Pietro Tundo · Liang-Nian He
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Editors

Chemistry Beyond Chlorine

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Foreword

On 25 September 2015, the United Nations Sustainable Development Summit adopted the document “Transforming Our World: The 2030 Agenda for Sustainable Development”.

This agenda is considered to be a plan of action for people, planet and prosperity. The 17 sustainable development goals and 169 targets which have been announced in the document demonstrate the scale and ambition of this new universal agenda. They are integrated and indivisible and balance the three dimensions of sustainable development: the economic, social and environmental. They reflect complexity and interdisciplinarity of world’s realities.

I do hope that the reader-chemist will not stop here, puzzled with a question: “What has all this to do with “Chemistry Beyond Chlorine”?” The answer is as follows. It is not possible to achieve sustainable development goals without broadening the application of chemical science and technology in all fields of human activities. However, the development of chemical industry poses novel challenges to humankind: the urgent problems are the safety of industrial processes and safe management of chemicals, especially the ones, which have no analogues in nature. Green chemistry – the scientific direction, which is actively supported by IUPAC – is addressed to solve these problems. “Chemistry Beyond Chlorine” demonstrates multiple examples of practical applications of principles of green chemistry. Twenty-two chapters cover a wide range of topics: new synthetic pathways, chlorine-free reagents, chlorine-free catalysts, phosgene replacement, utilization of CO_2 derivatives as chlorine replacements and metrics for chlorine-free synthesis.

The international team of the authors led by professor Pietro Tundo, one of the pioneers of green chemistry, state that “Chemistry Beyond Chlorine” “… is not committed in any way against chlorine chemistry; this would be out of common sense. Conversely, it should be considered as a useful tool to seek alternative pathways beyond chlorine chemistry so to open the way to new discovers which is the ultimate aim of Green Chemistry”. This statement goes in line with the Goal 12 that calls to “Ensure sustainable consumption and production patterns”. The targets to achieve this goal are defined as follows:

12.4 By 2020, achieve the environmentally sound management of chemicals and all wastes throughout their life cycle, in accordance with agreed international frameworks, and significantly reduce their release to air, water and soil in order to minimize their adverse impacts on human health and the environment
12.5 By 2030, substantially reduce waste generation through prevention, reduction, recycling and reuse
12.6 Encourage companies, especially large and transnational companies, to adopt sustainable practices and to integrate sustainability information into their reporting cycle

Chemistry attracts a lot of public attention because of its intrinsic diversity. Here are some examples. Elaboration of novel chemical compounds and materials with desirable properties helps to solve such problems as provision of humanity with pure water, food and medicines. On the other hand, it is necessary to pre-empt possible negative consequences, caused by careless exploitation of chemicals. The generations of the Earth inhabitants have been admiring the austere beauty of the monumental building of fundamental chemistry, while nowadays chemophobia attacks more and more people as the consequence of lack of attention to chemical education and popularization of scientific knowledge. "Chemistry Beyond Chlorine" clearly demonstrates that chemists are ready to meet these challenges.

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Introduction on the Design of a Chemistry Beyond Chlorine

Pietro Tundo, Liang-Nian He, Claudio Mota, Ekaterina Lokteva, Fabio Aricò, and Andrea Vavasori

Preamble

International Union of Pure and Applied Chemistry (IUPAC) and Green Chemistry

The IUPAC dedicated considerable attention to sustainable development and has published many issues on this topic, such as the IUPAC Position Paper on Sustainable Development for Rio + 20, June 2012. Moreover, the monograph for secondary

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schools on global climate change was translated from Italian into English, Greek, Romanian, Portuguese, Spanish, and Russian.

As green chemistry is specifically concerned, the IUPAC Subcommittee on Green Chemistry was founded on July 2001 and since then has embraced the following definition for green chemistry[1]:

> *Green Chemistry includes the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances.*

The first *Pure and Applied Chemistry* (PAC) journal special topic issue dedicated to green chemistry was published on July 2000.[1] Since then, five PAC special issues have been published on the occasion of the related international IUPAC conferences on green chemistry:

- 1st International IUPAC Conference on Green-Sustainable Chemistry (ICGC-1), Dresden, Germany, 10–15 September 2006: Issue 2007, Vol. 79, *11*
- 2nd ICGC-2, Moscow, Russia, 14–20 September 2008: Issue 2009, Vol. 81, *11*
- 3rd ICGC-3, Ottawa, Canada, 15–18 August 2010: Issue 2011, Vol. 83, *7*
- 4th ICGC-4, Foz do Iguaçu/PR, Brazil 25–29 August 2012
- 5th ICGC-5, Durban, South Africa 17–21 August 2014: *in print*

Moreover, the Symposium-in-Print on Synthetic Pathways and Processes in Green Chemistry, PAC, 2000, 72, No. 7, 1207–1228, should be considered along with the book series on green chemistry: *Green Chemistry in Africa*, *Green Chemistry in Latin America*, and *Green Chemistry in Russia*.

On chlorine-related topics, the IUPAC has already published a few reports on the utilization of chlorine, i.e., a 1996 PAC special issue[2] referred to as a "IUPAC White Book on Chlorine" edited by R. P. Martin and G. A. Martens. This issue is a contribution to the debate on the effect of chlorine and chlorine-containing compounds on the environment; of particular relevance is the conclusion of Prof. Albert Fischli, president of the IUPAC, who stated that "It is the responsibility of the scientific community to develop this science base, of the media to help them to inform the public in an understandable and unbiased way, of the public authority to take the relevant decisions on the bases of sound science and not on emotional reactions and of industry to act responsibly, endorsing product stewardship and responsible care. This is true for chlorine and its chemistry as well as it is for all human activities."

In 2012, another PAC special issue dedicated to "Chlorine-Free Synthesis for Green Chemistry"[3] has been edited as part of IUPAC Project No. 2008-016-1-300. This latter publication constitutes the preamble of the present book. However, the main difference is that the 2012 PAC special issue was constituted by 30 original scientific articles, while this present publication includes review articles as this book is intended for a broader audience besides scientists and professor, i.e., scholars and students. The main topic is related to innovative synthetic pathways

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[1] For a short history of green chemistry, see P. Tundo and F. Aricò. *Chem. Int.* **29**, 5, 4 (2007).

[2] Pure Appl. Chem. 1996 Vol. 68, No. 9, pp. 1683–1824.

[3] Pure Appl. Chem. 2012, Vol. 84, Issue 3.

using clearly identified production drivers (e.g., environmental and health impact, energy consumption, economical feasibility, etc.) as alternatives to chlorine-based synthetic approaches.

This book takes origin from IUPAC Project No. 2013-057-3-300 which was carried out by the Subcommittee on Green Chemistry (Division III), in collaboration with Division VI and the IUPAC Committee on Chemistry and Industry (COCI).

The book intends to point out the challenge of chlorine-free synthesis, and it deals with the following topics: new synthetic pathways, chlorine-free reagents, chlorine-free catalysts, phosgene replacement, utilization of CO_2 derivatives as chlorine replacements, and metrics for chlorine-free synthesis.

Introduction

First of all, it must be pointed out that this book is not committed in any way against chlorine chemistry; this would be out of common sense. Conversely, it should be considered as a useful tool to seek alternative pathways beyond chlorine chemistry so to open the way to new discovers which is the ultimate aim of Green Chemistry.

Among halogens, chlorine is by far the most abundant in nature[4] and is also the easiest and cheaper to produce and to use. This explains its predominant and irreplaceable role in the chemical industry. Five hundred companies at 650 sites around the world have the capacity to produce over 58 million metric tons of chlorine and 62 million metric tons of its by-product, caustic soda, per year.

In 2014, the European chlor-alkali industry had a production of 9612 kt, 1.7 % above the level of 2013, at about 80 plants, mostly (about 95 %) via electrolysis-based techniques (chlor-alkali industry); the sector directly employs about 40,000 people in 20 EU countries.

Germany is Europe’s largest chlorine producer accounting for 43.5 % of European production.[5]

Due to their peculiar characteristics, halogens are widely used by all sectors of the chemical industry to produce solvents, catalysts, building blocks, additives, and drugs. Chlorine is a major building block in today’s chemistry. More than 90 % of pharmaceuticals contain or are manufactured using chlorine, which is also used in the production of 86 % of crop protection chemicals. Furthermore, halogens are contained in several commodities that we all use daily such as plastics (e.g., chlorine is contained in PVC, one of the most widely used plastic materials), solvents for dry cleaning and metal degreasing, textiles, agrochemicals and pharmaceuticals, insecticides, dyestuffs, household cleaning products, and disinfectants.

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[4] N. Winterton, Green Chemistry, 2000, **2**, 173–225.

[5] Chlorine industry review 2014–2015, Eurochlor magazine www.eurochlor.org

Table 1 Tons of CO_2 produced/tons of product referred to different industrial sectors

Industrial sector	Tons CO_2 per tons of product
Cement industry	0.65–0.92 tons CO_2 per tons of cement
Ammonia production	1.15–1.30 tons CO_2 per tons of ammonia
Steel production	1.8 tons CO_2 per tons of steel
Chlorine production	2.1 tons CO_2 per tons of chlorine

Sources are: (a) EPA 2014 http://www.epa.gov/climatechange/Downloads/ghgemissions/US-GHG-Inventory-2014-Chapter-4-Industrial-Processes.pdf; (b) Euro Chlor 2010 http://www.eurochlor.org/media/9385/3-2-the_european_chlor-alkali_industry_-_an_electricity_intensive_sector_exposed_to_carbon_leakage.pdf; (c) WorldSteel 2014 http://www.worldsteel.org/dms/internetDocument List/bookshop/Steel-s-contribution-to-a-Low-Carbon-Future-2014/document/Steel_s%20contribution%20to%20a%20Low%20Carbon%20Future%202014.pdf; (d) Data, reported in this table are collected from the references a-c in which the authors did not specify if the ton values are tons USA (short ton 907.1847 kg) or tons UK (long ton 1,016.047 kg) or metric tonnes (1,000.000 kg)

Chlorine is used extensively in organic and inorganic chemistry as an oxidizing agent (i.e., water disinfectant) and as a leaving group in substitution and elimination reactions. Chlorine compounds find use as intermediates in the production of a number of important commercial products that do not contain chlorine. Foremost examples are polycarbonates, polyurethanes, silicones, polytetrafluoroethylene, carboxymethyl cellulose, and propylene oxide.

Through a chain of chemical derivatives and relatively easily made compounds and intermediates, such molecules have utilized the intrinsic energy available through the use of chlorine primarily produced via electrolysis of sodium chloride.

Chlorine is therefore "an iconic molecule" for industry, and humankind had major benefits from its exploitation; however, its production by the electrolysis of sodium chloride is energy intensive: due to a large amount of electric energy consumed, the CO_2 emission is comparable to that of the iron and steel industry and higher than for cement (Table 1). This energy is required for the electricity consumed in the electrolysis cells for the production of Cl_2 and for the utilities (motors, pumps, and illumination). In this context, electricity price is a crucial driver for chlorine production costs.[6]

Besides, we should bear in mind that chlorine-based chemistry very often does not obey the principles of atom economy and waste minimization introduced, respectively, by B. Trost and R. Sheldon; in fact, halogen anions are by-products of many organic reactions and represent a waste to be disposed of. Furthermore, Cl_2 and other halogens have negative impacts on global environment and health, e.g., toxicity and ecotoxicity, ozone layer depletion, energy consumption, and climate change. In this prospect, there is indeed a need to go forward, more precisely to go beyond chlorine chemistry.

Following this path, some primary questions we should pose are as follows: can we pursue an intrinsically safer, cleaner, and more energy-efficient alternative to chlorine chemistry? Many of society's greatest challenges and fortune depended on

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[6] Data published by www.eurochlor.org

Table 2 OECD seven research areas on sustainable chemistry (*approved at the OECD meeting in Paris, June 6, 1999*)

1.	Use of alternative feedstocks
2.	Use of innocuous reagents
3.	Employing natural processes
4.	Use of alternative solvents
5.	Design of safer chemicals
6.	Developing alternative reaction conditions
7.	Minimizing energy consumption

the chlor-alkali industry development, but is the chlorine-based chemistry sustainable?

The result, as chemical companies struggled to deal with increasingly stringent environmental regulations, was an industry-wide movement toward new principles of processes design which are often called “green chemistry.” New ways of synthesis using no chlorine compounds and none of those compounds where “chlorine is used in the making” mean that we avoid electrolysis as a primary energetic source; this makes chemistry without chlorine considerably more difficult and illustrates why it has not been adopted before.

An effective increase in the rate of introduction of new cleaner processes could derive only from a change of perspective, in which greener technologies are not only seen as a strategy to improve the image of chemistry but also as a novel business strategy for innovation. The environmental and health constraints and the growing need for energy (energy efficiency, climate change) force us to take advantage of the available knowledge to develop new chemical strategies.

It should be also pointed out that four out of the seven topics endorsed by the Organization for Economic Co-operation and Development (OECD) belong to chlorine-free chemistry (specifically No. 1, 2, 5, and 7, Table 2).

Chlorine-based compounds are used in the making of a number of important commercial products that might contain or not chlorine in the final molecular structure. For these compounds, alternative synthetic pathways which adopt a holistic and proactive approach and use no chlorine derivatives may provide new products and processes. Therefore, important chemical industries are already carrying out researches focusing on chlorine-free approach in their production; however, these studies are yet unknown, as they are protected by confidentiality issues.

Relevant examples for alternatives to chlorine in industry and academic syntheses will be useful to facilitate this trend and to hasten the development of industrially significant and implementable breakthrough technologies. As a result, the perception of the role of (green) chemistry in subjects of general interest such as chlorine chemistry will take advantage by the exploitation of the chemistry beyond chlorine. Chemists deserve to be perceived as creative people providing high input into prosperity of mankind and able to carry out and address a dialogue together with politicians, economists, entrepreneurs, and philosophers on sustainable development, instead as polluters of the planet.

In this context, we expect that this book will actively contribute to spread a more realistic and positive image of chemistry and chemists giving benefits to the chemical industry while helping to stimulate linkages between academia and industry.

A simple but poignant example would be the selectivity issue which is of great importance in such "beyond-chlorine" approaches. The use of a more selective reagent means that more of the starting material is going to be converted into the desired product. On the other hand, high product selectivity does not always translate into high product yield (and less waste generated). Both high selectivity and high conversion must be achieved to generate little or no waste during synthetic transformations; in fact, for a process or a product to be functional and green chemistry successful, they must be economically sustainable too.

Utilizing highly selective reagents can mean that separation, isolation, and purification of the product will be significantly less difficult. Since a substantial portion of the burden to the environment that chemical manufacturing processes incur often results from separation and purification processes, highly selective reagents are very desirable in green chemistry.

Another key point issue arising from the reported research is establishing innovative solutions that allow substitution of processes consuming phosgene and thionyl chloride by economically competitive and eco-efficient alternatives; this is a huge challenge for chemists. Phosgene is currently greatly valued as a versatile activating agent and as such essential to the production of chemical intermediates, engineering plastics, agrochemicals, and pharmaceuticals. At 2.2 million tons, phosgene is the second largest European outlet of chlorine (17 % at 1.8 million tons), and globally it accounts for 5 million metric tons of chlorine consumption per annum. In addition to its energy-intensive production process from chlorine and carbon monoxide, phosgene is highly toxic (currently classified as viable chemical warfare agent), corrosive, and aggressive, and in most applications, its use results in the stoichiometric formation of large amounts of solid waste (1.2 ton of sodium chloride per ton of phosgene or equivalent amount of salt). Replacement of phosgene, thionyl chloride, methyl halides, etc., will definitively improve workers' safety in chemical industries and surrounding communities. For instance, this book could have a significant impact, especially for the higher-value and lower-volume but more polluting compounds. The aims are to be able to access new structures or existing intermediates selectively and efficiently while avoiding waste and, moreover, to avoid additional reaction steps since one-pot synthetic technique means also saving on processing costs and freeing up of production capacity.

All these issues are discussed in the chapters of this book, and the related challenges and problems arising from investigated alternative chlorine-free pathways are impartially addressed.

Book Content

Nowadays it is particularly timely to investigate if alternative reagents are available that are either more environmentally benign themselves or are able to carry out the necessary synthetic transformation in a more environmentally benign way. In order to provide some answer to this question, alternative reagents must be identified, and any hazardous properties that they possess must be compared with those associated with the reagent originally selected.

The rationale behind this book is to seek useful industrially and academically relevant examples for alternatives to chlorine in synthesis, so as to facilitate the development of industrially relevant and implementable breakthrough technologies. The 22 chapters have been incorporated in 5 thematic areas:

New Synthesis illustrates completely new pathways that substitute reagents for such reactions as Grignard and cross-coupling ones. Special attention is given to phosphorus chemistry without halogens which is an emerging research field.

Alternative includes catalysis, biocatalysis, and polymers. Catalysis concerns the substitution of phosgene into isocyanate production and the use of acid chlorine-free catalysis. Biocatalysis is another tool to achieve organic compounds, and then alternative products to chlorine will be polymers that don't contain chlorine.

Substitutives of Chlorine and Chlorine Compounds deals with the utilization of CO_2 as building block for the synthesis of dialkyl carbonates (DACs).

DACs Utilization concerns the utilization of dialkyl carbonates in organic synthesis.

Chlorine Derivative Utilization and Recycle deals with the present chlorine derivative utilization in the chemical industry together with the recycle of chlorine-containing compounds.

Metrics describes green metrics that are applied to the synthesis of dicyclohexylcarbodiimide with and without chlorine.

Illustration of the Book Content

New Synthesis

General Chemists have nowadays an amazing state-of-the-art capability to prepare millions of organic compounds. However, as what R. Noyori stated, chemists must also pursue "practical elegance."[7] This means that today the main synthetic challenge is to pursue processes that are safe, environmentally benign, as well as reasonable in terms of cost, resources, and energy.

Catalytic hydrogenation, oxidation, and carbonylation are good examples of highly atom-efficient and low-salt processes. It is a fact that industrial sustainable chemistry is not an emerging trend, but is already a reality thanks to the application of "green" chemistry and engineering expertise.[8] The generation of copious amounts of inorganic salts can similarly be largely circumvented by replacing stoichiometric mineral acids, such as H_2SO_4, and Lewis acids and stoichiometric bases, such as

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[7] R. Noyori, Chemm. Commun. 2005, 1807–1811.

[8] J. F. Jenck, F. Agterberg, M. J. Droescherc. *Green Chem.* 2004, 544.

NaOH and KOH, with recyclable solid acids and bases, preferably in catalytic amounts. A large number of industrial processes are based on the use of inorganic or mineral acids. While many of these processes are catalytic, some require stoichiometric amounts of Bronsted or Lewis acids.[9]

Catalytic Grignard-type addition of aryl C-H bonds to polar $C=O$ or $C=N$ bonds mediated by transition metals is a very attractive approach to synthesize alcohols, amines, and their derivatives by avoiding generating a stoichiometric amount of metal and halide wastes associated with the classical Grignard-type reaction. However, there are many challenges to be still solved such as the development of inexpensive catalysts with lower catalyst loading and the need to operate with directing groups (Chap. 1).

The transition metal-catalyzed cross-coupling reactions are one of the most powerful tools of organic synthesis widely used in both academy and industry.

In Chap. 2, the progress in the direct oxidative (dehydrogenative) transition metal-mediated C-C coupling reactions, run via formal double C-H bond activation, which doesn't require utilization of substrates activated by halogens, is very comprehensively reported.

1. *Catalytic Grignard-Type Addition of Aryl C-H Bonds to $C=O$ and $C=N$ Bonds* (F. Wang, W. Liu and C.-J. Li)
2. *The Halogen-Less Catalytic Transition Metal-Mediated Cross-Coupling Reactions: A Sustainable Alternative for Utilisation of Organohalides* (O. M. Demchuk, R. Jasiński, A. Formela)

Phosphorus Recently, a few authors have published papers on sustainable phosphorus chemistry, dealing with Wittig reaction not involving halogen derivatives.[10] The interest in this field is also demonstrated by the conferences dealing with this topic, i.e., the Second International Conference on Sustainable Phosphorus Chemistry (ICSPC) 2016 will be held in Berlin (the previous one was held in Florence, 4–5 Dec. 2014). The idea of considering alternative pathways is gaining interest also on production of other chemical element derivatives.

Organophosphorus compounds have a paramount role in our everyday life, and this is motivating a growing interest in the synthesis of these compounds, and an environmentally friendly approach which avoids the use of chlorine and other highly toxic compounds is of tremendous interest. Two main possible alternatives are herein discussed in Chap. 3: (a) the establishment of an efficient catalytic protocol which can directly convert elemental phosphorus into the desired organophosphorus derivative by using a transition metal as catalyst and (b) the use of hypophosphorus acid or its salts as "P source" to carry out the phosphorylation of organic building blocks in a selective way.

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[9] (a) D. Schinzer in *Selectivities in Lewis Acid Promoted Reactions*, Kluwer Academic Publishers, Dordrecht (1989); (b) H. Yamamoto in *Lewis Acids in Organic Synthesis*; Wiley-VCH: Weinheim (2000).

[10] J. J. Weigend et al *ChemSusChem* **4**, 1805 (2011).

The future challenge will be the transferring of the know-how from academia to the plant manufacturer with complete abandonment of the $PCl_3/POCl_3$-based technology and consequent reduction of the environmental impact linked to the preparation of organophosphorus derivatives.

The aspects of using hypophosphorus acid and its salts as reagents for organophosphorus compounds are summarized in Chap. 4 which is focused on synthesis of α-aminophosphinic acid, α-aminophosphinates, H-phosphinic acids, and H-phosphinates.

3. *Benign Chlorine-Free Approaches to Organophosphorus Compounds* (M. Caporali, M. Serrano Ruiz, M. Peruzzini)
4. *Hypophosphorus Acid and Its Salts as Reagents in Organophosphorus Chemistry* (A. Visa, B. Maranescu, G. Ilia)

Alternative

Catalysis Most of the industrial processes to produce fuels and chemicals comprise catalytic stages. Catalysis is one of the pillars of green chemistry due to its technological and economical importance. A book describing the chemistry beyond chlorine would not be complete without discussing catalysis beyond chlorine.

Hydrochloric acid is used in the synthesis of methylene-dianiline (MDA) from aniline, and phosgene is used in its conversion to the corresponding isocyanates (MDI). Huge quantities of sodium chloride are generated during the processes and they need to be disposed off. New processes have been studied in order to avoid the use of HCl and phosgene in such productions and make them completely chlorine-free.

Chapter 5 describes possible phosgene-free routes to produce either MDA or MDI. For the production of MDA, zeolites have been used as solid acid catalysts. Among the routes considered to eliminate phosgene for the production of MDI, the synthesis of carbamate alkyl esters with subsequent pyrolysis at elevated temperatures seemed to be the most feasible; this opens the way for an industrial process through the DMC synthesis step.

Aluminum chloride and hydrochloric acid are among the most traditional Lewis and Bronsted acid catalysts, respectively. $AlCl_3$ has been largely used in Friedel-Crafts and other related alkylations, yielding significant amounts of residues and corrosion problems. Today, many industrial alkylation processes use zeolites and other solid acids as catalysts, replacing the old and dirty aluminum chloride. The benefits of using zeolites include not only the reduction of environmental impact caused by chlorine-containing acid catalysts but also shape selectivity properties and wide variety of forms providing great possibility of producing the desired products in higher yields by minimization of secondary reactions due to proper choice of the composition and framework structure. This implies that catalysis has to be as efficient (not only effective) as possible, involving a high turnover. Alternative catalysts are discussed in Chaps. 6 and 7.

5. *Catalytic Processes for Environmentally Friendly Methylene Diphenyl Diisocyanate Production* (A. de Angelis, A. Bosetti, R. Millini and C. Perego)
6. *Chlorine-Free Heterogeneous Acid Catalysts* (C. J. A. Mota)
7. *Chlorine-Free Catalysis for the Synthesis of Dialkyl Carbonate via Oxidative Carbonylation of Alcohols* (S. Huang, Y. Dong, S. Wang, X. Ma)

Biocatalysis Today, biomass processing is becoming increasingly important due to the global warming. Hydrolysis of lignocellulosic materials is advancing rapidly to produce sugars that may be fermented into ethanol and other fuels and chemicals. This process involves several steps and the use of enzymes, instead of hydrochloric acid, is gaining increasing attention. This topic is also covered in the book, showing that a complete sustainable production of biofuels can be accomplished with the use of chlorine-free processes (Chap. 8).

Chlorine-based flocculants are commonly used to enhance the flocculation and sedimentation of particles in suspension in water and other liquids, while chlorine is the major element used for disinfection of drinking water. The replacement of inorganic chloride salts with bio-flocculants, biodegradable and food-grade flocculants for use in food and water treatment process, is discussed in Chap. 9, together with a description of a comparative coagulation-flocculation experiment.

8. *Chlorine-Free Biomass Processing*: *Enzymatic Alternatives for Bleaching and Hydrolysis of Lignocellulosic Materials* (M. Fernandes de Souza, R. Sposina Sobral Teixeira, A. SantAna da Silva, V. S. Ferreira-Leit, E. Pinto da Silva Bon)
9. *Substitution of Chloride Chemicals with Degradable Bio-flocculants for Sedimentation of Suspended Particles in Water* (Y. Shevah)

Polymers New chlorine-containing polymers with prospective consumer characteristics can be easily produced by simple methods; moreover, chlorine processes are technologically attractive for intermediate stages of polymer synthesis. Thus, the so-called "chloric cycle" of silicone production, which is important for polymer materials, involves an addition of chlorine to a silicon atom at the first stage and removal of chlorine on subsequent stages. The problems, connected with the replacement of such cheap and simple strategies of polymer production process design by more environmentally benign ones, are discussed in Chaps. 10 and 11. It has been shown that eliminating the need for chlorine-containing compounds in this sector is very challenging, but an achievable goal.

10. *A Green Method for Potentially Recycling Condensation Polymers*: *Ring-Chain Recycling* (P. Hodge)
11. *Polymers Beyond Chlorine* (A. Muzafarov)

Substitutive

CO_2 as a Feedstock for Dialkyl Carbonates (DACs) Synthesis

Burning fossil fuels is the primary source of nonnatural CO_2 emission, estimated around 1460 $MtCO_2 \cdot Year^{-1}$,[11] and is the basis of worldwide primary energy production. Power plants; oil refineries; production of ammonia, ethylene oxide, cement, iron, and steel; and chlorine chemistry are the main industrial sources of CO_2. However, crude oil is a nonrenewable resource. Thus, it is extremely important to develop a new green methodology capable to prevent any further increase in the level of atmospheric CO_2 and to develop alternative, sustainable starting materials for the chemical industry.

In this context, *c*hemical conversion of CO_2 as feedstock or promoter or reaction media for producing materials and fuels is attractive as an integral part of carbon cycle.[12] In particular, establishing large-scale production using CO_2 in industry as non-chloride carbonylating agent to produce, e.g., phosgene or methyl chloroformate would be a fascinating dream for synthetic chemists, but nevertheless they are energetically highly disadvantaged. The crucial challenge is to develop efficacious catalysts that are capable of activating CO_2 under low pressure (preferably at 1 bar) and thus incorporating CO_2 into organic molecules catalytically.[13]

In this section, several investigations on the use of CO_2 as a feedstock for DACs synthesis are reported. Specific chapters (Chaps. 12, 13, 14, 15, and 16) are focused on:

– Catalytic reactions of CO_2 and CO_2-derived material transformation to useful chemicals
– The use of CO_2 for the catalyzed synthesis of carbonyl-containing value-added chemicals
– Recent advances on two-step industrial technology of DMC production; recent progress in the direct and phosgene-free synthesis of DMC
– Studies on the mechanistic understanding of oxidative carbonylation of alcohols promoted by chlorine-free catalysts
– Preparation of organic cyclic carbonates and polycarbonates from CO_2 including their enantiomers, as well as their applications in organic synthesis, material fabrications, chemical industry, agriculture, and medical treatment
– Recent applications of organic carbonates in organic transformation reactions catalyzed by ionic liquids

12. *Synthesis of Carbonate Compounds Using Carbon Dioxide and Carbon Dioxide-Derived Materials* (S.-I. Fujita, H. Yoshida, M. Arai)

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[11] Aresta, M.; Dibenedetto, A.; Angelini, A. *J. CO_2 Util.* **2013**, 65.

[12] An-Hua Liu, Yu-Nong Li, and Liang-Nian He, Organic synthesis using carbon dioxide as phosgene-free carbonyl reagent, *Pure Appl. Chem.* **2012**, 84, 3, 581–602.

[13] Liang-Nian He, Carbon dioxide chemistry. Beijing, Chinese Science Press, **2013**.

13. *Research Progress in the Phosgene-Free and Direct Synthesis of Dimethyl Carbonate from CO_2 and Methanol* (Z. Fu and Y. Meng)
14. *Industrial Production of Dimethyl Carbonate from CO_2 in China* (M.-Y. Wang, H.-B. Wang, Q.-H. Qu, L.-N. He)
15. *Halide-Free Synthesis of Cyclic and Polycarbonates* (I. D. V. Ingram, M. North and X. Wu)
16. *Heterocyclic Synthesis Through C-N Bond Formation with Carbon Dioxide* (Q.-W. Song and L.-N. He)

DACs Utilization

CO_2-based organic compounds are among the most promising molecules which could aid the substitution of several chlorine-based chemicals. However, there is one major problem in the utilization of CO_2-derived organic chemicals; they are very stable, so they require an energy input to be activated and consequently to react. DACs and DMC, once synthesized by phosgene, are, since the 1980s, produced by clean processes.[14] DACs are renowned for possessing properties of low toxicity and high biodegradability, which make them true green solvents and reagents and thus appropriate alternatives to chlorine chemistry.

DMC is a versatile compound which represents an attractive eco-friendly alternative to both methyl halides (or dimethyl sulfate) and phosgene for methylation and methoxycarbonylation processes, respectively.[15] Nowadays, DMC is widely used for the synthesis of pharmaceutical intermediates, flavors and fragrances, surfactants, softeners, electronics, aromatic polycarbonates, optical organic glasses, methylisocyanate, polyurethanes, synthetic lubricants, etc.

Noteworthy, DMC and chlorine chemistries have numerous similarities; since its reactivity is tunable, DMC can be used either as a methoxycarbonylation or methylation agent replacing:

(a) $SOCl_2$: The carbonate derivatives can be used in S_N2 reactions as methylation and methoxycarbonylation agents instead of the corresponding chloro-derivatives such as alkyl and acyl chlorides.
(b) $COCl_2$: DMC and organic carbonates can be used in place of phosgene for the synthesis of urethanes, carbamates, and isocyanates.
(c) Chlorinated solvents: Organic carbonates can be used in place of CH_2Cl_2 and $CHCl_3$ making the synthesis safe.

Organic carbonates are an alternative to chloride chemistry: ex ante CO_2 and CO_2 derivate chemistry substitutes the chlorine-based chemistry providing the

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[14] Asahi Kasei Chemicals Corporation Patent, WO2007/34669 A1, 2007.

[15] (a) Tundo, P.; Anastas P. Eds. Dimethylcarbonate: Challenging Perspectives, Rivetti, F. Oxford University Press, 2000, 201; (b) Sweet, D. V. Ed. Registry of toxic effects of chemical substances, 1986, 2, 186; (c) Tundo, P.; Rossi, L.; Loris A. *J. Org. Chem.* **2005**, 70 (6), 2219.

reduction of the world chlorine demand and thus the CO_2 emission due to the decrease of energy consumption; ex post organic carbonates are synthesized starting from the CO_2 insertion into epoxides and this allows the reuse of CO_2 emitted.

In the last 20 years, the reactivity of DMC in particular and DACs in general has been widely investigated as shown by the exponential increase in the number of publications (50 % increase in the last 10 years). Thus, the knowledge on DMC is nowadays good enough to extend its boundaries into innovative and exciting directions in both basic and applied research. From a scientific and technical point of view, the most important appealing feature is the possibility to find new synthetic pathways to obtain absolutely new products as for the synthesis of heterocyclic and cyclic carbamates which opens up the way of DACs chemistry to new unexpected frontiers of research and applications.

Carbonates are implicated also in other reactions. In particular, rearrangements opened the way to new compounds which now turn out to be interesting as new monomers which may allow the synthesis of polyurethanes by polymerization of the alkene functionality.

The peculiar selectivity that DACs had showed over the years has led to numerous industrial applications and consequently many patents.[16]

Applications of DACs as beyond-chlorine reagents in organic transformation catalyzed by ionic liquids and for the preparation of linear and cyclic carbamates via dialkyl carbonate chemistry are herein discussed (Chaps. 17, 18, and 19).

17. *Beyond-Chlorine Reagents*: *Organic Carbonate Chemistry* (H. Jing)
18. *Application of Organic Carbonates in Organic Transformation Catalyzed by Ionic Liquids* (B. Wang, E. H. M. Elageed, G. Gao)
19. *Linear and Cyclic Carbamates* via *Dialkyl Carbonate Chemistry* (P. Tundo, F. Aricò and A. Aldoshin)

Chlorine Derivative Utilization and Recycle

Utilization It is aimless to discuss chemistry beyond chlorine without outlining the state of the art, main products, and problems of chlorine industry. Now a good few of organochlorine products are widely used by humankind. Between them, the mention could be made of epichlorohydrin, chloroprene, and vinyl chloride which are used to produce the various resins, polymers itself, as well as methyl chloride and chloroform which are widely used for the production of organosilicon and

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[16] Some industrial patents which involve the use of DMC are (a) Wu, X.; Park, Y. J.; Ryu, K. S.; Chang, S. H.; Hong Y. US Patent 20040105809, 2004; (b) Carey, J. T.; Thomas, J.; Oumar-Mahamat, H. US Patent 5962379, 1999; (c) Schlosberg, R. H.; Larson, T.; Yezrielev, A. I.; Ilya, A.; Knudsen, G. US Patent 6818049, 2004; (d) Goldberg, L.; Le Flohic, M.; US Patent 5346615, 2003.

organofluorine compounds. Between polymers, the most widespread is PVC. Modern technologies of production and application of these products, between them balanced schemes that prevent environment pollution by the waste hydrochloric acid, are discussed in this book (Chap. 20).

20. *State of the Art and Problems of Organochlorine Synthesis* (Y. Treger and M. Flid)

Recycle Till now significant amounts of chlorinated organic wastes need qualified disposal. The production of many dangerous chlorinated organic products such as polychlorinated biphenyls was banished or diminished. However, other chlorinated substances are produced in constantly growing amounts such as polychlorinated polymers, especially PVC. The PVC production in the world has grown from 24.7 million tons in 2000 to 32.3 million tons in 2009. It is expected to reach around 55.2 million tons in 2020.[17] In addition, due to widespread use of chlorinated organics in the past, careful monitoring of chlorinated waste presence in water, soil, and atmosphere is needed. Additional problem is connected with the combustion of industrial and household wastes which can contain chlorinated ingredients, because dioxin formation in vent gases is quite likely due to catalytic action of transition metal (e.g., Ni) compounds which are components of fly ash and pipeline materials.[18] Therefore, special attention is paid in the book to the issues connected with chlorinated waste disposal, with the emphasis on chlorinated polymeric waste recycle and transformation to form absorbents or other useful materials (Chap. 21).

21. *Disposal of Chlorine-Containing Wastes* (E. Lokteva, E. Golubina, V. Likholobov and V. Lunin)

Metrics

Metrics in green chemistry are indicators of environmental issues and pollution associated with chemical manufacturing. Green metrics provide information already in the design phase of a chemical process and indicate consumptions measured as material and energy flows and waste or toxic release emissions. Thus, by their application, chemists can improve their awareness of environmental issues related to new products as well as to existing ones.

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[17] http://www.businesswire.com/news/home/20110110006117/en/Research-Markets-Polyvinyl-Chloride-PVC-Global-Supply (accessed Jan. 2016)].

[18] Yang J, Yan M, Li X, Lu Sh, Chen T, Yan J, Olie K, Bueken A (2015) Formation of dioxins on NiO and NiCl2 at different oxygen concentrations. Chemosphere 133: 97–102].

Metrics evaluation is often required for the assessment of the operations of a process plant, as they indicate human toxicity, toxicity pathway, and ecotoxicity.[19]

From these bases, Andros built up meticulously the algebra of organic synthesis by employing green metrics.[20]

Green metrics are here determined for various synthesis plans for dicyclohexylcarbodiimide (DCC) covering material efficiency, environmental impact, safety-hazard impact, and energy input demands to identify the greenest plan available to make this important dehydrating reagent. Chlorine-based routes using phosgene chemistry are juxtaposed against non-chlorine-based routes.

The four-step plan involving dimethyl carbonate chemistry is the best performing non-chlorine-based route when material efficiency, environmental impact, and safety-hazard impact are considered; however, it is the worst with respect to energy input demands. Dicyclohexylthiourea chemistry is the winning plan with respect to least energy consumption, but ranks third with respect to the other three categories of analysis, very close behind the dimethyl carbonate route.

It is hoped that the kinds of analyses described herein may serve as a template for the examination of greenness of any set of synthesis plans to any specified target molecule (Chap. 22).

22. *Application of Green Metrics Analysis to the Synthesis of Dicyclohexylcarbodiimide (dcc) Comparison of Chlorine Versus Non-chlorine-Based Routes* (J. Andraos)

Conclusions

The beyond-chlorine field is an ideal area to conduct research on and to train young scientists. By its very nature, this research area requires inputs from several disciplines, as design and synthesis, engineering, and modeling issues are always intertwined with chemical ones in the solution of research problems. In addition, sustainability issues are extremely relevant to the younger generation in their career choices and offer a very appropriate training ground, as they combine novel chemical processes with a clean, green image.

By intensive research in novel reaction pathways, catalyst development, CO_2 and DACs utilization, and green metrics evaluation, we expect to develop several eco-efficient processes also through a non-petroleum route.

Beyond-chlorine chemistry could provide numerous other opportunities for alternative applications and derivatives resulting in new, competitive, and

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[19] a. T. Hudlicky, D. A. Frey, L. Koroniak, C. D. Claeboe, Jr. L. E. Brammer. Green Chem. 57 (1999). b. R. A. Sheldon. *Chem. Ind.* (*London*) 12 (1997). c. B. M. Trost. *Science* **254**, 1471 (1991). d. C. Jimenez-Gonzalez, C. S. Ponder, Q. B. Broxterman, J. B. Manley. *Org. Process Res. Dev.***15** (4), 912 (2011).

[20] J. Andraos in The Algebra of Organic Synthesis: Green Metrics, Green Metrics, Design Strategy, Route Selection, and Optimization, CRC Press (2012).

resource-efficient process knowledge, based on novel chlorine-free synthetic reactions, for the production of safe and eco-efficient chemical intermediates and materials relevant to many sectors. These technologies are expected to significantly enhance the long-term competitiveness of the industry as a whole, especially if this generic philosophy will be adopted by other resource-intensive sectors of the industry. The combination of innovative process technology and highly selective, multifunctional catalysts will serve as a model example and bring about a radical shift in the way chemical conversion processes will be designed allowing the chemical industry to set future sustainable standards and to be closer to customers' needs and requests.

We do understand that the topics covered by this book are incomplete for such a huge challenge. However, we are confident that the work done shall stimulate further researches and applications.

Part I
New Syntheses: *General*

Chapter 1
Catalytic Grignard-Type Addition of Aryl C-H Bonds to C=O and C=N Bonds

Feng Wang, Wenbo Liu, and Chao-Jun Li

Abstract As an alternative to the classical Grignard reaction, transition-metal catalyzed direct addition of aryl C-H bonds to carbonyl groups and their analogues have recently attracted increasing attention due to its atom economy, environmental benefits, abundance of C-H bonds as well as the scientific challenging to achieve mild C-H activations. This chapter briefly summarizes the recent progress in this field, categorized according to different metal catalysts. Applications to synthesize heterocycles and other useful molecules were highlighted as examples. Both the major challenges and the strategies to solve them are discussed in this chapter.

Keywords Aldehyde • Atom-economy • C-H activation • Grignard-type reaction • Imine

1.1 Introduction

The Grignard reaction is an important and classical method to construct C-C bonds by nucleophilic addition of Grignard reagents to carbonyl groups or their derivatives. Despite its high efficiency and broad application in organic synthesis, some limitations still remain. For example, Grignard reagents require strict anhydrous and anaerobic handling, and organic halides, commonly derivatized from C-H compounds, are employed as the precursors to generate Grignard reagents, which would release stoichiometric halide wastes in hydrolysis step. From the perspective of atom economy, using C-H bonds rather than C-X as the precursor of Grignard reagents, bearing an overall 100 % theoretical atom efficacy [1], is a greener methodology to overcome these drawbacks (Scheme 1.1). Over the past decades, transition metal-catalyzed coupling of C-H bonds to unsaturated alkenes and alkynes was well developed [2–4]; however, the addition of aryl C-H bonds to polar C=Y (Y = O, N) bonds was relatively rare due to the more covalent nature and weaker nucleophilicity of C-M (M = transition metal) bonds derived from C-H

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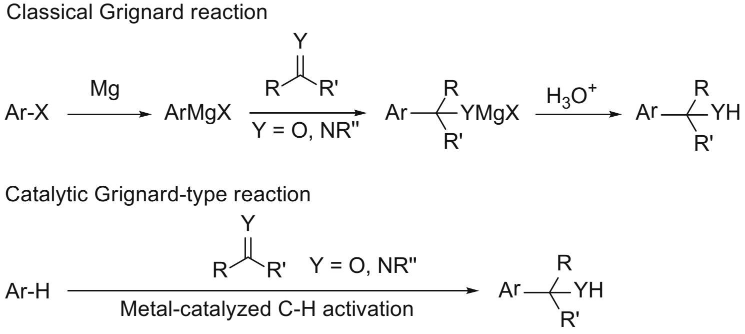
P. Tundo et al. (eds.), *Chemistry Beyond Chlorine*,
DOI 10.1007/978-3-319-30073-3_1



Scheme 1.1 Comparison of catalytic Grignard-type reaction and classical Grignard reaction

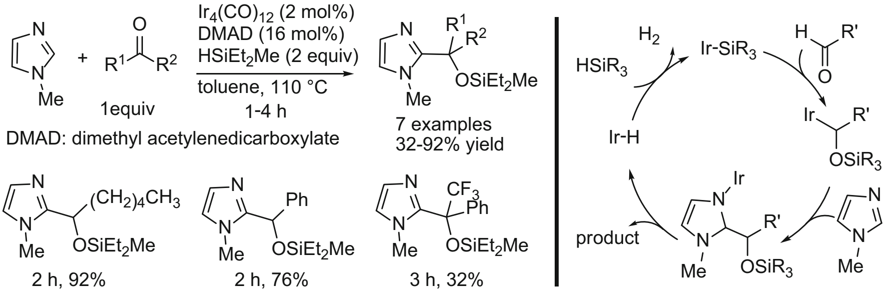
bonds, which make the addition untoward and the addition to C=O bond step reversible, thus the catalytic cycle difficult to proceed [5–8]. In order to solve this dilemma, various methods have been developed. Among these methods, silane capture, C-H activation/intramolecular annulations (or aromatization), and utilizing highly electron-deficient aldehydes as reaction partners have been the three important strategies.

This chapter will give a brief review of catalytic Grignard-type addition of aryl C-H bonds to C=Y bonds based on different types of transition metals. Due to very different mechanistic pathways, the catalytic addition of aryl C-H bonds to the C=O bonds of carbon monoxide and carbon dioxide is not included.

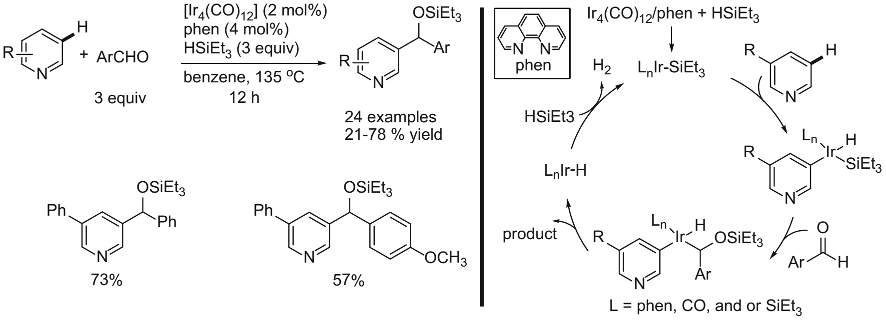
1.1.1 Iridium Catalyzed

In 2002, Murai and co-workers reported the first elegant example of Ir-catalyzed formal direct addition of imidazoles onto aldehydes in the presence of a co-reactant hydrosilane to produce 2-substituted imidazoles (Scheme 1.2) [9]. An air-stable iridium species, tetrairidium dodecacarbonyl [$Ir_4(CO)_{12}$], was applied as the metal catalyst. Using dimethyl acetylenedicarboxylate (DMAD) as a ligand greatly improved the yields. Experimental results indicated that diethylmethylsilane was essential to the reaction because no products could be detected in its absence. The authors speculated that the reaction was initiated by the reduction of aldehydes rather than the activation of the relative acidic C2 position C-H bonds of imidazoles by the iridium catalyst. The reaction gave higher yields with aliphatic aldehydes than aromatic aldehydes, whereas ketones had the lowest reactivity, which could react with silane to form the side products.

Using the same iridium catalyst, $Ir_4(CO)_{12}$, but a different ligand, Shi and co-workers successfully coupled pyridines with aryl aldehydes at the C3 position in 2011 (Scheme 1.3) [10]. This reaction fully displayed the power of silane capture methodology in the overall catalytic Grignard-type addition of aryl C-H bond to



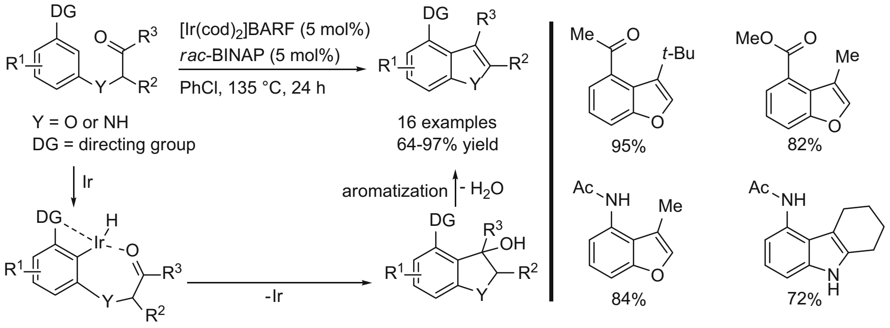
Scheme 1.2 Ir-catalyzed formal direct addition of imidazole onto aldehyde



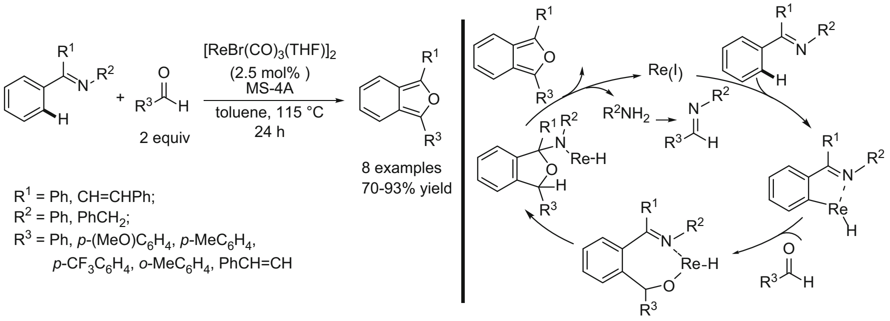
Scheme 1.3 Ir-catalyzed pyridine C3 C–H bond addition onto aryl aldehyde

C=O bond. Since most intermolecular C-H functionalizations of pyridines without activating or directing groups generally occur at the C2 position, Shi's work was the first example to functionalize the C3 C-H bond. The reaction gave higher yields for electron-deficient aromatic aldehydes than electron-rich aliphatic aldehydes, and aryl halides were compatible despite the tendency to undergo silylation or dehalogenation. Through mechanistic studies, the authors proposed that the reaction started from an active silyl iridium complexes and then underwent a *meta* selectively pyridyl C-H bond oxidative addition resulting in the key intermediates. The oxophilic property of silyl group in this key intermediate promoted the insertion of aldehyde C=O bond through the formation of strong Si-O bond. Finally, forming C-C bond through reductive elimination led to the addition products and an iridium hydride species which reacted with hydrosilane to regenerate the active silyl iridium catalyst.

In 2009, Shibata and co-workers successfully activated phenyl C-H bonds using a cationic [Ir(cod)$_2$]BARF catalyst with the assistance of directing groups [11]. Different from the silane capture strategy, they took the advantage of dehydration to form stable aromatic rings as the driving force to achieve the goal. A variety of substituted benzofurans and indoles were synthesized in high yields through this protocol intramolecularly (Scheme 1.4).



Scheme 1.4 Ir-catalyzed intramolecular addition of phenyl C–H bond onto ketone

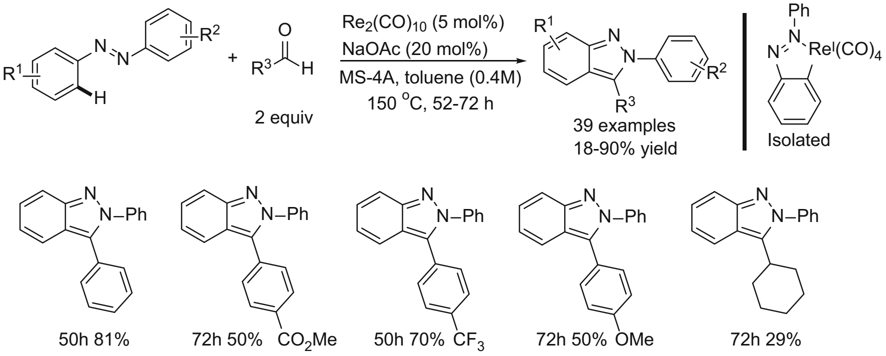


Scheme 1.5 Re-catalyzed ketimine C–H bond addition onto aldehyde C=O bond

1.1.2 Rhenium Catalyzed

In 2006, Takai and co-workers reported a groundbreaking result of a rhenium-catalyzed aromatic ketimines C-H bonds inserting into polar unsaturated C=O bond (Scheme 1.5) [12], representing an example of C-H activation/intramolecular annulations/aromatization methodology. Coordination of nitrogen atom from imine group to rhenium facilitated *ortho* C-H bond activation; and, more importantly, addition of the generated rhenium-carbon bond to aromatic aldehyde C=O bond was promoted by further intramolecular nucleophilic cyclization and aromatization process. Because of the formed aniline which reacted with 1 equiv aldehydes, 2 equiv aldehydes were thus required to complete the reaction. Addition of molecular sieves to remove water greatly enhanced the product yields. Using this rhenium catalyst, naphthalene derivatives were synthesized by further adding dienophiles to trap the cyclization product [13], whereas phthalimidine derivatives were formed in high yields when replacing the aldehyde by isocyanates [14].

Recently, Wang and co-workers reported a rhenium-catalyzed C-H bond activation of azobenzenes through azo functional group chelating assistance to obtain 2*H*-indazoles (Scheme 1.6) [15]. They characterized the cyclic Re^I complexes to



Scheme 1.6 Re-catalyzed addition of azobenzene C–H bond onto aldehyde C=O bond

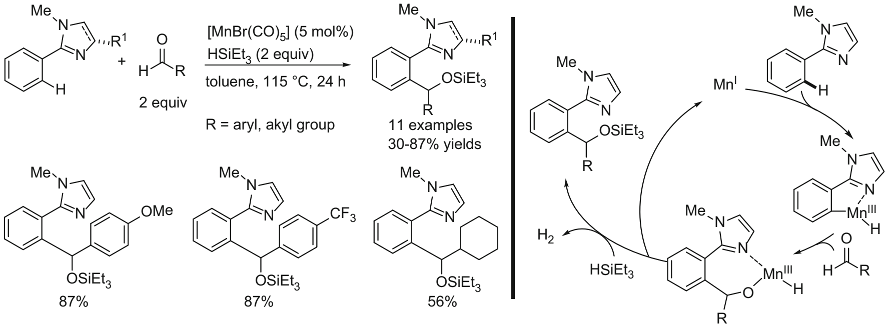
confirm a reversible deprotonation process, and further mechanistic studies revealed an irreversible aldehyde insertion process, which was in sharp contrast to Shi's and Bergman's work [16, 17]. Base was crucial to the reaction and acetate acted as a catalytic proton shuttle. The required prolonged reaction time at high temperature might be due to the low reactivity of aldehydes.

1.1.3 Manganese Catalyzed

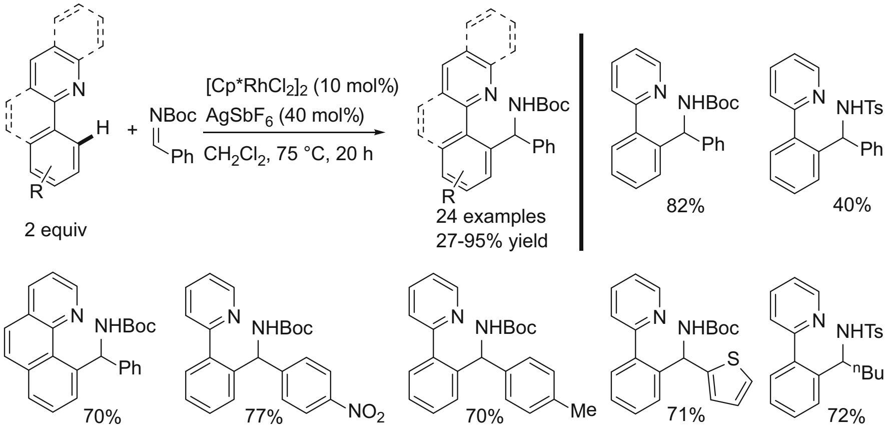
Manganese belongs to the fourth row *d* block transition metal, which is abundant and inexpensive compared to the fifth and sixth ones. However, manganese complexes are scarcely used as catalysts in C-H bond activation [18]. In 2007, Takai and co-workers reported a manganese-catalyzed phenyl C-H addition to aldehyde C=O bonds through using imidazole as directing group and co-reactant silanes to provide silyl ethers (Scheme 1.7) [19]. Similarly with the previous work, the success of this system was also attributed to the oxylic capture by silane.

1.1.4 Rhodium Catalyzed

Rhodium catalysts have been widely employed for C-H bond activation. At the beginning, nonpolar unsaturated double or triple carbon-carbon bonds were usually selected as reaction partners to form C-C bonds [20]. Then, moderately polar molecules such as α,β-unsaturated carbonyl compounds were used to synthesize acyclic or cyclic compounds [21, 22]. However, nucleophilic addition of C-H bonds to polar unsaturated C=O and C=N bonds in aldehydes, ketones, ketimines, and aldimines was difficult to achieve. Such additions were first achieved in 2011 independently by three groups: C=N bond addition by Bergman/Ellman [23] and Shi [24] and C=O bond addition by our group [25].



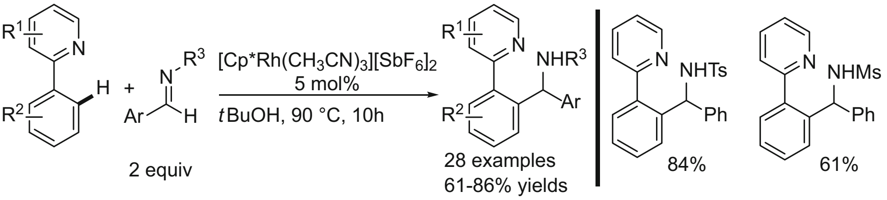
Scheme 1.7 Mn-catalyzed phenyl C–H bond addition onto aldehyde C=O bond



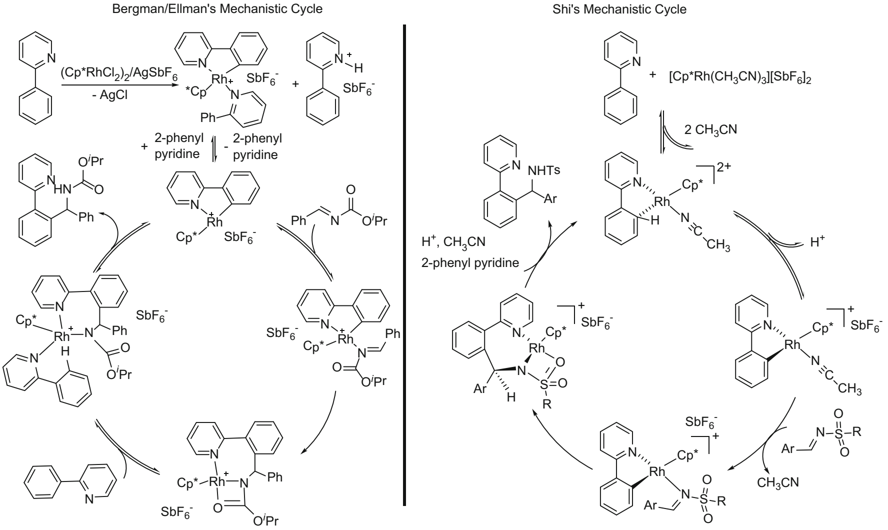
Scheme 1.8 [Cp*RhCl$_2$]$_2$/AgSbF$_6$-catalyzed aryl C–H bond addition onto C=N bond

1.1.4.1 Addition onto C=N Bond

In 2011, Bergman and Ellman published a protocol, in which through using nitrogen heterocycles as directing groups and rhodium^{III} as the catalyst, aryl C-H bond could be activated inserting into *N*-Boc-imines to afford *α*-branched amine products (Scheme 1.8) [23]. They indicated that [Cp*RhCl$_2$]$_2$/AgSbF$_6$ mixture was an efficient catalytic system and silver additive was crucial by removing halides from the rhodium. The reaction is robust and can tolerate various reactive functional groups such as esters, amides, aldehydes, and aryl chlorides. Further exploration of this reaction revealed that the addition was also effective for polar C=N bond of isocyanates to produce benzamides. Subsequently, they found that *N*-acyl amino directing groups were also effective for such reactions and they were also more readily available and easily removable [26].



Scheme 1.9 [Cp*Rh(CH_3CN)$_3$][SbF_6]$_2$-catalyzed aryl C–H bond addition onto C=N bond



Scheme 1.10 Mechanistic cycles proposed by Bergman/Ellman and Shi

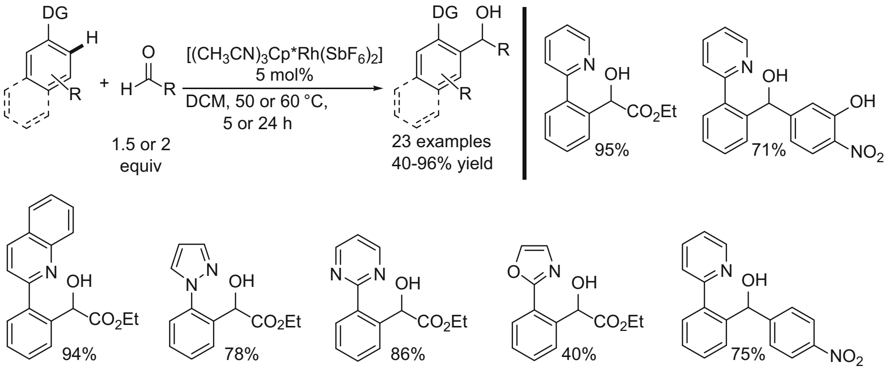
Independently, Shi's group reported a similar C=N bond addition in 2011 (Scheme 1.9) [24]. In Shi's work, they preformed catalyst [Cp*Rh(CH_3CN)$_3$][SbF_6]$_2$ instead of combining [Cp*RhCl_2]$_2$ with AgSbF_6. Notably, the reaction could be handled under air despite a small decrease of yield.

The two groups proposed two slightly different catalytic cycles both involving the same key steps (Scheme 1.10) [16, 17]. Firstly, pyridinyl directed reversible C-H activation and deprotonation forms the C-Rh bond. Secondly, coordination of aldimine to cationic Rh intermediates activates the C=N bond insertion to C-Rh bond to form the fused 7-membered rhodacycle complex intermediate. Both groups isolated and characterized this key intermediate, and further studies confirmed this insertion step was the rate-determining step. Finally, protonation releases the desired product and regenerates the active catalyst. In addition to pyridinyl, amide [27], *N*,*N*-dimethylcarbamoyl [28], and azophenyl [29] were also developed as directing groups to facilitate the rhodium-catalyzed addition of aryl C-H bond to imines.

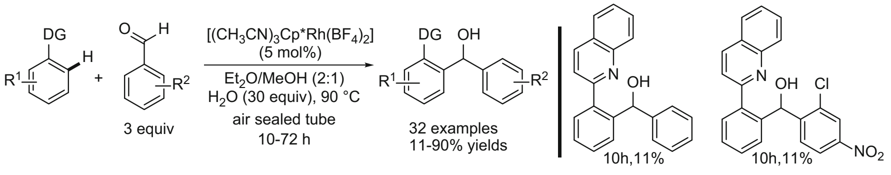
1.1.4.2 Addition onto C=O Bond

Through using highly electron-deficient aldehyde as reaction partner, the challenge of the reversible nature of inserting C-H bond across the C=O bond was overcome. In 2011, our group developed a rhodium-catalyzed Grignard-type arylation through directly adding C-H bond to C=O bond to produce alcohols in high yields (Scheme 1.11) [25]. A variety of nitrogen-containing heterocycles were effective as directing groups to give the Grignard-type addition products high yields. Ethyl glyoxylate and highly electron-deficient aromatic aldehydes were found to be satisfied substrates, while benzaldehyde failed. Remarkably, the reaction could proceed efficiently in the presence of water under an air atmosphere and could tolerate a variety of functional groups such as ester, halides, nitro, an additional aldehyde, and free hydroxyl. The proposed mechanism involves the following sequences: oxidative addition of the rhodium catalyst to the ortho C-H bond assisted by the nitrogen chelation to generate the arylrhodium complex, then aldehyde coordination to rhodium to activate both C=O and facilitate nucleophilic addition, and finally, protonation of rhodium alkoxide to release the Grignard-type addition product and regenerate the rhodium catalyst.

A similar rhodium-catalyzed aryl C-H addition to highly electron-deficient aldehydes C=O bond to produce biaryl methanols was also reported by Shi's group in 2012 (Scheme 1.12) [30]. *N*-directing group was essential to this



Scheme 1.11 Rh-catalyzed directly C–H bond addition onto C=O bond to produce alcohol

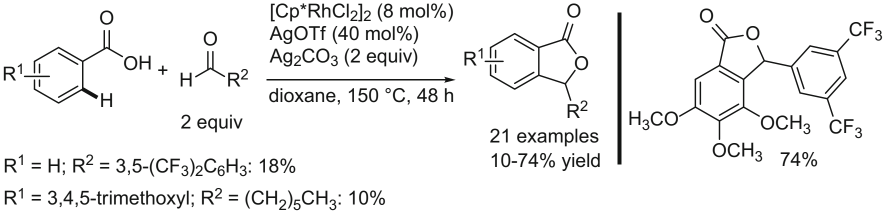


Scheme 1.12 Rh-catalyzed directly C–H bond addition onto C=O bond to produce biaryl methanol

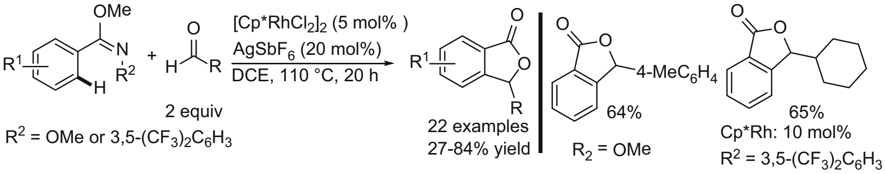
transformation. Intra- and intermolecular isotopic studies showed that the first step of C-H bond cleavage was reversible. Compared with aldehydes, ketones are less reactive because of their lower electrophilicity and higher steric hindrance. Based on their previous studies, Shi and co-workers successively developed an approach to directly add phenyl C-H bonds to ketones intermolecularly by using 2.5 mol% $[Cp^*RhCl_2]_2$ and 20 mol% $AgSbF_6$ catalysts [31].

Inspired by these transformations, our group further reported a tandem rhodium-catalyzed Grignard-type arylation of aldehydes, which was followed by an intramolecular lactonization to synthesize phthalides in 2012 (Scheme 1.13) [32]. Carboxyl group acted as both a directing group to activate *ortho* aryl C-H bond and a nucleophile intramolecularly to form the lactones. Although the reaction requires relatively high reaction temperature, long reaction time, and high loading of expensive rhodium catalyst, this cascade cyclization strategy provides a novel alternative to prepare phthalides.

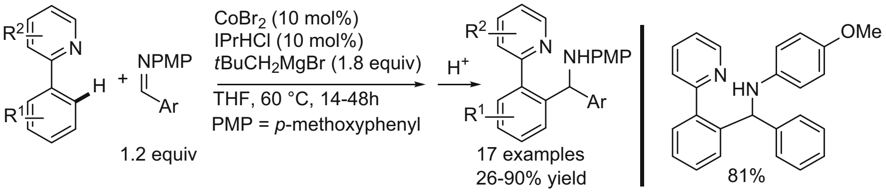
Through choosing proper directing groups, Bergman, Ellman, and co-workers successfully extended the substrate scope to electron-rich aromatic aldehydes and unactivated aliphatic aldehydes (Scheme 1.14) [33]. Imidate directing groups were found to not only activate the *ortho* C-H bonds of benzimidates but also capture the alcohol intermediate. In addition, such directing groups were also easier to remove than pyridinyl group. They also found that azo groups can also accomplish the C-H bond addition to aldehydes; by using 5 mol% $[Cp^*RhCl_2]_2$, 20 mol% $AgSbF_6$ catalysts, and $MgSO_4$ as the additive in THF for 20 h at 110 °C, 2*H*-indazole derivatives could be prepared [34]. Similarly, azo group not only played the role of directing group but also served as an intramolecular capture group for aromatiza-



Scheme 1.13 Rh-catalyzed Grignard-type arylation of aldehyde and intramolecular lactonization



Scheme 1.14 Rh-catalyzed imidate directed Grignard-type arylation of aldehyde to form phthalide



Scheme 1.15 Cobalt/NHC-catalyzed aryl C–H bond addition to aldimine C=N bond

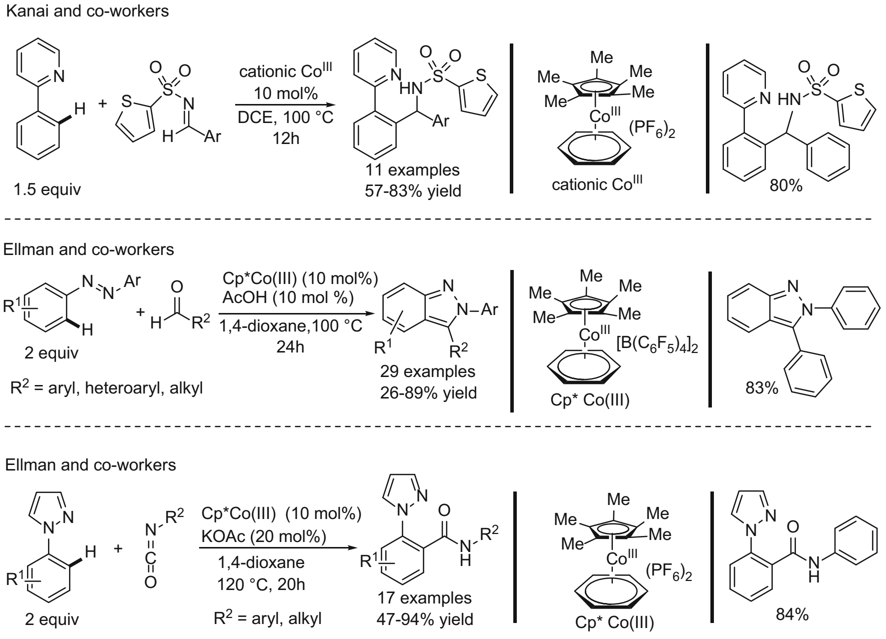
tion to form stable products. In 2014, Zhu and co-workers reported another example of this strategy. By using *N*-nitroso as the directing group, through a cascade [2+2] cycloaddition/fragmentation reaction, the indazoles can be synthesized in modest to high yields [35].

1.1.5 Cobalt Catalyzed

Although cationic Cp*Rh^{III}-catalyzed processes are powerful, the high price of rhodium limits their applications. Therefore, inexpensive and robust alternative catalysts are highly desirable. High-valent cobalt catalyst, being homologous with rhodium but a more abundant first-row transition metal, might possess the ability to promote similar C-H bond functionalization. Several groups investigated and achieved fruitful results.

In 2012, Yoshikai and co-workers reported a cobalt-*N*-heterocyclic carbene (NHC)-catalyzed arylation of aldimines through C-H bond functionalization (Scheme 1.15) [36]. The reaction, however, required the combination with a specific Grignard reagent ^{t}BuCH$_2$MgBr; unlike the Rh-catalyzed reactions reported by Bergman/Ellman and Shi, aldimines with *N*-Boc or *N*-Ts did not react under such conditions.

Using cationic high-valent Cp*Co^{III} complex, two groups, Kanai and Ellman, successfully developed Grignard-type addition of aryl C-H bonds to C=O bonds or C=N bonds (Scheme 1.16). In 2013, Kanai and co-workers established a new cationic high-valent Cp*Co^{III} complex to promote 2-phenylpyridine [37] and indole [38] C-H bond addition to sulfonyl imines. In 2015, Ellman and co-workers reported a novel air-stable cationic cobalt(III)-catalyzed C-H bond addition to aldehydes followed by in situ cyclization and aromatization to produce *N*-aryl-2*H*-indazoles [39]. Compared with rhodium catalyst, unfortunately, the cobalt catalyst system gave lower regioselectivities and inferior yields. A catalytic amount of acetic acid (10 mol%) was required as an additive and the reaction could be handled on benchtop in large scale. Using this cationic cobalt complex, Ellman also expanded isocyanates as the reaction partners to produce amides [40]. In addition to *N*-aryl-1*H*-pyrazole directing group, other nitrogen heterocycles such as 2-pyridinyl and 2-pyrimidinyl could also achieve good results.



Scheme 1.16 Cationic Cp*Co^{III}-catalyzed Grignard-type addition reaction

1.2 Conclusions and Outlook

Catalytic Grignard-type addition of aryl C-H bonds to polar C=O or C=N bonds mediated by transition metals is a very attractive approach to synthesize alcohols, amines, and their derivatives by avoiding generating stoichiometric amount of metal and halide wastes associated with the classical Grignard-type reaction. In spite of these preliminary success, there are still many challenges to be solved: (1) most reactions require directing groups to assist the coordination of aryl C-H with transition metal and some of the directing groups such as pyridinyl are not easy to remove; (2) some reactions require super-stoichiometric amounts of substrates in order to completely consume another substrate, which decreases the atom economy; and (3) the use of precious and toxic late transition metal catalysts, typically with high loadings, hampers their applications. Thus, expanding the substrate scope, without using directing groups, and developing inexpensive catalysts with lower catalyst loading will be the main research directions of this field.

Acknowledgments We are indebted to our colleagues, whose name are given in the list of references. We also thank the Canada Research Chair (Tier I) foundation; the CFI, NSERC, and FQRNT; and the CSC (China Scholarship Council) for a postdoctoral scholarship to Feng Wang.

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Chapter 2
The Halogen-Less Catalytic Transition Metal-Mediated Cross-Coupling Reactions: A Sustainable Alternative for Utilisation of Organohalides

Oleg M. Demchuk, Radomir Jasiński, and Adam Formela

To the memory of a pioneer in transition metal catalysis, Prof. Richard Frederick Heck (15.08.1931–10.10.2015). We pay tribute to his legacy, shedding the light on new generation of chemistry, inspired by his vision, his example and his sacrifice, which make the world a better place.

Abstract The transition metal-catalysed cross-coupling reaction, initially discovered by Richard F. Heck, Ei-ichi Negishi and Akira Suzuki in the late 1960s, became one of the most powerful tools of organic synthesis widely used in both academy and industry. The utilisation of readily approachably organic halides and pseudohalides allows straightforward selective and high-yielding synthesis of compounds not available formerly under mild and affordable conditions. The only bottleneck of standard cross-coupling approach was a necessity of the prior syntheses of properly decorated in the leaving group substrates (halides and organometallic) and necessity of dealing with organic and inorganic wastes, formed in the reaction. The modern economic and environmental considerations required, however, new methods of direct C-C bond formation free of that weaknesses. Herein we are exploring the progress in, discovered (but not developed) already in late 1960s direct oxidative (dehydrogenative) transition metal-mediated C-C coupling reactions, run via formal double C-H bond activation, which do not require utilisation of substrates activated by halogens.

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Keywords Twofold C-H activation • Dehydrogenative coupling • Cross-coupling • Arylation • Olefination • Insertion of unsaturated systems • Directing group • Direct coupling • Transition metal catalysis

2.1 Introduction

In about 40 years after their first discoveries [1–6], the palladium-catalysed cross-coupling reactions have completely revolutionised C-C bond formation and became one of the major synthetic instruments of chemists in both academia and industry. The applicability of these reactions had been greatly appreciated worldwide, and in 2010 the three giants of organic chemistry – Richard F. Heck, Ei-ichi Negishi and Akira Suzuki – who pioneered and independently developed the palladium-catalysed cross-coupling reactions (Fig. 2.1), shared the Nobel Prize in Chemistry "for palladium-catalyzed cross couplings in organic synthesis" [7].

Initially discovered for aromatic and olefinic iodides, reactions were rapidly extended to corresponding bromides and chlorides as well as to some pseudohalides. This quality leap was only possible because of the development of the new generation of highly active and selective transition metal complex catalysts [9–11]. Moreover, the asymmetric atroposelective couplings became possible with utilisation of properly designed chiral ligands [12]. Application of aryl halides for synthesis of biaryl compounds via cross-coupling reaction was subject of

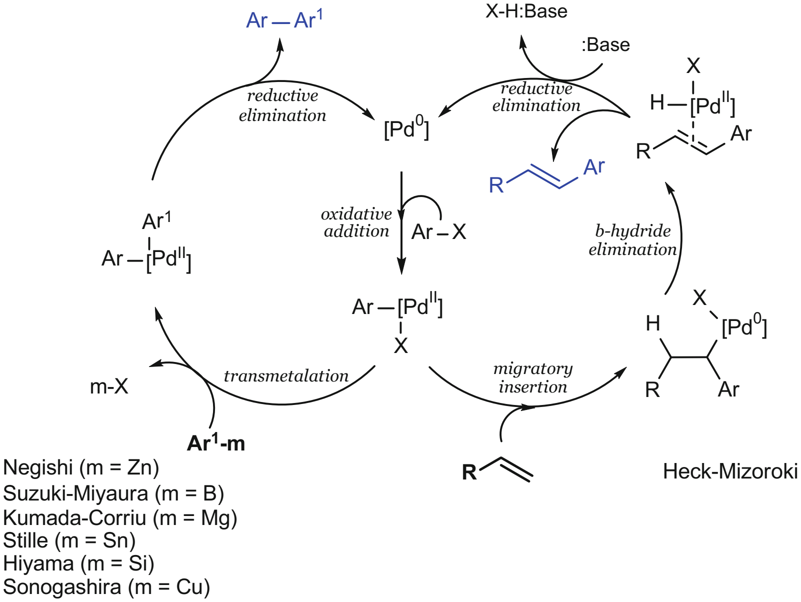


Fig. 2.1 Cross-coupling reactions [8]

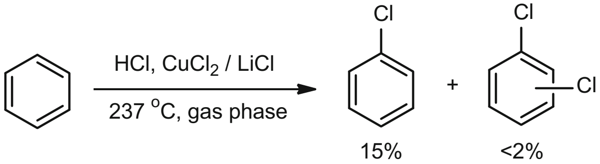


Fig. 2.2 An example of industrial way for preparation of parent chlorobenzene

experimental studies of many research groups [13]. It should be noted that especial attention to organic chlorides in this area could be easily explained from the economic point of view, because organic chlorides are relatively cheaper than bromides and iodides and do not require the recovering of the halogens from a toxic waste after the large-scale reactions [14, 15].

In the preparative scale, large spectrum of necessary halides is available. They may be prepared via classical Sandmeyer and Gattermann reactions, electrophilic substitution catalysed by Lewis acids as well as using several "green processes" [16]. Numerous methods for the preparation of heteroaryl halides are also known [17]. Unfortunately, most of these halides are difficult to prepare on industrial scale. Generally, only some synthetic ways are industrially applied for synthesis of aryl halides. Thus, oxyhalogenation process proceeds at elevated temperature (230–270 °C) in gas phase. In this approach, iron and copper halides are used as catalysts. Unfortunately, optimal degree of starting aryl conversion is lower than 20 %. For example, oxychlorination of benzene at 237 °C in the presence of $CuCl_2$/LiCl catalyst gives chlorobenzene with 15 % yield, with the addition of some amounts of regioisomeric dichlorobenzenes (Fig. 2.2) [18, 19].

Alternatively, aryl halides may be prepared in liquid phase. In this case, the degree of reagent conversion is satisfactory. Weak side of this strategy, however, is the necessity to use a corrosive mineral acids and relatively high pressures [20]. Another possibility for industrial scale of aryl halides preparation is electrochemical halogenations processes, which proceed via radical-cation intermediates [21, 22]. In this approach, total yield of aryl halides up to 50 % may be obtained. Unfortunately, corrosive mineral acids in this procedure are also used. As we can see from above, industrial process of aryl halides production is difficult, expensive and, additionally, environmentally unfriendly. Relatively most attractive for organic synthesis seem to be aryl iodides and bromides due to relatively lower C-X bond energy in comparison to C–Cl bond [23] – unfortunately, their large-scale preparation is more expensive and more difficult than of aryl chlorides.

Due to the above issues, as well as high toxicity [24], production of aryl halides has systematically decreased. For example, total industrial production of chlorobenzene in the United States has declined by nearly 60 %, from the peak production volume of 274,000 kg in 1960 to 112,000 kg in 1987 [25]. In Japan, production of chlorobenzene decreased from 35,000 kg in 1998 to 10,000 kg in 2002 [26].

Notable that from the point of view of cross-coupling reactions, the halogen is introduced into the structure of substrates only to be eliminated later in the course of preparation of boronic acids (Suzuki-Miyaura), organomagnesium or organozinc

Table 2.1 E factors in the chemical industry [27]

Industry segment	Annual production/[t]	E factor/(kg waste)·(kg product)$^{-1}$
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5–50
Pharmaceuticals	10–10^3	25–100

reagents (Negishi, Kumada) or directly in the course of cross-coupling reactions (Heck, Suzuki-Miyaura, Negishi, Kumada, etc.). Such situation increases the cost of the syntheses, as well as decreases already low atom economy (Table 2.1) [27] and overall environmental friendliness.

Thus, summarising the above, serious limitation of a modern chemistry of transition metal-mediated cross-coupling reactions is a necessity to use organic halides. Subsequently, great attention of organic chemists attracts alternative, halogen-less strategies of organic synthesis. This trend has been also applied in cross-coupling reaction. Important group of the aryl systems may be produced in a large scale, under dramatically milder conditions (as in the case of aryl halides) with utilisation of pseudohalide groups (OTf, OTs, OMs, OCbm, etc.) [28, 29]. In general, organic pseudohalides have similar reactivity in comparison to the corresponding chlorine compounds, but may serve the complementary "substitution pattern" in respect of high reactivity of phenols they had made from. There is also an additional possibility for regioselective reaction where catalyst of proper selection allows to activate chlorine or triflate site selectively [9, 30]. Nevertheless, also this approach does not really solve the problem, since pseudohalides are expensive and toxic, while the atom economy of the reactions, based on utilisation of pseudohalides, is even worse than in the case of organic halides. The only radical solution could be achieved when new C-C bond is formed on a way of formal metathesis of two C-H bonds (dehydrogenative reaction) with sufficient level of selectivity and under catalytic conditions (!) (Fig. 2.3). Due to this, the number of publication dealing with activation of C-H bond is growing rapidly. This dependence built, according to Thomson Reuters Science Citation Index on Web of Science database search, is presented in Fig. 2.4.

The most promising palladium-catalysed carbon-carbon bond-forming reaction should therefore run via twofold C-H bond activation. For example, these are dehydrogenative Heck reaction (arylation of alkenes and alkynes), dehydrogenative cross-coupling or homocoupling of (hetero)arenes as well as insertion of unsaturated systems to nonactivated C-H bonds. These reactions could be performed with excellent atom economy, in mild conditions and with utilisation of less expensive (nonactivated) substrates if a proper catalyst and conditions are selected. Our review is an attempt to shed light on preparative possibilities of dehydrogenative transition metal-mediated carbon-carbon bond-forming reactions run through twofold C-H bonds activation process. The state of the art in dehydrogenative coupling

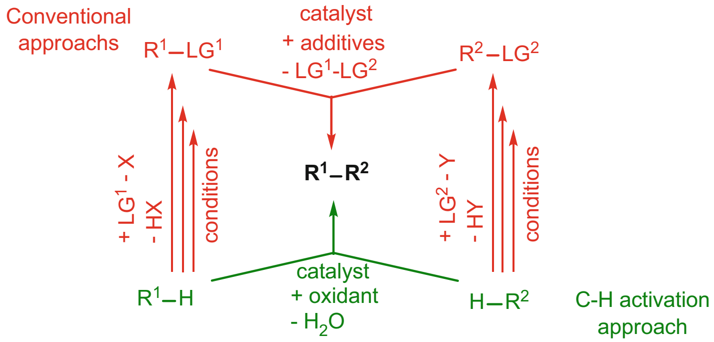


Fig. 2.3 Direct vs indirect C-H functionalisation

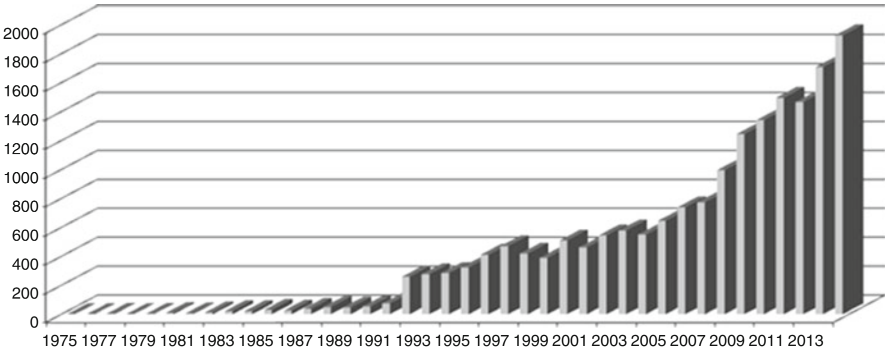
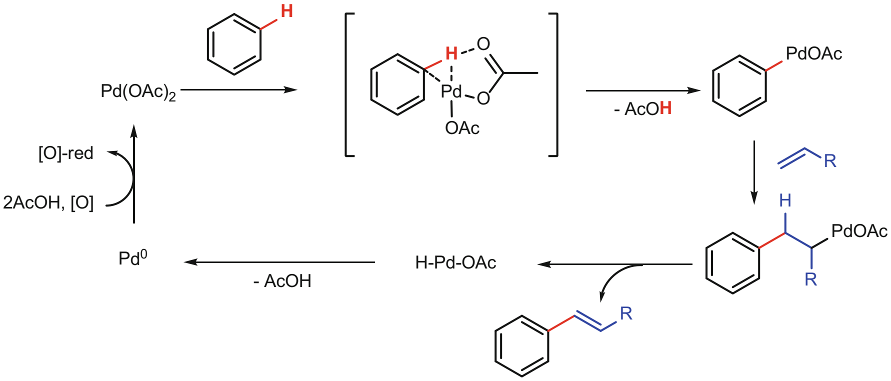


Fig. 2.4 The number of scientific publications in which C-H bond activation was mentioned

reaction, we discuss herein, consists of four thematic blocks which are devoted to (i) insertion of unsaturated systems to nonactivated C-H bonds, (ii) applications of direct dehydrogenative Heck reaction, (iii) the aryl-aryl coupling reaction run via twofold C-H activation and (iv) discussion of some mechanistic aspects of halogen-less cross-coupling reactions.

2.2 Direct Dehydrogenative Heck Reaction

The Mizoroki-Heck coupling (arylation of alkenes bearing mesomerically EWG) is probably historically the first TM-mediated C-C reaction recognised worldwide as versatile synthetic tool [1, 31–33]. In fact, Mizoroki-Heck condensation generally provides a very high regioselectivity; both steric and electronic factors favour the substitution at terminal position of alkenes. In the case of moderately hindered arenes and EWG-substituted alkenes, Heck coupling usually runs in high yields



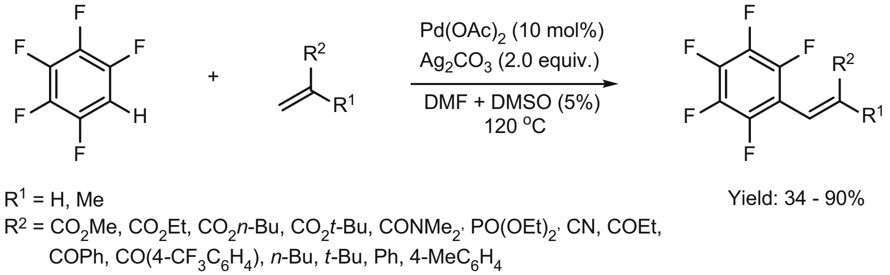
Scheme 2.1 Direct dehydrogenative Heck reaction

under mild reaction conditions. At the same time, Heck coupling is sensitive to the substituents in the alkene, and as a result, alkenes bearing substituents in *β* (regarding EWG position) are much less reactive, and this type of the coupling is quite rare. Despite the generally accepted opinion that EWG is required in Heck reactions, in some cases nonactivated alkenes may serve product in reasonably high yields [34]. The sources of aryl group in Heck reaction are aryl halides and pseudohalides, aroyl chlorides, iodonium and diazonium salts. In majority of the cases, an excess of base and some additives are used to assure high yields. As a result, the Heck reaction has moderate atom economy, and frequently, a formation of harmful low-molecular-weight products accompanies this condensation.

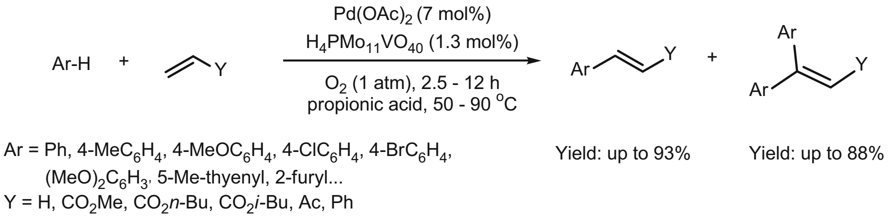
Typical Heck reaction catalytic cycle is initiated by a palladium (0) species activating the carbon-halogen bond (Fig. 2.1). Nevertheless, there is another possibility which does not require halogen, while under oxidative conditions, a catalytic cycle can be activated by palladium (II) species according to direct (oxidative) dehydrogenative Heck reaction (Fujiwara-Moritani reaction) protocol (Scheme 2.1) [32, 35–37].

First attempts of palladium-catalysed halogen-less arylation of olefins were taken up by Heck [1, 38–42] and Moritani [35, 43–45] in 1967–1969.

In these cases, single C-H bond undergoes the activation by reactive Pd (II) catalyst which also plays a role of oxidant. Obviously, a synthesis, which requires the stoichiometric amounts of palladium, does not have significant practical value, and therefore there is a need to use reoxidant to convert formed inactive palladium (0) to reactive Pd(II) form (Scheme 2.1) [35]. Despite the fact that different palladium sources were used, it looks that from mechanistic point of view, it is highly possible that the carboxylic acid residue is important for the C-H activation step[46]. At the same time, a wide range of reoxidants (O_2, Cu(II), Ag(I), t-BuO_2H, $(NH_4)_2S_2O_8$, benzoquinones, $NaNO_2$, $PhCO_3t$-Bu, etc.) have been successfully used in such reactions [24, 47–54].



Scheme 2.2 Dehydrogenative olefination of perfluoroarenes [48]

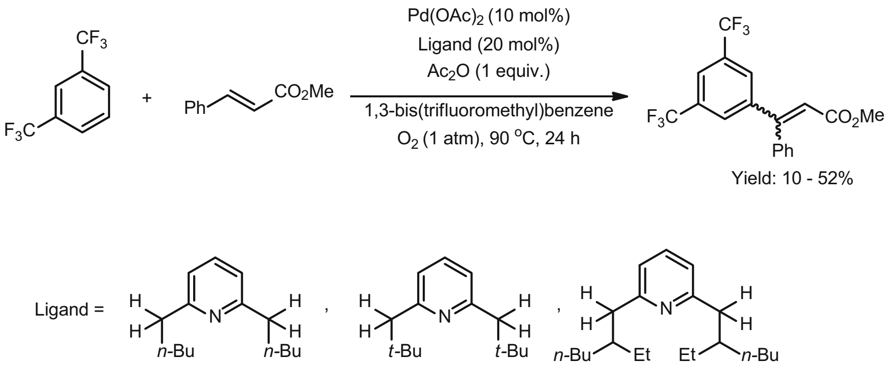


Scheme 2.3 Dehydrogenative olefination of simple aromatic compounds [60]

2.2.1 Undirected Direct (Oxidative) Dehydrogenative Heck Reaction (Fujiwara-Moritani Reaction)

The simplest case of a direct dehydrogenative arylation of olefins is realised when only one of the hydrogen atoms in the highly electronically pure aromatic ring is accessible. In this case, reactions run in moderate mild conditions with about 10 mol% catalyst loading in moderate to good yields. An example of such reaction was presented by Xingang Zhang et al. (Scheme 2.2) where inorganic silver salt was used as palladium reoxidant [48]. In general, highly electron π-deficient arenes are excellent donors of aryl group in cross-coupling reactions catalysed by palladium [55–57], copper [58] and nickel [59].

Another extreme case of a dehydrogenative arylation of olefins is the reaction run in excess of aromatic solvent playing also a role of a substrate. In case of symmetric aromatic compounds (e.g. benzene, p-xylene, mesitylene, etc.), the only one, less hindered, product may be formed [49]. Thus, in general, this reaction is not selective. For example, it has been shown that [60, 61] under air dioxygen oxidative conditions, catalysed by 10 mol% of palladium acetate, simple aromatics undergo the nonselective olefination in good yields. An addition of 2 mol% of molybdovanadophosphoric acid cocatalyst was crucial, since it assured an efficient electron transfer between palladium and dioxygen; also 10 mol% of acetylacetone was added to solubilise the palladium catalyst (Scheme 2.3).



Scheme 2.4 Pd(II)-catalysed olefination of electron-deficient arenes [64]

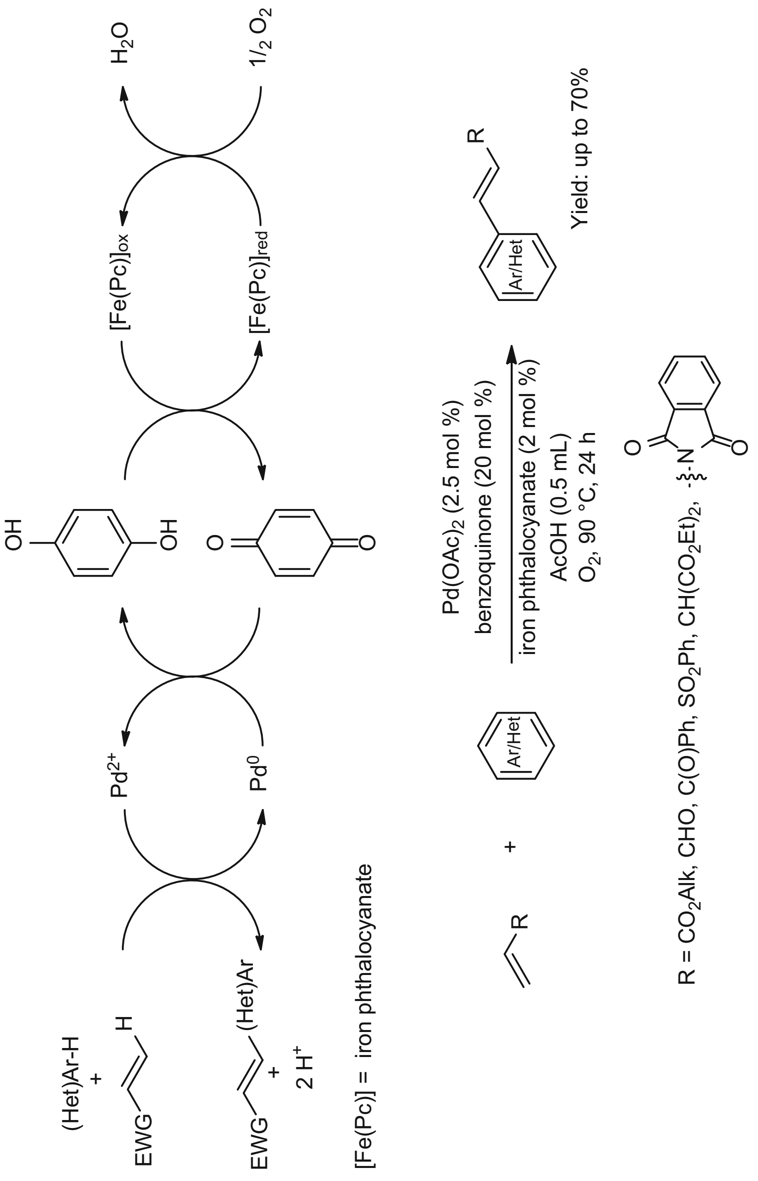
The acetylacetone is a good ligand for palladium (0); nevertheless it has low affinity to Pd(II) compounds [62, 63]; the palladium complexes of nitrogen ligands are more stable and can be also used to facilitate dehydrogenative olefination of aromatic compounds [64]. Notably, that in the case of pyridine-based ligand, any cocatalyst for reoxidation of palladium was not needed. In excess of arenes, the reaction smoothly runs at 90 °C in good yields, but unfortunately with low regioselectivity (Scheme 2.4).

It is worth to mention at this point that not only terminal alkenes but also internal alkenes undergo arylation under the direct oxidative Heck reaction conditions to form trisubstituted ethenes in usually good yields [47, 51, 64]. Similar to π-electron-deficient arenes, the electron-rich aromatic and heteroaromatic systems could be used in palladium-catalysed dehydrogenative arylation of unsaturated compounds under dioxygen oxidative conditions [60] as well as with utilisation of other oxidants, such as $(NH_4)_2S_2O_8$ [49] or Ag_2CO_3 in PivOH [65].

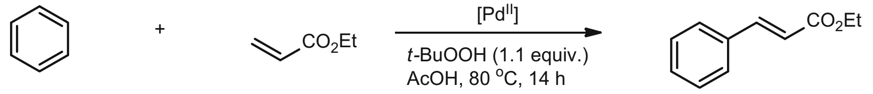
The efficiency of the reoxidation could be enhanced by applying a "biomimetic" approach, in which iron phthalocyanine oxidised by dioxygen accepts electrons of *p*-benzoquinone, and the last eventually oxidises (formed in reaction) Pd(0) to its active Pd(+2) form (Scheme 2.5) [66]. The same approach was used also in the arylation of unactivated olefins [67]. In this case good yields and regioselectivities were observed when symmetric arenes, giving a single product of substitution, were used.

A possibility to run dehydrogenative Heck coupling according to "flow reaction" protocol was demonstrated with utilisation of a single-site palladium (II) catalyst immobilised in 2,2′-bipyridine-grafted periodic mesoporous organosilica (Scheme 2.6) [37]. Different arenes and alkenes were tested in the reaction, and acceptable yields of products were obtained under low catalyst loading even after four-catalyst reusing.

The scope of alkenes could be extended to quinones, naphthoquinones and coumarins [49, 65], as well as enaminones [68]. Utilisation of strong reoxidant and formed in situ cationic palladium triflate catalyst allows to run arylation at room



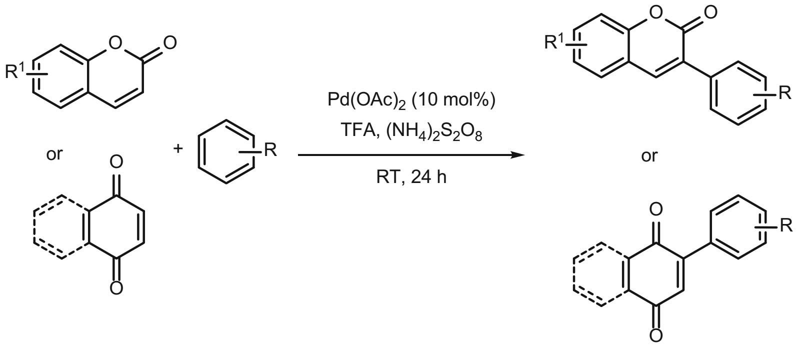
Scheme 2.5 Biomimetic aerobic dehydrogenative coupling [66]



$[Pd^{II}]$ = $Pd(OAc)_2$ or Pd^{II} on periodic mesoporous organosilica

Yield: up to 66%

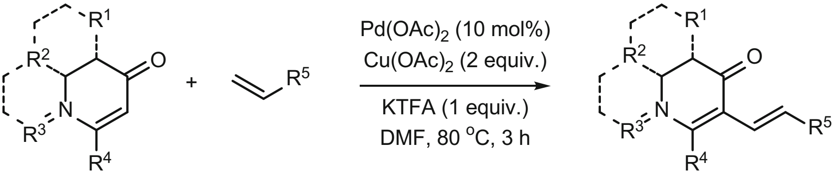
Scheme 2.6 Single-site Pd(II)-catalysed oxidative coupling of arenes with alkenes under plug-flow reaction conditions [37]



Yield: 41 - 94%

R = H, 4-MeO, (2-OMe, 5-Me), (3-Br, 4-OMe), $(3,4\text{-}Cl_2)$
R^1 = H, 4-Me

Scheme 2.7 Arylation of quinones and coumarins [49]



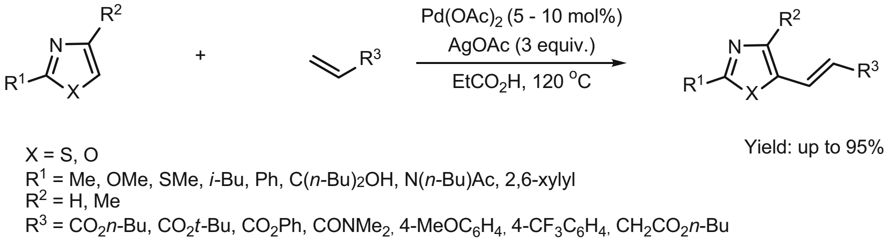
Yield: up to 95%

R^1 = H, Me, $-(CH_2)_4-R^2$
R^2 = H, $4\text{-}OMeC_6H_4$, Ph...
R^3 = H, Me, Ph, Bn, Cbz, $-(CH_2)_4-R^2$
R^4 = H, Me, NMe_2
R^5 = CO_2t-Bu, CO_2Me, Ac, CO_2n-Bu, $CONMe_2$, $S(O)_2Me$, n-BuO, CO_2H, $PO(OEt)_2$ CO_2Bn...

Scheme 2.8 Arylation of enaminones [68]

temperature (Scheme 2.7). Nevertheless, even in this case, the selectivity was not great [49]. Having analysed the observed reactivity, authors stated that the formation of Pd(+2) dication was important to achieve high yields of these reactions run in ambient temperature.

The efficiency of the reaction could be rendered by addition of suitable additives. For example, the influence of additive nature as well as solvent effect was studied in the case of enaminones arylation processes (Scheme 2.8) [68]. In



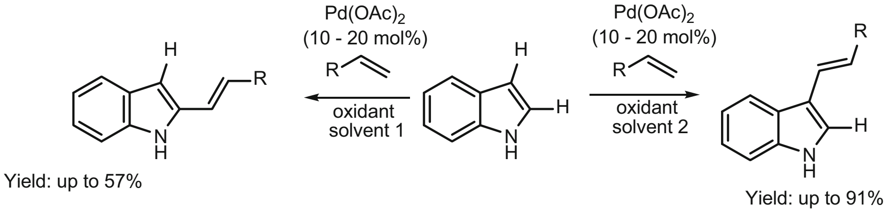
Scheme 2.9 Palladium-catalysed direct oxidative alkenylation of azoles [70]

particular, the yields of products increased depending on the solvent nature in the following order: DMSO, *t*-BuOH, DMA and DMF. The presence of carboxylate anions was crucial for the reaction run and $Cu(OAc)_2$ was better reoxidant than AgOAc and $PhCO_3tBu$. The addition of inorganic salts with non-carboxylate anion ($LiBF_4$) did not influence the reaction yield, while potassium carbonate and bismuth (III) chloride suppress the reaction. Addition of basic caesium acetate does not have a positive influence on the reaction yield, which may indicate that the only carboxylate moiety, in the coordination sphere of the palladium, participates in the catalytic cycle. The positive effect was achieved when non-nucleophilic carboxylate (KTFA) additive was used. Notably, positive influence of TFA was also mentioned in other cases of dehydrogenative arylations [49, 69].

The electron-rich five-membered heterocycles (e.g. thiazoles and oxazoles) are excellent substrates for dehydrogenative arylation (Scheme 2.9) [70]. The reaction with diversified alkenes (acrylates, methacrylates, acrylamides and styrenes) runs at elevated up to 120 °C temperature in the presence of 10 mol% of palladium catalyst and excess of AgOAc as reoxidant. Under these conditions and with carboxylic acids ($EtCO_2H$, *t*-$BuCO_2H$) used as solvents, the processes give good yields. In case of thiazoles and oxazoles, only products substituted in relatively electrophile-susceptible five-position were obtained. It has to be noted that a migration of a double bond of alkene was observed in the cases where methacrylates were used.

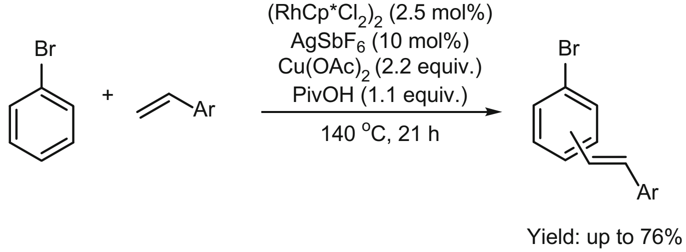
Dehydrogenative Heck reaction left some possibility to control its regioselectivity by the manipulation with such reaction conditions as a solvent and reoxidant used. Thus, Matthew J. Gaunt et al. presented the elegant approach to C2 and C3 alkenylation of indole, where the utilisation of polar coordination but aprotic solvents (DMF, DMSO) in combination with $Cu(OAc)_2$ (used as reoxidant) resulted in the formation of C3-alkenylated products in good to excellent yields and selectivities. At the same time, an addition of polar protic solvents (AcOH) and application of *t*-BuO_2Bz as reoxidant instead of $Cu(OAc)_2$ leads to C2-alkenylated products in good yields (Scheme 2.10) [71].

The complementary to regular Heck reaction reactivity of aromatic halides is presented on the case of dehydrogenative coupling of bromoarenes with styrenes (Scheme 2.11) [72]. Catalysed by cationic rhodium complexes, reaction run in acidic condition requires an addition of a copper acetate reoxidant and heating up to 140 °C. In fact, the reaction does not require a chelate-assisting directing group and therefore is not selective in respect to haloarene reagent; nevertheless it allows



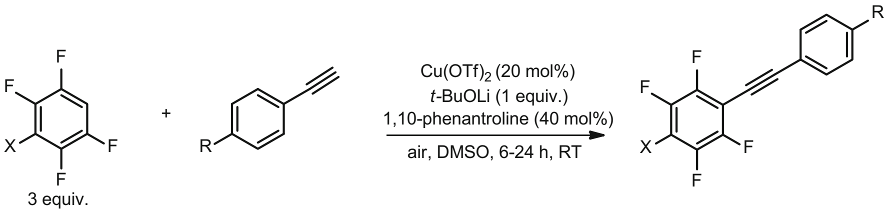
R = CO_2*n*-Bu, CO_2*t*-Bu, $CONMe_2$, CO*n*-C_5H_{11}, $PO(OEt)_2$, Ph, C_6H_{11}...
oxidant = $Cu(OAc)_2$, *t*-BuO_2Bz
solvent 1 = 1,4-dioxane, 1,4-dioxane/AcOH 3:1
solvent 2 = DMF, DMSO, DMF/DMSO 10:1, MeCN/AcOH 3:1, 1,4-dioxane/AcOH/DMSO 3:1:0.4

Scheme 2.10 Direct C2 and C3 selective alkenylation of indole [71]



Ar = Ph, 4-*t*-BuC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$CF_3C_6H_4$

Scheme 2.11 Direct dehydrogenative arylation of styrenes [72]



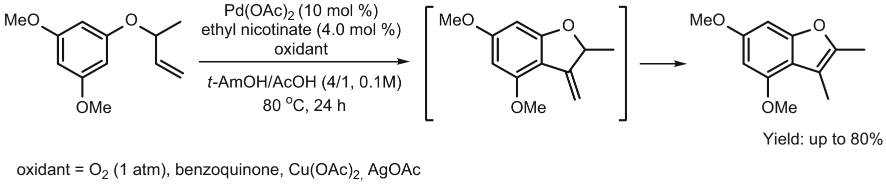
X = F, CF_3
R = H, Me, OMe, NMe_2, F, CO_2Me

Yield: 25 - 76%

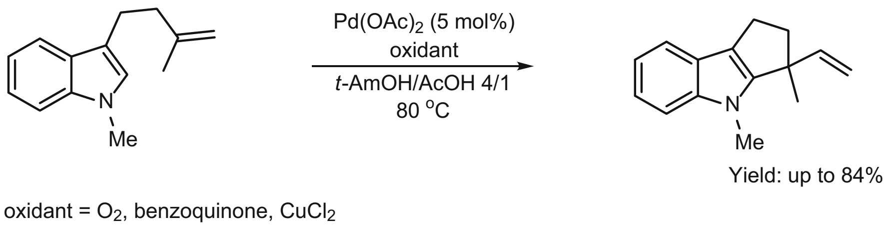
Scheme 2.12 Copper-catalysed dehydrogenative arylation of unsaturated compounds [78]

formation of bromo- and iodo-aryl-substituted styrenes in good yields in simple and unique way.

The palladium-catalysed dehydrogenative alkynylation of (hetero)aromatic systems is developed well [73–75]. At the same time, not only palladium, ruthenium and rhodium but also, much more demanded by pharmaceutical and perfumery industry, copper [76–79], nickel [79] and gold [80] catalysts could be applied in dehydrogenative arylation of substituted alkenes, alkynes and heteroarenes (Scheme 2.12).



Scheme 2.13 Approach to substituted benzofurans [81]



Scheme 2.14 Intramolecular *ortho*-alkylation of indoles [81]

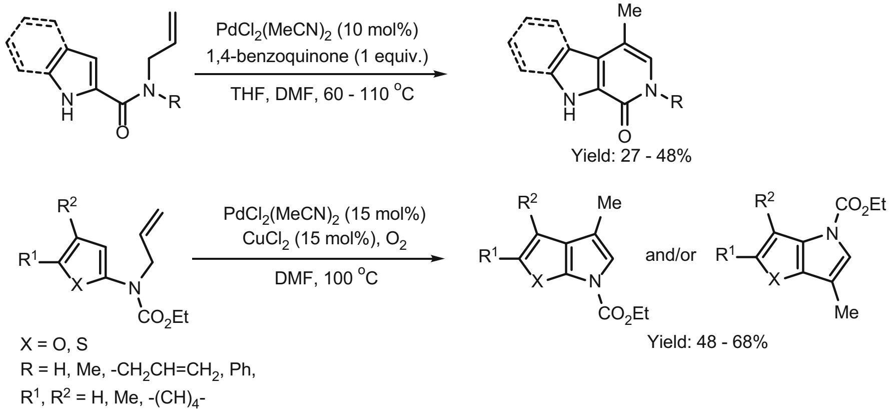
Thus, despite several serious drawbacks such as significant catalyst loading and not always good regioselectivity, the dehydrogenative (oxidative) Heck-type reactions which run via C-H bond activation could have even bigger synthetic potential than regular Heck couplings as they do not require preactivation of arene by halogenation and moreover may react with halogenoarenes with a retention of Ar-Hal bond. The main problem of dehydrogenative Heck-type coupling regioselectivity could be solved in a way of intramolecular reactions or by utilisation of proper directing metalation groups (DMG).

2.2.2 Intermolecular Dehydrogenative Annulation not Directed by Functional Groups

As it was already mentioned, the main drawback of dehydrogenative coupling reactions is their low regioselectivity. The intramolecular coupling reactions are usually deprived of this weakness. The entropic factor also favours the intramolecular transition metal-mediated dehydrogenative annulations. So, such condensations are quite well-known methods of synthesis of heterocycle compounds. In this way there were obtained highly substituted indoles and benzofurans [81], carbazoles [82] as well as other fused five- and six-membered heterocycles (Schemes 2.13 and 2.14) [83].

The dehydrogenative annulation could be also used in synthesis of indoles starting from aromatic imines according to Yoshikai's indole synthetic protocol [84]. Reaction runs in DMSO at 40–60 °C, while a palladium catalyst could be

Scheme 2.15 Approach to synthesis of substituted indoles [84]



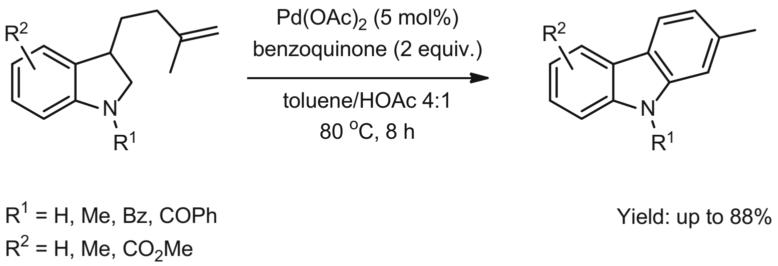
Scheme 2.16 Annulation of five- and six-membered heterocycles [83]

reoxidised by copper acetate or dioxygen (Scheme 2.15). Mild reaction conditions allow to use different substituted anilines and ketones and therefore obtained highly functionalised indoles not accessible by the Fischer indole synthesis.

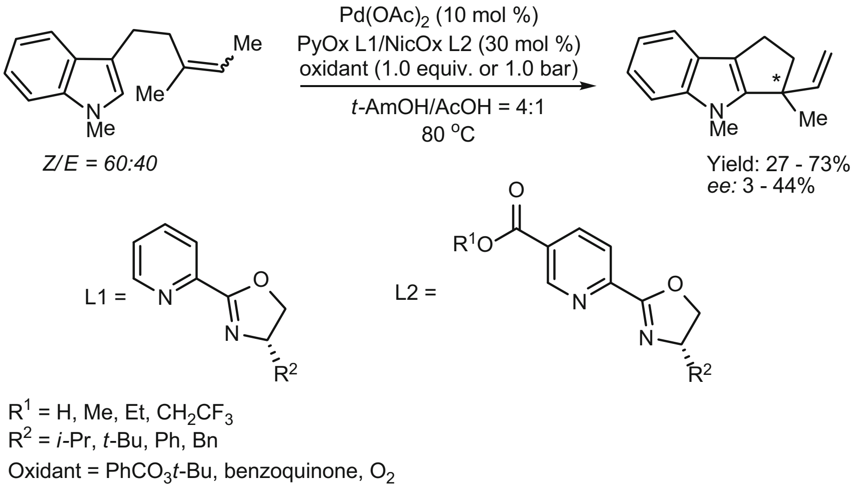
Creation of heterocyclic scaffold was demonstrated also in synthesis of thienopyrroles, pyrrolopyridines and carbolines [83], as well as pyrrolizinones [85]. In this case the palladium catalyst was reoxidised at 60–110 °C by dioxygen in the presence of catalytic amounts of copper salt (Scheme 2.16).

Alternative approach to heterocyclic compounds leads to creation of benzene ring. Thus, substituted carbazoles were obtained in annulation reaction of (but-3-en-1-yl)-indoles run in good yield at 80 °C in a solution toluene/AcOH in the presence of benzoquinone (Scheme 2.17) [82]. The mechanism of this reaction is not known, but the authors suggested that benzoquinone is required both for the reoxidation of catalyst and for the aromatisation of product formed (Scheme 2.17).

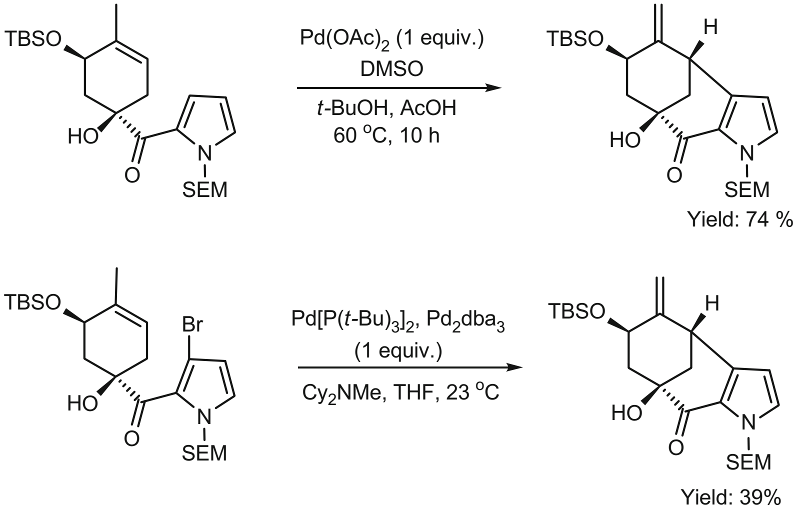
The high synthetic potential of dehydrogenative annulation could be demonstrated in a number of asymmetric reactions run in mild conditions in good yields and with high stereoselectivity mediated by chiral ligand complexes [86] (Scheme 2.18) or with utilisation of enantiomerically pure substrates (Scheme 2.19) [87, 88].



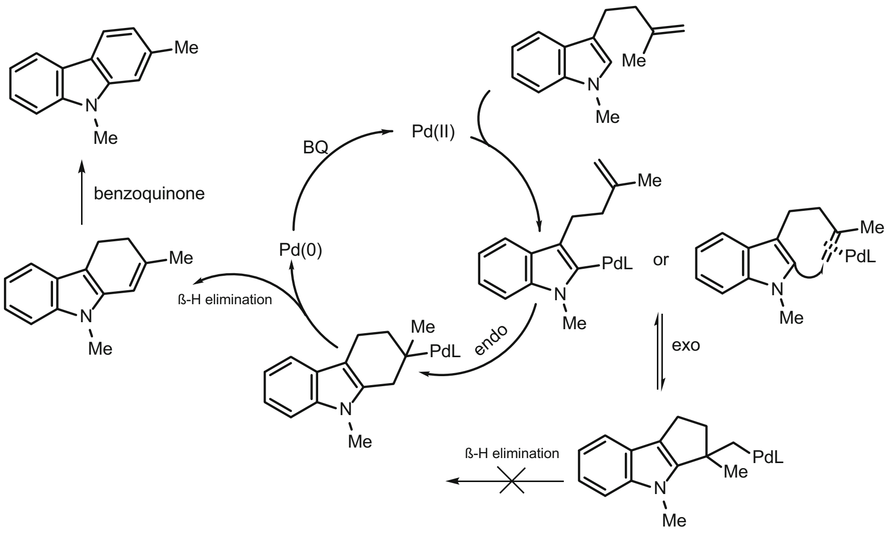
Scheme 2.17 Annulation of carbocyclic ring in carbazoles [82]



Scheme 2.18 Enantioselective dehydrogenative annulation [86]



Scheme 2.19 Diastereoselective dehydrogenative annulation [88]



Scheme 2.20 Annulation reaction mechanism [82]

Migration of alkene double bond was observed in almost all cases of intramolecular dehydrogenative Heck reactions. This observation strongly supports the mechanistic theory according to which (hetero)arylation of olefins follows a stepwise mechanism without concerted activation of olefin C-H bond, similarly like in Heck reaction (Scheme 2.20) [82, 83].

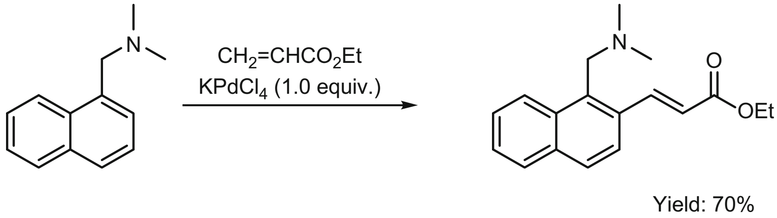
2.2.3 Functional Group-Directed Dehydrogenative Heck Coupling

Another approach to regioselective arylation of olefins is intermolecular dehydrogenative Heck reaction directed by DMG. It has been observed that in the case of (hetero)aromatic compounds possessing the coordinating transition metals (at higher oxidative state) functional groups (e.g. carbonyl, amine, hydroxyl and nitrile), an olefination usually undergoes in the *ortho*-position related to these groups.

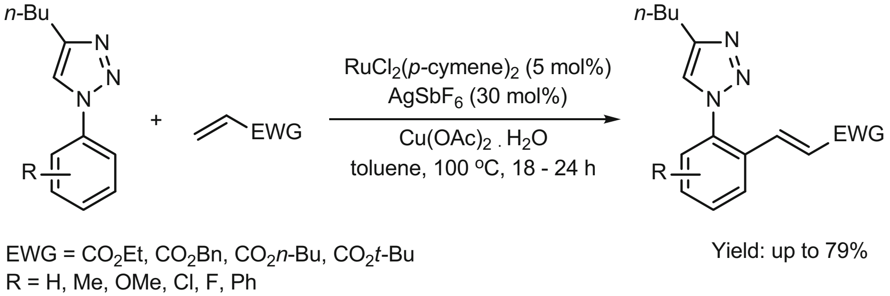
For example, the reaction 1-(*N*,*N*-dimethylaminomethyl)naphthalene with ethyl acrylate, oxidised by stoichiometric amounts of potassium tetrachloropalladate, leads to olefinated in position 2 product in 70 % yield (Scheme 2.21) [89].

Because of its high affinity to palladium, amino groups. play a role of excellent directing metalation (C-H activation) groups [90–93].

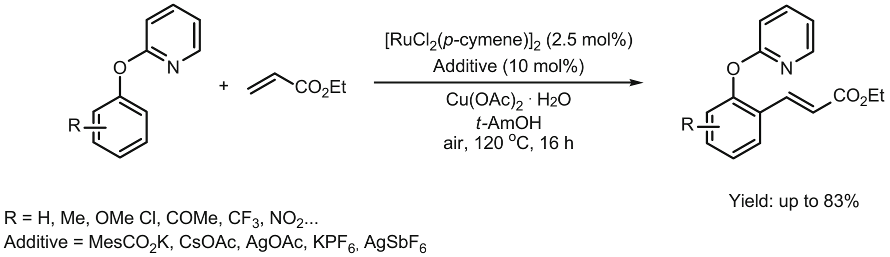
Similar to aliphatic amines, lone electron pair of nitrogen atom of heterobiaryls is excellent directing group which facilitates the selective *ortho*-olefination under ruthenium catalysis and $Cu(OAc)_2$ oxidative conditions (Scheme 2.22) [94]. The



Scheme 2.21 Direct olefination of 1-(*N*,*N*-dimethylaminomethyl)naphthalene [89]



Scheme 2.22 Directed Ru(II)-catalysed dehydrogenative C-H olefination of arenes [94]

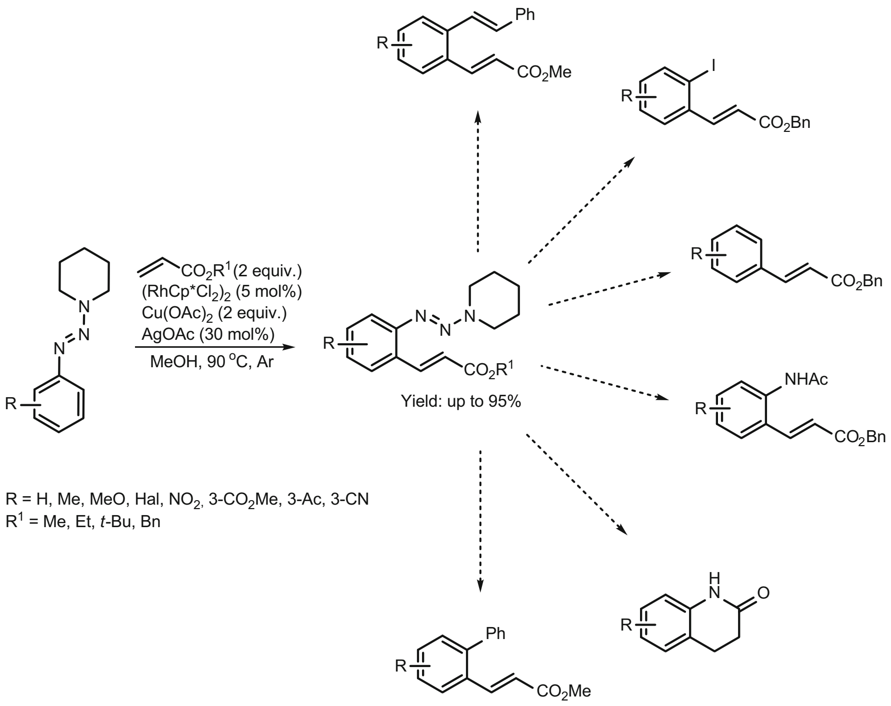


Scheme 2.23 Ru(II)-catalysed *ortho*-selective C-H olefination of phenols [95]

addition of catalytic amounts of non-nucleophilic silver salt was necessary for the efficient activation of the [RuCl$_2$(*p*-cymene)]$_2$ precatalyst and formation of products in high yields with excellent chemo-, regio-, site- and diastereoselectivities, as well as notable functional group tolerance.

Ruthenium-catalysed dehydrogenative alkenylation of phenol derivatives via directed C-H bond activation was realised with excellent chemo-, site- and diastereoselectivities when the transition metal coordinating 2-pyridyl group was introduced into the phenol structure (Scheme 2.23). The reactions were run in average 75–88 % yields at 120 °C in protic solvent and required copper acetate and atmospheric dioxygen for reoxidation of the catalyst [95].

The same concept was implemented in dioxygen reoxidative palladium-catalysed dehydrogenative Heck reaction, directed by 8-aminoquinoline moiety

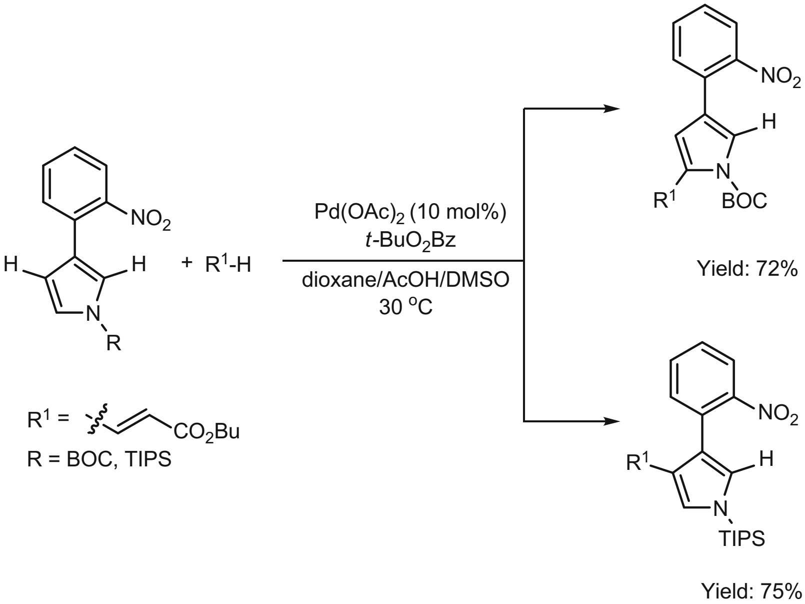


Scheme 2.24 Rh (III)-mediated C-H activation of arenes, directed by triazene function [97]

[96]. The notable directing potential of 8-aminoquinoline allows to achieve the high reaction yields in reactions with both EWG- and EDG-substituted olefins.

Similar behaviour was observed in the case of rhodium(III)-mediated C-H activation of arenes, directed by triazene function [97]. Notably, the great *ortho*-selectivity and high yields of the products were obtained when only 5 mol% of catalyst was utilised in readily achievable conditions. Moreover, the used triazene directing group could be easily transformed into a number of synthetically attractive substituents (Scheme 2.24).

The directing metalation effect of carbamoyl and other directing metalation groups (DMG) in D*o*M reactions is extremely well explored by Victor Snieckus' group. It was also compared with some transition metal-mediated C-H activation reactions [98–100]. So, it is not a surprise that in the case of *N*-Boc-substituted indoles, the C-H activation was directed to the position C2. The reactions were carried out at 35 °C in dioxane-AcOH-DMSO solvent system, where palladium catalyst was reoxidised by air dioxygen or t-BuO$_2$Bz [101]. In the same conditions, pyrroles, protected by non-coordinating TIPS group, underwent the olefinations at C3 position selectively (Scheme 2.25) [102]. The typical 70 % yields, observed in both cases, indicate high efficiency of directed dehydrogenative direct olefination. This approach was used later in the synthesis of natural product rhazinicine.



Scheme 2.25 Regioselective C-H alkenylation of pyrroles [102]

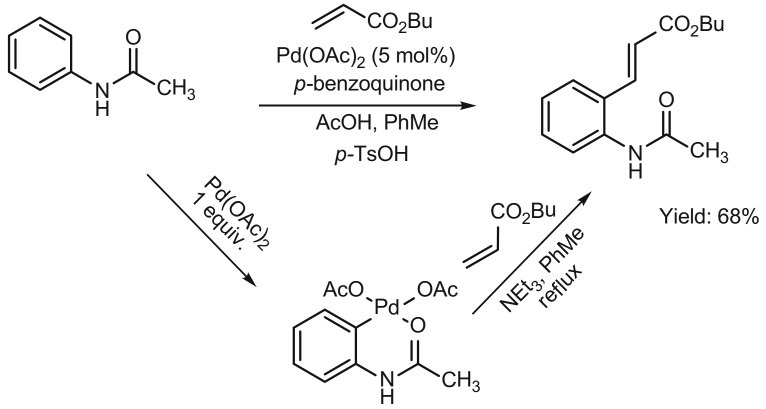
Similarly as *N*-Boc-protected pyrroles, *N*-benzoyl pyrroles and pyrazoles undergo the selective C-H activation. In fact, the formation of C3-substituted products was observed only when 2,5-dimethylpyrrole was utilised [54].

The substituted acetanilides also undergo this transformation. To prove the possible mechanism, the reactions run with stoichiometric and catalytic amounts of palladium acetate were analysed [103–105]. Formed in a high yield in the stoichiometric reaction, palladacyclic intermediate has been isolated and converted to the alkenylated product in the reaction with olefin (Scheme 2.26). The same type of products was also obtained in the catalytic direct and directed alkenylation reaction, also in that mediated by rhodium [106].

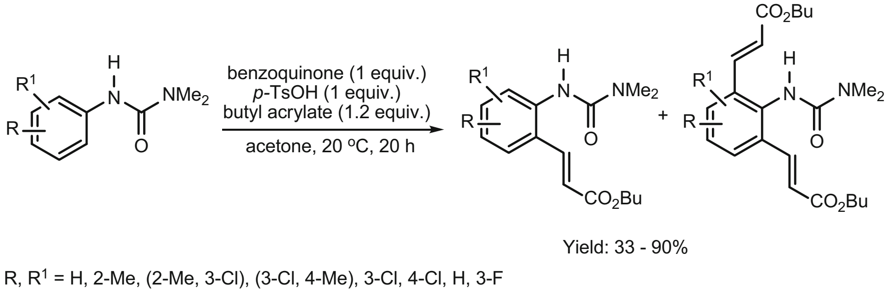
Such syntheses could be performed in a high yield at ambient temperature with utilisation of 6 mol% of palladium catalyst reoxidating with benzoquinone or hydrogen peroxide [105]. Application of the dioxygen oxidant requires moderate heating up to 60 °C [107]. This coupling could be also run at ambient temperature in water, which is considered as an additional ecological benefit of this green directed dehydrogenative Heck coupling reaction; nevertheless in such a case, a stoichiometric amount of benzoquinone in combination with two equivalents of silver nitrate was required [108]. The catalytic, in terms of both palladium and quinone, electrochemical approach had been also presented [109].

The same directing (to position *ortho* with regard to directing group) effect was observed in the case of arene-substituted ureas (Scheme 2.27) [110].

Similarly run the Pd-catalysed C-H olefination of aniline, benzylamine and phenethylamine derivatives possessed 2-pyridylsulphonyl group which acts both



Scheme 2.26 Direct directed alkenylation of anilides [103]

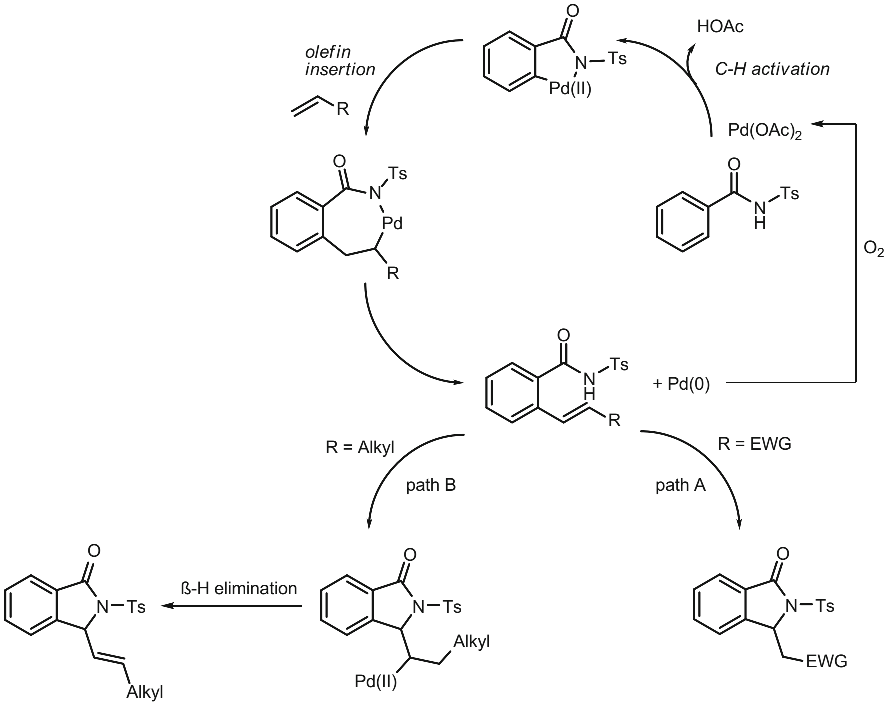


Scheme 2.27 Direct alkenylation of arenes directed by urea or amide groups [110]

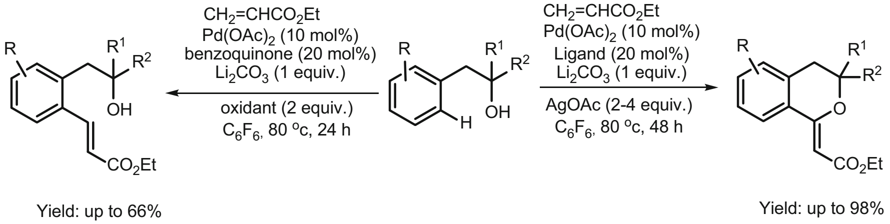
as a protecting group and DMG [111]. The corresponding products were obtained in usually high yields.

Interesting regioselectivity was observed in palladium-mediated reactions of tosylamides with EDG- and EWG-substituted olefins [112]. In the reaction of EWG-substituted olefins with various *N*-tosylbenzamides, the products of *ortho* (to carboxyl group)-olefination followed by annulation (via N-H bond addition to olefins) were obtained in excellent yields. In the same conditions, EDG-substituted olefins gave unsaturated product in good yields. The authors suggested that in the case of electron-rich olefins, tandem second oxidation occurred (Scheme 2.28).

The hydroxyl groups were also used to direct olefination in mediated by palladium acetate direct dehydrogenative Heck reaction, oxidised by dioxygen or silver acetate and run in the presence of benzoquinone, base as well as monoprotected amino acid (acting as a ligand) [113]. Depending on reaction condition and olefin used, the reaction may lead to expected Heck products or to 3,4-dihydro-1*H*-isochromenes, formed after second direct dehydrogenative cross-coupling reaction (Scheme 2.29). The use of monoprotected amino acids to promote the reaction represents a rare example of a ligand-promoted C-H activation reaction run selectively and in high yields under a mild reaction condition.



Scheme 2.28 Olefination of *N*-acylsulphonamides [112]



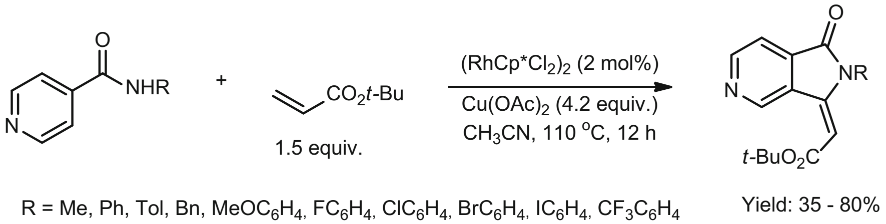
oxidant = O$_2$, Cu(OAc)$_2$, PhI(OAc)$_2$, Ag$_2$O, AgOAc

Ligand = BOC-Ala-OH, BOC-Val-OH, BOC-β-Cl-Ala-OH,
formyl-Ile-OH, PhSO$_2$-Pro-OH, BOC-Leu-NHOMe,
BOC-*t*-Leu-OH, BOC-Leu-OH, BOC-Leu-OH,
formyl-Leu-OH, MenthylOC(O)-Leu-OH

R = H, Me, Be, Cl, F, OMe, CF$_3$

R^1, R^2 = H, Me, Pr, Bu

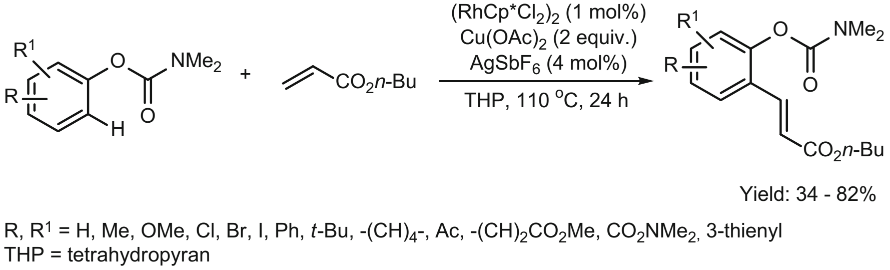
Scheme 2.29 Hydroxyl-directed dehydrogenative Heck reaction enabled by monoprotected amino acid ligands [113]



R = Me, Ph, Tol, Bn, $MeOC_6H_4$, FC_6H_4, ClC_6H_4, BrC_6H_4, IC_6H_4, $CF_3C_6H_4$

Yield: 35 - 80%

Scheme 2.30 Rhodium-catalysed direct olefination of aromatic amides [117]



Yield: 34 - 82%

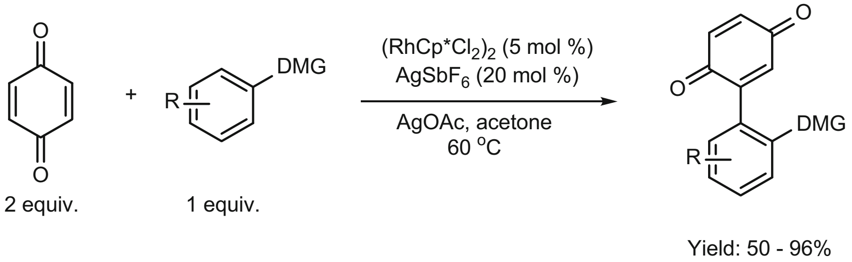
R, R^1 = H, Me, OMe, Cl, Br, I, Ph, *t*-Bu, $-(CH)_4-$, Ac, $-(CH)_2CO_2Me$, CO_2NMe_2, 3-thienyl
THP = tetrahydropyran

Scheme 2.31 Rhodium-catalysed direct olefination of aromatic carbamates [119]

Not only palladium but also ruthenium [114] and rhodium [112, 115–117] catalysts can mediate oxidative direct and directed alkenylation of aromatic amides, esters and ketones. For example, in the case of rhodium-catalysed olefination of nicotinamides, products are formed after formal activation of the three C-H bonds and one N-H bond (Scheme 2.30) [117].

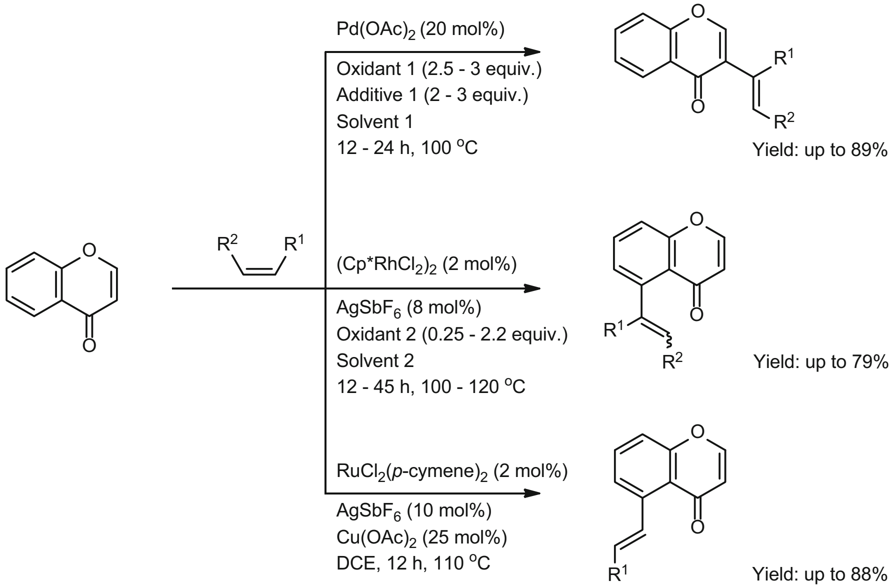
The ability of carbamate group to coordinate cations of metal is well known and is widely used in D*o*M and (D*o*M-cross-coupling nexus) chemistry. [118]. -Rhodium-mediated selective C-H activation/olefination of phenol carbamates was realised with utilisation of different types of EWG- and EDG-substituted terminal olefins and led to expected Heck-type products in usually good yields [119]. Generally, the less sterically hindered products were formed when two possible C-H activation sites, in the aryl core, were accessible (Scheme 2.31). The comparison of the C-H activating ability of carbamoyl and carbonyl groups was possible when 3-acetylphenyl dimethylcarbamate was utilised in a substrate role. The formation of a bis-olefinated product indicates the comparably directing power of two directing groups, while earlier studies suggested that ketone was a good directing group in Rh-catalysed C-H functionalisation [116].

In the presence of 5 mol% of $[RhCp^*Cl_2]_2$, quinones and naphthoquinones selectively undergo coupling reactions with substituted benzamides in mild conditions, furnishing products in high to excellent yields. In this reaction, silver salts were used as catalyst reoxidant. Similar to benzamides, in these conditions anilides, esters, ureas, nitrosamines, azobenzene and heterocyclic acid amides underwent reactions with quinones. This wide substrate scope may suggest that the role of directing C-H activation group in all cases plays the lone electron pair situated on oxygen atom of $C=O$ group (Scheme 2.32).



R = H, Me, F, Cl, Br, I, OAc, CO_2Me, CF_3, OMe, NO_2, Ph, CN, OCF_3, NMe_2
DMG = CONHAdamantyl, NHCOAdamantyl, $CONEt_2$, CO_2*t*-Bu, N(O)NPh, N(NO)Me, ...

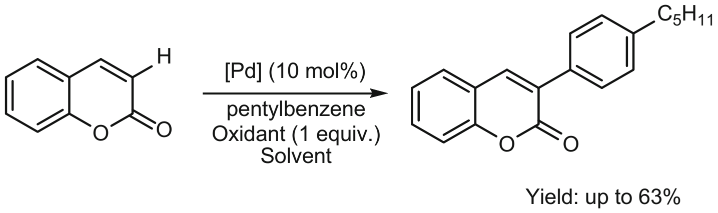
Scheme 2.32 Rhodium-catalysed arylation of quinones [115]



Solvent 1 = PivOH, 1,4-dioxane, TFA, AcOH, $PhCO_2H$, $EtCO_2H$, *t*-$BuCO_2H$
Solvent 2 = 1,4-dioxane, 1,2-DCE, 1,2-DME, *t*-AmOH, toluene, DMF
Oxidant 1 = none, $Cu(OAc)_2$, AgOAc, Ag_2CO_3
Oxidant 2 = $Cu(OAc)_2$, $Cu(OTf)_2$, AgOAc, Ag_2O, $AgOCOCF_3$, Ag_2CO_3
Additive 1 = none, K_2CO_3, AcOH, PivOH, TFA, Cs_2CO_3, Ag_2CO_3, AgOAc, AgO_2CF_3, AgOTf
R^1, R^2 = H, Me, CO_2*n*-Bu, Ac, Ph, Hal-C_6H_4, -C(O)C_6H_4C(O)-...

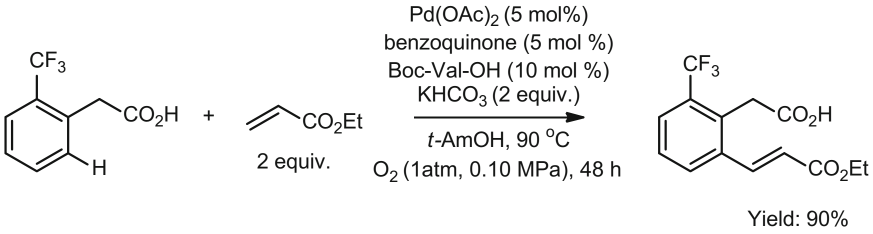
Scheme 2.33 Selective alkenylation of chromones [122]

The directing effect of carbonyl group was also observed in the palladium- [120], ruthenium- [121] and rhodium- [122]mediated reactions of chromones with alkenes. In the case of palladium catalysis, C-H activation underwent at position C3, while ruthenium and rhodium catalysis leads to C5-substituted products (Scheme 2.33).



[Pd] = $Pd(OAc)_2$, $PdCl_2$, $Pd(acac)_2$, $Pd(dba)_2$, $Pd(OCOCF_3)_2$
Oxidant = none, t-BuO_2H, Bz_2O_2, O_2, $K_2S_2O_8$
Solvent = t-$BuCO_2H$, TFA, TFAA-TFA, TFAA, TFAA-DMA, TFAA-1,2-$Cl_2C_6H_4$

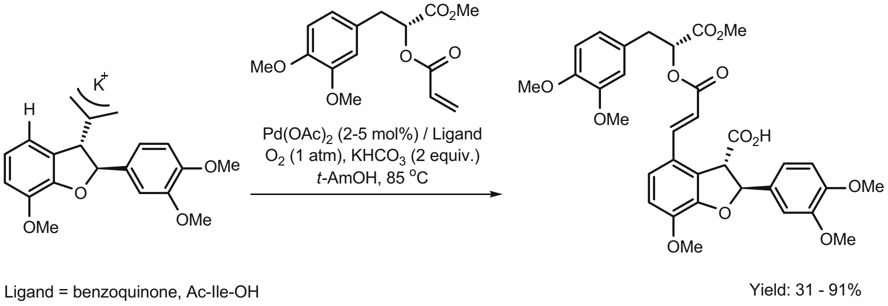
Scheme 2.34 Palladium-catalysed dehydrogenative arylation of coumarins [123]



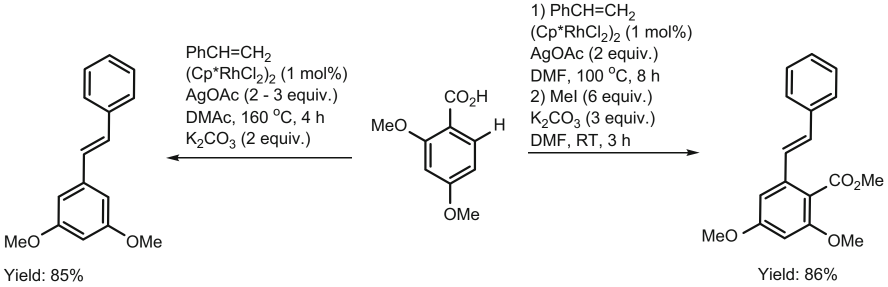
Scheme 2.35 Alkenylation directed by carboxyl group [125]

Jafarpour and co-workers explored the reactions between coumarins and pentylbenzene (Scheme 2.34) [123]. In contrast to reactions involving coumarins and arylboronic acids (which proceed via Suzuki protocol and lead to C4-addition product [124]), this approach provides possibility of the synthesis of C3-aryl derivatives. For this purpose, palladium acetate catalyst and TFA solvent are necessary. Under these conditions, expected products with yield higher than 60 % were formed. In similar synthesis involving $Pd(dba)_2$ catalyst precursor, instead of expected aryl-heteroaryl derivatives, only small amounts of products of self-condensation of pentylbenzene were formed.

Even carboxyl group of arylacetic acids could act as directing metalation group in slightly basic conditions [125–127]. Obviously, carboxylic anion may coordinate Pd (II) species, thus the proximity effect favoured *ortho*-metalation and next dehydrogenative Heck arylation reaction (Scheme 2.35). Notably, this reaction can run in the presence of 5 mol% of palladium catalyst and 5 mol% of benzoquinone, while dioxygen was used as a stoichiometric oxidant. Surprisingly, the products of α-functionalisation of phenylacetic acid were not formed in this reaction in significant amount. Thus, certainly direct (oxidative) dehydrogenative Heck reaction extends the usual pattern of regioselectivity, observed in the "classical" reactions. This reactivity had been already used in the synthesis of important natural product (+)-lithospermic acid, which is used in the treatment of cardiovascular disorders, cerebrovascular diseases, various types of hepatitis, chronic renal failure and dysmenorrhea with a potential to be used as nontoxic anti-HIV compound (Scheme 2.36) [128].



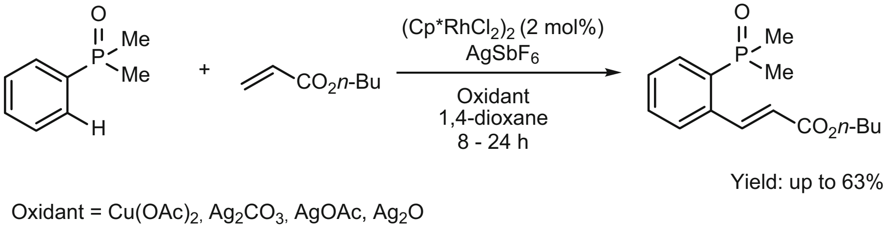
Scheme 2.36 Synthesis of lithospermic acid derivative [24]



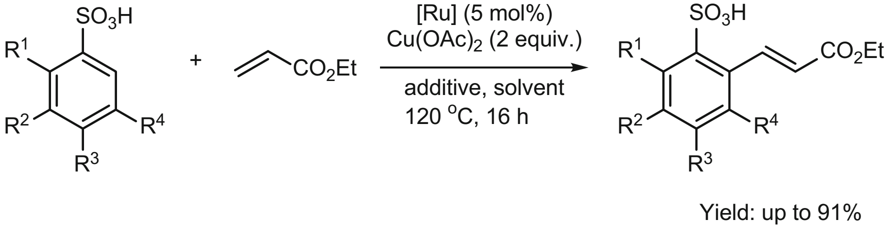
Scheme 2.37 Direct alkenylation of benzoic acids [129]

Directing effect of carboxyl group was also found in dehydrogenative alkenylation of benzoic acids catalysed by rhodium complexes used in 0.5 mol%. In the reaction run at about 100 °C in polar aprotic solvents, the active catalyst was reoxidised by silver or copper acetates. It was also found that in the conditions of the reaction, the carboxyl group underwent hydrodecarboxylation reaction unless it was protected in situ by methyl group (Scheme 2.37). This method could have been used for the preparation of *meta*-substituted stilbenes as well as 1,3- and 1,4-distyrylbenzene derivatives from readily available benzoic acids and styrenes through precisely ordered oxidative and dehydrogenative *ortho*-alkenylation followed by decarboxylation, run under rhodium catalysis. In these reactions, the carboxylic group acted as a unique removable directing group.

In the same conditions, tertiary (hetero)arylphosphine oxides, in reaction with activated as well as nonactivated alkenes, selectively undergo the dehydrogenative *ortho*-olefination via twofold C-H bond activation with good functional group tolerance. The reactions run in moderate to high yields when copper acetate was used as reoxidant (Scheme 2.38). For the good reaction yields, an addition of catalytic amounts of AgSbF$_6$ was very important. It is possible that silver salt undergoes the metathesis reaction with rhodium precatalyst to form catalytically active cationic rhodium complex.

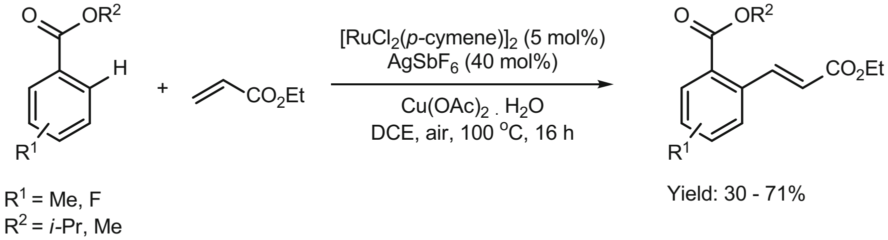


Scheme 2.38 Direct alkenylation of tertiary (hetero)arylphosphine oxides [130]



[Ru] = $[RuCl_2(p\text{-cymene})]_2$, $RuCl_3$, $[RuCl_2(PPh_3)]_2$
additive = $AgSbF_6$, NaOAc, KPF_6, AgOTf, $AgPF_6$, $AgBF_4$
solvent = H_2O, toluene, 1,4-dioxane, DMA, *t*-AmOH, NMP, DMF, DCE
R^1, R^2, R^3, R^4 = H, Me, Et, *n*-Pr, OMe, F, Cl

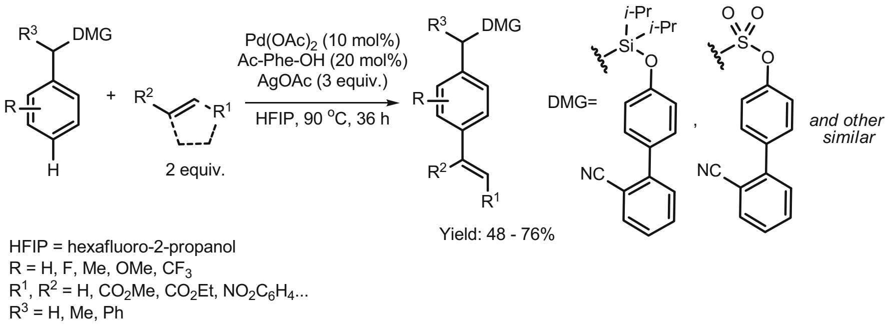
Scheme 2.39 Direct alkenylation of benzenesulphonic acids [133]



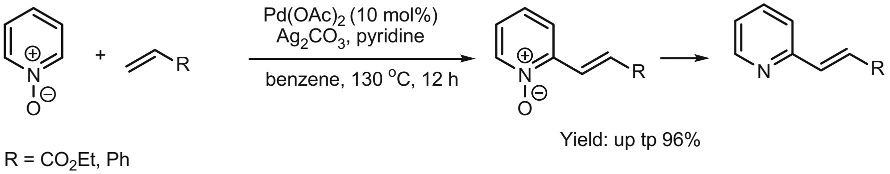
Scheme 2.40 Direct alkenylation of alkyl benzoates [131]

Similar to benzoic acids, but under ruthenium and rhodium catalysis, alkyl benzoates [131, 132] as well as sulphonic acids and their derivatives (such as sulphonyl chlorides and sulphonamides) [133] undergo the directed dehydrogenative Heck alkenylation in high to excellent yields. In the optimised conditions, they were used to obtain desirable alkenylated products derived from numerous of electron-deficient alkenes (Schemes 2.39 and 2.40).

Interesting remote *para*-olefination approach was presented by Debabrata Maiti [134]. The biphenyl-directing group-bearing palladium-coordinating nitrile



Scheme 2.41 Remote para-C-H functionalisation of arenes [134]



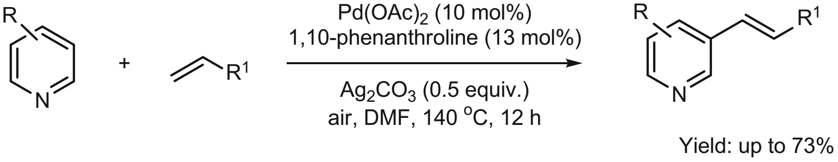
Scheme 2.42 Direct selective alkenylation of pyridine *N*-oxides [135]

function was introduced into the molecules of phenylacetic acids, phenylmethane sulphonic acids and toluene derivatives via C-O, S-O or C-Si bonds, allowing to perform remote *para*-C—H functionalisation of arenes in excellent yields and selectivities (Scheme 2.41).

Oxygen atom of N-O moiety could be used as a directing group in dehydrogenative olefination reactions mediated by palladium in oxidative conditions [135]. Utilisation of 10 mol% of catalyst and 150 % of Ag_2CO_3 reoxidant allows to achieve high to excellent yields of products in coupling reactions between different nitrogen heterocyclic *N*-oxides and EWG- as well as EDG-substituted olefins. Even in the case when benzene was used as a solvent, the main product still was the product of dehydrogenative Heck reaction. Obviously, the conditions of the deprotection of nitrogen lone electron pair reaction were also reported (Scheme 2.42).

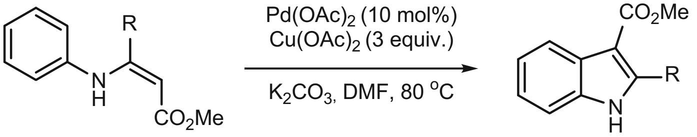
The high-yielding C-3 selective C-H olefination of pyridines could be assured by utilisation of bis-nitrogen chelating ligands and palladium (II) catalyst in the presence of air and catalytic amounts of Ag_2CO_3 as reoxidants. According to the authors' assumption, the origin of high C3 selectivity is strong trans-effect of the bispyridine ligands (Scheme 2.43) [136].

In some cases dehydrogenative Heck reaction could be directed to untypical α- position of EWG-substituted olefins. Thus, in carefully optimised conditions, annulation of *N*-aryl enamines leads to substituted indoles in high yields (Scheme 2.44) [137]. Authors state that to reach high yields and selectivities, it was very important to use proper amounts of palladium acetate catalyst (5–10 mol%),



R = H, Me, CF_3, CO_2Me, CO_2Et, OMe, F
R^1 = CO_2Et, CO_2n-Bu, CO_2t-Bu, $CONMe_2$,

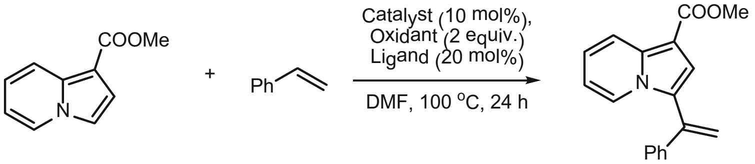
Scheme 2.43 Ligand-promoted C-3 selective C-H olefination of pyridines [136]



R = H, Me, Ph

Yield: up to 85%

Scheme 2.44 Direct oxidative synthesis of indoles [137]



Catalyst = $Pd(OAc)_2$, $PdCl_2$, $Pd(dba)_2$

Yield: up to 84%

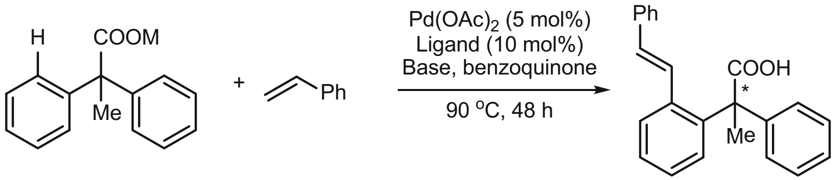
Oxidant = Ag_2CO_3, AgOAc, AgOTf, $CuCl_2$
Ligand = none, PPh_3, pyridine, 1,10-phenantroline, 2,2'-bipyridyl, 1,2-bis(diphenylphosphino)ethane...

Scheme 2.45 Direct ligand-controlled α-selective dehydrogenative Heck reaction [138]

$Cu(OAc)_2$ reoxidant (3 equiv.) and K_2CO_3 base (3 equiv.). The presented method is an attractive alternative to standard Heck coupling reactions, which require the use of *ortho*-halogen-substituted anilines. Initial mechanistic studies indicate that reaction does not run according to an electrophilic aromatic palladation of the aniline ring but follows the α-C-H bond metathesis pathway.

Highly regioselective palladium-mediated dehydrogenative Heck-type α-heteroarylation of styrenes via twofold C-H bond activation was realised in a basic condition with utilisation of 3 mol% of $Pd(OAc)_2$, 20 mol % of 2,2′-bipyridine as a bidentate ligand, 1 equiv. of Ag_2CO_3 and 2 equiv. of KOAc in DMF at 100 °C. Importantly, the crucial impact on regiochemistry of this reaction gave bidentate 2,2′-bipyridine ligand, in the presence of which the α-product being mainly obtained (Scheme 2.45) [138].

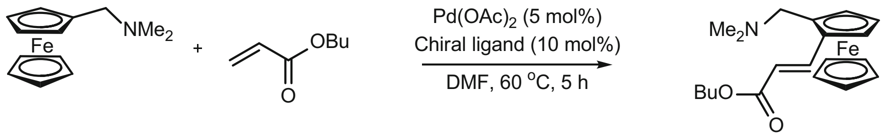
The highest synthetic potential of the dehydrogenative Heck reaction could be demonstrated on the cases of asymmetric coupling reactions leading to a product of



Ligand = BOC-Ile-OH
Base = $NaHCO_3$, Na_2CO_3, Cs_2CO_3, K_2HPO_4, Li_2CO_3, NaOTs, $NaHCO_3$, $KHCO_3$, K_2CO_3
M = H, Na, K, Cs, NH_4

Yield: 25 - 61%
ee: 79 - 91%

Scheme 2.46 Direct stereoselective dehydrogenative desymmetrisation of phenylpropionic acids [139]



Chiral ligand = Boc-L-Tle-OH, Boc-L-Phe-OH
Boc-L-Ala-OH, Boc-L-Val-OH
Boc-L-Leu-OH, Boc-L-Ile-OH,
Boc-L-Cys(Trt)-OH, Boc-L-Asp-O*t*-Bu,
Fmoc-L-Phe-OH, Ac-L-Phe-OH,
Boc-L-Phe-OH

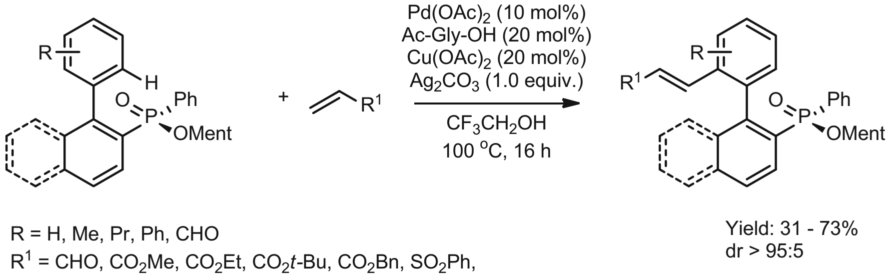
Yield: 62 - 98%
ee: 12 - 99%

Scheme 2.47 Direct stereoselective dehydrogenative desymmetrisation of *N*,*N*-dimethylaminomethylferrocene [93]

different kind of chirality (central, planar and axial) in which both unique reactivity and selectivity were ultimately exposed. The enantioselective dehydrogenative reactions require oxidation-resistant chiral ligand, coordinating Pd(II) species and assuring the significant level of spatial control at kinetically controlled key reaction steps.

One of the first enantioselective dehydrogenative Heck reactions was demonstrated in 2010 on the example of stereoselective desymmetrisation of diarylpropionic acids (Scheme 2.46) [139]. The site of the alkenylation of the substrates, in this case, was directed by carboxyl group, while *N*-BOC-protected amino acids were used as efficient ligands for palladium acetate, allowing the formation of products in up to 73 % yield and up to 99 % *ee*. Notably, even in this case, only 5 mol% of catalyst, reoxidised by O_2/benzoquinone couple, was applied.

A planar chirality at ferrocene core was also induced by chiral palladium (II) complex catalysts based on *N*-BOC-protected amino acid ligands (Scheme 2.47) [93]. Presented in the substrate structure, trimethylamino group has high affinity to Pd(II) and therefore effectively directs the olefination, which resulted in much better chemical yields obtained under mild reaction conditions. Surprisingly, since the ferrocene may participate in redox reactions, the active catalyst was reoxidised by atmospheric dioxygen with no need to add copper or benzoquinone additive.



Scheme 2.48 Directed diastereoselective dehydrogenative remote olefination of biaryls [140]

Axially chiral biaryls were obtained in good yields and excellent diastereomeric ratio in diastereoselective, direct and directed by P = O group, remote dehydrogenative olefination, mediated by 10 % of Pd(II) catalyst, and reoxidised by copper acetate (Scheme 2.48) [140]. An atroposelective mild C-H activation occurs through dynamic kinetic resolution and kinetic resolution towards the synthesis of alkenylated atropisomeric biaryl bearing phosphorus group of central chirality at the phosphorus atom.

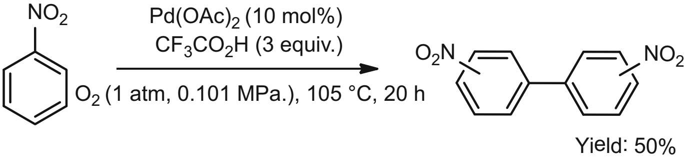
The key mechanistic features of enantioselective C-H bond activation were also theoretically studied [141].

2.3 Dehydrogenative Aryl-Aryl Bond Formation

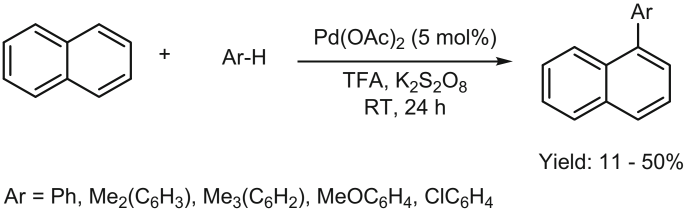
Aromatic systems are very resistant as components of addition reactions. For example, only some, very rare arene cycloaddition processes are known [142, 143]. In consequence, a formation of aryl-aryl bond is usually a challenging issue. Before the discovery of Pd-catalysed cross-coupling reactions, biaryls were prepared almost exclusively by Ullmann coupling [28], Meyers reaction [144], Gomberg-Bachmann reaction [145] and oxidative dimerisation of hydroxyarenes [146–149]. Obviously, these methods require arene preactivation, which involves costly manipulations and proper leaving group introduction prior to the coupling. Only the alternative direct arylation approach, leading through twofold C-H activation, is an environmentally benign, atom economic and has significant commercial potential.

2.3.1 Undirected Aryl-Aryl Bond Formation

In the pioneering studies on dehydrogenative (oxidative) dimerisation of unactivated arenes, the stoichiometric amounts of palladium "catalysts" were utilised [150–152]. Because of marginal economic value of such stoichiometric



Scheme 2.49 Direct oxidative dimerisation of simple aromatics [153]



Scheme 2.50 Direct dehydrogenative cross-coupling of simple aromatics [154]

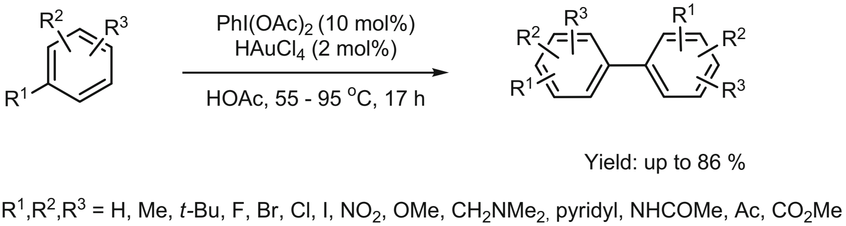
reactions, this (dehydrogenative **aryl-aryl bond formation**) method had not been extensively developed for a long time. Its renaissance is dated only in the beginning of this century, when efficient catalytic approaches were found.

The dimerisation of simplest aromatic compounds run in strong acidic medium, catalysed by about 10 mol% of palladium acetate, and reoxidised by dioxygen is not regioselective even in the presence of strongly EWG groups (i.e. NO_2) in the ring (Scheme 2.49) [153]. The yields of these types of reactions did not exceed 50 %. Notably in the case of dimerisation of nitrobenzene five (!) regioisomeric products are formed. This observation indicates that the reaction does not run via aromatic S_E2 metalation mechanism, which should favour *meta*-substitution.

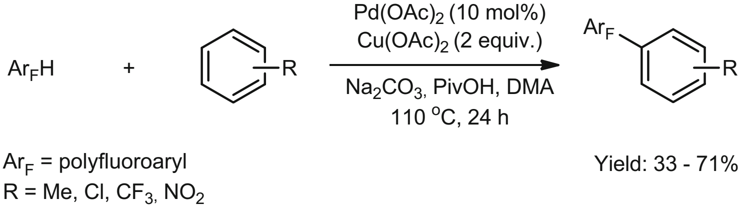
The possibility to stimulate the regioselectivity in the cross-dehydrogenative coupling reactions, which run under oxidative conditions in the presence of palladium catalyst, was also demonstrated (Scheme 2.50) [154]. Preparation of unsymmetrical biaryls as the major or sole products via twofold aromatic C-H activation has been achieved just by tuning the concentrations of the arenes and TFA in the system $Pd(OAc)_2/TFA/K_2S_2O_8$.

In fact, the authors were able to obtain products of cross-coupling reaction, but the mixture of isomers was obtained when it was allowed by substitution pattern of the reagents.

The better regiocontrol of the coupling could be achieved when symmetric arenes, giving single, monosubstituted products, are used. This approach was demonstrated on the case of gold-mediated oxidative dehydrogenative dimerisation of *para*-xylene (Scheme 2.51) [155]. In contrast to the palladium-mediated couplings, syntheses based on gold catalysis seem to follow aromatic S_E2 mechanism at metalation reaction step. Thus, gold-mediated (oxidative) dehydrogenative dimerisation of substituted arenes, run in acetic acid, under $HAuCl_4$ catalysis, furnishes a mixture of biaryl products. Regioselectivity of these processes can be



Scheme 2.51 Dehydrogenative dimerisation of arenes [155]



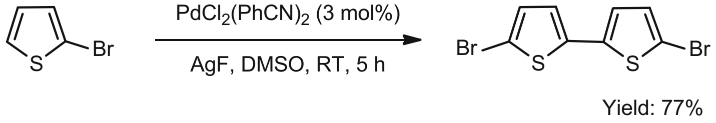
Scheme 2.52 Dehydrogenative arylation of polyfluoroarenes [156]

clearly explained on the basis of steric and electronic properties of substituents [155]. The reactions were carried out under mild conditions with application of only 2 mol% of catalyst. Unfortunately, expensive oxidant (e.g. $PhI(OAc)_2$) was required to assure high yields.

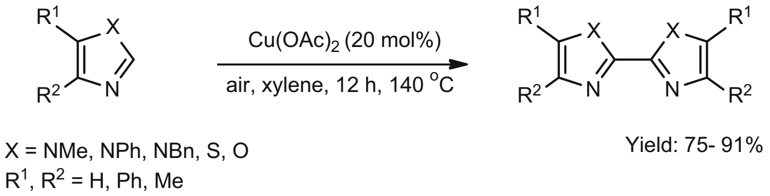
Obviously, the simplest way to guarantee the stereospecificity of the reaction is to run it with substrates which allows the formation of a single product. In this way, symmetric polyfluoroarenes were subjected to the dehydrogenative arylation reaction run under oxidative conditions in the presence of palladium and copper [156] or palladium and silver acetates (Scheme 2.52) [157]. The notable high yields of desirable products were obtained under conditions only where phenyl group was introduced into the arene. Nevertheless, reaction run with substituted aromatics furnished a mixture of biaryls substituted in less hindered position, with no visible correlation between the arylation position and value of Hammett constant of the substituents. The same approach could be used for perfluoroarylation of heteroaromatics [158].

Much better, both selectivities and reaction yields could be achieved in the dehydrogenative arylation reaction of less aromatic five-membered heteroarene systems. Thus, selective C2 dimerisation of thiophenes could be realised with high yields under palladium catalysis in DMSO at ambient temperature (Scheme 2.53) [159]. It should be noted that a wide range of substituents (e.g. halogens, carbonyl, carboalkoxyl, etc.) is tolerated in this reaction.

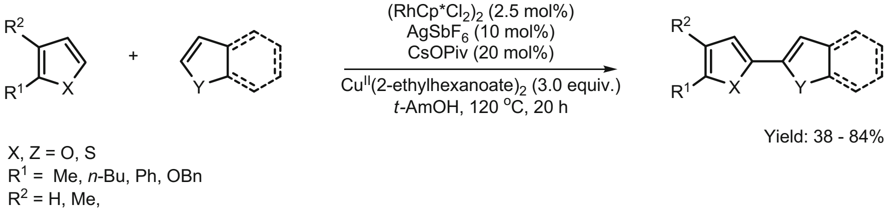
The dimerisation of electron-rich heteroarenes underwent smoothly copper (II) catalysis in the presence of atmospheric dioxygen as reoxidant [160–162]. That type of coupling is high yielding and C2 selective. There is also a limited evidence for the radical mechanism of this reaction (Scheme 2.54) [162].



Scheme 2.53 Dehydrogenative dimerisation of thiophenes [159]



Scheme 2.54 Copper-catalysed dehydrogenative dimerisation of five-membered heteroaromatic compounds [162]

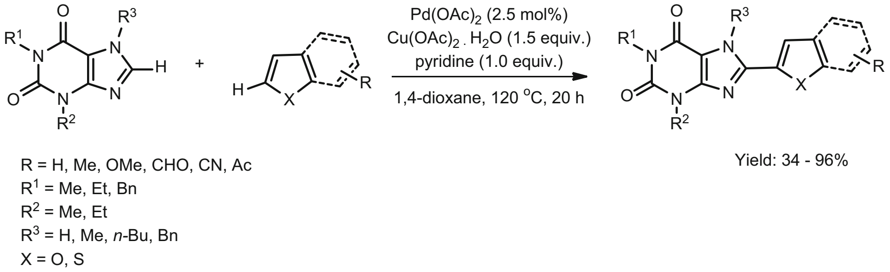


Scheme 2.55 Rhodium-catalysed dehydrogenative cross-coupling of five-membered heteroaromatics [163]

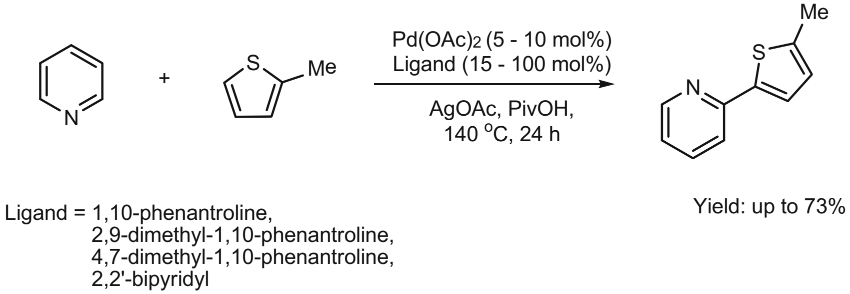
Quite general approach to cross-coupling of five-membered heteroaromatics was demonstrated by Glorius (Scheme 2.55) [163]. Under rhodium catalysis conditions, and in the presence of silver or copper oxidants as well as caesium pivalate, high yields and high levels of selectivities of the cross-coupling reactions between substituted indoles, pyrroles, (benzo)furans and (benzo)thiophenes were observed .

Similar to rhodium catalysis, an efficient and regioselective oxidative cross-coupling of heteroaromatic compounds via twofold C-H activation could be achieved at low Pd(II) catalyst loading. The use of substoichiometric Cu(II) salt, as a reoxidant, had been found important to enhance reactivity of electron-rich *N*-containing heteroarenes (e.g. xanthines, azoles, indolizines, thiophenes and furans) as well as electron-poor heteroarenes, pyridine *N*-oxides, in cross-coupling reactions (Scheme 2.56) [164].

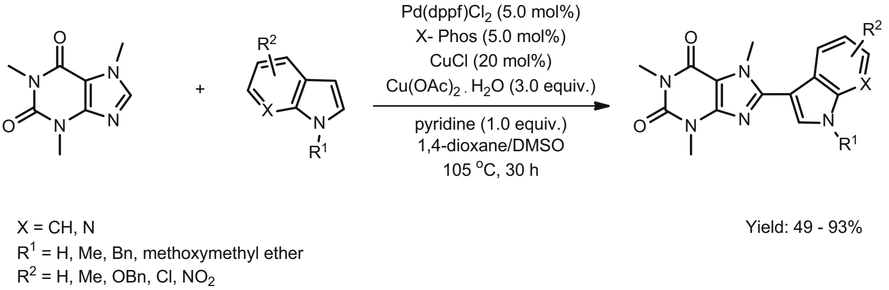
Liu and You [165] described interesting case of bis-C2 selective creation of a new single bond between electron-rich five-membered heteroaromatics and electron-deficient pyridines (Scheme 2.57). This palladium-mediated process leads exclusively to expected heterobiaryls. Notably, that in contrast to Yu assumption (about the role of phenanthroline ligand "trans-effect" for C3-selective



Scheme 2.56 Palladium-catalysed dehydrogenative cross-coupling of five-membered heteroaromatics [164]



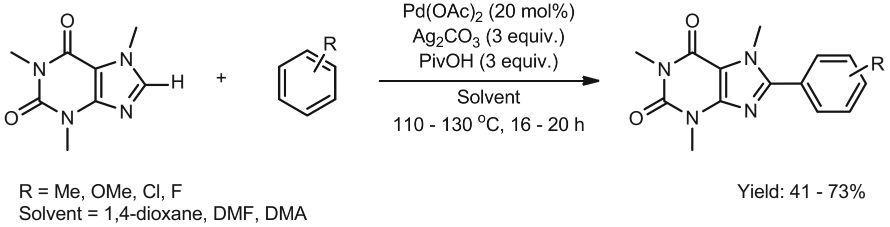
Scheme 2.57 Twofold C2 oxidative heteroarylation of pyridine [165]



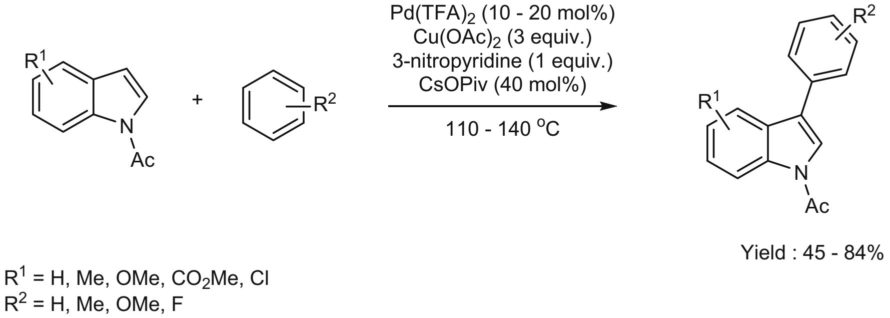
Scheme 2.58 Selective C3 heteroarylation of indoles and pyrroles [167]

functionalisation of pyridines) [136, 166], Liu and You observed in this case C2 regioselectivity.

Selective C3 heteroarylation of indoles and pyrroles was possible when source of palladium (II), in combination with two different bident phosphorus ligands (X-Phos and dppf), was utilised as a catalyst and copper(II) acetate was applied as a reoxidant, while Cu(I) chloride as an additive (Scheme 2.58). This reaction, run at about 100 °C for 30 h in DMSO/dioxane mixture, also required an addition of pyridine as a base. Despite all requirements mentioned above, the products of



Scheme 2.59 The palladium-catalysed direct C-arylation of xanthines with arenes [168]



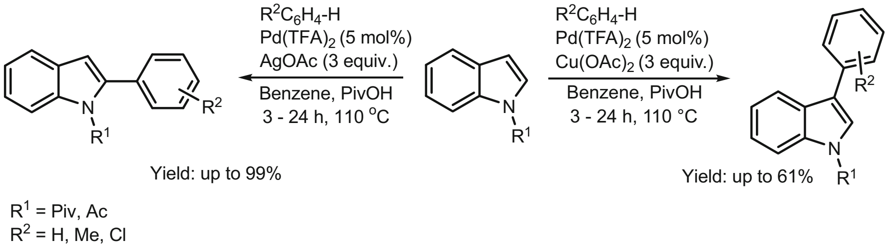
Scheme 2.60 C3 selective oxidative direct dehydrogenative arylation of *N*-acetylindoles [169]

C3-selective oxidative cross-coupling of indoles and pyrroles with a variety of electron-rich and electron-deficient heteroarenes were obtained in high yields [167].

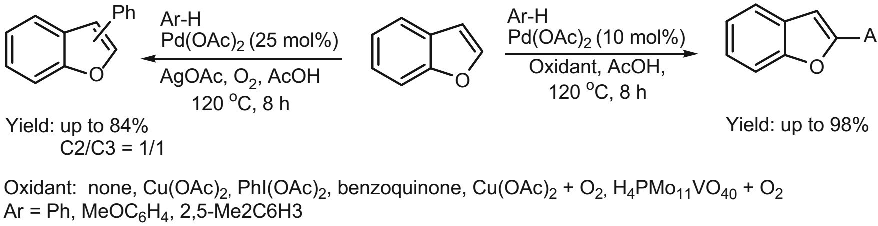
The palladium-catalysed direct C-arylation of xanthines with arenes could be realised with utilisation of Ag_2CO_3 and dioxygen as reoxidants. (Scheme 2.59). Nevertheless, reaction was not usually selective in relation to arenes and a mixture of *meta*- and *para*-substituted products were formed when it was possible [168].

C3-selective oxidative direct dehydrogenative arylation of *N*-acetylindoles runs via twofold C-H activation mediated by palladium catalyst and copper reoxidant presented by Fagnou (Scheme 2.60) [169]. It was also found that microwave-assisted synthesis gave usually higher yields in shorter timeframes than syntheses run in oil bath. Nevertheless, thermal heating was used in reactions with chloro-substituted indoles because small amounts of hydrodechlorination were observed under microwave heating. The utilisation of Pd(TFA)$_2$ catalyst and an addition of caesium pivalate as well as nitropyridine ligand was important to achieve high reaction yields. The only utilisation of symmetric arenes giving a single product of monosubstitution was reported; at the same time, still some amounts of C2 arylindoles and C2,3-bisarylindoles were obtained also.

Notably, the regioselectivity of the oxidative direct dehydrogenative arylation of indoles could be reversed simply by an additive change (Scheme 2.61) [170]. The C2 selectivity phenylation of indole system strongly depends on the reaction conditions.



Scheme 2.61 Elements of regiocontrol in palladium-catalysed arylation of indole [170]



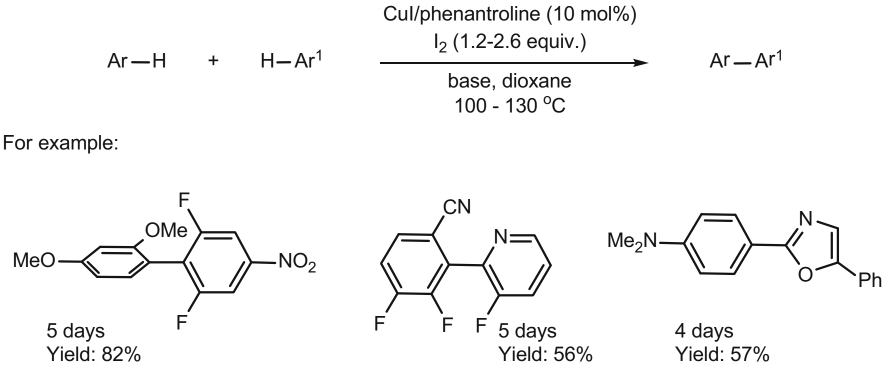
Scheme 2.62 Palladium-catalysed arylation of benzofuran [171]

Arylation without copper (II) reoxidant, but in the presence of large excess of caesium acetate, proceeds with regioselectivity higher than 99 % and leads to C2-functionalised derivative (in yields comparable with the amount of Pd(II) used). In contrast, similar reaction without caesium additive proceeds with reverse regioselectivity and gives C3 arylindoles as major products. The addition of Cu $(OAc)_2$ reoxidant enhances C3 selectivity and yield of the arylated products, while AgOAc reoxidant allows to obtain C2-functionalised derivatives in high yields.

Similar C2-selective arylation reactions involving benzofuran were also studied (Scheme 2.62) [171]. In particular, palladium-catalysed reaction between benzofuran and benzene, in the presence of silver oxidant, leads to a mixture of regioisomeric C2- and C3-phenyl benzofurans. $Cu(OAc)_2$, $PhI(OAc)_2$, heteropolymolybdovanadic acid ($H_4PMo_{11}VO_{40}$) and dioxygen reoxidants favour the formation of C2-arylated products. Synthesis without presence of oxidant requires higher amounts of palladium acetate, but proceeds with high regioselectivity to 2-phenylbenzofuran.

The phenomenon of oxidant-controlled regioselectivity in the dehydrogenative arylation reaction was also reported for processes involving *N*-acetylindoles [172].

Detailed mechanistic studies on the origin of C2/C3 selectivity of dehydrogenative direct arylation of electron-rich five-membered heteroaromatics were also undertaken [173]. Nevertheless, there is still no sufficient data allowing for a comprehensive mechanistic discussion. At least, two general mechanisms can be considered [174, 175]. One involves sequential activation of the indole and benzene at a single Pd(II) centre, followed by reductive elimination of the product



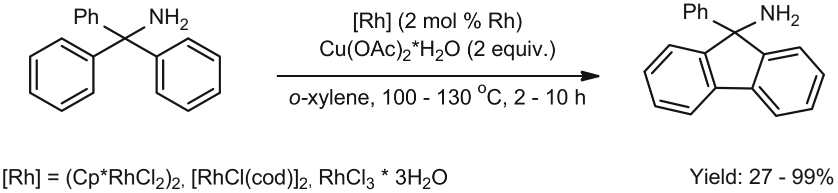
Scheme 2.63 Copper-catalysed arene cross-dimerisation [176]

and reoxidation of Pd(0). An alternative pathway involves activation of indole and benzene at independent Pd(II) centres, followed by transmetalation to afford the Pd (phenyl)(indolyl) intermediate that undergoes reductive elimination of the product. Distinguishing between these possibilities and exploring the basis for the reaction regioselectivity will be an important focus of future works.

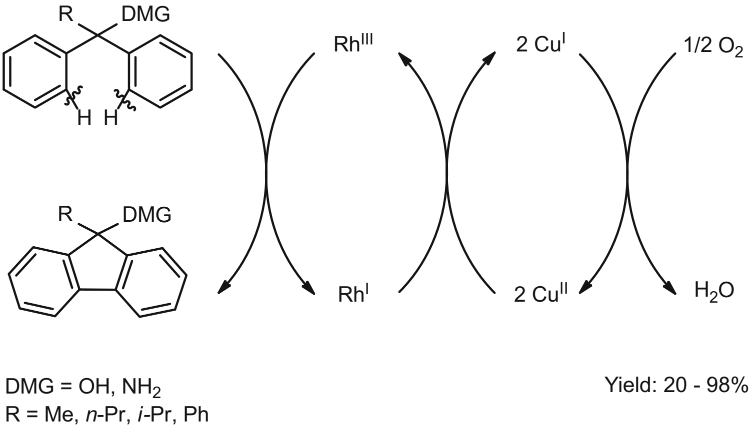
The undirected dehydrogenative cross-coupling reaction rarely runs in regioselective manner. There are only single cases of the regioselective coupling reactions not assisted by proper functionality in the aromatic systems. The cross-coupling of both EDG- and EWG-substituted aromatic and heteroaromatic compounds could be also achieved in the reactions oxidised by iodine. Since the regioselectivity of the reaction was corresponding to classical S_N2Ar reactivity, the authors suggested that in these cases reaction could proceed by iodination of one of the coupling components followed by arylation of the most acidic C-H bond of the other coupling component pathway (Scheme 2.63) [176].

2.3.2 Directed Aryl-Aryl Bond Formation via Twofold C-H Activation

Despite of high synthetic potential of undirected (hetero)aryl-(hetero)aryl bond-forming reactions, more selective, and therefore more useful, strategy involves formation of a new C-C bond in a way directed by certain Directing Metalation functional Groups (DMG) C-H bond activation. The directing effect of DMGs has an origin in their transition metal (TM) coordination nature; at the same time the proximity of precoordinating catalyst to an unreactive C-H bond assures the selective activation followed by a formation of (hetero)aryl-TM intermediate. Depending on the type of these directing groups as well as on the nature of a catalyst and selected reaction conditions, various biaryls could be formed in DMG-assisted reactions.



Scheme 2.64 Rhodium-catalysed intramolecular cyclisation of (diphenylmethyl)amine [177]

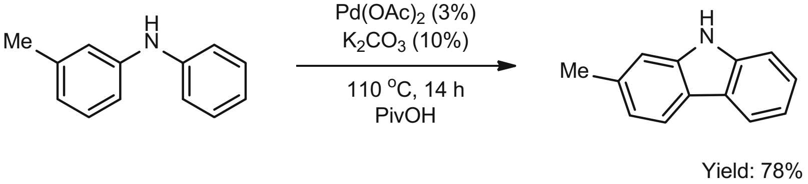


Scheme 2.65 Rhodium-catalysed intramolecular cyclisation using air as terminal oxidant [178]

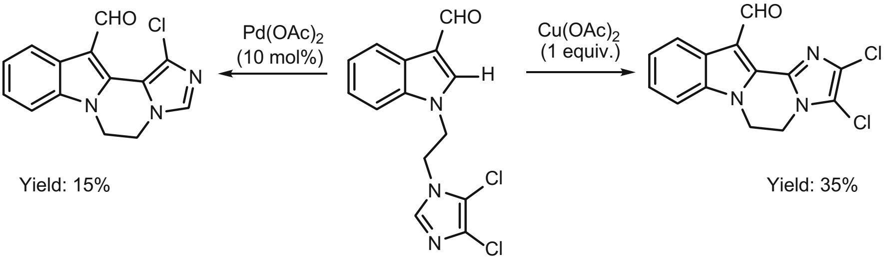
Indeed, formation of new aryl-aryl bonds, via twofold C-H activation, may proceed intramolecularly. Also in this case, the high regioselectivity of C-H activation could be defined by proper coordinating functional groups, which eventually resulted in high reaction yields. Miura and co-workers found that in the course of rhodium(III)-mediated intramolecular cyclisation of (diphenylmethyl) amines, the corresponding fluorenone derivatives were formed in 65 % to almost quantitative yields, depending on the catalyst used (Scheme 2.64) [177]. The reoxidation of formed in the reaction inactive Rh(I) species to its active Rh(III) form had been realised by an addition of copper acetate.

Fluorene derivatives may also be obtained via intramolecular cross-coupling process using rhodium-copper catalyst pair under oxidative conditions in atmospheric dioxygen (Scheme 2.65) [178].

Intramolecular, cross-coupling reactions give also possibility for synthesis of heterocyclic systems. For example, carbazoles were obtained in high yields in palladium-catalysed cross-coupling reaction starting from the diarylamines (Scheme 2.66) [179]. Notably, the atmospheric dioxygen was used as only a reoxidant in this coupling, while the pivalic acid additive favours cleaner reaction run. This annulation could be speeded up by microwave excitation in acid-free conditions [180].



Scheme 2.66 Example of palladium-catalysed intramolecular cyclisation of diarylamine [179]



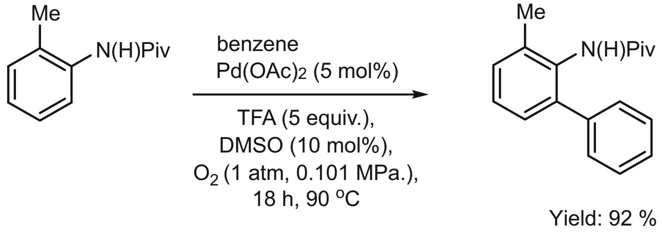
Scheme 2.67 Intramolecular dehydrogenative annulation of heteroarenes in the presence of Pd(OAc)$_2$ and Cu(OAc)$_2$ [182]

The highly developed case of such annulation was presented by Kanai and Kuninobu [181]. In palladium-mediated reaction, run in oxidative conditions in DMF or pivalic acid, series of diversified heteroatom-containing π-conjugated polycyclic systems (up to ten rings) possessing benzothiophene, benzofuran and indole skeletons were obtained in high yields after closing of new five- or six-membered ring.

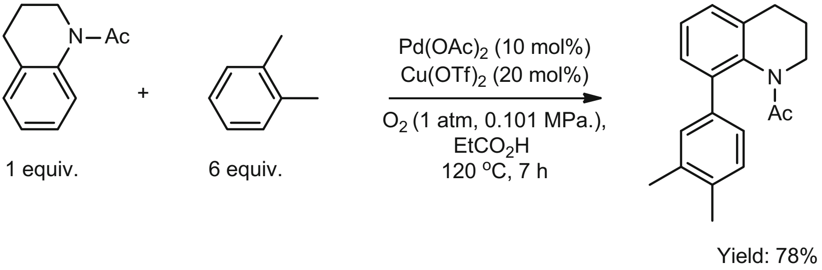
Similarly in intramolecular copper-catalysed and silver-oxidised reaction, interesting polyheterocyclic systems were obtained in usually good yields with different regioselectivities than those observed under palladium catalysis (Scheme 2.67) [182].

Intermolecular dehydrogenative aryl-aryl bond formation is quite challenging reaction. The selective arylation of nonactivated aromatics could only be possible when efficient directing group (of high affinity to palladium(II) species) is incorporated in the structure of the substrates. Palladium acetate is generally a universal catalyst for dehydrogenative arylation processes (the effect of acetate anion in C-H activation process had been already discussed) and therefore was used in the majority of cases of direct and directed aryl-aryl bond formation [46].

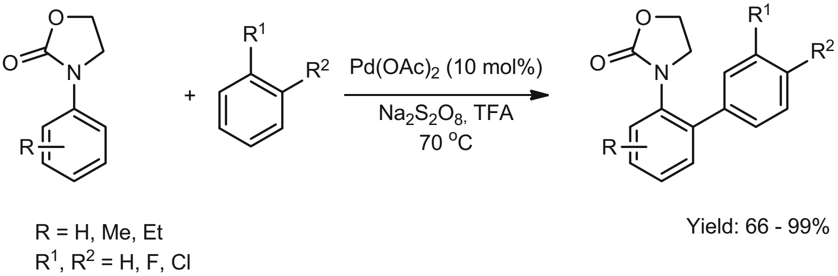
The efficient reaction systems, in which aryl-aryl bond is formed, have been examined by Buchwald [183]. It was found that in the presence of palladium acetate, *ortho*-functionalised anilides easily undergo the reaction with benzene (Scheme 2.68). Reaction proceeds with full regioselectivity and gives only one product, in which phenyl group is situated in *ortho*-position relatively to NHAlk functional group. Many alkyl-, polyalkyl- and alkoxy-substituted benzenes underwent the reaction with anilides according to analogous protocol.



Scheme 2.68 Palladium-catalysed phenylation of anilide [183]



Scheme 2.69 Palladium-catalysed arylation of acetanilide [184]

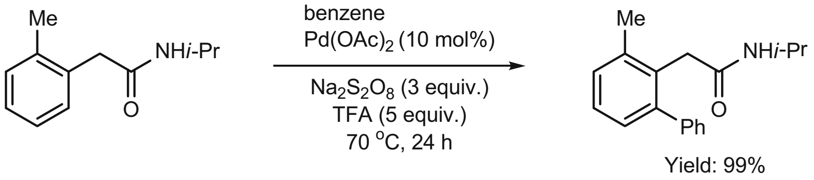


Scheme 2.70 Oxidative *ortho*-directed arylation of *N*-aryloxazolidinones [185]

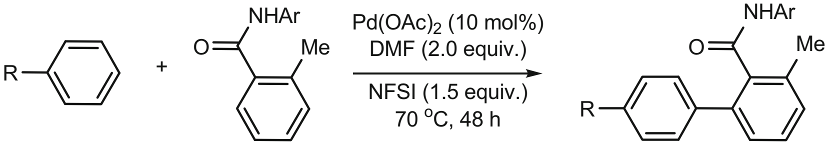
Cyclic acetanilides undergo reactions with substituted benzenes to furnish expected biaryl systems in high yields (Scheme 2.69) [184].

Another class of cyclic aniline derivatives, *N*-aryloxazolidinones, underwent *ortho*-directed, palladium-catalysed arylation under oxidative conditions in the presence of TFA (Scheme 2.70) [185]. Surprisingly, the reaction was very demanding to the reoxidant nature, and among the series of tested oxidants and conditions, only the use of sodium persulphate in the presence of five equivalents of TFA allows to achieve excellent conversion of the substrate and high yields of the *ortho*-arylated products as well as good regioselectivity of arylation towards to the formation of less sterically hindered biaryls.

Introduction of phenyl group into the *ortho*-position of nonactivated arylacetamides was demonstrated on the case of direct oxidative dehydrogenative



Scheme 2.71 Palladium-catalysed phenylation of arylsubstituted acetamide [186]



Ar = 4-$CF_3C_6H_4$
R = H, Me, CD_3, Et, *i*-Pr, F, Cl, Br, OMe
NFSI = N-Fluorobenzenesulfonimide

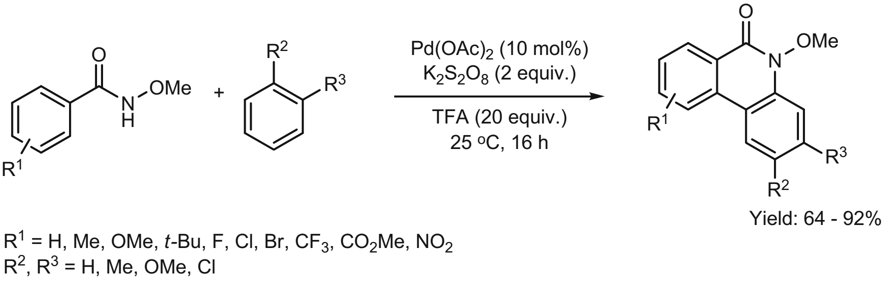
Scheme 2.72 Pd(II)-mediated para-selective C-H arylation of monosubstituted arenes [187]

coupling of *N*-isopropyl (2-methylphenyl) acetamide with benzene (Scheme 2.71) [186]. In the presence of sodium persulphate reoxidant, reaction proceeds in practically quantitative yield. In contrast, similar process, where other oxidants were applied or run with no TFA added, yielded less than 75 % of target products. The same reaction conditions were used for the phenylation of benzamides and anilides.

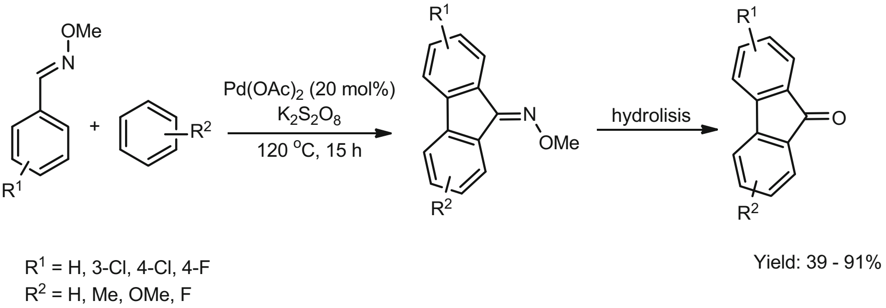
It should be underlined, however, that similar reactions involving benzamides oxidised by N-fluorobenzenesulphonimide (NFSI) proceed in good yields and furnish corresponding *ortho*-arylated benzamides with significant *para*-selectivity in relation to monosubstituted aryls. (Scheme 2.72) [187]. Importantly, the authors also demonstrated that bromoarenes underwent the arylation reactions with retention of the bromine in the product structure.

N-Methoxybenzamides were also used in direct dehydrogenative arylation (Scheme 2.73) [188], mediated by 10 mol% of Pd(II) catalyst reaction run under very mild conditions with notable high selectivity (in regard to substituted arene and *N*-methoxybenzamide) to form less hindered products in high to excellent yields. At the first reaction step, a new aryl-aryl bond is created by twofold C-H activation, followed by newly formed biaryl product undergoing the annulation via tandem direct C-N coupling involving C-H and C-H bond activation. The present methodology appears to be very useful for the synthesis of natural products that contain the phenanthridinone core, for example, crinasiadine [189, 190].

Unusual directing group was used in the case of dehydrogenative cross-coupling between oxime ethers and monosubstituted benzenes, catalysed by palladium acetate, and reoxidised by potassium persulphate (Scheme 2.74) [191]. In the



Scheme 2.73 Pd(II)-mediated directed dehydrogenative arylation of *N*-methoxybenzamides [188]

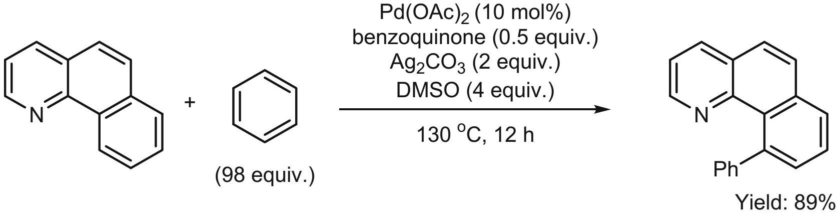


Scheme 2.74 Palladium-catalysed reactions between oxime ethers and simple aromatics [191]

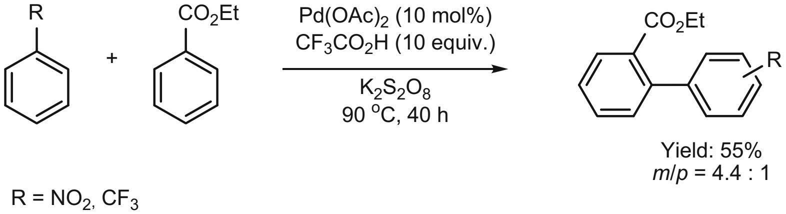
reaction course, four tandem activations of C-H bonds, directed by the same oxime group, occurred in a regioselective manner. This led to creation of two new C-C bonds, which in turn constituted the newly formed five-membered cyclic system. This methodology provides synthesis of fluoren-9-ones that avoids the use of aryl halides, aryl boronic acids and expensive metal oxidants. Surprisingly, the reaction seems to be also selective in relation to substituents presented in both substrates.

The same *O*-methyl oxime DMG was used in rhodium-mediated direct and directed dehydrogenative heteroarylations of arenes run in oxidative conditions with relatively wide substrate scope and a broad tolerance of functional groups, which provides a straightforward access to bi(hetero)aryl scaffolds [192].

A presence of nitrogen atom in azafenantrene and 2-arylpyridines molecules facilitates the selective C10 C-H bond activation followed by arylation on the activated position. These types of reactions, catalysed by palladium acetate, carried out in the presence of excess of reoxidant (Ag_2CO_3) and catalytic amount of benzoquinone, acting as electron-transfer mediator, in DMSO at 130 °C run in excellent yields. Unfortunately, reaction was not selective in relation to arenes. In consequence, mixture of isomeric products was obtained when possible (Scheme 2.75) [193]. Surprisingly, the selectivity in relation to the arene of this reaction could be significantly improved and even reversed simply by addition of some amounts of carboxylic acid and changing the amount of benzoquinone used [194].



Scheme 2.75 Palladium-mediated arylation of azaphenanthrene and 2-arylpyridines [193]

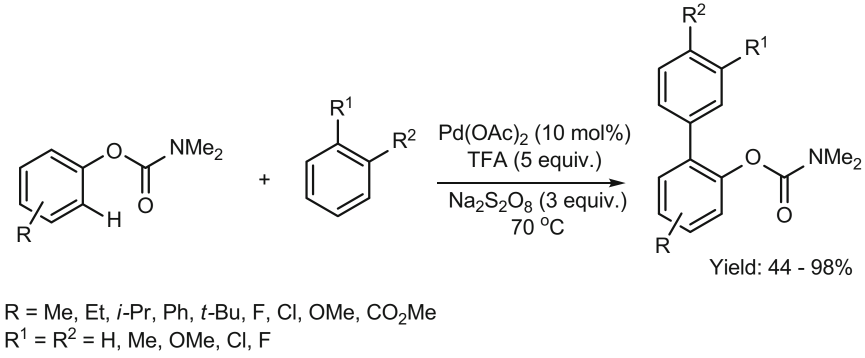


Scheme 2.76 Catalytic cross-coupling of ethyl benzoate with nitrobenzene or (Trifluoromethyl) benzene [153]

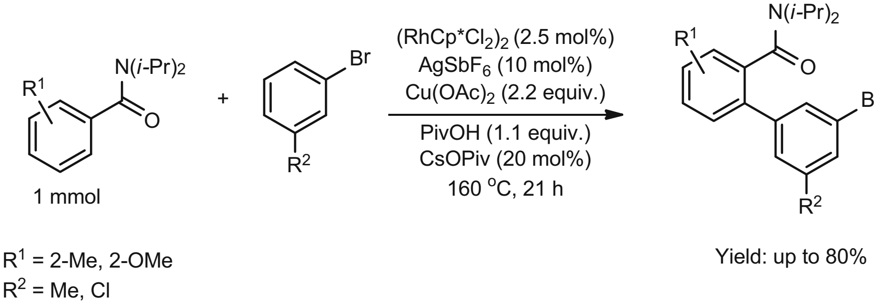
Esters also offer the possibility of selective direct and directed dehydrogenative arylations likely because of coordination palladium with lone electron pair of carboalkoxy group (Scheme 2.76) [153]. The precoordination of the Pd(II) catalyst assures high level of *ortho*-selectivity of the arylation reaction and the reactivity towards unreactive EWG-substituted aromatics. Such arylation reaction runs in the presence of non-nucleophilic strong acid (TFA) and oxidant ($K_2S_2O_8$) at 90 °C in average 55 % yield. For the contrast, dimerisation of nitrobenzene, run in the same conditions, was completely unselective.

The directing metalation reaction (D*o*M) ability of carbamoyl group is well known and comprehensively studied by Snieckus group [118, 195–197]. This ability of carbamoyl group to coordinate the metal cations was used in palladium-mediated direct dehydrogenative coupling of *O*-aryl *N*,*N*-alkyl carbamates with *ortho*-disubstituted arenes possessing such substituents as Me, F, Cl and OMe (Scheme 2.77) [198]. The synthesis of corresponding biaryls is strongly dependent on an oxidant nature. In particular application of oxone as well as copper or silver oxidants is totally ineffective. On the other hand, in the presence of 1.5 equivalents of sodium persulphate, reaction yield increased up to 73 %. Utilisation of higher amounts of oxidant leads to the products of double condensation.

It should be highlighted at this point that direct and directed dehydrogenative cross-coupling of aryls, run via twofold C-H activation under oxidative conditions, could be a “green” alternative to traditional D*o*M approach. Moreover, it may tolerate significantly wider range of substituents bearing in the substrates. The main drawback of this approach is the necessity to use large excess of the arene.



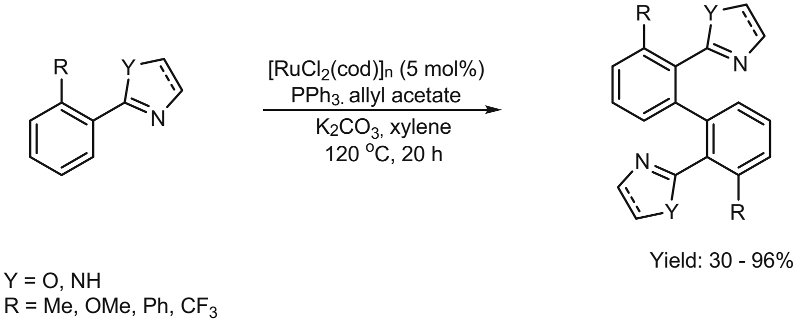
Scheme 2.77 Carbamoyl group-directed dehydrogenative arylation of *O*-arylcarbamates [198]



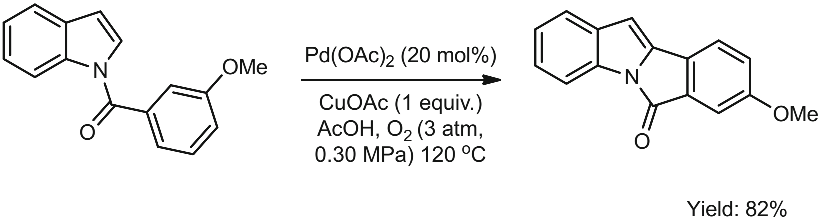
Scheme 2.78 N,N-dialkylbenzamides in rhodium-catalysed reactions with bromoarenes [199]

Several other transition metals may catalyse directed dehydrogenative arylation. Glorius and co-workers described Rh(III)-mediated dehydrogenative cross-coupling of substituted benzamides and bromobenzenes (Scheme 2.78) [199] or [200]. In this reaction, only one (from several possible) regio- and stereoisomeric products was formed. It is interesting that the yields of the reaction clearly depends on the nature of substituents of bromoarene. For example, replacement of methyl group in meta-position with chlorine facilitates an increase of reaction yields.

The rare case of double-directed dehydrogenative arylation was presented on the example of ruthenium-catalysed oxidative dimerisation of arenes substituted by oxazolinyl group [201]. Thus, 2-(2-methylphenyl)-1,3-oxazoline dimerised in the presence of [RuCl$_2$(cod)]$_n$ into the sterically crowded *ortho*-*ortho*-functionalised derivatives as only reaction products formed in high yields (Scheme 2.79). Unlike in majority of dehydrogenative coupling cases, the allyl acetate was used as an oxidant in this directed dimerisation. Several five-membered heterocyclic substituents were suitable for the dimerisation, and the good yields were observed in the case of oxazoline-, oxazole-, thiazole- as well as imidazole-substituted arenes which bear few additional EWG and EDG. Similar reactivity was also found to be inherent to 2-arylpyridines [202].



Scheme 2.79 Double-directed C2-C2 selective dimerisation of arenes [201]



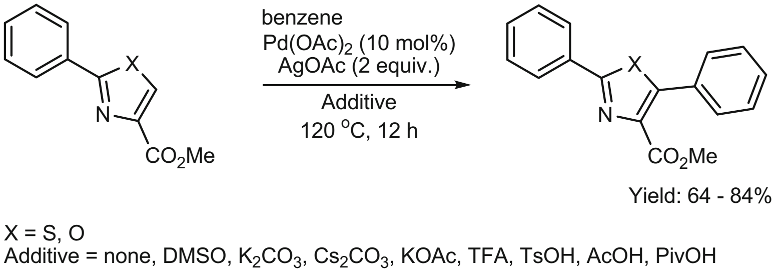
Scheme 2.80 Intramolecular aerobic oxidative coupling of *N*-benzoylindoles [171]

The heterocyclic compounds seem to be more active in the cross-dehydrogenative coupling. Intramolecular aryl-heteroaryl cross-coupling reaction of substituted *N*-benzoyloindole runs under palladium acetate-catalysed conditions in the presence of acetic acid and equimolar amounts of copper acetate. Nevertheless for better reoxidation of a catalyst, the reaction was carried out under 3 atm pressure of dioxygen (Scheme 2.80) [171].

Catalysed by palladium acetate, arylation of five-membered heterocycles furnishes C5-arylated azole-4-carboxylates through double C-H bond cleavage with good functional group tolerance [203]. Similarly like in the case of intramolecular aerobic oxidative coupling of *N*-benzoylindoles (Scheme 2.80), in this reaction (Scheme 2.81), the metalation process is directed by carboxylic group; nevertheless, since only a single substitution site is available in the used azole-4-carboxylates, this assumption is not verified. Together with the arylated azoles, the products of heteroaryl-heteroaryl condensation are formed in this reaction.

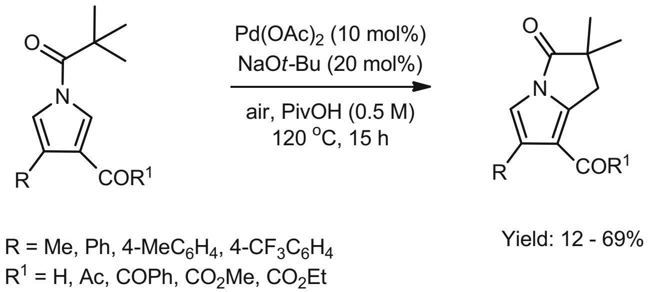
The intramolecular dehydrogenative sp^3-sp^2 coupling run via twofold C-H activation is also known [204]. The reaction runs in good to high yields in usual palladium-catalysed oxidative dehydrogenative cross-coupling conditions with participation of atmospheric dioxygen as a reoxidant (Scheme 2.82) [204]. The mechanistic studies of such transformations were also undertaken [205].

Pyridine *N*-oxides structure provides excellent possibility for *ortho*-directed dehydrogenative arylation. Directed by oxygen atom of *N*-oxides moiety and mediated by Pd(II) catalyst, cross-dehydrogenative coupling between arenes and



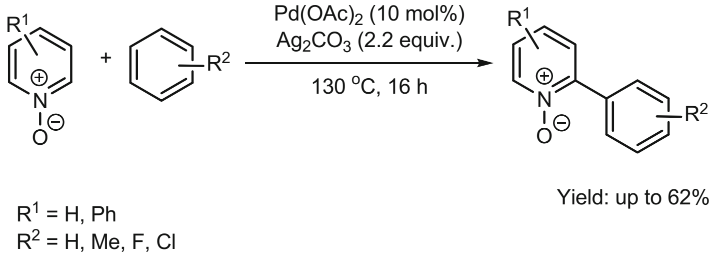
X = S, O
Additive = none, DMSO, K_2CO_3, Cs_2CO_3, KOAc, TFA, TsOH, AcOH, PivOH

Scheme 2.81 Palladium-catalysed phenylation of 2-aryl-azole-4-carboxylates [203]



R = Me, Ph, 4-MeC_6H_4, 4-$CF_3C_6H_4$
R^1 = H, Ac, COPh, CO_2Me, CO_2Et

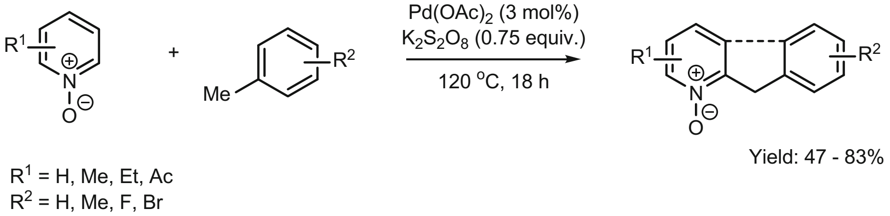
Scheme 2.82 Palladium-catalysed intramolecular coupling of arenes and unactivated alkanes in air [204]



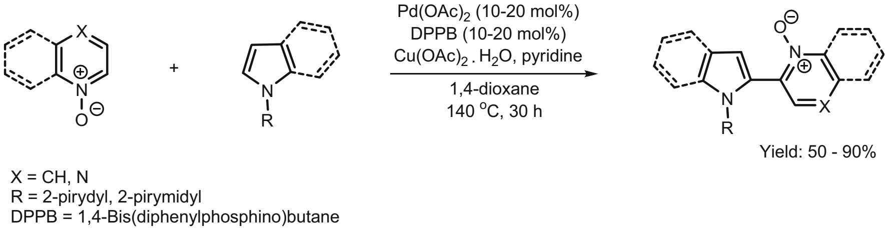
R^1 = H, Ph
R^2 = H, Me, F, Cl

Scheme 2.83 Direct C2-arylation of pyridine *N*-oxides [135]

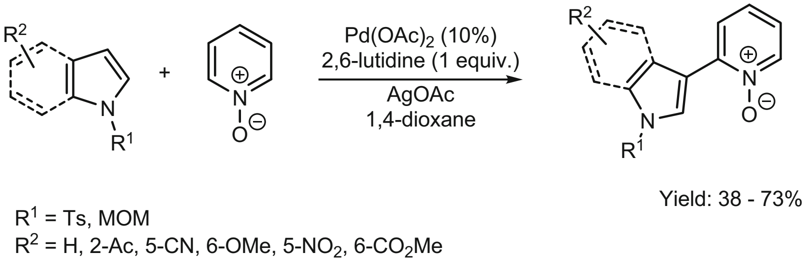
pyridine *N*-oxides was explored by Chang and co-workers (Scheme 2.83) [135]. They found that in the presence of excess of arene and silver carbonate, several different arylated pyridines, quinolines, isoquinolines, benzoquinolines, quinoxalines and pyrazine *N*-oxides could be obtained in good yield and good selectivity (also in regard to aryl reagents). Obviously, the simple procedure of deoxygenation of nitrogen atom was also presented there. Unfortunately, under the reaction conditions, some amounts of bis-condensation products were formed as well.



Scheme 2.84 Regioselective benzylation–annulation of pyridine *N*-oxides with toluene derivatives [206]



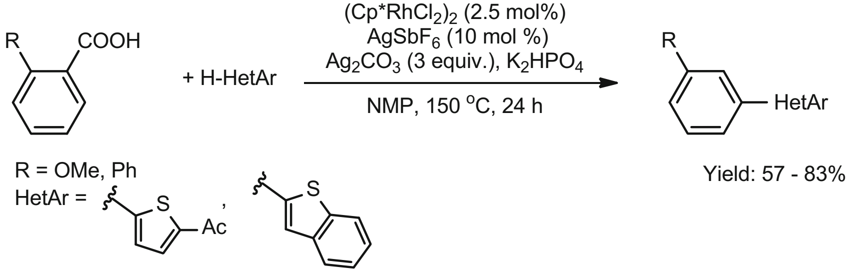
Scheme 2.85 Double-directed C2-C2 selective cross-dehydrogenative coupling of heteroaromatic N-oxides with pyrroles and indoles [207]



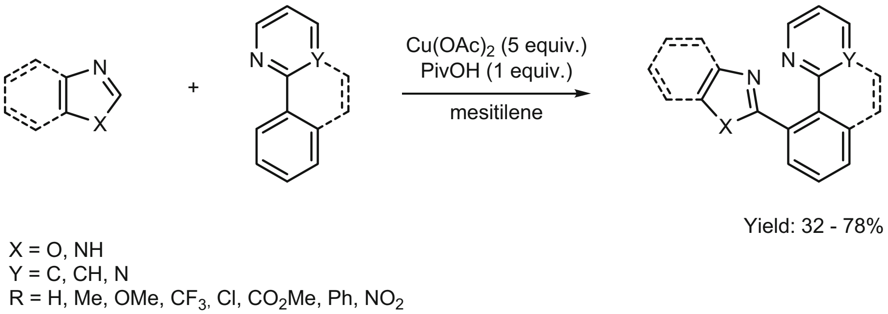
Scheme 2.86 C2-C3 selective directed cross-dehydrogenative coupling of heteroaromatic *N*-oxides with indoles [209]

Creation of a new cycle is possible after the formal bis-dehydrogenative coupling involving fourfold C-H activation. Thus it was shown that pyridine *N*-oxides undergo the selective directed reaction with toluene derivatives furnishing in simple and mild conditions, 2-benzylpyridine *N*-oxides and azafluorene *N*-oxides (Scheme 2.84) [206].

The generality and selectivity of this methodology were confirmed by a construction of biaryl systems from the two heteroaromatic molecules [167, 207, 208]. Moreover, copper acetate and pyridine (or lutidine) may be used instead of more expensive silver salt for the reoxidation of the catalyst allowing to obtain high yields of target products. (Schemes 2.85 and 2.86). Notably, the manipulation with directing groups and reaction conditions allows to shift selectivity of heteroarylation of indoles towards to C2 [207] or C3 [167, 208, 209] sites.



Scheme 2.87 Ruthenium-catalysed heteroarylation of aromatic carboxylic acids [210]

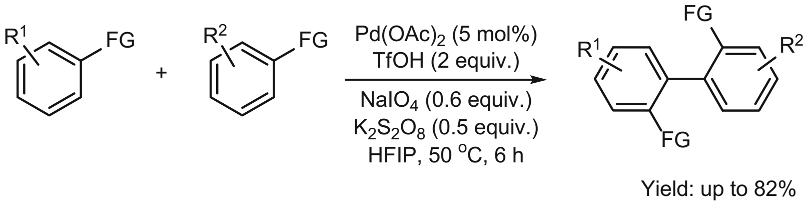


Scheme 2.88 Copper-catalysed arylation of benzazoles [211]

Directed by carboxyl group, *ortho*-heteroarylation (with thiophenes, furans, indoles, indolizines, azoles and xanthines) of substituted benzoic acid proceeds with good yields in the presence of Rh(III) catalyst and silver reoxidant (Scheme 2.87) [210]. Notably, under the conditions of the reaction, the product underwent the spontaneous decarboxylation and therefore the carboxylic group was used as a “traceless directing group”. This efficient synthesis of the formal *meta*-substituted adducts from *ortho*- and *para*-substituted aromatic carboxylic acids, and the *para*-heteroarylated adducts from *meta*- substituted substrates, looks like an interesting alternative for usual multistep synthesis of such compounds.

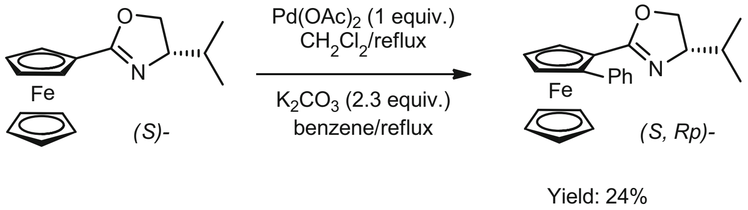
Interesting alternative for palladium-, as well as rhodium- and ruthenium-catalysed processes, is syntheses catalysed by less expensive and less toxic copper acetate. An example is a reaction between benz-1,3-oxazole molecule and 2-phenylpyridine (Scheme 2.88) [211]. This process required significantly high temperature and protection by inert atmosphere, but still it proceeded in fully regioselective manner, furnishing in high yields the expected *ortho*-substituted derivatives, in addition to (when possible) some amounts of bisheteroarylated products.

Similar cross-coupling of pyridine and quinoline *N*-oxide with substituted oxazoles and imidazoles could be realised under the copper-mediated conditions (with no Pd catalyst added) [212]. In this case, the oxygen of *N*-oxide plays a role of both DMG and oxidant.



FG = weakly coordinating groups including ketone, ester, carbamate etc.
HFIP = hexafluoro-2-propanol
R^1, R^2 = H, Me, OMe, Cl, F

Scheme 2.89 Weak coordination group promoted regioselective oxidative cross-coupling of aryls [213]



Scheme 2.90 Asymmetric dehydrogenative direct cross-coupling directed by oxazoline group [214]

Obviously, the C-H activation reactions do not usually follow the substituent-induced selectivity (as it is in the case of S_E2_{Ar}) and (if possible) a mixture of regioisomers is formed. This drawback of dehydrogenative cross-coupling could be overridden by using a DMG strategy. Eventually the double-directed dehydrogenative cross-coupling of two aryls strategy was presented (Scheme 2.89) [213]. As substrates in this unique reaction used ketones, esters and carbamates. At the same time both the oxidants, additive and solvent play critical roles in this reaction. It was shown that HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) was a solvent of choice, while combination of $NaIO_4$ and $K_2S_2O_8$ in the presence of triflic acid was important to have high yields of heterocoupling products. The reaction demonstrates broad functional group tolerance, excellent reactivity and high yields.

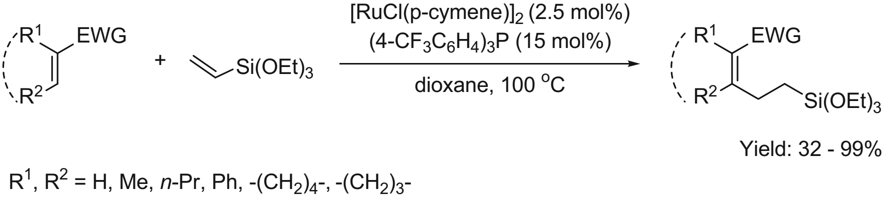
The utility and selectivity of the dehydrogenative cross-coupling approach demonstrate its asymmetric case (Scheme 2.90) [214]. Thus, in diastereoselective reaction, chiral ferrocenyl oxazoline underwent *ortho*-selective direct arylation to furnish a single diastereomer of product in 25 % yield. The second diastereoisomer, with reversed planar chirality, could be obtained when starting ferrocenyl oxazoline was protected first by TMS group and next arylated according to dehydrogenative protocol followed by desilylation of the product formed. The asymmetric arylation was performed with utilisation of stoichiometric amount of palladium acetate; nevertheless in the catalytic version of this reaction, $Pd(OAc)_2$ was used in 10 mol% amount and two equivalents of $Cu(OAc)_2$ were added for its reoxidation.

2.4 Insertion of Unsaturated Systems to Nonactivated C-H Bonds

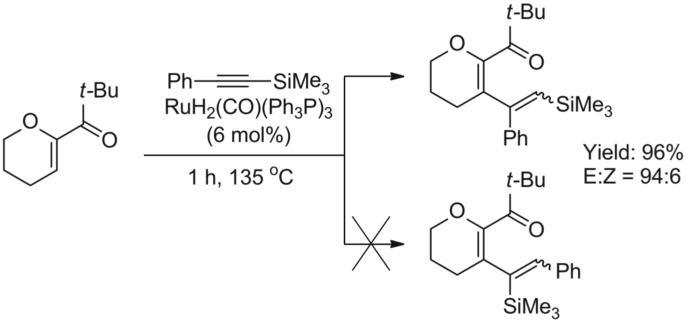
An insertion of unsaturated systems to nonactivated C-H bonds (according to alternative nomenclature: additions of unactivated C-H bonds to multiple bonds) is a special group of halogen-less cross-coupling reactions, which proceed with complete atom economy. For this purpose, transition metal catalysts based on ruthenium, rhodium, rhenium and nickel complexes were generally applied.

Addition processes involving relatively simple sp^2 systems have been discussed by Darses and co-workers (Scheme 2.91) [215]. They found that cycloalkenes functionalised by EWG groups (i.e. CO_2Me, COMe, CONHR) in ß position easily undergo reaction with (triethoxysillyl)ethene at 100 °C in the presence of ruthenium catalysts. These reactions give expected adducts with yields above 80 %. Similar reactions, in which the EWG-substituted alkenes were used instead of (triethoxysillyl)ethene, proceed with significantly lower yields.

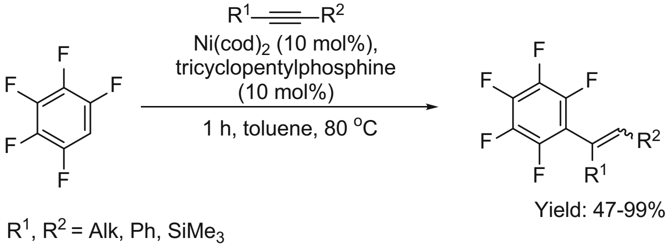
Murai and Kakiuchi explored some addition reactions of unsaturated, cyclic molecules to trimethylsilyl-substituted alkynes [216]. These additions, catalysed by $RuH_2(CO)(PPh_3)_3$ complex, proceed rapidly, with complete regioselectivity as well as high stereoselectivity (the E-products were formed in more than 95 %) (Scheme 2.92). Analogous protocol was successfully applied for addition involving other acetylenic molecules (including non-silyl-functionalised compounds).



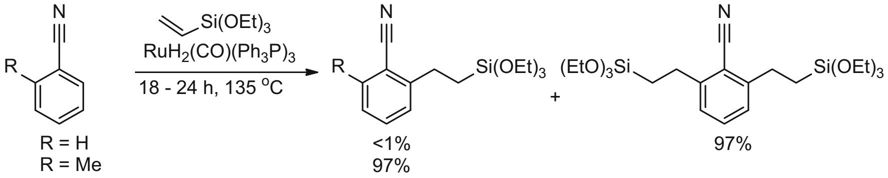
Scheme 2.91 Ruthenium-catalysed alkylation of EWG-functionalised cycloalkenes [215]



Scheme 2.92 Ruthenium-catalysed addition of acetylenes to conjugated enone system [216]



Scheme 2.93 Nickel-catalysed alkenylation of pentafluorobenzene [217]

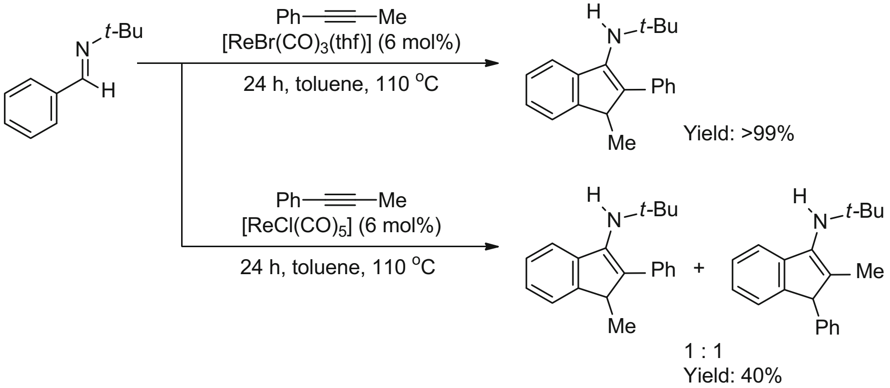


Scheme 2.94 Ruthenium-catalysed addition of triethoxysilylethene to benzonitrile [218]

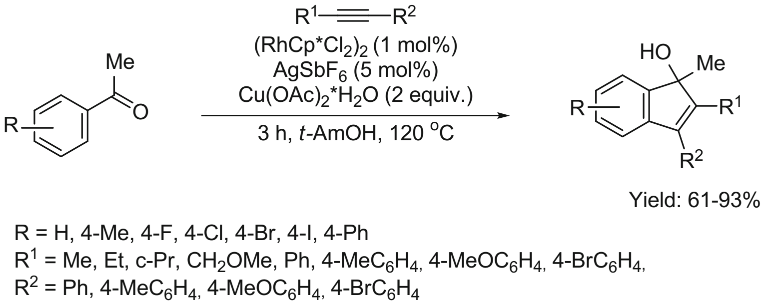
Interactions of silylated alkynes with aromatic molecules have also been studied. Hiyama found that reactions between π-deficient pentafluorobenzene and 1,2-dialkyl-substituted acetylenic compounds in the presence of nickel complex run under the relatively mild conditions. These processes proceed in regio- and stereoselective manner and lead to expected styrenes with higher than 95 % yields (Scheme 2.93) [59]. Under similar conditions, some trimethylsilylalkynes also undergo reaction with pentafluorobenzene, however in slightly lower yields.

Ruthenium-catalysed addition of (triethoxysilyl)ethene (as model electron-rich alkene) to a benzonitrile was examined by Murai and Kakiuchi (Scheme 2.94) [218]. This reaction proceeds at relatively high temperature and leads to functionalised arene with full regioselectivity. Unfortunately, in the case of addition to benzonitrile, primary reaction product is trapped rapidly by next (triethoxylsillyl)ethene molecule. In consequence, bis-functionalised adduct is predominant in post-reaction mixture. Single-addition protocol is possible, however, only in the case of starting materials with alkyl(aryl)-protection in *ortho* to a nitrile group positions.

Ruthenium and rhodium catalysts are inactive in addition reaction of internal acetylenes to phenyl rings of aromatic imines leading to bicyclic hydrocarbons [219]. For this purpose, rhenium catalytic systems were dedicated (Scheme 2.95). However, yields and regioselectivity of these rhenium-mediated reactions are significantly dependent on catalyst nature. For example, addition of 3-phenylprop-1-yne to *anti*-*N*-(*t*-butyl)-*C*-phenylimine catalysed by $ReCl(CO)_5$ gave two regioisomeric products in about 20 % yields. On the other hand, application of more advanced $[ReBr(CO_3)(thf)]$ complex caused that reaction proceed with almost full regioselectivity and in 99 % yield.



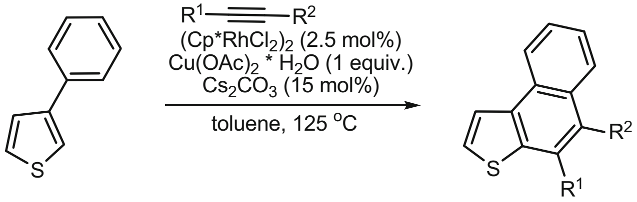
Scheme 2.95 Rhenium-catalysed addition of internal alkyne to *anti-(t*-butyl)*C*-phenylimine [219]



Scheme 2.96 Ruthenium-catalysed addition of internal alkynes to benzaldehyde derivatives [220]

Another type of alkyne-carboarene addition reaction has been described recently by Cheng and co-authors [220]. Authors demonstrated synthesis of several bicyclic hydrocarbons, starting from aryl ketones and internal unsaturated compounds mediated by $[RhCp^*Cl_2]_2$ complex reactions (Scheme 2.96). In contrast to the Kuninobu experiments [219], these additions proceed with full regioselectivity. In the case of reaction involving biarylacetylenes, the total yields of the products were about 70–90 %. Replacement of one aryl group by alkyl substituent resulted in small decrease of reaction efficiency. Similar study on addition reaction of aryl ketones to alkynes was explored by Glorius group [221].

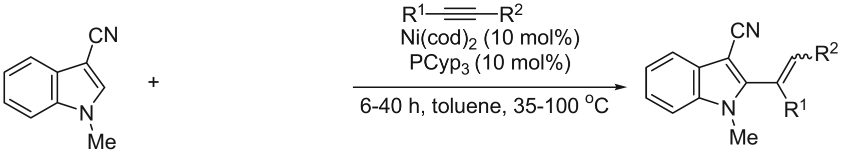
Above examples demonstrated processes of addition of unsaturated systems to aryl compounds, in which new five-membered cyclic moiety is formed in consequence of two new single-bond formation. However, additions yielding vinyl-functionalised\aryl systems were also described. The addition reaction of internal alkynes to 3-cyano-1-methylindole catalysed by nickel complex proceeds with full regioselectivity and more than 95 % stereoselectivity (Scheme 2.98) [222]. The



Yield: up to 90%

R^1, R^2 = *n*-Pr, *n*-C_7H_{15}, $C(OH)Me_2$, CO_2Me, Ph, 4-MeC_6H_4, 4-*t*-BuC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, 4-BrC_6H_4, 4-AcC_6H_4, 4-$CF_3C_6H_4$

Scheme 2.97 Sulphur-containing five-membered hetoroaryls in reactions with internal alkynes [223]



Yield: 67 - 97%
E:Z => 95:5

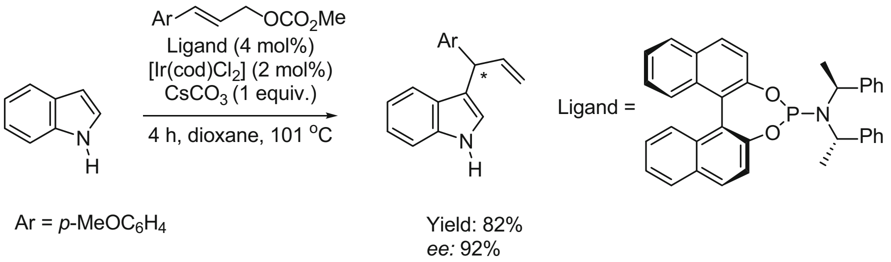
R^1, R^2 = (Pr, Pr), (Me, *i*-Pr), (Me, TMS), (Ph, TMS)
$PCyp_3$ = tricyclopentylphosphine

Scheme 2.98 Nickel-catalysed alkenylation of 3-cyano-1-methylindole [222]

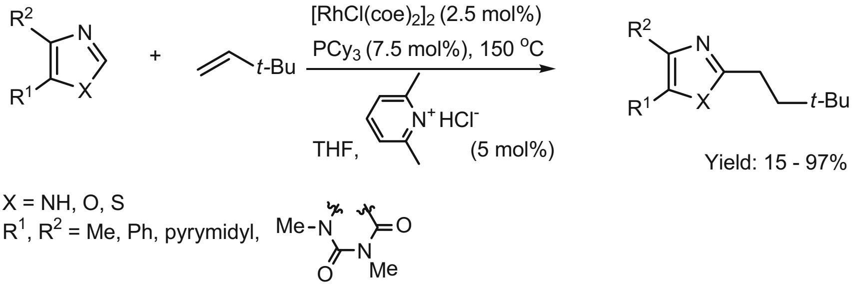
reactivity of alkynes is strongly dependent on nature of substituents. In particular, dialkyl-substituted acetylenes undergo reaction with 3-cyano-1-methylindole at 35 °C and give final adducts in higher than 90 % overall yields. Replacement of one of alkyl substituent to a trimethylsilyl group dramatically decreases the reactivity of alkyne. For example, reaction involving 1-trimethylsilyl-2-phenylethyne carried out at 100 °C gave expected product after 35 h in 67 % yield only. It should be noted that under similar conditions, sulphur-containing five-membered hetoroaryls also undergo reaction with internal alkynes (Scheme 2.97) [223].

Addition of alkene moiety to indole derivatives has also been explored. You and co-workers found that addition of β-unsaturated carboxylates to indole in the presence of iridium complex leads to 3-alkenyl-functionalised derivative, which is a product of a spontaneous decarboxylation of formed saturated ester (Scheme 2.99) [224]. The decarboxylation reaction stage is stimulated by the presence of strongly basic caesium carbonate. It should be noted that an addition of alkene to indoles proceeds in a highly enantioselective (up to 93 % *ee*) manner. Recently, similar protocol has been applied in Ni-mediated C3 selective processes involving wide range of EWG- and EDG-substituted olefins [225].

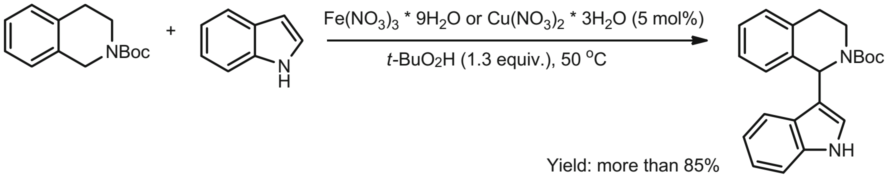
The intermolecular, catalysed by phosphine-rhodium complexes, addition of azoles to olefins was carefully studied by Bergman group (Scheme 2.100)



Scheme 2.99 Enantioselective, iridium-catalysed functionalisation of indoles [224]



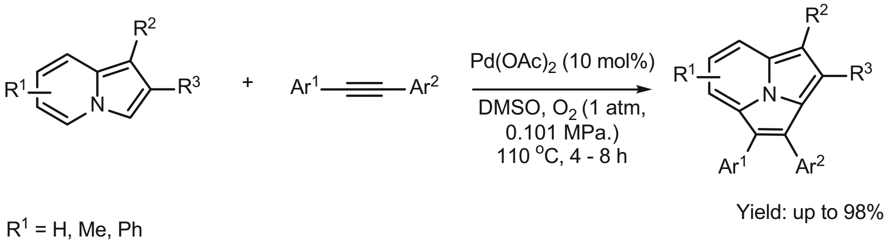
Scheme 2.100 Rhodium-catalysed alkylation of some five-membered, unsaturated heterocycles [226, 227]



Scheme 2.101 Addition of C-H to formed in situ imines [229]

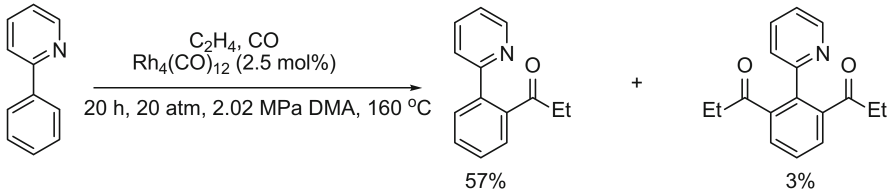
[226, 227]. It was found that these reactions provide an easy and practical route to synthesis of 2-alkylazoles bearing -N-C=N-, -N=C-S-, -N=C-O- moieties in heterocyclic ring and diversified EDG and EWG in an alkyl chain.

Schnürch and co-workers found that reactions between indole and imines (generated in situ from tetrahydroquinoline derivatives) proceed according to quite similar scheme (Scheme 2.101) [228, 229]. Additional advantage of these types of processes is the possibility to apply relatively inexpensive catalysts based on simple inorganic copper salts. However, reaction yield significantly depends on the nature of substituent at nitrogen atom in tetrahydroquinoline derivative. In particular, *N*-acetates give final products with yields more than 45 %, whereas *N*-pivalates only about 20 %. In contrast, *N*-tosylates give only trace amount of expected products.



R^1 = H, Me, Ph
R^2 = CO_2Me, CO_2Et, CN, CO_2t-Bu, CO_2n-Bu
R^3 = H, Ph, CO_2Me, CO_2Et, CN, CO_2n-Bu
Ar^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 3-BrC_6H_4, 4-$NO_2C_6H_4$, 4-EtC_6H_4, 2-thienyl, 4-$MeOC_6H_4$
Ar^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 3-BrC_6H_4, 4-$NO_2C_6H_4$, CCPh, 2-thienyl

Scheme 2.102 Dehydrogenative Heck annulation of indolizine with diaryl acetylenes [230]



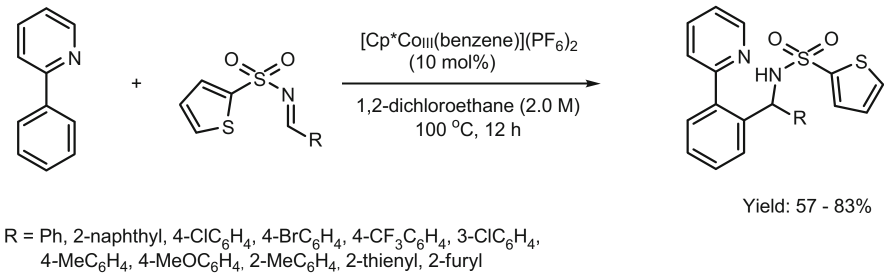
Scheme 2.103 Ruthenium-catalysed β-functionalisation of α-piryd-2-yl-substituted arenes [231]

Intramolecular cross-coupling reactions involving indolizine derivatives are an attractive strategy for the preparation of condensed, three-cyclic aromatic systems with nitrogen as central atom (pyrrolo[2,1,5-*cd*]indolizines). These processes, carried out in DMSO and mediated by palladium acetate, furnish highly substituted heterocyclic products in excellent yields when dioxygen was used as the only oxidant under base-free conditions (Scheme 2.102) [230]. The addition of catalytic amount of 2,6-difluorobenzoic acid was crucial for the successful accomplishment of the transformation.

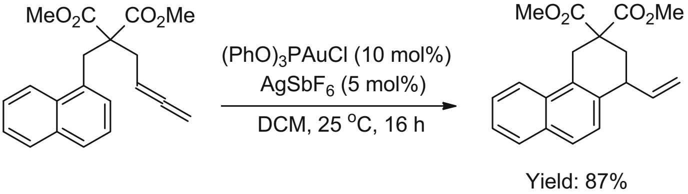
Addition of 2-phenyl pyridines run in the presence of carbon monooxide under ruthenium catalysis leads to corresponding alkyl-biaryl ketones in yields not exceeding 60 % (Scheme 2.103) [231]. Some bis-addition by-products are formed under the reaction conditions as well.

Directed by pyridine nitrogen atom into the remote position, synthesis of secondary amine derivatives by an addition of imines to unactivated aromatic C-H bond was carried out with utilisation of cationic complex cobalt catalyst (Scheme 2.104) [232]. Importantly, the similar conditions and catalyst were also successfully applied in the addition reaction of conjugated olefins to the diversified 2-arylpyridines.

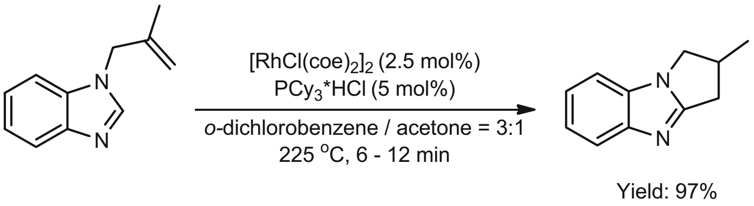
Obviously, addition of olefins to aromatic C-H bond moiety may proceed also intramolecularly. Gagne and Tarselli described an example of such intramolecular, catalysed by gold(I) phosphite complex, reaction of allene-substituted benzenes



Scheme 2.104 Cobalt-catalysed β-functionalisation of α-pyridyl-substituted arenes [232]



Scheme 2.105 Gold-catalysed, intramolecular *ortho*-alkylation of arenes [233]

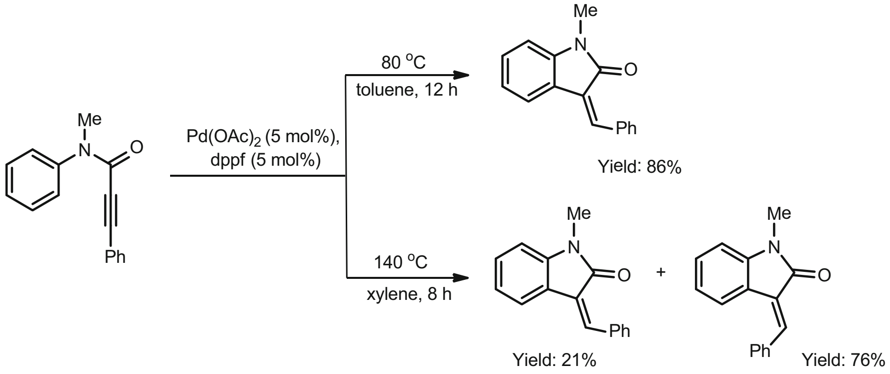


Scheme 2.106 Rhodium-catalysed, intramolecular *ortho*-alkylation of heteroaryl systems [234]

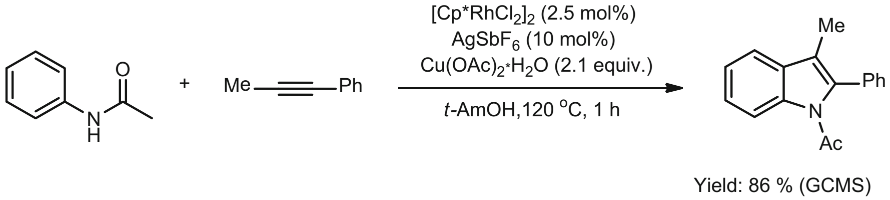
(Scheme 2.105) [233]. Reaction proceeded under mild conditions and led to new six-membered cyclic system with full chemoselectivity.

Another case of intramolecular coupling, which proceeds according to an addition scheme, is cyclisation involving *N*-(but-3-en-1-yl)-benzimidazoles furnished in good to excellent yields corresponding to tricyclic systems with new five- or six-membered ring formed (Scheme 2.106) [234]. Unfortunately, these reactions, catalysed by rhodium complex, proceed under relatively harsh conditions.

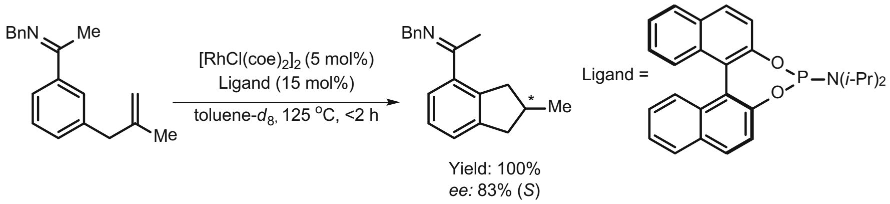
Alkynes may be also considered as components of intramolecular additions to aromatic C-H bonds. The model, catalysed by palladium phosphine complex, at 80 °C reaction of *N*-phenylprop-2-ynamides proceeds with full stereochemical control and after 12–36 h leads to expected benzopyrolines in moderate to high yields (Scheme 2.107) [235]. However, it was found that process carried out at higher temperature proceeds with less stereoselectivity and gives two isomeric adducts of different configuration on vinyl moiety.



Scheme 2.107 Palladium-catalysed, intramolecular addition of alkyne moiety to aryl system [235]



Scheme 2.108 Rhodium-catalysed addition of internal alkynes to aryl system [236]



Scheme 2.109 Rhodium-catalysed, intramolecular, enantioselective β-alkylation of aryl systems [237]

Similarly, in rhodium-catalysed process, acetanilides undergo reactions with internal alkynes, which were used in the synthesis of indoles (Scheme 2.108) [236].

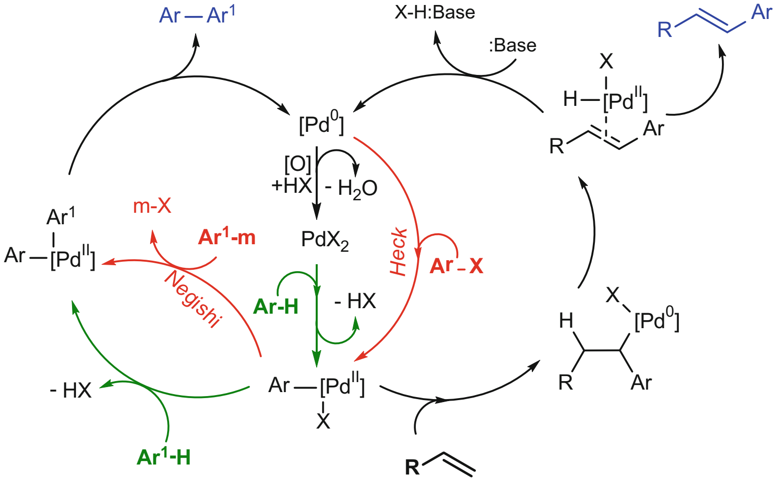
Lastly, it should be noted that intramolecular addition processes may also proceed in enantioselective manner. For example, cyclisation of *N*-benzyl-C-methyl-C-[3-(2-methylprop-2-ene)-imine, mediated by rhodium catalyst in the presence of chiral ligand, gives in a short time expected bicyclic system with yields up to quantitatively and enantiopurity higher than 80 % (Scheme 2.109) [237].

Thus, in the light of above facts, insertion of unsaturated systems to nonactivated C-H bonds should be considered as attractive and universal strategy for functionalisation of many different aryl as well as heteroaryl systems. Discussed examples obviously do not exhaust the vast area of these type of reactions; only few more representative examples were discussed, while this wide topic may constitute the subject of a separate book.

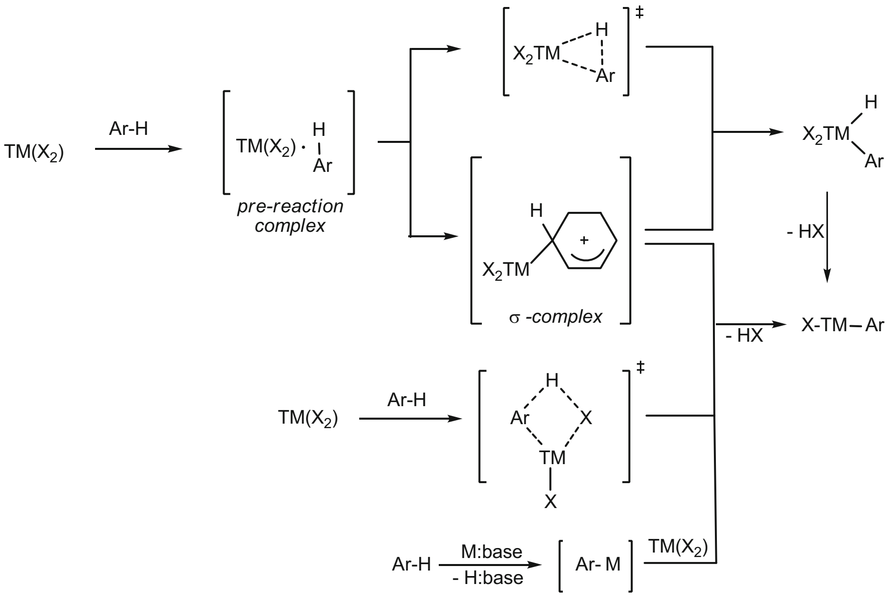
2.5 Mechanistic Aspects of C-H Activation-Based Cross-Coupling Reactions

In general, the mechanism of dehydrogenative cross-coupling reactions is compatible with the mechanism of usual palladium-mediated couplings involving aromatic halides (Scheme 2.110).

Mechanistic aspects of halogen-less cross-coupling reactions are object of intensive study of many research groups. Actually, it is assumed that first, key stage of these types of reactions is a C-H bond activation process which usually takes place after the precoordination of transition metal catalyst. The first observations about the possibility of transition metal-catalysed activation of aromatic C-H bonds are dated by 1937 where Farkas reported the exchange between gaseous benzene and D_2 proceeded on a platinum film [238]. One of the first evidences of C-H activation reactions was presented in 1965 by Chatt and Davidson [239] and little later in 1971 by Ibekwe, B. T. Kilbourn, U. A. Raeburn and D. R. Russell [240]. These authors described reactions of $RuCl_2(dmpe)_2$ with benzene, naphthalene and other aromatic systems, which give arylruthenium hydride complexes. The term “C-H activation” has been widely accepted in chemical literature only since the middle of 1970s [241, 242] and used to define such transition metal-mediated C-H functionalisations, which proceed by coordination of a starting molecule to the



Scheme 2.110 General mechanism of cross-coupling reactions



M = Li, Na, K
TM = transition metal complexes
X = OAc, Cl...

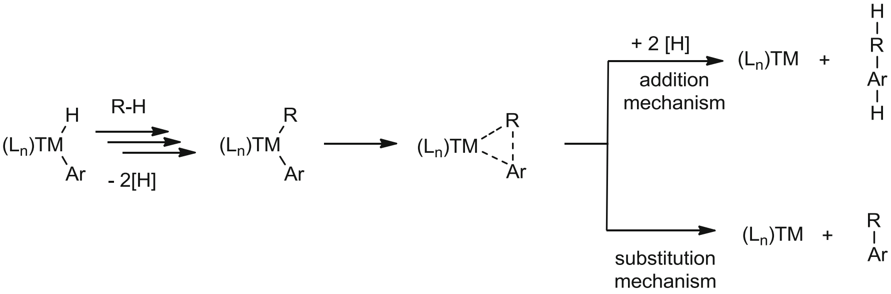
Scheme 2.111 General overview of theoretically possible mechanisms for C-H bond activation

inner sphere of a metal, either via an intermediate “alkene or arene complex” or a “M−C” and/or “M-H” intermediates [243–246], or even run via three-centred CMH transition state [247]. In many cases the proper reaction pathway cannot be easily distinguished since the same products may be obtained in reactions following Heck, Friedel-Crafts, $S_{E(Ar)}$ or one-step (“concerted”) C-H activation mechanisms [248].

In fact, the C-H activation stage may be realised according to several mechanisms (Scheme 2.111), which have been theoretically considered. However, latest studies indicate that two possibilities should be considered in practice first of all: (i) oxidative insertion of transition metal (TM) (which may be considered as special type of metathesis reaction) or (ii) electrophilic reactions which proceed according to substitution ($S_{E(Ar)}$) or addition ($A_{E(Ar)}$) scheme.

The oxidative insertion of transition metal is realised via three-membered transition state, which probably is formed in consequence of conversion of early pre-reaction and orientation π-π complex stabilised by van der Waals interactions between π-orbitals from both unsaturated (aromatic) systems [247].

Electrophilic substitution ($S_{E(Ar)}$) and electrophilic addition mechanism ($A_{E(Ar)}$) have a similar nature to a classical electrophilic substitution reaction [46, 249, 250]. In these cases, nonaromatic σ-complex is formed, in consequence of interaction of transition metal with sp^2 centre of primary, pre-reaction π-π-complex. Next stage is re-aromatisation process. In case of $S_{E(Ar)}$ scheme, re-aromatisation stage



Scheme 2.112 General overview of mechanism of cross-coupling reaction including C-H activation stage

proceeds in consequence of dehydrogenation of σ-complex. In the case of $A_{E(Ar)}$ scheme, final aromatic active form is obtained via hydrogen shift. $A_{E(Ar)}$ is characterised by good selectivity for electron-rich arenes [251–253]. In 2006 it was discovered that a recently described proton transfer palladation mechanism [254] can exhibit complementary reactivity to the $A_{E(Ar)}$ pathway [55, 255].

Nature of C-H bond, transition metal properties and coordinated ligands decide what type of mechanisms actually proceeds. Generally, this stage of halogen-less cross-coupling reactions is better known [256, 257].

After C-H activation, "transmetalation" stage proceeds [175]. As a first step, addition of new, π-electron system to the activated starting material should be considered. As substrates for this reaction may be considered alkene, alkyne or other unsaturated compounds, as well as aromatic components. This step proceeds via new unsaturated molecule complexation and, next, in consequence of electron density redistribution, formation of new σ-bonds, which linked them with metal centre. Next step is an insertion of a new moiety between transition metal and activated carbon centre. Last is the elimination of organometallic molecule and reconstruction of primary catalyst structure. In the case of addition mechanism (addition to multiple bond processes), this stage proceeds without elimination of small molecules, but via hydrogen migration. Alternatively, in the case of substitution processes (direct dehydrogenative Heck reaction and aryl-aryl bond formation via twofold C-H activation), reoxidation of catalytic system is necessary. General overview of this type of transformation is presented in Scheme 2.112.

Overall, typical halogen-less cross-coupling process clearly illustrated theoretical study about cross-coupling between benzene and *N*-acetylindole molecules (Fig. 2.5) [175]. In the first reaction stage, pre-reaction complex (**I-1**) is formed. This process is practically irreversible. In the next step, new σ-bond between palladium and indole derivative is formed (**TS-1**). This stage requires small activation energy, which is equal to about a few kcal/mol. Further conversion of reaction system leads to intermediate in which benzene molecule is coordinated on palladium (**I-3**). This molecule, via high-energetical transition state (**TS-2**), converts to next intermediate (**I-4**) in which benzene molecule is bonded directly with palladium. This stage limited overall rate constant. Next, via reductive

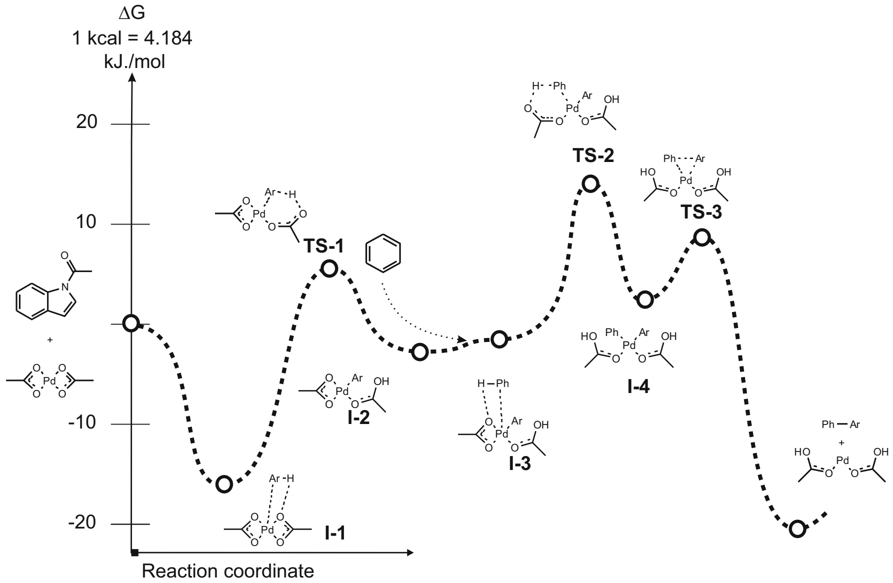
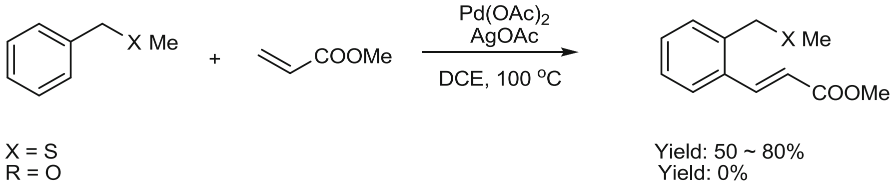


Fig. 2.5 Mechanism of model arylation of *N*-acetylindole molecules



Scheme 2.113 Palladium-catalysed reaction of benzyl-methyl ether with methyl acrylate [256]

elimination process, new σ bond between aryl molecules is formed. This process requires relatively low activation energy, and leads in totally irreversible manner, and via three-membered transition state (**TS-3**) to final biaryl system, which is (on this stage) coordinated by palladium. Last reaction step, on which palladium catalyst is regenerated, requires only few kJ·mol^{-1} activation energy and in consequence proceeds rapidly. It should be noted at this point that simultaneously, alternative mechanism with benzene-palladium complexation on first stage proceeds. This scenario, however, should be considered as forbidden from kinetic point of view. Additionally, pre-reaction complex between benzene and palladium acetate is more than 7 kcal·mol^{-1} (29.3 kJ·mol^{-1}) less stable as compared to the one involving *N*-acetylindole.

Fang and Zhang performed theoretical study about competition between arene-activation and alkene-activation mechanisms, in the case of cross-coupling involving benzyl-methyl ether and methyl acrylate (Scheme 2.113) [256].

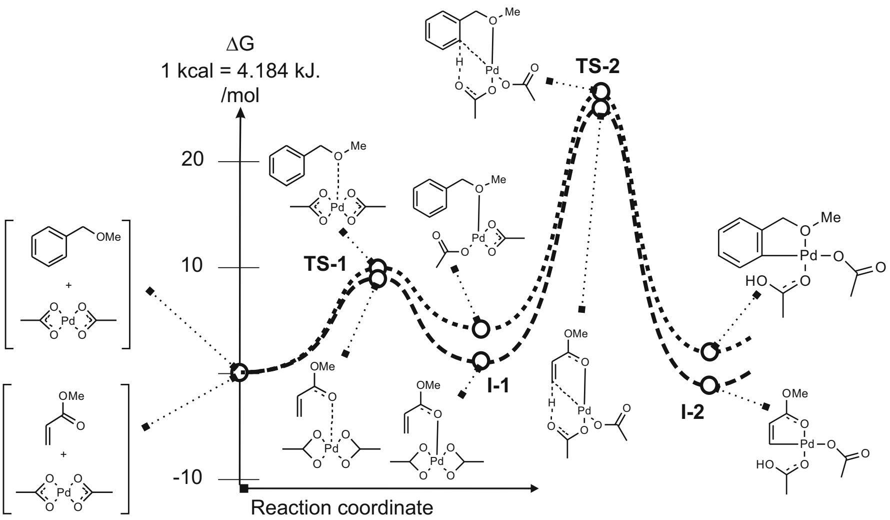


Fig. 2.6 Competition between C-H arene-activation and C-H alkene-activation mechanisms in reaction of benzyl-methyl ether with methyl acrylate [256]

They found, in both analysed mechanisms, that C-H activation stage proceeds via two transition states (Fig. 2.6). Analysis of activation parameters shows that both processes should be considered as allowed from kinetic point of views. So, in contrast to the above example, kinetics of formation of primary intermediate (**I-2**) has not stimulated further reaction course. Differentiation of kinetic preferences on competitive reaction paths takes place on the second, migratory insertion reaction step. In particular, in case of a process which proceeds via arene-activation mechanism, this stage requires less than 18 kcal·mol^{-1} (75.3 kJ·mol^{-1}) activation energy, whereas in the case of a process which proceeds via alkene-activation mechanism, similar activation barrier is higher than 33 kcal·mol^{-1} (138 kJ·mol^{-1}) and must be considered as forbidden from kinetic point of view.

Mechanistic aspects of cross-coupling reactions are discussed also in many other works. It should be noted, however, that these are generally results of DFT computational studies (e.g., [256–258]). Detailed kinetic, mechanistic studies, so far, have not been performed.

2.6 Conclusions and Outlook

In several years after the Nobel price was awarded to R. Heck, A. Suzuki and E. Negishi, the organic chemistry has experienced a flurry of new studies pointed on the development of advanced methodologies of direct catalytic C-C bond formation which are based on reactions included unreactive C-H bond activation step. The

"C-H bond activation" reactions already gained popularity as powerful tools with which the organic chemist (both from academy and industry) may construct complex molecules of practical value, natural products, pharmaceuticals and functional materials. Special interest was attracted to the dehydrogenative coupling reaction, mediated by transition metals and run via twofold C-H bond activation. The attractiveness of these reactions could be easily explained by their unique features such as notable function group tolerance (even active halogens are tolerated), simple preparative procedures, mild conditions, affordable price of starting material (the reactivity of which was not rendered by functionalisation), ability to control (even reverse) the selectivity, good stereoselectivity, high yields, complete atom economy, sustainability, no requirements to protect reaction by inert gases, etc. In addition, the application of proper directing groups (from the large pallet) made possible to direct the reaction in a desirable position with almost no need to consider steric and electronic effects. This all makes the dehydrogenative coupling reactions the green reactions of significant industrial value [259]. Almost in all the cases where standard cross-coupling reaction-based approach was applied, the alternative straightforward synthesis, based on dehydrogenative coupling, could be designed. It looks that in many cases (found in recent literature), the reason not to apply the dehydrogenative cross-coupling was simply lack of tension to try new synthetic approach as well as lack of understanding of the process or knowledge about such possibility.

Obviously, the dehydrogenative cross-coupling reactions have a weak side too – they have low selectivity observed in nondirected cases, relatively big catalyst loading and, frequently, the necessity to use late transition metals. In some cases, the reaction pathway is not known, which makes the rational design of catalysts and reaction conditions impossible. Thus, trends observed nowadays allow to foresee further development of transition metal-mediated cross-coupling reactions. First of all, the studies giving deep insight into understanding the nature of C-H activation both on theoretical and experimental levels will be undertaken. They allow to design and carefully optimise reaction conditions and improve the selectivity of the reactions, also on a way of application of a new tailored (to a given process) directing metalation groups. The utilisation of "traceless" DMG and what could be transformed to a desirable function will make double-directed dehydrogenative cross-coupling the reactions of first choice in everyday organic synthesis. On the other hand, the development in rational catalyst design clearly follows the creation of a new generation of transition metal catalysts – the efficient artificial enzymes, designed for a total control of regio- and stereoselectivity of direct (and directed by catalyst surrounding) cross-coupling reactions run through twofold C-H bond activation step. The environmental concerns are playing a significant role in the selection of suitable synthetic tools, especially in industrial-scale synthesis. Since it is not only a fashion trend but has a solid economic background (an issue of waste management, negative influence of contamination on human health, high cost of multistage synthesis, etc.), the influence of environmental (in a wide sense) factors in chemistry will rise. This may focus the academic chemist to seek an efficient catalyst based on less toxic transition metal such as Fe, Cu, Au and Ag (instead of

Pd, Pt, Rh, Ru) that operate at mild temperature and low loadings. The first steps in this direction has already been made.

Herein we present a short review of most interesting and representative syntheses based on twofold C-H activation reactions. Some other reviews on that and similar topics were published in several books [8, 11, 260–273].

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Part II
New Syntheses: *Phosphorous*

Chapter 3
Benign Chlorine-Free Approaches to Organophosphorus Compounds

Maria Caporali, Manuel Serrano-Ruiz, and Maurizio Peruzzini

Abstract Organophosphorus compounds have widespread use throughout the world, as agricultural chemicals, medicinal agents, flame retardants, plasticizing and stabilizing agents, selective extractants for metal salts from ores, additives for petroleum products and corrosion inhibitors. Moreover, they are also endowed with metal binding properties, for this reason they have a paramount role in catalysis, being able to direct the activity and selectivity of a metal. Currently, organophosphorus compounds are produced on industrial scale using white phosphorus and chlorine, through an environmentally harmful process which generates equimolar amount of chlorinated waste. In the quest for alternative environmentally benign technology, several routes have been envisaged starting either from elemental phosphorus or from one of its direct low-valent derivative as hypophosphite.

In this contribution, we summarize the latest findings on “green” synthetic approaches towards organophosphorus derivatives. Reactions of elemental phosphorus with organic molecules by means of photochemical irradiation, through a radical mechanism, by electrophilic/nucleophilic addition, mediated by a transition metal or by electrochemical means, will be described. Moreover, a synthetic strategy that uses hypophosphorus acid and its alkali salts as phosphorylating agents towards organic molecules will be as well depicted.

Keywords Elemental phosphorus • Hypophosphite • Organophosphorus • Carbenes • Transition metals • Electrochemistry • Phosphate

3.1 Metal-Mediated Formation of P-C Bond from White Phosphorus

Currently, organophosphorus compounds are produced on industrial scale using white phosphorus as large scale commodity which is first halogenated to phosphorus chloride, PCl_3. In a subsequent step, the chlorine atoms are substituted with

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Scheme 3.1 "Chlorine" route for the bulk production of organophosphorus compounds from white phosphorus

$$1/_4\,P_4 + 6\,Cl_2 \longrightarrow 4\,PCl_3$$

$$PCl_3 + 1/_2\,O_2 \longrightarrow (O)PCl_3$$

$$(O)PCl_3 + 3\,ROH \longrightarrow (O)P(OR)_3 + 3\,HCl$$

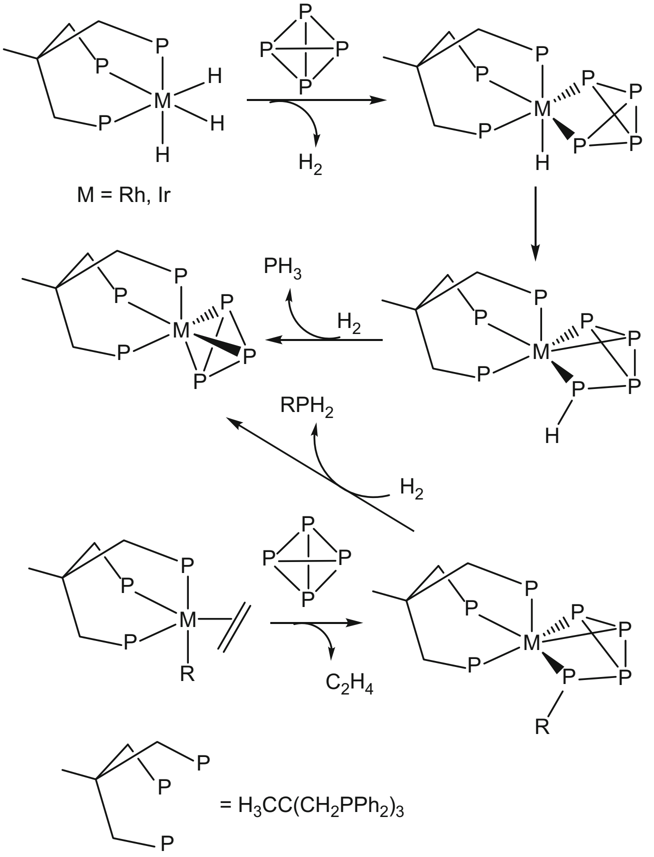
$$PCl_3 + 3\,RMgBr \longrightarrow R_3P + 3\,MgBrCl$$

organic groups by salt metathesis, generating the desired phosphane R_3P and three molar equivalents of chlorinated waste. On the other hand, reaction of $OPCl_3$ with an alcohol affords the corresponding organic phosphate, $(O)P(OR)_3$, and three times the molar amount of HCl (Scheme 3.1). In other words, the current industrial technology is atom- and energy inefficient and utterly remote from being a sustainable and environmentally benign process. Therefore, the direct and selective processes are needed to avoid the use of chlorine gas, whose production and transportation is highly risk and to circumvent the formation of halogenated intermediates and by-products, which are environmentally harmful and require a high cost to get rid of [1].

Many efforts in academia have been devoted to produce phosphanes, phosphates and phosphites through an alternative route. These compounds are indeed highly valuable in many important industrial fields. Thus, phosphanes as ligand towards a metal center play a key role in catalysis, triorgano phosphates, phosphonates and phosphinates are used as additives to polymers, since are endowed with peculiar properties and can act as plasticizers and flame retardants. Plasticizers play a key role because they increase the flexibility of the polymers and make them easier to process. Additionally, they contribute to lower the glass transition temperature of the polymer, making it more suitable for low temperature applications. Nowadays, the most common plasticizers are phthalates, anyway triorgano phosphates still attract the market in some particular applications thanks to their stability, their rheological properties at low temperature and flame retardants properties. According to the EU legislation [2], halogen-based flame retardants are banned, which is pushing both the academia and the industry to search and develop new materials which behave as efficient flame retardants and do not contain any halogen. Several aryl phosphates fulfill the rule of laws and among them, both triphenyl and tritolyl phosphate are sold commercially as flame retardants, the latter being more common due to its compatibility with PVC.

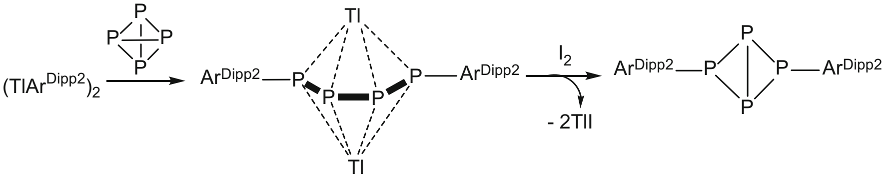
In the quest for alternative ways of the production of organophosphorus compounds, a huge amount of knowledge about P_4 chemistry has been developed in the last decades, though direct functionalization methods are still scarce and applicable mainly on a laboratory scale [2].

One of the most spread approaches is based on the use of a transition metal, either early or late, that can firstly activate white phosphorus through coordination to the metal center, and afterwards the coordinated P_4-moiety is prone to react further with a suitable organic reagent. On this regard, a milestone has been the work by Ginsberg and Lindsell in 1971 [3], who showed for the first time that white phosphorus can bind to a transition metal-ligand system, namely the



Scheme 3.2 Summary of the reactivity of [(triphos)MH_3] (M = Rh, Ir; triphos = MeC(CH_2PPh_2)$_3$) and [(triphos)RhR(C_2H_4)] (R = H, Me, Et, Ph) with P_4

rhodium Wilkinson's complex. Since then, more than 40 years of studies have focused on the key role played by a transition metal, or a main group element or compound, which in principle can carry out the activation and subsequently either aggregation or fragmentation of P_4 to yield a variety of naked Px units ($x \leq 24$) well suited to bind one or more metals. Although subsequent functionalization of the P_4 moiety and liberation reactions from the metal centers are not common due to the strong bond between the metal and the P_4 moiety [4]. In this regard, the Florentine group lead by Peruzzini discovered that rhodium and iridium trihydride complexes bearing as ancillary ligand a tripodal phosphane named triphos (1,1,1-tris(diphenylphosphanylmethyl)ethane) were prone to react with P_4, which upon the displacement of molecular hydrogen was coordinated to the metal center in a di-hapto fashion, see Scheme 3.2. The remaining hydride, being in *cis* position respect to the P_4 moiety, can interact and migrate on the phosphorus moiety, resulting in the formation of a P-H bond. Applying a hydrogen pressure to this



Scheme 3.3 Synthesis of Phosphane derivatives from P_4 and dimeric “dithallene”

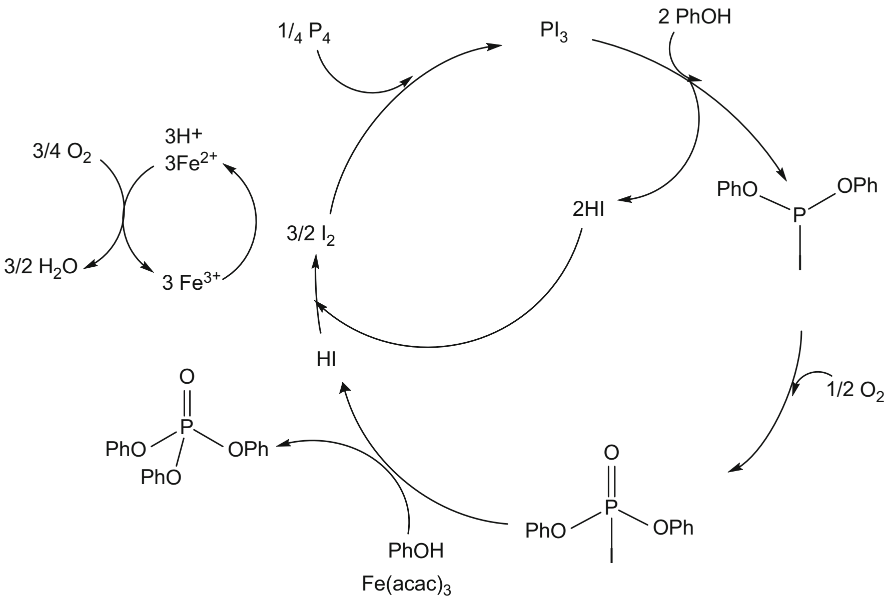
derivative, it is observed formation of PH_3 and the other three P atoms (coming from P_4) forms a highly stable cyclotriphosphorus unit η^3-coordinated to the metal. The latter represents a resting state that does not evolve to an active species able to activate either molecular hydrogen or P_4. Therefore, the reaction of the trihydride metal precursor, P_4, and hydrogen is stoichiometric and cannot be catalytic.

Similarly, the reaction of the ethylene complex [(triphos)RhR(C_2H_4)], R=H, alkyl, aryl, with P_4 in the presence of positive hydrogen pressure gave a stoichiometric amount of the corresponding phosphane RPH_2 and cyclo-triphosphorus rhodium complex [5a–b], see Scheme 3.2.

Another example of a stoichiometric route to access a phosphane derivative starting directly from P_4 in the presence this time of a main group metal was shown by Power in 2005 [5c]. Surprisingly, by reacting the weakly dimerized “dithallene” $[TlAr^{Dipp2}]_2$ ($Ar^{Dipp2} = C_6H_3$-2,6-(C_6H_2-2,6-$i$$Pr_2)_2$) with white phosphorus, the tetrahedral structure of the latter was completely disrupted, resulting in an open chain of four P atoms sandwiching the two metal atoms, see Scheme 3.3. Notably, the two aryl groups Ar^{Dipp2} (= C_6H_3-2,6-(C_6H_2-2,6-$i$$Pr_2)_2$) were transferred from the metal to the two opposite end of the phosphorus chain. Subsequent mild oxidation with iodine resulted in the quantitative formation of a tetraphosphabicyclobutane derivative, $Aryl_2P_4$, with the elimination of thallium iodide. Later, in Sect. 3.4, we will discuss the formation of tetraphosphabicyclobutane derivative, in the absence of a metal.

Concerning the “chlorine free” production of di- and tri-alkyl phosphates, di- and tri-alkyl phosphites, a remarkable catalytic protocol was developed in the 1990s by Dorfman and Abdreimova [6]. They carried out a mild catalytic oxidative alkoxylation of P_4 dissolved in arene/alcohol solution, using Cu(II) or Fe(III) as catalysts in aerobic conditions, being O_2 necessary as oxidant. Intriguingly, it was observed in the case of copper that the product distribution was strongly influenced by the nature of the ligands. In the presence of copper halides, the main product was alkyl phosphate, while copper sulfate or acetate enhanced the formation of alkyl phosphite. However, these catalytic systems did not work well with phenol or aryl alcohols and lack of narrow selectivity.

A further relevant contribution on this regard comes from Kilian, who recently found out that P_4 can react with phenol in aerobic conditions in the presence of iodine and Fe(acac)$_3$ (acac = acetylacetonate) as catalyst affording quantitative



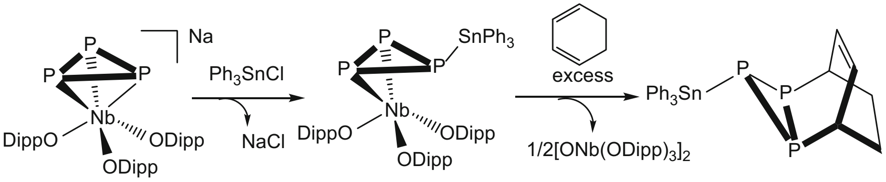
Scheme 3.4 Catalytic synthesis of triphenyl phosphate from white phosphorus

conversion of the desired triphenyl phosphate [7] producing only water as by-product. Mechanistic studies were carried out to understand the reaction pathway and in particular the rate-limiting steps in order to optimize the process. Iodine, also used in catalytic amount, served to oxidize P_4 to phosphorus(III) by forming instantaneously PI_3. Additionally, it was observed that the reaction did not proceed under anaerobic conditions, being oxygen indispensable first to oxidize P(III) to P (V) in the catalytic step where PI_3 reacted with phenol. Secondly, O_2 was responsible for the reoxidation of the by-product HI back to iodine as shown in Scheme 3.4. The reaction, carried out at 80 °C and with 25 mol% $Fe(acac)_3$ loading, was applied successfully also to functionalized phenols giving high conversion and very good selectivity.

Another advantage of this process is that iron is a desirable metal for the catalysis of industrial processes due to its low toxicity, low cost and ready availability.

However, phosphites cannot be synthesized through this route since the iron/ iodine catalyst system does oxidize phosphites to phosphates.

Unlike main-group and late-transition metal mediated activation of P_4, the applications of early transition metals in this field are far less common. Aiming to circumvent the use of PCl_3 as an intermediate in the synthesis of organophosphorus compounds and in the search for a catalytic process producing organophosphanes directly from white phosphorus, Cummins [8] has put a lot of efforts to study the activation of white phosphorus mediated by early transition metals. Indeed, niobium and molybdenum complexes have been shown by Cummins et al. to carry out



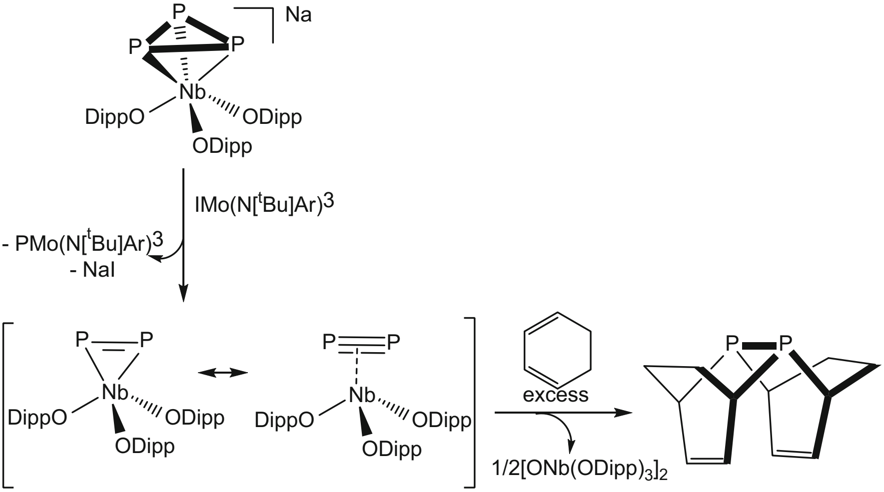
Scheme 3.5 Release of the P_3^- fragment from the niobium complex and subsequent cycloaddition reaction

in an efficient way the activation of molecular dinitrogen and to promote N-transfer reactions, thus synthesizing, for instance, organo-nitriles. This study was extended to other early transition metals and, intriguingly, it was observed that a niobium complex could firstly coordinate P_4 and, then, the phosphorus moiety could be transferred to an organic substrate. A beautiful example of this chemistry is shown in Scheme 3.5, where complex $[Na(thf)_3][(\eta^3\text{-}P_3)Nb(ODipp)_3]$ (Dipp = 2,6-$i$$Pr_2C_6H_3$), easily prepared by reduction of $[Cl_2Nb(ODipp)_3]$ in the presence of P_4, has an anionic nature which imparts to the P_3 ring a strong nucleophilic character which makes possible the straightforward reaction with a range of mild electrophiles [9]. For instance, the reaction with Ph_3SnCl, proceeds quickly at room temperature forming $[(\eta^3\text{-}Ph_3SnP_3)Nb(ODipp)_3]$ while sodium chloride is eliminated. To free from the metal center the triphosphirene moiety, Ph_3SnP_3, a stoichiometric amount of pyridine-*N*-oxide together with an excess of 1,3-cyclohexadiene were used. The latter serves as a trapping agent of the phosphirane, yielding the desired Diels-Alder adduct $Ph_3SnP_3(C_6H_8)$ as shown in Scheme 3.5.

The stable $Ph_3SnP_3(C_6H_8)$ can be regarded as a P_3^- synthon, since the reactive P-Sn bond can be cleaved with elimination of Ph_3SnCl and the cyclic olefin, formed by trapping the P=P unit with 1,3-cyclohexadiene, can be readily lost as it has been shown that retrocycloaddition reactions are accessible for such protected diphosphanes [10]. Significantly, the Ph_3Sn^+ moiety can be replaced by other electrophiles as Ph_3C^+, Ph_3Si^+ and Me_3Si^+ by the salt elimination procedure. This modularity may allow the assembly of a library of P_3^- transfer reagents opening the way to the synthesis of a wide range of organophosphorus compounds. Formal abstraction of P^- from $Na[(\eta^3\text{-}P_3)Nb(ODipp)_3]$ was mediated by the molybdenum complex $IMo(N[^tBu]Ar)_3$ and resulted in the formation a labile niobium complex [11] bearing a P_2 side-on coordinated ligand as shown in Scheme 3.6.

In the presence of a 20-fold excess 1,3-cyclohexadiene, the P_2 unit is released from the metal center and a formal [4 + 2] Diels-Alder cycloaddition takes place affording the diphosphane (Scheme 3.6).

Replacing the ancillary ligands ODipp at niobium center with the more hindered $(OC[^2Ad]Mes)_3$ where ^2Ad = 2-adamantylidene, Mes = 2,4,6-trimethylphenyl, Cummins discovered [12] that by reacting four equivalents of $[NbI\{(OC[^2Ad]Mes\}_3(thf)]$ with two equivalents of P_4, a new niobium complex was formed, $[(P_8)\{Nb(OC[^2Ad]Mes)_3\}_2]$, which is a unique dinuclear species having a P_7

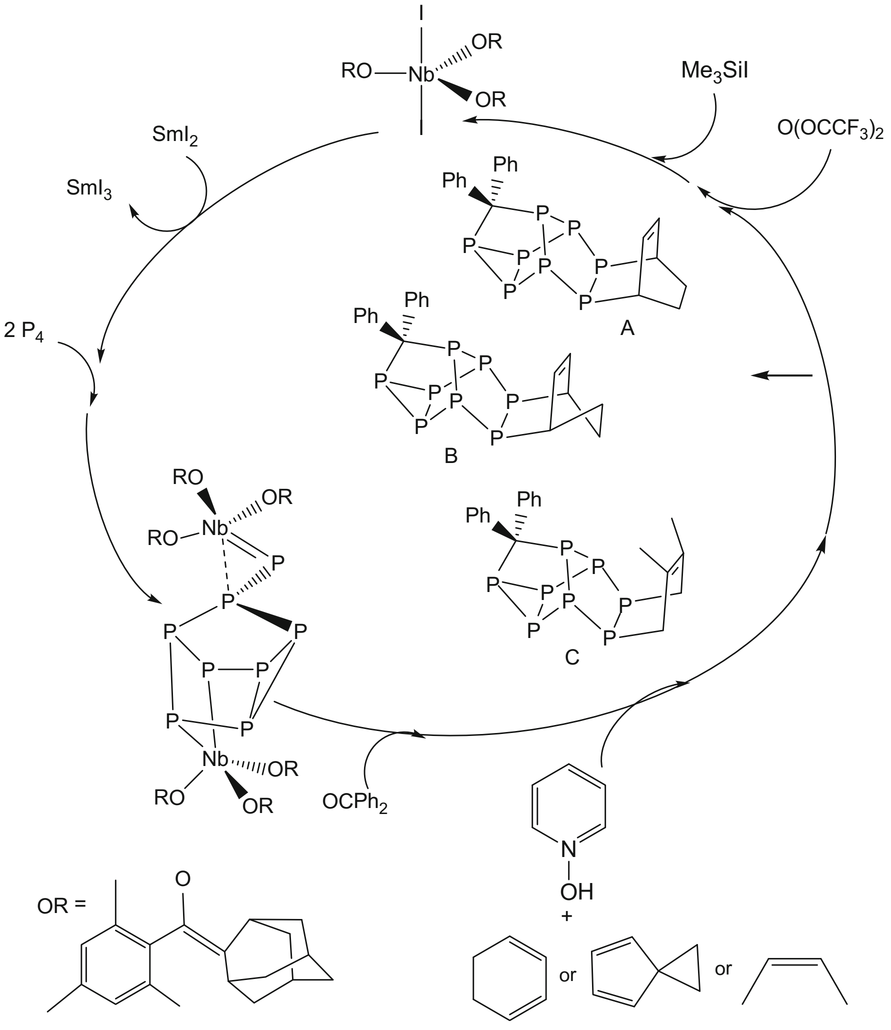


Scheme 3.6 Abstraction of P^- and trapping of the P_2 fragment by cycloaddition reaction

nortricyclic core with a phosphino-phosphinidene moiety connected to one of the two niobium center, as shown in Scheme 3.7. The phosphino-phosphinidene moiety is endowed with a special reactivity and easily reacts with a suitable organic substrate as benzophenone detaching the coordinated niobium fragment as oxide. Since the remaining niobium-phosphorus interaction in the complex can be regarded as a side-on coordination of a diphosphene unit (RP=PR) to a strongly π-donating d^2 niobium center, a 20-fold excess of 1,3-cyclohexadiene together with pyridine-*N*-oxide were added. The corresponding Diels-Alder cyclo-adduct A was obtained in good yield, eliminating a second niobium-oxo fragment as above. Herein, the synthetic cycle could be completed by addition of triflic anhydride (2 equiv) followed by Me_3SiI (4 equiv) to recycle the two niobium-oxo complexes to the catalytic precursor, $[I_2Nb\{(OC[^2Ad]Mes\}_3]$ as shown in Scheme 3.7. The latter in the presence of samarium (II) iodide, undergoes the displacement of one iodide, generating a coordinatively unsaturated species $[INb(thf)\{(OC[^2Ad]Mes\}_3]$, prone to react with P_4 [13].

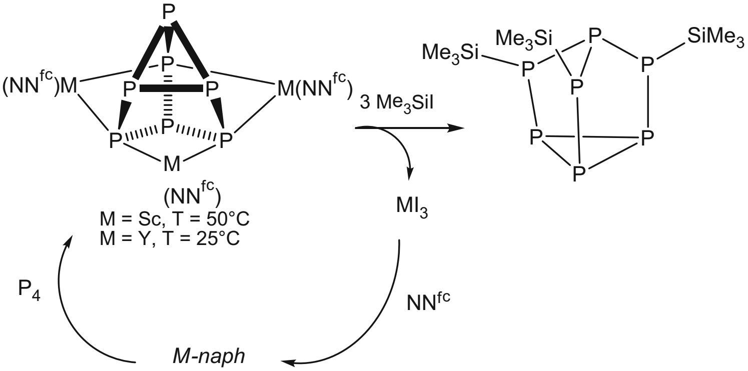
Noticeably, instead of 1,3-cyclohexadiene, spiro[2.4]hepta-1,6-diene and 2,3-dimethylbutadiene were also tested in the catalytic cycle. They resulted to be very reactive Diels-Alder diene, in particular the first one, and trapped efficiently the carbophosphorus cluster contained in the key intermediate complex $[Ph_2CP_8Nb(OC[^2Ad]Mes)_3]$ giving respectively the organophosphanes B and C (Scheme 3.7), in good yield.

Despite their potentially strong reducing nature, group 3 and 4f-block metals have been sparely considered for the activation of white phosphorus, presumably because of the hard-soft mismatch between the electropositive metal and soft phosphorus. The direct activation of P_4 using group 3 metal was only recently achieved in mild conditions by Diaconescu et al. [14]. Unexpectedly, the reaction



Scheme 3.7 Niobium-mediated cycle for the direct transformation of white phosphorus into organophosphanes A, B or C

between the scandium naphthalene complex, $[\{(NN^{fc})Sc\}_2(\mu\text{-}C_{10}H_8)]$ (*Sc-naph*: $NN^{fc} = 1,1'\text{-fc}(NSi^tBuMe_2)_2$, fc = ferrocenylene) and white phosphorus afforded two different metal complexes, containing respectively $[P_8]^{4-}$ and $[P_7]^{3-}$ unit, that could be separated thanks to their different solubilities. The bonding motif of $[P_8]^{4-}$ in the cluster Sc_4P_8 recalls a realgar-type structure with four $(NN^{fc})Sc$ fragments standing at the corners, each of them bonding to two phosphorus atoms, while the cluster Sc_3P_7 contains the $[P_7]^{3-}$ unit having a heptaphosphanortricyclane structure and represents the first example of the Zintl anion $[P_7]^{3-}$ obtained directly from P_4



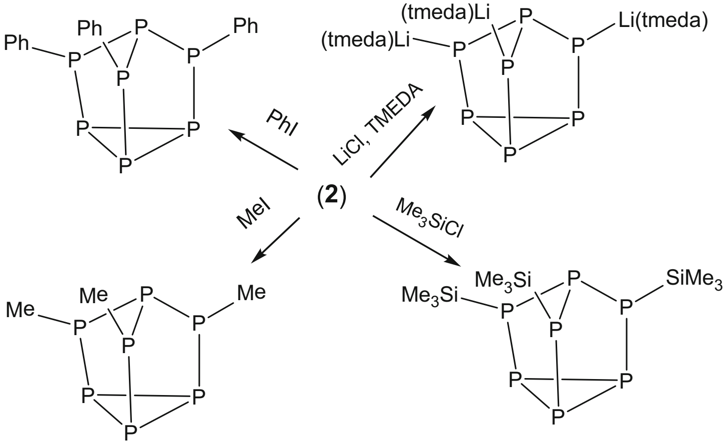
Scheme 3.8 Transferring a polyphosphide unit $[P_7]^{3-}$ from a metal center to an organic species

without using an alkali metal or its equivalent as a reducing agent. Interestingly, the reaction of white phosphorus with the yttrium analogue, $[\{(NN^{fc})Y(THF)\}_2(\mu\text{-}C_{10}H_8)\}$ went to completion at room temperature in a much shorter time and afforded uniquely the product Y_3P_7.

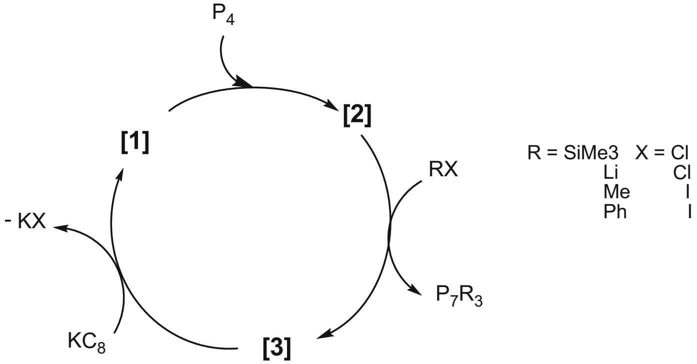
Aiming to activate the polyphosphide from the clusters Sc_3P_7 and Y_3P_7, these were allowed to react with three equivalents of Me_3SiI as shown in Scheme 3.8. These reactions led to $(Me_3Si)_3P_7$ and gave as by-product the scandium/yttrium iodide, which in turn can be recycled to synthesize the starting metal arene complex. This constitutes the first example of transferring the Zintl anion $[P_7]^{3-}$ to an organic species and establishes a synthetic cycle for the direct transformation of P_4 to organophosphorus compounds.

Studies on P_4 activation and functionalization mediated by 5f metals are exceptionally rare, there is one report concerning thorium [15] and a few about uranium [16, 17]. In the first publications concerning uranium [16], it was shown this metal can favor the cleavage of a P-P bond forming a $[P_4]^{2-}$ ring, but no fragmentation or catenation of P_4 was observed [16]. Recently, Liddle and co-workers [17] showed that a diuranium(V)-arene-tetraanion complex (**1**) reductively cleaves P_4 to form a triuranium cluster tris(triamidouranium)μ^3-η^2:η^2:η^2-heptaphosphanortricyclane (**2**) containing a heptaphosphanortricyclane cage connecting the three uranium centers. This represents not only the first example of fragmentation and catenation of P_4 to a higher oligomer promoted by uranium but also the first example of a molecular actinide $[P_7]$ Zintl complex. As shown in Scheme 3.9, by reaction of **2** with three equivalents of Me_3SiCl, the derivative $P_7(SiMe_3)_3$ was quantitatively afforded together with $[(Ts^{TOL})U(Cl)(\mu\text{-}Cl)U(THF)_2(Ts^{TOL})]$ (**3**) as a by-product where $Ts^{TOL} = HC(SiMe_2NAr)_3$, Ar = 4-$MeC_6H_4$. Other electrophiles have been tested, like LiCl, MeI and PhI, and in all cases the corresponding organophosphorus derivative was obtained in good yield while complex **3** was released.

This new pathway is of great relevance, since it makes feasible and straightforward the preparation of alkali-metal or organic derivatives of $[P_7]^{3-}$ that is



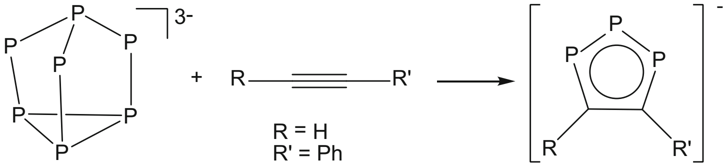
Scheme 3.9 Reaction of a tris(triamidouranium)μ^3-η^2:η^2:η^2-heptaphosphanortricyclane (**2**) towards diverse electrophiles



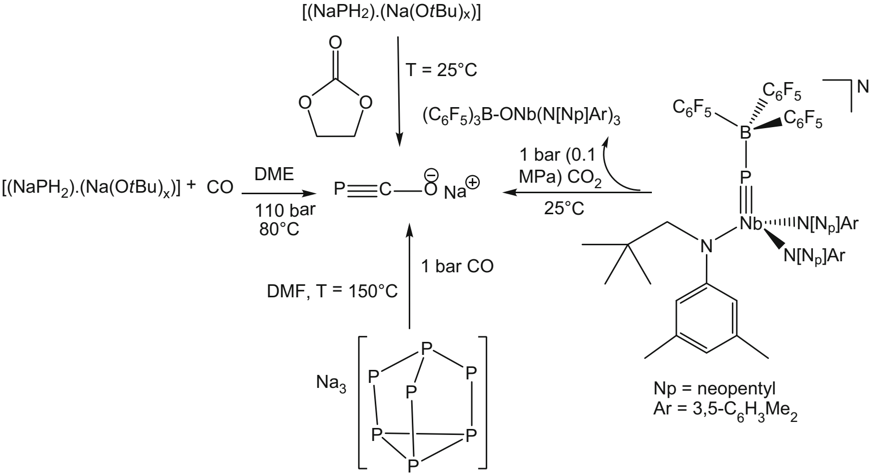
Scheme 3.10 Synthetic cycle for the direct transformation of P_4 into organophosphorus derivatives P_7R_3 mediated by an uranium complex

otherwise challenging. Moreover, the reduction of **3** with potassium graphite can restore complex **1** and in this way two turnovers can be achieved, demonstrating the ability of uranium complexes to activate and liberate P-functionalized organic molecules, working effectively as in a catalytic cycle (Scheme 3.10).

While in the past $[P_7]^{3-}$ and its derivatives were considered as a dead end in synthetic phosphorus chemistry, recent works involving the demolition of P_7 cage into P_5 and P_2 fragments indicate that P_7 compounds can be seen as useful platforms in the field of phospha-organic chemistry [18]. Recently, Goicoechea's group has shown that $[P_7]^{3-}$ clusters are reactive towards unsaturated organic substrates [19], in particular they react with alkynes with transfer of a $[P_3]^-$ unit to form an unusual class of cyclopentadienide analogue, the 1,2,3-tripnictolides (Scheme 3.11).



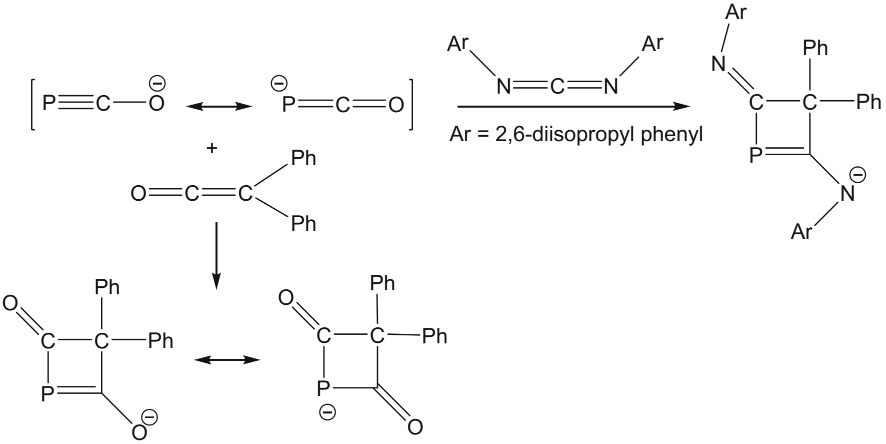
Scheme 3.11 Synthesis of 1,2,3-[P_3C_2RR']-anions



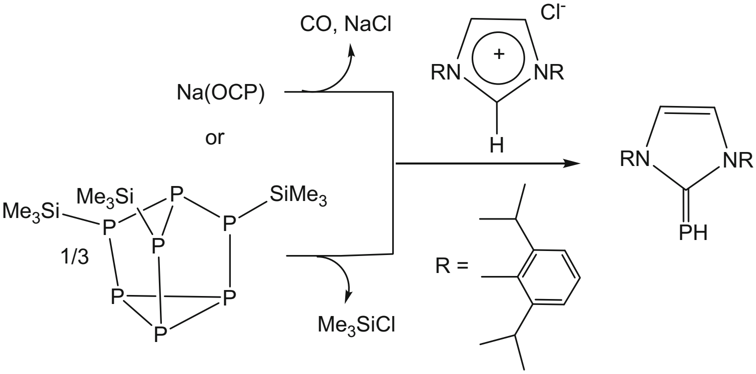
Scheme 3.12 Different ways to access Na(OCP)

The reaction mechanism that leads to the products is still unraveled, presumably the driving force for the formation of the 1,2,3-tripnictolide anions is their aromaticity. Routes to access this class of compounds are still scarce and underdeveloped, with only a few examples existing in literature [20]. Intriguingly, $[P_7]^{3-}$ is endowed with a special reactivity towards carbon monoxide, in refluxing dimethylformamide good yield of the phosphaethynolate anion, $[PCO]^-$ as $[K(18\text{-crown-}6)]^+$ salt, can be formed [21], see Scheme 3.12. This anion is known since decades [22], but no chemistry has been performed upon it, only recently it has been a renaissance and several studies have flourished. Among them, Grützmacher's group [23] has refined the synthesis obtaining Na(O-C≡P) through a large-scale procedure (hundreds of grams) based on the phosphination of carbon monoxide using $NaPH_2$ us "P" source or from the reaction of $NaPH_2$ with diethyl carbonate as source of CO (Scheme 3.12).

Cummins demonstrated that Na(OCP) can be synthesized also through a completely different way [24], using a niobium phosphide complex as source of "P" and carbon dioxide as source of CO, see Scheme 3.12. The salt Na(OCP) is remarkably stable and can be seen as a valuable building block for the synthesis of organophosphorus compounds. For instance, Goicoechea found out



Scheme 3.13 [2 + 2] cycloaddition of $[PCO]^-$ to diphenylketene and bis(2,6-diisopropylphenyl) carbodiimide



Scheme 3.14 [Na(OCP)] and $[P_7]^{3-}$ as valuable “P” synthon

that the reaction of [K(18-crown-6)][PCO] with diphenylketene or bis (2,6-diisopropylphenyl)carbodiimide, see Scheme 3.13, gives in both cases an anionic four-membered ring [21] resulting from a [2 + 2] cycloaddition product of P≡C triple bond across the C=C or C=N double bond.

This constitutes the first example of an isolated monoanionic four-membered phosphorus-containing heterocycle.

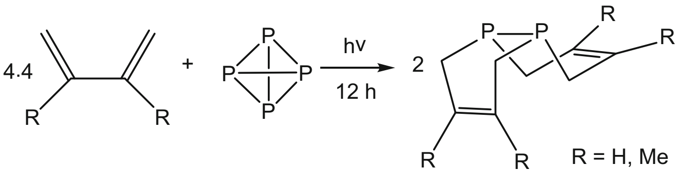
The $[OCP]^-$ anion can be regarded as an adduct of carbon monoxide and P^-, so it can work as a “P” transfer reagent, the by-product being simply gaseous CO, which facilitates the reaction work-up. On the other hand, $P_7(SiMe_3)_3$ (or similar derivatives) can also be regarded as a phosphorus donor, thus becoming highly promising building blocks to access organophosphorus derivatives in a sustainable way, avoiding the use of chlorine. An outstanding example of the synthetic relevance of the above-mentioned synthons is offered in Scheme 3.14, where starting from either Na(OCP) or $P_7(TMS)_3$, the N-heterocyclic carbene adduct was synthesized in high yield on the gram scale [25].

3.2 P-C Bond Formation by Photochemical Irradiation

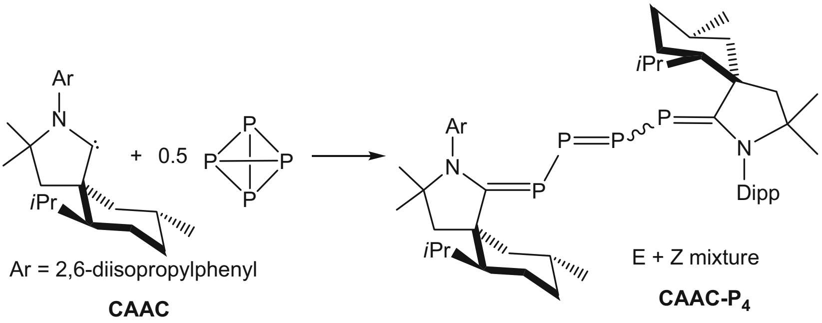
As underlined in the beginning of the chapter, a well-recognized imperative for the industrial synthesis of organophosphorus compounds is to avoid PCl_3 as an intermediate and to develop instead methods for the direct incorporation of phosphorus atoms into organic molecules using as building block elemental phosphorus, white or red. An old paper by von Rathenau [26] reported that photolysis of P_4 at room temperature using a mercury lamp induced polymerization of white phosphorus which is transformed into the less reactive red allotrope. Most importantly, he stated that the possible intermediate in this reaction is the transient species P_2, higher congener of N_2, generated by UV irradiation. A recent work by Cummins et al. has been inspired by this result and has shown that photolysis of white phosphorus under UV light generates a diphosphorus unit P_2 which may be immediately trapped by a diene molecule. The final product is consistent with a double Diels-Alder addition, affording the diphosphane derivative shown in Scheme 3.15. The process converts, in a straightforward way, P_4 into a phosphane; however the yield of the cycloadduct is moderate [27].

3.3 Carbene-Mediated Functionalization of P_4 as a Route to Organophosphorus Compounds

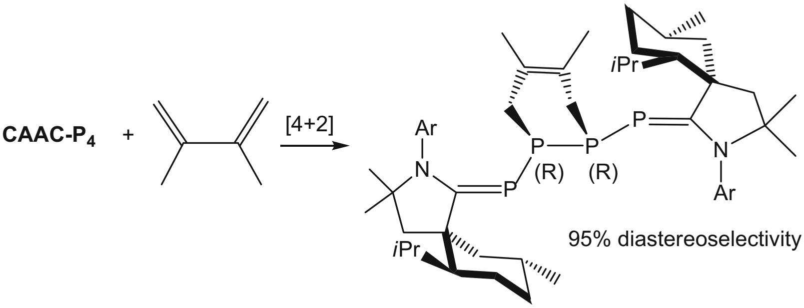
It is well known that transition metals can activate small molecules as white phosphorus and can stabilize highly reactive species. The group of Bertrand verified whether singlet carbenes may behave in a way similar to transition metals in the presence of P_4. It was shown that a bulky and rigid cyclic alkyl amino carbene, CAAC, see Scheme 3.16, is able to open P_4 and at the same time can stabilize the resulting highly reactive species, without inducing fragmentation or aggregation of



Scheme 3.15 One-pot synthesis of diphosphanes from white phosphorus by photochemical irradiation



Scheme 3.16 Reactivity of half equivalent of P_4 with CAAC

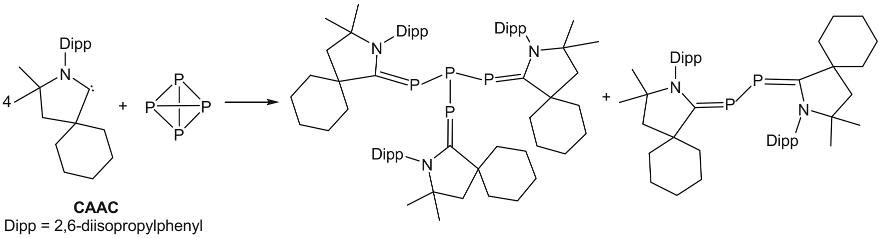


Scheme 3.17 Diastereoselective [4 + 2] cycloaddition of CAAC-P_4 adduct and 2,3-dimethylbutadiene

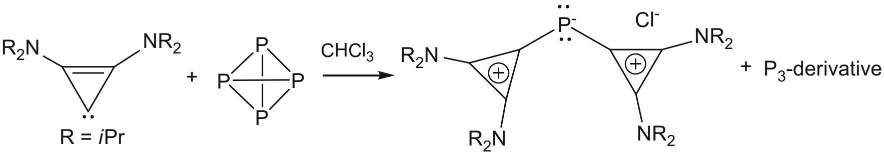
P_4. In this way, 2,3,4,5-tetraphosphatrienes constituted by an open chain of four P atoms bridging the two carbene units were isolated in good yields [28].

Moreover, it was studied the reactivity of the *(E)*-diphosphene with 2,3-dimethylbutadiene and surprisingly the reaction proceeded cleanly giving quantitatively the Diels-Alder product coming from a [4 + 2] cycloaddition of the diene with the phosphalkene, see Scheme 3.17. In this way, two phosphorus-carbon bonds were constructed and the isolated product shows very good diastereoselectivity.

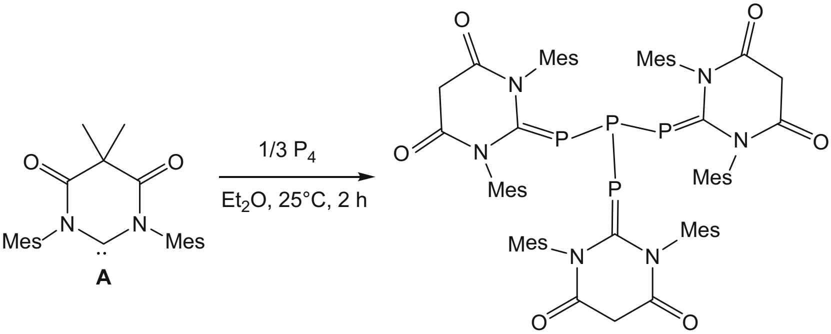
Since the chemical behavior of cyclic alkyl amino carbenes, CAACs, is usually different than that of N-heterocyclic carbenes, NHCs, these results pushed to investigate the reactivity of NHCs towards P_4. Bertrand and co-workers showed [29] that NHC not only reacts easily with P_4 but also induces an aggregation of three P_4 units and a P_{12} cluster is formed in high yield and stabilized by two NHC units. The architecture of P_{12} core is unprecedented and differs from that found in transition metal complexes having as ligand P_{12} derived from metal-mediated activation of white phosphorus [30]. Though it is not the largest cluster obtained from P_4: recently, a contribution by Scheer et al. was published [31] and demonstrated that via cobalt-mediated activation of P_4, a huge cluster of 24 phosphorus



Scheme 3.18 Reaction of P_4 with the non-hindered CAAC



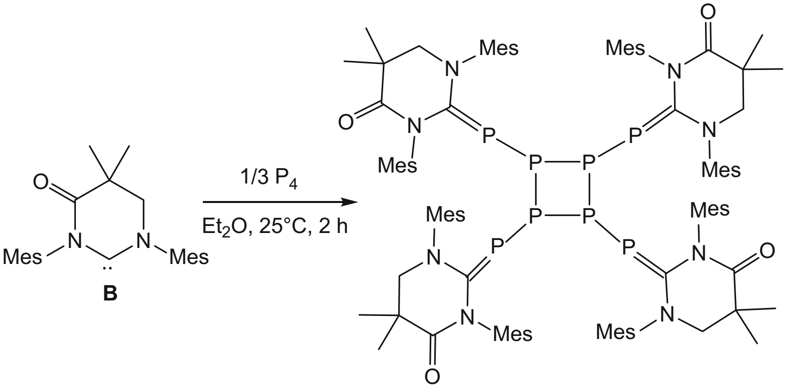
Scheme 3.19 Reaction of P_4 with cyclopropenylidene



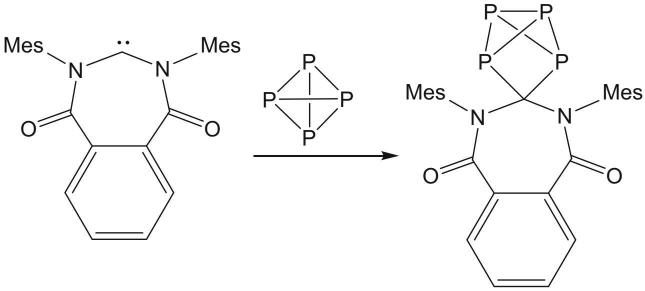
Scheme 3.20 Reactivity of white phosphorus towards carbonyl-functionalized carbene

atoms can be prepared. These results prove that singlet carbenes are excellent organic building blocks for the formation of organophosphorus compounds directly from white phosphorus without any need of a metal. Since the most synthetically useful organophosphorus compounds contain only one or two P atoms, it was mandatory to study the possible fragmentation, if any, of white phosphorus in the presence of a suitable carbene. Depending on the nature of the latter, carbene-stabilized P_3, P_2 and P_1 species have been isolated by Bertrand and co-workers [32] as shown in Schemes 3.18 and 3.19.

Carbonyl-decorated carbenes have been shown [33] to exhibit a rich and versatile reactivity, this motivated Hudnall and co-workers to investigate their reactivity towards white phosphorus. Gratifyingly, treatment of the latter with three equivalents of the highly electrophilic carbene **A** shown in Scheme 3.20 resulted in a rapid



Scheme 3.21 Reactivity of white phosphorus towards carbonyl-functionalized carbene



Scheme 3.22 Activation of P_4 mediated by a highly electrophilic carbene

activation at room temperature and formation of a triscarbene-P_4 cluster [34], analogue to the one prepared by Bertrand shown in Scheme 3.18.

Interestingly, the reaction of the less electrophilic carbene **B**, see Scheme 3.21, with white phosphorus in identical reaction conditions, provided a drastically different product, a neutral tetrakiscarbene-P_8 cluster. The X-ray analysis revealed a central P_4 butterfly structure that is capped at each P atom with a phosphalkene moiety. Taking into account that a tetraanionic P_8 cluster was previously prepared by Wiberg et al. [35] via a [2 + 2] cycloaddition dimerization of a linear P_4-diphosphene, Hudnall repeated the reaction of P_4 with carbene **B** by adding 2,3-dimethyl-1,3-butadiene and the corresponding Diels-Alder cycloaddition product was isolated, confirming the hypothesized reaction pathway. Therefore, it is evident the dramatic influence of the electrophilicity of the chosen carbene on the identity of the final product.

In the same time, Bertrand's group was working on this matter, and shortly after Hudnall, published that the tetrakis carbene P_8 cluster can be obtained from P_4 and the cyclic six-membered diamido carbene (as shown by Hudnall) and also by using a less electrophilic carbene as cyclic(alkyl)(amino)carbene [36]. Moreover, he demonstrated that a carbene can insert into a single P-P bond of P_4, resulting in the formation of a carbene-P_4 adduct (Scheme 3.22). Thus the extremely electrophilic seven-membered cyclic benzamido carbene can behave as a transition metal towards P_4 showing a η^2-coordination.

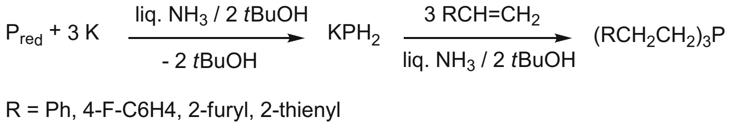
Future efforts will be necessary to investigate these compounds coming from the carbene-mediated activation of P_4, as potential phosphorus transfer reagents for the preparation of useful organophosphorus compounds.

3.4 Synthesis of Organophosphorus Compounds by Nucleophilic Addition

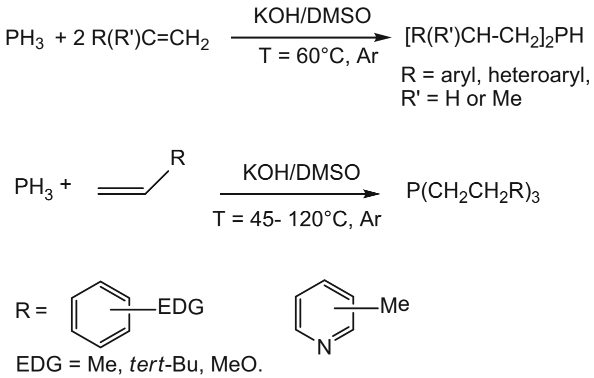
In this section, we review two main different approaches: (a) phosphorus-centered anion, usually directly derived from elemental phosphorus, which does a nucleophilic attack (addition) on organic substrates; (b) carbon-centered anion, which does a nucleophilic attack (addition) on P_4; in both cases a new P-C bond is formed.

Concerning the chemistry of phosphorus-centered anion, it is worth mentioning the work developed by Trofimov and Gusarova. They choose red phosphorus as "P"-source to accomplish the phosphorylation of unsaturated organic compounds, as alkenes and alkynes. Since red phosphorus has a polymeric chain-like structure which reduces strain and reactivity in comparison to the white allotrope giving greater stability, harsher treatments are required for the activation of the red allotrope. Strongly basic conditions, as aqueous potassium hydroxide in dimethylsulfoxide under heating or microwave irradiation were used, and the final reaction mixtures gave primary, secondary and tertiary phosphanes and phosphane oxides. A similar procedure was applied by the same authors to carry out the direct phosphorylation of alkenes and alkynes with P_4, but using milder conditions, as shorter reaction time and heating at lower temperature [37]. From the mechanistic point of view, it is believed that in such heterogeneous and strongly basic media, highly active *P*-centered nucleophiles (as polyphosphides and polyphosphinites) are formed and prone to interact with the suitable electrophile (styrenes, vinylpyridines, acetylenes and similar). This methodology avoids the use of chlorine but has the disadvantage to produce mainly oxidized products, i.e. phosphane oxides.

In the late 1990s, Brandsma and Trofimov [38] refined this methodology and triggered a way to avoid the formation of the oxide selectively achieving the desired phosphane. They reacted the elements, red phosphorus and potassium in liquid ammonia and using *tert*-butanol as mild source of protons, potassium phosphide, KPH_2, was formed quantitatively (Scheme 3.23). Subsequent addition of an alkene brought the formation of tertiary phosphane and the reaction is supposed to proceed through a series of nucleophilic addition of the phosphides, formed *in situ*, to the double bond of the alkene. Importantly, the reaction generated selectively and exclusively tertiary phosphanes. Electrophilic alkenes are preferred being able to



Scheme 3.23 Synthesis of tertiary phosphanes from red phosphorus



Scheme 3.24 Selective synthesis of secondary and tertiary phosphanes from PH_3

react with the phosphorus-centered anion $[PH_2]^-$, while less electrophilic alkenes were left un-reacted.

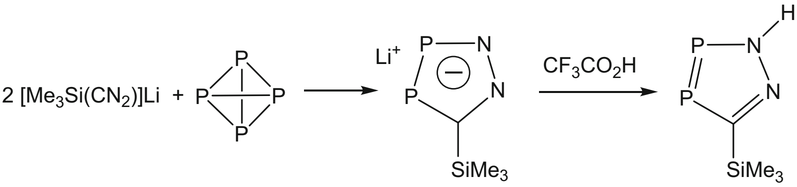
A similar method was followed for the preparation of primary alkylphosphanes [39].

Since the pioneer work of Rauhut et al. [40] and later by King et al. [41] described the nucleophilic addition of phosphane, PH_3 and R_2PH, respectively, to the C-C double bond of acrylonitrile and $[Ph_mP(CH{=}CH_2)_n](m{=}1{,}2;\ n{=}2{,}1)$ respectively, in the presence of bases, further contribution to this field came from Trofimov and co-workers [37] who foresee in the use of PH_3 as P-source replacing elemental phosphorus, a great advantage from the atom economy point of view, which is fully respected in the presence of phosphane.

Using as phosphorylating agent PH_3 produced *in situ* from the basic hydrolysis of red phosphorus, the hydrophosphination of weakly electrophilic double bonds of aryl- and heteroarylethenes was performed affording selectively secondary phosphanes previously unknown or difficult to prepare phosphane (Scheme 3.24).

As in the phosphorylation carried out with elemental phosphorus, strong basic conditions are required in this process as well, which is believed to proceed via a nucleophilic addition to the olefinic bond of the phosphorus-centered anion, PH_2^-, which can be generated only by action of a strong base on PH_3.

Complete and selective formation of tertiary aryl(heteroaryl) phosphanes was accomplished at atmospheric pressure of PH_3 in KOH/DMSO heating in the range 45–120 °C and with additional introduction of the alkene (styrenes or vinylpyridines) in the reaction mixture at the end of the process, see Scheme 3.23. Notwithstanding the reaction goes to completion in a selective way, working at



Scheme 3.25 Synthesis of 1,2,3,4-diazadiphosphole ring from P_4

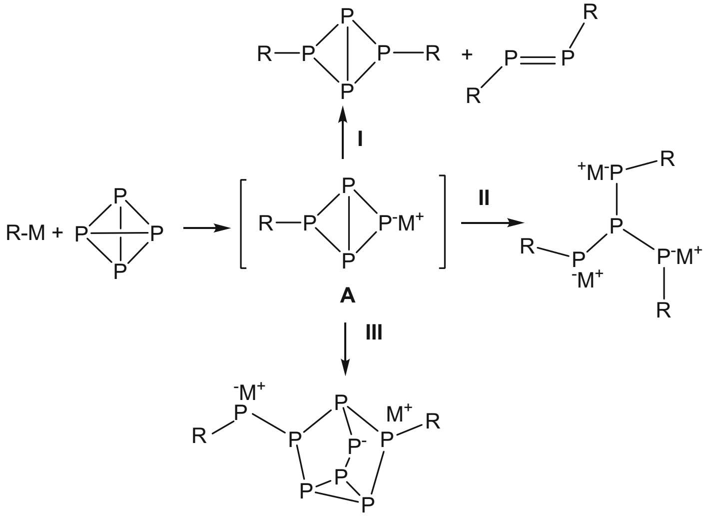
atmospheric pressure of PH_3 constitutes a great advantage, considering the flammability and toxicity of this gas. Previously, PH_3 was added to styrene in the presence of a radical initiator under elevated phosphane pressure [42] but a mixture of primary, secondary or tertiary phosphanes difficult to separate was obtained.

The first example of a suitable anionic carbon centered-nucleophile used to activate directly P_4 was published by Rauhut et al. in 1963. He reacted organo-alkali reagents with white phosphorus obtaining a complex mixture of polyphosphides and upon hydrolysis primary and secondary phosphanes were isolated in moderate yield [43]. Afterwards, the nucleophilic functionalization of P_4 has been widely explored using milder conditions and softer reagents with the aim to direct it selectively to one main product.

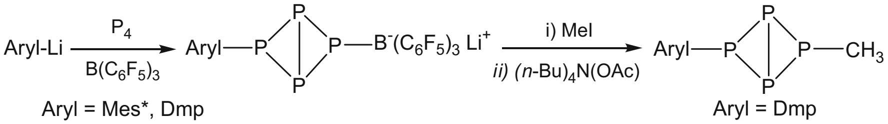
Mathey and co-workers studied the reaction of lithium(trimethylsilyl) diazomethanide with white phosphorus, considering that the first reagent can be seen as the synthetic equivalent of a $[RC]^-$ fragment and in principle could provide a direct way to get $[RCP_4]^-$ thanks to the driving force of the reaction due to the aromatic stabilization of the final five-membered ring. The reaction proceeded cleanly as a formal [3 + 2] cycloaddition between a P_2 unit, [P≡P], extruded from P_4, and the diazomethyl anion, giving as a sole product the previously unknown aromatic 1,2,3,4-diazadiphospholide anion, shown in Scheme 3.25. The protonation of the latter by trifluoroacetic acid at low temperature afforded the stable 2*H*-1,2,3,4-di-azadiphosphole. This work [44] showed for the first time that white phosphorus can be a useful starting material for the direct synthesis of new aromatic polyphosphorus compounds.

In the last decades, several efforts have been carried out to accomplish the direct synthesis of organophosphorus compounds by nucleophilic addition of an organic reagent to P_4 bypassing the use of a metal and are summarized in Scheme 3.26. The common intermediate in all these reactions is believed to be the highly reactive bicyclo[1.1.0]tetraphosphabutane anion **A** formed upon a P-P bond cleavage of the P_4 tetrahedron, which is susceptible of degradation and re-aggregation forming a complex mixture of products.

Fluck et al. found out that P_4 in the presence of Mes*Li (Mes* = 2,4,6-$C_6H_2{}^tBu_3$) is opened to give a di-substituted butterfly compound in low yield (Scheme 3.26, route I) and a diphosphene [45]. Lerner et al. [46] by using a threefold excess of the less bulky MesLi (Mes = 2,4,6-$C_6H_2Me_3$) obtained a complete degradation of the P_4 tetrahedron and isolated a trianionic tetraphosphide (Scheme 3.26, route II). Direct reaction of P_4 with hypersilyl complex $[(Me_3Si)_3Si]$



Scheme 3.26 Nucleophilic addition of carbon-centered anion to P_4



Scheme 3.27 Arylation and subsequent alkylation of white phosphorus

(K(18-crown-6)] gave a Zintl-type P_7-cage compound [47], probably arising from dimerization of anion **A** (Scheme 3.26, route III). A few years ago, Tamm and co-workers studied the behavior of P_4 in the presence of a frustrated carbene-borane Lewis pair. In this condition, the selective heterolytic cleavage of one of the six P-P bonds of the P_4 tetrahedron took place, and the resulting highly reactive P_4 butterfly was stabilized by formation of a P-C and P-B bond respectively at the two opposite site of the butterfly cage [48]. Recently, Lammertsma and his group [49] accomplished the activation and functionalization of P_4 with a bulky nucleophile as ArylLi [Aryl = Dmp (2,6-dimesitylphenyl), Mes*] in the presence of a Lewis acid as $B(C_6F_5)_3$, mimicking a frustrated Lewis pairs approach, similar to Tamm's group. Methylation of the P_4 butterfly derivative as shown in Scheme 3.27 favored the elimination of Lewis acid $B(C_6F_5)_3$ and the formation of a new P-C bond in quantitative yield.

This represents a new method enabling the formation of organophosphorus compounds starting directly from white phosphorus, forming two P-C bonds in a controlled stepwise fashion and avoiding chlorinated reagents.

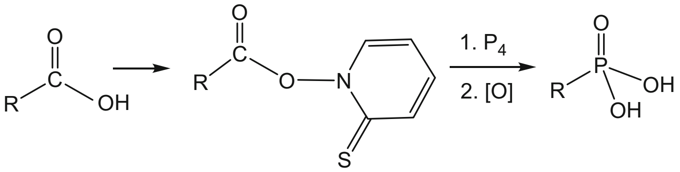
3.5 P-C Bond Formation Mediated by Radicals

White phosphorus can be an efficient radical trap and can react with carbon-centered radicals in solution under mild conditions. The work developed by Barton et al. [50] shows the great ability of P_4 to react in a long radical chain reaction with carbon radicals generated from carboxylic acids via photolysis of the corresponding Barton PTOC ester. Subsequent oxidation with aqueous hydrogen peroxide affords the phosphonic acid derivatives in good yields. In this way, a wide range of carboxylic acids, including those derived from natural products, as oleic and linoleic acid, can be converted into the corresponding phosphonic acids, see Scheme 3.28. Moreover, a clear mechanistic picture for the addition of carbon radicals to P_4 has been presented, where the chain reaction is initiated by the reaction of dioxygen with P_4.

Subsequent to the work of Barton, it has been shown by Sato et al. that P-P bonds other than those in P_4 may serve as a trap for organic radicals; for instance Ar · radical, coming from ArX, can react with the diphosphane $Ph_2P\text{-}PPh_2$ accomplishing in this way a radical phosphination of organic halides [51].

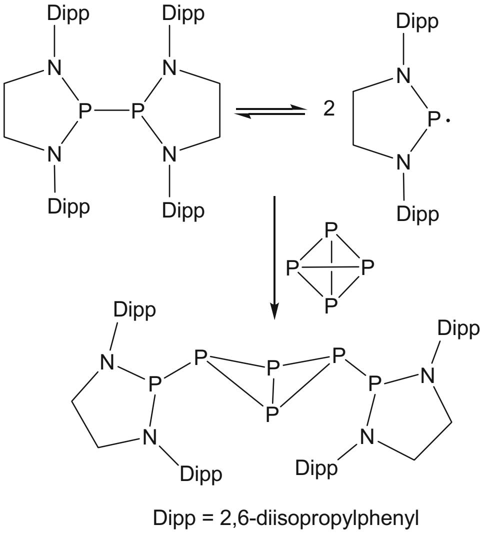
Lappert prepared the diphosphane $[P\{N\text{-}(Me_3Si)_2\}(NPr^i{}_2)]_2$ which reversibly dissociates in solution to phosphinyl radical and when refluxed for short time in toluene in the presence of white phosphorus, generated as main product a tetraphosphabicyclobutane derivative, present in solution as a 1:1 mixture of *meso*- and *rac*-diastereoisomers [52]. Similarly, the diphosphane $[(\{Me_3Si\}_2CH)_2P]_2$ is known in the literature as a molecular “jack in the box” radical [53] since it is endowed with potential energy stored in the central P-P bond, due to the strained rotation of the bulky peripheral trimethylsilyl ligands. As a result, the P-P bond in the diphosphane can easily undergo homolysis forming two equivalents of the phosphinyl radical. The latter can react at room temperature with half equivalent of P_4, causing the cleavage of one P-P bond of the tetrahedron, and the resulting tetraphosphabicyclobutane is stabilized by the highly hindered substituents on the heterocycle. The structure, shown in Scheme 3.29, was confirmed by X-ray crystallography [54] with the molecule assuming a *trans,trans* configuration to minimize steric interactions.

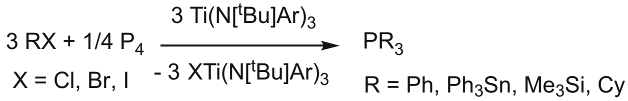
The contribution to this chemistry from Cummins and co-workers is based on the discovery that the three-coordinate titanium(III) complex $Ti(N[^tBu]Ar)_3$ ($Ar = 3,5\text{-}C_6H_3Me_2$) is a powerful abstractor of halogen-atoms, as chloride, bromide, iodide, from various donor molecules at room temperature in aprotic organic media



Scheme 3.28 Radical synthesis of phosphonic acids from P_4

Scheme 3.29 Reactivity of P_4 with a phosphinyl radical





$$3\,RX + 1/4\,P_4 \xrightarrow[-\,3\,XTi(N[^{t}Bu]Ar)_3]{3\,Ti(N[^{t}Bu]Ar)_3} PR_3$$

$X = Cl, Br, I$ $R = Ph, Ph_3Sn, Me_3Si, Cy$

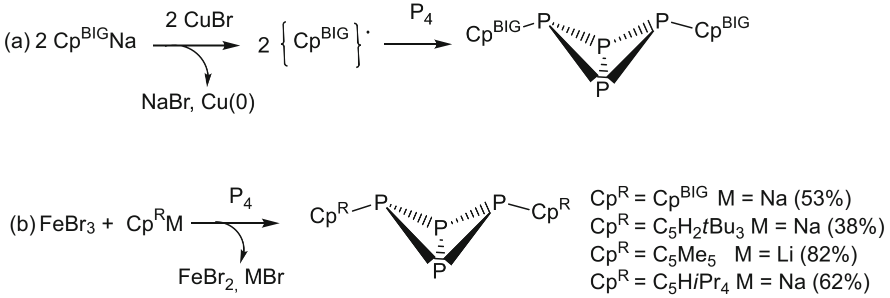
Scheme 3.30 Radical synthesis of tertiary phosphanes from P_4 catalysed by Ti(III) complex

[55]. On these basis, Cummins developed a high yield synthesis of phosphanes, PR_3, starting from P_4 and an alkyl or aryl halide in the presence of $Ti(N[^{t}Bu]Ar)_3$ as promoter [56], according to the equation shown in Scheme 3.30. In terms of recycling, the titanium by-product $XTi(N[^{t}Bu]Ar)_3$ ($X = Cl$, Br, I) can be reduced by Na/Hg amalgam back to the active species $Ti(N[^{t}Bu]Ar)_3$.

This represents a powerful and clean method to prepare a wide array of phosphane directly from P_4; based on the ability of P-P bonds to work as efficient radical traps, the next step will be trying to make this process catalytic.

A recent paper by Scheer et al. [57] shows a new methodology involving the intermediary formation of Cp^R radicals that selectively open one P-P bond of the P_4 tetrahedron. The process is mediated by a transition metal which is in the end eliminated as a salt by-product, and the main product is a carbon-substituted bicyclic P_4 butterfly compound as shown in Scheme 3.31. Two different methods have been used: the first one (a) is based on the addition of a stoichiometric amount of Cu(I) salt, which readily reduces to Cu metal allowing the oxidation of $(Cp^{BIG})^-$ to Cp^{BIG} radical [$Cp^{BIG} = C_5(4\text{-}^{n}BuC_6H_4)_5$], and the second (b) can activate P_4 yielding a modest amount of $(Cp^{BIG})_2P_4$.

Any attempt to extend the reaction to smaller Cp^R radicals failed, probably the latter being less hindered and more reactive than Cp^{BIG}, which made a radical

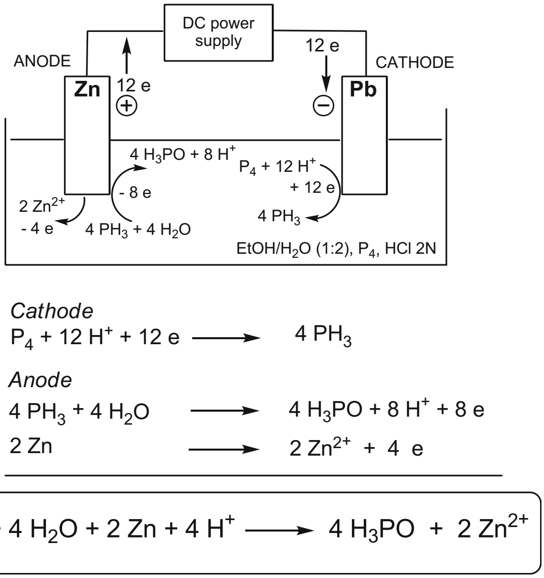


Scheme 3.31 Functionalization of P_4 mediated by a metal radical

decomposition faster than the reaction with P_4 so that the formation of the desired P_4 butterfly does not proceed. It is known [58] that $[\{Cp'''Fe(\mu\text{-}Br)\}_2]$ [Cp''' = 1,3,5-CpH^tBu_3) reacts with one equivalent of P_4 leading to the formation of $[\{Cp'''Fe\}_2(\mu,\eta^{4:4}\text{–}P_4)]$ as well as to the carbon-substituted butterfly compound $(Cp''')_2P_4$ together with a small amount of $FeBr_2$, meaning in the process an oxo-reduction takes place bringing initial Fe(III) to Fe(II) and $[Cp^R]^-$ to $[Cp^R]^{\cdot}$ radical. On this basis, Scheer et al. carried out the straightforward reaction of $FeBr_3$ and Cp^RM ($M = Na$ or Li) in the presence of white phosphorus. The desired, symmetrically substituted, P_4-butterfly shown in Scheme 3.31, was isolated with good yield. Interestingly, while the "copper" route is feasible only in the presence of Cp^{BIG}, the "iron" route has a wider applicability.

3.6 Electrochemical Activation of P_4: An Alternative Way to Access Organophosphorus Compounds

Electrochemistry can be considered as a "green" technique since it uses electrons as reagents and generally the electrochemical processes proceed under mild conditions where the rate and selectivity of the process can be easily adjusted by tuning both the working electrode potential and electric current. Therefore, a chemical process can be directed in a very clean way, obtaining high purity products and avoiding the formation of waste. For all these reasons, electrochemical methods become attractive for synthesizing pharmaceuticals and fine chemicals. An outstanding contribution to the development of electrochemical synthesis of inorganic and organic phosphorus compounds starting directly from white phosphorus comes from the Arbuzov Institute of the Russian Academy of Sciences in Kazan [59]. It was shown that depending on the experimental conditions, as solvent (water or alcohol), electrode material (graphite, platinum, mercury) temperature and pH, the electrochemical process may be modulated to give predominantly the desired phosphorus derivatives. It is believed [60] that the first step is the reduction of P_4 at the cathode electrode with formation of a highly reactive phosphido radical anion



$$P_4 + 12\,H^+ + 12\,e \longrightarrow 4\,PH_3$$

$$4\,PH_3 + 4\,H_2O \longrightarrow 4\,H_3PO + 8\,H^+ + 8\,e$$

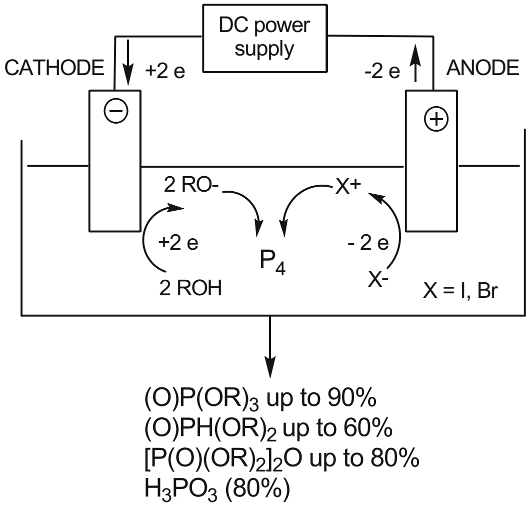
$$2\,Zn \longrightarrow 2\,Zn^{2+} + 4\,e$$

$$\boxed{P_4 + 4\,H_2O + 2\,Zn + 4\,H^+ \longrightarrow 4\,H_3PO + 2\,Zn^{2+}}$$

Schema 3.32 Electrochemical generation of H_3PO in acidic ethanol/water solution from white phosphorus

$[P_4]^-$. Soon after, a fast protonation of this species takes place being the process carried out in protic media, resulting in cleavage of P-P bonds and formation of P-H bonds. Several studies have been carried out on the electrochemical hydrogenation of white phosphorus, which can be considered as the suitable method for *in situ* generation of highly pure PH_3 directly from P_4. Gaseous PH_3, meanwhile is generated, can be collected in another reaction vessel in presence of the appropriate organic reagent to synthesize the desired organo-phosphorus derivative [60]. The yields of PH_3 vary in the range 60–83 % at the lead cathode in an aqueous solution of NaOH in a range of temperature from 70 to 100 °C. In a classical chemical process, operating without electrochemistry, boiling a basic emulsion of P_4 ends up with a mixture of products: hypophosphite (50 %), phosphite (25 %) and PH_3 (25 %) together with hydrogen evolution. Noteworthy, the electrochemical process transforming selectively P_4 into hypophosphorus acid has been studied [61] analyzing carefully the reaction mixture at equal interval of time by ^{31}P NMR spectroscopy. This allowed to intercept for the first time, a key intermediate, H_3PO, which is formed at the zinc anode as an oxidation product of PH_3 released at the lead cathode, as shown in Scheme 3.32.

The generation in solution of H_3PO was completely unexpected, being known as highly labile species that previously was generated only under extreme conditions and characterized in argon matrices [61]. A detailed study evidenced that the formation of this species is related to electrode-surface processes and it is observed only in the presence of a zinc electrode as anode and operating in acidic ethanol/water mixture.



Scheme 3.33 Electrochemical process for the transformation of P_4 into phosphates and phosphorous oxyacids

$$P_4 + 12\ ROH + 4\ H_2O \xrightarrow{\pm 20\ e^-} 4\ (RO)_3PO + 10\ H_2$$

Scheme 3.34 Electrochemical synthesis of organophosphates

$$P_4 + 12\ R_2NH + 4\ ROH \xrightarrow{\pm 20\ e^-} 4\ (NR_2)_3PO + 10\ H_2$$

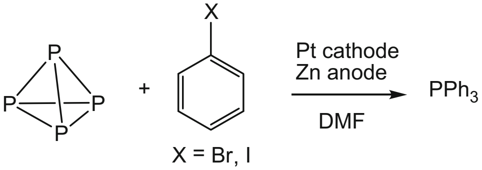
Scheme 3.35 Electrochemical synthesis of triamidophosphates

When the electrochemical reduction of white phosphorus is performed in the presence of alcohols and ammonium salts used as supporting electrolyte, in principle a mixture of esters of different phosphorus oxyacids may be produced. The accepted mechanism is based on the reduction of the alcohol at the cathode with formation of the alkoxide anion, RO^-, which does a nucleophilic attack on P_4; meanwhile at the anode, the oxidation of the halide coming from the supporting electrolyte takes place, generating an electrophilic reagent. The joint action of the alkoxy anion and the electrophile on P_4 results in various derivatives as shown in Scheme 3.33, depending on the nature of the alcohol, on the ratio water/P_4 and on the temperature used to carry out the process,

Under specific conditions, trialkyl phosphates were prepared in a quantitative yield; Scheme 3.34 shows the equation for the overall process which looks like highly clean, only gaseous hydrogen is formed as by-product [59].

Electrolysis of an emulsion of white phosphorus in the presence of an alcohol and an amine generates the corresponding triamidophosphates, as shown in Scheme 3.35 [60].

Interestingly, the electrolysis of an emulsion of P_4 and an aromatic halide in dimethyl formamide leads to triphenylphosphane without using any metal catalyst



Scheme 3.36 Electrochemical synthesis of triphenylphosphane directly from white phosphorus

as shown in Scheme 3.36. The process patented by Budnikova et al. works under mild conditions [62] and results in the selective formation of triphenylphosphane with up to 82 % yield relative to P_4.

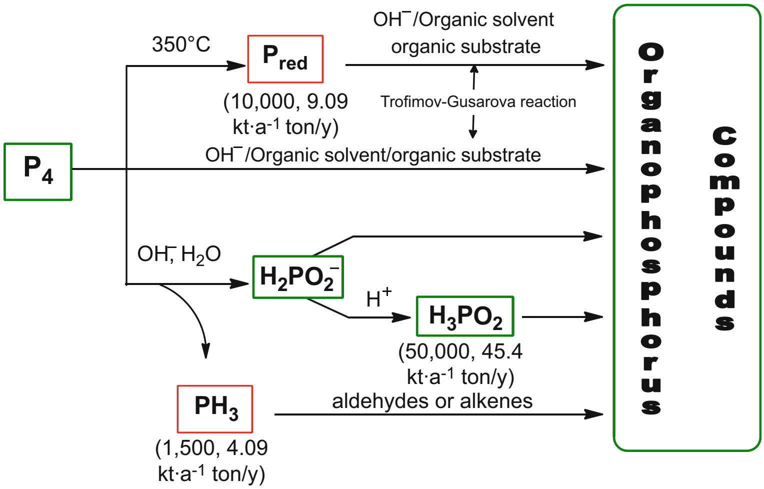
To shed light on the reaction mechanism, it was investigated the reactivity of organozinc species, as diphenylzinc, in the presence of white phosphorus outside the electrochemical cell. In the final reaction mixture, only phenylphosphane and diphenyl phosphane were identified, demonstrating that via the transition-metal mediated synthesis the process is not selective and stops at the product with maximum two phosphorus-carbon bonds [63]. On the other hand, under electrochemical conditions using zinc as sacrificial anode, the interactions of electrogenerated organozinc reagents with P_4 causes the opening of all P-P bonds of the tetrahedron, resulting in the selective formation of organophosphorus compounds with three phosphorus-carbon bonds.

In conclusion, the interest in the electrosynthesis of organophosphorus compounds from P_4 arises from a series of advantages compared to common chemical methods: (a) mild conditions required by the process (ambient pressure and temperature); (b) atom economy (the supporting electrolyte can be recycled at the end of the process); (c) high environmentally safety, avoiding the use of chlorinated reagents; (d) the electrosynthesis can be highly selective, affording high purity products.

3.7 Hypophosphorous Pathway: From H_3PO_2 and Its Alkali Salts to Organophosphorus Compounds

In the way to avoid PCl_3 as P-source for the preparation of organophosphorus compounds, many efforts have been devoted either to functionalize directly elemental phosphorus, both allotropes, white and red, or to transform elemental phosphorus into a variety of different inorganic phosphorus compounds as phosphane (PH_3) [64], hypophosphorous acid (H_3PO_2) and its alkali salts [65] as shown in Scheme 3.37.

However, white and red phosphorus usually uses hard conditions such as the superbasic system: aqueous solution KOH (86 %)/DMSO or HMPA/organic substrate (Trofimov-Gusarova reaction), and PH_3 is a highly toxic and pyrophoric gas. Nevertheless, as stated in the beginning of this chapter, all of them, together with the highly reactive and hazardous PCl_3, are currently the basis of organophosphorus manufacturing [66].

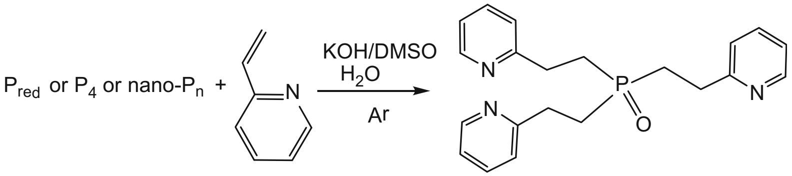


Scheme 3.37 Access to organophosphorus compounds avoiding the use of chlorine

The use of hypophosphorus acid and its derivatives in the synthesis of organophosphorus compounds is nowadays becoming a widespread methodology, due to its low toxicity and low environmental impact in comparison with PCl_3.

3.7.1 Phosphorylation with Elemental Phosphorus

While white phosphorus is formed by single tetrahedral molecules endowed with a certain tension due to ring strain, which makes it highly unstable and reactive, red phosphorus has a polymeric structure, where one of the P-P bond of the P_4 tetrahedron is broken and one additional bond is formed with a neighboring tetrahedron to form a chain-like structure. This polymeric network of P-atoms reduces strain and reactivity in comparison to the white allotrope and gives greater stability. The activation of red phosphorus requires therefore harsher treatments. According to the procedure developed by Trofimov and Gusarova in the late 1980s, using “superbasic” conditions, as aqueous KOH/DMSO under heating or microwave irradiation, directly convert a mixture of red phosphorus and unsaturated organic compounds, as alkenes and alkynes, into primary, secondary and tertiary phosphanes and phosphane oxides. A similar procedure was applied by the same authors to carry out the direct phosphorylation of alkenes and alkynes with P_4, but using milder conditions, *i.e.* shorter reaction time and heating at lower temperature. From the mechanistic viewpoint, it is believed that in such heterogeneous highly basic media, KOH/DMSO (or HMPA), KOH/organic solvent/phase-transfer catalyst as shown in Scheme 3.38, highly active *P*-centered nucleophiles



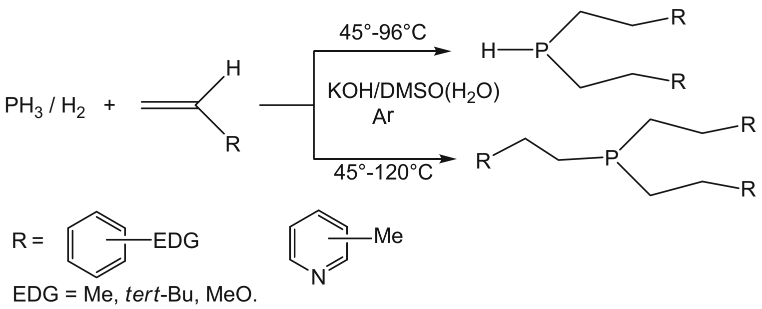
Scheme 3.38 Phosphorylation of elemental phosphorus using "superbasics" conditions (Trofimov-Gurasova reaction)

(as polyphosphides and polyphosphinites) are formed and prone to interact with the suitable electrophile (styrenes, vinylpyridines, acetylenes and similar) [67].

A further development has been lately introduced by Trofimov et al. which consists in the preparation of nanocomposites of red phosphorus, nano-P_n, with carbon, graphite or organophosphorus inclusions, obtained by radiation-induced polymerization (^{60}Co γ-radiation) of P_4 at room temperature [68]. Nano-P_n contain mainly phosphorus (80 %), the rest is carbon, oxygen and hydrogen and consist of nanoparticles having diameter in the range of 30–50 nm. Interestingly, nano-P_n have shown higher reactivity in the phosphorylation of styrene and its derivatives compared to common red phosphorus, see Scheme 3.38.

3.7.2 *Phosphorylation with PH_3*

The approach based on elemental phosphorus, white or red, does not solve the problem of phosphorus atom economy, since not all P-atoms of the reagent are found in the final product, but some are lost in the process usually as unidentified by-products. In this respect, PH_3 and MH_2PO_2 (M = H, metal, alkyl) have the potential to incorporate all the phosphorus content into an organic product. Alkali hypophosphites (and consequently hypophosphorus acid) and PH_3 come from the alkaline hydrolysis of white phosphorus, which is still nowadays a process not fully understood and its improvement would be desirable. PH_3 is a highly toxic and pyrophoric gas requiring very careful handling, its use is therefore strongly limited to small amounts in the electronic industry and as a starting material for the synthesis of trialkylphosphanes, R_3P, and related compounds. Since the pioneer work of Rauhut et al. [40] and later by King et al. [41] who described the nucleophilic addition of PH_3 to the C-C double bond of alkenes bearing strong electron-withdrawing substituents, in the presence of bases, further developments have been studied by Trofimov and co-workers [37]. Using as phosphorylating agent the mixture PH_3/H_2 coming from the basic hydrolysis of red phosphorus, they performed the hydrophosphination of weakly electrophilic double bonds of aryl- and heteroarylethene affording previously unknown or difficult to prepare secondary or tertiary phosphanes as shown in Scheme 3.39.



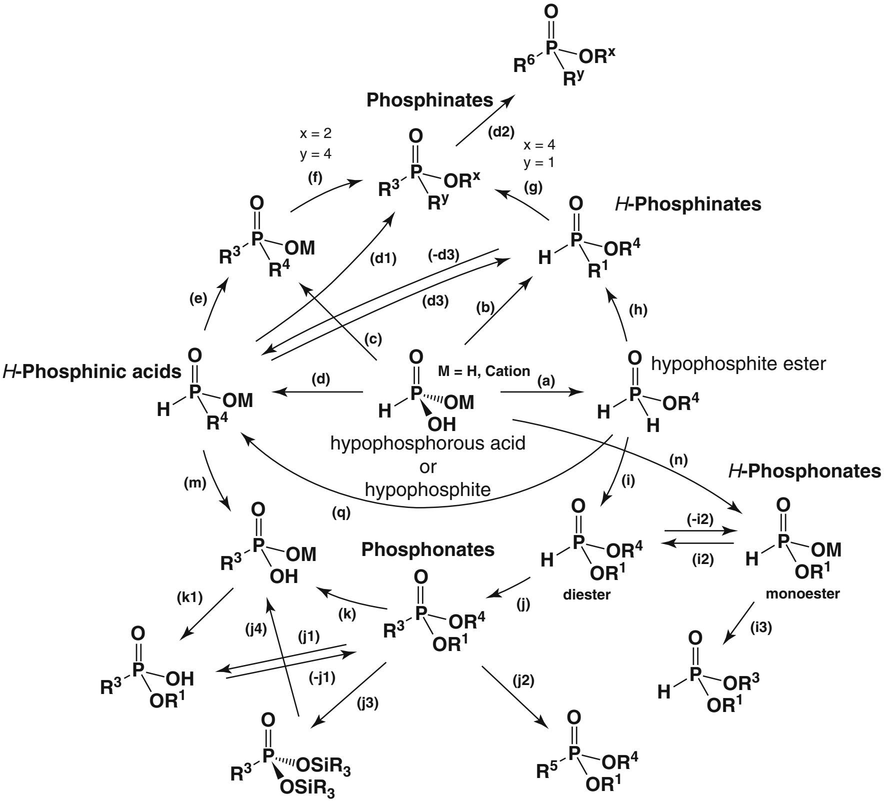
Scheme 3.39 Phosphorilation of PH_3 using alkenes under harsh conditions

As in the phosphorylation with elemental phosphorus, strong basic conditions have been used, notwithstanding the reaction goes to completion in a selective way, working at atmospheric pressure of PH_3, which constitutes a great advantage. Previously, PH_3 was added to styrene in the presence of a radical initiator under elevated phosphane pressure [42] to give a mixture of primary, secondary or tertiary phosphanes. In the process discovered by Trofimov, the pathway is not radical but entails a nucleophilic addition of PH_2^-, generated from PH_3 under strong basic conditions, to the olefinic bond in the presence of water.

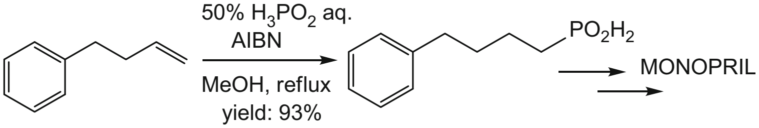
3.7.3 Organophosphorus Compounds from H_3PO_2 or Its Salts

Owing to the problem of toxicity and handling related to PH_3, only MH_2PO_2 and/or their derivatives represent a real alternative to PCl_3. The higher homologue, H_3PO_3, currently produced from the hydrolysis/alcoholysis of PCl_3, is much less reactive than H_3PO_2, so it is not a valuable option. Hypophosphorous acid, which can be prepared by boiling white phosphorus with an inorganic base and subsequent acidification, represents a much more environmentally benign phosphorous source than PCl_3, coming from the high temperature reaction of white phosphorus and chlorine. Hypophosphorous acid and its salts, being more easily handled and less toxic than other P-sources (P_4, red P, PCl_3, PH_3), constitute an industrial commodity, inexpensive and highly versatile. The key challenge is to find out the shortest pathway leading to the desired organophosphorus compound from the hypophosphorous acid or its derivatives, in particular *H*-phosphinate, *H*-phosphinic acid, *H*-phosphonate diester, *H*-phosphonate monoester, phosphonate, phosphinate and hypophosphite esters have the great advantage to offer access to various functional groups, see Scheme 3.40.

Unexpectedly, hypophosphites have not received a great attention yet from the industry, one of the best examples is the production of the heart drug Monopril, in



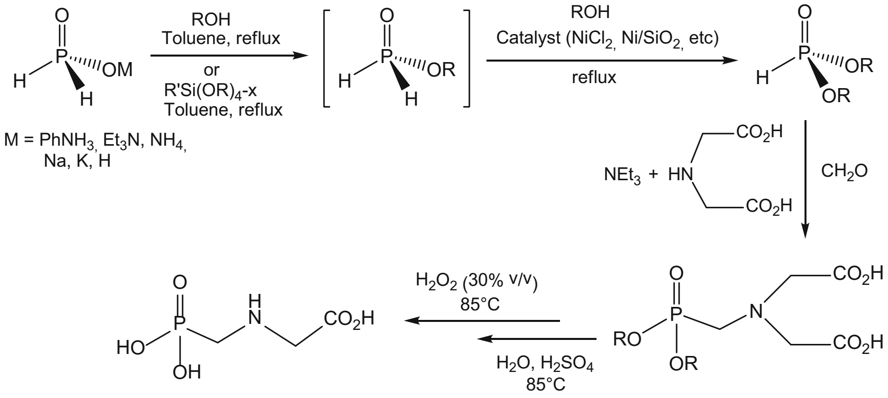
Scheme 3.40 Synthetic versatility of hypophosphorous acid its salts and their derivatives. (*a*) (*b*) [70, 83, 158], (*c*) [131–134], (*d*) (*e*) [69, 83, 131, 132, 135, 136, 144, 145, 147], (*e*) (*m*) [139, 147], (*f*) [69, 136], (*g*) [75–87], (*h*) (*i*) [65, 70, 83, 149], (*j*) [70, 88–112], (*k*) [70, 83, 109], (*m*) [83, 144, 145], (*d1*) (*d2*) [83, 146], (*d3*) [87, 147, 148, 158], (*−d3*) [149], (*n*) [83], (*q*) [158], (*i2*) [103], (*−i2*) (*i3*) [150], (*j1*) [83, 151], (*−j1*) [152–155], (*j2*) [113–137], (*j3*) [157], (*j4*) [155, 157], (*k1*) [155, 156]



Scheme 3.41 Radical addition of H_3PO_2 to a terminal double bond in the synthetic pathway to the drug Monopril

which the radical addition of H_3PO_2 to olefins, initiated by AIBN, is employed (Scheme 3.41) [69].

The other industrial process patented [70] and developed by Montchamp et al. is the synthesis of the herbicide Glyphosate, in which H_3PO_2 or its salts are converted



Scheme 3.42 Conversion of phosphinate to *H*-phosphonate and glyphosate

first to an alkyl phosphinate and then to an *H*-phosphonate diester, thus avoiding the use of PCl_3 as shown in Scheme 3.42.

The addition of H_3PO_2 to olefins under radical conditions was discovered by Williams and Hamilton [71] in 1955. Since then, improvements to the reaction were carried out by Nifant'ev, though the low solubility of H_3PO_2 and of its sodium salt in organic solvents, the need of high initiation temperature and large amounts of initiator, usually AIBN, make this reaction quite unfeasible.

In 2001, Montchamp [72] published that the radical addition of hypophosphorous derivatives to unsaturated hydrocarbons is feasible in mild conditions at room temperature by using a trialkylborane and air as the initiator. Another advantage of this methodology is its wide applicability with respect to the kind of alkene and phosphinate reagent. Another important discovery by the same group was the hydrophosphinylation of alkenes catalysed by palladium or nickel [73]. It was shown that in the presence of a suitable phosphane ligand, *i.e.* Xantphos, a low loading of palladium was enough to reach a complete conversion. An heterogenous catalyst, stable in aqueous environment, was prepared by supporting palladium on polystyrene and this allowed to carry out the reaction in water, which was advantageous since in this medium hypo acid and hypophosphite are perfectly soluble. On the other hand, the nickel-catalyzed hydrophosphinylation was less effective, since it gave only up to 70 % of conversion.

In the case of alkynes, the hydrophosphinylation in the presence of Et_3B worked well only for terminal ones, a nickel-catalysed reaction was developed to add alkyl phosphinates to internal alkynes [74]. Pd_2dba_3 together with a suitable phosphane ligand was used as a catalyst to accomplish a regioselective hydrophosphinylation of terminal alkynes to either (*E*)- or (*Z*)- alkenes. Both palladium- and nickel-catalyzed hydrophosphinylation proceed under microwave heating to deliver a high yield of the desired product in a few minutes.

In the last years, the most used precursors in the synthesis of organophosphorus compounds have been *H*-phosphinates [75–87], *H*-phosphonates [88–112], phosphonates [113–137] and *H*-phosphinic acids [138–149]. Although most of the precursors are still synthesized from chlorinated derivatives, some research groups, as Montchamp's [65, 83], are exploring new synthetic pathways based on hypophosphites and *H*-phosphinates. These synthetic procedures are working well at laboratory scale, therefore the challenge in the coming years will be to transfer the new synthetic routes based on hypophosphite to an industry level.

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Chapter 4
Hypophosphorous Acid and Its Salts as Reagents in Organophosphorus Chemistry

Aurelia Visa, Bianca Maranescu, and Gheorghe Ilia

Abstract In the last decades, the interest in the organophosphorus compound preparation using chlorine-free reagents has been of great importance, due to significant applications of phosphorus compounds as reagents in future synthesis. Usually, organophosphorus derivatives are obtained starting from phosphorus trichloride or phosphoryl chloride, although the final products do not have reactive phosphorus–chlorine bonds. In the last period the interest is to replace the halogen-containing compounds with other starting reagents using environmentally safe paths. In this chapter we tried to summarize the aspects of using hypophosphorous acid and its salts as reagents for organophosphorus compounds. The chapter is focused on the synthesis of α-aminophosphinic acid, α-aminophosphinates, H-phosphinic acids, and H-phosphinates. These reactions are discussed in classical conditions and, as microwave-assisted synthesis, in the presence or absence of metal catalysts or reaction solvents. Phosphonate metal organic frameworks are an important class of materials, which achieves dramatic growth in the last 15 years. Therefore a brief overview of the reactivity of phosphinic acids used to obtain phosphonic acids is provided.

Keywords Organophosphorus compounds • Chlorine-free reagents • Hypophosphorous acid

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4.1 Introduction

Phosphorus, a combination of two Greek words *phos* and *phorus* which means light bringing, was the first element discovered in 1669 by Hennig Brand in the most unusual manner, by boiling 60 buckets of urine. Phosphorus is the eleventh element in order of abundance in the earth's layer because the phosphate rocks, the source of phosphorus , occupy about 0.1 % of the earth's crust, and it does not exist in the elemental form [1].

Hypophosphorous acid is a colorless compound with low melting point (m.p. 26.5 °C); is soluble in water, alcohols, and dioxane; and usually is supplied as a 50 % aqueous solution [2]. The formula for hypophosphorous acid is generally written H_3PO_2, but a more adequate presentation is $HOP(O)H_2$ which highlights its monoprotic character. The hypophosphorous acid salts are called phosphinates (hypophosphites) [3]. $HOP(O)H_2$ (major tautomer, sometimes called phosphinic acid) exists in equilibrium with another tautomer $HP(OH)_2$ (sometimes called hypophosphorous acid) having minor compounds as outcome. It is proposed and the third structure $H^+(H_2PO_2)^-$.

The first structure, $H_2P(=O)–(OH)$, having one hydroxyl group, a phosphoryl oxygen, and two P–H bonds, i.e., a pentavalent phosphorus atom, was the result of the NMR study by spin–spin splitting of aqueous H_3PO_2 solutions [4]. The second structure, $H–P(OH)_2$, containing two hydroxyl groups attached to a trivalent phosphorus atom, was suggested on measurements of magnetic susceptibility of several inorganic and organic phosphorus compounds [5].

$H^+(H_2PO_2)^-$ structure was suggested on the basis of a Raman study of several oxygen-containing phosphorus compounds [6].

In industry the acid is prepared via a two-step process. The hypophosphite salts of alkali and alkaline earth metals result from the treatment of white phosphorus with hot aqueous solution of the appropriate hydroxide followed by treatment with a strong acid such as sulfuric acid.

$$P_4 + 3\,OH^- + 3\,H_2O \rightarrow 3\,H_2PO_2{}^- + PH_3 \tag{4.1}$$

When phosphine is prepared from the reaction of white phosphorus and a base, the remaining solution contains the $H_2PO_2{}^-$ ion (Eq. 4.1). If barium hydroxide $Ba(OH)_2$ is used as base and the solution is acidified with sulfuric acid, barium sulfate, $BaSO_4$, precipitates and an aqueous solution of hypophosphorous acid results (Eq. 4.2).

$$Ba^{2+} + 2H_2PO_2^- + 2H_3O^+ + SO_4{}^{2-} \rightarrow BaSO_4 + 2H_3PO_2 + 2H_2O \tag{4.2}$$

Alternatively, H_3PO_2 can be obtained by the oxidation of phosphine with iodine in water (Eq. 4.3).

$$PH_3 + 2I_2 + 2H_2O \rightarrow H_3PO_2 + 4I^- + 4H^+ \qquad (4.3)$$

The pure acid cannot be isolated simply by water evaporation because hypophosphorous acid can easily oxidize to phosphoric acids (and elemental phosphorus) and its disproportionation to phosphine and phosphorous acid. To obtain pure acid, the extraction of its aqueous solution by diethyl ether can be used [7].

Another way is to pass direct current, through the insoluble anode to cathode in electrical contact with the aqueous solution to generate H^+, to form hypophosphorous acid solution. The process is simple, inexpensive, and highly efficient. The production is environmentally friendly without wastewater and residue [8].

Hypophosphorous acid and its sodium salt (sodium hypophosphite) are used as powerful reducing agents in various fields:

- Pharmaceutical aid as antioxidant
- Retrieval of nonferrous metals
- Component of electroless plating solutions
- Water treatment agent
- Meat preservative
- Prevent the discoloration of polymers
- Production of chemicals

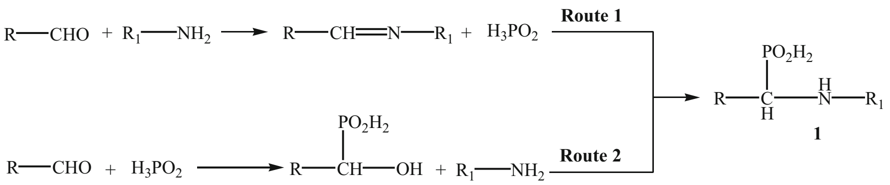
In this chapter we will discuss about hypophosphorous reagent in the synthesis of other organophosphorus compounds, being a special case of free chlorine phosphorus derivative, and will not discuss about the use of hypophosphorous acid as a reducing agent. Since H_3PO_2 is extensively used in a variety of functional group transformations, we will describe the reaction of H_3PO_2 with amines, alcohols, alkenes, and alkynes.

4.1.1 Synthesis of α-Aminophosphinic Derivatives

In the literature two mechanisms are described in order to obtain 1-aminophosphinic acid or 1-aminophosphinates (**1**). The mechanisms are described in Scheme 4.1 following two different routes:

Route 1 indicates a nucleophilic attack of an amine at the carbonyl bond of an aldehyde which leads to the formation of a Schiff base. The formed Schiff base reacts with the hypophosphorous acid with the formation of azomethine bond.

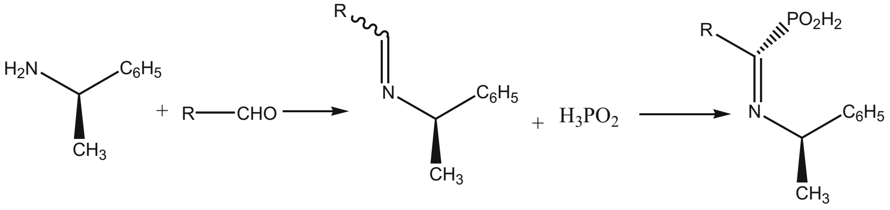
Route 2 indicates in the first step the attack of hypophosphorous acid to an aldehyde forming the α-hydroxyphosphinic acid, which undergoes a nucleophilic substitution, and its transformation into α-aminophosphinic acid [9, 10].



Scheme 4.1 Two routes for the synthesis of 1-aminophosphinic acids

4.1.1.1 α-Aminophosphinic Acid via Schiff-Based Intermediates: Route 1

Lewkowski and coworkers have investigated the reactions of six model Schiff bases using route 1: *N*-furfurylidene (**2a**), *N*-benzylidene (**2b**), *N*-cyclohexylmethylidene (**2c**), *N*-*p*-nitrobenzylidene (**2d**), *N*-*o*-methoxybenzylidene (**2e**), and *N*-(3-phenylallylidene) (**2f**). The reactions of heteroaromatic, aromatic, α,-β-unsaturated, and aliphatic aldehydes depicted in Eq. 4.4 were studied.



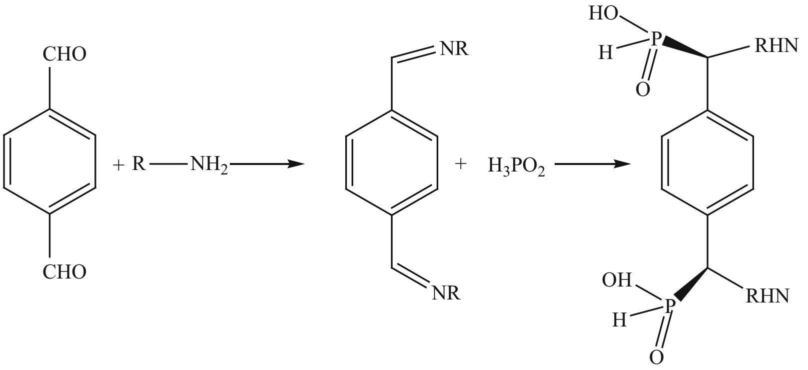
2 a-f **3 a-f**

R= **a** 2-Furyl; **b** C_6H_5; **c** *c*-C_6H_{11}; **d** *p*-$NO_2C_6H_4$; **e** *o*-CH_3O-C_6H_4; **f** C_6H_5-CH=CH

(4.4)

In all cases the addition of hypophosphorous acid to the azomethine bond of the *N*-(*R*)-α-methylbenzyl Schiff bases lead to only one diastereoisomeric form (**3a-f**), proved by ^{1}H and ^{31}P-NMR spectroscopy. From optical rotation values and compared with literature data [11], the exclusively formed diastereoisomer involves the formation of S configuration around the recently formed chirality center.

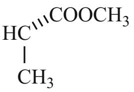
Following the mechanism proposed in route 1, terephthalic Schiff bases were obtained which are followed by the nucleophilic addition of hypophosphorous acid to form 1,4-phenylene-bis-*N*-alkyl-aminomethanephosphinic acids in yields varying from 40 to 90 % (Eq. 4.5) [12].



4 a-k

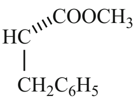
R= **a** -$CH_2C_6H_5$; **b** CH_2Furfuryl; **c** -$C(CH_3)_3$; **d** -$CH(C_6H_5)_2$; **e** *p*-$CH_3OC_6H_4$; **f** *m*-$CH_3OC_6H_4$

g *p*-$CH_3C_6H_4$; **h** *m*-$CH_3C_6H_4$; **i**



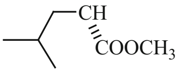
$CH(CH_3)COOCH_3$

; **j**



$CH(CH_2C_6H_5)COOCH_3$

; **k**



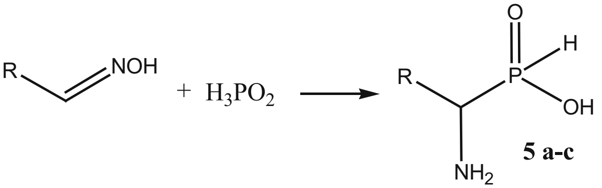
(4.5)

The addition of hypophosphorous acid to achiral *N*-alkyl terephthalic imines was described in the literature [13] to be 100 % selective and leads to a *meso*-form, while in the reactions carried out on *N*-aryl imines, the dependence of the substituent nature on aromatic ring has been observed [12, 14].

Analyzing the obtained aminophosphinic acids (**4a–k**), it was observed that the addition reaction is not diastereospecific for all cases. One diastereoisomer formation was observed for four reactions: N-benzyl (**4a**), *N*-tert-butyl (**4c**), *N*-benzhydryl (**4d**), and *N*-*p*-methoxyphenyl (**4e**). Pairs of diastereoisomers were formed for *N*-furfuryl-substituted product (**4b**), *Nm*-methoxyphenyl (**4f**), *N*-*p*-methylphenyl (**4 g**), and *N*-*m*-methylphenyl (**4 h**) in the following R:S ratio: 1:1, 5:2, 2:1, and 3:1, respectively. ^1H and ^{31}P-NMR spectroscopy demonstrated that the acids (**4i–k**) were formed as a mixture of all three possible diastereoisomeric forms in a 2:1:1 ratio. Because of this no chiral assistance occurred in this situation.

4.1.1.2 α-Aminophosphinic Acid via Oximes

Another way to obtain α-aminophosphinic acid is the reaction of H_3PO_2 with oximes [15]. The addition of hypophosphorous acid to aldoximes gives (α-aminoalkyl)phosphinic acids (Eq. 4.6).



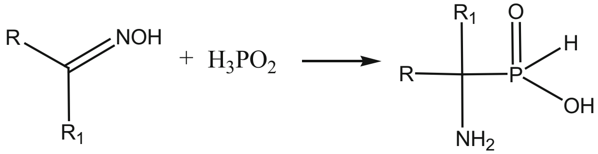
5 a-c

(4.6)

R= **a** CH_3; **b** *i*-Pr; **c** *i*-Pr-CH_2

The addition of H_3PO_2 at the C = N bond is preceded by the reduction of the N–O bond. This mechanism of N–O bond reduction followed by H_3PO_2 in addition to the imine double bond is expected to occur in the formation of (α-aminoalkyl) phosphinic acids. The phosphinic analogues of alanine (**5a**), valine (**5b**), and leucine (**5c**) were obtained in moderate yields ≈ 50 %.

Osipova and coworkers demonstrated that the reaction of H_3PO_2 with aliphatic ketoximes, including functionally substituted ketoximes, and with acetophenone oxime occurs fairly smoothly to give the corresponding amino phosphinic acids in 13–50 % yields (Eq. 4.7). Lower yield was obtained only for the compound (**6a**) about 5.6 % [16].



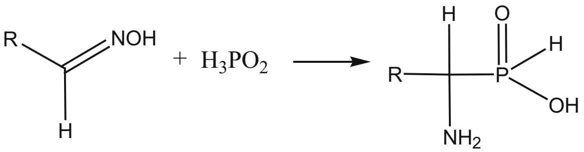
6 a-f

(4.7)

	a	**b**	**c**	**d**	**e**	**f**
R	CH_3	CH_3	CH_3	C_4H_8	CH_3	$CH_2{=}CHCH_2OCH_2$
R_1	CH_3	C_2H_5	C_6H_5	C_4H_8	$CH_3SCH_2CH_2$	$CH_2{=}CHCH_2OCH_2$

The structures of the synthesized aminophosphinic acids were confirmed by their ^{1}H NMR and mass spectroscopy. It was observed that a twofold excess of H_3PO_2 favors an increase in the yield of the products.

Belyankin and coworkers [17] have for the first time demonstrated that the reaction of aryl and aralkyl aldoximes could be transformed into the corresponding α-aminophosphinic acids (**7a–c**) under the action of H_3PO_2.

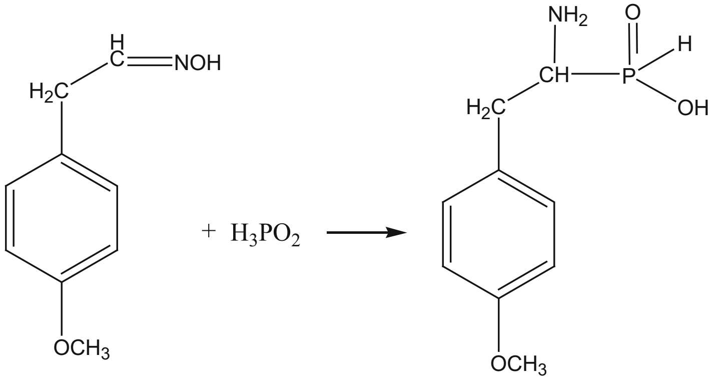


7 a-c

(4.8)

R= **a** $C_6H_5CH_2$; **b** 3,4-$(OH)_2$-C_6H_3; **c** C_6H_5

The yields of aminophosphinic acids formed depend on the reaction conditions. For the synthesized compounds, the yield varied between 26 and 56 %.



8

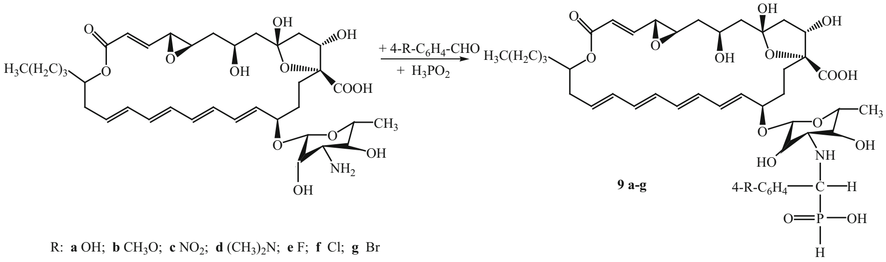
(4.9)

It was observed that the reaction carried out in methanol gives good yields which are improved by the use of a high excess (tenfold) of H_3PO_2 and the exclusion of the solvent in the case of benzaldoxime (**8**) (Eqs. 4.8, and 4.9).

4.1.1.3 Antibiotic Formation

The wide use of polyene macrolide antibiotics in clinical practice [18] as potential antimycotics is promising, and therefore, the researchers search different ways to synthesize these compounds in good yields. Derivatives of lucensomycin and pimaricin will be described.

Belakhova and coworkers studied the reaction of polyene macrolide antibiotic lucensomycin with aromatic aldehydes and hypophosphorous acid. In the first stage an addition of primary amino group of carbohydrate unit of lucensomycin molecule occurs to a carbonyl group of aromatic aldehyde with the formation of azomethine intermediate, following the presented route 1 [19]. In the second stage the interaction of hypophosphorous acid at a C = N bond of the azomethine intermediate occurs to form hydrophosphoryl derivatives of lucensomycin (**9a–g**). Hypophosphorous acid, a phosphorylating compound, was used in the reaction with the following aldehydes: 4-hydroxybenzaldehyde (**a**), 4-methoxybenzaldehyde (**b**), 4-nitrobenzaldehyde (**c**), 4-(dimethylamino) benzaldehyde (**d**), 4-fluorobenzaldehyde (**e**), 4-chlorobenzaldehyde (**f**), and 4-bromobenzaldehyde (**g**) (Eq. 4.10).

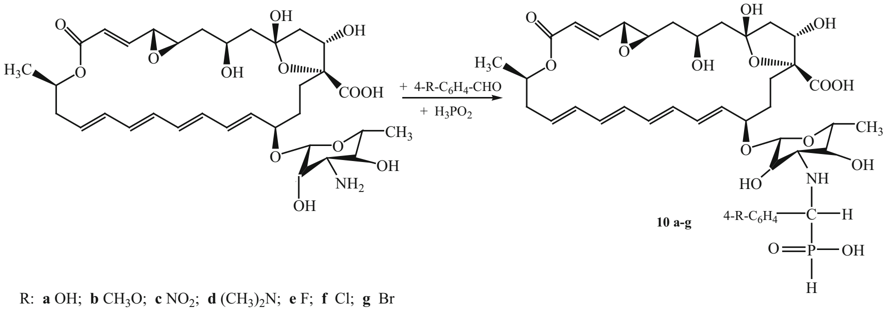


R: **a** OH; **b** CH_3O; **c** NO_2; **d** $(CH_3)_2N$; **e** F; **f** Cl; **g** Br

(4.10)

The resulting products of lucensomycin (**9a**–**g**) are solid crystalline compounds of white or cream color. The structure of the derivatives is established by ^1H, ^{13}C, ^{31}P-NMR, IR, and UV spectroscopy. Reactions of the polyene macrolide antibiotic pimaricin with aromatic aldehydes and hypophosphorous acid are shown to afford pimaricin hydrophosphoryl derivatives. Physicochemical and biological properties of these compounds were investigated [20]. The biological studies show that the pimaricin hydrophosphoryl derivatives are low-toxic agents holding a high antifungal activity.

It was shown that pimaricin reacts with aromatic aldehydes and hypophosphorous acid to form hydrophosphoryl derivatives of the antibiotic. The studied reaction is a variety of the Kabachnik–Fields reaction [21]. In the first step, the primary amino group of the pimaricin carbohydrate is added to the carbonyl group of the aromatic aldehyde to form an azomethine intermediate. In the second step, hypophosphorous acid reacts at the C = N bond of the azomethine fragment to afford pimaricin hydrophosphoryl derivatives (**10a–g**). The phosphorylation agent used was hypophosphorous acid (Eq. 4.11).



R: **a** OH; **b** CH_3O; **c** NO_2; **d** $(CH_3)_2N$; **e** F; **f** Cl; **g** Br

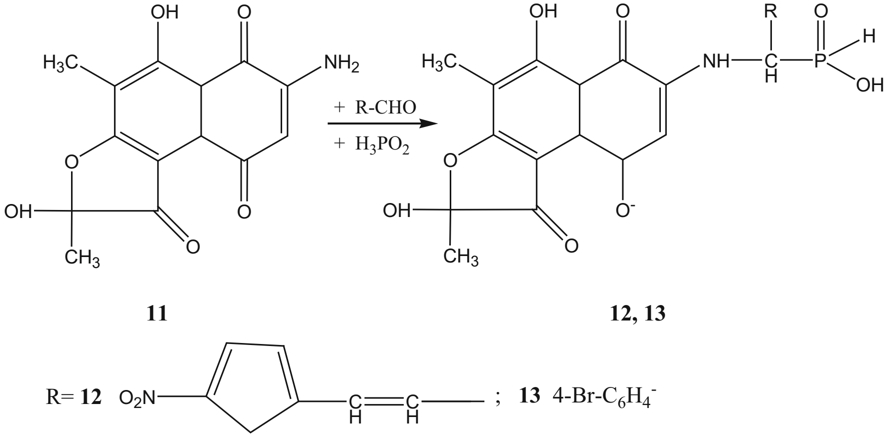
(4.11)

The following aromatic aldehydes were used in this work: 4-hydroxybenzaldehyde (**a**), 4-methoxy-benzaldehyde (**b**), 4-nitrobenzaldehyde (**c**), 4-(dimethylamino)benzaldehyde (**d**), 4-fluorobenzaldehyde (**e**), 4-chlorobenzaldehyde (**f**), and 4-bromobenzaldehyde (**g**). Pimaricin derivative

(**10a–g**) structure was confirmed using ^{1}H, ^{13}C, ^{31}P-NMR, FT-IR, and UV spectroscopy.

Known organophosphorus antibiotics of both natural origin (phosphomycin, macarbomycin, diumycin) and semisynthetic origin (derivatives of penicillin, lincomycin, asparagine) were obtained by the chemical modification of biosynthetic products. This is a fruitful method for the preparations of medicinal compounds.

Yudelevich and coworkers used this method in the synthesis of new organophosphorus derivatives based on 2-amino-1,4-naphthoquinone chromophore (**11**), a known product of the hydrolysis of the rifamycin S antibiotic. In the reaction of 2-amino-1,4-naphthoquinone chromophore with hypophosphorous acid and aldehydes, N-substituted 1-aminoaryl-(heteryl)methanephosphonous acids are formed with an unpaired electron at the oxygen atom in the 1-position of the aromatic ring, as confirmed by EPR spectra [22].



(4.12)

The compounds were synthesized in about 18 % (**13**) and 25 % (**12**) yield.

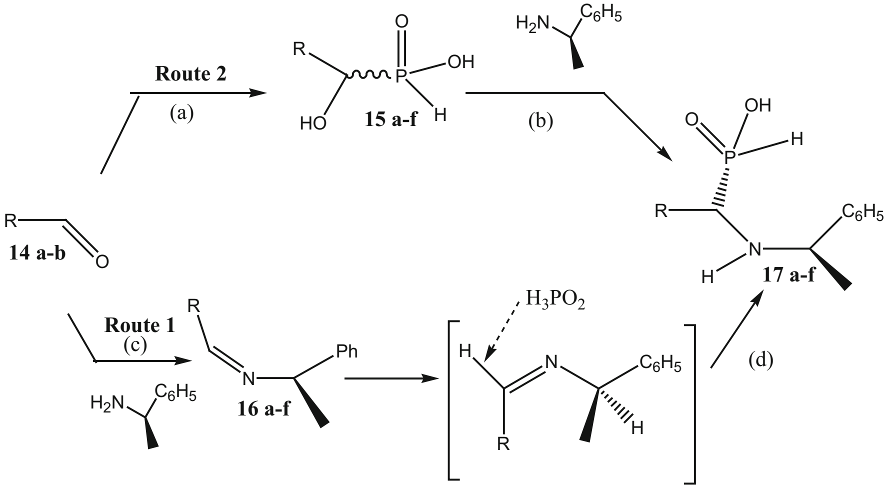
4.1.1.4 α-Aminophosphinic Acid via 1-Hydroxyphosphinic Acid Intermediates: Route 2

In order to explain the stereochemistry of this reaction mechanism, both routes were investigated using PM3 and AM1 semiempirical methods [23]. The addition of the chiral α-methylbenzylammonium hypophosphite to an aldehyde was investigated regarding the stereoselectivity. Both mechanisms (the first allowing the formation of α-hydroxy phosphonous acids as intermediate (route 2) followed by the nucleophilic substitution with a chiral amine and the second allowing the formation of a Schiff base (route 1) followed by the addition of hypophosphorous acid to an azomethine bond) were investigated by semiempirical method using the Molecular Dynamics protocol in a MM2 packet included in the ChemOffice 7.0. The semiempirical theoretical studies were investigated using the previous experimental studies available in literature [11, 24].

Minima of all experimentally obtained RS diastereoisomers (**17a–f**) as well as all supposed RR diastereoisomers (**17a–f**), starting aldehydes (**14a–f**), the α-hydroxyphosphonous acids as intermediate (**15a–f**), Schiff bases (**16a–f**), (*R*)-α-methylbenzylamine, hypophosphorous acid, and water were searched by the use of Molecular Dynamics protocol in a MM2 packet included in the ChemOffice 7.0. Geometries of resulting models were optimized by the use of the AM1 and PM3 methods. Semiempirical RHF PM3 and AM1 computations were performed using GAMESS for ChemOffice 7.0 pack (Scheme 4.2).

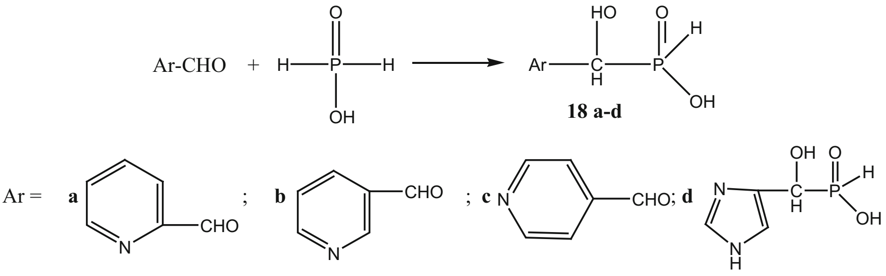
The computational data taken from PM3 semiempirical method demonstrated that differences in total energies among diastereoisomers RS **(17a–f)** and RR **(17a–f)** of acids varied from (3.8 to 6.3) kcal·mol^{-1}, i.e. (15.9 to 26.4) kJ·mol^{-1}. The geometric predictions of bond lengths and angles by PM3 methods proved to be better than those of AM1 method. The analysis of the total energies achieved using the AM1 method gave results much more consistent with the experimental results.

Olszewski and coauthors [25] developed an easy and efficient method for the synthesis of (α-hydroxymethyl)phosphinic acids in a pyridine and imidazole series from their corresponding aldehydes and 50 % aqueous hypophosphorous acid. The synthesized phosphinic acids (**18a–d)** are illustrated in Scheme 4.2. The obtained pure (α-hydroxymethyl)phosphinic acid (**18a–d)** products were isolated in good yields of 32–55 %, calculated after crystallization from methanol. The obtained compounds (**18a–d)** were racemic mixtures due to the presence of a chiral carbon atom attached to a pseudoasymmetric phosphorus atom (Eq. 4.13).



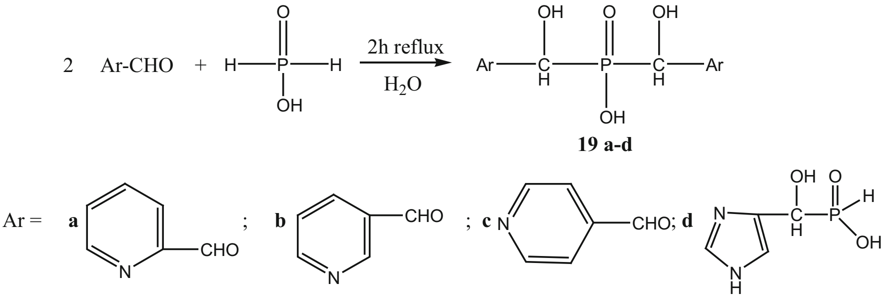
R: **a** *i*-Pr; **b** *i*-Bu; **c** C_6H_5; **d** $CH_2C_6H_5$; **e** 2-Furyl; **f** *c*-C_6H_{11}

Scheme 4.2 Semiempirical computational calculation



(4.13)

Varying the molar ratio of reagents from 1:1 to 2:1, heterocyclic bis(-α-hydroxymethyl)phosphinic acids (**19a–d**) were synthesized. From the preparation of (α-hydroxymethyl)phosphinic acids, the authors found that besides (**18a–d),** also small amounts of the corresponding bis(α-hydroxymethyl)phosphinic acids were formed. For that reason, the molar ratio of reagents to obtain heterocyclic bis (α-hydroxymethyl)phosphinic acids (**19a–d**), as exemplified in Eq. 4.14, was modified. The yield of the synthesized pure bis(α-hydroxymethyl)phosphinic acids (**19a–d**) was between 30 and 87 %.

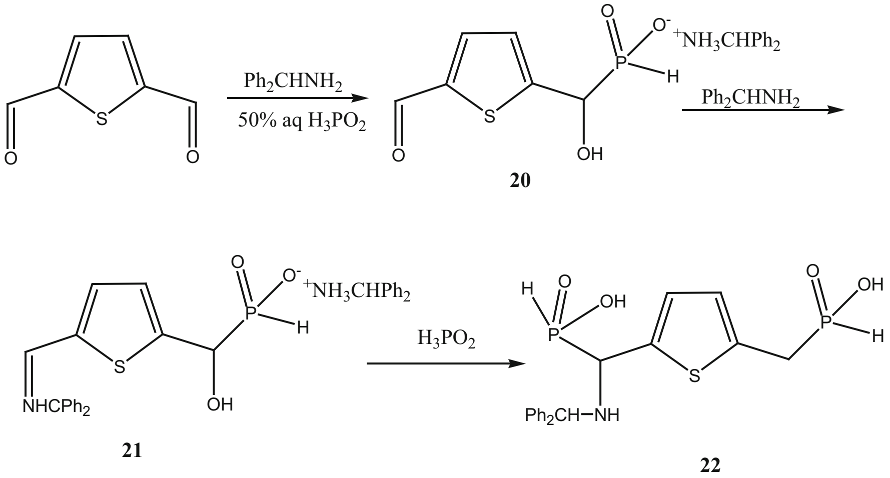


(4.14)

The thermal hydrophosphinylation of aldehydes with the highly unstable methyl phosphinate, produced in situ from anhydrous H_3PO_2 and methyl orthoformate, was first reported in the literature by Fitch in 1964 [24].

Preparation of α-amino-H-phosphinic acids consists usually of heating anhydrous hypophosphorous acid with a Schiff base and Mannich-type reactions of amines with aldehydes and anhydrous hypophosphorous acid [11]. Using this method Hamilton and coworkers obtained pure diastereoisomers by reaction of hypophosphorous acid salts of (R)(+) or (S)(−) – N-α-methylbenzylamine with aldehydes.

The first direct structural information on the α-hydroxyalkylphosphinate class of compounds were provided by reaction of 2,5-diformylthiophene with Ph_2CHNH_2 and hypophosphorous acid depending on reaction conditions [26]. The presence of the α-hydroxy group in compound (**20**) was confirmed by X-ray structure analysis



Scheme 4.3 Synthesis of α-aminoalkylphosphinate derivative

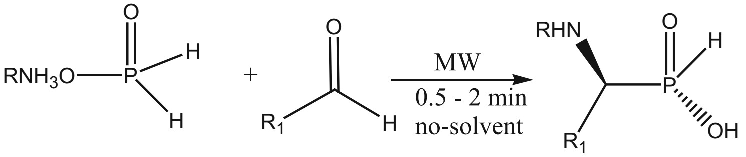
of the (diphenylmethyl)ammonium salt and the structure of the ions. Those are linked by a hydrogen bond between one of the phosphinate oxygen atoms and a proton of the ammonium cation at 1.86 Å(0.186 nm) distance.

The capability to derivatize only one of the two aldehyde groups to afford the mono(α-hydroxyalkylphosphinate) opens up the possibility that the leftover carbonyl group can be used in further reaction with an amine [e.g., Scheme 4.3, compound (**21**)]. This second carbonyl group can be used in various coupling to biological macromolecules or polymers for selective metal complexation applications. The addition of hypophosphorous acid to the mono-imine derivative (**21**) converts the imine to the α-aminoalkylphosphinate. In the presence of excess, hypophosphorous acid reduces the α-hydroxy functional group to yield compound (**22**).

4.1.1.5 α-Aminophosphinic Acids Under Microwave Irradiation

The use of microwave energy to accelerate organic reactions is of growing interest and presents numerous advantages over conventional techniques [27, 28]. Aminoalkylphosphinic acids, the phosphinic acid analogues of 1-amino carboxylic acids, are important compounds that exhibit a variety of interesting and useful properties. In contrast to the widely studied α-aminoalkylphosphonic acid derivatives [29, 30], relatively a few papers have reported on the chemistry of 1-aminoalkylphosphinic acids. There are quite a few evidences that prove the α-aminophosphinic acids are pharmacologically active compounds.

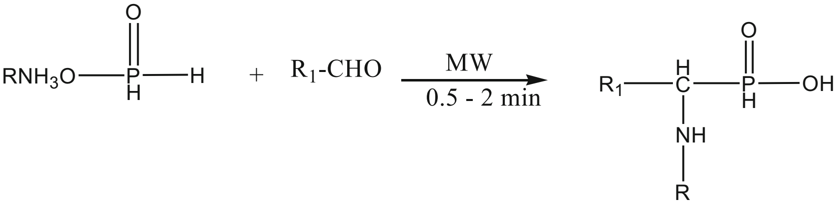
A more efficient technique to prepare α-aminophosphinic acid consists in the reaction of hypophosphorous salts [31] with aldehydes under microwave irradiation. The advantages of using the microwave method are as follows: short reaction time, solvent-free reaction, and avoidance of the problems associated with handling anhydrous H_3PO_2 [32].



(4.15)

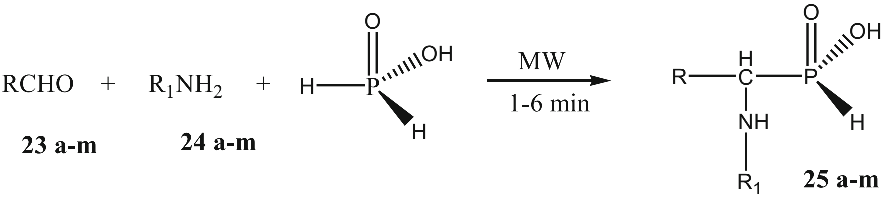
R= Ph; Cy; (R)-(+)-1-phenylethyl-
R_1= Aryl; Alkyl

Kaboudin and coworkers developed a simple and efficient method for the synthesis of α-aminophosphinic acids from hypophosphorous acid under solvent-free conditions using microwave irradiation. α-Aminophosphinic acids were obtained in high yield under mild conditions by reaction of hypophosphorous acid with various aldehydes in the presence of amines under microwave irradiation (Eq. 4.16) [33].



(4.16)

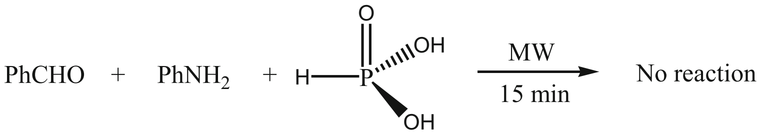
In the same research group, the convenience of microwave-assisted reactions for the synthesis of different organophosphorus compounds was explored [34, 35]. - One-pot reaction for the preparation of α-aminoalkylphosphinic acids from a mixture of aldehyde and amine was performed in the presence of hypophosphorous acid under microwave irradiation in solvent-free conditions for 1–6 min depending on the reagent (Eq 4.17).



(4.17)

Entry	**R**	**R_1**	**Entry**	**R**	**R_1**
a	C_6H_5-	C_6H_5-	**h**	2-$C_{10}H_7$-	p-$O_2NC_6H_4$-
b	p-$CH_3C_6H_4$-	C_6H_5-	**i**	o-$CH_3C_6H_4$-	o-$CH_3OC_6H_4$-
c	1-$C_{10}H_7$-	C_6H_5-	**j**	p-FC_6H_4-	o-$CH_3OC_6H_4$-
d	p-$(CH_3)_2CHC_6H_4$-	m-$O_2NC_6H_4$-	**k**	m-$CH_3C_6H_4$-	1-$C_{10}H_7$-
e	m-FC_6H_4-	m-$O_2NC_6H_4$-	**l**	m-$CH_3OC_6H_4$-	1-$C_{10}H_7$-
f	p-ClC_6H_4-	m-$O_2NC_6H_4$-	**m**	C_6H_5-CH = CH-	C_6H_5-
g	m-$CH_3OC_6H_4$-	p-BrC_6H_4-			

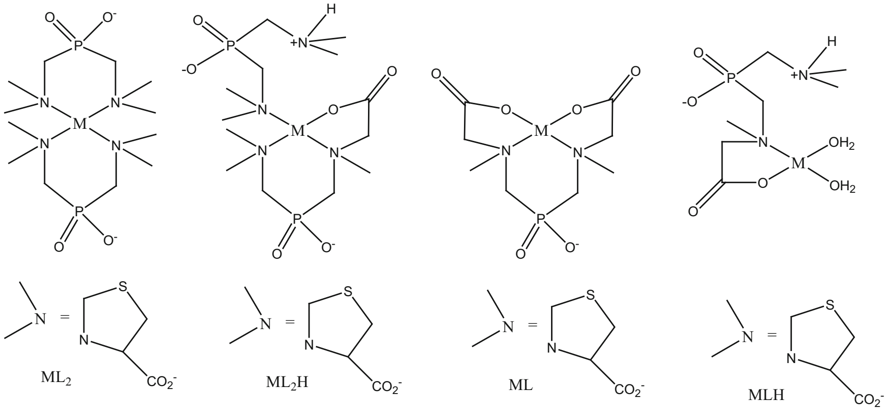
Synthesis, which normally requires a long reaction time, can be achieved conveniently (58–79 % yields) and quickly (1–6 min) in a microwave oven obtaining the compounds (**25a–m**). The first reaction, one-pot mixture of benzaldehyde (**23a**), aniline (**24a),** and hypophosphorous acid , was selected as a model reaction for the one-pot synthesis of 1-aminophosphinic acid (**25a)** under microwave irradiation. This reaction afforded the product (**25a**) in 79 % yield. The strong electron-withdrawing property of the nitro group in p-nitroaniline (**24 h**) decreases the nucleophilicity of the amine group. A mixture of p-nitroaniline and 2-naphthaldehyde (**23 h**) in the presence of hypophosphorous acid under microwave irradiation gives α-aminophosphinic acid (**25 h)** in 66 % yield. Starting from these promising results, the reaction was performed replacing the hypophosphorous acid with phosphorus acid. As first trial, the reaction of benzaldehyde with aniline (**24a)** in the presence of phosphorus acid was carried out under microwave irradiation (Eq. 4.18).



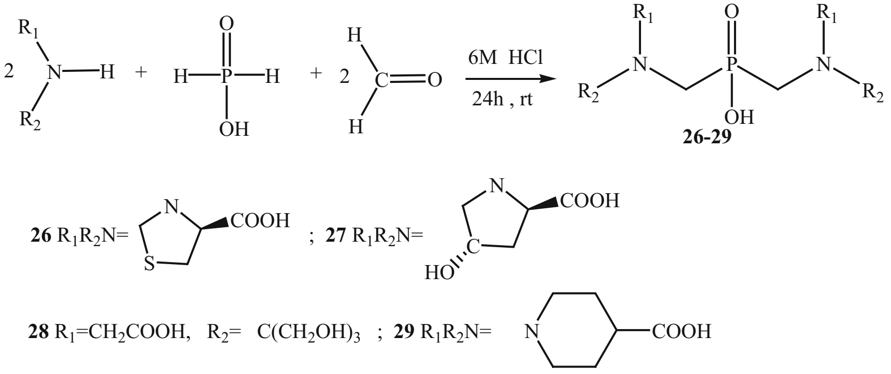
(4.18)

Unfortunately, after 15 min of irradiation, the reaction was stopped and no product was detected.

α-Aminophosphinic acids are phosphorus analogues of natural amino acids and are selective inhibitors of various proteolytic enzymes, particularly metalloproteases [36]. Starting from N,N-bis(phosphinomethyl)amines, new α-amino-H-phosphinic acid containing two phosphinic moieties with C2-symmetry axis was reported in Eq. 4.19. Physical and chemical properties to identify their potential complexation properties (Scheme 4.4) of this new compounds were investigated [37, 38].

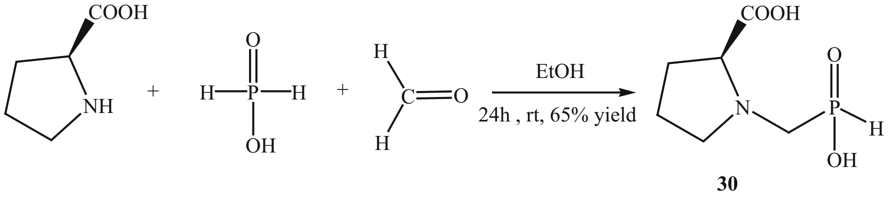


Scheme 4.4 Proposed structures of complexes



(4.19)

The aminophosphinic acid ligand **30** was synthesized via Mannich-type reaction (Eq. 4.20). For this a modified procedure of a known reaction was used [39].



(4.20)

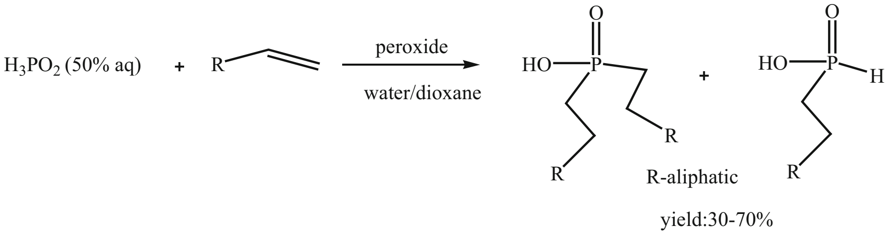
The novel chiral ligand of bis(aminomethyl)phosphinic acids (**26–30)** was treated with transition metals such as Co^{2+}, Ni^{2+}, Zn^{2+}, Fe^{2+}, Cu^{2+}, and Cd^{2+} and lanthanide ions such as La^{3+} and Gd^{3+} in aqueous solution. The stabilizing capability of formed complexes was investigated by the pH-potentiometric method.

The stability constants of complexes of the following metal ions, Zn^{2+}, La^{3+}, and Gd^{3+}, could not be calculated by pH potentiometry, due to precipitation of these metal ions in the pH range 2–12 in the presence of the ligand (**26**). Best complexation results were obtained with ligand (**26**). Studies on the complexation of other ligands (**27**–**30**) with metal ions did not give significant information [40].

4.1.2 P–C Bond Formation by Reaction of Hypophosphorous Acid and Its Salts, Alkenes and Alkynes

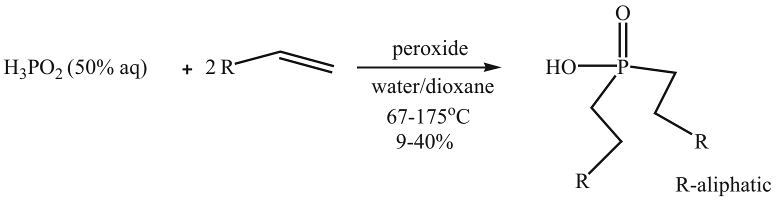
4.1.2.1 Free-Radical Hydrophosphinylation Reactions of Alkenes and Alkynes

The formation of P–C bond represents an important process in phosphorus chemistry. Radical addition of phosphorus-centered radicals and P–C bond forming were known for several decades. Williams and Hamilton reported in 1955 for the first time the addition of aqueous H_3PO_2 to olefins using a peroxide, at high temperatures (Eq. 4.21) [41].

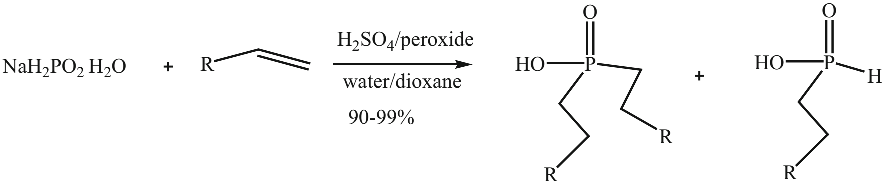


(4.21)

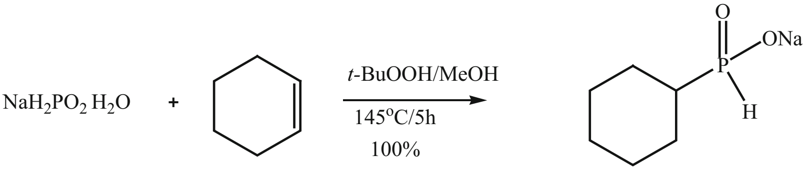
Nifant'ev and coworkers [42, 43] used H_3PO_2 or sodium or potassium hypophosphite salts which were added to alkenes and alkynes in the presence of peroxides and mineral or organic acids which enabled lowering the temperature of the reaction by helping the breakdown of the peroxide initiators. The method became one of the most convenient methods for the synthesis of phosphinic acids (Eqs. 4.22, 4.23, and 4.24).



(4.22)



(4.23)

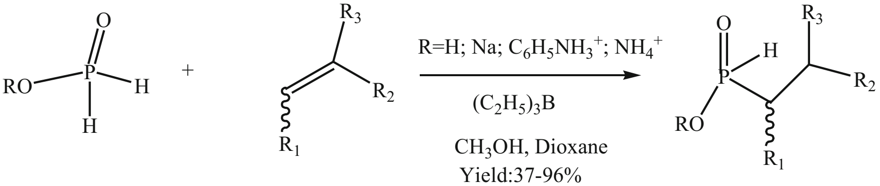


(4.24)

Karanewsky discovered that even AIBN could be used in refluxing EtOH as hydrophosphinylation agent providing a major practical breakthrough in this process [44].

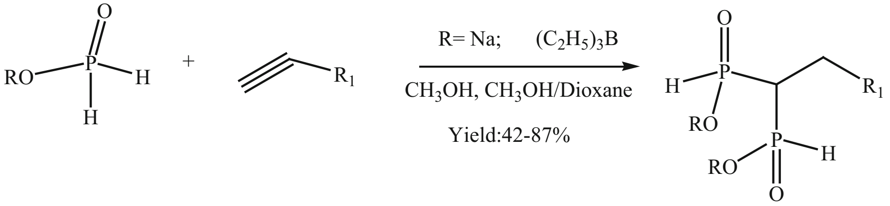
A more efficient approach was reported recently for the free-radical addition of hypophosphorous derivatives to unsaturated compounds **(27, 28)** (Eqs. 4.25, and 4.26). When H_3PO_2, its salts (anilinium hypophosphite (AHP) and $NaOP(O)H_2$), or even alkyl phosphinates are added to alkenes in the presence of Et_3B/O_2 as initiators the reactions occur at room temperature, in an open flask. The mild and neutral conditions of this reaction are in contrast to previous literature conditions [45].

Using hypophosphite salts, the yields of adducts are very high, but the isolation can be difficult with relatively polar alkenes, and at least 0.5 equiv. of Et_3B is required for reproducible results. The choice between hypophosphorous ester and salt will be dictated by the particular reaction.



27

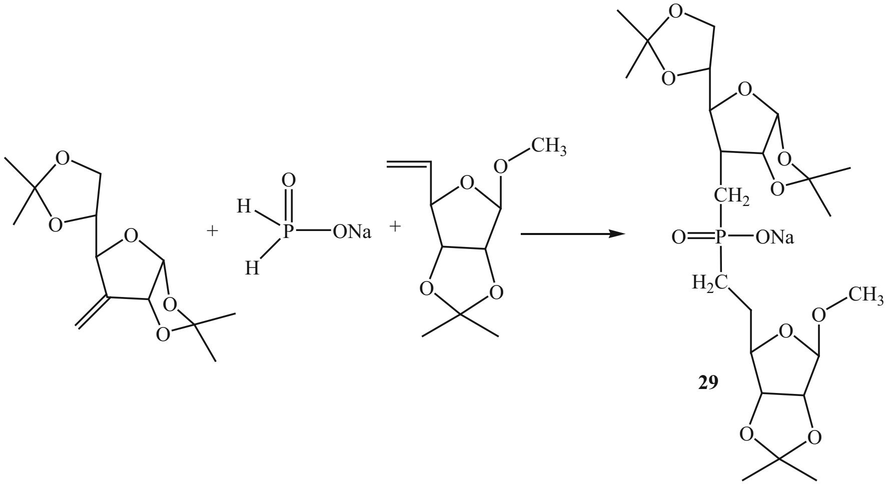
(4.25)



28

(4.26)

When AIBN is used as initiator for hydrophosphinylation of alkenes and alkynes with alkyl phosphinates, the reaction proceeds effectively at 80 °C [46]. The methodology was used by other research groups in the preparation of α,-α-difluoro-H-phosphinic acids [47] or 3-furanosyl-6′-furanosylphosphinate **29** (Eq. 4.27) [48].

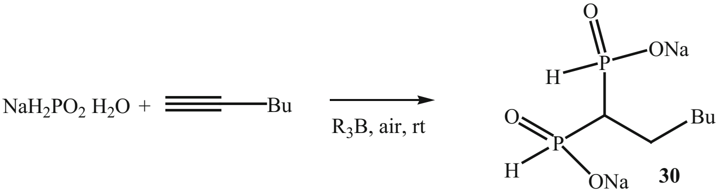


29

(4.27)

The sodium salt of hypophosphorous acid acts as a double radical precursor in a two times, sequential radical addition on 3-*exo*-methylenefuranose derivative 4-ethylenefuranose.

The potential of 1,1-bis-H-phosphinates to function as precursors of bisphosphonates was investigated using as model study the reaction of sodium hypophosphite with 1-hexyne in the presence of Et_3B/O_2. Methanol was selected as solvent, since sodium hypophosphite is almost insoluble in other solvents. 1,1-Bis-H-phosphinate was always obtained as the major product [49]. The 1,1-bis-H-phosphinate disodium salt precipitated from the reaction mixture, allowing easy isolation (Eq. 4.28).



30

(4.28)

Epiandrosterone was reacted with propargyl chloroformate to form the corresponding carbonate in quantitative yield followed by reaction with NaH_2PO_2 which then afforded 1,1-bis-H-phosphinate as a white solid. Oxidation with ozone produced the bisphosphonate–steroid conjugate (Scheme 4.5).

Radical addition of hypophosphorous acid and sodium hypophosphite to unsaturated derivatives of adamantane led to adamantly containing phosphonous and phosphinic derivatives [50].

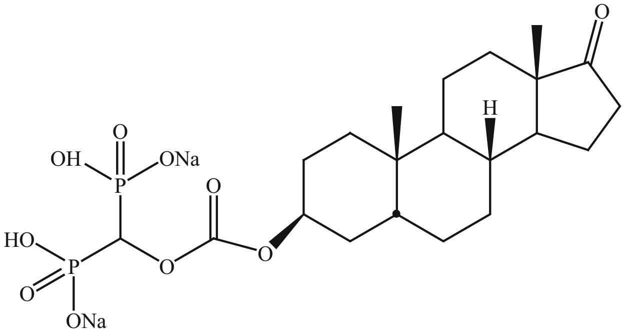
Using *tert*-butyl hydroperoxide as initiator, adamantylalkylphosphonous acids **31, 32** were obtained by heating a mixture of the corresponding unsaturated compound with 50 % aqueous hypophosphorous acid in propan-2-ol (Scheme 4.6).

Reaction of sodium hypophosphite with 2 equivalents of the unsaturated adamantyl compounds was performed in methanol at 120 °C in the presence of *tert*-butyl hydroperoxide and yield sodium salts of bis(adamantylalkyl)phosphinic acids (**33, 34)** which were treated with aqueous hydrochloric acid to give the corresponding phosphonic acids (Scheme 4.7).

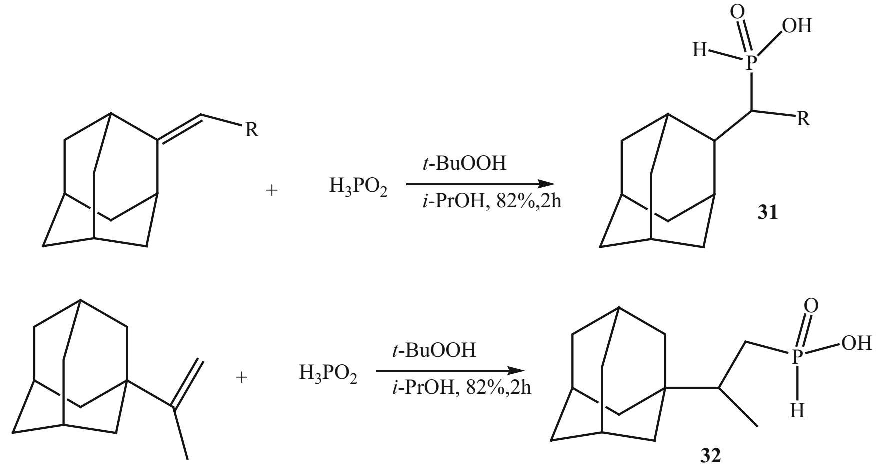
Adamantyl derivatives exhibit antiviral activity against herpes simplex virus, influenza A, respiratory syncytial virus, and adenovirus.

4.1.2.2 Metal-Catalyzed Hydrophosphinylation

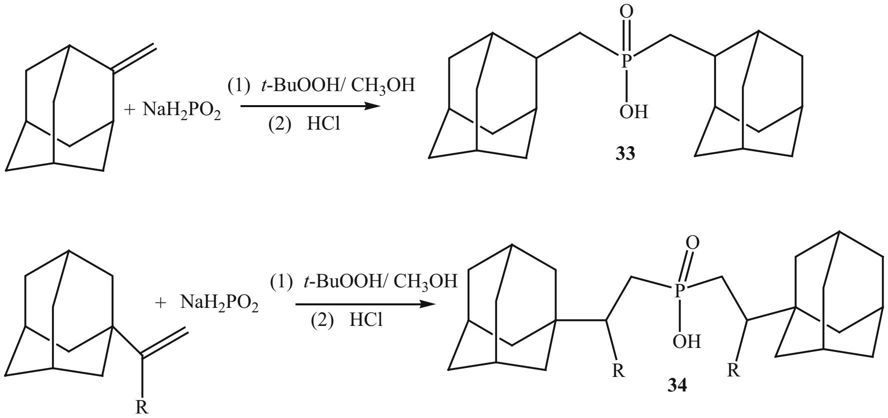
The addition of phosphorus–hydrogen bonds to unsaturated substrates catalyzed by transition metal complexes is already known [51, 52]. The transfer hydrogenation of alkenes, alkynes, aldehydes, ketones, and aryl halides takes place with H_3PO_2 or its sodium and amine salts, under the influence of almost all transition metals



Scheme 4.5 Structure of a steroid–bisphosphonate conjugate

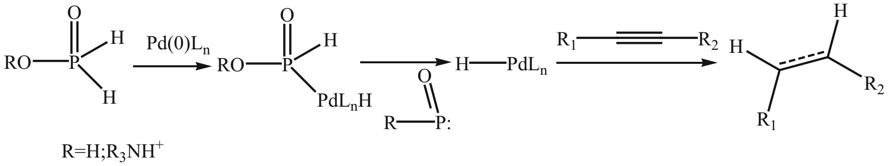


Scheme 4.6 Synthesis of adamantyl-containing phosphinic acids



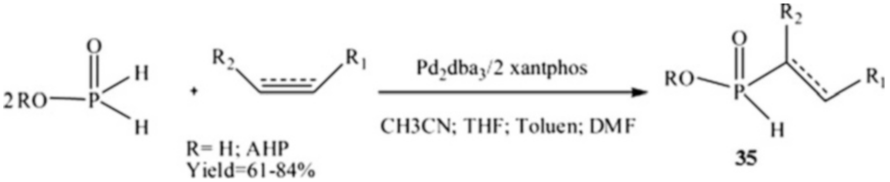
Scheme 4.7 Synthesis of bis(adamantylalkyl)phosphinic acids

[53–56], and the process probably occurs via insertion of the metal into a P–H bond with subsequent formation of a metal hydride, which is the catalytically active reducing agent (Eq. 4.29).



(4.29)

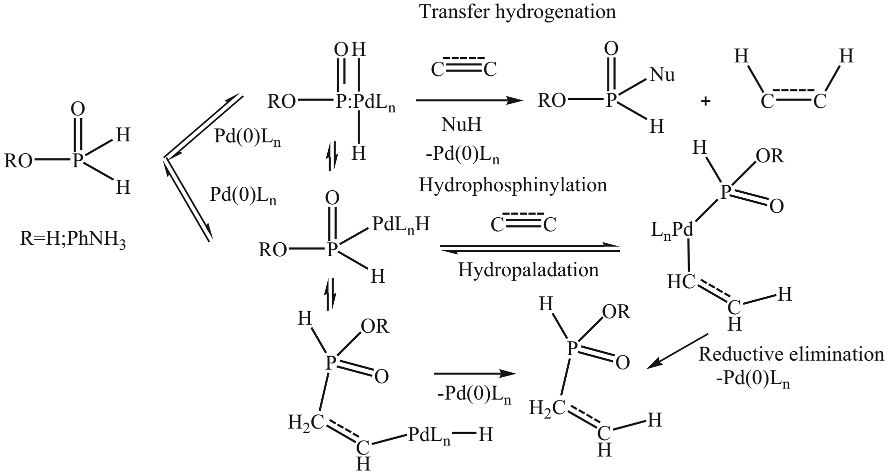
Montchamp and coworkers [57, 58] developed a general Pd-catalyzed addition of H_3PO_2, AHP, and alkyl phosphinates to alkenes and alkynes under homogeneous catalytic conditions when H-phosphinic acid derivatives (**35**) in high yields are obtained (Eq. 4.30).



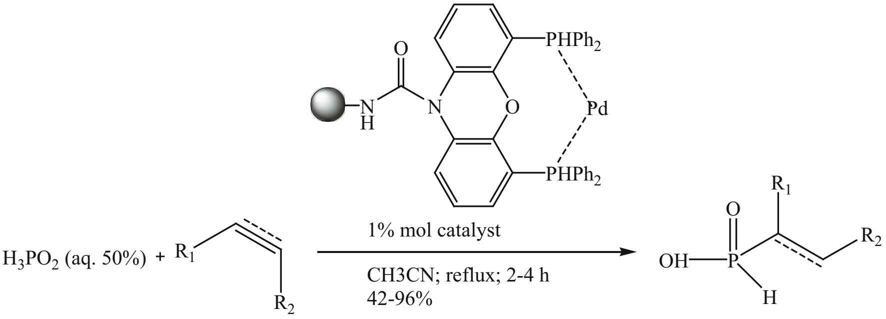
(4.30)

Pd_2dba_3/xantphos is the most useful catalytic system, where loadings as low as 0.02 mol% Pd provide good conversions. The mechanism for this reaction indicates the necessity of a selection of ligands around the Pd center in order to exploit the reactivity of the phosphinyl palladium intermediate before its decomposition to palladium dihydride species, leading the reaction toward addition (Scheme 4.8).

An environmentally friendly process was developed using a recyclable polymer-supported catalyst (Eq. 4.31) [59].

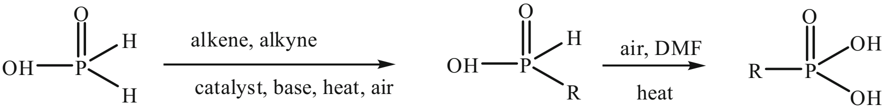


Scheme 4.8 The mechanism of Pd-catalyzed addition of H_3PO_2, AHP, and alkyl phosphinates to alkenes and alkynes



(4.31)

The polymer-supported hydrophosphinylation catalyst is water and air tolerant and gives good yields for a variety of substrates [60].



(4.32)

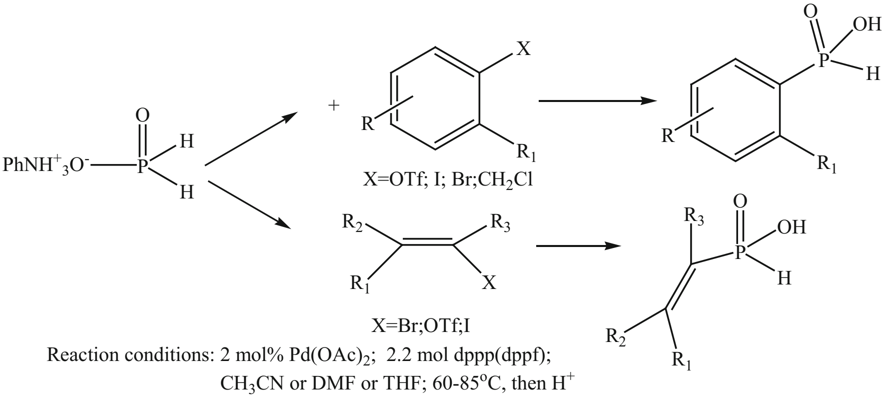
The procedures involving atom-economical and environmentally friendly functionalization reactions of hypophosphorous acid (H_3PO_2) and H-phosphinic acids [RP(O)(OH)(H)] are new ways to obtain phosphonic acids by Pd-catalyzed tandem carbon–phosphorus bond formation–oxidation processes (Eq. 4.32). The influence of the catalyst, solvent, temperature, air, and water was investigated.

4.1.3 Cross-Coupling Reactions with Electrophiles

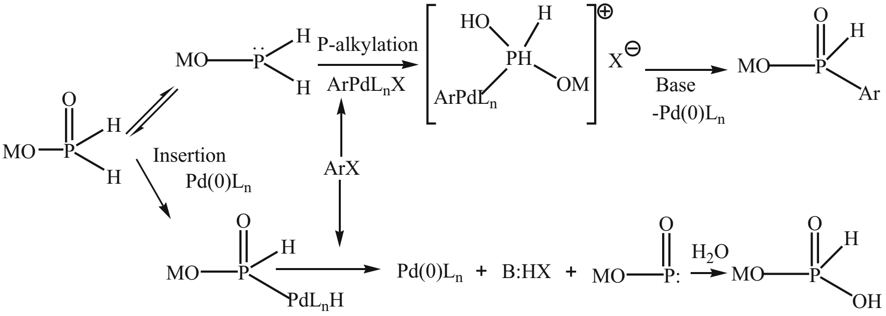
In the past, only a few publications regarding the cross-coupling of hypophosphorous derivatives are found. Holt reported an example of the cross-coupling between triethylammonium hypophosphite and a steroid-derived dienyl triflate [61], and Schwabacher using Fitch's orthoformate method developed a palladium-catalyzed cross-coupling of aryl iodides with methyl or *tert*-butyl phosphinates, which requires anaerobic and anhydrous conditions and is limited to be used with very reactive aryl iodides due to the competing transfer hydrogenation with the rapid thermal decomposition of the alkylphosphinates [24, 62, 63].

Montchamp developed a Pd catalyst for cross-coupling reactions of hypophosphite salts with aryl halides, alkenyl bromides, and triflates (Eq. 4.33) (Scheme 4.9) [32].

The possible mechanism indicates that oxidative addition of the metal into the C–X and P–H bonds is one competitive process and that the ligand around the metal controls the partition between them (Scheme 4.10).



Scheme 4.9 Pd catalyst for cross-coupling reactions

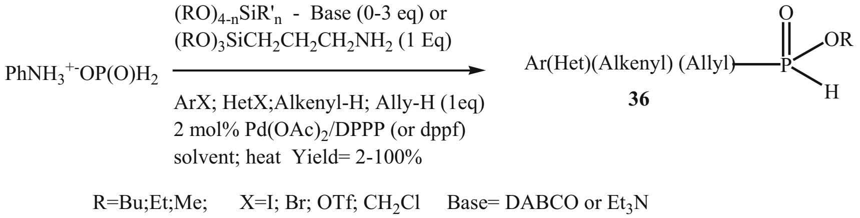


Scheme 4.10 Cross-coupling versus transfer hydrogenation mechanism

The reduction process is decreased when Pd(OAc)$_2$/1,3-bis(diphenylphosphino) propane (dppp) is used as catalyst. In the case of alkenyl electrophiles, steric hindrance due to *Z*-substitution required a ligand switch from dppp to 1,1′-bis (diphenylphosphino)ferrocene (dppf).

Alkenyl bromides and triflates undergo palladium-catalyzed cross-coupling with anilinium hypophosphite to afford monosubstituted phosphinates. The best reaction conditions are observed with Pd(OAc)2/dppp as catalyst, in refluxing tetrahydrofuran or benzene. This reaction is applied to the synthesis of (1,2,3,6-tetrahydropyridin-4-yl)-methylphosphinic acid (TPMPA), a selective competitive antagonist for GABAC receptors. The synthesis proceeds through protected (1,2,3,6-tetrahydropyridin-4-yl)phosphinic acid. This synthetic intermediate can be a precursor to other biologically interesting GABA analogues [64].

Also Montchamp [65, 66] developed a direct cross-coupling of phosphinates with a different aryl, heteroaryl, and alkenyl and even some allylic electrophiles using alkoxysilane method to obtain various H-phosphinates (**36**) as shown in Eq. 4.33.

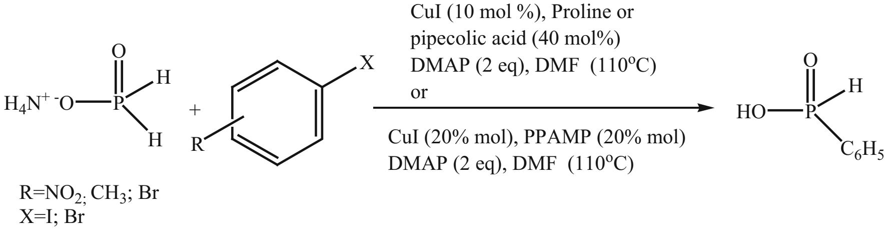


(4.33)

A process for obtaining H-phosphinate esters was developed by employing aminoalkoxysilanes to facilitate the workup and isolation of the products. Alkenyl halides and alkenyl triflates are good substrates for the cross-coupling, whereas allylic compounds apparently react in a reduction–hydrophosphinylation sequence. The reactions cover a broad scope of substrates beyond Schwabacher's aryl iodides and offer a new way to access H-phosphinate esters. The development of a catalytic desymmetrization of alkyl phosphinates for the preparation of P-chiral H-phosphinate esters represents a significant challenge for substrates other than aryl iodides.

Hypophosphorous derivatives ($MOP(O)H_2$, M = H, R_3NH) participate in metal-catalyzed C–P bond-forming reactions with activated allylic electrophiles, dienes, and allenes to avoid or reduce the competitive reductive transfer hydrogenation pathway available to hypophosphorous acid derivatives. The reactions establish an efficient synthetic method, not only to prepare allylic H-phosphinic acids but also their esters via one-pot tandem processes [67].

Another cross-coupling of hypophosphorous compounds is the Cu-catalyzed reaction of ammonium hypophosphite with aryl halides, when CuI and pyrrolidine-2-phosphonic acid phenyl monoester (PPAPM) or CuI and proline or pipecolinic acid is used (Eq. 4.34) [68, 69].



(4.34)

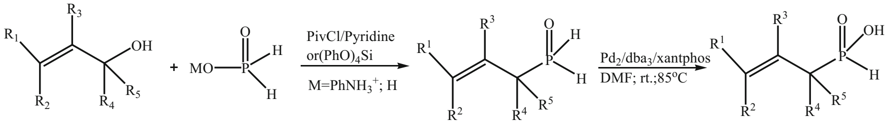
The method can be of practical application for obtaining arylphosphonates, arylphosphinates, and arylphosphine oxides as biological molecules and catalytic ligands containing phosphorus.

4.1.4 P–C Bond Formation by Reaction of Hypophosphorous Acid and Its Salts with Alcohols

4.1.4.1 Allylic H-Phosphinates

Unsaturated H-phosphinic acid with P–H-reactive bond was obtained in the esterification reaction of hypophosphorous acid with dimethylethynylcarbinol or propargyl alcohol. Using different reaction conditions, various compounds were obtained [70]. The reaction temperature is also very important (Scheme 4.11).

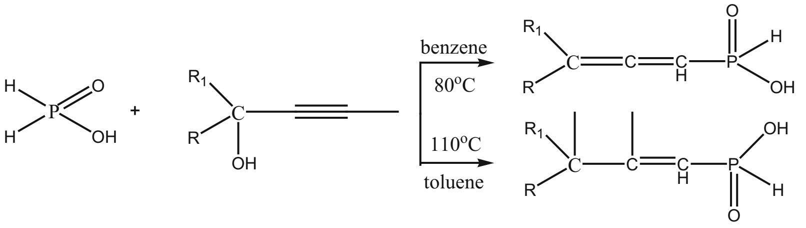
Having a very reactive allene system, the compounds (**37**) and (**38**) can react with amines and convert rapidly into crystallizable ammonium salts of aniline, *p*-bromoaniline, and dimethylaniline. The synthesis of allylic-H-phosphinic acids was performed using from a novel palladium-catalyzed by allylation of H_3PO_2 with allylic alcohols (Eq. 4.35) [71].



(4.35)

In the case of allylic alcohol with 1–3 equivalents of H_3PO_2 in DMF at 85 °C, the allylic H-phosphinic acids were obtained in 54 % yield. In the case of cinnamyl alcohol with H_3PO_2 in DMF at 85 °C, the allylic H-phosphinic acids were obtained in 98 % yield. Using cyclohexanes as solvent at reflux, no reaction was observed. Primary H-phosphinic acids were obtained in good yields, while secondary H-phosphinic acids react slowly. In the Montchamp research group [71], a possible mechanism for the catalytic mechanism for the Pd-catalyzed allylation of H_3PO_2 with allylic alcohols was proposed (Scheme 4.12).

Starting from the idea that allylic phosphinate can form through a Fischer-like esterification of H_3PO_2 with an allylic alcohol (**41**) and taking into account that hypophosphorous compounds are present in a tautomeric equilibrium between the P (V) and P(III) forms due to the presence of a phosphinylidene moiety (P(O)H), compound (**42**) can be generated.

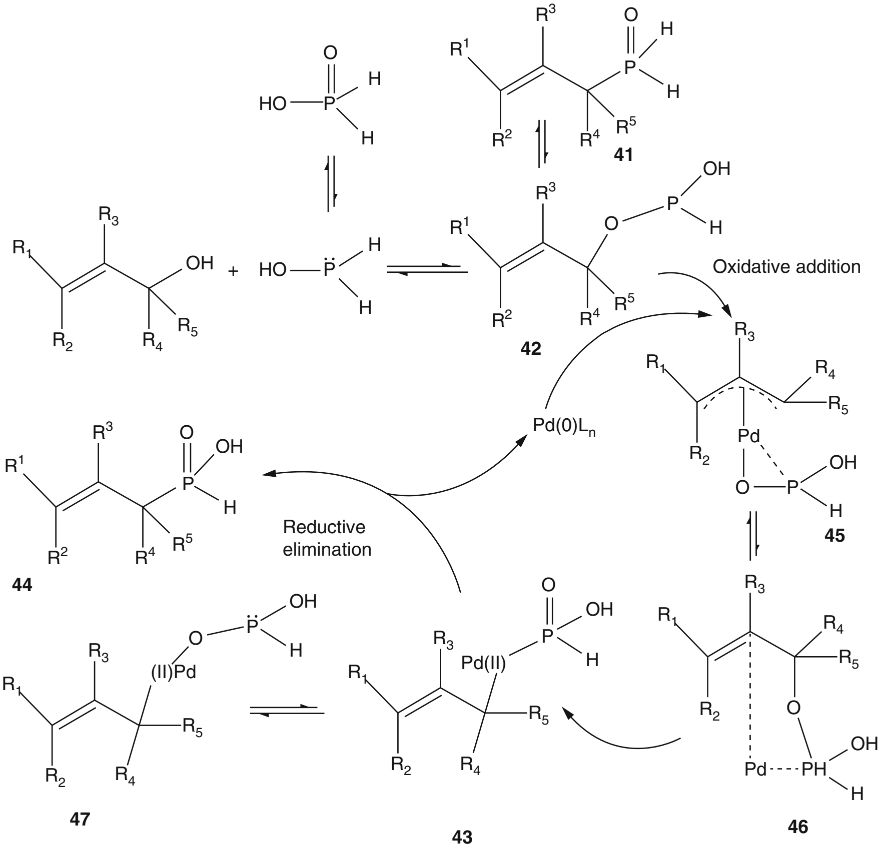


37, 38

39, 40

37, 39: R=R$_1$=H; **38, 40**: R=R$_1$=CH$_3$

Scheme 4.11 Unsaturated H-phosphinic acid

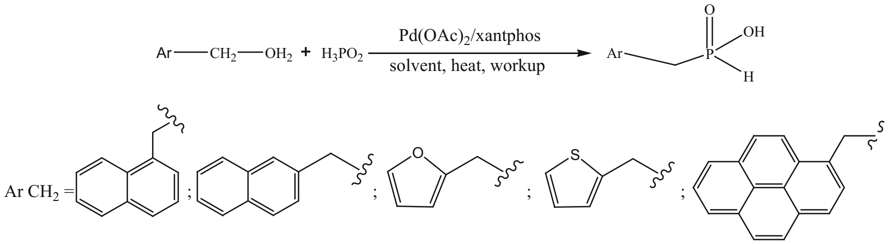


Scheme 4.12 Catalytic mechanism for the Pd-catalyzed allylation of H_3PO_2 with allylic alcohols

Coordination of a Pd(0) species to the P(III) and to the alkene in (**42**) may favor the oxidative addition of Pd(0), which can conduct to the following species: (**43**) and (**46**). After this step a rearrangement of (**43**–**46**) species followed by reductive elimination of (**43, 47**) and (**44**) compounds provides the C–P bond formation of allylic H-phosphinic acids.

4.1.4.2 Benzylic H-Phosphinates

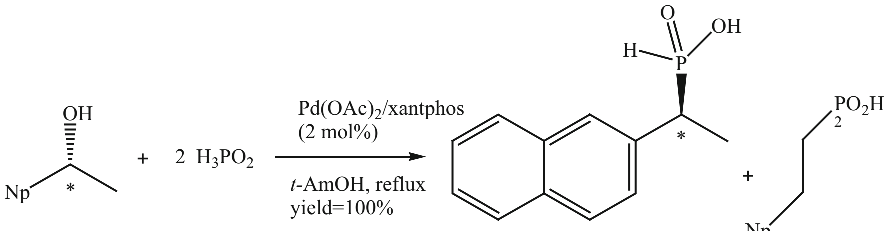
Recognized that this type of reaction should form a general model of reactivity, the reaction of benzylic alcohols in place of allylic alcohols in order to accomplish the catalytic synthesis of benzylic H-phosphinates without the need for any prior activation was investigated (Eq. 4.36) [72].



(4.36)

A broad range of substrates were converted into the corresponding H-phosphinic acids directly. This reaction offers a valuable and simple way to benzylic H-phosphinic acids and their derivatives. This method increases the benzylic H-phosphinic acid synthesis yields compared with alternate synthetic methods [31, 66, 73–76]. The acids are formed in good yields around 50–84 %. The obtained H-phosphinic acids may be isolated analytically after a simple extractive workup or can be separated by precipitation as the ammonium salt.

The possibility for an asymmetric variant of this benzylation was examined with the commercially available chiral (R)-1-(2-naphthyl)ethanol (97 % ee). Starting from this chiral alcohol, the corresponding H-phosphinic acid was obtained in 77 % ee (Eq. 4.37).

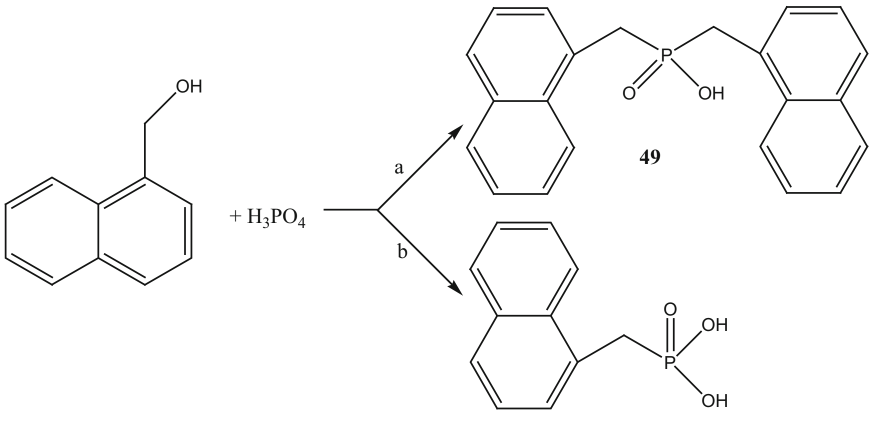


48

(4.37)

This method provides a significantly enantio-enriched H-phosphinic acid **48** (the enantiomeric excess is comparable to or better than that of other asymmetric reactions with benzylic electrophiles) [77, 78] which can be a precursor to a variety of other organophosphorus compounds.

Another example of catalytic transformations in which the benzylation can be employed to prepare other compounds is exemplified in Scheme 4.13. Under catalytic benzylation, the *H*-phosphinic acid provides the compounds (**49**), and one-pot benzylation–oxidation reaction leads to phosphonic acids, compound (**50**), in a catalytic and environmentally friendly approach [79]. The compound (**49**) was obtained at reflux of 2-methyl-2-butanol in 78 % yield using 0.5 equivalents of H_3PO_2, since compound (**50**) was obtained in DMF at 110 °C in 75 % yield using 2 equivalents of H_3PO_2 as reagent. The catalytic allylation of benzylic H-phosphinic acids can also be achieved [60].



49

50

Scheme 4.13 Tris(dibenzylideneacetone)dipalladium-catalyzed tandem transformations through benzylation

In general, the direct benzylation of H_3PO_2 is an original and efficient catalytic reaction, which improves the use of atom-wasteful process.

The necessity for new and improved properties has been a driving force for the growth of novel materials and technologies produced in an environmentally friendly manner further than those available for conventional materials.

Acknowledgements This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS – UEFISCDI, project number PN-II-RU-TE-2014-4-1398. The chapter is dedicated to the 150th anniversary of the Romanian Academy.

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Part III
Alternatives: *Catalysis*

Chapter 5
Catalytic Processes for Environmentally Friendly Methylene Diphenyl Diisocyanate Production

Alberto de Angelis, Aldo Bosetti, Roberto Millini, and Carlo Perego

Abstract Isocyanates are industrially produced using strong mineral acids (e.g. HCl), in the condensation of aniline to produce methylenedianiline (MDA), and phosgene, in the conversion of MDA to the corresponding isocyanates. Huge quantities of sodium chloride, contaminated with organic compounds, are produced during process, and their disposal is a relevant issue.

New processes during the last 20 years have been studied in order to avoid the use of both HCl and phosgene obtaining the production of methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), completely chlorine-free.

Keywords Isocyanates • MDA • MDI • TDI • Phosgene • Hydrochloric acid • Solid acid catalysts

5.1 Introduction

Isocyanates (in particular di- and poly-isocyanates) constitute an important class of molecules, industrially used for the preparation of polyurethanes (PUs) through the copolymerization with diols. The first polyaddition reaction of diisocyanates and diols to polyurethanes was claimed in 1937 [1a] and successively described in 1947

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[1b]. This class of polymers finds several applications in all areas of our daily life (i.e., medical, automotive, and industrial) and has shown high growth rates for a long time [2]. Classic polyurethane formulations are soft or rigid foams, elastomers, as well as hard solid or flexible plastics displaying low density, excellent strength to weight ratio, energy absorbing performance, and comfort features [3]. In 2011, the PU market share within all polymers in Europe was 7.0 % [4], mainly due to polymers deriving from methylene diphenyl diisocyanate (MDI, ~60 %) and toluene diisocyanate (TDI, ~35 %). Just to give an idea of the dimension of the market, it is enough to say that the global capacity for MDI in 2011 amounted to 5.15 $Mt \cdot a^{-1}$, with nine producers, of which the top five own over 75 % of capacity. In the next years, this figure is expected to grow since three new companies in China, India, and Iran are expected to enter in the market.

MDI demand is expected to increase globally up to 6.02 $Mt \cdot a^{-1}$ in the coming years, with the majority of the growth expected to take place in China. This is due to the great number of markets of MDI-based PUs, such as construction, insulation, automotive, coating, and footwear.

The industrial processes for the preparation of PUs make use of dangerous and toxic raw materials and reagents and produce large quantities of byproducts; in other words, they all present severe safety and environmental concerns. As a matter of fact, the industrial processes for the production of isocyanates, based on the phosgenation of amines (e.g., methylenedianiline, MDA; toluene diamine, TDA), imply the use of the highly toxic phosgene and produce huge amounts of aqueous NaCl solution contaminated with organics, which should be treated before being disposed.

The copolymerization of diisocyanates with diols is carried out in the presence of tertiary amines (Fig. 5.1) as basic catalysts, and this also presents environmental and safety problems.

The development of alternative synthesis routes, which avoid the use of toxic reagents (e.g., phosgene) and reduce the environmental impact of the overall process (e.g., by eliminating or, at least, reducing the amounts of byproducts), is therefore highly desirable. To do that, attention has been focused on the preparation

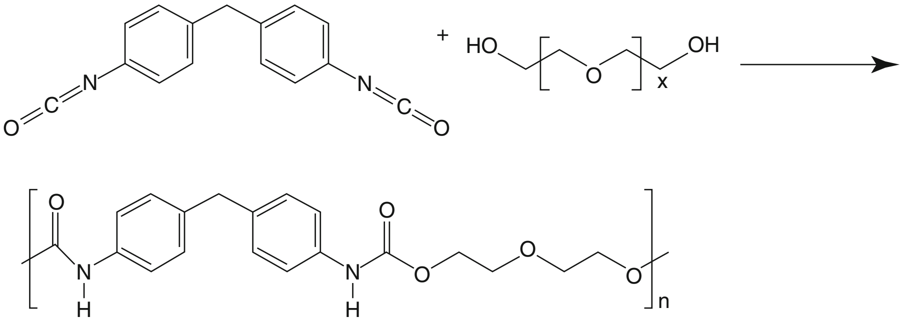

Fig. 5.1 Simplified scheme for polyurethane synthesis

of the isocyanates, and here we examine the status of the research focusing on the most important product, i.e., MDI.

5.2 Methylenedianiline (MDA) Production

The synthesis route to MDI passes through the preparation of methylenedianiline (MDA), which is prepared by reacting aniline (as hydrochloride) with formaldehyde in agitated reactor at 100–160 °C for ca 1 h (Fig. 5.2) [5]. The reaction mixture is then treated with an excess of aqueous NaOH to neutralize the products, producing two phases: the aqueous phase containing NaCl and contaminated by traces of organic amines and the organic phase constituted by the products and unreacted aniline. The latter is separated by distillation, leaving a mixture of condensation products composed by 4,4′-MDA (70–75 %), 2,2′-MDA, and 2,4′-MDA (3–5 %) and oligomeric MDA formed by three to four units (PMDA, 20–25 %). As for 4,4′-MDA, also PMDA are interesting products, industrially employed for the preparation of the corresponding isocyanates.

The most unwanted reaction, however, is the N-methylation of aniline, which occurs according the redox Plöchl reaction [6]:

$$RNH_2 + 2CH_2O \rightarrow RNHCH_3 + HCOOH$$

The formation of the N-methylated products should be avoided because they do not form the corresponding isocyanates through reaction with phosgene and, if present, they interrupt the polymerization chain, lowering the average molecular weight of

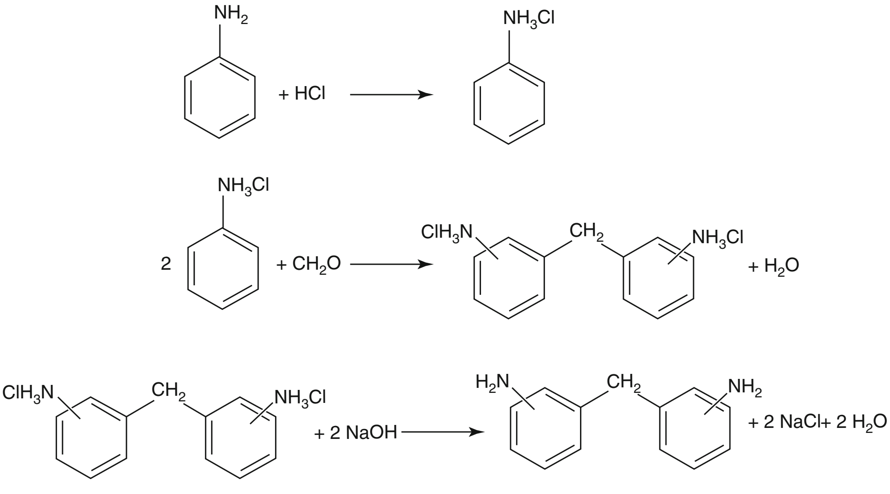

Fig. 5.2 Simplified scheme of MDA production

the polymeric material. Therefore, the content of N-methylated products should be limited to 0.5 mol%.

The above reported conditions can be varied in order to modulate the products' distribution. In particular:

- The increase of the aniline/formaldehyde molar ratio increases the MDA content and decreases the PMDA formation; however, larger amounts of aniline must be distilled off and recycled, and this implies the increase of the volume of the distillation apparatus and, finally, of the costs.
- The increase of the HCl concentration favors the formation of 4,4′-MDA at the expenses of the other two isomers; the drawback is the higher amount of NaOH solution to be used and NaCl solution to manage; moreover, the corrosiveness of HCl is also a concern, requiring the appropriate choice of the materials.
- The increase of the temperature decreases the 4,4′-MDA content, favoring the formation of the other isomers; it should be avoided unless 2,2′- and 2,4′-MDA are needed for other purposes (e.g., for adding the corresponding diisocyanates to MDI for reducing the melting point).

In all cases, huge amounts of NaCl solution contaminated with organic amines are produced, and its disposal is a critical issue because it requires a dedicated treatment plant for removing the contaminants before being disposed. It should be outlined that most of the aromatic amines have been reported to be carcinogens and mutagens. For all these reasons, academic and industrial research groups were looking for the replacement of HCl with other more convenient acids.

At this regard, recently Tian et al. proposed the use of SO_3H-functionalized ionic liquids (SFILs) as acid catalysts for the synthesis of 4,4′-MDA in homogeneous solution [7]. A series of SFILs derived from N-methylimidazole were synthesized and used as catalyst in the condensation of aniline with formaldehyde. The appropriate amount of SFIL is dissolved in dry aniline and heated at 50 °C under stirring: successively aqueous formaldehyde solution (37 wt.%) is added dropwise and the temperature increased to 80 °C and maintained for 8 h. The molar ratios aniline/formaldehyde and SFIL/formaldehyde were kept 5/1 and 3.5/1, respectively. The best results were achieved with the SFIL containing $CF_3SO_3^-$ as a counterion (36.3 % aniline conversion, 87.9 % selectivity to 4,4′-MDA, 79.4 % yield of 4,4′-MDA). When recovered and reused without any treatment, SFIL showed a significant decay in the selectivity and yield of 4,4′-MDA, while the aniline conversion was practically unchanged. On the contrary, when the recovered SFIL was treated with trifluoromethanesulfonic acid at 80 °C for 6 h, the original activity was recovered, and only slight decrease of the 4,4′-MDA yield was observed after the first regeneration (from 79.4 % to 72.7 %) and then remained practically unchanged for the successive three regenerations [7]. This example of application of the ionic liquids (ILs) is interesting under the scientific point of view, but hardly it will find a practical application due to not excellent catalytic performances and the complexity of the regeneration procedure.

Given that the mineral acid and the ILs operating in homogeneous conditions are characterized by severe drawbacks, the possible alternatives must be found in other systems, the most promising being the solid acid catalysts.

5.2.1 Solid Acid Catalysts

In general, the use of solid heterogeneous catalysts is preferred with respect to those operating in homogeneous phase (e.g., mineral acids) for several reasons, the most important being the facile separation from the reaction medium, the regenerability and reusability, the overall life, and the substantial absence of corrosiveness. Furthermore, some specific families of catalysts, in particular the crystalline microporous ones (e.g., zeolites), are also characterized by higher selectivity towards the desired products.

In the case of MDA production, the attempts for replacing HCl by solid acid catalysts date back to the 1960s, when started the catalytic tests on different families of materials [8].

A non-exhaustive list of acid catalysts tested in the synthesis of MDA is reported in Table 5.1. It is evident the efforts devoted to find the most suitable catalyst among different families of materials, from the non-oxidic intermetallic compounds and salts to carbon-based materials (modified graphite, sulfonated resins), from amorphous alumina and/or silica-based phases to the most classical phyllosilicates

Table 5.1 Heterogeneous acidic catalysts proposed for the synthesis of MDA

Catalysts	Materials	References
Non-oxidic compounds, salts		
Boride, nitride, aluminide, silicide, sulfide	BaN_3, MoB_2, $AlSi_3$, WSi_2, WS_2, WB, W_2B, WB_5, W_2B_3, Mo_3Al	[9–13]
$Zr(O_3PC_6H_4SO_3H)(O_3PH)$	Sulfonated zirconium benzenephosphonate-phosphite	[14]
$Sc(SO_3CF_3)_3$	Mesostructured scandium triflate	[15]
Carbon and polymers		
$CF_{0.8-0.9}$	Fluorinated graphite	[16]
Ion-exchange resin	Sulfonated styrene-divinylbenzene polymers	[14, 17–21]
Nafion	Sulfonated polyperfluoroalkene polymers	[21]
Oxides		
$Al_2O_3 \cdot MgO$	Magnesium-aluminum mixed oxide	[22]
$SiO_2 \cdot MgO$	Magnesium-silicon mixed oxide	[23]
$SiO_2 \cdot Al_2O_3$	Silica-alumina	[23–30]
$Al(Fe)_2O_3.nH_2O$	Iron containing hydrated alumina (Bauxite)	[24–28]
Phyllosilicates	Magnesium and/or aluminosilicates (clays)	[23–28, 31–35]
Zeolites	Microporous crystalline aluminosilicates	[36–48]

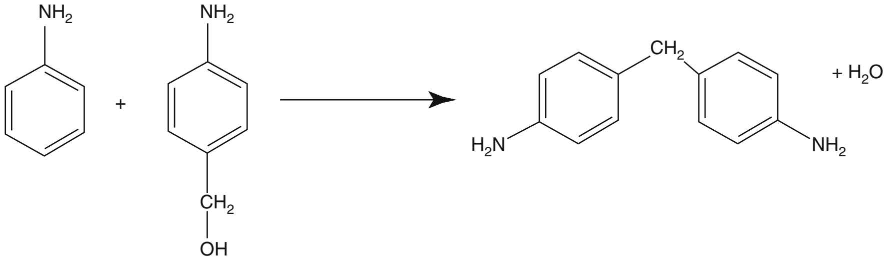

Fig. 5.3 Scheme of MDA synthesis according to Parvulescu et al. [15]

(clays) and zeolites. The results of the catalytic tests showed significant differences among the different families of materials. For instance, non-oxidic compounds (BaN_3, MoB_2, $AlSi_3$, WSi_2, WS_2, WB, W_2B, WB_5, W_2B_3, Mo_3Al, etc.) were extensively studied by Texaco during the 1980s [9–13]. Although very stable and non-corrosive, their acid strength is too low to have an activity comparable to that of HCl, even at high temperatures (200 °C). As a matter of fact, an incomplete conversion of formaldehyde to MDA was usually achieved, while significant amounts of intermediate (3–6 mol% of the products) were always detected. Most important, however, was the concentration of the noxious N-methylated products, which amounted to 6–9 mol%, well above the tolerable limit of 0.5 mol% (*vide supra*). On the other hand, the overall concentration of the three MDA isomers was found in the range 45–48 mol% (the remaining being PMDA), clearly too low for considering these materials possible candidates for the replacement of HCl.

The use of $Zr(O_3PC_6H_4SO_3H)(O_3PH)$ was claimed in a patent by Catalytica Assoc. Inc., but no catalytic data were reported [14]. In principle, this layered material might be promising because of the contemporary presence of microporosity (generated by the substitution of the sulfonated phosphonic groups by phosphites) and sulfonic groups, whose acid strength should be sufficient for promoting the condensation reaction.

Of a certain interest is a recent paper by Parvulescu et al. who reported the use of mesostructured scandium triflate as a catalyst for the condensation reaction of aniline with 4-aminobenzyl alcohol to MDA [15] (Fig. 5.3).

The reaction is performed batchwise at 80 °C for 24 h using two moles of aniline for each mole of 4-aminobenzyl alcohol in acetonitrile as a solvent. The catalyst is between 5 and 10 wt.% with respect to the reactants.

The best results were achieved with 31.4 % conversion of aniline and 85.7 % selectivity to C- alkylation (>99.9 % 4,4′-MDA), the remaining being alkylated on N. Interestingly, the increase of the temperature to 140 °C led to 40.2 % conversion of aniline and 88.9 % selectivity to C-alkylates (>99.9 % 4,4′-MDA) after 24 h of conventional heating and only 3 h of microwave heating. Recycling the catalyst for four times at 80 °C was not accompanied by any visible loss of conversion and selectivity to C-alkylates (>99.9 % 4,4′-MDA) [15].

Due to its low yield (54 %) and productivity, the interest of this approach remains scientific only and the industrial development of this catalyst is not likely to happen in a short time, since the catalyst used is very expensive and thermal regeneration cannot be used to restore its initial activity. Carbon-based materials were also investigated as catalysts of MDA production. With the exception of fluorinated graphite ($CF_{0.8–0.9}$), which gave unsatisfactory results in terms of high selectivity to N-methylated products (concentration of 1.9–5.9 mol% in the products) and reusability (it cannot be recycled at the end of the reaction) [16], a certain interest was aroused by the use of ion exchange resins containing sulfonic acid groups with two different frameworks: (a) styrene-divinylbenzene [14, 17–20] and (b) tetrafluoroethylene-perfluorovinylether (Nafion ©) [21].

In all cases, complete formaldehyde conversion is obtained, at 100–110 °C, provided that the by-produced water is removed through distillation from the reaction mixture. The selectivity to MDA is very high, always >80 %, with a low content of unwanted 2,2′-MDA (~1 mol%). PMDA content is always <10 mol% with <1 mol% of heavier molecular weight condensation products. On the contrary, the productivities reported for these catalysts are not adequate to an industrial development. In fact, using styrene-divinylbenzene resin as catalyst [20], maximum productivities of 4.95 and 2.47 $g_{MDA}/g_{catalyst}$ are obtained, depending on the ratio formaldehyde/aniline. On the other hand, the productivity using Nafion [21] reaches the maximum value of 12 g MDA/g catalyst, still not high enough for a practical use of this catalyst.

More extensively studied are the oxidic phases. The early studies date back to the 1960s and were aimed at verifying the catalytic performances of mixed oxides (Mg/Al/O [22], Mg/Si/O [23], Fe/Al/O (bauxite) [23–28], Si/Al/O [23–29]), clays [23–28, 30–34], and zeolites [35–48]. Most of the information is reported in the patents, and it is therefore rather difficult to draw a rational picture of performances of these catalysts, especially with regard to the unstructured (amorphous) mixed oxides. We will therefore report few interesting data for demonstrating the potentialities of these systems.

Focusing the attention on the Si/Al/O system, the use of silica-alumina cracking catalyst usually led to production of MDA mixtures with a higher content of 2,4′- and 2,2′-MDA isomers with respect to 4,4′-MDA. In a patent assigned to Jefferson Chemical Company, silica-alumina was used as co-catalyst together with oxalic acid [27], but since the latter is claimed to be an active catalyst in MDA synthesis, it is hard to understand whether the silica-alumina is a true catalyst itself. In any case, this catalytic system actually favors the formation of MDA mixtures rich in 4,4′-MDA isomer (60–80 mol% on the products). In another patent, E. T. Marquis and H. Schulze [28] employed silica-alumina catalyst to transalkylate PMDA with aniline to produce MDA, but in this case, due to the high reaction temperature, a relevant ratio of 2,4′-MDA (~20 mol%) and 2,2′-MDA (3–4 mol%) was produced.

Silica-aluminas with different average pore size ranging between 30 and 200 Å were claimed to be active catalysts for MDA synthesis [29, 30]. The process involved first a non-catalytic condensation of aniline with formaldehyde to N, N′-diphenyldiaminomethane (aminal) carried out at 40 °C for 1 h and with a

Table 5.2 Composition and textural properties of the silica-alumina catalysts tested in the aminal conversion to MDA

Catalyst	SiO_2/Al_2O_3	SSA/($m^2.g^{-1}$)	SPV/($cm^3.g^{-1}$)	10 APD/nm
J 639	100	318	1.44	207
13-110	11.4	480	1.02	94
SA	100	509	0.24	13
PK200[a]	15.3	480	0.43	35
MSA	102	928	0.74	32
ERS-8	100	1196	0.62	16
MCM-41	39	1140	0.83	21
HMS	75	948	0.96	19

SSA specific surface area, *SPV* specific pore volume, *APD* average pore diameter [29, 30]
[a] Used in the fixed bed reaction test only

molar ratio aniline/formaldehyde = 4. At the end of the reaction, the organic phase containing aminal and the unreacted aniline was separate from the aqueous phase and dried over anhydrous Na_2SO_4; the dried mixture, containing 1.25 wt.% of residual water, was used in the successive catalytic tests performed both in batch and in fixed bed conditions using powdered and extruded catalysts, respectively. A number of silica-aluminas with different compositional, textural, and structural characteristics were used in the batch aminal conversion tests using aniline as a solvent (Table 5.2). They included three mesoporous commercial catalysts (J 639 and 13–110 by Grace, PK200 by Kali-Chemie), a proprietary mesoporous silica-alumina (MSA by Eni), a proprietary microporous silica-alumina (ERS-8), two ordered mesoporous materials (MCM-41 and HMS), and a microporous silica-alumina (SA), with relatively low specific surface area and specific pore volume (Table 5.2). For the sake of comparison, a sample of zeolite Beta ($SiO_2/Al_2O_3 = 22$) exchanged in acidic form was tested both in batch and in fixed bed conditions.

All these catalysts were tested in batch conditions and just few of them (J 639, MSA, PK200, and SA) also in fixed bed reactor in form of pelletized particles (100% active phase, 70–100 Mesh) or after extrusion with 50 wt.% alumina binder (MSA). The results of the tests performed in batch conditions are reported in Table 5.3.

In the batch tests, complete aminal conversion was generally achieved with the exception of microporous silica-alumina (SA), which gave only a partial conversion of the substrate to MDA and PMDA (52.73 mol%). Apart from HMS, mesoporous catalysts showed very similar product distributions: 4,4′-MDA was the main product (64–68 mol% selectivity), while 2,4-MDA isomer was produced with ~10 mol% selectivity. On the contrary, 2,2′-MDA isomer was not detected in the products. The selectivity to PMDA was in the range 21–26 mol%, the trimers prevailing over the heavier products. With HMS the selectivity toward PMDA was the highest (40.17 mol%), but the content of N-methylated products (0.70 mol%) and the 4,4′/(2,4′ + 2,2′) MDA isomers ratio (6.71) were very similar to those

Table 5.3 Results of the catalytic tests of conversion of aminal to MDA in batch conditions

Composition (mol/%)						4,4′/(2,4′ + 2,2′)
Catalyst	Amines	Benzylamines	N-methylated	MDA	PMDA	Mole ratio
J 639	99.61	0	0.39	73.51	26.10	6.53
13–110	99.31	0	0.69	78.44	20.86	6.37
SA	52.73	46.80	0.47	7.43	45.3	6.51
MSA	99.18	0	0.82	73.49	25.68	5.99
ERS-8	99.27	0	0.73	75.29	23.98	5.50
HMS	99.30	0	0.70	56.74	40.17	6.71
Beta	99.57	0	0.43	83.98	15.53	2.55

Reaction conditions: 4 g aminal mixture, 10 g aniline as solvent, 250 mg catalyst, 150 °C, 6 h [30]

Table 5.4 Results of the catalytic tests of conversion of aminal to MDA in fixed bed reactor. Reaction conditions: tubular reaction (i.d. 12.5 mm, length 390 mm) loaded with 5 ml of pelletized catalyst crushed at 70–100 Mesh; feed, aminal (10 vol.% in aniline), 180 °C, 4 bar, LHSV = 7.2 h^{-1}. The data reported are collected after 72 h of stream [29]

		Selectivities (mol%)			
Catalyst	Aminal conv./%	4,4′-MDA	2,4′-MDA	Trimers	PMDA
J 639	99	71	16	11	2
MSA[a]	99	71	20	6	3
PK200	99	72	16	10	2
SA	37	6	2	61	31

[a] Extruded with 50 wt.% alumina binder and crushed at 70–100 Mesh; 10 ml of catalyst used in the tests

obtained with the other mesoporous silica-alumina. Finally, the zeolite catalyst (H-Beta) showed the highest selectivity to MDA (83.98 mol%) but the lowest 4,4′/(2,4′ + 2,2′) MDA isomer ratio (2.55) indicating its larger isomerization activity with respect to silica-alumina [30].

Some of the catalysts were tested in the fixed bed reactor, and the results are reported in Table 5.4.

They substantially confirmed what is observed in batch conditions, the only significant difference being the higher selectivity to 4,4′-MDA (71–72 mol%) and, in particular, to 2,4′-MDA (16–20 mol%) at the expenses of PMDA. This is obviously a consequence of the shorter contact times, which limit the consecutive reactions of MDA to PMDA. MDA productivities as high as 120 $g_{MDA}/g_{catalyst}$ were achieved with MSA in the fixed bed reaction, after optimization of the reaction conditions [30]. This productivity, however, should be compared with the 300 $g_{MDA}/g_{catalyst}$ obtained with H-Beta in the same conditions. Moreover, the zeolite catalyst proved to be more stable than silica-alumina, since it maintained the aminal conversion close to 100 % for 200 h test in fixed bed, while silica-alumina catalysts showed a decay of the conversion after 50–120 h [30]. The tests were usually performed with aniline as a solvent, but other solvents (e.g., chlorobenzene, dichlorobenzene) proved to be suitable as well. Finally, silica-alumina

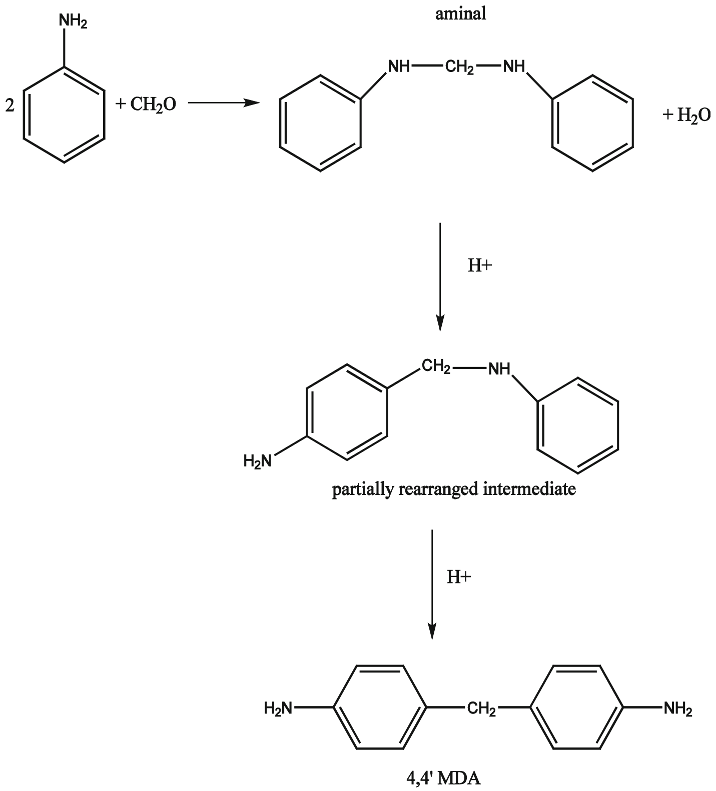

Fig. 5.4 Scheme of MDA synthesis according to Upjohn's patents

catalysts tolerate up to 3 mol% of water in the reaction mixture, and this is a clear improvement with respect to other catalytic systems (e.g., clays), for which water resistance is a critical issue.

Upjohn Company investigated clays as active catalysts in MDA synthesis, using the five-step process schematized in Fig. 5.4 [31–34]:

1. Non-catalytic condensation of aniline and formaldehyde to produce aminal
2. Separation of the organic phase, containing aminal and unreacted aniline, from the aqueous phase produced during the reaction
3. Catalytic partial rearrangement of aminal to mixture of MDA isomers and PMDA at mild temperature
4. Distillation under vacuum of most of the unreacted aniline from the reaction mixture
5. Complete catalytic rearrangement of aminal to MDA and PMDA products at high temperature

The catalysts used were mainly clays, but other catalysts such as diatomaceous earth and zeolites were claimed. A complete aminal conversion was usually achieved, while the reaction conditions were modulated to favor the formation of PMDA [31] or MDA [32].

When the reaction was performed batchwise at 180 °C in the presence of a clay catalyst, a mixture of roughly 50 wt.% of MDA and PMDA (mainly tri- and tetramines) was obtained. The MDA mixture, in turn, was composed of 72–75 wt.% of 4,4′-MDA, 21–25 wt.% of 2,4′-MDA, and 2–3 wt.% of 2,2′-MDA [31]. If the reaction is performed in a fixed bed reactor always with a clay catalyst, but at a lower temperature (up to 100 °C), up to 94 wt.% of the product was constituted by the MDA isomers, the remaining fraction being PMDA. The selectivity to 4,4′-MDA was very high (up to 85 mol%), but it dropped down to 78 mol% when the reaction temperature was reduced to 80 °C [32]. A drawback related to the use of clay catalysts concerns their high sensitivity to water, whose content in the reaction mixture used in the rearrangement of aminal (step 5) should not exceed 1500 ppm. This represents a critical issue that, combined with the complexity of the entire production process, probably hampers the industrial development of this technology.

Among the different families of materials potentially useful as heterogeneous catalysts for MDA production, zeolites may offer interesting advantages related to their relevant acidic strength combined to their shape selectivity properties, which may be exploited for driving the reaction toward the desired MDA isomers, limiting the formation of heavier products (e.g., PMDA).

In a patent filed in 1989, Mitsui Petrochemical Industries claimed the use of dealuminated Y-type zeolites as active catalysts for the synthesis of MDA through the rearrangement of the aminal prepared by non-catalytic condensation of aniline and formaldehyde (Fig. 5.4). A large number of catalysts were tested, consisting of the dealuminated Y-type zeolite as such or after treatment with fluoride ions as such, treated with an ammonium fluoride solution or with a variety of different metal ions [36]. The best results were obtained with the fluoride and metal-treated catalysts, which led to an almost complete aminal conversion (up to 97.5 mol%) and a very high selectivity to 4,4′-MDA (up to 90 mol% of the MDA mixture).

However, the weakness of these catalysts concerns their poor water resistance, which obliges to maintain the water content in the aminal mixture below 0.1 mol%. Another negative aspect is related to the concentration of partially rearranged intermediate in the reaction mixture, which remained too high (2–3 mol%) [36].

In 1988, Clerici et al. claimed the use of various zeolites, including Y, ZMS-5, and silicalite-1 eventually isomorphously substituted with Ti, B, and Fe, for the preparation of MDA by reacting aniline with trioxane in an inert solvent (benzene, but even other aromatic, chloroaromatic, nitroaromatic, aliphatic solvents) at 120 °C for the required time [37]. Complete conversion of aminal to MDA was never obtained with 8–30 mol% residual content of partially rearranged intermediate in the products, depending on the catalyst employed.

Later on [38], zeolites active in MDA synthesis were selected according to their spaciousness index (SI), which, according to Weitkamp et al., provides a measure of the effective width of the zeolite pores [39]. The catalytic tests were performed batchwise, by treating the preformed aminal (prepared by non-catalytic

Table 5.5 MDA synthesis with zeolite catalysts with different spaciousness index (SI) [38]

Zeolite	SI	Aminal conv./%	Selectivities (mol/%)		
			4,4′-MDA	2,4′-MDA	PMDA
Beta	19	99.3	58.5	22.9	18.6
Mordenite	7	98.3	71.1	15.1	13.8
ERB-1	8	99.9	59.0	22.2	18.8
ZSM-12	3	98.3	54.5	30.4	15.1
Y	21	83.4	28.8	3.5	67.7
ZSM-5	1	78.8	8.0	1.9	90.1

condensation of aniline and formaldehyde and still containing 1.25 wt.% of water>) at 150 °C for 6 h. The best results were obtained with zeolites characterized by SI in the range 2.5–19 (Table 5.5) and, in particular, with Beta (a large pore zeolite with 12R openings and SI = 19) and ERB-1 (medium pore zeolite with the *MWW* topology, characterized by two independent 10R channel systems and 12R pockets on the [001] crystal surface; SI = 8) [38]. With these two zeolites, in fact, complete aminal conversion was obtained, with no partially rearranged intermediate. Reaction products contained ~59 mol% of 4,4′-MDA and 22–23 mol% of 2,4′-MDA, the remaining part being PMDA (mainly trimers and tetramers) (Table 5.5). Interesting are also the performances of mordenite (*MOR*), a large pore zeolite with a monodimensional linear channel system with 12R openings. In fact, among the zeolites examined, it displayed the highest selectivity to 4,4′-MDA (71 mol%) and, consequently, the lowest selectivities to 2,4-MDA and PMDA, but the aminal conversion was not complete (98.3 mol%, Table 5.5).

Reaction tests were performed also in a fixed bed reactor obtaining similar product distribution; in these tests, the maximum MDA productivity (260 $g_{MDA}/g_{zeolite}$) was obtained with zeolite Beta. Interestingly, the zeolite catalysts can be regenerated by the usual procedure, involving an in situ high-temperature thermal treatment in air, recovering the initial conversion and selectivity.

In general, the catalytic performances of the different catalysts also depend on the solvent employed. With aniline, the aminal conversion is usually close to completeness while is slightly lower than that obtained by using other solvents (e.g., *m*-dichlorobenzene); the major effect, however, is on the selectivity to MDA (in particular, to the 4,4′- isomer) which is usually much higher with aniline.

The product distribution obtained using a zeolite Beta implies a higher amount of 2,4′-MDA than in the product distribution achieved using HCl as catalyst (22.8 vs. 3–5 mol%). This is an effect of the reaction temperature on the isomerization reaction, as demonstrated by the data reported in Table 5.6. In fact, the reaction performed with HCl occurs at significantly lower temperature (100 °C) compared to that required by zeolite catalysts (150 °C or higher), and this favors the isomerization reaction. In fact, when the temperature is increased to 190 °C in the presence of HCl, the selectivity to 2,4′- and 2,2′-MDA isomers dramatically increases at the expenses of the 4,4′-MDA isomer.

Table 5.6 MDA isomers distribution obtained with different catalysts [5]

Catalyst	T (°C)	MDA selectivities (mol/%)		4,4′/(2,4′ + 2,2′) mole ratio
		4,4’	(2,4′ + 2,2′)	
HCl	100	94	6	15
HCl isomerization	190	49	51	0.96
Beta	150	72	28	2.5

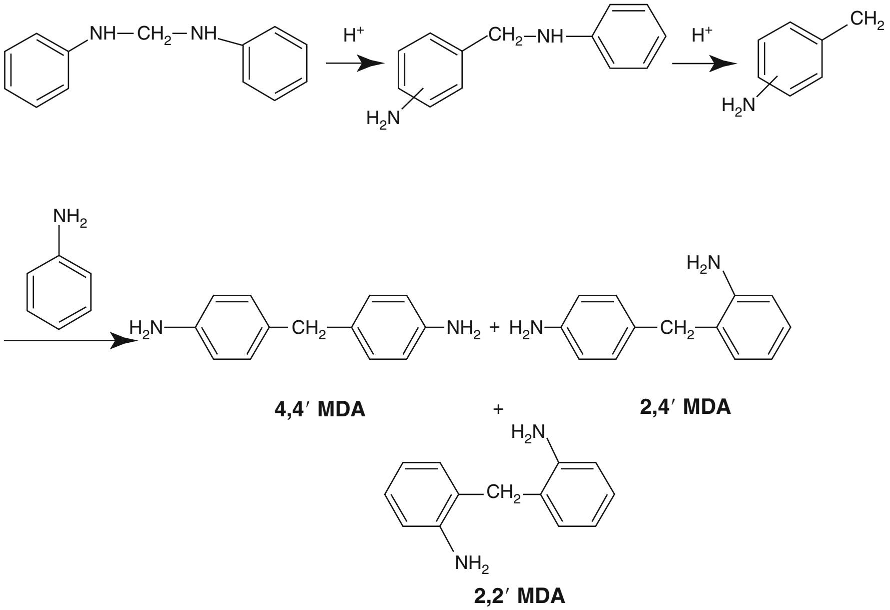

Fig. 5.5 Aminal rearrangement

The acid-catalyzed rearrangement of aminal starts with the formation of benzylamines, by the electrophilic substitution on an aromatic ring carrying a strong activating *ortho*-*para* orienting group, e.g., $-NH_2$. This reaction is relatively rapid, and the formation of *p*-bonded benzylamines is favored according to the lower steric hindrance of *p*- versus *o*-position. Then the dissociation of benzylamines follows, giving rise to the formation of a benzylic carbenium ion, which reacts with aniline forming MDA (see scheme Fig. 5.5 [30]). This reaction is considered the rate-determining step of the overall process [5]. According to the steric hindrance, *p*-isomer (4,4′-MDA) is favored at low temperature; however, 4,4′-MDA can isomerize to 2,4′- and 2,2′-isomers at high temperatures via an acid-catalyzed protodealkylation [41].

Possible solutions to the unwanted isomerization reaction have been proposed. One of them involves the treatment of the zeolite crystal surface with silylating agents, which actually increases the selectivity to 4,4′-MDA while decreasing that to 2,4′-MDA (Table 5.7) [42].

Table 5.7 Results of the catalytic tests performed with zeolite H-Beta treated with silylating agents [42]

Silylating agent	Aminal conv. (mol/%)	Selectivity (mol/%)			4,4′/(2,4′ + 2,2′) mole ratio
		4,4′-MDA	2,4′-MDA	PMDA	
TEOS	99.9	49.1	18.6	32.3	2.6
TPOS	99.9	54.1	20.1	25.8	2.7
TBOS	99.9	54.8	20	25.2	2.7
OMTS[a]	99.9	53.5	11.9	34.6	4.5
OMTS[b]	99.9	58.1	10.1	31.8	5.8
H-Beta[c]	99.3	58.5	22.9	18.6	2.2

TEOS tetraethylorthosilicate, *TPOS* tetrapropylorthosilicate, *TBOS* tetrabutylorthosilicate, *OMTS* octamethylcyclotetrasiloxane

[a] One treatment

[b] Three consecutive treatments

[c] Pristine untreated sample

In the treatment of the zeolite crystals either with organic orthosilicates of general formula $Si(OX)_4$ or with cyclic silylating agents (e.g., octamethylcyclotetrasiloxane, OMTS), the 2,4′-MDA content could be sharply reduced without lowering aminal conversion and catalyst life. In fact, the isomerization of 4,4′-MDA cannot take place inside the pores of zeolite Beta. The critical diameter (i.e., the smallest diameter of a cylinder through which the molecule can pass through without distortion) of 2,4′- and 2,2′-MDA is comparable (~0.8 nm) and slightly larger than that of 4,4′-MDA (0.7 nm). As the pore openings of zeolite Beta are 0.76 × 0.64 nm and 0.55 × 0.55 nm, the isomerization will likely take place outside the pore on the zeolite external surface. Therefore, a reasonable explanation of the increased selectivity to MDA could be the inertness of the external surface of the zeolite, subsequent to silanization [43].

Kugita et al. also compared the catalytic performances of some conventional zeolites including ZSM-5, Beta (with Si/Al molar ratio ranging from 120 to 10), and Y, but instead of feeding aminal, they used directly aniline and formaldehyde [44]. The results of the catalytic tests are reported in Table 5.8.

It is clear that the activity of zeolites increases in the order Beta > Y > ZSM-5, the latter displaying the worst performances probably for steric reasons (10R channels too small for allowing the adsorption/easy diffusion of reactants and products). On the other hand, the activity of zeolite Beta proved to be dependent on the composition since the activity and the selectivity to 4,4′-MDA increased with the decrease of the Si/Al ratio. On the other hand, zeolite Y displayed the highest selectivity to 4,4′-MDA but also lower activity than Beta.

Besides type and composition of the zeolites, the authors found that also the aniline/formaldehyde and catalyst/formaldehyde ratios influenced the yield and the MDA isomers distribution. The best results (81.3 % yield of 4,4′-MDA) were achieved when zeolite Y (Si/Al = 10) was used with aniline/formaldehyde and catalyst/formaldehyde ratios of 30 (molar) and 1.2 (Mass), respectively (44).

Table 5.8 Catalytic performances of zeolite catalysts in MDA synthesis

Catalyst		Yields[a]/%		MDA isomers distribution/%		
Zeolite	Si/Al	Aminal	MDA	4,4′-MDA	2,4′-MDA	2,2′-MDA
–	–	3.1	0	–	–	–
ZSM-5	45	25.6	6.3	19.5	7.9	72.6
Beta	40	9.6	49.1	47.8	39.9	12.3
Beta	10	9.5	47.6	54.1	28.9	17.0
Y	10	9.4	26.5	71.9	8.9	19.2

(reaction conditions: mole ratio aniline/formaldehyde = 5; weight ratio catalyst/formaldehyde = 0.4; 120 °C, 3 h) [44]

[a]Calculated on formaldehyde

The different behavior of zeolites is recently examined by Salzinger and Lercher who elucidated the reaction network and mechanism of the synthesis of MDA from aminal on microporous acidic materials [45]. After an accurate examination of the experimental data collected on zeolite catalysts without (Beta with Si/Al = 12.7 from Süd-Chemie) and with mesopores (dealuminated Y zeolite CBV-760 with Si/Al = 29.5 from Zeolyst), they demonstrated that the first step of the reaction (the aminal decomposition) is limited by pore diffusion in both microporous structures. On the contrary, the rearrangement of N-alkylbenzylaniline intermediate is limited by pore diffusion over Beta but not over dealuminated Y zeolite. In other words, the presence of intracrystalline mesoporosity in the latter catalyst eliminates the mass transport limitations dramatically improving the catalytic activity of the otherwise poorly performing large crystals of the parent H-Y zeolite. The most important indication coming from this study was that solid Brønsted acid catalysts with small crystal size and a pronounced mesoporosity offer ideal green catalytic routes for MDA synthesis. These catalysts with hierarchical micro-mesoporous systems constitute ideal candidates for replacing HCl avoiding the formation of stoichiometric amounts of NaCl in the process [45]. The authors concluded announcing that a systematic study of the detailed role of the pore size, geometry, and extent of mesoporosity was in progress. In this study, published just few weeks later [46], a number of different zeolite structures were considered including ZSM-5 (*MFI*), mordenite (*MOR*), Beta and Y (*FAU*). For each structure, samples with different composition (in terms of Si/Al ratio) were tested. In the case of Y zeolites, the dealuminated commercial samples already contained intracrystalline mesopores, while in the case of zeolites Beta, they were generated by desilication with bases. Furthermore, MCM-22 (*MWW*) was also examined as such, after delamination (ITQ-2) or swelling and pillaring with TEOS (ITQ-36). The catalytic activity of the different catalysts was expressed in terms of turnover frequency (TOF) determined by normalizing the initial rates of 4,4′-MDA and 2,4′-MDA formation (below 10 % 4,4′-MDA yield) to the amount of employed catalyst and the concentration of Brønsted acid sites, provided that all these sites contribute equally to the overall acidity useful for the reaction, as previously shown by the same research group [45]. Quite interesting information was obtained from this detailed study.

Table 5.9 MDA synthesis on delaminated zeolites and comparison with the corresponding zeolites

Catalyst	Aminal conv. (mol/%)	Selectivity (mol/%)			4,4′/(2,4′ + 2,2′) mole ratio
		MDA	PMDA	Others[b]	
MCM-22	95.9	79.3	16.6	4.1	4.3
ITQ-2	98.4	83.8	14.6	1.6	1.0
Ferrierite	60.3	53.7	6.6	39.9	5.0
ITQ-6	98.1	79.9	18.2	1.9	1.4
NU-6	73.7	64.9	9.8	25.3	4.7
ITQ-18A[a]	90.7	71.9	18.9	9.3	4.4
ITQ-18B[a]	89.3	71.3	18.0	10.7	4.3

(batch reaction conditions: aniline/formaldehyde = 3.0 (with <1 wt.% water); T = 150 °C, 20 wt.% catalyst, TOS = 1 h) [48]

[a] Different levels of delamination

[b] Σ(sec-amines+N-methylated+quinazolines)

In particular, it was clearly shown that when the mass transport limitations prevail, as in the case of *MFI*- and *MOR*-type samples, the TOF remains close to zero (i.e., they are substantially inactive catalysts). Zeolite Beta showed a relatively low catalytic activity in the pristine form (TOF = 0.8–1.0 s^{-1}), which increased only slightly after desilication (TOF = 1.4 s^{-1}). On the other hand, the best results were achieved with hierarchical (dealuminated) micro-mesoporous Y zeolites. It should be noted that, in its pristine form, also for Y the mass transport limitations prevail and the TOF is very low (0.2 s^{-1}), but the generation of intracrystalline mesoporosity greatly enhanced the catalytic activity, with the TOF reaching values of 7.0–7.8 s^{-1}. In the case of *MWW* type of catalysts, as expected MCM-22 did not show any activity (TOF = 0 s^{-1}); however, upon delamination (ITQ-2) and, particularly, swelling and pillaring of the layers (MCM-36), the activity dramatically increased (TOF = 3.4 and 7.4 s^{-1}, respectively), demonstrating once more that the mass transport limitations play a decisive role in the reaction [46].

The fact that delaminated zeolites might be efficient catalysts for increasing the selectivity to 4,4′-MDA was not new, being already been proposed by Corma et al. in 2004 [47] and confirmed later [48]. In particular, three different delaminated zeolites were tested in the aminal conversion to MDA in batch and fixed bed conditions: ITQ-2 (delaminated MCM-22), ITQ-6 (delaminated ferrierite), and ITQ-18 (delaminated Nu-6).

Table 5.9 reports some selected results of the catalytic tests performed in batch conditions. Compared to the corresponding conventional zeolites, it is evident how delaminated catalysts are more active as a consequence of the easier diffusion of reactants and products and increased accessibility of the acid sites (at this regard, it should be pointed out that *MWW*, *FER*, and NU-6 are all medium pore zeolites with 10R channel openings). In the case of ITQ-2 and ITQ-6, however, the selectivity to the desired 4,4′-MDA isomer was very low, probably because of the high isomerization activity of these catalysts. On the other hand, ITQ-18, independently on the level of delamination, displayed lower aminal conversion and MDA selectivity but the highest yield of the desired 4,4′-MDA isomer. The amount of unwanted N-methylated MDA is quite low (1.3 %) even though higher than industrial N-methylated content (<1 %). The catalysts ITQ-18 proved to be stable, in a fixed bed reactor, for more than 70 h, and it can be easily regenerated through thermal treatment under air flow at 540 °C.

5.3 MDI Production

MDI is produced by reacting MDA with phosgene in inert solvent (e.g., chlorobenzene or dichlorobenzene) according to Fig. 5.6. The initial fast reaction produces carbamoyl chloride at 50–70 °C. This compound is then heated up to 180 °C at moderate pressure (3–4 bar) to produce MDI that is distilled to obtain a composition of 97–98 % of 4,4′-isomer and 2–3 % of the 2,4′-isomer [5].

The ratio of PMDI to monomeric MDI is around 4:1 and can be adjusted according to the customers’ specification and the end-use applications.

Phosgene is an extremely poisonous and toxic gas that was used as a chemical warfare agent during the First World War and is therefore a very controversial substance in many regions around the world. It is used to produce diisocyanates, polycarbonates, acid chlorides, chloroformates, and organic carbonates. Phosgene is under the supervision of OPCW (Organization for the Prohibition of Chemical Weapons), and every production facility exceeding 30 tons per year must be declared and can be inspected at any time. Because of its toxicity, it requires rigorous standards to protect the health and safety of handling personnel. It has a T+ classification of the directive of dangerous substances set by the REACH program [49].

The effects of phosgene on inhaling are the production of hydrochloric acid in the alveoli, which reacts with the capillary wall of the lung and produces an edemal fluid that causes suffocation.

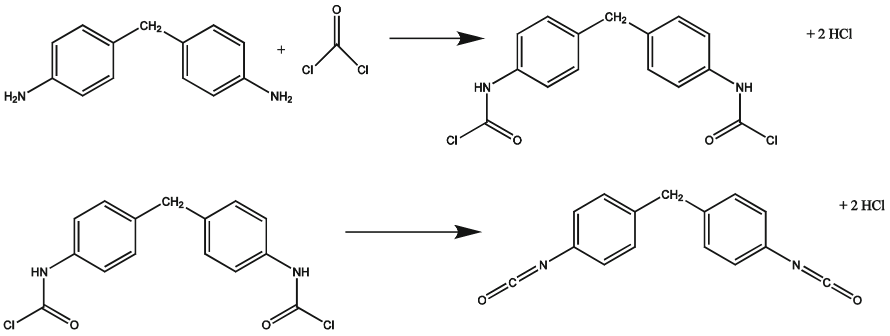

Fig. 5.6 Scheme of MDI synthesis

Phosgene is mainly produced and consumed on site in United States, Europe, and Asia. Very little trade of phosgene takes place because of legislative difficulties. It has been estimated that the consumption growth of phosgene has been 4.3 % between 2006 and 2011. The polycarbonate market is already in a transition to phosgene-free production processes, as a result of the enforcement of stricter governmental regulations. This enforcement, however, is strictly related to the availability of suitable alternative production process.

A competitive phosgene-free production process of MDI would find wide recognition among the environmental movements. This competitive alternative would make it possible to enforce stricter regulations for new MDI production facilities that exclude the use of phosgene.

Thus, it is not surprising that an enormous effort has been applied to the development of phosgene-free routes to isocyanates. Among possible alternatives, only three appear to have the potential for large-scale applications: the reductive carbonylation of aromatic nitro-compounds, the oxidative carbonylation of amines, and the reaction of amines with dimethylcarbonate.

5.3.1 Reductive Carbonylation of Aromatic Nitro-compounds

A promising and sustainable pathway to aryl isocyanates is the reductive carbonylation of nitro-arenes [50]. For the synthesis MDI, this is an excellent alternative method compared to the phosgenation of MDA. Already in 1967, Hardy and Bennett described the direct conversions of aromatic nitro-compounds with carbon monoxide on Rh/C catalysts at high pressure and temperatures (Figs. 5.6 and 5.7) [51].

Several catalysts can be used for this thermodynamically favored, highly exothermic process. Normally, nontoxic transition metals of groups 8–10 are employed, but also sulfur, selenium, and tellurium catalyze this reaction [50]. However, highly toxic catalyst residues were detected in the final products, and thus, this route is until now inapplicable for an industrial polyurethane synthesis [52]. The generally accepted reaction mechanism starts with the formation of a metallacycle intermediate from the nitro-arene in the presence of carbon monoxide and the

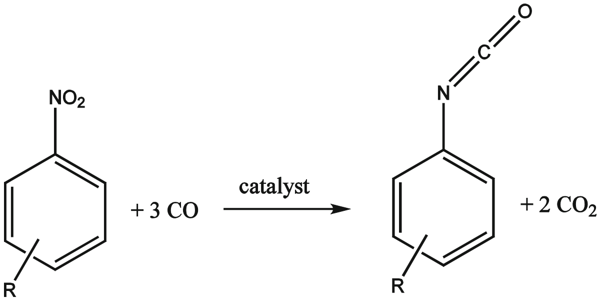

Fig. 5.7 Reductive carbonylation of nitro-arenes to isocyanates

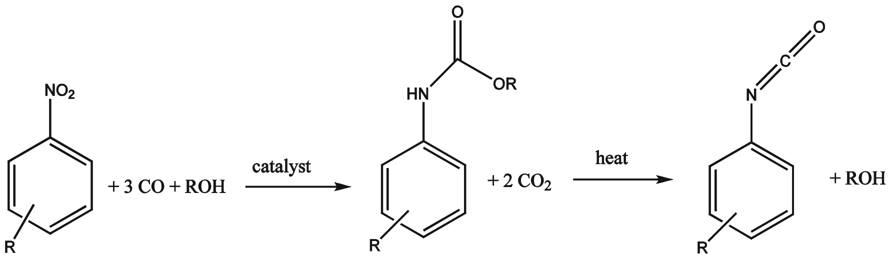

Fig. 5.8 Reductive carbonylation of nitro-arenes to carbamates followed by thermal decomposition to isocyanates

catalyst [53]. This intermediate fragments by decarboxylation, but the nitroso group remains bound to the metal. Subsequently, the insertion of CO occurs, followed by decarboxylation. The formed nitrene species, as a key intermediate, can be carbonylated to give the resulting isocyanate.

Another approach is a two-step synthesis in which the first is the carbonylation to N-phenylcarbamates in the presence of alcohols, followed by subsequent thermal decomposition to isocyanates (Fig. 5.8) [50].

Several catalysts and ligands are described for this process. Common homogeneous catalysts are based on ruthenium carbonyl complexes having chelating ligands [54], palladium(II) complexes with bipyridine and phenanthroline ligands [55], as well as rhodium carbonyl compounds [56]. N-phenylcarbamate is then reacted with formaldehyde to yield a dicarbamate, which is subsequently thermolytically decomposed to form MDI [57].

The reductive carbonylation of nitrobenzene is enhanced by the presence of aniline. Therefore, the reaction is conducted with a high concentration of aniline. In a patent of Haldor Topsøe, a molar feed ratio of 13.5/1/1/0.002 for methanol/aniline/nitrobenzene/catalyst is reported [58]; under CO atmosphere at 70 bar and 160 °C, nitrobenzene is nearly completely converted to methyl phenylcarbamate (MPC) in 3.5 h.

5.3.2 Oxidative Carbonylation of Aniline to Produce MPC

Another access to carbamates is the metal-catalyzed oxidative carbonylation of amines (Fig. 5.9).

In 1984, Fukuoka et al. reported a novel catalytic synthesis of carbamates by oxidative alkoxycarbonylation of primary amines and anilines with alcohols in the presence of platinum group metals and alkali metal halides [59]. The yields of methyl- and ethyl-carbamates were in most cases above 90 % when palladium and alkali metal iodides were used as catalyst. One year later, Alper and Hartstock showed a mild, catalytic alternative for the conversion of amines into carbamates [60]. Anilines were converted to methyl- and ethyl-carbamates using a catalytic

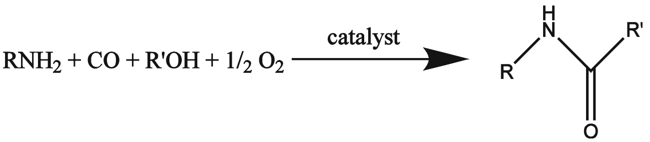

Fig. 5.9 Oxidative carbonylation of primary amines in the presence of alcohols

mixture of $PdCl_2$ (10 mol%), $CuCl_2$ (20 mol%), and traces of hydrochloric acid at room temperature. The obtained yields ranged from 16 % in the case of sterically hindered anilines up to 99 % for unsubstituted aniline. In the 1990s, Monsanto developed a technology to produce MPC by reacting aniline and carbon dioxide at 25 °C and 5.5 bar in presence of methyl chloride and caustic soda and issued several patents [61].

In 1992, Leung and Dombek reported that metallomacrocyclic compounds, such as metalloporphyrins, are excellent catalysts for the oxidative carbonylation of amines to carbamates [62]. Bayer has filed two recent patents for making MPC from oxidative carbonylation of aniline, in the presence of homogeneous cobalt (II) complexes with different ligands as catalysts [63]. The reaction takes place at 165 °C, 4 bar (0.4 MPa) of oxygen and 36 bar (3.6 MPa) of carbon monoxide; a quantitative yield (99 %) in MPC can be achieved.

5.3.3 The Dimethyl Carbonate Approach to the Synthesis of Isocyanate from Amine

Dimethylcarbonate (DMC) is a versatile and environmentally safe building block for the chemical industry. Its industrial use was very limited until 1984 when it started its production from phosgene and methanol [64]. Successively, EniChem has developed the production of DMC directly from CO and methanol according to the reaction in Fig. 5.10 [65].

DMC manufactured through this process presents high purity, absence of organic chlorine impurities, and no residual acidity. It finds extensive applications as a solvent, octane booster in gasoline to meet oxygenate specifications and raw material for organic synthesis [66].

DMC has two carbon centers at which a nucleophile may react: the carbonyl and the methyl groups. When a nucleophile attacks the carbonyl atom, the cleavage of acyl-oxygen bonds results in a methoxycarbonyl derivative. Therefore, DMC can replace phosgene as a safe starting material for carbonic acid derivatives. When a nucleophile attacks at the methyl carbon, the reaction produces a methyl functionalization due to the alkyl-oxygen bond cleavage. In this form, DMC acts as methylating agent, as a substitute for dimethyl sulfate [67].

Sometimes, the two different nucleophilic reactions occur in a competitive manner, leading to the formation of the main product together with undesired

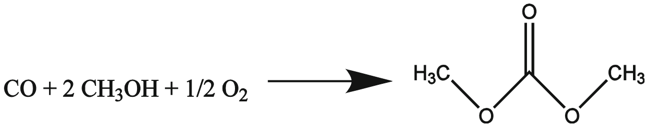

Fig. 5.10 DMC synthesis according to the EniChem process

byproducts. Indeed, DMC is particularly suitable to be used as carbonylating agents. It can be used for making polycarbonate resins or as a replacement of phosgene in making isocyanates. As stated before in this chapter, phosgene route to isocyanates for polyurethanes presents many drawbacks, among them its high toxicity. Therefore, several routes without phosgene are underway [5, 68]. One of the most feasible ways is based on DMC reaction with an amine in order to produce useful carbamates, $RNHCOOCH_3$:

$$RNH_2 + DMC \rightarrow RNHCOOCH_3 + CH_3OH$$

Methylcarbamates (or methylurethanes) can be schematically considered as esters of instable carbamic acid. Indeed, carbamates might be produced not only from amine and DMC but also from other substrates and through different synthetic routes [69]. Here we focused our attention mainly to the DMC process starting from aromatic amine, e.g., MDA. The reaction with DMC can be carried out under much milder conditions compared with the carbonylation of nitro- or amino-compounds [67], and carbamates can be transformed onto isocyanates by thermolysis [70]:

$$RNHCOOCH_3 \rightarrow RNCO + CH_3OH$$

This is an endothermic and highly reversible reaction, and because of the reactivity of the -NCO group, several undesired side reactions may occur, and they must be managed in order to minimize the formation of undesired byproducts. Indeed, it is a delicate reaction in which operative conditions and reactor design must be well controlled to obtain maximum performance. The reaction can be catalyzed and performed in gaseous or liquid phase [71].

Several patents claim the synthesis of carbamates from alkylcarbonates and amines by using Lewis acids such as Ti, Sn, Pb, and Zn compounds as catalysts [72, 73]. From an industrial point of view, DMC appears as the more feasible alkylcarbonate due to its chemical characteristics, specially its low molecular weight and low boiling point [74].

5.3.4 Synthesis of Methylene Diphenyl-4,4′-Diisocyanate from Dimethylcarbonate

MDI synthesis through the production of the diurethane appears as an environmentally friendly reaction performed in mild conditions. Actually, literature reported

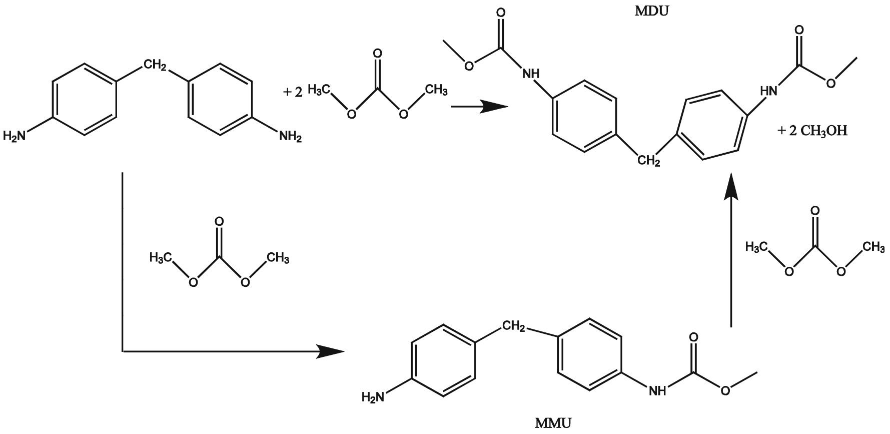

Fig. 5.11 Methoxycarbonylation of 4,4’-MDA with DMC

catalyzed MDI synthesis also using diphenylcarbonate (DPC) as carbonylating agent [75]. Indeed, DPC (prepared from DMC and phenol [76]) generally leads to high urethane yields, but its use is industrially less appealing because it is more expensive than DMC~~.~~

The methoxycarbonylation of the 4,4′-MDA with DMC is schematized in Fig. 5.11.

Normally, DMC acts as a reagent and solvent due to its good capacity to dissolve polar organic compounds, and a DMC/MDA molar ratio can vary from stoichiometric to 40/1.

In the reaction, there are two important aspects that deserve attention: the need to rapidly transform the two amine groups and the presence of methanol formed during the reaction. The first aspect means that once the substrate is monofunctionalized (MMU, methylene monourethane), this mono-intermediate should further proceed to react with DMC to form the desired product (methylene diurethane, MDU) avoiding the formation of byproducts with the consequent lowering of the overall selectivity. The main byproducts are represented by urea derivatives [77] and by N-methylated derivatives (e.g., $R\text{-}NHCH_3$ or $R\text{-}N(CH_3)_2$), whose formation occurs when DMC can act as methylating agent [78]. Furthermore, N-methylurethanes (e.g., $R\text{-}N(CH_3)\text{-}COOCH_3$) could also form. The problem can be overcome, for example, by choosing a high active catalyst or optimizing the reaction conditions (amount of MDA with respect to DMC, reaction time, temperature, and pressure). It should be noted that a temperature tuning is crucial in order to have high yields and good selectivity, remembering that urethanes are ready to be transformed by heat into isocyanates. An isocyanate formation in this DMC transformation, due to -NCO high reactivity with amine, for example, affords a severe lowering of the selectivity. As already described, the industrial polymeric MDA substrate is produced by the acid-catalyzed condensation of aniline with formaldehyde. The presence of MDA isomer and of polymeric MDA mixture enhances the complexity of the system. However, a large excess of employed DMC might be a problem in an industrial process asset due to the large recycle streams and the heating need of a high diluted media.

The second aspect concerns the presence of methanol in the reaction affording a DMC-MeOH azeotrope that should be managed in the recovery of DMC at the end of reaction.

Relatively few works were published on MDU synthesis from MDA, mainly using zinc acetate. Among them, Zhang et al. screened inorganic catalyst candidates (e.g., $ZnCl_2$, $Zn(OAc)_2$, $Pb(OAc)_2$, PbO, ZnO, and so on) [77]. The best one was methanol-pretreated PbO affording the diurethane with about 80 % of selectivity. Anhydrous $Zn(OAc)_2$ catalyst gave diurethane with a low selectivity in the used experimental conditions (160 °C, 3 h); however, it was reported that zinc acetate on SBA-15 gave an 87 mol% selectivity of MDU after 4 h at 170–180 °C, with a 1:21 MDA-DMC molar ratio [79]. Vidal-Ferran et al. observed again that 1.0 mol% zinc acetate is an excellent catalyst to synthesize dicarbamate of MDA in almost quantitative yields via reaction with DMC [80]. The reaction conditions with DMC were quite drastic since high temperature (180 °C) and a MDA-DMC molar ratio of 1:25 were needed in order to reach high selectivity (98 %) and yields. Dihydrate zinc acetate performed better than anhydrous one even if no explanations were given.

A synthesis of MDI from DMC over solid catalysts was developed in three steps [81]. In the first step, aniline and DMC were reacted to produce MPC. Then MPC condenses with formaldehyde to produce dimethyl-methylene-diphenyl-4,4-′-dicarbamate. This compound was thermically decomposed to MDI. MPC maximum yield with zinc acetate on activated carbon was 78 % with a 98 % selectivity. Unfortunately, the paper was focused on catalyst screening and characterization with less attention to the whole process yield and selectivity to MDI from aniline. Besides that, the use of already synthetized MDA as substrate industrially allows the reuse of existing equipment of MDA manufacturing.

One of the more interesting industrial DMC approaches appeared in patent literature in the period 1997–2001 assigned to Ministero dell'Università e della Ricerca Scientifica e Tecnologica, EniChem, and eni SpA. The patent group was dealing how to use the Lewis acid catalysts (mainly zinc derivatives) with DMC and MDA, even if some of the patents were mainly focused onto toluene diisocyanate (TDI) production [82–84]. Two new zinc catalysts were claimed in the synthesis of 4,4′-MDA with DMC, and the results are summarized in Table 5.10 [82].

The MDA conversion was almost quantitative with both catalysts, while zinc basic carbonate gave higher MDU selectivity with respect to zinc carbamate. The zinc basic carbonate is a peculiar catalyst in which two different coordination metal sites are present, probably offering a better DMC activation. The zinc carbamate indeed is a μ-oxo diethylcarbamato complex of zinc having a preformed carbamato derivative and therefore in principle able to coordinate DMC or more ready to exchange with DMC the urethane moiety [85]. Even if with lower selectivity, the zinc carbamate is more reactive with MDA.

Table 5.10 Zn catalysts for MDU synthesis claimed in [82]

Catalyst	Catalyst[a] (mol/%)	Reaction t / °C	MDA conversion (wt/%)	MDU selectivity (mol/%)
$ZnCO_3 \cdot 2Zn(OH)_2 \cdot H_2O$	13	160 (6 h)	>99	73
$Zn_4O(OOCNEt_2)_6$	1.5	160 (3 h)	>99	62

[a] With respect to MDA

A breakthrough in the preparation of MDU was reported in a patent filed in 2000 [83]. Here, the amount of produced methanol in the reaction media was managed in order to enhance the yield and the selectivity of the MDU. In fact, the accumulation of the produced alcohol in the reaction environment caused a lowering of reaction kinetics and a consequent possibility for the compounds to react in secondary reactions to form, for example, N-methylated or urea compounds. Other patents claimed the complete removal of methanol using specific reaction conditions [86], but the selectivity to urethane was low due to the main formation of urea products by the reaction

$$RNH_2 + RNHCOOCH_3 \rightarrow RNH - CO - NHR + CH_3OH$$

The whole removal of methanol meets the requirements of increasing the conversion of the starting amine but with an unwanted urea formation.

In this case, using zinc acetate dihydrate as catalyst, the tuning of methanol concentration in the media allowed to increase yield and selectivity. This was obtained using an apparatus as reported in Fig. 5.12.

4,4′-MDA was charged in reactor A in DMC (molar ratio DMC/MDA equal to 31/1), and zinc acetate dihydrate was added (3.4 % mole catalyst/mole MDA). The reactor was then pressurized to 2 bar and heated to 140 °C. The autoclave was directly connected to an alcohol removal system consisting of a condenser B at 115 °C (in which a fractionation of an enriched MeOH phase in DMC was performed) and a final condenser C at 10 °C. The condensate was finally collected in D vessel. In 1.5 h, the reaction was complete, and the dedicated system allowed the removal of about 57 % of the total produced methanol leaving a residual methanol concentration in A of about 27 %. The other produced methanol was converted into methyl acetate or in byproducts. The conversion of 4,4′-MDA was >99 % in weight, and the selectivity in 4,4′-MDU was about 97 %. These results, obtained in milder conditions than other works, open the industrial feasibility to produce MDI through the DMC synthesis step, in which the optimal methanol concentration is designed enhancing catalyzed methanol carbamate functionalization of amino groups.

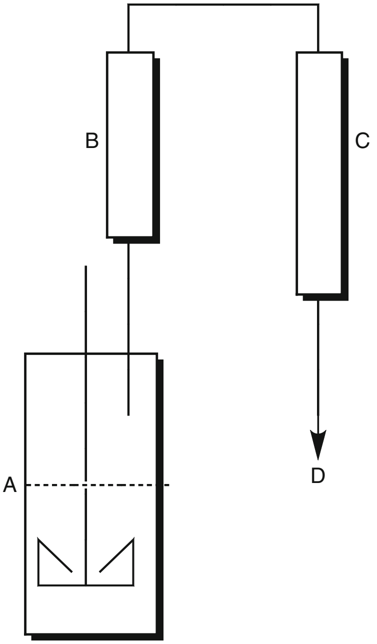

Fig. 5.12 Scheme of the apparatus to manage MeOH concentration during the reaction. (**a**) Reactor vessel. (**b**) First condenser. (**c**) Second condenser. (**d**) Condensate vessel

5.4 Conclusions

In the latter part of the twentieth century, the increasing awareness that many syntheses practiced on a large scale were detrimental to the environment led to a movement toward reshaping the science of chemical synthesis. It was the birth of green chemistry. Green chemistry is the design of chemical products and processes that reduce or eliminate the generation of hazardous substances. The primary pathways for green chemistry include, among others, waste minimization in the chemical production process and replacement of existing products with less toxic alternatives. The evolution of these practices is being driven by a combination of technical, regulatory, consumer preference, and economic factors.

In this scenario, this paper describes possible phosgene-free routes to produce MDI, an important building block for the manufacture of polyurethanes, thermoplastics, and foams. The manufacture of MDI proceeds via classical process chemistry, i.e., from aniline condensation with formaldehyde to the corresponding diamine (MDA) catalyzed by HCl and subsequent reaction with phosgene to MDI. However, handling corrosive acid and very reactive and toxic phosgene presents a serious threat to the living environment to the extent that the use of this chemical is severely restricted by environmental regulations and permits in order to prevent disasters.

For the production of MDA, several different kinds of solid acid catalysts have been patented as useful substitutes for HCl, and zeolites seem to be the most promising alternatives. In particular zeolites, having SI between 2.5 and 19, showed the best catalytic performances. Therefore, it is possible to produce MDA avoiding the utilization of HCl and the side production of huge amounts of NaCl contaminated by aromatic amines. Actually, this last fact renders the disposable of the waste chemicals cumbersome and expensive.

Among the route considered to eliminate the phosgene for following production of MDI, the synthesis of carbamate alkyl esters that with subsequent pyrolysis at elevated temperatures would give the isocyanate seems the most industrially feasible.

The MDA functionalization to carbamate using dimethylcarbonate resulted more feasible and robust only when it was found the appropriate way to manage the concentration of methanol in the reaction medium. In this way it was possible to improve the yield and selectivity to the desired product.

Using simple zinc acetate dihydrate as catalyst and tuning the concentration of produced MeOH in the reaction media, high conversion of 4,4′-MDA and high selectivity in 4,4′-MDU were achieved. These results, obtained in milder conditions than other previous works, open the industrial feasibility to produce MDI through the DMC synthesis step.

Therefore, even though the phosgene-free technology is not competitive today, these studies indicate that they do have the potential to become cost-competitive. It is likely that governments and legislative institutions could impose stricter legislation and thereby stimulate the development and the scaling up to an actual commercial production facility of the phosgene-free technology and enforce a transition in this market.

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Chapter 6
Chlorine-Free Heterogeneous Acid Catalysts

Claudio Jose de Araujo Mota

Abstract Chlorine-containing compounds are highly used as catalysts. $AlCl_3$ is a traditional Lewis acid, whereas HCl is commonly used as Bronsted acid, either pure or in aqueous solution. Nevertheless, these acidic substances can be replaced by solid acid materials, such as zeolites, metal oxides, and clays, among others, all presenting high catalytic activity and yielding significant less hazardous wastes. In addition, many heterogeneous acid catalysts can be reused, contributing to greener and more sustainable processes.

We wish to show in this chapter some application of solid acid catalysts in alkylation, etherification, acetalization/ketalization, esterification, and carbonation reactions to replace chlorinated acidic systems. In contrast, we will show a positive role of chlorinated compounds as water suppressor agent in the carbonation of methanol with CO_2 to produce dimethyl carbonate.

Keywords Acid catalysis • Zeolites • Clays • Metal oxides • Alkylation • Etherification • Esterification • Carbonation

6.1 Chlorine-Containing Catalysts

$AlCl_3$ is a traditional Lewis acid. It is commonly used as catalyst in Friedel-Crafts alkylation and acylation to produce alkyl and acyl aromatic compounds, respectively (Scheme 6.1). In these reactions, the $AlCl_3$ catalyst interacts with the nonbonded electron pairs of the alkyl halide (RX) or acyl halide (RCOX) to yield an electrophilic species, which attacks the aromatic ring. For acyl halides, the interaction with the $AlCl_3$ usually yields an acyl cation (RCO^+) as the acylating agent, whereas for alkyl halides, carbocations (R^+) are generally believed to be the intermediates, when 2° and 3° alkyl groups are involved. Notwithstanding, high loadings of the $AlCl_3$ catalysts, usually the stoichiometric ratio, are necessary,

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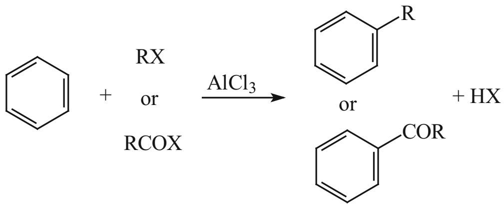


Scheme 6.1 $AlCl_3$-catalyzed Friedel-Crafts alkylation and acylation (*R* stands for and alkyl group; *X* stands for an halogen atom)

Scheme 6.2 Formation of alkyl chloride and ethers from alcohols and HCl

$$\mathrm{ROH + HCl \longrightarrow RCl + H_2O}$$

$$\mathrm{R'OH + Na \longrightarrow 1/2\,H_2 + R'ONa \xrightarrow{RCl} ROR' + NaCl}$$

because of the interaction with the formed HX to yield $HAlCl_3X$ complexes. In addition, work-up procedures usually generate high amounts of chlorinated wastes, which are not environmentally friend.

HCl is a traditional Bronsted acid. It may be used pure or in concentrated aqueous solution to catalyze many reactions. HCl is also a reactant to produce alkyl halides and ethers from alcohols (Scheme 6.2).

The use of HCl is a problem in many industrial processes. It is highly corrosive and attacks stainless steel, requiring the use of vitrified or ceramic reactors. In addition, neutralization of the remaining HCl requires the use of basic solution, yielding significant amounts of wastes.

Although $AlCl_3$ and HCl were important catalysts in the infancy of organic chemistry, helping the discovery of new reactions and processes, their use, today, is neither desirable nor sustainable. The principles of green chemistry [1] state that the generation of residues, by-products, and wastes must be minimized. Hence, other Bronsted and Lewis acid catalysts should replace HCl and $AlCl_3$ in these reactions.

6.2 Chlorine-Free Catalysts for Alkylations

Zeolites are crystalline aluminosilicates of pores with molecular dimensions [2]. Figure 6.1 shows a part of the structure of zeolite Y. Each corner represents a tetrahedral Si or Al atom, linked by oxygen atoms (not shown in the figure). The pore aperture of zeolite Y is around 7.4 Å (0.74 nm), but the internal cavity is 13 Å (1.3 nm) wide.

Since the Al atom is tetracoordinated in the zeolite structure, it bears a negative charge, which must be compensated by a positive one (Fig. 6.1). Thus, zeolites are cation-exchange materials. The zeolite Y is usually synthesized with Na^+ as counterion, but it can be easily exchanged by other monovalent, divalent, and trivalent cations.

The use of iron-exchanged zeolites as catalysts for traditional Friedel-Crafts alkylation with alkyl halides has been studied [3, 4]. Ethylbenzene may be alkylated

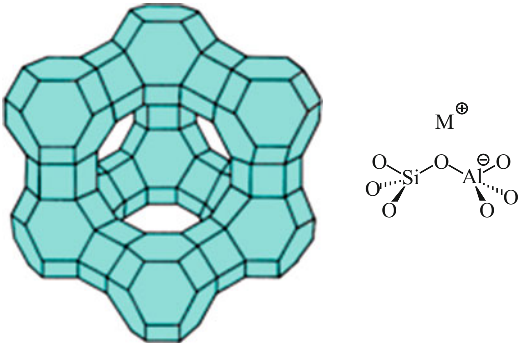
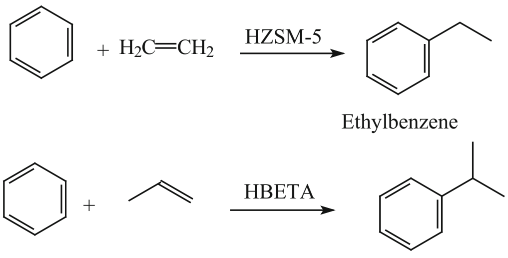


Fig. 6.1 Representation of part of the zeolite Y crystalline structure and of the active site, showing the tetrahedral aluminum atom and the counterbalance cation

Table 6.1 Results of ethylbenzene alkylation using FeY as catalyst at 60 °C and 180 min

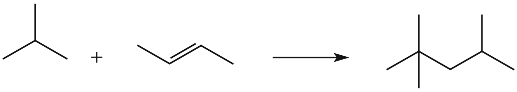
RCl	Conversion/%	Selectivity to monoalkylation	Isomer distribution		
			o	m	p
n-Butyl	4.3	100	nd	nd	nd
Isobutyl	2.7	100	nd	nd	nd
sec-Butyl	99	100	26	25	49
tert-Butyl	96	97	–	21	79



Scheme 6.3 Mobil-Badger process of ethylbenzene production using HZSM-5 zeolite and EniChem process for the production of cumene using HBETA zeolite

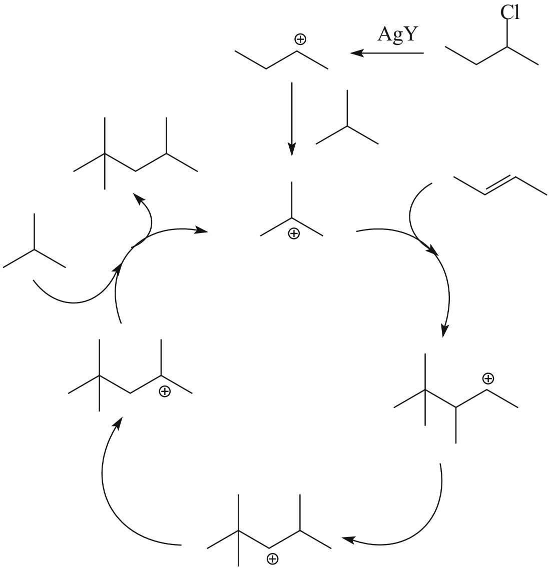
with tert-butyl chloride in the liquid phase at 60 °C. After 30 min, the conversion is 95 % with 97 % selectivity to the monoalkylated isomer. Table 6.1 shows the results of ethylbenzene alkylation with different alkyl halides over FeY. It can be observed that conversion is low for primary alkyl halides, but it is satisfactory for secondary and tertiary ones. High selectivity to the monoalkylated product was observed. The para-alkylated ethylbenzene was the main product, which may reflect the shape selectivity properties of zeolites [5].

Protonic zeolites are used for Friedel-Crafts alkylations with alcohols and olefins. In fact, present industrial processes of ethylbenzene and cumene synthesis from the alkylation of benzene with ethene and propene, respectively, use acidic zeolite catalysts (Scheme 6.3), in replacement of old processes, based on $HCl/AlCl_3$ and HF catalysts [6].



Scheme 6.4 Alkylation of isobutane with 2-butene. Common catalysts are H_2SO_4 and anhydrous HF

Scheme 6.5 Proposed mechanistic pathway for alkylation of isobutane with 2-butene over AgY catalysts. The initial step is the formation of the carbocation through the interaction of 2-chlorobutane with AgY



Another interesting use of zeolite catalysts is in the alkylation of isobutene with 2-butene. This process produces high octane gasoline, with high content of branched alkanes (Scheme 6.4). The available commercial technologies still use concentrated sulfuric acid or anhydrous HF as catalysts [7]. Thus, significant amounts of hazardous wastes are generated. $HCl/AlCl_3$ can also be used as catalyst in this reaction, but it is not sustainable either.

The reaction mechanism involves protonation of the hydrocarbons to form carbocations. Zeolites and other solid acids are good catalyst for this reaction [8], but the main problem is the rapid deactivation due to formation of coke. Olefins tend to be preferentially adsorbed over solid acid catalysts, leading to oligomerized products that do not desorb from the acid site.

We worked [9] on a different approach, using metal-exchanged zeolites as catalyst in alkylation of isobutane with 2-butene. Instead of protonating the hydrocarbons to generate the carbocation, we used a small amount of alkyl halide to yield the carbocations, through interaction with the metal cation. The formed carbocations undergo a self-catalyzed reaction cycle, yielding the branched alkanes (Scheme 6.5). Deactivation is significantly slower compared with a protonic zeolite catalysts (Fig. 6.2). Therefore, this type of approach could be used to replace HF and other strongly acidic solution as catalyst for alkylation of isobutane.

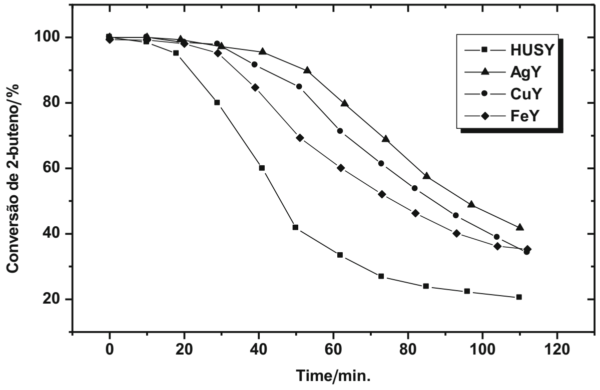


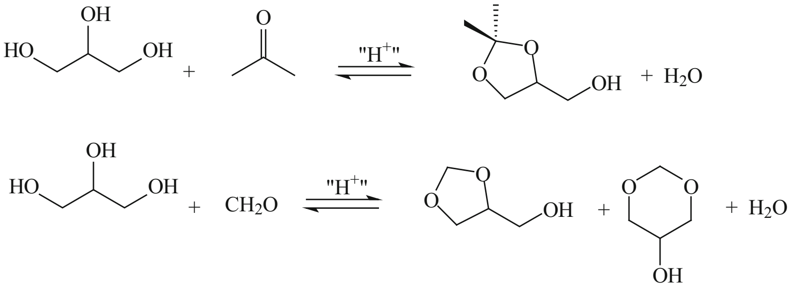
Fig. 6.2 2-Butene conversion against time on stream for the alkylation of isobutane over protonic zeolite (HUSY) and metal-exchanged zeolite Y

6.3 Chlorine-Free Catalysts for Acetalization/Ketalization

Acetals and ketals are produced upon the reaction of aldehydes and ketones with alcohols, respectively. The reaction is reversible and carried out in the presence of Bronsted acid catalysts.

We have studied the use of different types of heterogeneous acid catalysts in the acetalization and ketalization of glycerol with formaldehyde and acetone [10]. Glycerol, also called glycerin, is a by-product of biodiesel production through the transesterification of vegetable oils and fats. In recent years, there is a strong interest in the development of glycerol-derived products to add value to the biodiesel chain [11–14]. The product of the acid-catalyzed reaction of acetone and glycerol is solketal, a five-membered cyclic ketal, whereas the reaction with formaldehyde affords a mixture of acetal isomers, with five- and six-membered rings (Scheme 6.6). These results may be explained by the relative stability between the five- and six-membered isomers. While in the case of the cyclic acetals the energy difference is about 0.7 kcal·mol^{-1} (2.9 kJ·mol^{-1}), favoring the six-membered ring isomer, for the solketal isomers, this difference is around 1.7 kcal·mol^{-1} (7.1 kJ·mol^{-1}), favoring the five-membered ring structure [15]. The substituent methyl groups in solketal face more repulsive interactions in the six-membered ring isomer than in the five-membered ring one. This type of repulsion is not present in the case of the acetals of glycerol and formaldehyde. Solketal has been shown to be a good additive for gasoline, decreasing the gum formation and increasing the octane number [16].

Figures 6.3 and 6.4 present the glycerol conversion to solketal and glycerol/formaldehyde acetal isomers. The reaction is faster with acetone, showing conversion of more than 95 % after 40 min of reaction time. Amberlyst-15 acid resin was the most active catalyst, whereas zeolite HUSY and HZSM-5 presented lower activity than the homogeneous catalysts, p-toluenesulfonic acid. The reaction with formaldehyde is slower than with acetone over all the studied catalysts. Only zeolite HBETA showed conversion higher than 90 % after 60 min of reaction time. Amberlyst-15 presented a significantly lower activity in comparison with the reaction with acetone, whereas zeolites HUSY and HZSM-5 were virtually



Scheme 6.6 Acid-catalyzed reaction of glycerol with acetone and formaldehyde to form, respectively, solketal and a mixture of acetal isomers

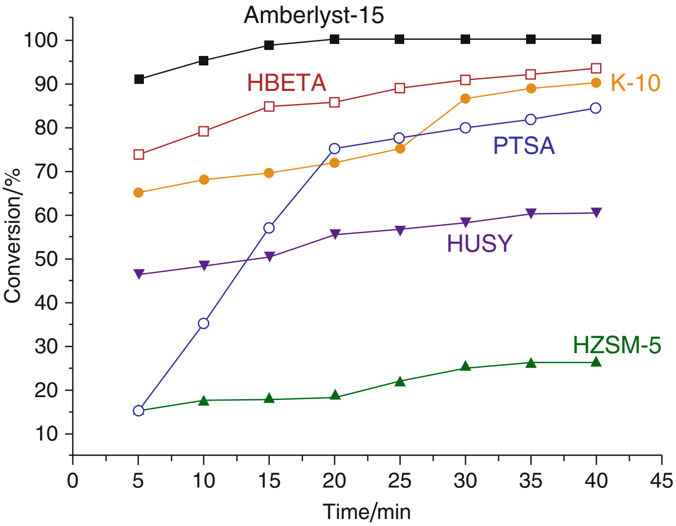


Fig. 6.3 Kinetics of the glycerol reaction with acetone at 70 °C over various acid catalysts. PTSA stands for p-toluenesulfonic acid

inactive. These results may be explained by the hydrophobicity of the zeolites. This is an important property of these materials and is related with the Si/Al content [17]. Silicon-rich zeolites are more hydrophobic, whereas aluminum-rich zeolites are hydrophilic. The zeolite HBETA used presented a total Si/Al ratio of 16, whereas this ratio was about 2.5 for the zeolite HUSY (including the extra-framework aluminum atoms) and around 25 for HZSM-5. The reactions to produce the acetal isomers employed a 37 % aqueous solution of formaldehyde. The excess of water in the medium favors the reverse reaction and compete with the reactants for the acid sites. Thus, most of the catalysts showed reduced activity in comparison with the reaction with acetone. On zeolite HBETA however, the hydrophobic environment inside the pores prevents the entrance and diffusion of water in the

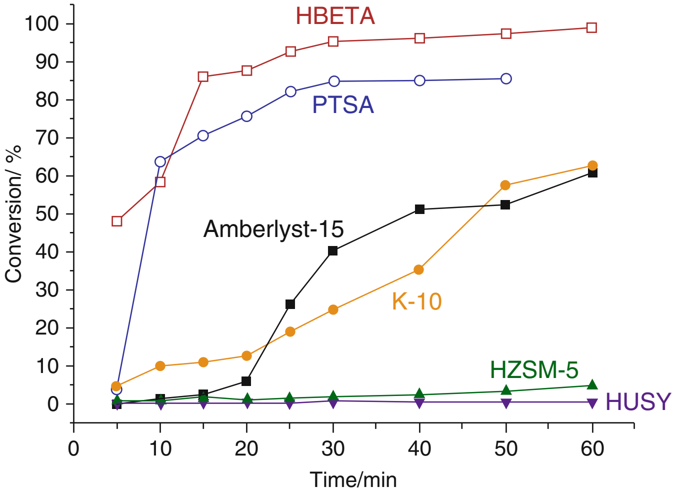


Fig. 6.4 Kinetics of the glycerol reaction with aqueous formaldehyde at 70 °C over various acid catalysts. PTSA stands for p-toluenesulfonic acid

Table 6.2 Composition and reactivity of a crude glycerol from a Brazilian soybean biodiesel plant

Composition	wt%
Glycerol	80
Methanol	7
Water	0.2
NaCl	12.8
Conversion to solketal[a]	50 %

[a] Reaction carried out at 70 °C, 60 min with Amberlyst-15

medium to the acid sites, preserving their strength while expelling off the water formed during the acetalization process. Therefore, this catalyst presented the highest activity among the acid systems studied. HZSM-5, although being a silicon-rich zeolite, may present pore constraint problems which impair the formation of the products. In fact, its activity in the reaction with acetone may be ascribed to the external acid sites, which would be virtually inactive in the presence of excess of water. HUSY has the lowest Si/Al ratio, being hydrophilic. In the reaction with acetone, this zeolite presents moderated activity, which can be explained by the fact that as the water from the ketalization reaction is formed, it remains adsorbed on the acid sites affecting the overall activity. However, in the reaction with formaldehyde solution, the amount of water in the system virtually prevents the reactants to interact with the acid sites, thus leading to an extremely low activity.

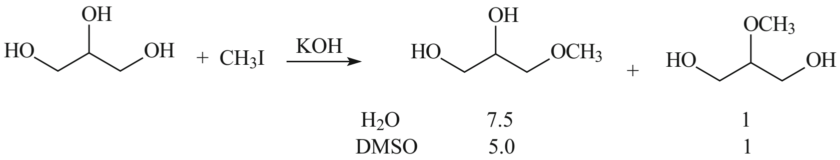
Crude glycerol from biodiesel production plants has many impurities. Table 6.2 shows some typical composition of crude glycerol produced in a Brazilian soybean biodiesel plant. There is a significant amount of water and NaCl, formed upon the neutralization of the dissolved basic catalyst with HCl. The conversion of this crude glycerol to solketal using Amberlyst-15 is significantly lower, compared with pure glycerol. Doping a pure glycerol with similar amounts of each contaminant indicated that the decrease in catalytic activity was due to the presence of NaCl and water [18], which may partially neutralize the acid sites of the catalyst. In fact, when concentrated HCl was used as catalyst in the reaction of pure glycerol with acetone, only 20 % conversion was observed, showing that it is not a good catalyst for this reaction.

6.4 Chlorine-Free Etherification

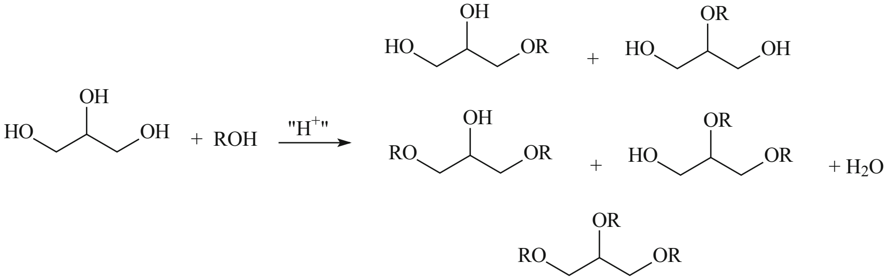
There are two major routes for the production of ethers: the synthesis of Williamson, where an alkoxide reacts with an alkyl halide, and the acid-catalyzed dehydration of alcohols. We studied these two methods with glycerol with the purpose of producing alkyl glyceryl ethers that would be useful as fuel additives.

The reaction of glycerol with dimethyl sulfate or methyl iodide in the presence of KOH yields methyl-glyceryl ethers. Depending on the stoichiometric amount used, mono-, di-, and trimethyl glyceryl ethers can be produced. The medium also affects the selectivity toward the hydroxy group of glycerol that would be methylated. In aqueous KOH solution, the ratio of 1-methyl-glyceryl monoether to the 2-methyl isomer is 7.5, whereas in DMSO the ratio decreases to 5 (Scheme 6.7). This finding can be explained by the solvation of the alkoxide. In water, the glycerol alkoxide is mostly stabilized by intermolecular hydrogen bonds, with the solvent playing a decisive role. Thus, the less sterically hindered primary alkoxides are better stabilized. On DMSO, besides the stabilization by ion-dipole interaction, there is significant stabilization by intramolecular hydrogen bonds, which favor the secondary alkoxide.

Besides the problem of using hazardous reactants, such as dimethyl sulfate or methyl halides, the methylation of glycerol may be extremely exothermic with great evolution of heat. Therefore, the production of the ethers through the acid-catalyzed reaction of glycerol with alcohols could be a better pathway (Scheme 6.8). Table 6.3 shows the glycerol conversion and selectivity to mono-, di-, and triethers over Amberlyst-15 acid resin at 180 °C [19]. The glycerol conversion was usually high, but the selectivity depends on the molar ratio and time of reaction. The monoether was mainly produced with di- and triethers being in lower amounts.



Scheme 6.7 Monoetherification of glycerol with methyl iodide in the presence of KOH. Ratio of the 1-methyl ether to the 2-methyl ether in water and DMSO



Scheme 6.8 Acid-catalyzed reaction of glycerol with alcohols to afford mono-, di-, and triethers

Table 6.3 Etherification of glycerol with different alcohols at 180 °C in the presence of Amberlyst-15 acid resin

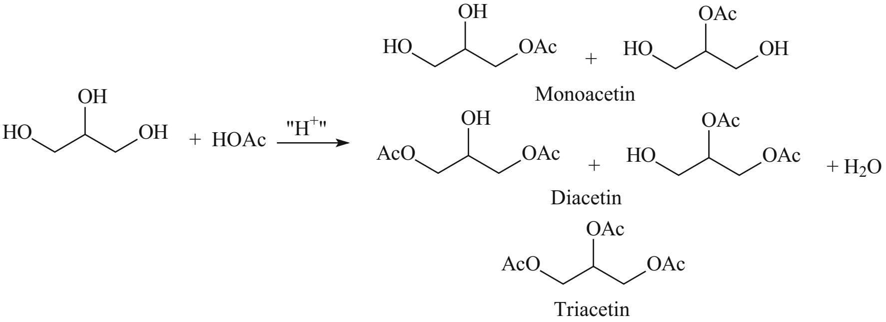
Alcohol	Mole ratio[a]	Time/h	Conversion/%	Selectivity/% Monoether	Diether	Triether
Methanol	3	4	62	74	19	7
Methanol	3	8	84	72	18	10
Methanol	6	4	79	74	16	10
Methanol	6	8	100	68	20	12
Ethanol	3	4	90	87	5	8
Ethanol	3	8	96	65	19	16
Ethanol	6	4	95	79	12	9
Ethanol	6	8	89	87	7	5
Isopropanol	3	4	98	79	19	1
Isopropanol	3	8	95	82	16	2
Isopropanol	6	4	98	76	22	2
Isopropanol	6	8	94	82	17	1
tert-Butanol	3	4	95	63	28	9
tert-Butanol	3	8	98	51	44	5
tert-Butanol	6	4	98	68	22	10
tert-Butanol	6	8	100	66	25	9

[a] Alcohol/glycerol molar ratio

The ethyl glyceryl ethers can be used as additives to improve the cold flow properties of biodiesel [19].

6.5 Chlorine-Free Esterification

Esters can be produced by the acid-catalyzed reaction of alcohols with carboxylic acids. Although sulfuric acid is mostly employed as catalyst in this reaction, HCl can be used as well. Another method of producing esters is through the reaction of



Scheme 6.9 Acid-catalyzed esterification of glycerol with acetic acid to afford monoacetin, diacetin, and triacetin

anhydrides or acyl halides with alcohol, either alone or in the presence of an acid catalyst.

We have studied [20, 21] the esterification of glycerol with acetic acid using different heterogeneous acid catalysts and reaction conditions (Scheme 6.9). Table 6.4 shows the glycerol conversion and selectivity toward mono-, di-, and triacetin derivatives.

The formation of triacetin from acetic acid and glycerol is not favored over all catalysts studied. In fact, it has been shown [22] that the last acetylation step is endothermic and not favored by thermodynamic, which may explain the poor selectivity to triacetin in this reaction. The best results were observed with Amberlyst-15 acid resin using a 4:1 molar ratio of acetic acid to glycerol during 120 min. The observed selectivity to triacetin in this case was 24 %. Zeolites are not good catalyst for this reaction either. HZSM-5 and HUSY showed low glycerol conversion at 30 min of reaction time, whereas HBETA presented similar conversion and selectivity of the blank, uncatalyzed reaction after 120 min of reaction time. In the case of HUSY, the explanation may be related with its hydrophilicity, as in the case of the formation of glycerol/formaldehyde acetals. HZSM-5 has pore constraint problems, which may impair the formation of the acetins. Notwithstanding, the results with HBETA zeolite is surprising, because this zeolite is hydrophobic and has large pores.

We have also studied the reaction of acetic anhydride with glycerol in the presence of different acid catalysts [21] and the results are presented in Table 6.5. The thermodynamic of the reaction with the anhydride favors the formation of triacetin [22]. In all reactions the glycerol conversion was 100 %, showing the higher reactivity of the anhydride compared with acetic acid. Using 4:1 molar ratio of anhydride to glycerol, triacetin could be formed in 100 % selectivity over HBETA and K-10 montmorillonite after 20 min of reaction time and at 60 °C. The same selectivity could be observed with Amberlyst-15 acid resin, but at longer time. Niobium phosphate showed 100 % selectivity to triacetin only at 120 °C and 120 min of reaction time; a result slightly better that the non-catalyzed reaction at the same conditions. At the stoichiometric ratio, the selectivity to triacetin was

Table 6.4 Esterification of glycerol with acetic acid with different heterogeneous catalysts and conditions

Catalyst	t/°C	Time/ min	Mole ratio[c]	Conv./%	Selectivity/% Monoacetin	Diacetin	Triacetin	Acetol[d]
Amberlyst-15[a]	120	30	3	97	31	54	13	2
Amberlyst-15[b]	120	120	4	100	18	55	24	3
K-10[a]	120	30	3	96	44	49	5	2
K-10[b]	120	120	4	100	36	52	6	6
Nb_2O_5[a]	120	30	3	30	83	–	–	17
$NbOPO_4$[b]	120	120	4	100	38	49	7	5
HZSM-5[a]	120	30	3	30	83	10	–	7
UUSY[a]	120	120	3	14	79	14	–	7
HBETA[b]	120	120	4	94	48	39	4	9
Blank[b]	120	120	4	91	50	40	4	7

[a] Ref. [20]
[b] Ref. [21]
[c] Acetic acid/glycerol mole ratio
[d] Acetol is hydroxyacetone

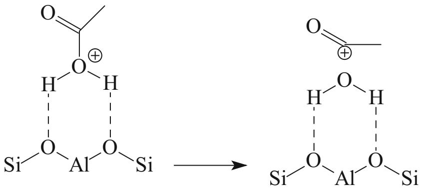
Table 6.5 Esterification of glycerol with acetic anhydride with different heterogeneous catalysts and conditions

Catalyst	Mole ratio[a]	t/°C	Time/min	Selectivity to acetins % Monoacetin	Diacetin	Triacetin
HBETA	4	60	20	–	–	100
HBETA	3	60	120	–	38	62
K-10	4	60	20	–	–	100
K-10	3	60	120	–	22	78
Amberlyst-15	4	60	80	–	–	100
Amberlyst-15	4	60	20	–	10	90
$NbOPO_4$	4	60	120	–	53	47
$NbOPO_4$	4	120	80	–	–	100
Blank	4	60	120	10	56	34
Blank	4	120	120	–	6	94

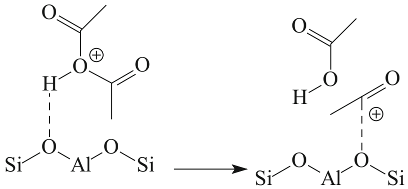
[a] Acetic anhydride/glycerol mole ratio

lower, with significant amounts of diacetin present in the medium. Monoacetin was only detected in the blank experiment at 60 °C.

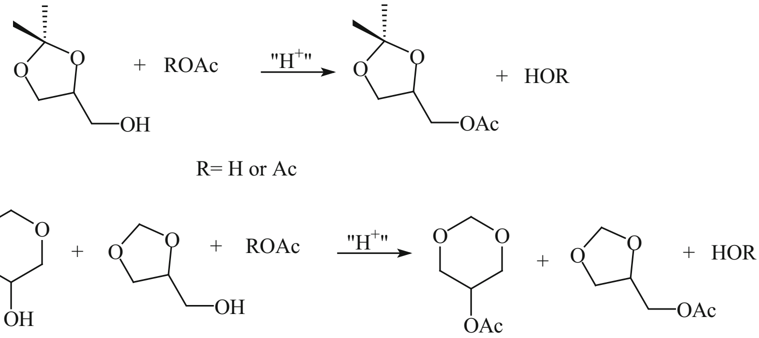
The good performance of zeolite HBETA in the acetylation of glycerol with acetic anhydride contrasts with its poor performance in the acetylation with acetic acid. This result suggests that the interaction of acetic acid and acetic anhydride with the acid site of the zeolite does not occur in the same manner, to yield a common intermediate. The explanation may arise from the formation of the acetyl



Scheme 6.10 Proposed structure of the protonated acetic acid on the zeolite surface and its dehydration to the acetyl cation (no zeolite assistance)



Scheme 6.11 Proposed structure of the protonated acetic anhydride and its transformation to the acetyl cation (zeolite-assisted)



Scheme 6.12 Acid-catalyzed acetylation of solketal or glycerol/formaldehyde acetals (R = H or Ac)

cation, through the $A_{AC}1$ mechanism of ester formation. In the case of acetic acid, there is no assistance from the framework oxygen atoms of the zeolite structure in the formation of the acetyl cation from the adsorbed acetic acid (Scheme 6.10), leading to a higher energetic pathway. On the other hand, for acetic anhydride, the formation of the acetyl cation may be assisted by the framework oxygen atoms (Scheme 6.11), leading to a more favorable reaction mechanism. It is worth mentioning that adsorption of hydroxylated compounds occurs through hydrogen bonding with the framework oxygen atoms [23–25], similarly to the structure shown in Scheme 6.10. In addition, other electrophilic reactions take place with nucleophilic assistance from the zeolite structure [26], supporting the present mechanistic view.

Another interesting application of acetic acid and acetic anhydride is in the acetylation of solketal (Scheme 6.12) or glycerol/formaldehyde acetals. These

Table 6.6 Acetylation of solketal and glycerol/formaldehyde acetals at different conditions

Catalyst	Acetylating agent[a]	Conversion/%	Selectivity/%[b]
Solketal			
Amberlyst-15	HOAc	56	92
Amberlyst-15	Ac_2O	94	85
$NbOPO_4$	HOAc	29	28
$NbOPO_4$	Ac_2O	13	100
Glycerol/formaldehyde			
Amberlyst-15	HOAc	51	44
Amberlyst-15	Ac_2O	100	95
$NbOPO_4$	HOAc	28	28
$NbOPO_4$	Ac_2O	75	100

[a] Molar ratio of 1:1

[b] Selectivity to the acetylated solketal or glycerol/formaldehyde acetals

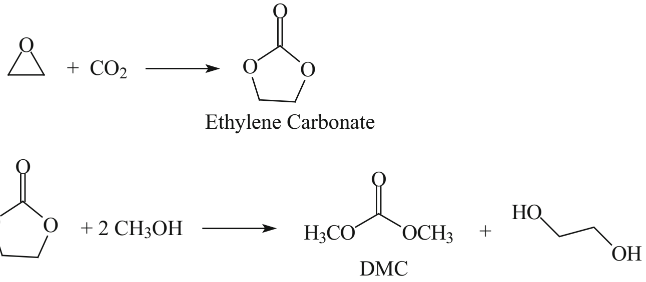
products are potential additives for biodiesel [27], but processes for their production are still poorly studied.

Table 6.6 shows the results of acetylation of solketal and glycerol/formaldehyde acetals with different catalysts and acetylating agents [28]. The conversion using acetic anhydride is higher than with acetic acid, reflecting its increased reactivity. Nevertheless, the selectivity to the acetylated solketal is somewhat lower when the anhydride was used as reactant. Triacetin and other by-products were detected and associated with other processes taking place in the medium [28]. Nevertheless, the use of HOAc and solid acid catalysts prevents the use of acyl halides in the reaction.

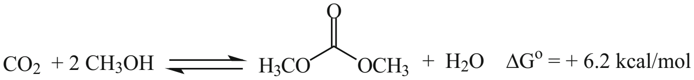
6.6 Chlorine-Free Carbonation

Organic carbonates are important chemicals. Dimethyl carbonate (DMC) is used in the production of polymers and is also an antiknocking additive for gasoline [29]. Cyclic carbonates, such as ethylene (EC), propylene (PC) and glycerol (GC) carbonates, are also valuable chemicals and solvents.

The production of DME may be achieved through the reaction of phosgene ($COCl_2$) with methanol. This process has been discontinued, and today [30], DMC is industrially produced in two steps by the reaction of CO_2 with ethylene oxide to afford EC, which subsequently reacts with methanol to yield DMC (Scheme 6.13). This technology, developed by Asahi Kasei Chemicals, avoids the emission of 1730 ton of CO_2 into the atmosphere for each 10,000 ton of polycarbonate produced. Although the production of DMC through this route is significantly greener than the route from phosgene, it still involves hazardous reactants, such as ethylene oxide. Therefore, the development of a direct route involving the reaction of methanol with CO_2 is highly desired.



Scheme 6.13 Asahi Kasei Chemicals route to DMC from CO_2



Scheme 6.14 Reaction of CO_2 with methanol to produce DMC

The reaction of CO_2 with methanol is not favored by thermodynamics [31] (Scheme 6.14). The equilibrium may be shifted toward DMC by the removal of water, as well as by the use of excess of methanol. Alkyl and alkoxy tin compounds, such as Bu_2SnO, have been used as catalyst in this reaction, along with water suppressor agents to shift the equilibrium. Nevertheless, depending on the nature of the suppressor, several by-products may be formed, which makes the whole process not significantly green and sustainable.

The key to a successful green and sustainable process for DMC production from the reaction of CO_2 and methanol involves the use of a suppressor that reacts faster with water than DMC itself, and that could be recycled at the end of the reaction. Many suppressors studied in the literature involve nitriles, which produce amides and carboxylic acids as final products. In many instances, these chemicals cannot be easily reconverted in the nitrile for reuse, being regarded as wastes.

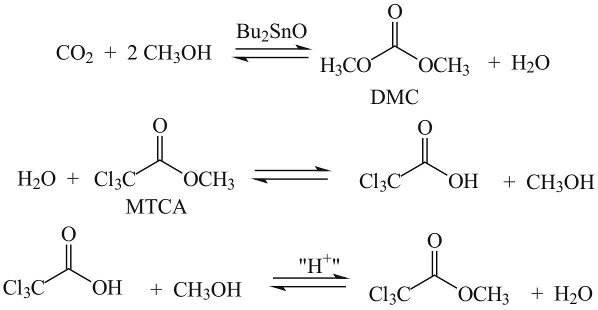
The use of methyl trichloroacetate (MTCA) as water suppressor in the synthesis of DMC looks quite promising. Table 6.7 shows the results of DMC formation from CO_2 and methanol, in the presence of tin catalyst and different water suppressors. One can see that the production of DMC, expressed as the turnover number (TON) in g of DMC formed per gram of catalyst used, is significantly high when MTCA was used as suppressor. The results are particularly interesting when compared with 2,2-dimethoxypropane, which, although presented the highest TON, required a significantly longer time and higher pressure. Another advantage of the use of MTCA is that the product of hydrolysis is methanol, which contributes to shift the equilibrium of the reaction. In addition, the formed trichloroacetic acid may be recycled upon esterification with methanol (Scheme 6.15). Therefore, there is practically no undesirable waste in this process.

The high efficiency of MTCA as water suppressor in the direct carbonation of methanol to produce DMC is associated with the electron-withdrawing property of the CCl_3 substituent, which increases the reactivity of the carboxyl group toward

Table 6.7 Reaction of CO_2 with methanol to produce DMC in the presence of tin catalysts and water suppressors

Suppressor	Catalyst	Reaction conditions	DMC yield (Turn Over Number)
DCC[a]	$Sn(OEt)_4$	150 °C, 12 h, 363 psi	2.3
2,2-Dimethoxypropane[b]	$Bu_2Sn(OMe)_2$	180 °C, 20 h, 4351 psi	30
$Si(OMe)_4$[c]	Bu_2SnO	142 °C, 12 h, 580 psi	3
MTCA[d]	Bu_2SnO	170 °C, 6 h, 700 psi	21.5

[a] Ref. [32]
[b] Ref. [33]
[c] Ref. [34]
[d] Ref. [35]



Scheme 6.15 Synthesis of DMC in the presence of MTCA as water suppressor. Recycling of the formed trichloroacetic acid upon acid-catalyzed reaction with methanol. No chlorinated waste was generated

hydrolysis. This is a nice positive role of chlorine in the process, which does not contribute to the generation of waste.

Glycerol carbonate (GC) is a somewhat new molecule that is gaining increased applications in the past years as solvent, emulsifier, and plasticizer, among other uses [36]. It is usually produced through the reaction of urea and glycerol, in the presence of a Lewis acid catalyst. $ZnCl_2$ is among the catalysts mostly commonly employed in this reaction [37]. Ammonia is a by-product and must be captured for reconversion in urea. There are few studies of the direct carbonation of glycerol with CO_2 (Scheme 6.16). Tin complexes were used as homogeneous catalysts for this reaction, affording 5.5 % of GC after 15 h at 180 °C and 50 bar (5.0 MPa) of pressure [38]. This is mostly the equilibrium conversion without the use of water suppressor systems [39].

Metal-impregnated zeolite catalysts have been tested in the reaction of CO_2 and glycerol [40]. Table 6.8 shows the yield of GC over the different catalysts. The active phase is probably the metal oxide formed upon the impregnation and calcination of the metal salts over NaY zeolite, because the calcined metal salts themselves are also active in the reaction. The parent NaY showed no conversion to GC. Figure 6.5 shows the results in terms of turnover number (TON), expressed as % of GC formed per mol of active metals on the medium. It can be clearly seen that

Scheme 6.16 Reaction of glycerol and CO_2 to produce glycerol carbonate

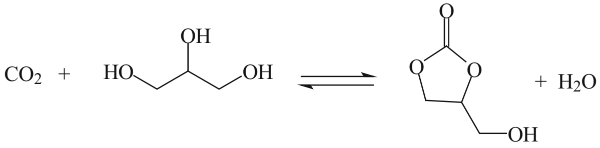


Table 6.8 Yield of GC in the reaction of glycerol with CO_2 at 180 °C, 100 bar, and 3 h

Catalyst[a]	Yield of GC/%
NaY	0.0
AgY	5.6
ZnY	5.8
SnY	5.1
$AgNO_3$	3.5
$Zn(NO_3)_2$	2.7
$SnCl_2$	2.6

[a]Calcined at 450 °C for 3 h

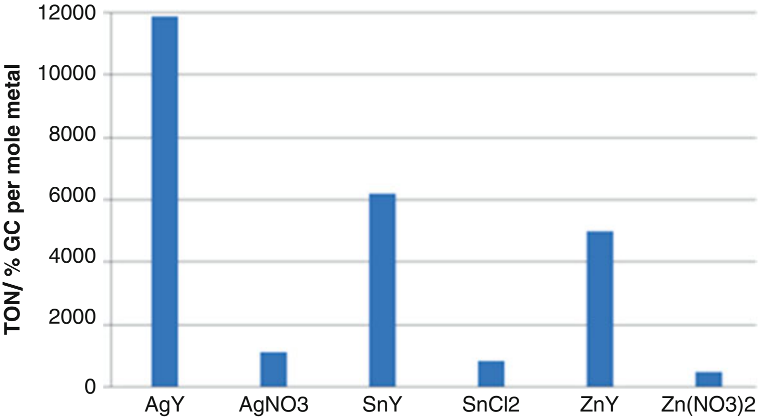


Fig. 6.5 Turnover number (TON), expressed in yield of GC (%) per mol of the metal on the catalyst. The values for $AgNO_3$, $SnCl_2$, and $Zn(NO_3)_2$ correspond to the calcined samples

the metal-impregnated zeolites are significantly more active than the calcined metal salts. This is probably due to the formation of dispersed metal oxide phases over the outer zeolite surface.

6.7 Final Remarks

$AlCl_3$ and HCl are widely used Lewis and Bronsted acids, respectively, in organic chemistry. Nevertheless, they cause corrosion problems, as well as generate significant amounts of wastes. These acids can be efficiently replaced by zeolites, clays, acid resins, and metal oxides in alkylations, etherifications, and esterifications, with high conversion and selectivity to the desired product. An additional advantage of solid acid catalysts is the possibility of reuse, because they are easily separated from the reaction medium, which is not simple when $AlCl_3$ and HCl are employed. Therefore, these materials can certainly contribute to the development of more sustainable processes, decreasing the generation of waste and yielding the possibility of reuse.

Chlorine-containing compounds, such as phosgene and $ZnCl_2$, are also involved in the synthesis of important organic carbonates. Phosgene is highly toxic and its use has been phased out in the industrial production of DMC. Nevertheless, the present industrial process still employs hazardous chemicals, such as ethylene oxide, and makes use of metal chlorides as catalysts. The direct carbonation of methanol may be carried out, but requires the addition of water suppressor reactants, to shift the equilibrium. The use of methyl trichloroacetate (MTCA) as water suppressor is highly promising. In this case, chlorine atoms have a positive role, due to their electron-withdrawing properties.

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Chapter 7
Chlorine-Free Catalysis for the Synthesis of Dialkyl Carbonate via Oxidative Carbonylation of Alcohols

Shouying Huang, Yuanyuan Dong, Shengping Wang, and Xinbin Ma

Abstract With the global phase-out of the phosgenation processes, oxidative carbonylation of alcohols to synthesize short-chain dialkyl carbonates (especially DMC, DEC) is considered as a promising route under the guidance of "green chemistry." Despite the good initial performance of chlorine-containing catalyst, including CuCl, $CuCl_2$, $PdCl_2$, $CuCl_2$-$PdCl_2$, etc., the loss of chlorine during reaction results in the catalyst deactivation, equipment corrosion, and environmental problems. The chapter is to review the progress in oxidative carbonylation of alcohols promoted by chlorine-free catalysts. The catalyst development and process improvement as well as mechanistic understanding are discussed.

Keywords Dialkyl carbonates • Oxidative carbonylation • Catalyst • Cu-zeolites • Copper and copper oxides on carbon • Methyl nitrite • Pd/NaY

7.1 Introduction

In the last decades, the environmental impact associated with chemicals production and application has been fully recognized as a major concern from the public [1]. This public health and environment protection pressure results in more severe laws related to both production and utilization of chemicals [2]. As a consequence, the initiative of "green chemistry" and "sustainable development" have gained momentum, involving the design of environmentally benign compounds, clean and highly efficient synthesis processes, as well as the development of new catalysts [3].

Dialkyl carbonates, especially short-chain dialkyl carbonates such as dimethyl carbonate (DMC) and diethyl carbonate (DEC), are considered as eco-friendly alternatives because of their biodegradability, low toxicity and diversified chemical

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properties. As building blocks, they are widely used as carbonylation and alkylation agents to replace toxic and cancerogenic chemicals (e.g., phosgene, dimethyl sulfate (DMS), methyl iodide (MeI)) in the manufacturing of agrochemicals, pharmaceuticals, antioxidants, etc. and potential green solvents for coating, adhesives, and electrolytes in lithium-ion batteries [4]. Table 7.1 summarizes and compares the toxicological properties of DMC, DEC, and several alkylation and carbonylation agents [1, 5]. Besides, DMC and DEC are strong contenders as effective oxygenates for fuel additives compared with MTBE [6].

Up to the 1980s, the traditional industrial synthesis of DMC and DEC are phosgene alcoholysis process. Despite the high yield of dialkyl carbonates, it suffers from the drawbacks such as using corrosive gases of chlorine and excessive pyridine, producing large amounts of waste NaCl salts [7]. More importantly, phosgene as an extremely hazardous compound decomposes in the lungs to form carbon monoxide and hydrochloric acid, which endangers human health seriously. Nowadays, phosgenation process has been totally abandoned worldwide. Concerned by the principles of "green chemistry," several phosgene-free routes for dialkyl carbonates production (e.g., oxidative carbonylation, transesterification of propylene or ethylene carbonate and alcohols, alcoholysis of urea, direct carbonylation of alcohols, etc.) have been put forward and drawn much attention from both academic and industrial communities. Among them, direct oxidative carbonylation and indirect oxycarbonylation via methylnitrite (MN) are promising routes due to their high atom economy, abroad and cheap raw materials, favorable thermodynamics, and mild reaction conditions.

7.2 Direct Oxidative Carbonylation from O_2, CO, and Alcohols

The direct oxidative carbonylation of alcohols to dialkyl carbonates uses CO, O_2, and alcohols as raw materials (Eq. 7.1).

$$\begin{aligned}&2\mathrm{ROH}+\mathrm{CO}+0.5\mathrm{O_2}\rightarrow(\mathrm{RO})_2\mathrm{CO}+\mathrm{H_2O}\\&\mathrm{R}=-\mathrm{CH_3},\Delta_\mathrm{r}G_{298\mathrm{K}}=-250.8\ \mathrm{kJ\cdot mol^{-1}},\Delta_\mathrm{r}H_{298\mathrm{K}}=-311.9\ \mathrm{kJ\cdot mol^{-1}};\\&\mathrm{R}=-\mathrm{C_2H_5},\Delta_\mathrm{r}G_{298\mathrm{K}}=-247.5\ \mathrm{kJ\cdot mol^{-1}},\Delta_\mathrm{r}H_{298\mathrm{K}}=-309.5\ \mathrm{kJ\cdot mol^{-1}}.\end{aligned}\tag{7.1}$$

In 1983, the EniChem's process (liquid-phase oxycarbonylation) has been transferred to the industrial scale successively in a slurry by exploiting cuprous chloride (CuCl) as catalyst. An extreme excess of CO is necessary for acquiring ideal yield of DMC [8]. Meanwhile, the selectivity of dialkyl carbonates is strongly influenced by Cl/Cu ratio of the catalyst. Considering the loss of chlorine with time on steam, hydrochloric acid needs to be added to maintain the Cl/Cu ratio in order to resist the catalyst deactivation. Although high space-time yield (STY) of DMC/DEC can be achieved in liquid-phase process, it is inherently difficult to solve the problems

Table 7.1 General properties of several alkylation agents, including DMC, DMS, MeI, and methanol

	DMC	DEC	Phosgene	DMS	MeI	MeOH
Oral acute toxicity (rats)	LD_{50} 13,800 mg kg^{-1}	LD_{50} 1570 mg kg^{-1}		LD_{50} 440 mg kg^{-1}	76	5700
Acute toxicity per contact (cavy)	>LD_{50} 2500 mg kg^{-1}				LD_{50} 110 mg kg^{-1}	
Acute toxicity per inhalation	LC_{50} 140 mg L^{-1} (4 h)	LD_{50} 8500 mg kg^{-1} (subcutaneous)	LC_{50} 16 mg m^{-3} (1.25 h)	LD_{50} 1.5 mg L^{-1} (4 h)		64 mg l^{-1} (4 h)
Mutagenic properties	None	Equivocal tumorigenic		Mutagenic	Possible teratogen	
Irritating properties	None	None	Severely irritate and burn skin and eyes	Causes burns	Irritant to skin	Irritant to skin, eyes
Hazard identification	Highly flammable	Highly flammable	Very toxic and corrosive	Very toxic and corrosive	Very toxic	Toxic and highly flammable
Biodegradability	>90 % (28 days)		Rapid hydrolysis	Rapid hydrolysis		

involving equipment corrosion, product and catalyst separation, and operation of high reaction pressure. Besides, the generated H_2O gives rise to the deactivation of CuCl catalyst. Gas-phase oxycarbonylation is directly derived from the liquid-phase method, but operates at lower pressure and dispenses with catalyst separation procedure. Furthermore, the timely removal of H_2O with gas flow results in mitigation of catalyst deactivation and DMC or DEC decomposition. To date, heterogeneous $CuCl_2$ and Pd-Cu bimetallic chloride supported on various carbonaceous materials seem to be the most profitable catalysts of the systematic studies for DMC and DEC synthesis. However, the stability of these catalysts caused by chlorine loss is still the most frustrating issue. Although several strategies are applied for restoring the catalyst activity involving ex situ regeneration using HCl [9] or methyl chloroacetate [10], continuous addition of ppm levels of CCl_4 [11], as well as stabilization through coordinating with ligands [12], the negative effects of chlorine loss on the catalyst and equipment cannot be overcome completely. Hence, the development of non-chlorine catalysts is becoming a predominant research direction.

7.2.1 *Cu-Zeolite Catalyst*

The pioneering work by King reported that Cu-exchanged zeolite prepared by solid-state ion exchange (SSIE) showed good activity in oxidative carbonylation of methanol. It was the first time to confirm that the presence of chloride was not necessary in oxidative carbonylation of alcohols to synthesize dialkyl carbonates [13]. According to the mechanism of CuCl-catalyzed oxidative carbonylation proposed by Romano et al., chloride was actually not directly involved (shown as Eqs. 7.2 and 7.3), so the negatively charged anionic zeolite lattice (Ze^-) probably played a role in the replacement of chloride anion to provide a required local environment for catalyzing the reaction [14]. Besides, the catalyst presented excellent stability without loss of chloride. It opened up the study of chlorine-free catalysis in this reaction.

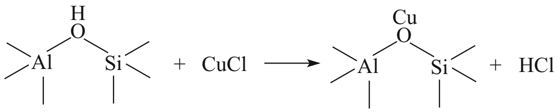
$$2CH_3OH + 1/2O_2 + 2Cu^+Cl^- \rightarrow 2(CH_3O - Cu)^+Cl^- + 2H_2O \tag{7.2}$$

$$2(CH_3O - Cu)^+Cl^- + CO \rightarrow (CH_3O)_2CO + 2Cu^+Cl^- \tag{7.3}$$

7.2.1.1 Identification of Cu Active Sites

In Cu-zeolites, the amounts of Cu species and its property and local environment had an influence on catalytic performance. Cu(II)-zeolites obtained from conventional ion exchange in aqueous solution were proved almost inactive, while the formation of dimethyl carbonate (DMC) was remarkably facilitated by Cu(I)-

zeolites from SSIE [13]. Spoto et al. proposed the mechanism of SSIE of various zeolites with CuCl (Eqs. 7.4 and 7.5): Brønsted acidic sites were substituted by Cu^+ cation under high temperature, accompanied by the release of gaseous HCl. Therefore, isolated Cu(I) cations coordinating with zeolitic framework were considered as the active sites in oxidative carbonylation. Besides, a complete exchange could be achieved by SSIE, which provided much more Cu^+ sites than ion exchange in aqueous solution. Bell and his coworkers investigated the oxidation state, local coordination, and bond distances of Cu and Al in Cu-Y by X-ray absorption spectroscopy (XAS) and concluded that only those Cu cations located in site II and III′ (Fig. 7.1) were accessible to the reactants and hence are catalytically active [15]. Li et al. employed $CuCl_2$ as precursor to replace the utilization of CuCl, which decomposed to CuCl and Cl_2 during SSIE [16].



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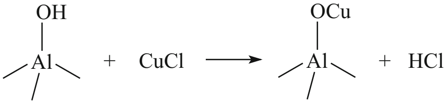


(7.5)

Besides SSIE with CuCl, other preparation approaches were also applied to synthesize Cu-zeolites for oxidative carbonylation of alcohols in recent years. In contrast to isolated Cu^+ cations bound to framework in Cu-zeolite through SSIE, the catalysts obtained from these preparation methods always contained heterogeneous species, including isolated Cu^+, CuO_x, Cu^0, etc. Drake et al. reported that Cu-SBA-15 prepared via molecular precursor grafting method from $[CuOSi(O^tBu)_3]_4$ possessed highly dispersed Cu^+ cations on small particles of noncrystalline

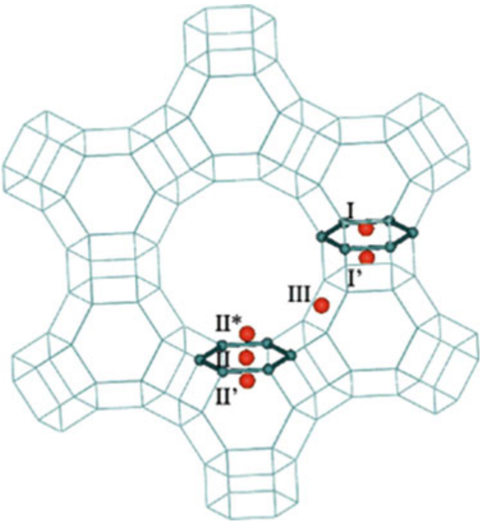


Fig. 7.1 Possible Cu sites of Y zeolite [33] (Copyright 2008 American Chemical Society)

CuO, resulting in an enhancement of $S_{DMC/CO}$, $S_{DMC/MeOH}$, and activity [17]. Richter et al. reported that Cu-Y prepared by incipient wetness impregnation allowed space-time yield of DMC up to 632 g·lcat^{-1}·h^{-1} [18]. The activation of catalyst under inert gas was necessary, which initiated the dispersion of CuO, auto-reduction of Cu^{2+}, and redistribution of Cu^{+} ions with enrichment in the supercages of zeolite Y. Meanwhile, CuO_x agglomerates accelerated oxidation of methanol to generate methoxy species. Ma and coworkers found that ammonia evaporation could promote the ion-exchange level of Cu appreciably and lead to coexistence of CuO_x, Cu^0, and Cu^+ ions [19]. Additionally, Cu precursors exerted profound effects on the textural and chemical properties of Cu-Y, and their catalytic behaviors were in line with the proportions of Cu(I) species. Li's group discovered that Cs dopant into the supercage of Cu-Y zeolite significantly improved its catalytic activity, because Cs^+ species at adjacent site increased the adsorption energy of co-adsorbed CO and stabilized the transition state for CO insertion reaction [20]. Recently, Cu-SAPO-37 was successfully synthesized by SSIE with Cu (II) acetylacetonate and showed a comparable activity with Cu-Y zeolite [21]. The auto-reduction and re-dispersion of Cu species during activation procedure was similar to Cu-Y zeolite reported by Richter et al. [18].

Through the above preparation approaches, chloride is completely avoided and no deactivation is observed. However, the complexity of Cu species in these Cu-zeolite catalysts puts forward new challenges to establish the relationship between different Cu species and catalytic performance. On the other hand, it also provides new possibilities to tune the nature and amount of Cu species in Cu-zeolite catalysts for the synthesis of dialkyl carbonates.

7.2.1.2 The Influence of Zeolite Support

The effect of zeolite structure and chemical composition was intensively investigated on both DMC and DEC synthesis. Root and colleagues found that Cu-X showed a better catalytic performance than Cu-ZSM-5 for DMC production because weak adsorption of CO onto Cu-X favored for methoxide formation [22]. Bell's group proposed that Cu-Y exhibited higher activity and selectivity for DMC, while dimethoxymethane (DMM) was the main product on Cu-ZSM-5 and Cu-MOR [23]. Due to a lower Si/Al ratio of Cu-Y, the weak binding of CO to Cu^+ cations made insertion of CO into Cu–OCH_3 much easier, which was the rate-limiting step of the reaction. By comparing the catalytic behavior of Cu-faujasite with various Si/Al ratios, Ma and coworkers concluded that it was more reasonable to relate the Brønsted acidic sites in supercages to catalytic activity rather than Cu contents, considering aggregation and accessibility of Cu species [24]. Furthermore, the distribution of Brønsted acidic sites also influenced on Cu localization, and thus on catalytic performance. DFT study demonstrated that Cu-Y zeolite with a Si/Al ratio = 6.5 exhibited the best catalytic activity, which was in a good agreement with experimental results. Alkaline treatment was applied to introduce meso- and macropores in zeolite Y by inducing defects and promoting dealumination in ion exchange. The formed hierarchical pore structure and more accessible Cu active sites were responsible for the improvement of DEC yield [3]. When SPAO-37 (belong to the same FAU structure family like aluminosilicate zeolite Y) was employed as support, Cu-SAPO-37 showed an unchanged selectivity of DME in the range from 120 to 220 °C because of different and more effective blockage of acid sites than Cu-Y [21]. It was noteworthy that β zeolite displayed a shape selective catalysis in DEC synthesis due to its unique three-dimensional interconnected channel system, which was different from Cu-Y [25]. Extraction of extra-framework silicon by $NH_3 \cdot H_2O$ treatment resulted in a better catalytic activity because the steric hindrance of SiO_2 blocked the attack of Cu^+ to O atom during the preparation [26].

The residual Brønsted acid sites on catalysts, resulted from incomplete exchange during the catalyst preparation, dominated the decomposition of dialkyl carbonates, especially at high temperature. It limited the positive effect on yield of dialkyl carbonates by increasing operating temperature. Several strategies were proposed to block or remove acid sites of Cu-zeolite catalysts. Compared to adsorption of pyridine or trimethyl phosphate, aqueous-phase exchange of Li^+ ions after Cu loading reduced the rate of DMC decomposition dramatically at both low and high temperature without affecting copper performance [27]. Moreover, moderate acid sites on Cu-zeolite were considered to be contributive to accelerate condensation reaction of aldehyde with alcohols [19].

Considering oxidative carbonylation of alcohols as exothermic reactions, local thermal effect gave rise to acceleration of DME and CO_2 formation, especially in fix-bed reactors. Keller and coworkers introduced thermoconductive β silicon carbide into Y zeolite as support. The obtained Cu-Y/β-SiC catalyst offered a better control of the catalytic bed temperature as well as limited production of DME and CO_2 [28].

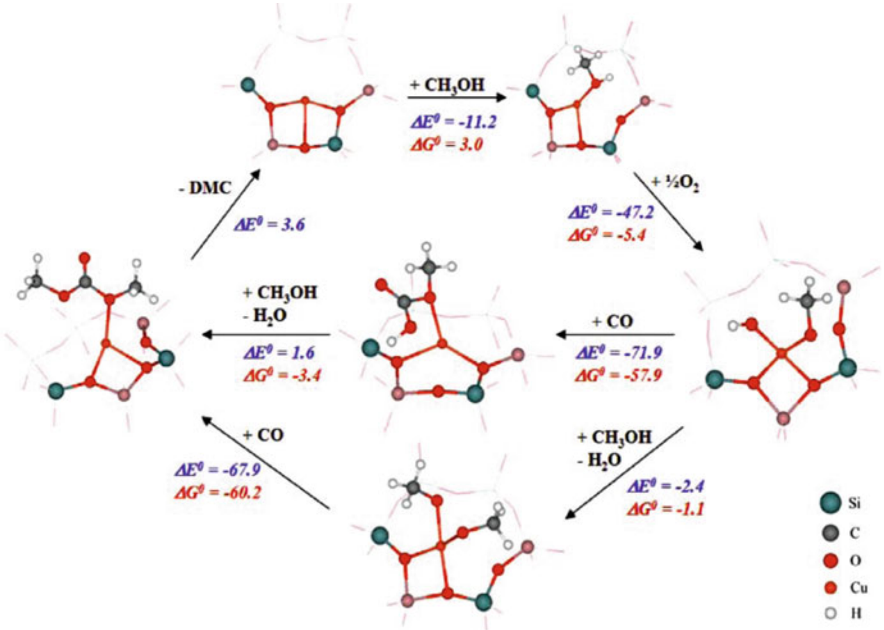
7.2.1.3 Reaction Mechanism Over Cu-Zeolites

The catalytic mechanism of oxidative carbonylation of alcohols over both chlorine-containing and chlorine-free catalysts includes two key steps: (a) oxidation of methanol and (b) insertion of CO. In the case of chlorine-containing catalysts (e.g., $CuCl_2$, $CuCl_2$-$PdCl_2$, etc.), chlorine plays an important role in the production of DMC as well as regeneration of catalysts [2, 29]. DFT results showed that the presence of Cl atoms could facilitate activation of H–O bond of methanol to produce methoxide. However, HCl is easily formed and escapes from the surface of catalysts during the reaction, which leads to the catalyst deactivation. Based on the CuCl-catalyzed process, King suggested that the similar redox cycle could be carried out inside the channels of Cu-zeolite [30]. The in situ FTIR study revealed that methanol was oxidized on Cu(I) to form Cu(II)–methoxide followed by the insertion of CO to form carbomethoxide (CH_3O–CO–Cu^+). Finally, methanol and oxygen reacted with carbomethoxide to generate DMC [30]. The Eley–Rideal mechanism was also convinced by kinetic study of Root and his coworkers, in which insertion of gaseous CO into the adsorbed methoxide was the rate-controlling step. At low CO pressure, nearly first-order kinetics with respect to CO pressure, slightly positive order to O_2 pressure, zero order to methanol pressure, and −0.4 order to water pressure over Cu-X zeolite catalyst were derived (Eq. 7.6) [31]. However, the competition between direct adsorption of nonreactive CO and reaction of CO with the formed methoxide resulted in decreasing benefits for DMC formation at high CO pressure [22].

$$R_{DMC} = \frac{k_3 K_1 K_2 P_{MeOH} P_{CO} P_{O_2}^{\frac{1}{4}} / P_{H_2O}^{\frac{1}{2}}}{1 + K_1 P_{MeOH} + \frac{K_1 K_2 P_{MeOH} P_{O_2}^{\frac{1}{4}}}{P_{H_2O}^{\frac{1}{2}}} + K_{10} P_{H_2O}} \tag{7.6}$$

Bell’s group built the reaction network of oxidative carbonylation of methanol on Cu-exchanged Y zeolite by combining in situ spectroscopy and DFT method [32, 33]. DMC was suggested to be formed through two distinct pathways: (a) reaction of CO with dimethoxides and (b) interaction of methanol with monomethyl carbonate (MMC) (Scheme 7.1). In comparison with the mechanism hypothesized by King, there were two different aspects: The intermediate derived from the addition of CO into methoxide groups was identified as MMC rather than a carbomethoxide species; secondly, another pathway was assumed that DMC would be originated from the insertion of CO to dimethoxide species. These experimental observations were strongly supported by theoretical investigation. Furthermore, co-adsorption of molecular methanol and CO led to the decrease of the CO adsorption energy and red-shift of the C–O bond from 2134 to 2117 cm^{-1}. Methoxide groups bound to Cu^+ cations located in lite II* were formed in the presence of gaseous O_2, which inhibited the adsorption of CO completely. These predictions agreed well with experimental observation. The two principal by-products (DMM and methyl formate (MF)) were surmised to proceed via a hemiacetal intermediate produced by the reaction CH_2O with CH_3OH. Theoretical study indicated that the dissociation of O_2 occurred readily, followed by the reaction with methanol to form methoxide on Cu-β catalyst under reaction conditions [34].

As mentioned above, several novel preparation methods were applied to synthesize Cu-zeolite catalysts that contained multiple Cu species. Therefore, it made the reaction mechanism become more complicated. In previous study, Bell’s group and King suggested that O_2 was required during oxidation of methanol, whereas Bentrup and coworkers claimed that the lattice oxygen of CuO_x aggregates rather than O_2 participated in both oxidation and oxycarbonylation process based on results of an *operando* SSITKA/DRIFTS/MS study, which pointed to a Mars–van Krevelen mechanism [35, 36]. Gaseous oxygen was used to re-oxidize the catalyst but favored also unselective oxidation reactions of MeOH and CO. Thus, O_2 pressure had a significant impact on selectivity of DMC, DMM, and MF. They also found that only monodentate-like MMC (I) species were active in DMC

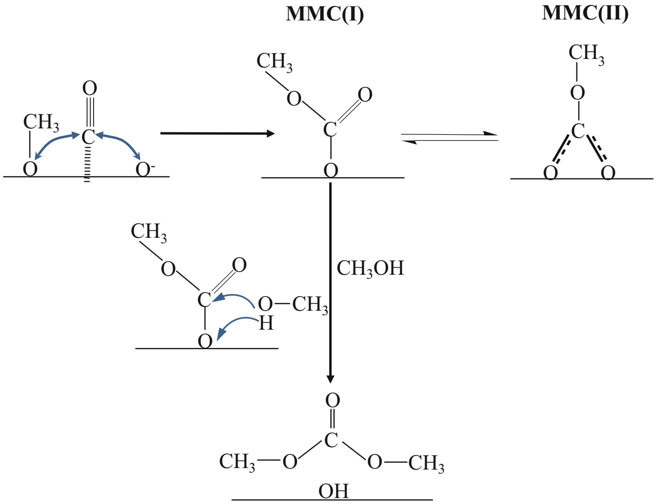


Scheme 7.1 Proposed reaction mechanism for DMC synthesis (Reprinted with permission from Ref. [33]. Copyright 2008 American Chemical Society)

formation owing to the strong adsorption of bidentate-like MMC (II) species on the catalyst surface (Scheme 7.2).

7.2.2 *Supported Oxide Catalyst*

Carbonaceous materials have been extensively used as catalyst supports because of their superior electronic conductivity, abundant pore structure, and tunable surface properties. In chlorine-containing catalysts, carbonaceous materials (e.g., active carbon (AC) [37], carbon nanofibers [11], and ordered mesoporous carbon [38]) are considered as excellent supports to promote the dispersion of metal active component and play a key role in good catalytic properties during the synthesis of dialkyl carbonate via oxidative carbonylation. Since Wang et al. firstly reported the utilization of CuO-La_2O_3/AC catalyst in DMC synthesis, copper oxides and Cu^0 supported on AC showed potential in oxidative carbonylation due to their competitive catalytic performance and stability. Several non-chlorine copper sources, such as $Cu(NO_3)_2$ and $Cu(CH_3COO)_2$, were applied as precursors, which completely avoided the disadvantages caused by loss of chlorine during the catalyst preparation and reaction.



Scheme 7.2 Proposed mechanism for DMC formation (Reprinted with permission from Ref. [36]. Copyright 2012 Royal Society of Chemistry)

7.2.2.1 Identification of Cu Active Sites

Although researchers have made great effort to identify catalytic active species in carbon-supported catalysts, it is still a controversial issue. Wang et al. suggested that CuO and Cu_2O were active components, whose transformation completed the catalytic cycle [39]. The ratio of them influenced the activity remarkably. Subsequently, Li and workers paid much attention to the development of CuO_x/AC catalyst, especially via pyrolysis of copper precursors including $Cu(CH_3COO)_2$ or $Cu_2(NO_3)(OH)_3$. Their investigation revealed that the temperature of thermal treatment dominated the valence state of Cu species [40] and low temperature maintained Cu components in their reduced form (Cu^0 and Cu_2O). Catalytic properties evaluation showed that Cu^0, Cu_2O, and CuO were all active, and the activity increased in an order of $CuO < Cu_2O < Cu^0$. They also investigated the activity and selectivity of copper oxides supported on AC prepared by hydrazine hydrate reduction for DMC synthesis [41]. Compared with the other two species, Cu_2O was the most stable one during the reaction so that it was deemed as the main catalytic active center. Recently, the physicochemical properties of CuO_x/AC catalysts at different reaction time were characterized by means of XRD, TEM, H_2-TPR, AAS, XPS, and O_2-TPD [42]. The results indicated that Cu^0, as the main copper species in fresh Cu/AC catalysts, was easily oxidized to Cu_2O by oxygen in feedstock. The well-dispersed Cu_2O species on the surface of AC provided Cu (I) active sites and lattice oxygen for oxycarbonylation of methanol. The deactivation was attributed to aggregation of copper species and its oxidation to CuO.

7.2.2.2 Effects of Additives

Considering that Cu_2O and Cu^0 possess good activity for oxidative carbonylation of alcohols, the addition of appropriate promoter is beneficial to the dispersion and reduction of Cu species. Introduction of Ce after Cu impregnation resulted in an improvement of catalytic performance, owing to a more uniform dispersion of Cu^0 and Cu_2O species on the surface of the catalyst [43]. The dopant of moderate content of lithium facilitated the auto-reduction of copper oxides to Cu^0, leading to well-dispersed Cu nanoparticles with more uniform grain size [44]. Besides, the existence of Li made CO weak adsorption centers increased, which favored the insertion of CO molecules into Cu–OCH_3 intermediates and thus effectively enhanced the catalytic activity.

7.2.2.3 Effects of Support

As a series of promising materials for catalytic application, carbon materials are able to anchor metal particles and promote their dispersion on a substrate because of large surface area and various functional groups. Ma and coworkers modulated the number of surface oxygen-containing groups (OCGs, including phenol, lactone, carboxyl groups, etc.) by different concentrations of HNO_3 solution and found that the surface OCGs had an impact on Cu loading [45]. The optimality of the Cu content as well as catalytic activity increased linearly with the amount of OCGs. The Cu_2O nanoparticles coordinated to the OCGs on the carbon surface were presumed to be active species in the reaction. Li et al. discovered that treatment with nitric acid or ammonia led to the formation of the new nitro-groups, increase of CO and COO groups, and significant decrease even disappearance of C=O species on the surface of AC [46]. It was suggested that nitro-group electron donation and abundant COO groups contributed to promoting the reduction of Cu^{2+} to Cu^+, which was a response for unique and well-dispersed Cu_2O-supported catalysts and enhanced catalytic activity. Ren et al. prepared the Cu/C catalyst using sol–gel method with starch and $Cu(NO_3)_2$ as carbon source and Cu precursor, respectively, followed by high-temperature carbonization and KOH activation [47]. The controllable Cu particle size, resulting from the large surface area and microporosity of carbon support, led to a good yield of DMC. And the highest activity was achieved at optimized KOH/C ratio and applicable carbonization temperature.

7.2.2.4 Reaction Mechanism Over CuO_x/AC Catalyst

Generally speaking, the experimental research (e.g., spectroscopy and kinetic study) on the mechanism of oxidative carbonylation over copper or copper oxide on AC has been rarely reported until now. However, several theoretical investigations by DFT method have been published to discuss about the dissociation of O_2, formation of CH_3O, as well as the whole reaction network at molecular level [48–50]. According to the calculated results by Zhang et al., it was more favorable both thermodynamically and kinetically for dissociation of molecularly adsorbed O_2 into two O atoms on the deficient surface than that on the perfect surface, which improved the catalytic activity of Cu_2O obviously [48]. This result was in good agreement in experimental study. Furthermore, two possible pathways of CH_3O formation over oxygen-precovered (O_{pre}) $Cu_2O(111)$ surface via CH_3OH adsorption and dissociation were proposed (Eqs. 7.7 and 7.8): (1) the O−H bond breaking along with H migration to O_{pre} and (2) the C–O bond cleavage together with CH_3 migration to O_{pre} to form CH_3O_{pre} [49]. The first pathway had the lower activation barrier and the oxygen-precovered $Cu_2O(111)$ surface exhibited a high reactivity for generating CH_3O species.

$$CH_3O - H + O_{pre} + * \rightarrow CH_3O + HO_{pre} \tag{7.7}$$

$$CH_3 - OH + O_{pre} + * \rightarrow CH_3O_{pre} + HO \tag{7.8}$$

Then, a further theoretical analysis about DMC formation via oxidative carbonylation of methanol on Cu_2O catalyst was studied systematically [50]. As shown in Eqs. (7.9), (7.10), (7.11), (7.12), (7.13), (7.14), and (7.15), two proposed pathways over Cu_2O were very similar to that on Cu-zeolites. Ren and his colleagues took the interaction between the active components (Cu^0) and AC into account during the theoretical investigation [51]. The results demonstrated that Cu^0 tended to adsorb at unsaturated sites on AC and the mechanism of DMC formation was the same as that on Cu_2O: it was much more competitive that CO inserted into methoxide species to produce monomethyl carbonate species (rate-determining step), and then, monomethyl carbonate species reacted with methoxide to form DMC in comparison with the path through CO insertion to dimethoxide species. The activation barrier on Cu^0 (87.9 kJ/mol) was lower than Cu_2O (161.9 kJ/mol). However, the presence of solvent apparently reduced the activation barrier of the elementary reaction of CO insertion to methoxide. That was why higher yield of DMC could be achieved in a liquid-phase slurry.

$$CH_3OH + * \rightarrow (CH_3OH)* \tag{7.9}$$

$$(CH_3OH)* + O* \rightarrow (CH_3O)*(OH)* \tag{7.10}$$

$$\text{Pathway 1} \quad (CH_3O)*(OH)* + CH_3OH \rightarrow (CH_3O)_2* + H_2O \tag{7.11}$$

$$(CH_3O)_2* + CO \rightarrow (DMC)* \tag{7.12}$$

$$\text{Pathway 2} \quad (CH_3O)* + CO \rightarrow (CH_3OCO)* \tag{7.13}$$

$$(CH_3OCO)* + (CH_3O)* \rightarrow (DMC)* \tag{7.14}$$

$$(DMC)* \rightarrow (DMC) + * \tag{7.15}$$

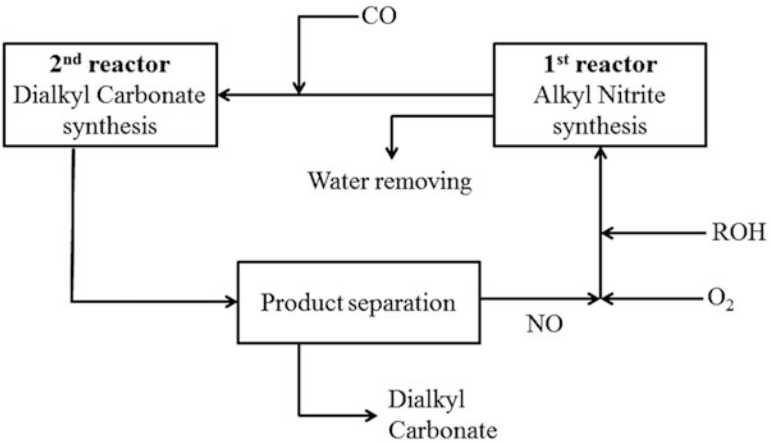
7.3 Indirect Oxidative Carbonylation via MN as Intermediate

7.3.1 Introduction

Despite the simple synthesis process and preferable thermodynamics, relative low conversion of alcohols and selectivity of dialkyl carbonate limit its further commercialization. UBE exploited a process on the synthesis of DMC via carbonylation of MN over a Pd-based bimetallic catalyst, as illustrated in Scheme 7.3 [2]. It includes two main processes: synthesis of alkyl nitrite from NO, O_2, and alcohol (1st reactor, Eq. 7.16) that is non-catalytic and formation of dialkyl carbonates catalyzed by $PdCl_2$-$CuCl_2$/AC catalyst from CO and gaseous alkyl nitrite (2nd reactor, Eq. 7.17). It is obvious that the synthesis of dialkyl carbonates is not accompanied by the generation of H_2O, so that the negative effect of H_2O on catalyst is eliminated and equipment corrosion caused by loss of chlorine is mitigated. Meanwhile, the division of the synthesis into two separated parts decreases the energy consumption of product separation, owing to the disappearance of ternary azeotrope (methanol-water-DMC) in products. Moreover, utilization of alkyl nitrite as oxidative agent instead of oxygen reduces the risk of explosion raised by the coexistence of CO and O_2, which has been recognized as a potential security problem in direct oxycarbonylation.

$$2NO + 2ROH + 0.5O_2 \rightarrow 2RONO + H_2O \tag{7.16}$$

$$CO + 2RONO \rightarrow (RO)_2CO + 2NO \tag{7.17}$$



Scheme 7.3 Schematic view of the UBE process (Reprinted with permission from Ref. [2]. Copyright 2010 Elsevier)

7.3.2 Catalyst and Catalytic Mechanism

Similar to direct oxidative carbonylation, the loss of chlorine is also believed to be responsible for catalyst deactivation. UBE reported Pd/NaY exhibited excellent catalytic activities even in the absence of ligands such as chlorine. By optimizing the preparation parameters such as Pd-loading, calcination temperature, and so on, the initial yield of DMC could reach 353 g·(L-cat_h)$^{-1}$ and maintain relatively stable at about 200 g·(L-cat_h)$^{-1}$ even after 700 h on stream, as displayed in Fig. 7.2 [52]. On the other hand, it is acknowledged that decomposition of alkyl nitrite depending on acidity of catalysts is one of the major factors for the selectivity of dialkyl carbonates [53, 54]. Therefore, moderate acidity as well as proper coordination environment provided by supports plays a crucial role in catalytic performance for Pd-based catalyst without chlorine. Based on the results of EXAFS and XPS, Okamoto and colleagues concluded that Pd^{2+} species were transformed into Pd^0 metal clusters during the reaction and the anchoring effect of protons as well as molecular-sized pore structure of NaY suppressed the migration and sintering of Pd clusters [52]. Ma's group investigated the effect of zeolite supports and concluded that NaY zeolite was the optimal carrier because of its appropriate amount of weak acid sites [55]. The TOFs increased linearly with the enhancement of Lewis acid sites in the Pd/FAU catalysts [56]. Combined with the data from XPS, it was inferred that Lewis acid sites, as electron acceptors in this catalyst system, helped the Pd species to retain at electron-deficient state, which promoted the formation of dialkyl carbonates. Yamamoto et al. offered the catalytic cycle over Pd/NaY on the analogy of the mechanistic reaction pathway over $PdCl_2$ catalyst, as

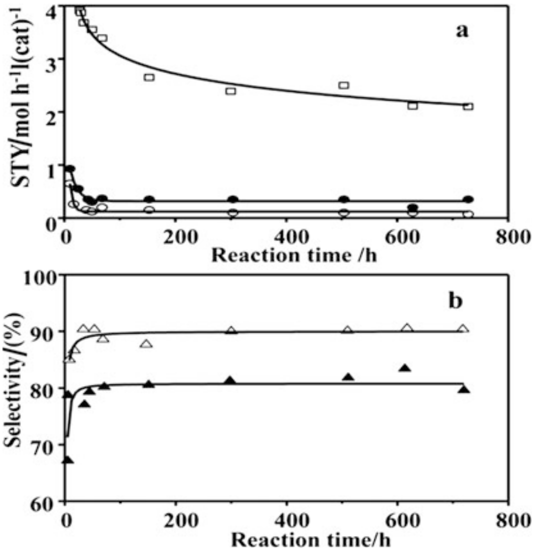
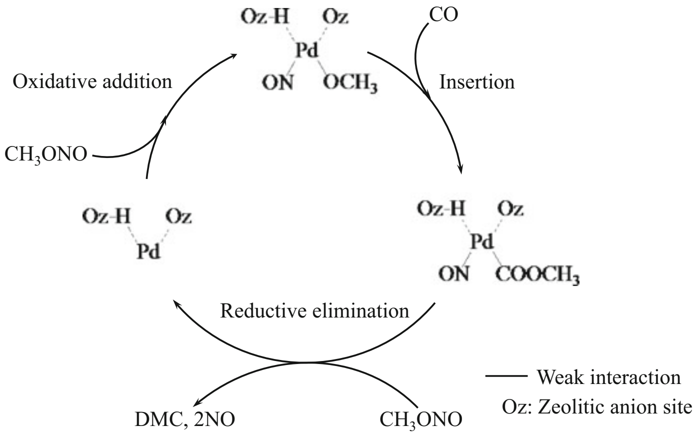


Fig. 7.2 Catalytic behavior of 1 wt.% Pd/NaY for DMC synthesis as a function of reaction time. (**a**) Formation rates of DMC (□), MF (○), and DMM (●) and (**b**) selectivities of CO (Δ) and MN (▲) to DMC (Reproduced with permission from Ref. [52]. Copyright 1997 American Chemical Society)



Scheme 7.4 Catalytic cycle during the DMC synthesis by methylnitrite carbonylation (Reproduced with permission from Ref. [52]. Copyright 1997 American Chemical Society)

presented in Scheme 7.4. However, the mechanism was speculative and lacked supportive experimental evidence.

7.4 Summary and Future Perspectives

Recently, the utilization and production of green chemicals are becoming an important theme. Short-chain dialkyl carbonates have attracted increasing interests due to their environmental friendliness and extensive potential applications in various aspects of chemical industry and daily life. With the global phase-out of phosgenation process, chlorine-free routes for dialkyl carbonates synthesis as alternatives have become the trend of industrial development. Direct and indirect vapor-phase oxycarbonylation approaches are proposed in coincidence with the guidance of “green chemistry.” Herein, we highlight these two processes by exploiting non-chlorine catalysts, which exhibits acceptable activity and excellent stability. Meanwhile, the use of metal-doped zeolites and copper or copper oxides supported on carbonaceous materials instead of Cu, Pd, or bimetallic chloride catalyst have shown promising prospect, which is regarded as an effective approach to completely avoid the problems of catalyst deactivation and equipment corrosion caused by the loss of chlorine. However, the activity and selectivity of non-chlorine catalyst system are still not competitive with chlorine-containing catalysts, which become the main limited factor for commercial application. In recent years, the rapid advances of operando or combined characterizations as well as computational chemistry contribute to the identifying structure-performance of catalysts, elucidating catalytic mechanism at molecular level and further rational design of catalysts. The exploration of novel materials (e.g., hierarchically porous materials, metal organic frameworks, etc.) offers more possibility to enhance catalytic activity through eliminating diffusion limitation of microporous aluminosilicate zeolites, modifying the local environment of metal active sites as well as controlling products distribution. Besides, process intensification such as reactive distillation, reaction coupling, and monolithic catalysts are anticipated as effective methods to relieve negative effect of H_2O and heat generated during reaction.

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Part IV
Alternatives: *Biocatalysis*

Chapter 8
Chlorine-Free Biomass Processing: Enzymatic Alternatives for Bleaching and Hydrolysis of Lignocellulosic Materials

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and Elba Pinto da Silva Bon

Abstract This chapter presents biocatalytic alternatives for the processing of lignocellulosic materials with chlorine compounds in the pulp and paper industry and in the hydrolysis of lignocellulosic materials for the production of biomass sugar syrups and, ultimately, biofuels and chemicals. The advantages and disadvantages of the current chemical processes, their effects on the organisms and the environment, and the options for biocatalytic routes are discussed with the aim of contributing to the shift toward innovative and sustainable industrial processes. This shift is not an easy task due to economic reasons and to the impact on the operation logistics of the chemical industry worldwide. However, this investment is a necessary step for the future, when green processes will improve production and be required by the ever-growing restrictive regulations for the industrial sector.

Keywords Green processes • Chlorine-free process • Lignocellulosic materials processing • Pulp and paper industry • Biofuels • Xylanases • Cellulases

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8.1 Introduction

This chapter presents two examples of enzyme-catalyzed replacements for chlorine-based processes. The first topic focuses on the use of chlorine compounds for bleaching lignocellulosic materials and the efforts to reduce its use and thus decrease the concentration of organic chlorides in effluents. The pulp and paper industry offers an excellent model for the introduction of biocatalysts in a chemical-based industry where microorganisms and, particularly, their secreted or extracted enzymes have been studied and applied to pulping and bleaching to replace or reduce the use of chemicals.

The pulp and paper industry, in both traditional and emerging processes, is a major source of environmental pollutants. At present, global production of chemically manufactured pulp stands at around 100 million tons per year, and the demand will likely increase [1]. This industry consumes a significant amount of water and chemicals, including chlorine and chlorine dioxide, and produces large volumes of effluent. The effluent generated often contains, depending on the applied pulping and bleaching processes, high chemical oxygen demand (COD), low biodegradability, color, and over 700 organic and inorganic compounds, including phenolic compounds and organic chlorides that are recalcitrant and toxic [2, 3]. A brief review of the key pollutants released directly into the wastewater and the wastewater treatment methods for this industry was recently published [4]. Because of such pollution, central issues in the pulp and paper sector include lowering the environmental impact of pulping and bleaching, saving energy and water, recycling fibers, and minimizing effluent to protect natural bodies of water. Therefore, the application of biotechnology in the pulp and paper industry has emerged with the objective of decreasing processing time, improving product quality, lowering total processing costs, and/or reducing harmful waste streams.

The second topic focuses on lignocellulosic biomass processing, which is a very promising renewable substrate for the biofuel and chemical sectors, considering a biorefinery concept. The sequential steps of pretreatment, hydrolysis, fermentation, and distillation for the production of ethanol from lignocellulosic materials are well known [5–8]. However, although lignocellulosic ethanol is a renewable fuel, its processing can be more sustainable and greener if the hydrolysis step applies enzymes instead of acids. Although enzymatic hydrolysis of biomass has been paving the way as a preferred option over the use of acid, there is still research done on the use of acid and industries that still use acid for biomass processing. Lower oil costs hinder lignocellulosic ethanol competitiveness; nevertheless, important industrial initiatives worldwide aim to decrease technology costs. Sizeable advances have been made in the enzymatic hydrolysis step, which is still under cost optimization, where the enzymes' cost contribution to ethanol's final price decreased from 50 % in 2010 to 15–25 % in 2015 [9].

This chapter focuses on the use of enzymes to replace traditional chemical methods for lignocellulosic material processing in cellulose pulp production and in the production of biomass sugar syrups. The transition to greener and more sustainable processes is not easy, as important environmental issues of paramount importance are not yet regarded as pressingly relevant. However, in addition to developing new processes that are technically and economically viable, new paths are already underway to minimize waste disposal and emissions and to save energy and water. The choice for environmentally friendly procedures is often seen as an investment for the future, as optimized processes will likely become less expensive than traditional ones, which will also improve production processes and prepare the industrial sector to meet future legal regulations [10, 11].

8.2 Lignocellulosic Biomass Structure and Composition

Lignocellulosic biomass is composed mainly of cellulose, hemicellulose, and lignin, with a small percentage of ash, extractives, proteins, and pectin; its composition varies depending on the plant species [12]. The biomass macrostructure is made of hollow tubes with walls of a lignocellulosic nature whose composition is 40–50 % cellulose, 20–40 % hemicellulose, and 18–35 % lignin [13].

Cellulose is the main component of plant cell walls, and it accounts for about one third of plants' organic matter [14, 15]. This linear polymer is formed by approximately 10,000 glucose residues, joined together by β-1,4-glycosidic bonds. Its structural unit is cellobiose, a glucose dimer [16]. Although it has a simple chemical composition, together, cellulose chains form insoluble structures called microfibrils, which contain highly ordered crystalline regions and other disordered amorphous regions. These cellulose chains are packed in such a tight configuration that even small molecules such as water cannot permeate them [17]. Microfibrils interact through hydrophobic interactions and hydrogen bonding between its hydroxyl groups [18], creating larger fibrils that form lamellas to make the cellulose fiber more resistant [19]. Cellulose's crystalline structure has been studied since the nineteenth century, and although several models have been proposed, its complex structure is still not fully understood.

Hemicelluloses are heteropolysaccharides, found in the cell walls of higher plants [20, 21]. They have a fundamental role in cell wall structure, supporting the cellulose microfibrils by cellulose–hemicellulose hydrogen bonds [22].

Hemicellulose chains contain pentoses, hexoses, and uronic acids, and their main backbone may be composed of one monosaccharide unit, such as xylans, which are composed of xylose, or several, such as glucomannans, arabinogalactans, xyloglucans, and arabinoxylans [21]. As such, hemicelluloses are complex polysaccharides that require several enzymes for their degradation. Nevertheless, they present an amorphous structure and are therefore more susceptible to hydrolysis than cellulose.

Lignin is a complex macromolecule, highly branched, and with an amorphous and random structure. It functions as a natural barrier to enzymatic and microbial degradation, which, besides giving it mechanical strength, protects plant cell walls [21]. This makes lignin a very recalcitrant substrate for enzymatic degradation.

Lignin is composed of three main subunits – guaiacyl (G), syringyl (S), and p-hydroxyphenyl (H) – which are formed by the peroxidase-mediated oxidation of conyferil, sinapyl, and p-coumaryl, respectively [23]. This molecule is what gives wood its brownish color and is therefore the target of bleaching processes. Lignin removal from the lignocellulosic matrix can cause biomass swelling, increasing its surface area [24].

Lignocellulosic biomasses can be divided into three types – softwood, hardwood, and grasses – all of which have different compositions. Softwood comes from gymnosperm trees, which have G unit-rich lignin with a small number of H units; these are usually evergreen conifers, such as pine, spruce, or cedar. Hardwoods, on the other hand, have a lignin composed of approximately the same number of G and S units [25]; these trees are dicot angiosperms with broad leaves, such as mahogany, maple, and oak. The third type are the grasses, such as sugarcane, rice, and wheat, which are monocot angiosperms and have a lignin that contains G, S, and H units in different ratios depending on the type of grass [26]. There are also significant differences between the types of hemicelluloses in hardwood and softwood species [27]. Softwoods are mainly composed of galactoglucomannans and glucuronoarabinoxylans, while hardwoods are composed of glucuronoxylan [28].

Lignin does not link directly with cellulose, but it connects to hemicellulose through covalent bonds, such as ester and ether linkages. Studies indicate that these bonds occur between lignin and the side chains of the hemicellulose instead of the backbone. For example, in spruce, lignin is linked to an L-arabinosyl side chain of a xylan backbone and a D-galactosyl side chain in a galactoglucomannan [28].

8.3 Lignocellulose Biomass Processing

8.3.1 The Pulp and Paper Industry: Pulping and Bleaching

Paper is mainly produced from pulp, which consists of cellulose fibers from softwood (e.g., pine), hardwood (e.g., eucalyptus), and non-wood plants, such as crops (e.g., cotton) and agricultural residues (e.g., sugarcane bagasse). The process of paper production may be divided in two main steps: pulping and bleaching. Pulping refers to the separation of vegetable fibers by the use of chemicals or mechanical or thermomechanical energy. Depending on the pulping process, wood pulps are categorized as mechanical pulp, chemical pulp, or chemo-thermomechanical pulp (CTMP). In general, mechanical pulping has a higher recovering yield (90–95 %) compared to chemical-based processes (40–50 %), but the quality of these products is significantly lower in terms of strength [29, 30].

Chemical processes are the most widely used due to their broad applicability to different types of woods, the high resistance of the pulps obtained, and the possibility of reusing chemicals. The chemical pulps are generally classified as (i) kraft or sulfate pulp, which is obtained by the alkaline treatment of wood chips at high temperatures (around 160 °C) with sodium hydroxide and sodium sulfide, and (ii) sulfite pulp, which is formed by using the various salts of sulfurous acid [12].

Kraft pulp is the most common process, because it produces a pulp with the desired characteristics, such as high strength and low lignin content, from various wood species [31]. Chemical pulping through the kraft process accounts for 70 % of total global production [32]. The main objective of kraft pulping is to release cellulosic fibers by removing more than 90 % of the lignin from the material [4]. The remaining fibers have a brown color, mainly due to the presence of residual lignin. Hemicellulose chain fractions, which may be linked to lignin fragments, modified lignin, and/or partially degraded derivatives, may also reprecipitate on the fibers at the end of the pulping process, when the temperature and the alkali concentration decrease. The hemicellulose reprecipitates in a crystalline form due to the loss of its side chains. This reprecipitated hemicellulose is less soluble than the native one, hindering the solubilization of its residual lignin – the residual lignin is relatively nonreactive and can only be removed by intensive treatment with reagents containing chlorine or oxygen, which is done in the bleaching step of paper production [4].

The bleaching step may be applied to brown pulp to remove the residual lignin, improving brightness while maintaining strength, making it suitable for papermaking. This is the most complex step, and it produces various pollutants: dissolved lignin, color, chemical oxygen demand (COD), inorganic chlorines, adsorbable organic halogens (AOXs), extractable organic halides (EOXs), volatile organic compounds (VOCs), chlorophenols, and halogenated hydrocarbons [4].

It is worth noting that lignin remains almost intact during mechanical pulping, and mechanical pulp is generally brightened by hydrogen peroxide, a process that generates no chlorinated organic compounds. On the other hand, several bleaching agents can be used for bleaching chemical pulps, such as hypochlorite (ClO^-), elemental chlorine (Cl_2), chlorine dioxide (ClO_2), hydrogen peroxide (H_2O_2), oxygen (O_2), and ozone (O_3). Those chemicals have a large oxidation potential and are recognized as very effective bleaching agents. Traditionally, the pulp and paper industry uses a highly efficient and cost-effective but environmentally unsound bleaching technique that uses elemental chlorine. The traditional bleaching process for kraft pulp starts with a chlorination stage in which the chlorine attacks and modifies the structure of lignin to form several acidic groups. The chlorination stage is then followed by an alkali extraction stage in which the modified lignin, which is mostly hydrophilic, is dissolved in an aqueous solution and then removed to produce a pulp with a low kappa number, i.e., low lignin content. The chemistry of chlorine reactions with lignin is an extensive subject. In the past several decades, various studies and reports have proposed numerous reaction mechanisms and process improvements to improve bleaching [33–37].

Although the traditional method using elemental chlorine is extremely efficient, effluents generated by this process are not suitable for chemical recovery or burning due to the presence of chloride ions, which are potentially corrosive; thus, they require special treatment. These effluents also contain considerable amounts of harmful organic chlorides, including the persistent environmental pollutant dioxin, resulted almost entirely from reactions between lignin and the chlorine compounds used. Dioxins are among the most toxic man-made substances and are not considered safe at any concentration. They can cause serious human health problems, affecting reproductive, developmental, immunological, and hormonal systems, and are also carcinogenic [38]. Human exposure to dioxins is primarily through contaminated food such as meat, fish, and shellfish; contamination is exacerbated by the hydrophobic character of dioxin and its accumulation in fatty tissues throughout the food chain. The world was first alerted to the danger of dioxin in a 1976 industrial disaster in Seveso, Italy. The storage tank of the ICMESA chemical plant broke, releasing several kilograms of dioxin TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) into the atmosphere, spreading the product over a large area between Milan and Lake Como. Due to contamination, 3000 animals died, and 70,000 animals had to be sacrificed to prevent the entry of dioxin into the food chain.

Therefore, since the late 1980s, there has been growing environmental concern to reduce the use of chlorine to eliminate organic chlorides from the effluents of the pulp and paper industry. Limits for total AOX (including organic chlorides such as dioxin), biological and chemical oxygen demand (BOD and COD, respectively), and total suspended solids in pulp and paper industry effluents were first proposed in 1991. However, these proposed limits were postponed, and each country established individual criteria for the AOX released in wastewater discharges. Typical goals were 1.5–2.5 kg AOX per ton of pulp produced, but several countries proposed further reduction. More information about the regulatory policies and AOX limits in each country, and plant by plant, can be found in a report from the Organisation for Economic Co-operation and Development (OECD) [39].

As a result, since the 1990s, traditional bleaching processes have been replaced by elemental chlorine-free (ECF) and totally chlorine-free (TCF) sequences [40]. ECF and TCF processes employ oxygen-based bleaching agents, mainly oxygen, hydrogen peroxide, and ozone. ECF bleaching may also use chlorine dioxide and hypochlorite instead of elemental chlorine, reducing the production of organic chlorides five times. In terms of bleaching, the ECF process is more effective than the TCF one, as it produces a pulp with better brightness and quality due to the use of chlorine dioxide, which has high specificity to lignin. The oxidizing agents used in the TCF process have low specificity and may promote depolymerization of cellulose via secondary reactions [41].

Even though the ECF process still uses chlorine compounds and discharges organic chlorides, the US Environmental Protection Agency (EPA) and the European Community considered it to be the best available technology (BAT), as it usually meets standards for the release of AOX. Thus, the ECF process has become predominant worldwide and, because of the large amount of capital already invested, it is unlikely that the process will be replaced in the near future. However, to eliminate or reduce the production of organic chlorides, improved methods still need to be implemented, as the regulatory limits on AOX will likely be more restricted in the future. The introduction of enzymes from microorganisms as delignification agents during the pulping and bleaching steps, in processes known as biopulping and biobleaching, has become one initiative that could further reduce chlorine dioxide use.

8.3.2 *The Pulp and Paper Industry: Biopulping and Biobleaching*

The application of biotechnology to the pulp and paper industry has been the object of many research studies [29, 42–52]. Microorganisms or their secreted or extracted enzymes can be used to degrade lignin or facilitate its removal from lignocellulosic substrates during the papermaking process. Generally, the whole microorganism is grown in raw lignocellulose materials to improve the pulping process, while their secreted or extracted enzymes are tested for pulp bleaching. These procedures have the potential to reduce not only the environmental impact of traditional pulping and bleaching but also their energy costs [29, 44]. Improvements in paper strength properties have also been reported [44, 45].

8.3.2.1 Biopulping

The biopulping treatment is usually done before the pulping step, and its aim is to delignify the lignocellulosic material and/or to modify its lignin to soften the material to facilitate its processing in a subsequent step. Among microorganisms, the white-rot fungi have been the most studied for biopulping, and several screening studies have revealed that these fungi could degrade lignin over cellulose depending on the cultivation conditions [29, 50].

Most research on biopulping has cultivated fungi on raw substrates and tried to correlate ligninolytic enzyme production with lignin removal. The addition of a biopulping treatment to wood and non-wood materials has been found to be beneficial for both mechanical pulping [44, 53] and chemical pulping [54–57]. Such studies included the fungi *Phanerochaete chrysosporium* [58], *Ceriporiopsis subvermispora* [56, 59–62], *Pleurotus ostreatus* [50, 61, 63], *Trametes versicolor* [64], and *Phlebia brevispora* [65], among others, which produce ligninolytic enzymes such as laccases (EC 1.10.3.2), manganese peroxidases (EC 1.11.1.13), and lignin peroxidases (EC 1.11.1.14). These enzymes catalyze the depolymerization of lignin by β-O-4 ether cleavage and degrade lipophilic extractives [66], thus reducing the pitch content and effluent toxicity [67]. Moreover, other reactions may occur in the presence of oxidative mediators, increasing the enzymes' oxidative potential and enabling non-phenolic oxidation, which is described in the subsequent section on biobleaching.

One of the first papers on screening lignin-degrading fungi investigated 72 fungi [68]. However, biopulping received little attention until the 1980s, when a pretreatment with *P. chrysosporium* was found to decrease energy requirements and increase the paper strength [69]. Biopulping was put forward as a procedure that deserved a comprehensive evaluation, so several works have been published since that time. Kirk et al. [29] detailed the early work on biopulping.

The most significant advantages of biopulping are the energy savings for wood and pulp refining (estimated to be at least 30 %), increased potential in mill throughput for mechanical pulping, enhanced paper strength properties, improved yield, and reduced environmental impact [66, 70]. It is well known that the pretreatment of lignocellulosic materials with microorganisms, such as *C. subvermispora*, softens and swells cell walls, which leads to increased porosity [56]. Likewise, the increased porosity of biopulping fibers facilitates their processing and improves the accessibility of chemicals, reducing the energy and chemical requirement for pulping and bleaching [56, 70].

This reduced environmental impact is frequently mentioned [56, 57, 66, 70]; however, only a few papers have shown the percentage of elemental chlorine and chlorine dioxide reduction from biopulping. Yadav et al. [56] studied the effect of biopulping hardwood chips with *C. subvermispora* on the subsequent bleaching step and reported that around 5 % less chlorine was consumed in comparison to a control process without biopulping. Yadav et al. [57] reported a reduction of around 10 % and 20 % of chlorine and chlorine dioxide, respectively, after direct bleaching a mixture of eucalyptus and bamboo chips (4:1) after biopulping with *Phanerochaete* sp. for 20 days. These authors also tested the combination of biopulping and a pre-bleaching step with xylanases and reported a reduction of 37 % and 20 % for chlorine and chlorine dioxide on the subsequent bleaching step, respectively.

However, biopulping processes have some significant disadvantages that hinder their industrial implementation: (i) long treatment times (reported from 5 to 40 days); (ii) system heterogeneity, i.e., wood chips are large particles with significant intraparticle diffusion resistance; (iii) difficulty of process monitoring and control; and (iv) risk of contamination during treatment.

8.3.2.2 Biobleaching

The biobleaching process aims to remove and/or modify the residual lignin that remains in the pulp to facilitate its degradation and/or extraction in subsequent steps. It is commonly studied as a pre-bleaching step, before conventional bleaching. Typically, enzymes from white-rot fungi or produced by engineered bacteria or fungi were used instead of the microorganisms. The use of enzymes for pre-bleaching the pulp has a significant impact on the whole process, as these enzymes can substitute in part for the use of chlorine dioxin, decreasing the formation of organic chlorides. One of the first works on pulp biobleaching, which tested several enzymes capable of degrading lignin or hemicellulose, was developed at the VTT Biotechnical Laboratory in cooperation with the Finnish Pulp and Paper Research Institute in 1986 [71]. Since that time, many enzymes involved in lignin modification or removal have been identified, and at least two strategies of enzyme utilization for pulp bleaching have been extensively evaluated.

The first strategy is to directly oxidize lignin by ligninolytic enzymes such as lignin peroxidases (EC 1.11.1.14), manganese peroxidases (EC 1.11.1.13), and laccases (EC 1.10.3.2). Although several reports have shown the use of manganese peroxidases and lignin peroxidases for bleaching [43, 46, 72, 73], the most effective oxidative enzyme for pulp biobleaching is the phenoloxidase laccase [47–49, 51, 52, 74]. Laccases use oxygen as the final electron acceptor, while manganese peroxidases and lignin peroxidases require hydrogen peroxide as the final electron acceptor, which is highly corrosive for tanks and, therefore, not feasible for industrial applications [52].

Laccases mainly catalyze the oxidation of the hydroxyl groups of phenolic substrates to phenoxy radicals, reducing oxygen to water [52, 75], which may also promote the bond cleavage of β-O-4′ and 4-O-5′ bonds in lignin models. The active phenoxy radical may induce different reactions on the structure of lignin. Munk et al. [52] proposed that three main reactions may occur on the activated lignin: (i) bond cleavage and depolymerization of lignin, (ii) functional group modification, and (iii) coupling reactions leading to grafting or polymerization of lignin. However, the ability of laccase to catalyze the oxidation of native or complex lignin, which contains high amounts of non-phenolic subunits, is restricted by its limited redox potential. This restriction can be overcome by the presence of a mediator, which works as an electron carrier between laccase and the substrate [76]. In this laccase-mediator system (LMS), the mediator is first oxidized by laccase to become a strong oxidizing agent that has redox potential higher than those of non-phenolic compounds in native or complex lignin. Laccase mediators can be classified as natural or synthetic, depending on their origin [52, 77]. Natural origin mediators are usually lignin degradation products and other phenolic compounds from plants (e.g., 4-hydroxybenzyl alcohol, p-cinnamic acid, sinapic acid), and their inherent presence makes it difficult to distinguish the solo action of laccases. Synthetic origin mediators such as HBT (1-hydroxybenzotriazole,), ABTS (2,2′-azinobis 3-ethylbenzothiazoline-6-sulfonate), and TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) are commonly used in LMS studies. Additionally, another improvement promoted by oxidized mediators is that they can diffuse into cell walls, overcoming an accessibility limitation that may occur because laccase cannot penetrate deep into the fibers due to its molecular mass of around 70,000 Da. Therefore, LMS has the advantage of being easily implemented in most bleaching sequences.

Polymerization and depolymerization of lignin have been reported for both laccase and LMS; it seems that the resulting course of action may depend on both the reaction conditions and the properties of the mediator [78, 79]. Most of the studies demonstrate laccase or LMS depolymerization of lignin by measuring the increase in pulp brightness and the decrease in kappa number. However, these parameters may be modified by an enhanced solubility of the lignin polymer due to radical grafting of sulfonated mediators on lignin [49, 78] and not by lignin removal, as intended by the bleaching process. Thus, these results should be analyzed with caution, and other techniques allied to a spectrophotometric method should be used to analyze the reaction products or remaining structure of lignin. For this reason, recent works have used pyrolysis gas chromatography/mass spectroscopy (Py-GC/MS) and two- or three-dimensional nuclear magnetic resonance (2D or 3D NMR) to prove the depolymerization action of LMS on the structure of lignin [80, 81].

Although the biobleaching process using laccases shows promising results, it has some drawbacks that hinder its industrial implementation: (i) the high cost and toxicity of synthetic mediators, (ii) unresolved problems concerning mediator recycling, and (iii) the complexity of controlling reaction pathways.

The second strategy is an indirect way to remove lignin by the hydrolysis of hemicellulose using xylanases (EC 3.2.1.8). Xylanases catalyze the hydrolysis of β-1,4-xylosidic linkages from the xylan backbone at random or specific positions, producing short-chain oligosaccharides with different lengths [82]. The depolymerization of xylan affects the separation of lignin from cellulose and increases swelling of fiber cell walls, further increasing the diffusion of enzymes and chemicals [83]. For instance, a xylanase dosage of 2–5 IU per gram of dry pulp has the potential to improve lignin removal up to 30 %, by fiber swelling and by the hydrolysis of xylan that is reprecipitated with lignin on cellulose after the cooking step [84]. The results of this process are (i) increase in pulp brightness; (ii) reduction in the demand of bleaching chemicals, such as chlorine-based compounds, caustic soda, hydrogen peroxide, and activated oxygen, used in ECF or TCF bleaching sequences; (iii) reduction of AOX and dioxin formation; and (iv) improved pulp and paper quality. However, xylanases can only substitute for a fraction of the chlorine and chemicals used in ECF and TCF bleaching, respectively. It is also important to mention that other enzymes, such as endo-1,4-mannanases (EC 3.2.1.78), may play a crucial role, depending on the origin of the pulp (e.g., many softwoods have mannan covalent links to lignin and their hydrolysis could affect lignin removal) [85]. In addition, enzymes that are hyperthermophilic and stable and active at alkaline conditions are ideal for bleaching processes to avoid the additional steps of temperature and pH adjustment [86, 87]; a formulation free of cellulases is also required.

To enhance the delignification ability of the enzymatic step, a combination of laccase or LMS and xylanases has been evaluated for pulp biobleaching, denoted as LX, LXS, LMXS, or LMS+X [88–90]. Although a synthetic system using commercial laccase and xylanases was reported to be ineffective for biobleaching [91], many authors have reported improved brightness results and decreased kappa numbers using LXS [88–90]. In addition, the use of xylanase followed by laccase has been shown to decrease the demand for laccase load and mediator dosage by 30 % and 80 %, respectively, with a 45 % shorter reaction time for bleaching kraft-pulped eucalyptus [92]. Alternatively, biobleaching can be done by growing whole microorganisms on pulp, especially white-rot fungi [93, 94], similar to the biopulping process. This is a cost-effective strategy; however, it requires long cultivation times on unbleached hardwood and softwood pulps to be effective. Recently, however, Sharma et al. [95] achieved expressive results via a novel,

Table 8.1 Overview of recent scientific studies on the reduction of chlorine consumption by the use of a pre-bleaching step with laccase, laccase-mediator systems (LMS), and laccase or LMS/xylanase systems (LXS) on lignin polymers

Strategy	Enzyme origin	Biomass	Chlorine save	Reference
Laccase	*Ganoderma* sp. rckk-02	Eucalyptus kraft pulp	25 %	[95]
LMS	*Pycnoporus cinnabarinus* and a chimeric laccase-CBM	Mixed softwood kraft pulp	15 % and 28 %	[99]
LXS	*Lentinus lepideus*	Wheat straw pulp	29 %	[88]
Xylanase followed by laccase	*B. pumilus* MK001 and *Ganoderma* sp. rckk-02	Eucalyptus kraft pulp	35 %	[95]
Xylanase	*Thermomyces lanuginosus* SSBP and xylanase P from Iogen	Bagasse unbleached soda, hardwood post-oxygen soda–aq (anthraquinone), and softwood post-oxygen kraft pulps	Up to 30 %	[100]
Xylanase	*B. pumilus* MK001	Eucalyptus kraft pulp	15 %	[95]
Xylanase	*Bacillus halodurans* C-125	Wheat straw pulp	10 %	[101]
Xylanase-producing *Bacillus halodurans* FNP 135	–	Eucalyptus kraft pulp	20 % for SmF; 10 % for SSF	[103]
Xylanase + mannanase + LMS	*Bacillus halodurans* FNP 135, *Bacillus* sp., gamma-proteobacterium	Mixed wood kraft pulp (bamboo, 14 %; poplar, 8 %; eucalyptus, 78 %)	30 %	[90]

SmF Submerged fermentation, *SSF* Solid state fermentation

faster approach by using the xylanases-producing *Bacillus halodurans* FNP 135, instead of a fungi-based system, for biobleaching kraft pulp through submerged and solid-state fermentation.

Most of the aforementioned works emphasize the positive environmental impact of laccases, LMS, and/or xylanases on chlorine and chlorine-free pulp biobleaching processes [56, 57, 96–98]. The implementation of an enzymatic pre-bleaching step resulted in reductions of 10–35 % in chlorine consumption, depending on the pulp type and reaction conditions. Table 8.1 shows recent studies that reported the use of these enzymes and their potential to lower the consumption of chlorine-based compounds for pulp bleaching, thereby reducing AOX generation in bleach effluents. In addition, COD can be reduced by about 85 %, and other parameters, such as brightness and strength, can be increased when implementing an enzymatic step.

Furthermore, application of an enzymatic step with LMS and/or xylanases was also reported to improve the quality of pulp and reduce the need for chemicals in TCF bleaching. The LMS improved the brightness up to 82 % ISO brightness, compared with 60 % in the peroxide-bleached control, and resulted in very low kappa number [102]. Similarly [90] tested the bleaching of mixed wood kraft pulp with a combination of xylanase, mannanase, and LMS and reported a reduction of 44 % on H_2O_2 consumption.

8.3.2.3 The Commercial Process for Biopulping and Enzymes for Biobleaching

A research consortium composed of the USDA Forest Service, the Forest Products Laboratory in Madison, and the Universities of Wisconsin and Minnesota scaled the biopulping process from the laboratory to a 50-ton (45 kt) semicommercial scale [44, 70, 104]. Twenty-three pulp and paper companies, as well as related companies and the Energy Center of Wisconsin, supported this research over 12 years, which established a commercial and economically feasible biomechanical pulping with advantages such as electrical energy saving, pulp strength enhancement, increased throughput, reduced pitch content, and reduced environmental impact. This technology has been licensed to a US company, Biopulping International Inc. (BII), which is promoting and commercializing the patent licensing arrangements, the supply of fungal inoculum, the design and supply of the appropriate equipment, and, most importantly, the technical knowledge.

Several laccases, LMS, and xylanases from different sources have been tested for biobleaching on both bench scales and in larger pilot studies and demonstration scales. For example, Sharma et al. [95] reported that a sequential enzyme treatment (xylanases followed by laccases) on a pilot scale (50 kg pulp) resulted in a 34 % reduction of AOX levels in bleach effluents and improved pulp properties. This enzymatic step could easily be implemented in existing ECF and TCF bleaching sequences, leading to not only a partial replacement of chlorine compounds or other chemicals but also to cost reduction, in addition to the other aforementioned advantages. Consequently, many laccases and xylanases have been identified as candidates for commercialization for the pulp and paper industry, and several patents for using LMS [105–109] and xylanases [110–113] for pulp pre-bleaching have been filed. One of the first processes with laccases and the mediator HBT (*N*-hydroxybenzotriazole), which has been successfully tested in several pilot plant trials, has been patented under the trade name Lignozym®-process [114].

The use of xylanases as an enzymatic step to assist pulp bleaching has been implemented by Domtar (Canada) and Oji Paper (Japan). Domtar uses the xylanase commercialized by the Iogen Corporation (Canada), enabling the company to reduce the amount of chlorine dioxide used for bleaching by 10–15 %. Domtar also reported a reduction in the cost of bleaching chemicals by 10–15 % and of organically bound chlorine in wastewater by 60 %. Oji Paper (Japan) produces its own xylanase in situ, which reduces the cost of xylanase production. This company reduced chlorine dioxide and organically bound chlorine in wastewater in similar percentages as those observed by Domtar. Table 8.2 presents the laccases and xylanases that have been commercialized; ones that are currently available are

Table 8.2 Overview of commercialized xylanases and laccase-mediator systems (LMS) for biobleaching. Currently available enzymes are highlighted in bold and italic

Product	Enzyme content	Optimum pH	Optimum temperature/°C	Company
Irgazyme 10®	Xylanase	5–7	35–55	Genencor, Finland
Irgazyme 40®	Xylanase	6–8	35–70	Geigy, Switzerland
Cartazyme HS®	Xylanase	3–5	30–50	Clariant, England
Cartazyme HT	Xylanase	5–8	60–70	Clariant, England
Ecopulp®	Xylanase	5–6	50–55	Alko Rajamaki, Finland
VAI Xylanase®	Xylanase	6–7.5	65–75	Voestalpine, Austria
Pulpzyme HA®	Xylanase	6–8	50–55	Novozymes, Denmark
Pulpzyme HB®	Xylanase	6–8	50–55	Novozymes, Denmark
Pulpzyme HC®	Xylanase	6–9.5	60	Novozymes, Denmark
Bleachzyme F®	Xylanase	n.d.	n.d.	Biocon India, Bangalore
AU-PE89	Xylanase	6–9.5	45–55	Sukahan, China
Optipulp L-8000 ®	Xylanase	6.5	55	Solvay Interox, EUA
Luminase™ PB-100	*Xylanase*	*5–8*	*40–70*	*Verenium, EUA*
Luminase™ PB-200	*Xylanase*	*5–9*	*60–90*	*Verenium, EUA*
GS-35®	Xylanase	5.2–7.8	47–58	Iogen, Canada
HS-70®	Xylanase	5.3–7.5	45–55	Iogen, Canada
Xylanase P	Xylanase	n.d.	n.d.	Iogen, Canada
Novozym 51003	Laccase	n.d.	n.d.	Novozymes, Denmark

Data taken from *Enzymes in Biotechnology* by Bon et al. [115] and the websites of specific companies
n.d. – not determined

indicated in bold and italic. Note that most of the commercialized enzymes are xylanases, due to their aforementioned advantages.

Bajpai et al. [116] conducted one of the first studies to test commercialized enzymes; they reported that the use of commercial xylanases (Novozyme 473, VAI xylanase, and Cartazyme HS-10) not only reduced chlorine consumption by 31 % and decreased the total organic chlorine content in bleach affluent by 30 % but also increased brightness and tensile strength of eucalyptus kraft pulp by 3 % and 26 %, respectively. Because they are from mesophilic microorganisms, many of the previously commercialized enzymes are not applicable to the pulp and paper industry, which requires enzymes that are stable and active at a high temperature and alkaline pH. However, it is worth noting that the currently available commercialized enzymes, highlighted in Table 8.2, meet the requirements for biobleaching.

Therefore, although at present commercialized enzymes for ECF and TCF biobleaching are being considered as only partial substitutes for chemicals, they have the potential to modify or eliminate certain stages of bleaching. Advances in enzyme technology, such as complex hyperthermophilic enzyme formulations, would enable the implementation of an enzyme-assisted TCF process in the pulp and paper industry, saving energy and chemicals and eliminating chlorine compounds.

8.3.3 The Hydrolysis of Lignocellulosic Biomass

The biorefinery concept has been applied to processing facilities that integrate equipment and conversion processes to produce solid and liquid fuels, value-added chemicals, power, and heat [117]. In this context, considering the use of lignocellulosic biomass as a raw material, cellulose and hemicellulose can be hydrolyzed to generate monomeric sugars that serve as the platform molecules for the production of liquid fuels and chemical feedstock such as acetic acid, ethane, lactic acid, acrylic acid, and polymers via biochemical or chemical routes [118]. In addition, the valuable phenolic macromolecule lignin may enter another processing route for the production of solid fuel, due to its high calorific power of 26 $\mathrm{MJ \cdot kg^{-1}}$ [119], and lignin-derived chemicals, such as benzene and substituted benzenes, cyclohexane, phenols, methoxy phenols, lignosulfonate, lignin fertilizer, resins, and lignin carbon fibers [120]. However, access to the biomass monomeric sugars and lignin has been hindered by the recalcitrance of the plant cell walls, despite extensive worldwide research efforts that have been carried out in the last 30 years to establish a robust bio-based fuel and chemical industry [121].

The production of monomeric sugars from heterogeneous feedstock can be done chemically, using mineral acids, or enzymatically, using biomass-degrading enzymes such as cellulases and hemicellulases, after a pretreatment step to disrupt the plant cell wall structures [122]. The process for the acid hydrolysis of lignocellulosic materials was developed in the nineteenth century and commercialized in the early twentieth century [123]. Meanwhile, the alternative enzymatic route was only considered in the late 1990s, when the use of enzymes began increasing in importance with the emerging field of industrial biotechnology [124]. Nowadays, most research efforts are concentrated on the enzymatic hydrolysis process, which suits better the microbial conversion of the resulting biomass syrup [125]. However, some efforts to accelerate acid hydrolysis are still being undertaken, mostly when the resulting biomass sugar syrups will be processed via chemical methods. The comparative advantages and disadvantages of acid and the enzymatic hydrolysis are discussed later in this chapter.

8.3.3.1 Acid Hydrolysis

Processes for biomass acid hydrolysis can be conducted using either diluted or concentrated acids. In these processes, the temperature and operational mode vary and aim to increase the yield of monomeric sugars derived from cellulose and hemicellulose, avoid lignin degradation that produces phenol, and avoid sugar degradation that leads to the formation of inhibitors such as furfural, 5-hydroxymethylfurfural, acetic acid, levulinic acid, uronic acid, 4-hydroxybenzaldehyde, vanillic acid, and vanillin [126]. The most commonly used acids are sulfuric (H_2SO_4) and hydrochloric acid (HCl), with the latter offering several advantages over the former. HCl can permeate the lignocellulosic biomass more easily than H_2SO_4 and is more volatile, making the crucial recovery step easier, with economic and environmental benefits. However, the use of concentrated HCl has severe drawbacks related to its highly corrosive nature and its formation of an azeotrope with water in concentrations between 21 % and 25 %, depending on the pressure, which increases the difficulty of its recovery [127].

The mechanism generally accepted for acid hydrolysis is the penetration of the acid through the cellulose structure, causing the hydrogen bonds to rupture. This leads to cellulose swelling and, finally, to the breaking of the glycosidic bonds, which releases sugars in their monomeric forms [123].

One example of concentrated acid hydrolysis at low temperature is the concentrated hydrochloric acid process (CHAP). This process is primarily indicated for biomasses that are rich in cellulose and poor in hemicellulose because the concentrated acid can easily hydrolyze the hemicellulosic fraction and then degrade the resulting pentoses to furfural, which inhibits microbial fermentation. However, the resulting high calorific power, lignin-rich fraction is contaminated with HCl, whose combustion emits dioxins [128].

In 1937, commercial cellulosic ethanol plants, based on acid hydrolysis with concentrated HCl, were built in Germany [123], and, to meet increased fuel demand, the Bergius–Rheinau process was developed during World War II. There is no consensus on how these plants operated, besides having used HCl [127, 129, 130].

Studies aiming to improve the process economically developed the modified Udic–Rheinau process, whereby the use of more than one hydrolysis step (two or three, depending on the source) minimized the pentose degradation reported in CHAP. Thus, in a first pre-hydrolysis step, carried out at room temperature, HCl with low or intermediate concentration would be used to hydrolyze the hemicellulosic fraction, thus generating a liquid pentose-rich stream and a solid cellulose–lignin-rich residue. The cellulose content of the solid residue would then be hydrolyzed by a more concentrated HCl, also at room temperature, yielding a glucose-rich liquid stream and a solid lignin residue [127, 130].

Although HCl has often been substituted by lower-cost sulfuric acid, some recent studies have still been conducted with HCl. For example, Pulidindi et al. [131] used a microwave system instead of conventional heating for the acid hydrolysis of commercial cellulose, reaching a 63 % cellulose-to-glucose conversion.

Besides conventional acid hydrolysis, a new ionic liquid-based technology has emerged using acids as catalysts for the solubilization and simultaneous hydrolysis of lignocellulosic biomass. The first report, by Li and Zhao [132], which used sulfuric acid as the catalyst in a BMimCl medium, was followed by reports in which HCl was used instead. Indeed, in a recent study, Wang et al. [133] reported the use of HCl with the ionic liquid BMimCl and several metal chlorides as co-catalysts for the hydrolysis of bamboo powder. The authors reported a 67 % reducing sugars yield within 4 h of hydrolysis at 100 °C when using CuCl2 as co-catalyst.

Although acid hydrolysis results in the fast release of sugars without the need for a biomass pretreatment step, inorganic acids are toxic and corrosive, and their use requires reactors that are resistant to corrosion, which increases the cost of the process. Furthermore, the need to neutralize the liquid streams, which generates salt, and the extensive washing of the solid stream for acid removal make the process harmful for the environment [134].

For these reasons, the enzymatic hydrolysis route has been perceived as a sound alternative regarding final sugar yields and low environmental impact. Even though this process requires enzymes and a costly biomass pretreatment step to lower biomass recalcitrance, it is considered worldwide as a technology of choice for biomass processing. Nevertheless, some industrial plants run with acid hydrolysis technology in the USA, i.e., Masada, in Alabama, and Arkenol, in Las Vegas. Arkenol's technology has been also used by the US company Bluefire in its production plant in Izumi, Japan (operated by JGC Corp.) and in a new plant in Fulton, Mississippi. The Tavda hydrolysis plant in Russia has also been using this technology since 1943.

8.3.3.2 Enzymatic Hydrolysis

Enzymatic hydrolysis of biomass carbohydrates is carried out by cellulases and hemicellulases, which, opposed to acids, are highly specific catalysts, resulting in the formation of the reducing sugars of interest. Moreover, their reaction does not form sugar's dehydration products, which are inhibitory molecules for the biochemical routes used in processes that produce fuels and chemicals from biomass sugar syrups. Furthermore, unlike acid hydrolysis, enzymatic hydrolysis is carried out at mild conditions, with a pH of around 5.0 and a temperature of 50 °C, and does not create serious equipment corrosion problems [134–136]. However, as plant cell walls are highly recalcitrant, enzymes in untreated biomass produce very low hydrolysis yields. Therefore, before enzymatic hydrolysis takes place, the biomass needs to undergo a pretreatment step to open up cell wall structures for enzymatic attack. We do not comment on the pretreatment step in this chapter, as reviews on this subject can be found elsewhere [5–7].

One disadvantage of enzymatic hydrolysis of biomass is that, depending on pretreatment conditions, it usually takes between 48 and 72 h for hydrolysis with

Table 8.3 Comparison of acid and enzymatic hydrolysis of biomass

Parameter	Concentrated acid hydrolysis	Diluted acid hydrolysis	Enzymatic hydrolysis
Hydrolysis duration	Low 🟢	Low 🟢	High 🔴
Cost of catalyst	Moderate 🟠	Low 🟢	High 🔴
Specificity	Moderate 🟠	Low 🔴	Very high 🟢
Corrosiveness	High 🔴	Moderate 🟠	Very low 🟢
Equipment maintenance	High 🔴	Moderate 🟠	Low 🟢
Hydrolysis yields	High 🟢	Moderate 🟠	Moderate/high[a] 🟠
Inhibitory by-product formation	Low 🟢	High 🔴	Very low 🟢
Generation of toxic effluents	Very high 🔴	High 🔴	Low 🟢
Reaction conditions	Mild temperatures, low pH 🔴	High temperatures, low pH 🔴	Mild temperatures, mild pH 🟢

[a] Depending on pretreatment conditions

solid content up to 10 % and 96–120 h for hydrolysis with high solid content, whereas acid hydrolysis can occur in few minutes. Additionally, it is still difficult to obtain high yields of concentrated sugar syrups, due to the stirring difficulties of hydrolysis reactions with high solid content and the inhibition of enzymes by their final hydrolysis products [137, 138]. Finally, the cost of the pretreatment step, together with the price of enzymes, is still high. Table 8.3 shows a comparison of acid and enzymatic hydrolysis of biomass.

For the widespread and economical use of enzymes, they need to be robust and display high activity on various different types of lignocellulosic biomass that have been pretreated with different pretreatment methods, such as sugarcane bagasse, corn stover, wheat straw, and energy crops. The types of enzymes needed for biomass hydrolysis and their current application in commercial plants for the production of cellulosic ethanol are detailed in the following section.

Enzymes and Accessory Proteins for Cellulose Degradation

The classic scheme for cellulose enzymatic degradation involves enzymes that hydrolyze the β-1,4-D-glucan linkages in cellulose to primarily produce glucose, cellobiose, and cello-oligosaccharides by the synergistic action of three distinct classes of enzymes [124, 139, 140]:

- Endoglucanases, which randomly hydrolyze internal β-1,4-glycosidic linkages in the cellulose chain
- Exoglucanases, or cellobiohydrolases, which act on reducing and nonreducing ends of the cellulose chain, liberating cellulose units from its ends
- β-Glucosidases, which convert cellobiose to glucose

During the enzymatic attack of crystalline cellulose, endoglucanases and exoglucanases act cooperatively to release cello-oligosaccharides and cellobiose. The endoglucanases have the ability to catalyze the hydrolysis of the low crystalline and amorphous regions of the cellulose fiber, creating free chain ends and releasing oligosaccharides. The exoglucanases further degrade the sugar chain by removing cellobiose units from the reducing and nonreducing free chain ends and create more substrate for endoglucanases by disrupting the crystalline substrate and/or exposing previously inaccessible less-ordered substrates for the endoglucanases to attack [15]. The resultant cellobiose is then hydrolyzed to glucose by β-glucosidase, which can also hydrolyze, to a lesser extent, other small cello-oligosaccharides to glucose [141].

Cellulases are produced not only by a wide variety of microorganisms such as fungi, bacteria, and protozoans but also by plants and animals [142]. However, only a few fungi and bacteria produce high levels of extracellular cellulases that are capable of acting extensively on cellulose. Many fungi produce more than one isoform of each enzyme, apparently with redundant activity, but that may have affinities for different sites in the cellulose chain, such as different ends or specific crystal faces [8, 141, 143]. Variation in affinity may in part be a consequence of the presence of carbohydrate-binding modules in exoglucanases and in some endoglucanases. For example, *Trichoderma reesei*, one of the most studied fungi for cellulase production, produces two exoglucanases, five endoglucanases, and two β-glucosidases [144].

All these enzymes are hydrolases, i.e., they cleave glycosidic bonds by the addition of a water molecule. However, it has been recently discovered that fungi also produce enzymes called lytic polysaccharide monooxygenases (LPMOs), formerly classified as GH61 and CBM33, capable of cleaving polysaccharide chains in the crystalline parts by an oxidative mechanism [145, 146]. LPMOs are copper-dependent monooxygenases that oxidize polysaccharides at C1 and/or C4, initiating chain breakage [147]. LMPOs were included in commercialized enzyme preparation, such as Cellic CTec2 and CTec3 (Novozymes), only few years after their discovery because they were proven to boost cellulose degradation and improve ethanol production from biomass [148, 149].

Other accessory proteins that have gained attention for cellulose degradation are the expansin-like proteins, such as swollenins, which are reported to disrupt hydrogen bonds, loosening the packaging of cellulose fibril and exposing individual cellulose chains, thus increasing the accessibility of cellulose to the enzymes [150].

Nowadays, commercialized enzyme cocktails are tailor-made in accordance with specific characteristics of the target biomass after pretreatment processing; they present different proportions of enzyme activities and accessory proteins to maximize sugar yields from cellulose while decreasing costs.

Enzymes for Hemicellulose Degradation

A low-severity pretreatment is desired for lignocellulosic biomass processing to reduce capital costs and to minimize the production of inhibitory compounds for the subsequent sugar fermentation step [151]. However, low-severity pretreatments do not completely remove the hemicellulose, which then requires enzymes to hydrolyze the residual hemicellulose during the cellulose enzymatic hydrolysis step, thus increasing cellulose-degrading enzymes' access to cellulose [152].

Depending on the type of biomass, a completely different set of hemicellulases are required. Most biomass sources considered for commercial processing are agricultural wastes that have xylan as the primary component of their hemicellulose. Xylan consists of a backbone of xylose residues that can be substituted with arabinose, galactose, acetate, glucuronosyl, and 4-O-methyl glucuronosyl residues and feruloyl arabinofuranosyl side chains [153].

The diversity of linkage types between sugar residues and types of branching contributes to the complexity of the structure of hemicellulose, which requires a similarly complex enzymatic system for its full degradation. Complete enzymatic hydrolysis of xylan and its substituents requires many different enzymes, such as endoxylanase, β-xylosidase, α-L-arabinofuranosidase, α-glucuronidase, α-galactosidase, acetylxylan esterase, and ferulic acid esterase [154]. On the other hand, the absence of crystallinity and a microfibrillar structure, as observed in cellulose, makes hemicellulose more susceptible to enzymatic hydrolysis [155].

Depending on the type of pretreatment, pretreated biomass contains different amounts of hemicellulose or even keeps its hemicellulose content. Taking this into account, commercial manufacturers of biomass-degrading enzymes are designing enzyme cocktails that are rich in hemicellulases and can be blended with the mix of primary cellulases according to specific requirements.

The Commercial Use of Enzymes for Biomass Hydrolysis

Until recently, enzymes for biomass hydrolysis have corresponded to nearly half the cost of cellulosic ethanol. Thus, providing cost-effective biomass-degrading enzymes has been a challenge for industrial application in this area. Many enzyme producers such as Novozymes, DuPont, Dyadic, and DSM have brought down the production cost of enzymes so that their contribution to the biomass ethanol cost was reduced from \$2 per gallon (0.53 US\$$\cdot$L^{-1}) in 2010 to an estimated cost of \$0.30–0.50 per gallon (0.08 to 0.13 US\$$\cdot$L^{-1}) in 2014 [9]. In comparison, the enzyme cost for hydrolyzing starch to produce corn-based ethanol is around \$0.03 per gallon (0.008 US\$$\cdot$L^{-1}) [156]. Current estimates suggest that the cost of producing cellulosic ethanol is \$2.00–2.30 per gallon (0.53 to 0.61 US\$$\cdot$L^{-1}) [157], so enzymes are estimated to account for approximately 15 % of the cost of cellulosic ethanol.

The first commercial facilities to produce cellulosic ethanol in Europe, the USA, and Brazil demonstrate that the biochemical is preferred over the acid route to deploy this technology [158–160]. The first industrial plant to produce cellulosic ethanol started production in 2013 in Crescentino, Italy, with capacity of 20 million gallons (75.7×10^6 L) of ethanol per year; this plant is owned by Beta Renewables, which has a partnership with Novozymes as its preferred enzyme supplier [161].

In 2014 in Brazil, GranBio became the first commercial plant in the southern hemisphere to produce cellulosic ethanol from sugarcane bagasse and straw, with an annual capacity of 21.6 million gallons (81.8×10^6 L) of ethanol; GranBio uses similar technology as the Italian plant, with Beta Renewables and Chemtex of the Italian chemical group Mossi and Ghisolfi providing process technologies and engineering and Novozymes supplying the necessary enzyme technology [160].

The other three commercial plants, which are all based on enzymatic hydrolysis technology, are located in the USA, with POET-DSM Liberty Project being the first one to open in 2014. This plant, which has an installed annual production capacity of 20–25 million gallons ($(75.7 \text{ to } 94.6) \times 10^6$ L) of ethanol, had its enzymes supplied by Novozymes before transitioning to DSM enzymes [157]. The other two plants, constructed by Abengoa and DuPont, respectively, are nearing production. Abengoa's plant plans to produce 25 million gallons of ethanol per year, using enzymes produced on-site by a microorganism licensed from Dyadic [9]. DuPont's plant will have the largest production capacity of all operating or soon-to-be-operating plants, with 30 million gallons per year; it will also use its own enzymes, known as Accellerase® [162].

As a result of those efforts, the industry will soon have real numbers on the competitiveness of cellulosic ethanol production based on enzymatic hydrolysis in relation to other sources, such as corn-based and sugarcane juice-based ethanol. According to Dyadic [9], if cost reductions and volume increases match current estimates, the enzyme market could reach $5 billion in a decade. Therefore, a major emphasis on research to reduce the cost of hydrolytic enzymes is likely to continue.

8.4 Conclusion

The use of enzymes for the hydrolysis of the polysaccharide portion of lignocellulosic materials, to produce biomass sugar syrups, is already a technology of choice due to the use of the liquid syrup stream in microbial processes for the production of fuels and chemicals. As such, the very nature of this liquid syrup's application is directing the shift from acid hydrolysis, which is more prone to producing inhibitory molecules, toward the enzymatic route. Research and development initiatives from both the industry and the academy have been of paramount importance in increasing the economic feasibility of using enzymes at the industrial scale required for biomass ethanol production.

Advances in the use of enzymes in the bleaching process of lignocellulosic materials, however, is lagging behind due to the nature of the end product, which is not further processed by microbes but sold as a commodity by the pulp and paper industry. Nevertheless, environmental issues and legislation are pushing toward innovation at an increasingly fast pace. Indeed, contamination prevention is the best approach for the environment and for public health; such prevention is only possible with a shift away from traditional chemical processes. However, this type of approach is still in its infancy, being a common practice of the end of pipe decontamination. It is imperative that the pulp and paper industry changes its bleaching process, which is the most complex step and produces numerous pollutants. The pulp and paper industry is one of the most economically important industrial sectors worldwide; managing its resulting pollutants is still a challenge that must be tackled. Similarly, from an industry perspective, environmentally based motivations are not strong enough to promote changes in traditional production processes in the chemical industry. Regulations and incentives for implementing less-polluting processes, coupled with heavy fines on environmental pollution and increasing worldwide awareness of environmental issues, may exert greater pressure in this direction.

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Chapter 9
Substitution of Chloride Chemicals with Degradable Bioflocculants for Sedimentation of Suspended Particles in Water

Yehuda Shevah

Abstract Chlorine-based flocculants are commonly used to enhance the flocculation and sedimentation of particles in suspension in water and other liquids, while chlorine is the major element used for disinfection of drinking water. The chlorine chemicals which are highly effective and low cost are also nondegradable and after use the compounds and their derivatives can be detected in the environment and in estuaries. In the case of pretreatment of seawater for RO desalination, a plant producing 100 million m^3 of water per year could discharge with the filter backwash water up to 1500 ton/year (1.362 $kt \cdot a^{-1}$) of spent ferric chlorinated chemicals forming a nonesthetic red-brown mat, affecting light penetration and biological productivity, as well as being a potential eutrophication agent of coastal water. The likely replacement of inorganic chloride salts with environmentally friendly biodegradable and food-grade flocculants for use in food and water treatment process is discussed together with a description of a comparative coagulation-flocculation experiment testing patented bioflocculants (Seleno-X) as against traditional chemical flocculants for the destabilization of colloidal and particulate matter in seawater feeding RO membranes. The bioflocculants were found to yield comparable results in terms of NTU and silt density index (SDI). But, the results are inconclusive to validate the practical application and commercial use of bioflocculants in water, and further research is required in an attempt to substitute and reduce the use of chloride chemicals in general and in water treatment in particular.

Keywords Bioflocculants • Chlorinated chemicals coagulation-flocculation • Desalination • Disinfection

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9.1 Introduction

9.1.1 The Coagulation and Flocculation Process

The process of contact and adhesion whereby particles in dispersion form larger-size clusters is termed a coagulation and flocculation process [1]. In the first step, the destabilization of suspended colloidal materials – *coagulation* – is achieved by the addition of coagulant salts which reduce, neutralize, or invert the electrical repulsion between particles. Because these particles all carry the same surface charge (usually negative), their mutual repulsion is enough to prevent them from settling, and the particles remain suspended for long periods of time. In the second step – *flocculation* – the destabilized particles are aggregated to form a fragile structure, the floc or flake which can be settled or float that can be removed from the system by flotation or sedimentation.

In the process, flocculants reagent in a form of polymers or other small-charged multivalent cation such as aluminum, iron, calcium, or magnesium molecules may be added to enhance the interaction with negatively and positively charged particles and molecules in the media. Synthetic high molecular weight polymer flocculants of polyacrylamide chemistry are conventionally used in the treatment of waste suspension [2] to form large aggregates which can be further flocculated or separated from the media. The aggregates may float to the top of the liquid (creaming), settle to the bottom of the liquid (sedimentation), or be readily filtered or centrifuged from the liquid.

The coagulation and flocculation process is essential in various disciplines and industrial processes; in chemical, mining, and food industries and fermentation processes; as well as in the water sector to improve the quality of drinking water and in wastewater treatment [3, 4]. The process is dependent on the doses of the flocculants and other factors which promote the coagulation-flocculation process including the velocity gradient, the time, and pH. Under appropriate pH and other conditions, colloids react with water to form insoluble hydroxides which, upon precipitating, link together to form long chains or meshes, physically trapping small particles into the larger floc [2].

9.1.2 The Coagulants and Coagulation Agents

Flocculants are chemicals that stimulate flocculation by aggregation of colloids and other suspended particles, forming a floc [5]. A wide range of organic coagulants based on polyamines and blends are available including anionic, nonionic, and cationic polymers of various molecular weight. Products used as coagulants and flocculants include organic compounds such as polyacrylamides, polydiallyldimethyl ammonium chloride, and polyamines. Inorganic products include such materials as alum, iron salts, polyaluminum chloride (PAC), and blends of an inorganic with an organic polymer, classified as follows.

9.1.3 Synthetic Flocculants: Polymers

Polymers are natural or synthetic, water-soluble, macromolecular compounds that have the ability to destabilize or enhance flocculation of the constituents of a body of water. Polymers can be given anionic character by copolymerizing acrylamide with acrylic acid. Cationic polymers are prepared by copolymerizing acrylamide with a cationic monomer. These polymers have a very specific effect, dependent upon their charges, their molar weight, and their molecular degree of ramification. Coagulants having positive ions with high valence are preferred. An anionic flocculent will usually react against a positively charged suspension (positive zeta potential). That is the case of salts and metallic hydroxides.

9.1.4 Natural Flocculants

The most common natural flocculants are:

- The starch derivatives
- The polysaccharides
- The alginates

9.1.5 Mineral Flocculants

They are colloidal substances including:

- Activated silica
- Certain colloidal clays (such as bentonite)
- Metallic hydroxides with a polymeric structure, including:
  - Aluminum sulfate
  - Aluminum chloride
  - Sodium aluminate

  And

- Iron including:
  - Ferric sulfate
  - Ferrous sulfate
  - Ferric chloride
  - Ferric chloride sulfate

The most common coagulants are mineral salts: aluminum sulfate, ferric chloride, lime, calcium chloride, and magnesium chloride. Generally, aluminum is applied as $Al_2(SO_4)^3$-(alum) and iron as either $FeCl_3$ or $Fe_2(SO_4)_3$ that oxidize to Fe3+ during aeration. The effectiveness of aluminum and iron coagulants arises principally from their ability to form multi-charged polynuclear complexes with enhanced adsorption characteristics. Combined with modern separation techniques, they produce a very dense sludge that can be directly treated in a dewatering unit.

9.1.6 Inorganic Chlorine-Containing Coagulants

Of the various flocculants, metal chlorides aluminum and iron chlorides are major catalysts in synthesis and as flocculants, and some of them are applied at industrial scale in water treatment [6,7]. Among halogens, the most active class of chemical elements, chlorine is by far the most abundant in nature and is also the easiest to produce and to use. This explains its predominant and irreplaceable role in the chemical industry, in all industrial sectors and in our day-to-day life [8]. Numerous products, such as polymers, chemicals or pharmaceuticals, and ultrapure metals, which often do not actually contain chlorine, are produced using either chlorine or its derivatives. They are essential in all industrial sectors and in our daily lives, used in health, agro-food, building, textiles, transport, leisure activities, cosmetics, etc. More than 85 % of all pharmaceuticals and more than half the products marketed by the chemical industry are derivatives of chlorine chemistry [9].

9.1.7 Inorganic Chlorine-Containing Derivatives and Impact on the Environment and Health

Since the Industrial Revolution, chlorine has featured as an iconic molecule in process chemistry even though its production by electrolysis of sodium chloride is very energy intensive. Owing to its high energy and reactivity, chlorine allows the manufacture of chlorinated derivatives such as $AlCl_3$, $ZnCl_2$, $COCl_2$, etc., in a very easy way, serving in turn as intermediates in the production of numerous everyday goods.

9.2 Water Treatment

In recent years, potable water has become a vital natural resource whose quality and increasing scarcity are paramount for the survival of human and the ecology globally. Human activities contribute markedly to particulate matter deposition into water bodies, resulting in a dramatic increase in total suspended solids of water bodies that are to be removed during the water-purification process.

Water treatment involves two types of processes:

- Physical removal of solids (mainly mineral and organic particulate matter)
- Chemical disinfection (killing/inactivating microorganisms)

9.2.1 Coagulation and Flocculation Process

The physical process includes a coagulation and flocculation process in which chemicals are added to raw water to aggregate particles into masses that settle more readily than individual particles and sedimentation, clearing the water of much of the solid debris. The sedimentation process is followed by filtration in which the suspended particles not previously removed by sedimentation are trapped in layers of sand, gravel, coal, or activated charcoal.

Flocculation, coagulation, and sedimentation are widely employed in the purification of drinking water as well as sewage treatment, storm-water treatment, and treatment of other industrial wastewater streams. The processes facilitate the removal of total suspended solids (TSS) and colloidal microscopic particles, finer than 0.1 μm particles which would otherwise cause the water to be turbid (cloudy) and which would be difficult or impossible to remove by filtration alone. Nowadays, the coagulation and flocculation process is required to consistently produce treated water having a turbidity value of less than 0.1 NTU to guard against pathogen contamination, reducing suspended solids and organic matters.

9.2.2 Chlorine and Its Derivatives

Chlorine and its derivatives are commonly used in water treatment and disinfection. The treatment has relied upon halogenated iron ($Fecl_2$) and aluminum ($AlSO_4$) salts throughout the last century to provide the bulk removal of contaminants from source waters containing natural organic matter (NOM). These chemicals represent the most widely used coagulant across the world [10] and, in the case of ferric, the most effective coagulant for enhanced NOM removal [11].

Metal salts widely used in water coagulation treatment include:

Aluminum chloride [AlCl3] – Applications include metal removal, oil and grease separation, and water clarification.

Poly-aluminum chloride [PAC] – This describes a wide variety of materials containing more than one aluminum atom in the molecule up to about 13. Aluminum chlorohydrate is an example of a PAC.

Aluminum chlorohydrate – This is used as a flocculent in water-purification and wastewater treatment processes to remove dissolved organic matter and colloidal particles present in suspension. In water purification, this compound is preferred in some cases because of its high charge, which makes it more effective at destabilizing and removing suspended materials than other aluminum salts. Further, the high degree of neutralization of the HCl results in minimal impact on treated water pH when compared to other aluminum and iron salts [12].

Ferric chloride [$FeCI_3$] – This is used as a catalyst in organic synthesis and as a flocculent in sewage treatment and drinking water production. Applications include phosphate removal, sludge conditioning and dewatering, trace metal removal, and odor control. Iron (III) chloride is toxic, highly corrosive, and acidic. The anhydrous material is a powerful dehydrating agent. Ingestion of ferric chloride can result in serious morbidity and mortality.

Ferrous chloride [$FeCI_2$] – Applications include phosphate removal, odor control, heavy metal removal, toxic sulfide generation control in anaerobic digesters, oil and grease removal, and sludge conditioning.

Calcium chloride [$CaCl_2$] – Applications include phosphate and metal removal, organic reduction, and water clarification.

9.2.3 Flocculants Market (North America)

The North America inorganic flocculants account for about half of the market, and the share of the water sector is 45 %. The total market value is $1.25 billion (US$ $1.25 \text{x} 10^9$) increasing at about 3 %. The increase is due to increase in the use in papermaking, improved water quality standards (Safe Drinking Water Act), stringent limits on discharges of wastewater, and environmental regulation operating performance [13].

9.2.4 Doses of Metal Flocculants

The amount of flocculent that is necessary to obtain a good solid/liquid separation is very small. The average range of dosage is:

- 0.5–3 g per cubic meter of diluted mineral suspension
- 2–20 g per cubic meter of concentrated mineral suspension
- 25–300 g of flocculants per ton (per 0.454 kg) of solid for the filtration or centrifugation of a mineral slurry
- For metal chloride derivatives, the dose usually varies between ((10 and 90) mg ^{197} $Fe^{3+} \cdot L^{-1}$), but when salts are present, a higher dose needs to be applied.

9.2.5 Limitations of Halogenated Flocculation Chemicals

Because of stringent water quality requirements, there is now a strong drive for water treatment processes to be able to provide more DOC removal than that which can be provided by the chemical coagulants. This drive is incited by an increase in NOM levels in source waters across the world, as well as the inability of treatment works to cope with elevated NOM flux and excessive demand for coagulant [14] as well as the associated reduction in floc strength when high NOM loads enter the water treatment works, resulting in poor removal of NOM in solid/liquid separation processes [15]. Poor removal of NOM adversely affects the disinfection process and increases the production of the undesirable formation of DBPs, such as THM [14].

As a possible solution to both floc strength reduction and inadequate NOM removal, Jarvis et al. [16] tested novel zirconium (Zr) coagulant salts, as an alternative metal ion assuming to have increased positive charge compared with Al and Fe. The Zr coagulant outperformed the other coagulants tested at both bench and pilot scale. Improvements were demonstrated in terms of larger and stronger floc properties and lower residual of dissolved organic carbon (DOC) and reduced production of THMs formed.

9.2.6 Water Disinfection

Water with or without a prior physical treatment is subjected to chemical treatment in order to kill or inactivate pathogen organisms in water supply as well as to remove many disagreeable tastes and odorous compounds, hydrogen sulfide, ammonia, and other nitrogenous compounds that have unpleasant tastes and hinder disinfection. Adequate residual disinfectant in the treated water is also required to prevent the regrowth of microorganisms [17].

For these purposes, chlorine is the most commonly used and is the main disinfectant used worldwide because of its potency and low cost. It is also highly effective in inactivating microorganisms that are difficult to control including protozoan parasites, e.g., *Cryptosporidium parvum* and *Giardia lamblia*. A chlorine-based process, as elemental chlorine (chlorine gas), sodium hypochlorite solution, or dry calcium hypochlorite, is used for water disinfection [18].

9.2.7 Safety Hazards

However, the use of chlorine in gaseous form or as a solution can cause safety hazards. The use of chlorine is also associated with the formation of toxic disinfection by-products (BPs) in the form of chlorinated hydrocarbons, such as trihalomethanes (THMs) and halo-acetic acids which are known to be carcinogenic

[19, 20]. The use of chlorine-based flocculants in the treatment of water has resulted in a positive association between aluminum in drinking water and cases of Alzheimer's disease [21]. Current disinfection regulations require water systems to limit THMs and other DBPs in drinking water [22] which might force water utilities to discard chlorine disinfection and implement alternative technologies.

9.2.8 Disposal of the Returned Sludge

In addition, the use of chemical flocculants and the formation of metallic hydroxide cause the production of a substantial amount of backwash water and sludge. Millions of dry tons of alum and ferric sludge are produced every year in water treatment plants worldwide. In parallel to high effectiveness and low cost, the chlorinated flocculants are nondegradable [23], and the spent materials are discharged back to the environment. The discharged sludge has a significant negative effect on the aquatic life as a whole. In the case of the pretreatment of seawater used for desalination, a plant treating 735,000 m^3/day (735,000 $m^3 \cdot d^{-1}$) could discharge back to the sea up to 1500 ton per annum (1.362 $kt \cdot a^{-1}$) of ferric chloride which form a nonesthetic deep red-brown color mat that disperses over a considerable distance, affecting light penetration and biological productivity, and is a potential eutrophication agent of coastal water [24].

9.3 Chlorine Substitutes

Due to the environmental and health constraints (toxicity and ecotoxicity, ozone layer depletion) and the growing need for energy (energy efficiency, climate change), there is the growing need for the substitution of chlorine in end products. The combination of innovative process technology and highly selective, multifunctional catalysts will allow the chemical industry to set up new sustainable standards, leading to an era of "beyond-chlorine chemistry" [25]. Rigorous legislation is now in effect to limit the impact of such residuals on the environment. The regulations require proper treatment of the wastewater and the concentration of the chemicals to the point that they can be hauled and disposed to a landfill. Such treatment is very expensive, and the substitution of the chemical flocculants with biodegradable substances is highly desirable [2].

To reduce the formation of the hazardous chlorinated compounds produced by chlorine and hypochlorite in the disinfection process, multiple barrier approaches are considered including reliable physicochemical removal, e.g., coagulation, flocculation, sedimentation, and media or membrane filtration followed by photon based and or chemical inactivation. Disinfection agents that have been used in water and wastewater treatment over the last decades are available including chloramine, hydrogen peroxide (H_2O_2), ozone (O_3), UV, chlorine dioxide (ClO_2), potassium permanganate and nanofiltration, photo-Fenton, semiconductor photocatalysis, electrolysis, ultrasound irradiation, and wet air oxidation, among others [25].

Sequential disinfection schemes such as UV/combined Cl and ozone/combined Cl and ultraviolet irradiation following ClO_2 (UV/ClO_2) and H_2O_2 in combination with UV are being considered. Chlorine dioxide which seldom produces chlorinated by-products is used in water treatment as a pre-oxidant prior to chlorination of drinking water to destroy natural water impurities that produce THMs [26]. These alternatives are not always effective as chlorine. For example, viruses although effectively controlled by ozone are resistant to UV disinfection, while ozone can form the DBP carcinogen bromate ion in water containing bromide ions [27, 28] that may be more toxic and carcinogenic than those associated with free chlorine.

Futuristic disinfection techniques involve the combined use of photons and engineered nanostructures. UV light is capable of activating photocatalytic materials such as titania (TiO_2) which are capable of inactivating viruses [29]. New photocatalysts such as TiO_2 doped with nitrogen TiON or co-doped with nitrogen and a metal such as palladium can be activated with visible light to inactivate viruses and other waterborne pathogens with much lower energy use than UV [30]. Optical fibers could be used to bring photons into compact configurations such as monolithic reactors [31].

All disinfection methods, old and new, have unique benefits, limitations, and costs, but, as of now, only chlorine-based chemicals provide “residual disinfectant” levels that prevent treated water from recontamination and microbial regrowth and help to protect treated water throughout the distribution system. Novel nanomaterials having high catalytic properties that could provide unprecedented opportunities for more efficient water-purification catalysts able to inactivate viruses and other light and photocatalytic-resistant protozoa cysts and oocysts without producing DBPs or extensive use of chemicals are yet to be developed.

9.4 Development and Use of Bioflocculants

9.4.1 Bio-Based and Biodegradable Polymers

Bio-based polymers are attracting increased attention due to environmental concerns and the realization that global petroleum resources are finite and the need to find non-fossil fuel-based polymers. Bio-based polymers not only replace existing polymers in a number of applications but also provide new combinations of properties for new applications [32]. Bio-based and biodegradable polymers are materials which are produced from renewable resources, whose physical and chemical properties undergo deterioration and completely degrade to carbon dioxide (aerobic) processes, methane (anaerobic processes), and water (aerobic and anaerobic processes) [33].

The first generation of bio-based polymers focused on deriving polymers from natural resources, such as corn potatoes and legume seeds and agricultural feedstock. Other classes of natural bio-based polymers are proteins, nucleic acids, and polysaccharides (collagen, chitosan, chitin, fatty acids and various polysaccharides and proteins, etc.). However, with the current, extremely high demand for corn and potato as food for human consumption, the focus has shifted to move away from food-based resources to *Moringa oleifera* plant seeds and bacterial fermentation processes by synthesizing the building blocks (monomers) from lignocellulosic biomass (starch and cellulose and organic waste) followed by polymerization (e.g., poly-lactic acid, polybutylene succinate, and polyethylene) [34].

An overview of the development and flocculating efficiencies of plant-based bioflocculants including processing methods, flocculation mechanism, and the application of natural bioflocculants in food and beverage, mineral, paper and pulp, and oleo-chemical and biodiesel industries was prepared by Chai et al. [35], while the development of microbial flocculants was reviewed by Zhang et al. [36] and Huang et al. [37] highlighting bacteria, algae, fungi, actinomyces, and other microorganisms able to produce bioflocculants, followed by a review of factors that affect microbial flocculation and the optimization of the flocculation conditions by Bao-jun and Jiang-mei [38].

The flocculation efficacy of renewable resources such as lignocellulosic biomass and other natural bio-based polymers to create monomers and polymers that can replace petroleum-based polymers was evaluated on various microalgae genera belonging to *Chlamydomonas*, *Chlorococcum*, *Botryococcus*, and *Chlorella*. While ferric chloride was found to be the most efficient for most of the microalgal strains, the widely available cheaper biopolymers such as rice starch, maize, and potato starch were found to be promising flocculants due to their better harvesting efficiency (>80 %) and low price [39]. Similarly, mucilage and pectin extracted from cactus leaves of *Opuntia ficus-indica* showed more than 98 % of the flocculating activity in clay suspension and in synthetic turbid water treatment using a dosage of mucilage and pectin of 2 ~ 8 mL and 2 ~ 6 mL per liter of turbid water [40].

9.4.2 Use of Bioflocculants

The bioflocculants which have gain a great interest for coagulation and flocculation processes due to their biodegradability and the harmless of their degradable intermediates in the environment can be effectively used to destabilize colloidal and particulate matter in water without the use of inorganic chloride salts [30]. It is assumed that biodegradable anionic flocculants can be used for clarification combined with filtration to remove suspended organics which contributes to bacterial regrowth in the water distribution networks leading to less chlorine consumption and less disinfection by-products in drinking water.

Excretion of a potent macromolecular flocculant by the benthic cyanobacterium was found to bring about the flocculation and subsequent sedimentation of suspended clay particles in a water column [41]. Cationic starch extracts were reported to be an efficient, nontoxic, cost-effective, and widely available flocculants for harvesting the small size and often found in low concentration in the culture medium microalgal biomass, with no addition of chemical flocculants [42]. Also, *Opuntia ficus-indica* mucilage was tested as an eco-friendly flocculants for textile wastewater treatment resulting with a high removal of COD (88.8 %) and turbidity (91.7 %) [43].

Using a bioflocculent composed of 66 % uronic acid and 31 % protein produced by a consortium of two bacteria belonging to the genera *Cobetia* and *Bacillus*, at a dosage of 0.8 mg/mℓ ($mg \cdot mL^{-1}$), pH of 8, and with Ca_2^+ as a coagulant aid, Ugbenyen and Okoh [44] reported 90 % flocculating activity removing turbidity and reducing COD in brewery wastewater, dairy wastewater, and river water. Similarly, a bioflocculant produced by *B. licheniformis* that was applied to treat sugarcane-neutralizing juice to remove colloids, suspended particles, and coloring matters showed clarification values that were almost the same as those acquired following treatment with polyacrylamide (PAM), the most widely applied flocculent in sugar industries [45].

These studies indicate that the utilization of biodegradable flocculants seems to have a great potential for the treatment of water due to their biodegradability and their environmentally inert nature [30]. In water treatment, the application of eco-friendly bioflocculants is assumed to have a high removal capability in terms of solids, turbidity, color, and dye although less effective than the synthetic polyacrylamide-based flocculants, on equivalent dosage basis. A moderate flocculating property and short shelf life restrict their development.

Further research is required to enhance the flocculating ability of natural polysaccharides which derive from plants and microorganisms as was found in the preliminary experiment in which bioflocculants were tested for the pretreatment of seawater prior to desalination using RO membranes, as described in the following.

9.5 Evaluation of a Specific Bioflocculent: Seleno-X

9.5.1 The Product

The use of bioflocculants to destabilize colloidal and particulate matter in seawater was tested using patented bioflocculants (Seleno-X) for the pretreatment of seawater feeding seawater desalination plant. Seleno-X is a bioflocculant which is a patented product produced by Dead Sea Medica Ltd.

Patent: Dead Sea Medica Ltd (2008) Seleno-X. Israel Patent 150346, July 4, 2008
Patent: Dead Sea Medica Ltd (2010) Seleno-X. US Patent 7645389B2, January 10, 2010
Patent: Dead Sea Medica Ltd (2010) Seleno-X. Canadian Patent 2490076, issued August 17, 2011

The product is based on selenium which is found naturally at high concentrations (up to 500 μg/l) (500 mg·L^{-1}) in the Dead Sea springs or artificially synthetized. The base source is used to produce cationic and anionic solutions – Seleno-X/BI and Seleno-X/BII by polymerization adding single or a mix of natural large molecule proteins, such as chitin and polysaccharides from a marine source (cationic solution) and gum, fiber, or cellulose of vegetable origin for the anionic product.

9.5.2 Seleno-X Characteristics

Ingredients: Extracts of bio-source.
Appearance: Transparent liquid or gel.
pH: 7–5.
Aerobic bacteria: <100/g. (100 g^{-1})
Fungi: <100/g. (100 g^{-1})

9.5.3 Activity

Removal of toxic and beneficial floated and suspended particles from municipal, industrial, and agricultural sources.

9.5.4 Regulatory Information

Seleno-X contains no dangerous chemicals and has no adverse effect on human animal or aquatic life. Seleno-X is exempt from licensing under EU directive 93/112/EC, 67/548/EEC, and 88/389/EEC as well as their relevant amendments. The substance is exempted from registration as it is not dangerous and has not been chemically modified according to EU Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) (2006). The product is a biodegradable 100 % natural and food-grade approved for use as a bioflocculent for the treatment of raw water intended for drinking purposes. The product is biological nontoxic compound which is environmentally friendly.

9.5.5 Preliminary Tests

Preliminary tests were undertaken with Seleno-X on artificial suspensions containing particulate matter of inorganic, organic, and biological origin and of positive, negative, and neutral charge (zeta potential) over a range of pH values.

Also, field tests were conducted to test the Seleno-X for the treatment of municipal and agricultural and industrial wastes, including:

- Potato factory – Fritolay Israel
- Oil industry – Syncrude, Alberta, Canada
- Florida municipal water – Everglades polluted water
- Drinking water – Ami'ad, Israel

The preliminary tests indicated that Seleno-X is effective in promoting flocculation, causing colloids and other suspended particles in liquids to aggregate, forming a flock. It was assumed that the substance is suitable for the purification of water substituting the undesirable chemical products.

9.5.6 Pretreatment of Seawater Before RO Desalination

Seawater desalination technology offers the potential to substantially reduce water scarcity by converting the almost inexhaustible supply of seawater into new sources of freshwater. As such, there has been an exponential increase in desalination capacity both globally and nationally, particularly in water-scarce regions, in localities experiencing rapid population growth, or where users are able and willing to pay for a high-quality, reliable new supply [46]. Nowadays, RO technology has become the fastest-growing technology and the most prevalent desalination technology and an affordable solution to cope with the shortage of water in the globe's arid and semiarid regions [47, 48].

9.5.7 Seawater Composition

The separation of salts in the reverse osmosis process is carried out by infiltration of the seawater through thin-film spiral-wound composite membranes which are subject to fouling by the suspended materials present in the seawater. The seawater contains in addition to dissolved salt minerals (calcium, magnesium barium, or strontium sulfates and carbonates) expressed as TDS also microorganisms (bacteria, viruses, protozoan), sand, and clay. Suspended solids are expressed as TSS, turbidity, organic and inorganic complexes, and microalgae. Colloids, natural organic matter (NOM), and humic and fulvic acids are expressed as silt density index (SDI). These particles have to be removed prior to the infiltration process.

The seawater composition includes salts, minerals, and impurities that include mineral nonorganic and organic substance, as given in Table 9.1.

Table 9.1 Seawater composition (1 ppm = 10^{-6})

Temperature		15–30 °C	
pH		8.1	
Total dissolved solids		40,700 ppm	
Total hardness as $CaCO_3$		~7680 ppm	
Alkalinity as $CaCO_3$		~231 ppm	
Turbidity		<5 NTU	
Total suspended solids (TSS)		<20 ppm	
Total organic carbon (TOC)		<1 ppm	
Oil and grease		<0.1 ppm	
Hydrocarbons		<0.1 ppm	
Silt density index (SDI)		~10–80	
Anions		*Cations*	
Chloride (Cl)	22,599 ppm	Sodium (Na)	12,200 ppm
Sulfate (SO_4)	3186 ppm	Potassium (K)	481 ppm
Carbonate (CO_3)	9 ppm	Calcium (Ca)	481 ppm
Bicarbonate ($HCO_{3)}$	162.1 ppm	Magnesium (Mg)	1557 ppm
Nitrate (NO_3)	0 ppm	Boron (B)	≤5.3 ppm
Conductivity in μScm^{-1}		62,000~	

9.5.8 Pretreatment of Seawater

Using RO membranes for desalination of seawater, a precise pretreatment stage is required ahead of the reverse osmosis plant. To avoid fouling and protection of the membranes, the pretreatment stage includes the removal of particles and colloids by coagulation and flocculation using chemical flocculants, flocculant aids, followed by sand filtration or ultrafiltration and fine filtration (5-micron) before the RO membranes. An antiscalant solution is dosed into the filtrate to disperse calcium carbonate and sulfate precipitates before the reverse osmosis membranes in order to avoid scaling.

In general, chlorine-based flocculants is used to enhance the flocculation and sedimentation of suspended particles. A dose ranging between 1 and 6 mg/l (1 and 6 $mg{\cdot}L^{-1}$) of coagulant is injected into the system, and the used coagulants are returned with the filter backwash that is discharged with the brine back to the sea. The spent material could reach upto 1500 ton per annum (1.362 $Mt{\cdot}a^{-1}$) for a desalination plant treating a capacity of 735000 m^3/day (735,000 $m^3{\cdot}d^{-1}$), and in the sea it forms a nonesthetic deep red-brown color mat that disperses over a considerable distance, affecting light penetration and biological productivity, and is a potential eutrophication agent of coastal water. Thus, other pretreatment techniques are highly desirable, taking into account the quality of feed water, local conditions, and economics.

9.5.9 Testing the Bioflocculants: Seleno-X for the Pretreatment of Seawater

In this study, Seleno-X was evaluated for the pretreatment of seawater prior to seawater desalination using reverse osmosis (SWRO) technology.

9.5.10 Objectives

- To expand on previous studies that were mostly conducted at a laboratory and desk scale studies
- To evaluate the effectiveness of Seleno-X for the pretreatment of seawater prior to desalination using reverse osmosis membranes (SWRO)
- To produce filtered water that meets or exceeds the water quality requirements for RO feed

(SWRO membrane manufacturers typically require a turbidity less than one NTU and less and less than 3 SDI.)

9.5.11 Bench-Scale Tests

Coagulation trials were undertaken on a jar tester using cylindrical jars and tested for turbidity and SDI. Samples of 1 l of seawater were mixed with 1, 2, and 4 ppm of Seleno-X, and in parallel, similar seawater samples were treated with chemical flocculants (Fe_2SO_4) at a concentration of 6.5 ppm or left blank and used as control. Mixing involved a 60 s rapid mix stage at 200 rpm followed by a 15 min flocculation stage at 30 rpm and a 15 min settlement period, allowing formation and settling of the flocci. Settled water aliquots were analyzed for NTU and SDI.

The results of the bench scale flocculation tests in terms of turbidity (NTU) and SDI are given in Table 9.2.

In terms of NTU and SDI, the results show that the Bio-Seleno-X yielded comparable levels to those obtained with ferric sulfate. The results indicate that the tested substance is efficient for the removal of impurities, as required for seawater desalination.

9.5.12 Pilot Plant Experiment

Based on the preliminary bench scale test results, a series of experiments were conducted, using a continuous full-scale pilot-scale treatment system having a

Table 9.2 Bench scale turbidity tests of seawater using chemical and bioflocculants

	Control	Fe_2SO_4	Seleno-X		
Dose/ppm (1 ppm = 10^{-6})	0	6.5	1	2	4
Turbidity level (NTU)	(0.7–1.2) 0.89	0.32	0.16	0.14	0.3
SDI (desk experiment)				2.84	
SDI (commercial plant)				2.41	

SDI of less than three is acceptable for SWRO

Photo 9.1 The Pilot Plant (10 m^3/hr) used for the experimen showing the raw seawater pretreatment stage

10 $m^3 \cdot h^{-1}$ capacity. The pilot plant (Photo 9.1) is situated at Ashkelon SWRO Desalination Plant and mimics the pretreatment process of the plant which treats up to 800,000 m^3 of seawater a day, using flocculants and flocculant aids followed by dual-media filtration (DMF) and micronics filtration before the treated seawater is fed into the RO vessels.

The water for the pilot was taken from the same source that feed the commercial full-scale plant, drawing water from a lengthy and wide-constructed sea intake structure that connects to the raw water pump station and to the pipe leading to the pilot plant. The filtration system included a single-stage, dual-media (silica sand and anthracite) filtration system, followed by microfiltration using automatic disk filter batteries, 200 micron to feed the SWRO skid with pretreated filtrate. The skid comprised 7 Filmtec SW30HR LE-400i elements, 40 in. long, 8" in dia. (1.02 m long, 20 cm in diameter), and a surface area of 400 $feet^2$ (37.2 m^2) placed into a high-pressure vessel. The plant has the capability for all operations including start-up, normal operations, and shutdown, automatically sequenced and controlled by a master control panel.

9.5.13 Results of the Pilot Plant Experiments

Raw seawater was pumped through the plant at 10 $m^3 \cdot h^{-1}$, and a fresh solution of coagulants was pumped into the coagulation tank using peristaltic pumps. Ferric chloride was used to coagulate. The feed water was mixed in the rapid mix stage at

200 rpm at a contact time of 20 min. The coagulated water was then mixed at 5 rpm in the flocculator tanks with a combined contact time of 24 min. The treated water then went on to the filter column operating at 8 m h^{-1}. The plant was run in continuous operation for 15–30 h, and the performance was continuously monitored, recording run time (hours), coagulant dosage ($mg \cdot L^{-1}$), permeate flow, DP, filtrate turbidity, and SDI.

9.5.14 Pilot Plant Performance Results

Test n°1

Date: January 29, 2009, to January 31, 2009. Total filtration time, 79 h06
Flocculants' dosing: Seleno-X – 2 ppm for 17 h of filtration
Flocculation activation: frequency, 40 Hz; contact time, 20mn

Test n°2

Date: February 1,2009, to February 4, 2009. Total filtration time, 80 hr.
Flocculant's dosing: Seleno-X – 2 ppm
Flocculation activation: frequency, 40 Hz; contact time, 20mn

9.5.15 Results

The continuous operation of the pilot plant using a bioflocculants resulted in a good removal of turbidity from the initial level of about 4 NTU to a level ranging between 1.5 and 2 NTU. Similarly, the SDI level was reduced from above four to about three throughout the duration of the test (Fig. 9.1).

9.5.16 Comparison with the Commercial Plant Performance

The performance of the pilot plant was compared with the performance of the commercial plant in relation to the removal of turbidity and impurities and filtration efficiency (filter head loss). The results of several tests, using different doses as compared to the commercial plant DSI levels after DMF and microfiltration are summarized in Table 9.3 and illustrated in Fig. 9.2. Table 9.3 has been changed to Table 9.2. Please check.No. There sre 2 tables ahead of Table 3, so table 3 is correct

The DSI values measured at the commercial plant after DMF and micronic filtration using chemical flocculent were found to range between 3–2.8 after DMF and 2.25–2.5 after micronic filtration, as compared to the SDI value of 3.8 which was obtained at the pilot experiment, as shown in Fig. 9.2.

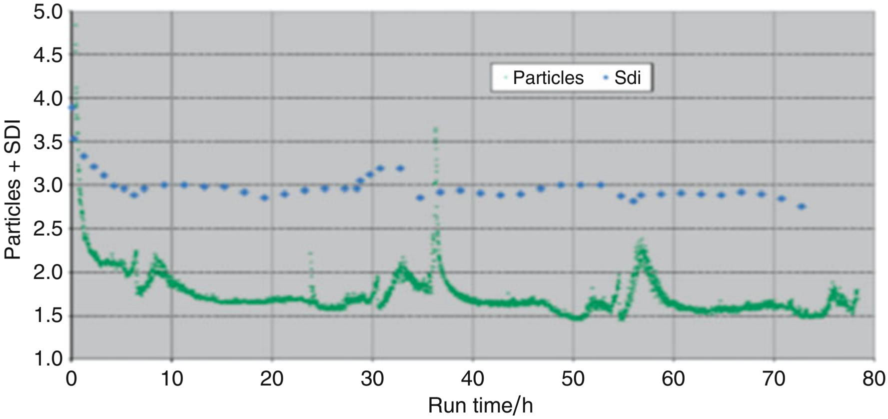

Fig. 9.1 Pilot plant bioflocculant performance: reduction of turbidity and SDI levels

Table 9.3 Commercial plant and pilot plant SDI results, using chemical and bioflocculants (1 ppm = 10^{-6})

Run date	Seleno-X dose (ppm)	Chemical dose (ppm)	SDI level		
			Pilot	Commercial plant	
				After DMF	After micronic filtration
1. 29/1	2	0	3.8		2.5
2. 1/2	2	0	3.4		2.5
3. 4/2	1	1	4	2.8	2.25
4. 24/2	1	0.2	3.8	3	2.5

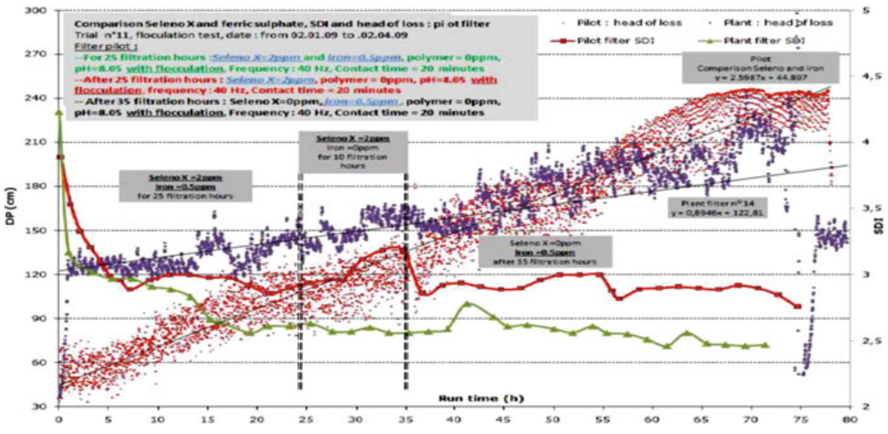

Fig. 9.2 SDI level and filter head loss of the pilot plant vs. the commercial plant

The figure shows clearly the higher performance of the chemical flocculent in terms of SDI (green line) as compared to the bioflocculent (red line), although the resulting SDI levels and the filtration efficiency (doted lines) are both satisfactory.

9.5.17 Result Summary

The results indicate that the pretreatment using the bioflocculant is capable of treating raw seawater to a quality that meets the predetermined water quality standards. But the results are inconclusive and the performance of the bioflocculants is slightly inferior to ferric sulfate. The results are indicative to the likely potential for substituting chemical flocculants with the bioflocculants. Additional tests are required to verify fully the advantages of the bioflocculants in general and for the pretreatment of seawater in particular.

9.5.18 The Use of Bioflocculent for Flocculation of Filter Backwash Water

Seleno-X was tested for the coagulation-flocculation of the DMF backwash which is rich with spent chemical flocculent (ferric sulfate). The addition of 5–10 mL of a 2 ppm Seleno-X solution to a 500 mL of filter backwash resulted with a formation of large floc and good and fast settling of the suspended material. A very clear permeate was obtained after paper filtration, as shown in Photo 9.2.

9.6 Discussion and Conclusions

The technological and future challenges in using biodegradable materials as a substitute to chlorinated chemicals to a wide range of applications, together with potential solutions, were discussed in general and in water treatment in particular.

Photo 9.2 DMF backwash water before and after dosing of bioflocculants and after filtration

The conventional low molecular weight, such as ferric sulfate, alum, other inorganic aluminum polycation salts, and other charged polymers (polyelectrolytes) which serve as coagulants, dramatically increase the settling rate of particles in treated water allowing effective separation and sedimentation of suspended materials. However, while the application of chemical additives has gained worldwide commercial success, their widespread use and failure to degrade rapidly may lead to environmental pollution.

To avoid substances that persist indefinitely in the environment or in landfill, it is desirable to replace them with those that are designed to degrade after use. The alternative is to use novel natural flocculants which are produced from biodegradable and renewable resources which are readily available. Bio-based polymers have shown enormous growth in recent years in terms of technological developments and their commercial applications, as recently discussed by Babu et al. [32] who reviewed recent trends, developments, and future applications of biodegradable flocculants.

Nowadays, bio-based polymers are commonly found in many applications from commodity to hi-tech applications due to advancement in biotechnologies and public awareness. As such, they are closer to the reality of replacing conventional polymers because of their possible applications in a large number of processes. In the water sector, the bioflocculants provide endless potential applications to purify water for domestic, industrial, and agricultural purposes, provided that their flocculation performances and efficacies are demonstrated to be good enough for a range of particulate matter found in aqueous suspensions.

However, despite these advancements, there are still some drawbacks that need to be addressed, especially the performance, efficiency, and competitive cost which prevent the wider commercialization of bio-based polymers in many applications [49]. When compared with conventional chemical compounds, the performance remains a significant challenge for bio-based polymers, as was also demonstrated in this study. The preliminary tests, as reported herewith, reflect the suitability of the biodegradable product for water treatment and indicated that these products would likely attract a wide interest. Thus, the commercial application of biodegradable and environmentally safe products is only a matter of time. Although, additional tests are still required in order to establish the effectiveness of these compounds for the pretreatment of water and wastewater.

A real progress in this issue will contribute to the reduction in the use of chlorine, making redundant the need for expensive treatment of spent materials.

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Part V
Alternatives: *Polymers*

Chapter 10
A Green Method for Potentially Recycling Condensation Polymers: Ring-Chain Recycling

Philip Hodge

Abstract This article discusses the synthesis of a range of condensation polymers by the relatively new method of entropically driven ring-opening polymerization (ED-ROP), a green method of polymer synthesis that has considerable commercial potential. It also discusses the synthesis of the required macrocyclic starting materials by the cyclodepolymerization (CDP) of the same condensation polymers. Both reactions are based on ring-chain equilibria (RCE), the latter being the classical equilibria that can exist between a condensation polymer and the corresponding family of macrocyclic oligomers. Taken together, ED-ROP and CDP form the basis of a potential new method for recycling certain condensation polymers, a method we refer to as "ring-chain recycling" (RCR). Some of the problems that need to be addressed to make the overall process commercially more attractive are discussed.

Keywords Ring-chain recycling • Ring-chain equilibria • Entropically driven ring-opening polymerization • Cyclodepolymerization • Ring-closing depolymerization

10.1 Introduction

The use of polymers in everyday life has increased dramatically in the last 50–60 years, and it has become increasingly important to consider how to synthesize and recycle them in an environmentally friendly manner. Commercially important polymers have been prepared by vinyl polymerization (e.g., polystyrene and various methacrylate polymers), by ring-opening polymerization of *strained* cyclic compounds (e.g., poly-ε-caprolactone and nylon-6), and by condensation polymerization (e.g., aromatic polyesters and high-performance polymers). This article discusses the synthesis of a range of condensation polymers by entropically driven ring-opening polymerization (ED-ROP), a novel green method that has considerable commercial

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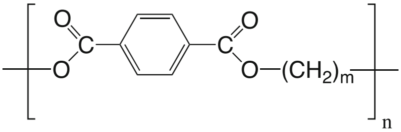
potential, and then the synthesis of the macrocyclic compounds which are the required starting materials for ED-ROP. Indeed, the macrocycles can be obtained by the cyclodepolymerization (CDP), otherwise known as ring-closing depolymerization, of the same condensation polymers. Clearly taken together, ED-ROP and CDP have the potential to form the basis of a method for recycling certain condensation polymers, a process we refer to as “ring-chain recycling” (RCR). “Thermodynamic recycling” of *small strained* cyclics has been discussed before by Höcker et al. [1], but RCR via *large strainless* rings has not. RCR increases considerably the scope for chemically recycling polymers.

$$-\!\!\left[(CH_2)_mCO_2\right]_n\!\!-$$

(**1**) : m = 10

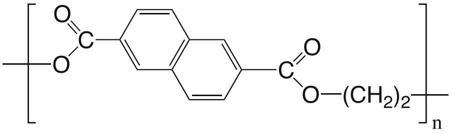
(**2**) : m = 15



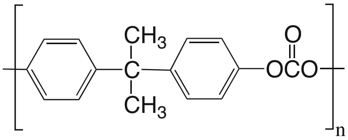
(**3**) : m = 2, PET

(**4**) : m = 4, PBT

(**5**) : m = 3, PTT



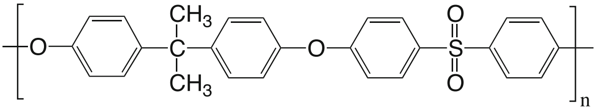
(**6**, PEN)



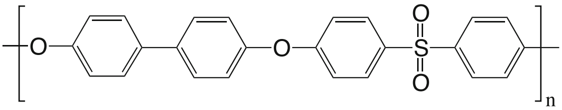
(**7**)

$$-\!\!\left[(CH_2)_6O\text{-}CO\text{-}O\right]_x\!\!-$$

(**8**)



(**9**, Udel™)



(**10**, Radel™)

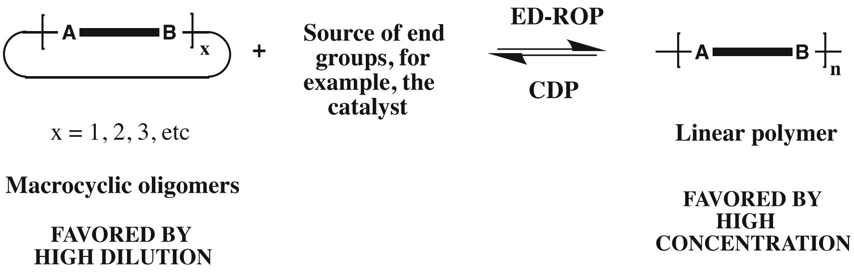
Chart 10.1 Structures of the polymers discussed in this chapter

The structures of the 10 polymers this article focuses on are shown in Chart 10.1. These include polyundecanoate (**1**), polypentadecanolactone (**2**), poly(ethylene terephthalate) (PET, **3**), poly(butylene terephthalate) (PBT, **4**), poly(trimethylene terephthalate) (PTT, **5**), poly(ethylene naphthalene-2, 6-dicarboxylate) (PEN, **6**), poly(bisphenol A carbonate) (**7**), poly(hexamethylene carbonate) (**8**), and polyethersulfones **9** and **10** (Udel$^{\text{TM}}$ and Radel$^{\text{TM}}$ respectively).

There are several important general points to bear in mind about polymer recycling [2]. First, in many cases, the polymeric materials will need to be collected, sorted into the different polymer types, cleaned (e.g., washed, labels and/or paint removed, etc.), and then broken down mechanically into more easily handled smaller pieces before processing can begin [2]. Then, there is the question of whether to use physical recycling or chemical recycling. In the former approach, appropriate fragments of the spent polymeric material are incorporated into new materials [2]. An example is the physical recovery of poly(vinyl chloride) (PVC) and mechanically processing the recovered material into new components [3]. In other cases, chemical recycling is more appropriate. An example is the reaction of poly(ethylene terephthalate) (**3**) with methanol to give dimethyl terephthalate and glycol [4]. These latter chemicals can then be used to prepare fresh polymer or used as starting materials for other applications. This chapter is concerned with chemical recycling.

10.2 Ring-Chain Equilibria

Both ED-ROP and CDP are based on ring-chain equilibria (RCE). These are the equilibria that can exist, under suitable reaction conditions, between a condensation polymer and the corresponding *family* of homologous macrocyclic oligomers (MCOs): see Scheme 10.1 [5, 6]. The MCOs can be analyzed easily by size-exclusion chromatography (SEC), using stationary phases specifically designed for the analysis of relatively small molecules, and by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI ToF MS) [7, 8]. Such analyses show that most of the family of MCOs present in an RCE



Scheme 10.1 A generalized ring-chain equilibrium

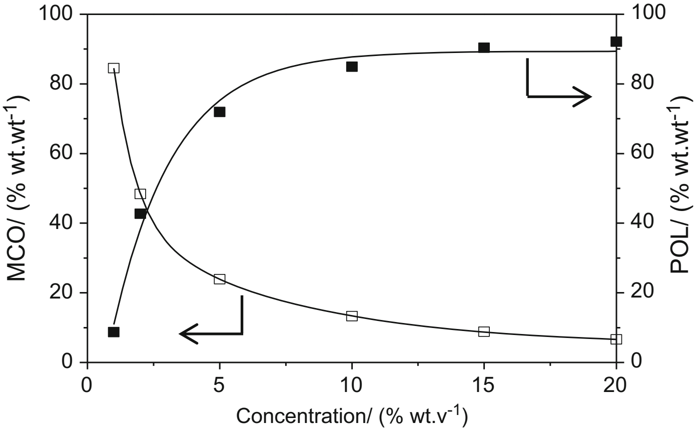


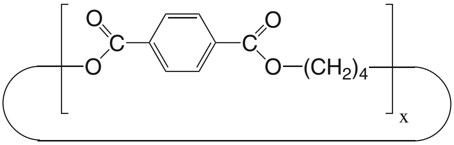
Fig. 10.1 Proportions of MCOs **11** (☐) and polymer **4** (■) obtained experimentally as a function of initial polymer concentration in the RCE of poly(butylene terephthalate) (**4**) (Reproduced with permission from Ref. [11])

have ring sizes ranging from *ca*. 14 ring atoms up to more than 100 ring atoms. The cyclics are, therefore, generally *strainless*.

RCE have been of *theoretical* interest for many years [5, 6], a major topic of interest being the proportions of the MCOs present in a family. According to the theory of Jacobson and Stockmayer [5], if the MCOs are *strainless* and full equilibration has been achieved, the amount of each cyclic oligomer present is predicted to decrease proportionally to $n^{-2.5}$, where n is the number of repeat units present [5].

Recently RCE have also become of practical interest because they provide a simple means to interconvert macrocycles and polymers and also because the position of the equilibria depends greatly on the concentration [9, 10]. The latter is because ED-ROP involves bimolecular reactions, i.e., reactions between MCOs and "reactive end groups," while CDP is a unimolecular reaction: see Scheme 10.1. The "reactive end groups" may actually be part of the catalyst. Thus, at *high concentrations the RCE lie heavily in favor of the polymer*, while at *low concentrations the RCE lie heavily in favor of the MCOs*. Figure 10.1 shows the proportions of polymer **4** and MCOs **11** as a function of concentration determined experimentally for the RCE of poly(butylene terephthalate) (**4**) [11]. It is clear that at high concentrations, ideally neat conditions, they lie heavily in favor of the polymer (as exploited in ED-ROP), while at concentrations $< 2\,\%$ w/v, the equilibria lie heavily on the side of the MCOs (as exploited in CDP). At intermediate concentrations, significant amounts of both the MCOs and the polymer are present. The key point is that the composition at equilibrium can be controlled simply by adjusting the concentration.

Linear oligomers are not usually formed to any significant extent in CDPs because their formation requires the availability of many “end groups” and usually few are present in the CDP reaction mixture. Indeed, under ideal CDP conditions, the only “end groups” present in the system are those derived from the starting linear polymer and, possibly, from the catalyst.



x = 2, 3, 4, 5, ... etc

(**11**)

Full equilibration may not always be achieved during the reaction period, especially for ED-ROPs. For example, during an ED-ROP the reverse (CDP) reaction in Scheme 10.1 might be slow to become fully established. This might be the case, for example, with certain enzyme-catalyzed reactions where the polymer might have some difficulty binding to the active site of the enzyme. In such cases, polymer is nevertheless formed in high yield but, in the limit, by a kinetically controlled process. The amounts of each oligomer present in a kinetically controlled CDP are predicted to decrease proportionally to $n^{-1.5}$ [12].

Clearly the combination of ED-ROP and CDP has the potential to be a means of recycling certain condensation polymers, a process we label RCR. A similar type of recycling called “thermodynamic recycling” has been discussed by Höcker [1]. This involves depolymerization to give volatile *strained* cyclics, such as 5–7-membered rings containing a heteroatom. The cyclics can then be repolymerized, generally by *enthalpically* driven processes [1].

In this article, we first consider the synthesis of polymers **1–10** by ED-ROP and some potential applications of this method of synthesis and then move on to the synthesis of the required MCO starting materials by CDP of the same polymers. Finally, the combination of the two types of reaction is considered.

10.3 Entropically Driven Ring-Opening Polymerization

This section focuses on how polymers **1–10** (shown in Chart 10.1), and some closely related polymers, may be prepared in high yield using ED-ROPs. It is, therefore, not comprehensive. A more comprehensive review of ED-ROPs has been published recently [9].

10.3.1 Some General Points

ED-ROPs are achieved by taking an individual MCO, or an homologous family of MCOs, at high concentration and establishing the RCE. Due to the high concentration, polymer is formed in high yield. Generally about 2 % of MCOs remain (see Fig. 10.1 for a specific example), but, since in most cases these are much more soluble than the corresponding polymer, the polymeric product can be isolated, if necessary, simply by precipitating the final equilibrated mixture into an appropriate nonsolvent for the polymer.

ED-ROPs have many attractive features [9]. These include the fact that such polymerizations are generally green. Thus, the polymerization takes place without the release of any small molecules, and, since most if not all of the MCOs are strainless, little or no heat is generated. Furthermore, as it is necessary to have high concentrations of the MCO(s), it is often convenient to carry out the polymerizations without solvent. It should be noted, however, that if full equilibration is to be achieved, there must be some molecular mobility in the system and this even needs to be the case when the mixture consists of $> 90\,\%$ polymer. Hence, with a neat reaction mixture, even if only relatively briefly, the polymerization temperature should exceed the T_g of the product and most probably also the T_m. This explains why many ED-ROPs are carried out at relatively high temperatures, for example, > 300 °C. Provided the RCE is fully established, the dispersity of the product is expected to be 2.0, that is, the same as that expected for all classical step-growth polymerizations.

To obtain linear polymers, it is clearly necessary to have a source of end groups: see Scheme 10.1. These may come from the catalyst itself, traces of linear oligomers or similar species present in the reaction mixture, or adventitious compounds, for example, water. The number of end groups present in the ED-ROP can have a major impact on the molecular weights of the polymeric products, and if very few end groups are present as, for example, in an entropically driven ring-opening *metathesis* polymerization (ED-ROMP) where no olefinic compounds other than the catalyst, MCO(s), and polymer are present, very high molecular weights may be obtained [13].

10.3.2 Synthesis of Polyesters by ED-ROPs

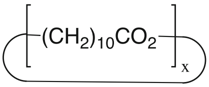
Many polyesters have been prepared by ED-ROP [9]. The reactions generally proceed via transesterifications, and various compounds of tin, titanium, bismuth, antimony, or aluminum have been used as catalysts [9]. Such catalysts are generally considered to be environmentally friendly, but a long-term goal is to replace the metal-containing catalysts by enzymes or to avoid altogether the need for a catalyst (see later).

Table 10.1 Comparison of some physical properties of polymer **2** and LLDPE[a]

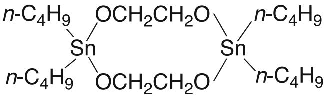
Polymer **2**	LLDPE
Soft, flexible	Soft, flexible
t_m *ca.* 100 °C	t_m 100–115 °C
t_g *ca.* – 30 °C	t_g – 120 °C
% Cryst 50–70	%Cryst 40–60
Elongation at break (%) *ca.* 700	Elongation at break (%) *ca.* 800

[a] Data taken from Ref. [21]

A simple example of an ED-ROP is the synthesis of polyundecanoate (**1**) [14]. When a film of MCOs **12** plus a catalytic amount of distannoxane **13** was cast on a microscope slide and the film heated to 170 °C for 4 h, polymerization occurred and a self-standing polymeric film was formed. The polymer had M_n 46,200 and M_w 81,600.



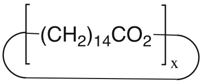
(12)



(13)

In a separate project with polyundecanoate (**1**), the mixture of MCOs **12** was subjected to careful column chromatography. This afforded pure samples of each of the cyclic dimer, trimer, tetramer, and pentamer [15]. All these MCOs in toluene at 70 °C polymerized well when treated with commercially available polymer-supported *Candida antarctica* lipase B (PS-CALB). The successful polymerization of the cyclic pentamer indicates that the lipase can ring-open 60-membered lactones [15].

The ED-ROP of pentadecanolactone (**14**) has been studied many times [16–18]. In part this is because the monomer is widely available for use in the odorant industry but also because polypentadecanolactone (**2**) is almost certainly biodegradable. Furthermore, the polymeric product **2** is sometimes considered to be a potential green alternative to polyethylene as many of the physical properties of the two polymers are similar [16, 19, 20]. Table 10.1 compares some physical properties of **2** and linear low-density polyethylene (LLDPE) [21]. An excellent catalyst for the polymerization of **14** is the aluminum-salen complex **15** [18]. Using this catalyst in toluene solution at 100 °C for 4 h, polymer **2** was obtained with M_n 100,000 and M_w 240,000 [18]. The polymerization can also be catalyzed by polymer-supported *Candida antarctica* lipase B (PS-CALB) [36]. Thus, treatment of a solution of the lactone **14** in toluene at 70 °C with PS-CALB for 4 h gave polymer in an isolated yield of 93 % with M_n 64,500 and M_w 129,000 [19]. Copolymers of **14** and trimethylene carbonate were also prepared using PS-CALB (see later) [22].



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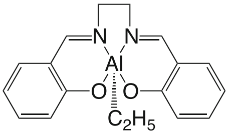
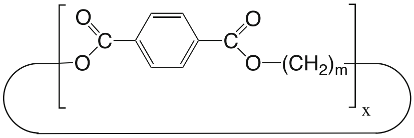


(15)

The synthesis of aromatic polyesters by ED-ROP is less straightforward than the synthesis of aliphatic esters in that the MCOs used for the former generally have higher melting points and lower solubilities than the latter, as do the polymeric products. Moreover, the products can crystallize rapidly, thus limiting diffusion of unreacted MCOs and other reactants in the reaction mixture, especially toward the end of the polymerization. Many metal-containing catalysts are very effective, but unfortunately, to date, no enzymes have been found that react well with aromatic esters.

Many ED-ROPs that produce aromatic polyesters of commercial importance have been studied. For example, poly(butylene terephthalate) (**4**) has been prepared by ED-ROP [11, 23–25]. MacKnight's research team looked at this polymerization in some detail [25]. Using MCOs **11** without solvent and *n*-butyltin chloride dihydroxide as the catalyst at 205 °C for several minutes, polymer **4** was obtained in 97 % yield with M_n 50,010 and M_w 130,030. Poly(trimethylene terephthalate) (**5**) has been prepared by treating the mixture of MCOs **16** with a catalytic amount of di-*n*-butyltin oxide at 300 °C for 2 h [8, 26]. The product had M_v 22,500.

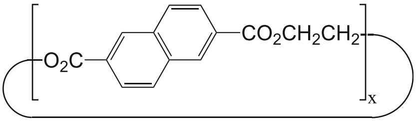
The syntheses of poly(ethylene terephthalate) (**3**) and poly(ethylene naphthalene-2,6-dicarboxylate) (**6**) by ED-ROP are less straightforward than those of **4** and **5** due to the poor solubilities of some of the MCOs and their relatively high melting points, but they are nevertheless commercially important polymers. The synthesis of poly(ethylene terephthalate) (**3**) in particular has been much studied [8, 9, 27–29]. For this ED-ROP, the mixture of MCOs **17** is much more satisfactory than an individual pure MCO [27, 28]. Antimony oxide and bismuth oxide in the presence of "a source of end groups" are satisfactory catalysts [28, 29]. For example, use of antimony oxide at 293 °C for 15 min in the presence of moisture gave polymer **3** with M_n 25,300 [28].



x = 2, 3, 4, 5, ... etc

(**16**) : m = 3

(**17**) : m = 2

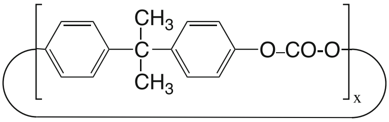


(18)

Poly(ethylene naphthalene-2,6-dicarboxylate) (**6**) has been obtained by ED-ROP by treating neat MCOs **18** with catalyst **13** at 280 °C for 60 min [30]. The polymer obtained had an inherent viscosity of 0.55 (as a 0.1 % solution in trifluoroacetic acid). After washing out the smaller molecules with chloroform (5 % weight loss), the viscosity increased to 0.73.

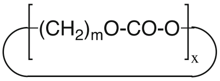
10.3.3 Synthesis of Polycarbonates by ED-ROPs

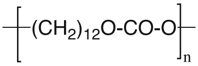
The preparation and ED-ROP of MCOs **19** to give the commercially very important polycarbonate **7** has been much studied by Brunelle's group at General Electric [31, 32]. In favorable cases, reaction times for the polymerizations carried out at 300 °C were 30 min, and the M_ws obtained were as high as 280,000. This approach has been extended to using bisphenols other than bisphenol A as starting materials, bisphenols that incorporate ether, amide, ester, urethane ether ketone, or sulfone groups [32].



(**19**)

Several aliphatic polycarbonates have been prepared by ED-ROPs. There are two particularly interesting points here. First, the ED-ROP can often be carried out simply by heating the neat MCOs to *ca.* 230 °C, i.e., *no catalyst is needed* [8]. This is obviously very attractive from an environmental point of view. As an example, heating MCOs **20** at 230 °C for 4 h gave polymer **8** in 98 % yield with M_n 15,000 and M_w 28,700 [8]. Second, the ED-ROPs can often be catalyzed, using temperatures below *ca.* 100 °C, by lipase enzymes [33]. For example, treating 26-membered macrocycle **21** in toluene solution at 75 °C for 48 h with PS-CALB gave polymer **22** in 98 % conversion with M_n 49,800 and M_w 76,690.





(**22**)

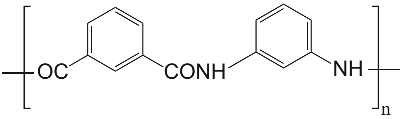
(**20**) : m = 6

(**21**) : m= 10; x = 2

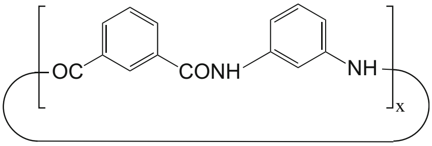
10.3.4 Synthesis of Polyamides and Polyurethanes by ED-ROPs Proceeding via Transamidations

Compared with polyesters and polycarbonates, relatively few polyamides or polyurethanes have been synthesized by ED-ROP. This is not surprising given the relatively low reactivity of amide and urethane linkages, and the high melting points of amide MCOs and the polymers produced.

Polyamide **23** (Nomex^{TM}) is one of the few polyamides that has been studied [34]. This is because it is commercially important, and, as the aromatic rings are *meta*-substituted, both the MCOs **24** and the polymer are more soluble than most. The aim in the ED-ROPs is to generate a nucleophilic N-center to react with an amide carbonyl group and so promote transamidation. Heating MCOs **24** (m.p. 400–440 °C) with a catalytic amount of sodium hydride to 430 °C gave a tough cross-linked polymeric product [34]. However, when a solution of MCOs **24** in dimethyl sulfoxide (8 % w/v), containing 8 % of calcium chloride to increase solubility [35], was heated and stirred at 170 °C for 6 h with a catalytic amount of sodium hydride, polymer **23** was obtained in 88 % yield with Mn 23,200 and Mw 46,000 [34].FORMULAE NUMBERS **23**, **24**, **25** AND **26** BELOW SHOULD BE IN BOLD FONT.



(23) : Nomex^{TM}



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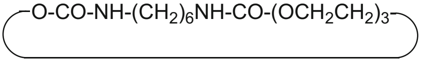

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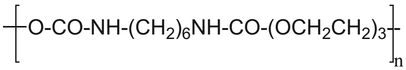


$\left[\text{O-CO-NH-(CH}_2\text{)}_6\text{NH-CO-(OCH}_2\text{CH}_2\text{)}_3\right]_n$

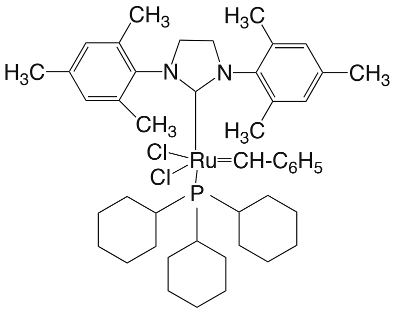
(26)

An example of polyurethane synthesis using ED-ROP is the polymerization of MCOs **25** by treatment with tetra-*n*-butylammonium tetrafluoroborate (TBATPB) at 230 °C for 6 h [36]. This gave polymer **26** with M_n 7500 and M_w 36,300. Thus, the dispersity index was significantly > 2.00. The latter suggests that the catalyst did not mix well with the neat cyclic monomer and that there were several sites where polymerization and/or side reactions were occurring. Any side reactions did, however, not lead to cross-linking as the products were easily dissolved in N, N-dimethylacetamide.

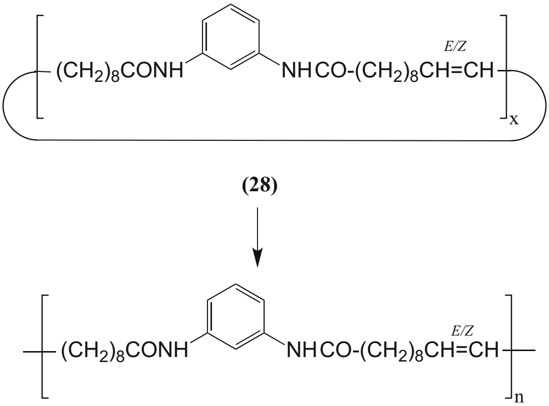
10.3.5 Polymer Synthesis by ED-ROPs Using Olefin Metathesis

Olefin metathesis is an area of interest not because commercial condensation polymers usually contain olefinic linkages but because of the potential future uses of olefin metathesis. It is a rapidly developing area, and it already has several attractive features in connection with the present topic. For example, the amounts of catalyst required can be very small, the reactions often proceed very rapidly under relatively mild conditions, metathesis catalysts are tolerant of many functional groups, and there are usually few side reactions.

ED-ROP, or more precisely in the present context ED-ROMP, of olefin-containing MCOs using the commercially available Grubbs catalyst **27** can, if no adventitious olefins are present, afford products with high molecular weights [13, 37]. With unsymmetrical olefins, the polymeric products are, of course, expected to contain repeat units in head-to-head, head-to-tail, and tail-to-tail arrangements. The following three examples illustrate these various points. First, the ED-ROMP of MCOs **28** in tetrahydrofuran with catalyst **27** and a reaction time of 24 h at 56 °C gave polymer **29** in 70 % yield with an M_n 15,300 and M_w 31,200 [38]. This polyamide synthesis is certainly a much easier synthesis by an ED-ROP than one proceeding via transamidation [34]. Second, the ED-ROMP of MCOs **30** in tetrahydrofuran with catalyst **27**, a reaction time of 20 h at 56 °C gave polymer **31** in 75 % yield with an M_n 16,100 and M_w 31,500 [38]. This provides a synthesis of polyether copolymer **26** via ED-ROP. Otherwise syntheses of polyethers by ED-ROP are very difficult as there is no linkage that can be easily and reversibly broken. Third, the ED-ROMP of macrocycle **32** in dichloromethane with catalyst **22**, a reaction time of 3 h at 20 °C gave polymer **33** in 99 % yield with an M_n 146,000 and M_w 273,500. This demonstrates that the reactions can be fast under mild conditions and that they can give very high molecular weights [13].

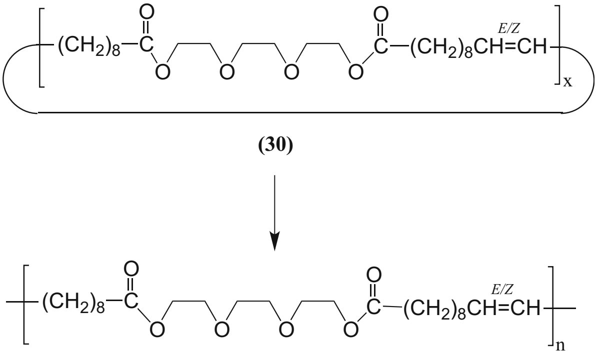


(**27**)



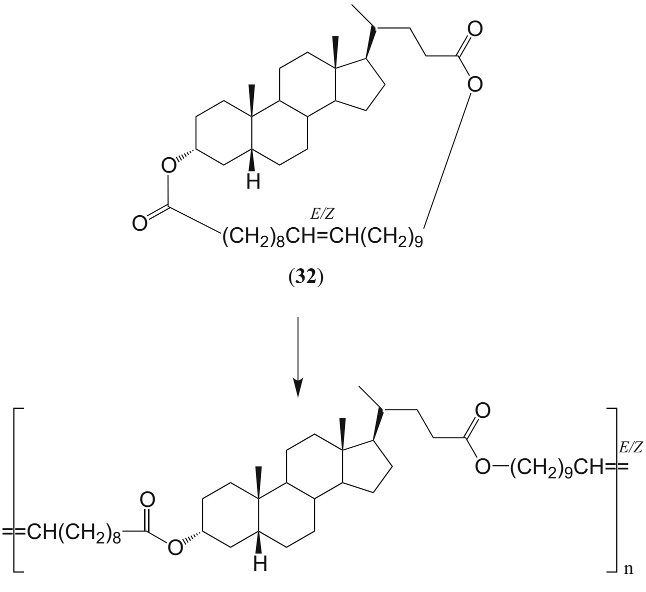
(28)

(29)



(30)

(31)

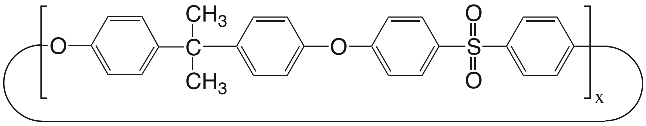


(32)

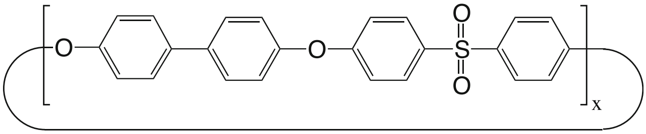
(33)

10.3.6 Synthesis of High-Performance Aromatic Polymers by ED-ROPs

Many ED-ROPs that give high-performance aromatic polymers involve aromatic ether-ketones, ether-sulfones, thioether-ketones, or thioether-sulfones. The reactions taking place are concerned with aromatic ether or thioether residues that are activated for nucleophilic aromatic substitution by the presence of ketone, sulfone, or other strongly electron-withdrawing groups in *para*-positions. Typical catalysts are alkali metal fluoride, chloride, or phenoxide salts [39]. Gibson's research team has compared the properties of the various catalysts [39]. A typical example is the ED-ROP of MCOs **34**. The reaction was carried out using the potassium salt of *para*-phenylphenoxide at 330 °C for 30 min. This gave polymer **9** (trade name Udel^{TM}) in essentially quantitative yield with M_n 26,000 and M_w 100,000. Polymer **10** (trade name Radel^{TM}) with M_n 29,500 and M_w 76,500 has been prepared similarly [40].



(**34**)

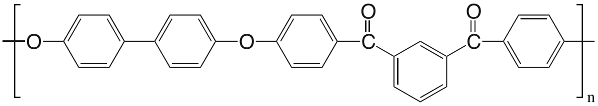


(**35**)

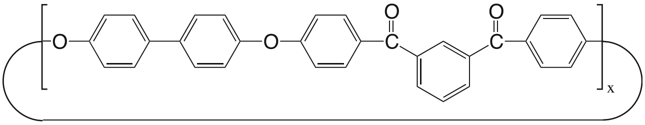
10.4 Some Applications of ED-ROPs

The novel features of ED-ROPs lead to several possible applications beyond simple recycling. As no small molecules are evolved during an ED-ROP and they are essentially thermally neutral, they are particularly suitable, for example, for reaction injection molding (RIM), for the application of coatings, and the preparation of composites [24, 41]. Thus, voids are not created in the products by the release of small volatile compounds, and temperature control of the reaction is relatively straightforward. Furthermore, the MCOs generally have significantly lower melt viscosities than the corresponding polymers so making it easier for them to penetrate into the finer recesses of the mold or network. The lower melt viscosities have been quantitatively demonstrated for ester-containing MCOs **11** [11], **16** [11], and **17** [11, 26] and aromatic sulfone MCOs **35** [42]. Mixtures of MCOs and polymer also have reduced melt viscosities, and the presence of 10–20 % of MCOs in a polymer can significantly reduce the melt viscosity [42]. Once in place, the MCOs are subjected to in situ ED-ROPs. Lower viscosities can also help processing [11].

The attractive features of ED-ROP noted above have been exploited to prepare many composites [24, 41, 43]. A simple example comes from the preparation of a composite of high-performance polymer **36** and a 150 μm mesh woven stainless steel cloth [43]. When the cloth and polymer were heated together (306 °C), the polymer and mesh did not interpenetrate significantly, but when the macrocyclic trimer **37**: $x = 3$ and 1 wt % of cesium fluoride were heated similarly in the presence of the steel cloth, the hot MCO flowed rapidly into the mesh, so that when ED-ROP occurred, the mesh became fully embedded in the polymer.



(**36**)



(**37**)

To gain an indication as to how small a pore the MCOs can penetrate attempts were made to mold microfibrils or tubes of polymer **10** in the pores of 0.1 μm (nominal pore size) alumina filters [44]. In these studies, after the polymer is formed in the pores of the filter, the alumina is dissolved away with alkali to leave the polymeric material. The ED-ROP of MCOs **35** gave tubes of high-performance aromatic polymer **10** that were 300 nm in diameter, while with the cyclic trimer **35**: $x = 3$, it gave 200–400 nm fibrils [44]. Thus, it is certainly possible to obtain very detailed features in high-performance polymer moldings using ED-ROP.

Another attraction of ED-ROPs is that the MCOs automatically have within each molecule the correct stoichiometry of repeat units needed to form the polymer. This means the polymerizations can be carried out on a small scale and so are ideal for high-throughput syntheses and, by mixing MCOs, the synthesis of polymer libraries. Libraries with up to 10 polymers have been prepared this way [23, 45].

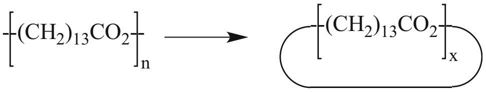
10.5 Cyclodepolymerization

This section focuses mainly on the CDP of polymers **1**–**10**, the syntheses of which were discussed above. CDPs have recently been reviewed comprehensively [8, 9].

There are two main ways of achieving CDPs. In one, which is very simple, an equilibrating RCE is established and one or more volatile MCOs is distilled out. As macrocycles are removed, more are formed as the RCE reestablishes. This approach obviously provides mainly macrocyclic monomers and/or dimers, and it is relatively easy to scale it up. However, it is of limited utility because few MCOs are sufficiently volatile.

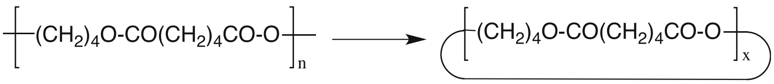
In the second, and more generally useful, way, the RCE is established starting with a *dilute* solution of the polymer: see Scheme 10.1. Under these conditions, when the RCE is reached, it lies heavily on the side of the MCOs. This latter method is widely used on a laboratory scale, but, as currently practiced, it needs large volumes of solvent and, usually, long reaction times.

Polyesters, especially aliphatic polyesters, are some of the most readily cyclodepolymerized polymers, and many such reactions have been studied. Indeed, as long ago as the 1930s, Spanagel and Carothers prepared more than 35 macrocyclic lactones in crude yields of 30–85 % by distilling out MCOs from equilibrating RCE [46, 47]. A typical example involves heating poly(14-hydroxytetradecanoate) (**38**) with magnesium chloride hexahydrate at 270 °C/1 mm pressure for 3.5 h and then distilling out the MCOs **39** (77 % yield). The distillate consisted of cyclic monomer (90 %) and cyclic dimer (6 %) [47]. On the other hand, using the high dilution approach, the CDP of polyundecanoate (**1**) was achieved by heating a 2 % w/v solution of the polymer in chlorobenzene at *ca.* 133 °C for 8 h with a catalytic amount of di-*n*-butyltin di-*n*-butoxide [14]. This gave the family of MCOs **12** in 90 % yield with the value of "*x*" ranging from 1 to > 8 [14]. Many other aliphatic polyesters react similarly [14]. These include the CDP of poly(pentadecanolactone) (**2**). When a 2 % w/v solution of the polymer in chlorobenzene was heated at *ca.* 133 °C for 6 h with a catalytic amount of di-*n*-butyltin di-*n*-butoxide, MCOs **14** were formed in 95 % yield [48].



(38) (39)

An interesting point about many of these aliphatic polyesters is that the CDPs can be catalyzed by lipase enzymes [49, 50]. Indeed Matsumara's research team suggested certain aliphatic polyesters could actually be recycled via enzyme-catalyzed RCE [50]. Furthermore, some such reactions have been carried out successfully in a flow system, for example, by passing a solution of the polymer **40** through a bed of commercial PS-CALB [50]. The product was MCOs **41**.



(40) **(41)**

The CDPs of several commercially important aromatic polyesters have been studied. These include poly(ethylene terephthalate) (**3**) [4, 51], poly(butylene terephthalate) (**4**) [7, 45], poly(trimethylene terephthalate) (**5**) [26, 45], and poly (ethylene naphthalene-2,6-dicarboxylate) (**6**) [30]. The CDP of poly(trimethylene terephthalate) (**5**) is typical [26]. This was carried out using a 1 % w/v solution of the polymer in 1,2-dichlorobenzene at *ca.* 180 °C with di-*n*-butyltin oxide (3 mol%) as catalyst. The reaction time was 72 h. The cooled reaction mixture was filtered to remove unreacted polymer and the solvent evaporated off. This gave MCOs **16** in 94 % yield of which 82 % was the cyclic dimer.

CDP of polycarbonate **7** in 1,2-dichlorobenzene at *ca.* 180 °C for 5 days using TBATPB as a catalyst gives MCOs **19** in high yield [8]. TBATPB also serves as a catalyst for the CDP of polymer **8** to give carbonate-containing MCOs **20**, but with these aliphatic polymers, a reaction time of only 3 days is required [8].

Aliphatic polycarbonates undergo *thermal* CDP relatively easily, and in general, a catalyst is not needed [8, 52]. In the 1930s, Carothers prepared more than a dozen macrocyclic carbonates by the thermal CDP of polycarbonates: the yields were not usually reported [52]. Since then, however, many aliphatic carbonate-containing MCOs have been prepared by first synthesizing a carbonate polymer from an α,ω-diol and, for example, diethyl carbonate, and then subjecting the polymer to thermal CDP. MCOs **20** and **21** have been prepared this way [53].

Many olefin-containing polymers have been subjected to CDP usually using Grubbs Second Generation catalyst **27** [37, 38]. The RCE are rapidly established. Olefin-containing MCOs prepared by CDP are **28** and **30** [38].

Many high-performance aromatic polymers have been successfully subjected to CDP. The reactions are generally based on nucleophilic aromatic substitution reactions, and the catalyst is either fluoride anion or a phenolate anion. The CDP of polymer **10** (Radel$^{\mathrm{TM}}$) is typical [40]. The reaction was achieved by treating polymer **10** in N,N-dimethylacetamide at 165 °C for 72 h with a catalytic amount of cesium fluoride. The yield of MCOs **35** was approximately 90 % with “*x*” ranging from 2 to $>$ 10 [28]. MCOs **34** have been prepared similarly from polymer **9** [54].

10.6 Recycling by the Combination of CDP and ED-ROP

It is clear from the above discussion that polymers **1–10** can be prepared efficiently by ED-ROP and also that the required MCOs can be obtained by CDP of the same polymers. Thus, RCR is a possibility for these polymers. This section discusses some of the problems that need to be solved in this area.

The ED-ROP reaction generally works well and is green in that no small molecules are released and in many cases no solvent is required. Scaling up is expected to be relatively straightforward. The MCOs could be used alone to generate new polymer (see applications in Sect. 10.4) or added into a standard condensation polymerization. An example of the latter is the successful incorporation of MCOs **34** into the reaction between bisphenol A and

4,4’-dichlorodiphenylsulfone, in the presence of base, to prepare polymer **9** [55]. The same technique could be used to prepare copolymers, by, for example, adding MCOs **35**.

The major obstacle to RCR is improving the CDP reaction. If a CDP just involves distilling cyclic monomer and/or dimer from an equilibrating RCE, scaling up is expected to be relatively straightforward. However, if a high dilution CDP is necessary, as it is in most cases where the MCOs are relatively involatile, for example, where they include aromatic rings, scaling up is more problematic. Such CDPs need a much more detailed investigation than hitherto in order to optimize the procedure.

At present there are essentially two significant problems with high dilution CDPs. The first problem is that relatively large volumes of solvent are usually required. One potential solution is to carry out the CDPs continuously and separate the MCOs from the reaction mixtures by means of, for example, size-selective membranes. Thus, with this approach, the formation of $>95\,\%$ MCOs may not be necessary. Starting with a significantly more concentrated solution of the polymer than usual such that at equilibrium there is, say, 20–30 % of MCOs present, see Fig. 10.1, may form the basis of a practical process. Clearly a membrane that is compatible with organic solvents, preferably at elevated temperatures, is required. A second possible solution based on the fact the presence of 10–20 % of MCOs in a polymer can significantly reduce the melt viscosity may mean that in some circumstances, the CDP reaction of the recycled polymer may only need to be carried out so as to produce this mixture directly. This would allow the CDP to be carried out at higher concentrations, that is, it would require less reaction solvent. Thirdly, a possible solution is to carry out the CDP in a flow system. As noted above, CDPs have been carried out successfully in flow systems before, and in one case, it has been claimed that less solvent is required than in a conventional high dilution CDP [49, 50]. Using a flow system requires an insoluble catalyst that can be packed into columns [50].

The second problem of high dilution CDPs is the long reaction times. This in part is a consequence of the low concentrations used, and the reaction times may extend into days. Solvents that allow higher reaction temperatures and/or better polymer solubilities would help. Ionic liquids may be helpful [56]. In the case of CDPs involving olefin metathesis, reaction times can, however, be just a few hours at modest temperatures [37, 38]. This suggests that in other systems, a major reason for the long reaction time is relatively poor catalyst activity. Better catalysts are needed [57], preferably organic catalysts and/or catalysts that can be used in larger amounts without causing separation problems. Polymer-supported catalysts, or clay- or silica-supported catalysts, may simplify the removal of the catalyst from the MCOs.

Another possible improvement in the processes is, where possible, to avoid the use of catalysts altogether. It is already clear that aliphatic polycarbonates undergo CDP simply by raising the temperature to *ca.* 230 °C, and similarly aliphatic macrocyclic carbonates undergo ED-ROPs just by heating [8]. Also various ED-ROPs can be carried out simply by heating aromatics MCOs containing *para*-thioketones groups [58]. In both cases, only a few such groups per polymer chain, say 5 %, may be needed.

10.7 Conclusions

Classical RCE can potentially be exploited to chemically recycle certain condensation polymers. Thus, the polymer can be prepared by ED-ROP and the required MCOs prepared by CDP of the polymer. The ED-ROPs generally work well and can probably be scaled up without major problems, but while CDPs can often be carried out in high yield, more work needs to be done to optimize many CDPs, in particular to reduce the need for large volumes of solvents and/or long reaction times. Suggestions are made for achieving this. ED-ROPs have various potential other applications, as in RIM and the synthesis of composites, and the starting MCOs for these applications may also be obtained by CDP.

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Chapter 11
Polymers Beyond Chlorine

A. Muzafarov

Abstract Chlorine is an important catching reagent used in polymer chemistry, as well as various other areas of organic and inorganic chemistry. The abundance of simple methods to substantially alter polymer characteristics by adding chlorine has resulted in increasing interest in obtaining and utilizing new chlorine-containing polymers. Chlorine processes are used on a large scale not only to produce chlorine-containing polymer compounds but also in the intermediate stages of polymer synthesis. However, chlorine-containing solvents used for the production of polymers represent a dangerous and poorly controlled threat to the environment. Cheap, incombustible and volatile, these freons are close to being prohibited by law in many countries due to the degree of their negative environmental impact. A large sector of important polymer materials – silicones – is based on the so-called chloric cycle, which involves an addition of chlorine to a silicon atom at the first stage, and then removal of chlorine during the process of producing silicones. It has been shown that eliminating the need for chlorine-containing compounds in this sector is very challenging, but achievable.

Keywords Alkoxysilanes • Polyorganosiloxanes • Silicones • Polycondensation • Direct synthesis • Chlorine-free process • Composite polymer materials • Environmental friendly materials

11.1 The Use of Chlorine in Polymer Composition

At present, humans are surrounded by artificial materials, which are, in general, polymers with various different structures and compositions. Over the last two centuries, polymer chemistry has made it possible to produce a diverse range of macromolecules, which meet various requirements of industry, medicine, daily

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tasks, etc. Nowadays, the aims of this field appear to be changing, moving towards the modification of both monomeric and polymeric compounds, and to the modification of methods of synthesis to create environmentally friendly, non-toxic, cheap, and recyclable materials with optimized consumer properties. This goal is probably more challenging than the original problem of designing new polymers.

The present paper is focused on one method of modernizing the chemical sector – the creation of a chlorine-free chemical industry. Unfortunately, extensively used materials and manufacturing technologies often employ such aggressive elements as chlorine. Along with actual chlorine-containing materials, other halogen-substituted polymers (e.g., fluorine-containing) are used. However, the prevalence of these other halogens is not comparable with that of industrial chlorine derivatives of polymers. The high prevalence of chlorine can be explained by the broad spectrum of beneficial consumer properties which chlorinated polymers possess, such as incombustibility, high firmness, oil, gasoline, heat and ozone proofing, influence on corrosive media, tolerance to microorganisms, high adhesion to various substrates, gas impermeability, etc. At present, the global large-scale polymer industry produces huge quantities of haloid modified polymers, such as polyvinylchloride (nearly 7 million tons (6.355 Mt) yearly in the USA, with only polyolefine being a more produced polymer), polyvinylidene chloride and its copolymers (nearly 9000 tons (8.17 kt) in Europe alone), chlorinated rubber, and polyesters of chlorostearic acid, which possesses superb mechanical properties and are widely used for various purposes. Polychloromethylstyrene (polyvinylbenzylchloride), polyepichlorohydrin, and so-called oxetane resin, a polymer based on bis-(chloromethyl)-oxacyanobutane, are utilized as plastics. Chloromethylated cross-linked copolymers of styrene with divinylbenzene or other cross-linking agents are used for the production of ion-exchange resins and polymer catalysts. Large quantities of chloroprene rubber, widely employed for various rubber technical-items (electrical insulation, wires, cable shells, convey or bands, drive belts, hoses, diving suits, engineering plates, and diverse protective coatings) are also produced. Adhesives made from chloroprene rubber and chloroprene latex are critical from an industrial perspective. Chlorine thermoplastic materials used in electrical technology and electronics (Fluoroplast-3 and -30) also contain chlorine. Moreover, the monomer used in their synthesis, trifluorochloroethylene, is toxic and highly explosive in mixtures with air.

Despite of all consumer advantages offered by chlorinated polymers, they also possess serious ecological and toxicological disadvantages. Even at the stage of polymer modification, difficult and dangerous "dissolving" technology, in which a polymer is dissolved in an organic solvent and gaseous chlorine runs through the solution, is applied. Every possible improvement to the technologies described above consists of the replacement of gaseous chlorine by chlorine-containing organic compounds, which unfortunately does not make the processes more environmentally acceptable.

Highly undesirable processes may also occur during the use of chlorinated polymer materials. Particularly dangerous is the detachment of chlorine ions and likely formation of HCl. The magnitude of the C-Cl bond energy is lower than the C-H bond energy, so chlorine-containing polymers eliminate HCl easily at relatively low temperatures. The dissociation of chlorine-containing compounds is the object of numerous investigations. Nevertheless, the mechanism of dehydrochlorination has not been fully elucidated. Dehydrochlorination of chlorine-containing compounds behaves randomly; first, a molecule of HCl departs from a location which is unstable due to certain structural anomalies. Such weak spots are double bonds at the ends of macromolecules, generated as a result of disproportionation in a polymerization process, as well as tertiary chlorides at the branching points. Hydrogen chloride released during the destruction of chlorine-containing polymers negatively affects their properties and catalyzes further dehydrochlorination processes. For example, widely used polyvinyl chloride (PVC) polymers have relatively low resistance to light and thermal exposure. Under the influence of these factors, dehydrochlorination and oxidative destruction of PVC plastics tend to occur. It is clear that linoleum, which is employed as floor-covering in buildings, among other polymer items, should not release toxic compounds, and a lot of research deals with the stabilization of such chlorine-containing polymers [1]. This stabilization could be achieved with the help of compounds able to: (1) add hydrogen chloride; (2) react with compounds containing unsaturated bonds; (3) work as antioxidants; and (4) reflect ultraviolet rays. The ability to add hydrogen chloride seems to be the most important of the above characteristics, because unabsorbed hydrogen chloride increases the rate of destruction due to its autocatalytic effect. This situation, of course, improves with the application of various expensive additives. However, the use of such materials in close contact with humans is not considered to be ecologically friendly.

Nevertheless, the most dangerous aspect of the use of chlorinated polymer materials is their combustibility. Linoleum, expensive self-adhesive and easily washable wallpapers, synthetic carpet strips and floorings, leatherette, synthetic clothes, unlicensed imported soft and plastic toys, electric cable shells, and some kinds of polymer wrapping can become serious hazards when combusted. When this occurs, a wide range of highly toxic chemicals and even toxic agents are formed within them. Synthetic carpet strips alone release up to 100 kinds of toxic compounds, such as phosgene, cyan hydric acid, and cyanogen chloride. If combustion takes place at temperatures lower than 1100 °C, chlorine-containing polymers convert to chlorinated polyaromatic hydrocarbons, including such highly toxic and carcinogenic compounds as dioxins and dibenzofuranes. Burning PVC plastic at 600 °C within sufficient oxygen provides an ideal situation for the formation of diverse dioxins. Under the same conditions small amounts of carbonyl chloride, commonly known as phosgene, could be formed. These constitute only a few of the gasses released during the combustion of PVC – no less than 75 potentially toxic gases could potentially be released [2]. According to foreign statistical data, more than half of the victims poisoned by gaseous products of combustion die almost immediately. Forty-two percent of surviving victims are severely poisoned, and one-third of them die in hospitals without regaining consciousness.

Although some advanced technologies exist for their cycling of PVC waste, the quality of the collection and sorting of this waste is not adequate for the scale of production. This means that, as of yet, a problem still remains that requires diverse solutions. Firstly, it is necessary to find a new field of use for PVC which retains the unique, effective technologies of its manufacture, but which does not necessitate close contact with humans. Searches for applications of PVC outside of everyday life have identified finishing and wrapping materials of mining operations as a viable option, e.g., unrecoverable construction elements or polymer parts of drilling soil could constitute the main way to solve this problem. The mineral environment would provide an additional guarantee of neutralization of active chlorine-containing components. Decomposition of PVC would proceed more rapidly, and harmful active compounds would react with the mineral environment.

11.2 The Use of Chlorine-Containing Solvents in Polymer Manufacturing Processes

In addition to various polymer materials, chlorine is often present in common solvents, such as tetrachloromethane, dichloroethane, tetrachloroethylene, chlorobenzene, and the less popular dichlorodiethyl ether. These compounds are extremely toxic, i.e., they stimulate the growth of specific cells, making them carcinogenic. At high temperatures, molecules of chlorine-containing organic solvents decompose releasing aggressive HCl molecules. Methylene chloride, trichloroethylene, and tetrachloromethane decompose and release hydrogen chloride even under solar UV-ray exposure. Chlorobenzene is extremely toxic, as well. At temperatures higher than 110 °C and in open flames, chloro-substituted hydrocarbons decompose, releasing phosgene.

However, chlorine-containing organic solvents possess a high dissolving capacity and low combustibility. This is that leads to their broad spectrum of applications: dry purification, degreasing of surfaces under various conditions, grain fumigation, and processing of textile materials. Chlorine-containing organic solvents are present in glues, soaps, dyes, oils, and silicones, as well. Chlorinated solvents are utilized regularly in various sectors of industry, including the railroad, military, automotive and aircraft sectors, as well as in the production of electronics, semiconductors, electric motors, shoes, etc. Chlorinated solvents are also widely used as household chemicals and chemicals for the maintenance of septic tanks. The quantity of solvents of this kind produced is enormous, e.g., as much as 1 million tons of dichloromethane, tetrachloromethane, and trichloroethane are produced in the USA alone.

Herein, we consider only one field of their application – as a solvent used for polymer synthesis. The use of tetrachloromethane, chloroform, or chlorobenzene as a part of the synthesis of chlorinated rubber through chlorination of natural or synthetic rubber in a chlorinated solvent medium is one of the oldest (developed in 1859) methods available, but it is still widely employed. In the process diluted (nearly 20 %) solutions are utilized; therefore, the involved solvent is quite expensive. Such solutions are used not only because of their high dissolving capacity but also due to the absence of additive processes with an active reagent, i.e., chlorine, with which the solution is saturated. Currently, there are some available emulsion technologies employed to obtain such compounds in an aqueous medium [3]; however, older technologies are widely used too, especially for obtaining lacquers, enamels, etc. In addition, the formation of chlorinated polyolefines (polyethylene and polypropylene) is still performed in a chloroform solution. Due to the large quantity involved in the manufacturing processes above, the amount of chlorinated solvents used is high. Polymerization in solution is frequently performed if the end product will be utilized in the form of a solution, e.g., lacquers, glues and bindings, or if other methods do not allow products with the required structure to be obtained, which is the case for polyvinyl acetate. The syntheses of various types of rubber (e.g., butyl rubber, butadiene-styrene rubber), high-density polyethylene, polypropylene, and polyisobutylene are also performed in solution. Chlorinated solvents, such as tetrachloromethane, are employed as solvents for the anionic polymerization of cycloolefines. Cationic polymerization of isoprene with catalysts, such as aluminum chloride, is performed in a chloroform solution, which makes it possible to obtain the trans-isomer of polyisoprene with a 90 % yield. Chloroprenes are polymerized in chlorinated solvents in the presence of Lewis acids. The increased rate and degree of polymerization under the influence of some chlorinated solvents suggest that they are fairly effective cocatalysts [4].

Reducing the consumption of chlorine-containing solvents is a difficult and multifaceted task. Wider use of supercritical CO_2, ionic liquids, and emulsion processes, as mentioned above, could constitute some feasible methods of solving this problem.

11.3 The Use of Chlorine-Containing Functional Groups

Chlorine is used in polymer chemistry and functional group chemistry, in both the formation of polymer chains and polymer analogous conversions. The activation of C-Cl bond in condensation reactions is employed particularly often during large-scale manufacture. For example, nylon, discovered in 1938 and widely used in various fields, is produced by polycondensation of dichloroanhydride and diamines. A broad spectrum of industrial polyamide polymers is also produced. However, large quantities of hydrogen chloride form during the synthesis, which incurs substantial cost. The synthesis of polysulfide elastomers, for example, is more efficient, because the sodium chloride byproduct formed is much easier to use. However, the chlorine-containing monomer is not volatile, and therefore is less aggressive in both of the above processes, meaning that industrial manufacture using dangerous reagents, such as phosgene, still occurs. For instance, one of the methods of synthesizing polycarbonates consists of polycondensation of the disodium salt of diphenyl carbonate (“A-Bisphenol”) with phosgene, which is performed in a chlorinated solvent medium. Phosgene is often employed as a reagent during the production of polymers and initial compounds, despite its obvious toxicity and risks associated with its use. The manufacture of various diisocyanates, i.e., initial compounds for producing industrial polyurethanes, uses phosgene. For instance, one way of obtaining polyurea consists of the interaction of diamines with phosgene. However, this is not the only alternative to the use of volatile toxic chlorinated monomers. For example, methylcellulose, widely used in the food industry and elsewhere, is obtained from methylation of natural cellulose by methyl chloride. High-heat stable polyphenylene sulfones, commonly used in the electronic, electrotechnical, automotive, and engineering industries, are produced from dichlorobenzene or dichlorodiphenyl sulfone through nucleophilic polycondensation with disodium salts or through homopolycondensation of monosulfochlorides.

What can be done for transition to non-chlorine polymer chemistry without sacrificing useful characteristics of materials? How can PVC, the second most commonly sold plastic, be changed while maintaining its low cost and versatility? It seems that finding a method that is very affordable and which provides such a diverse set of polymer structural properties may be impossible. Therefore, due to the negative characteristics mentioned above and the problems that must be overcome, it will be necessary to identify multiple alternatives for the different polymer functions, with each providing some definite properties.

The creation of hybrid materials is one of the most common approaches to the design of materials to replace mass polymers, during the production of which chlorine is generally used. This involves the formation of polymer composite materials, in which inorganic filler plays a more significant and deliberate role. By analyzing the unique characteristics of chlorine-containing polymers one by one, various approaches to yield properties analogous to non-chlorine polymer systems could be identified.

Incombustibility constitutes one of the most critical features of chlorine-containing polymers. To obtain this property, it is necessary to use macromolecules whose bond energy is higher than the carbon-carbon bond energy of an alternative polymer matrix. The presence of $C=O$, O-H, $P=O$, $S=O$, $C=N$, Si-O, $B=N$, or $P=N$ bonds in polymers decreases their combustibility. Adding aromatic rings to polymers raises their oxygen index. Polyesters with aromatic groups, such as polyketones, polycarbonates, and polyethyleneterephtalates, are the most promising candidates for further development in the area of reducing the production of highly toxic compounds during combustion. If polyolefines are relatively combustible, polycarbonates, in contrast, can be ignited only if the concentration of oxygen is higher than the atmospheric concentration (oxygen index of 26 %). Simple changes in their cycling conditions of such polymers make it possible to attenuate their tendency to ignite effectively even over open flames, by adding fire retardants, inorganic fillers, or metal nanoparticles into the composition of the polymer [5]. However, while these approaches exist, they have yet to be developed and advanced to the level of applicable technologies.

Replacements for harmful chlorine-containing compounds also tend to be fire-retardants. Efficient and ecologically safe systems are thus developed in conjunction. As such, adding mineral fillers (metal oxides, silicates, inorganic glass, powdery metals, etc.), stable up to temperatures as high as 1000 °C, to polymers is efficient. Hydroxides, carbonates, and hydrocarbonates of metals constitute other kinds of fillers; although they are not as heat-stable, they decompose with heat absorption, releasing aqueous vapor or carbon dioxide. Phosphorous and its compounds are among the most effective inhibitors of burning and smoldering processes for various polymers. Recently, not only low-molecular but polymer phosphorous-containing fire-retardants have been applied as well.

Through utilizing inorganic fillers, classic composite polymer materials with a range of beneficial qualities are obtained. It then becomes possible to improve both the thermal stability and mechanical characteristics of polymers through the consolidation of the properties of inorganic matrix (lightness, flexibility, plasticity) and inorganic materials (firmness, heat endurance, chemical stability). Thus, adding modified lamellar materials to a polymer matrix causes changes in: (1) mechanical properties, such as tensile, compression, bending, and breaking strength; (2) barrier properties, such as penetrability and resistance to solvents; (3) optical properties; and (4) other properties. In addition, fire and shock resistance are improved, and there is almost no increase in the weight of the polymer. The creation of nanocomposites using inorganic fillers, primarily silicate, metals, nanoclays, and nanocarbons produces positive effects. Carbon nanotubes and fullerenes are able to significantly improve the mechanical qualities of materials, to increase their electrical and thermal conductivity, and to confer new functional properties on nanocomposites. A large body of research on this subject points to the prospect of such materials and, at the same time, to the challenges of their creation, such as the probability of dispersion and immobilization of fractions inside the matrix, the necessity of preventing aggregation of nanoparticles during exploitation, etc. However, this pathway of creating ecological and high-tech polymer materials seems to be the most promising.

11.4 Chlorine-Free Manufacture of Silicones – Approaching Future Technologies

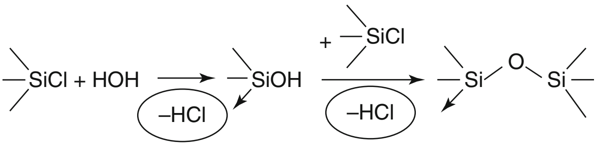
Silicones are some of the most promising candidates for the construction of alternative polymer systems. As mentioned above, it is necessary to create hybrid materials as an alternative to universal chlorine-containing polymers. Silicones are irreplaceable in the production of such hybrid materials. For example, it is well known that many fundamental modern life sectors (semiconductors and computer technology, aircraft and space instruments that run at extremely high and low temperatures, modern medical equipment, as well as everyday devices) could not exist without organosilicone polymers. Nevertheless, this branch of chemistry does not satisfy current requirements due to the high ecological impact of the processes associated with the manufacture, exploitation, and use of silicone polymers. Indeed, is it a proper alternative, given that it is based on the so-called chloric cycle, which consists of the addition of chlorine to a silicon atom during the direct synthesis process, with further release of chlorine in the course of silicone synthesis?

Silicon is a starting material for the production of silicones. In turn, silica and sand, practically in exhaustible raw materials, are sources of silicon. The scope of organosilicone manufacture is not comparable with that of organic polymer manufacture, but it is large and increasing. At present, as mentioned previously, the process of conversion of silicon from sand to a functional monomer consists of obtaining chlorosilane by direct synthesis with further removal of chlorine when transitioning to siloxane or carbosilane products. The deliverance of processes for obtaining silicones from the “chloric cycle” will, of course, cause a significant decrease in ecological load, as well as reduce the costs of the processes, given that the “chloric cycle” uses expensive and aggressive medium-resistant equipment, and involves expensive recovery of toxic waste.

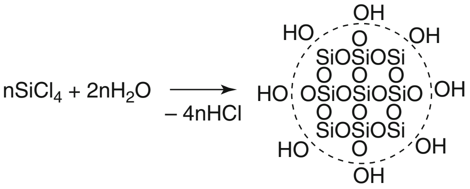
The processing of sand into a polymer consists of the following sequence: obtaining organochlorosilanes, hydrolysis of Si-Cl groups, which releases a lot of hydrogen chloride, and condensation of the newly formed hydroxyl groups, which results in the formation of a siloxane bond:

$$SiO_2 \longrightarrow Si \longrightarrow SiCl_4 \longrightarrow R_nSiCl_{4-n} \longrightarrow \text{-}[SiR_nO_{4-n}]\text{-}$$

Homo- or heterofunctional condensation will prevail depending on the pH, type, and amount of solvent used [6, 7].



The product obtained does not have a high molecular weight and consists of cyclic and linear macromolecules [8], which are predisposed to catalytic regrouping [9]. Hydrolytic polycondensation of mixtures of various organochlorosilanes followed by catalytic regrouping generates resins and lacquers, whose properties depend on the presence and ratio of M, D, T, and Q units in their structure [10].



Another manufacturing process, the production of fumed silica (silica with a particle size of 5–20 nm), exhibits similar imperfections due to the use of chlorosilanes. This type of silica, which is essential for various fields of industry, originates from silicon tetrachloride. At the time of the formation of one SiO_2 group, four chlorine ions, which require collection and utilization, are obtained.

Thus, almost all-global manufacture of silicones is based on the use of chlorinated derivatives of silicon. Initially, silicon is converted into chlorofunctional silanes, and then chlorine is removed when various siloxane structures are built. It is well known, however, that this scheme is technologically complicated, power-intensive, and environmentally unfriendly. Replacing chlorosilanes with another initial compounds and removing chlorine from the cycle would make the process more “green”:

$$SiO_2 \longrightarrow Si \longrightarrow R_nSi(OR')_{4-n} \longrightarrow \text{-}[SiR_nO_{4-n}]\text{-}$$

The transition of metal silicon to a functional silane by direct synthesis without chlorine participation is an essential part of new non-chlorine technologies. Although it is generally accepted that this is possible, no effective technological process has yet been developed.

There are a considerable number of studies related to the direct synthesis of alkoxysilanes through their action between metal silicon and alcohol in the presence of catalysts [11].

$$Si + ROH \xrightarrow{cat} Si(OR)_4 + HSi(OR)_3 + H_2$$

The liquid-phase process in boiling solvent [12] in which silicon conversion is up to 95 % is the most studied potential process. Nanosize particles of copper-containing compounds are efficient as catalysts [13]. Obtaining alkoxysiloxanes by processing a mixture of silicon, alcohol, and copper catalyst in the presence of microwave or radio-frequency radiation [14] is also a potential alternative. Various methods for the purification and activation of initial compounds and reagents, such as preliminary treatment and removal of air traces from the silicon surface in inert gas media or in vacuo with treatment by hydrin [15], are particularly considered in modern patents related to the direct synthesis of alkoxysiloxanes. Our investigations of liquid-phase process show encouraging results too. We have found out that there was no induction period, which does not correspond to the literary data. As methanol had been introduced the gas (mainly, hydrogen) evolution started immediately. The process is quite stationary (Table) [16].

Solvent	t/°C	Alcohol	Si conversion, %	Selectivity for $HSi(OMe)_3$/%
THERMINOL 66	270	Methanol	52	96
Oil		Methanol	60	94

These methods are sufficiently expensive in terms of using high-boiling solvents like TERMINOL; however, the selectivity of producing of trimethoxysilane is good enough (up to 95 %). Our good result is that less expensive oil exhibits the same conversion and selectivity.

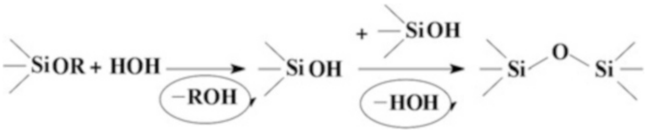
These methods are fairly expensive, as they use high-boiling solvents, such as TERMINOL; however, selectivity for the production of trimethoxysilane is adequate to justify the related expense (up to 95 %). On the other hand, the relationships between reaction rate, conversion of silicon, and reactor volume are not favorable. Specifically, there main products of high-temperature processes are dense, hardly convertible, and require difficult methods of purification. The fact that the addition of alkylhalides is used to improve the selectivity of the process [17] is disadvantageous, as well.

It has been suggested that processes occurring in the gaseous phase will not possess the above disadvantages. The amount of research devoted to gaseous phase direct synthesis is significantly smaller than that focused on liquid phase processes. The first description of processes for the production of alkoxysiloxanes in the gaseous phase [18] states that it results in both low selectivity of the processes and low conversion of silicon. Nevertheless, more successful applications of such methods are now known. The process of the interaction between metal silicon and alcohols (up to four carbon atoms) in the gas phase in vacuo has been achieved with selectivity to trimethoxy- and triethoxysilanes of up to 84 % [19]. The process of the interaction between metal silicon and alcohols in an aerated stratum has also been presented. The reaction can be processed at normal pressure (which is less expensive) or low pressure. High selectivity for trimethoxysilane (up to 98 % in the case of methoxy-groups, and up to 94.5 % in the case of ethoxy-substitutes) was achieved under 660 torr pressure. At present, processes at high pressures are being researched. It should be noted that in the case of a process with a high selectivity towards tetraalkoxysilane, it is possible to get the more applicable alkylalkoxysilane by the reaction [20]:

$$Si(OCH_3)_4 + C \xrightarrow{CH_3ONa} (CH_3)_nSi(OCH_3)_{4-n}$$

Overall, the technology for an initial step towards non-chlorine syntheses of polyorganosiloxane polymers is still not satisfactory, although similar technologies dealing with tri- and tetraalkoxysilanes are efficient.

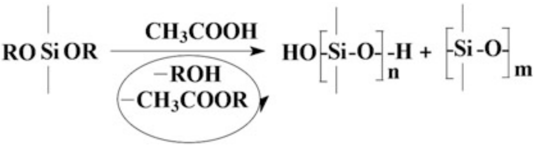
The conversion of alkoxy-functional organosilane monomers to various polymer products has required much exploratory effort. Organoalkoxysilanes are less reactive than chlorosilanes, and their hydrolysis and polycondensation reactions possess some peculiarities. In 1937, Soviet scientist Andrianov observed the ability of alkyl- and arylalkoxysilanes to convert into polymer organosilicon compounds as a result of hydrolysis, which leads to the synthesis of principally new macromolecules with only distant similarities to natural polymers. From the end of the 1930s onwards, he published a number of papers describing the hydrolysis of organoalkoxysilanes followed by condensation of the newly formed silanol-groups.



The peculiarity of this process is the role of water. In the first stage, water is injected as a reagent; in the second stage, water is released as a product of polycondensation. The additional water plays the role of reagent. In the process, all injected water will transform gradually to oxygen atoms in siloxane bonds. This allows the length of organosiloxane chains to be regulated by varying the ratio of initial reagents. These organosiloxanes were actually preceded by organosilicone polymers – siloxane chains framed by organic groups. However, after Rochow [21] created an effective way to produce organochlorosilanes by direct synthesis, these compounds became more affordable monomers than organoalkoxysilanes, which led to the creation of a silicone industry based on chlorosilanes. This is why research into hydrolytic polycondensation of organochlorosilanes and methods to obtain organosilicic products from organochlorosilanes excluded similar processes using alkoxysilanes for decades. Nevertheless, alkoxysilane chemistry is again a field that is attracting intense interest.

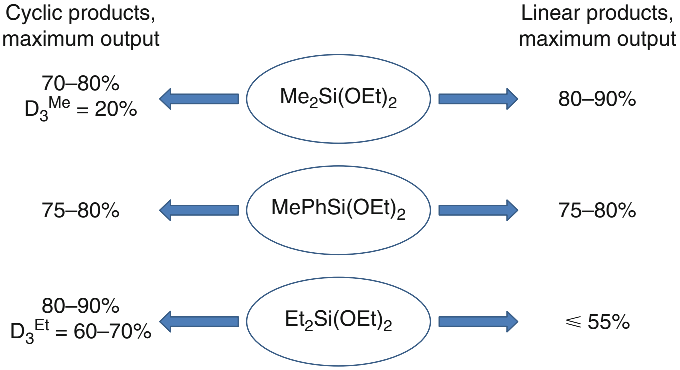
Ecological compatibility and the absence of the formation of hydrogen chloride, which is able to catalyze functional condensation of formed silanols and split the siloxane bond, disturbing the regulation of formed structures, constitute the main advantages of using alkoxysilanes instead of chlorosilanes. Furthermore, alkoxysilanes are more resistant to humidity than chlorosilanes, because alkoxy groups are less susceptible to hydrolysis. Due to the decreasing rate of hydrolysis in the case of alkoxysilanes, the behavior of hydrolytic polycondensation is less active. Alcohol, released because of the hydrolysis of alkoxysilanes, dilutes the reagents and products of the reaction. Due to the above conditions, hydrolytic polycondensation of organoalkoxysilanes is determined to be more effective to obtain polymers with the desired structure and characteristics.

The hydrolysis of organoalkoxysilanes has long been researched [22, 23]. It has been shown that when water is placed in the reaction mixture in the early stages, the process will be heterogeneous. Then, the process will become homogeneous, and an increase in temperature will lead to an increased hydrolysis reaction rate and to an increased rate of condensation of hydroxyl groups, i.e., to a greater fraction of higher molecular products. A number of published works have been devoted to the investigation of polycondensation of organoalkoxysilanes, that leads to the development of new and, in our opinion, successful technologies for the production of organosiloxane polymers. These processes take place in non-aqueous acetic acid media, in which acid participates as both reagent and solvent.



The process can be presented as a set of correlated reactions: acidolysis, hydrolysis, and condensation. The use of current methods does not require the additional injection of water, homogenizing solvents, or catalysts. Water, necessary for hydrolysis, is formed as a result of the etherification of acetic acid with alcohol which, in turn, is formed because of acidolysis of alkoxysilyl groups, and it is consumed *in situ*, not forming a separate phase. The results obtained make it possible to consider this method as an alternative to producing polyorganosiloxanes through the hydrolytic polycondensation of organochlorosilanes.

A considerable portion of the organosiloxane polymers presented commercially is copolymer systems. Copolymers are particularly widely used in the manufacture of siloxane liquids, rubbers, and organosilicic resins. It is well known that hydrolytic polycondensation of organochlorosilanes is accompanied by the formation of products whose structures and compositions are different from the specified ratio. This is caused by the significant difference between the reactivity of various organochlorosilanes. At present, the problem is solved by the introduction of a stage of catalytic regrouping into the process of producing copolymer siloxanes. The essence of the additional stage consists of averaging the composition of copolymer products. It was shown that polycondensation of organoalkoxysilanes in a non-aqueous acetic acid medium is an efficient method of obtaining copolymer products, as well the compositions of which are completely homogenous and correspond to calculated magnitudes. This distinguishes them in essence from analogues, obtained through hydrolytic polycondensation of corresponding chlorosilanes.



The prospect achieving a complete transition away from the "chloric cycle" is a topic to be actively considered in the next decade. The present paper analyzed some alternatives to chlorine-containing polymers. We considered hybrid materials as one of the most promising alternatives, in which silicones are the best candidates for components of such hybrids. Indeed, alkoxysilanes are the traditional reagents used to obtain hybrid materials by the so-called sol-gel method, or by a series of modern methods of injection of siloxane precursors into various polymer matrices [24–27]. Nevertheless, not only alkoxysilanes but also other siloxane polymers are appropriate candidates for a broad use regarding removal of chlorine from their production cycles. Siloxane-polyimidehybrids and modified polydimethylsiloxanes can be considered to be prospective components for new ecological polymer materials. The potential for their full regeneration to initial reagents or other useful products is a key and unique peculiarity of the development of silicones.

11.5 Conclusion

Taking into account the complexity and mutability of the problem of the reduction of chlorine use in the chemistry of polymer materials which interact with the various environments inhabited by humans, we have attempted to designate a sector of development of new polymers and polymer materials which focuses on the future development of less harmful alternatives to chlorine-containing systems to improve their consumer attributes. Searching for ways to modify the properties of chlorine-containing matrices to establish new markets constitutes another of our priorities.

It has been frequently asserted that all of the major problems of polymer chemistry were solved by the beginning of the twenty first century. This is an obvious overstatement. We should not only correct our past mistakes but create entirely new forms of polymers optimally designed for human contact. This goal is complicated by economic limitations caused by unintentional pressure from manufacturers who produce fine polymer items. These currently produced fine polymer items would need to be temporarily removed from the market and then returned in equally presentable, but much safer, forms.

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Part VI

Substitutives: *CO_2 as a Feedstock for DACs Synthesis*

Chapter 12
Synthesis of Carbonate Compounds Using Carbon Dioxide and Carbon Dioxide-Derived Materials

Shin-ichiro Fujita, Hiroshi Yoshida, and Masahiko Arai

Abstract The chemical transformation of carbon dioxide and carbon dioxide – derived materials such as urea into value-added chemicals may be significant from the viewpoint of green chemistry in replacing harmful reactants such as phosgene and recycling undesired carbon dioxide. The transformation may be achieved by using various catalysts including solid base catalysts, multi-component catalysts, ionic liquid catalysts, and so on, some of which include halogens. Our chapter is to review those catalytic transformation reactions of carbon dioxide and carbon dioxide – derived materials.

Keywords Carbonates • Carbon dioxide • Cyclic carbamate • Cyclic urea • Dialkyl urea • Transesterification • Methanolysis • Cycloaddition

12.1 Introduction

Green Chemistry is a widely accepted principle in designing and processing chemical synthetic reactions for the industrial production of chemicals, recommending the use of environmentally benign reactants, solvents, and catalysts [1, 2]. Carbon dioxide (CO_2) is one of the greenhouse gases but it is nontoxic, nonflammable, and naturally abundant. The transformation of CO_2 into useful organic compounds is therefore of significance for developing green chemical processes, which may replace current processes using harmful reactants such as CO and phosgene [3–5], and it might contribute to the reduction of undesirable CO_2 pollutant in the environment. The application of CO_2 as C1 feedstock is one of the desirable utilization technologies of CO_2.

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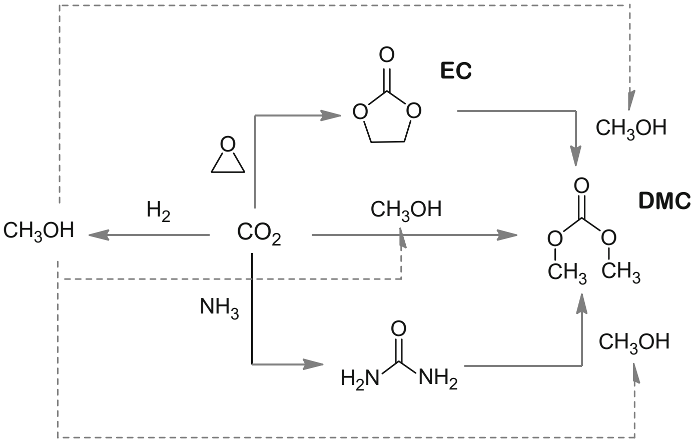
One of the promising transformation reactions of CO_2 is the synthesis of various carbonate compounds such as dimethyl carbonate (DMC) and ethylene carbonate (EC), which can find useful industrial applications [3–5]. A number of works on these reactions with CO_2 have so far been reported in the literature, and various catalysts have been tested in those works, including metals, metal oxides and metal complexes [6–8], and ionic liquids [9, 10]. In several cases, ammonium, phosphonium, and other halides are contained as catalysts and/or promoters. The use of halides would cause environmental pollution problems, and so these are desired to be excluded from industrial catalyst systems from Green Chemistry point of view. Considering those aspects, Li et al. place their concern on chlorine-free catalysts for the synthesis of cyclic carbonates in their review article in 2012 [6].

In this chapter, the authors will review the transformation of CO_2 into carbonate compounds with various catalysts, including indirect production of carbonate compounds from urea and methanol, for example, which can be obtained from CO_2. The performance of various catalysts will be compared to examine the practical usefulness of halogen-free catalysts in comparison to the halogen-containing catalysts. In the following, the first section deals with the synthesis of five-membered cyclic carbonates and the second one the synthesis of dimethyl carbonate (DMC) via different catalytic reactions using CO_2, methanol, ethylene carbonate (EC), and urea as starting materials (Scheme 12.1). Those carbonyl compounds such as DMC and EC can find industrial applications of solvents, octane booster, starting materials for organic synthesis via carbonylation and methylation, precursors of polycarbonate resins, and substitutes for poisonous phosgene and dimethyl sulfate reagents [4, 5]. DMC is currently produced via reaction with phosgenation and oxidative carbonylation reaction, which use poisonous phosgene and CO, and an undesired by-product of hydrochloric acid is



Scheme 12.1 Reaction pathways producing ethylene carbonate (EC) and dimethyl carbonate (DMC) from CO_2

$$2CH_3OH + COCl_2 \longrightarrow CH_3COOCH_3 + 2HCl \qquad (a)$$

$$2CH_3OH + CO + 1/2O_2 \longrightarrow CH_3COOCH_3 + H_2O \qquad (b)$$

Scheme 12.2 Production of DMC using phosgenation (**a**) and oxidative carbonylation (**b**)

formed for the latter (Scheme 12.2). These processes of DMC production would be replaced by greener ones using CO_2 and less harmful materials, in which some are CO_2-derived ones. It is required to design and develop effective green catalysts for practicing those different reactions. The last section reviews the synthesis of nitrogen-containing carbonyl compounds such as cyclic urea, substituted urea, cyclic carbamate, and so on from CO_2.

12.2 Synthesis of Cyclic Carbonate

12.2.1 CO_2 Cycloaddition to Epoxide

The five-membered cyclic carbonates are finding more extensive chemical application as solvents, selective reagents, fuel additives, and monomers for polymers and intermediates in the production of pharmaceuticals and fine chemicals [4, 5]. These cyclic carbonates are currently manufactured via the cycloaddition of CO_2 to epoxide (Scheme 12.1). Although the synthesis of cyclic carbonate via the CO_2 cycloaddition has been realized in industrial scales, development of more effective catalyst systems is still an important issue [8–10].

Inorganic heterogeneous catalysts generally possess high thermal stability and their recycling is easy. Yano et al. first employed a metal oxide catalyst of MgO for the reactions of CO_2 and a few epoxides. They showed that a commercial MgO could catalyze the reactions of CO_2 with propylene oxide (PO) and styrene oxide (SO) to give cyclic carbonates [12]. Styrene carbonate (SC) and propylene carbonate (PC) were obtained with 60 % and 41 % yields, respectively, at 135 °C and 2 MPa of CO_2 for 12 h in a solvent of dimethylformamide (DMF). CO_2 pressure showed no effect on the carbonate yield in a region between 0.2 and 2.8 MPa, suggesting that the activation of epoxide molecules is more significant for the reaction than that of CO_2 molecules.

Shortly later, Yamaguchi et al. used Mg–Al mixed oxides prepared from hydrotalcite for the reactions of CO_2 with several epoxides including PO and SO [13]. Corresponding cyclic carbonates were obtained with excellent yields at 100–120 °C and 0.5 MPa of CO_2 for 15–24 h in DMF. They also investigated the effects of Mg–Al ratio of the mixed oxide on its catalytic activity and showed that the best value was 5. Similarly, Dai et al. prepared Zn–Mg–Al, Zn–Al, and Mg–Al mixed oxides from hydrotalcite and used them for the PC synthesis from PO and CO_2 in the presence of trimethylamine at 140 °C and 2.5 MPa of CO_2 for 12 h

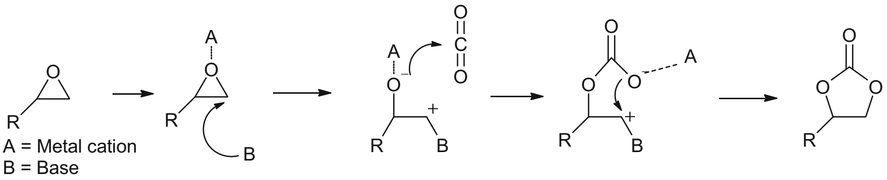
[14]. Among these catalysts, Zn–Mg–Al, Zn–Al, and Mg–Al gave 89 %, 84 %, and 86 % PC yields, respectively. Thus, the catalyst composition was not important for the reaction. Instead, the presence of the amine was significant for the reaction. The yield obtained with Zn–Mg–Al decreased to 67 % in the absence of the amine; however, the role of the amine in the reaction was not discussed.

No use of organic solvent makes the reaction system more preferable. A few groups have reported the CO_2 cycloaddition reactions under such conditions. Bhanage et al. employed several metal oxide catalysts of MgO, CaO, ZnO, ZrO_2, La_2O_3, CeO_2, and Al_2O_3 for the reaction of CO_2 and propylene oxide (PO) to propylene carbonate (PC) [15]. MgO was found to be the best among the metal oxides examined. It gave a PC yield of 32 % with a PC selectivity of 92 % at 150 °C and 8 MPa of CO_2 for 15 h. Although a higher PC yield of 54 % was obtained with La_2O_3, the PC selectivity was lower (75 %). Basic properties of these catalysts were investigated by temperature-programmed desorption (TPD) of adsorbed CO_2. It was suggested that both moderately and strongly basic sites are active sites for the reaction, and MgO has a large amount of moderately basic sites, resulting in its high activity and selectivity. The reaction of CO_2 and styrene oxide (SO) to SC was also examined with MgO. For this reaction, MgO gave a poor product yield (16 %) because of low selectivity. Yasuda et al. employed a Cs–P–Si mixed oxide catalyst for PC synthesis from CO_2 and PO [16]. This catalyst almost quantitatively produced PC, although a high reaction temperature of 200 °C was required. They also carried out the reaction in a fixed-bed continuous-flow reactor. Unfortunately, the PC yield gradually decreased with time on stream. This decrease was ascribed to dissolution of Cs and P into the product solution.

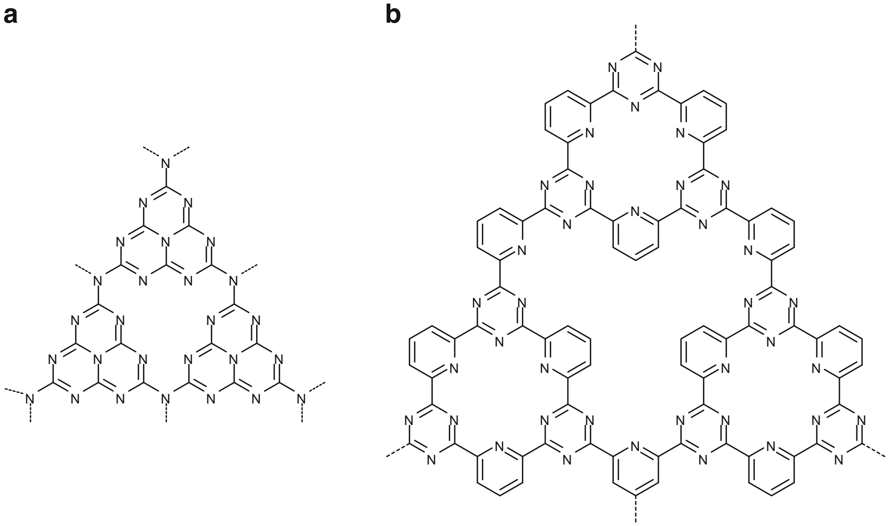
Smectite is one of the layered clay minerals in which one layer consists of one octahedral sheet sandwiched by two tetrahedral sheets. The octahedral sheet contains divalent or trivalent cations such as Mg^{2+}, Zn^{2+}, Fe^{3+}, and Al^{3+} surrounded by six oxygen atoms, and the tetrahedral sheet contains Si^{4+} cations surrounded by four oxygen atoms. Fujita et al. synthesized new types of catalysts based on Mg- and/or Ni-containing smectites, in which various amounts of alkali hydroxides were incorporated [17, 18]. These catalysts were highly active and selective for the PC synthesis from CO_2 and PO without organic solvent. The catalytic activity strongly depends on the amount of alkali atoms incorporated. The most active smectite catalyst gave a PC yield of 81 % with a PC selectivity of 94 % at 150 °C and 8 MPa of CO_2 for 15 h. The turnover number obtained with the most active smectite catalyst was about five times of that with MgO, which was considered to be the best catalyst among the conventional metal oxide catalysts tested, as mentioned above. TPD of adsorbed CO_2 suggested that the smectite catalysts had large amounts of strongly basic sites, resulting in their high activities. The CO_2 pressure did not significantly affect the conversion and the selectivity in the region between 3 and 10 MPa; however, both the conversion and the selectivity decreased sharply at 15 MPa. It is highly probable that the reaction system consists of three phases: CO_2–liquid–solid at the lower pressures, while it should be in a homogeneous phase at 15 MPa. Such a phase change would cause an increase in the volume at the location where the reaction proceeds. Hence, the concentration of the catalyst and/or PO would be low at 15 MPa, resulting in low PO conversion at this elevated pressure. The effect of reaction temperature on the reaction of PO and CO_2 was investigated. The PO conversion was found to increase with the temperature, as expected; however, the selectivity decreased at 170 °C, and thus the optimum reaction temperature was 150 °C.

As mentioned above, MgO gave a reasonable SC yield from CO_2 and SO at 135 °C in the presence of DMF; however, it gave a poor SC yield even at 150 °C in the absence of DMF, suggesting positive effects of DMF on the reaction. Yasuda et al. carried out the PC synthesis with MgO or Mg–Al mixed oxide in the presence and absence of DMF and showed that the presence of DMF enhanced the PC yield twice or more irrespective of the catalyst used [19]. Furthermore, Mori et al. reported that, when a catalytic amount of 4-(dimethylamino)pyridine (DMAP) was combined with zinc-based hydroxyapatite (ZnHAP), a good SC yield of 79 % was obtained at 100 °C and 0.5 MPa of CO_2 for 20 h, although ZnHAP had no activity and the activity of DMAP was very low [20]. Thus, it is highly probable that the occurrence of the synergetic effect is common in the bifunctional catalyst systems consisting of inorganic metal compounds and organic bases. A general reaction mechanism for those bifunctional catalyst systems can be drawn as Scheme 12.3. The Lewis acidic center of metal cation would interact with the oxygen atom of the epoxide, and the base would attack the less hindered carbon atom of the epoxide ring. Such cooperative activation of the epoxide should make the ring opening easier, being the reason of the promotional effects of the base. It is also possible that base activates a CO_2 molecule. In the absence of organic bases, the oxygen atoms on the metal oxide surface would act as Lewis base, but it would be less effective than the organic base.

Such bifunctional catalyst systems are possible by the combination of organic base and hydrogen bond donor. Sun et al. showed that 1,8-diazabicyclo[4.4.0]-undec-7-ene (DBU) gave 60 % PC yield from PO and CO_2 at 110 °C and 2 MPa of CO_2 for 2 h and the copresence of a small amount of cellulose could improve the PC yield to 85 % [21]. Other cyclic carbonates were also produced with high yields by this catalyst system. Similar improvements in the yield were also observed by combining DBU with polyethylene glycol, chitosan, and cyclodextrin. Such promotional effects were ascribed to the interactions between O atoms of epoxide molecules and H atoms of the hydroxyl groups of the cocatalysts. The use of such



Scheme 12.3 A possible reaction mechanism for CO_2 cycloaddition to epoxide catalyzed by acid–base bifunctional systems



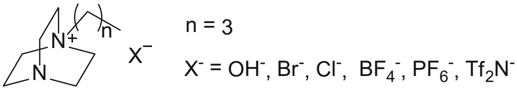
Scheme 12.4 Basal unit structures of (**a**) graphitic carbon nitride and (**b**) covalent triazine framework

abundant bio-resources as cellulose, chitosan, and cyclodextrin is of significance from the viewpoint of Green Chemistry.

Mesoporous graphitic carbon nitrides (MGCNs) (Scheme 12.4a) have recently attracted increasing attention as a new class of metal-free solid catalysts for several reactions [22–27]. Ansari et al. prepared a few MGCN materials from different carbon and nitrogen sources and used them for the CO_2 cycloaddition to PO. PC was obtained with medium yields (25–35 %) but with high selectivities (>90 %) at 100 °C and 80 psi of CO_2 for 2 h in DMF [26]. Roeser et al. reported the preparation of another type carbon nitride material called covalent triazine framework (CTF) whose unit structure is slightly different from that of MGCN (Scheme 12.4b) [28]. They employed CTF as a catalyst for the CO_2 cycloaddition to four different epoxides of epichlorohydrin (ClPO), PO, SO, and cyclohexene oxide (CHO) at 100 °C and 0.7 MPa of CO_2. Interestingly, the selectivity to cyclic carbonate greatly depended on the epoxide used. The highest selectivity of 96 % was achieved with ClPO, but it decreased in the order of ClPO>PO>CHO>SO. With SO, the selectivity was only 14 %. Side reactions were hydrolysis of epoxide and dimerization of carbonate formed. The reason for the differences among the epoxides is unknown. For the reaction of CO_2 and ClPO, the catalyst was recyclable at least five times without loss of the activity. But, to gain the initial activity, vacuum treatment of the recycled catalyst at 150 °C for 1 h was required to remove residual carbonaceous material causing active site blocking.

Ionic liquids (ILs) could contribute as solvents and catalysts to green organic synthetic reactions [29–31]. They are made of relatively large organic cations like imidazolium, ammonium, pyridinium ones, and inorganic anions. ILs have also been frequently employed as the catalysts for the CO_2 cycloaddition to epoxide [9, 10, 31]. In 2001, Peng and Deng reported the CO_2 cycloaddition to epoxide using ILs [32]. They prepared ILs based on 1-butyl-3-methylimidazolium ([BMIm]) and n-butylpyridinium ([BPy]) salts and used them for the PC synthesis from PO without additional organic solvents. The PC formation was effectively catalyzed by $[BMIm]BF_4$. PO was quantitatively converted to PC with 2.5 MPa of CO_2 at 110 °C for 6 h in the presence of 2.5 mol% $[BMIm]BF_4$. This IL catalyst was recyclable for the reaction. It was separated from the reaction mixture by distillation after the reaction and was recycled up to four times with only a minor loss in the catalytic activity. They also showed that the type of either cation or anion affected the activity of the ionic liquid. The activity decreased in the order of $[BMIm]^+ > [BPy]^+$ and of $BF_4^- > Cl > PF_6^-$. Shortly thereafter, Kawanami and coworkers reported the PC synthesis from PO using various imidazolium salts under supercritical carbon dioxide ($scCO_2$) that is highly miscible with IL [33]. The experimental results showed that both the type of anion and the length of alkyl chain in the cation have decisive effects on the conversion and selectivity. The performance of different ionic liquids of 1-ethyl-3-methylimidazolium cation ($[EMIm]^+$) with NO_3^-, $CF_3SO_3^-$, BF_4^-, and PF_6^- was investigated, and BF_4^- was again found to be the most effective. In addition, the carbonate yield increased markedly with an increase of the alkyl chain length (from C_2 to C_8). With 1-octyl-3-methylimidazolium ($[OMIm]BF_4$), PO was almost quantitatively converted to PC at 100 °C and 14 MPa of CO_2 in a short reaction time of 5 min. On the other hand, the yield and the selectivity obtained with $[EMIm]BF_4$ were 61 % and 87 %, respectively, even for the reaction time of 2 h. This enhancement by the alkyl chain length was attributed to higher solubility of both the epoxide and CO_2 into the IL having longer alkyl chain under the same pressure and temperature. The $[OMIm]BF_4$–$scCO_2$ reaction media could also give satisfactory yields for the synthesis of other carbonates. Following these studies, Seki et al. investigated the molecular interactions of pressurized CO_2 with imidazolium and pyridinium salts ($[BMIm]BF_4$, $[BMIm]PF_6$, $[BMIm]Tf_2N$, and $[BPy]BF_4$) by in situ ATR infrared spectroscopy [34]. They suggest that Lewis acid–base interaction between CO_2 and BF_4^- leads to the formation of a new anion species, $[BF_4–CO_2]^-$, which is more basic than the original anion of BF_4^-. Similar new anion species were also produced from PF_6^- and Tf_2N^-; however, they were less basic than $[BF_4–CO_2]^-$ because of the difference in the interaction strength of CO_2 with the anion. It was also shown that the basicity of $[BF_4–CO_2]^-$ was stronger for $[BMIm]BF_4$ than $[BPy]BF_4$, revealing that the interaction between CO_2 and BF_4^- also depends on the cation species of ILs. Thus, the basicity of the new anion species produced from CO_2 and the original anion of IL may explain the effectiveness order of $BF_4 > PF_6^-$ and of $[BMIm]^+ > [BPy]^+$ for the cyclic carbonate synthesis observed in the previous studies.

Yang et al. developed DABCO-based (1,4-diazabicyclo[2.2.2]octane) Lewis basic ILs (Scheme 12.5) and employed them for the PC synthesis from PO [35]. $[C_4DABCO]OH$ produced PC with 88 % yield at 140 °C and 1 MPa of CO_2 for 2 h. This yield was slightly higher than those obtained with halogen-containing ILs of $[C_4DABCO]Cl$ and $[C_4DABCO]Br$. The other ILs could give very low PC



Scheme 12.5 DABCO-based IL of $[C_4DABCO]X$

yields. Although the authors suggested the reaction of OH anion and CO_2 as a reason for the high activity of $[C_4DABCO]OH$, further detailed studies on this IL has not been reported. Very recently, Ema et al. reported the preparation of tetrabutylammonium hydroxide ([TBA]OH) and other quaternary ammonium hydroxides and the use of them for reaction of CO_2 with several different epoxides [36]. Among the ILs prepared, [TBA]OH and butyltrimethylammonium hydroxide gave very high hexene carbonate yields under the reaction conditions employed. The catalytic activity of [TBA]OH for the reaction was found to be comparable to that of [TBA]Br. They also prepared tetrabutylammonium bicarbonate ($[TBA]HCO_3$) and carried out the reaction using it. The reaction results obtained with $[TBA]HCO_3$ were the same with [TBA] OH. According to this finding, reaction results using a deuterated chiral epoxide, and density functional theory calculations, they proposed a reaction mechanism in which bicarbonate anion attacks the less hindered carbon atom of epoxide to produce an alkoxide anion. CO_2 is added to this species, giving a carbonate ion that is subsequently converted to a cyclic carbonate through the intramolecular cyclization.

Synthesis of ILs involving carboxylate or peroxiniobate anion was also reported [37, 38]. Galvan et al. prepared methyltrioctylphosphonium carboxylates and used them for the SC synthesis from SO [37]. Among the ILs prepared, methyltrioctylphosphonium acetate ([MTOP]AcO) was the most active. It could give a SO conversion of 20 % with 0.5 mol% loading under CO_2 at atmospheric pressure and at 100 °C for 23 h; however, 100 % conversion could not be achieved even by increasing temperature, CO_2 pressure, and the [MTOP]AcO loading. The catalyst was deactivated in the course of the reaction. NMR measurements of fresh and used IL samples revealed that [MPOP]AcO was converted to trioctylphosphine oxide, which was confirmed to be inactive for the reaction. It was proposed that combined action of epoxide and weakly nucleophilic carboxylate anion species caused such transformation of [MPOP]AcO to the inactive phosphine oxide. Structural transformations were also observed with $[DBUH]_3NbO_5$ [38]. When this IL was recycled for the PC synthesis, the PC yield gradually decreased up to the sixth run (from 96 % to 65 %), but the yield was kept almost constant in the seventh and eighth runs. Characterization of the fresh and rescued ILs showed that it was converted to $[DBUH]_3NbO_4$ during the first reaction run. Then, $[DBUH]_3NbO_4$ was gradually transformed to a more stable IL of $[DBUH]NbO_3$ in the course of the following reaction runs. For the latter transformation, two DBU molecules are evolved. When $[DBUH]NbO_3$ was separately prepared and used for the reaction, it showed excellent recyclability, and its activity was almost the same with that of $[DBUH]_3NbO_5$ on the basis of the number of [DBUH] cation involved in the catalyst used. The decrease in the yield observed during the catalyst recycling would be ascribed to the evolution of DBU molecules in the transformation of $[DBUH]_3NbO_4$ to $[DBUH]NbO_3$. Thus, one can say that DBU-niobate-based ILs can be stable catalysts, although some structural transformation can occur during the reaction.

In this subsection, several types of halogen-free catalyst systems for the CO_2 cycloaddition to epoxide have briefly been described. Table 12.1 compares the performance of several catalyst systems selected from the aforementioned ones for the reaction with those of the catalyst systems involving halogen atoms [39–42]. Metal oxide catalysts need small R/C ratios (large amounts of the catalysts) to give reasonable cyclic carbonate yields (entries 1–3). The combined system of ZnHAP/DMAP can give a high cyclic carbonate yield even at a very large R/C ratio (entry 4). This high activity is ascribed to the cooperative activation of epoxide molecule by the Lewis acid of ZnHAP and the base of DMAP. The DBU/cellulose system also had such cooperative function, but the R/C ratio employed was not large (entry 5). Compared to the metal oxides, a larger R/C ratio was enough to get a medium cyclic carbonate yield with MGCN (entry 6). There is only one paper reporting the use of MGCN for the CO_2 cycloaddition. Optimization of the catalyst preparation and the reaction conditions may improve the performance of this catalyst system. As mentioned above, the activities of hydroxide ILs are comparable to those of the corresponding halide ILs (entries 7, 8). As shown in Table 12.1, the combined systems of zinc halides and halide ILs gave good PC and SC yields with large R/C ratios under mild reaction conditions. This resulted from cooperative function of Lewis acid of zinc halide and basic nature of ILs. They seem to be more effective than most of the halogen-free systems listed in Table 12.1. However, considering the high activity of ZnHAP/DMAP system (entry 4) and the ones of hydroxide ILs that are comparable to those of halide ILs (entries 6, 7), the combination of ZnHAP and hydroxide ILs may also afford highly effective catalyst systems. Such examinations would be of interest and significance, and other types of ILs like carboxylates and niobates should also be tested. Furthermore, it was reported that hydrogen-bonding donors like water, phenol, alcohol, etc. could also improve the activity of a phosphonium IL [43], similar to the case of the DBU/cellulose system (entry 5). Thus, there are a number of halogen-free bifunctional catalyst systems that have not been examined and would be worth to be investigated to develop more efficient processes for the synthesis of cyclic carbonates.

12.2.2 Reaction of CO_2 and Glycol

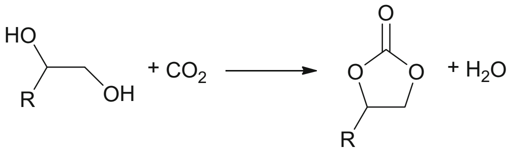
Another route to synthesize cyclic carbonate is the reaction of CO_2 with glycol (Scheme 12.6). Using the substrates of glycols cheaper than epoxides is of benefit. In addition, ethylene glycol (EG) is a coproduct of transesterification of ethylene carbonate (EC) and methanol producing DMC, as described in the next section. So if the effective transformation of EG to EC is realized, it would make the DMC synthesis via the transesterification more valuable. For this reaction, CeO_2–ZrO_2 mixed oxide [44–46], tin complexes [47], and metal acetates [48] were applied. Tomishige et al. examined the reactions of CO_2 with EG and propylene glycol

Table 12.1 Cycloaddition of CO_2 to epoxide using bifunctional catalyst systems of onium halides and metal halides

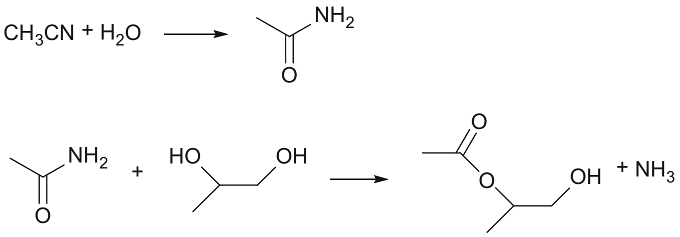
	Catalyst[a]	Epoxide[b]	R/C[c] (–)	CO_2/ (MPa)	*t*/°C and time/h	Yield/%	References
1	MgO	PO	1.7	8	150/15	31	[15]
		SO	1.7	8	150/15	16	
2	MgO/DMF	PO	1.0	0.2	135/12	41	[12]
		SO	1.0	0.2	135/12	60	
3	Mg–Al oxide/ DMF	PO	0.6	0.5	100/24	88	[13]
		SO	0.6	0.5	100/15	90	
4	ZnHAP/DMAP	PO	6667[d]	0.5	100/20	79	[20]
5	DBU/cellulose	PO	8.9	2	120/2	92	[21]
6	MGCN/DMF	PO	194	0.6	100/10	31	[26]
7	$[C_4DABCO]OH$	PO	100	1	140/2	85	[35]
	$[C_4DABCO]Br$	PO	100	1	140/2	79	
8	[TBA]OH	BO	200	1	120/24	76	[36]
	[TBA]Br	BO	200	1	120/24	84	
9	$ZnCl_2$/[TBA]I	PO	500[d]	0.1	25/24	98	[39]
		SO	500[d]	0.1	25/24	27	
10	$ZnCl_2$/[BMIm]Br	PO	5700[d]	1.5	100/1	95	[40]
		SO	3520[d]	1.5	100/1	86	
11	$ZnBr_2$/[BMIm]Cl	SO	88[d]	14	80/1	93	[41]
12	$ZnBr_2$/[TBA]I	SO	646[d]	8	80/0.5	92	[42]

[a] Compounds after slash represent solvents or cocatalysts
[b] PO propylene oxide, SO styrene oxide, BO butylene oxide
[c] Molar ratio of epoxide and catalyst
[d] Epoxide/metal ratio

(PG) using CeO_2–ZrO_2 mixed oxide catalysts [44, 45]. They optimized the catalyst composition (Ce/Zr ratio) and the calcination condition; however, even after the optimization, the carbonate yields obtained were very low (a few percents) because of the reaction equilibrium limitation. Recently, they carried out the reaction in the presence of CeO_2 as a catalyst and 2-cyanopyridine as a dehydration reagent [46]. Various cyclic carbonates were obtained from various diols with good to excellent yields with very high selectivity at 130–170 °C and 5 MPa of CO_2 for 1–48 h in the presence of 10 equivalents 2-cyanopyridine. Even selective production of six-membered cyclic carbonates was also possible with this catalyst system. Thus, removal of H_2O from the reaction system would be essential to obtain high yields of the carbonate. It was proposed that CeO_2 catalyzes not only the reaction of glycol and CO_2 but also the hydration of 2-cyanopyridine to 2-pyridine carboxamide. Huang et al. [48] reported that a PC yield of more than 20 % was obtained from PG with zinc acetate in the presence of acetonitrile, which was also considered to act as a dehydration reagent because the yield linearly increased with increasing the amount of acetonitrile up to some level. However, in their system, the selectivity to PC was



Scheme 12.6 CO_2 addition to glycol forming cyclic carbonate



Scheme 12.7 Hydration of acetonitrile and the reaction of acetamide and propylene glycol

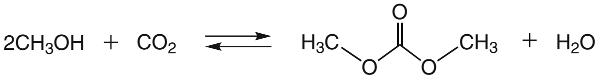
about 60 %, because of the formation of propylene glycol 2-monoacetate, which was produced from the hydration product of acetamide and PG (Scheme 12.7).

12.3 Synthesis of Dimethyl Carbonate

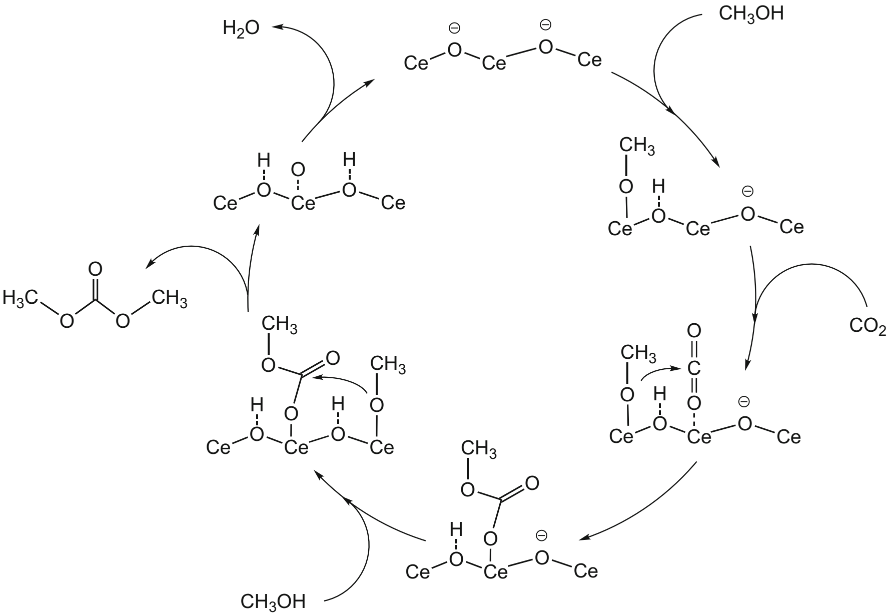
Dimethyl carbonate (DMC) has attracted much attention as an environmentally benign substitute for toxic phosgene, methyl iodide, dimethyl sulfate, and so on [49, 50]. It is widely used as a building block for the production of polycarbonate and other chemicals [15, 51, 52], electrolyte in lithium battery [53–55], fuel additive for the reduction of particulate emission from diesel engine [56], and an intermediate for the pharmaceutical production [57]. Conventional synthesis of DMC such as methanol phosgenation and oxidative carbonylation of methanol are highly hazardous for human health and environment, and, therefore, the present chapter will introduce some alternative routes for the synthesis of DMC using heterogeneous catalysts.

12.3.1 Direct Synthesis from CO_2 and Methanol

The direct synthesis of DMC from CO_2 and methanol is the most attractive and ideal route from the viewpoint of Green Chemistry (Scheme 12.8). There are several advantages such as high atom economy, safe process without using toxic and explosive substrates, and the formation of water as a single by-product, in addition to the effective use of CO_2 into a beneficial chemical.



Scheme 12.8 Direct synthesis of DMC from CO_2 and methanol



Scheme 12.9 Possible reaction mechanism of DMC synthesis from CO_2 and methanol on CeO_2

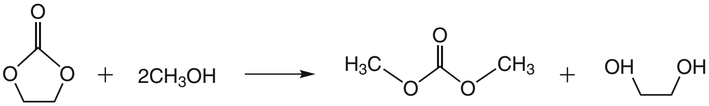
Many catalysts have been investigated for the direct synthesis of DMC from CO_2 and methanol using homogeneous [58, 59] and heterogeneous catalysts such as SnO_2-ZrO_2/SiO_2 [60], heteropolytungstate salts [61], Cu-KF/MgSiO [62], Cu-Ni-graphite [63, 64], Cu-Ni-V_2O_5-SiO_2 [65, 66], ZrO_2-MgO [67] CeO_2 [68–73], ZrO_2 [74], and solid solution of CeO_2 and ZrO_2 [75–81]. Among the catalysts investigated, CeO_2 and CeO_2-containing compounds are promising materials as highly active catalysts for DMC synthesis. The reaction mechanism on CeO_2 has been proposed on the basis of the results of in situ FTIR measurements [79] and XANES spectra [68] (Scheme 12.9). The first step is the dissociative adsorption of methanol on CeO_2 to form terminal methoxy species. Bridged methoxy species are also formed but these are inactive with CO_2. The adsorption of CO_2 on CeO_2 also occurs simultaneously, and Wada et al. point out that the amount of CO_2 adsorption is enhanced by H_2 reduction of CeO_2, which indicates that the adsorption of CO_2 on the defect sites (O vacancy) of CeO_2 is the key step for DMC synthesis [68]. The second step is the formation of Ce-methyl carbonate intermediate from CO_2 and methoxy species, which is a very fast step. DMC is formed by the reaction between this intermediate of Ce-methyl carbonate and another methanol adsorbed on CeO_2, which is the rate-determining step. Honda et al. investigated the details of this step using ^{18}O-labeled methanol and concluded that the nucleophilic addition of methoxy species to Ce-methyl carbonate species is likely to occur rather than the electrophilic addition. The reaction may proceed with similar reaction mechanisms on a solid solution of CeO_2 and ZrO_2 [75–78], and Zhang et al. showed that $Ce_{0.5}Zr_{0.5}O_2$ gave the highest catalytic performance due to their textural advantages such as BET surface area and pore diameter [78].

DMC synthesis is a thermodynamically unfavorable reaction, and so to overcome this limitation, the addition of dehydrating reagents into a reaction system is one of the effective ways, shifting the chemical equilibrium to the desired DMC of Scheme 12.7. A variety of dehydrating reagents have been investigated, such as butylene oxide [67], 2-cyanopyridine [71–73], 1,1,1-trimethoxymethane [78], 2,2-dimethoxy propane [81], dicyclohexyl carbodiimide [82], and acetals [83, 84]. Zhang et al. succeeded to increase the methanol conversion from 1.8 % to 10.4 % with 100 % DMC selectivity by the copresence of 50 wt.% 1,1,1-trimethoxymethane over $Ce_{0.5}Zr_{0.5}O_2$ catalyst at 12 MPa CO_2 for 34 h, and the conversion was significantly higher than the equilibrium value [78]. Recently, Honda et al. achieved the highest DMC yield based on methanol with a value of 94 % using a combination system of CeO_2 and stoichiometric amount of 2-cyanopyridine [71]. Their system is widely applicable to other alcohols for the synthesis of carbonates with CO_2 [72]. Another advantage is the reusability of 2-cyanopyridine; namely, 2-picolinamide formed by the hydration of 2-cyanopyridine can be separated from the reaction mixture by extraction and easily restored to corresponding 2-cyanopyridine by dehydration over Na_2O/SiO_2 [71–73].

The increase of hydrophobicity of heterogeneous catalysts may improve the efficiency of DMC synthesis. Unnikrishnan et al. prepared fluorine-modified ZrP_2O_7 and showed its good catalytic performance for DMC synthesis [85]. The adsorption of water on the active site may suppress the formation of DMC and promote the hydrolysis of DMC, resulting in a low yield of DMC, which can be prevented by the surface modification of the solid catalyst to hydrophobic state.

12.3.2 *Transesterification of Ethylene Carbonate with Methanol*

DMC synthesis by transesterification of ethylene carbonate (EC) with methanol is an environmentally benign route (Scheme 12.10), and the reaction also contributes to indirect chemical fixation of CO_2 because EC is easily formed by the



Scheme 12.10 Transesterification of EC with methanol to DMC and EG

cycloaddition of CO_2 to ethylene oxide as abovementioned. Furthermore, a by-product of ethylene glycol obtained through transesterification is also valuable from the industrial viewpoint.

The use of ionic liquid (IL) has been investigated as an effective catalyst for transesterification of cyclic carbonate with methanol [86–89]. Ju et al. reported the formation of DMC from EC and methanol in the presence of 1-alkyl-3-methylimidazolium ILs at 160 °C and 2 MPa CO_2 [86]. Wang et al. achieved 82 % yield of DMC with 99 % selectivity under the metal-free and halogen-free conditions using carboxylic functionalized imidazolium salt [87]. Yang et al. developed DABCO-based Lewis basic ILs (Scheme 12.5) [88]. The prepared DABCO-based ILs were active under mild conditions. These ILs could catalyze the reaction even at 80 °C, which was much lower than the temperatures required for the ammonium- and imidazolium-based ILs. The catalytic efficiency increased in the order of $Cl^- < Br^- < OH^-$ (n=3). [C_4DABCO]OH gave a DMC yield of 81 % with 90 % selectivity at 80 °C for 6 h. This IL catalyst could be recovered after separation of DMC and EG from the reaction mixture by distillation and reused for four times without loss in either DMC yield or selectivity. Furthermore, in comparison with the common basic catalysts, [C_4DABCO]OH showed higher activity than $N^+(CH_3)_3HO^-$-functionalized PS, [BMIm]Br and [Me_4N]Br. Although DABCO itself and NaOH showed higher catalytic activity for the reaction, these catalysts were hardly recyclable. The authors suggested that it could effectively activate methanol through tertiary nitrogen in the cation part of the IL in combination with hydroxide anion, producing methoxy anion. However, the separation of catalyst from the reaction medium is a crucial problem due to their homogeneous conditions. Wang et al. also have attempted to solve this problem and succeeded to immobilize ILs onto a highly cross-linked polystyrene resin that works as a heterogeneous catalyst, resulting in a continuous performance in a fixed-bed reactor for 200 h without obvious loss of activity [87].

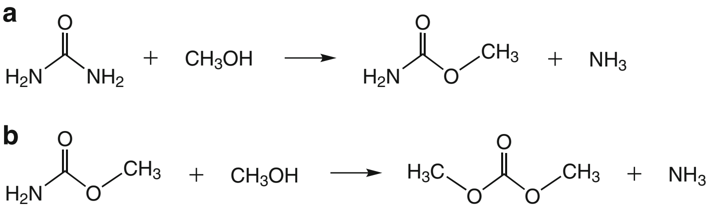
A variety of heterogeneous catalysts such as hydrotalcite [90, 91], alkali-metal hydroxide [92], smectite [93], metal oxides [94–97], anion-exchange resin [98], dawsonite [99], mesoporous carbon nitride [100], metal cyanide [101], tungstate-based catalysts [102], solid solution of cerium and lanthanum [103], and polymers [104] have been investigated for the transesterification of cyclic carbonate with methanol. In general, the transesterification is known as one of the nucleophilic addition reactions and can be catalyzed by either acid or base catalysts. Xu et al. prepared mesoporous ceria materials through a soft-templating method and investigated the influence of acidity and basicity on the catalytic activity for transesterification of EC with methanol [105]. In their work, the linear correlation between the catalytic activity and the amount of surface basic sites was observed, whereas there was no apparent relation between the amount of acid sites and the catalytic activity. Therefore, one can say that the basicity of solid catalyst plays a key role in promoting the transesterification from EC and methanol. Proton abstraction from methanol on Lewis-base sites results in an activation of methanol, which induces the nucleophilic addition reaction with EC for the formation of DMC.

Nitrogen-based carbon materials have attracted considerable attention as base catalysts in various organic reactions [25, 106–110], and these materials also have a potential for transesterification of EC with methanol. Xu et al. investigated the catalytic performance of mesostructured graphitic carbon nitride for the synthesis of DMC via transesterification, and a high DMC yield of 78.6 % was obtained with 99 % DMC selectivity after the reaction at 160 °C for 6 h [100]. Very recently, they further developed these carbon nitride materials doped with Zn on their surface and increased DMC yield to 84.2 % with 98.9 % DMC selectivity at 160 °C for 4 h [111]. Jagtap et al. used poly-4-vinyl pyridine (PVP) as a homogeneous recyclable base catalyst, and after optimization of reaction conditions, high yields of DMC (82 %) and ethylene glycol (75 %) were achieved at an EC conversion of 96 % using 20 wt.% PVP at 140 °C for 4 h without significant loss in the catalyst performance [104].

12.3.3 Methanolysis of Urea

The methanolysis of urea is one of the promising ways for the synthesis of DMC due to its environmentally benign and economical process [112]. The substrate of urea can be formed from NH_3 and CO_2, meaning that the methanolysis of urea is beneficial not only for the development of halogen-free process but also for indirect chemical fixation of CO_2. The reaction proceeds through two steps: the formation of methyl carbamate as an intermediate (Scheme 12.11a) and the consecutive nucleophilic substitution of methanol (Scheme 12.11b). The first step easily occurs in the absence of catalyst, and, therefore, the efficient catalyst for the reaction between methyl carbamate and methanol is required. A number of catalysts have been investigated including organotin derivatives [113], ionic liquids [114], metallic compounds [115], lanthanum compounds [116], polyphosphoric acid [117], supported catalyst [118], solid base catalysts [119], ZnO [120, 121], and Zn-containing materials [122–125]. A high DMC yield of 29 % was achieved over ZnO catalyst [120], and, however, the dissolution of ZnO into methanol was unavoidable. Zhao et al. reported that ZnO dissolved in reaction media formed $Zn(NH_3)_2(NCO)_2$ and worked as a highly active homogeneous catalyst for methanolysis of urea [121]. The development of heterogeneous catalysts is desirable for more practical application.

It is proposed that weak acidity and basicity promote the activation of urea and methanol. Wu et al. prepared several Zn/Al bifunctional catalysts with different



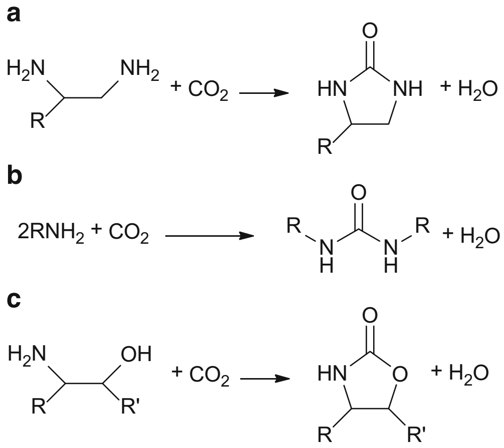
Scheme 12.11 The formation of DMC through methanolysis of urea

Zn/Al molar ratios and investigated the influence of their acid–base properties on a catalytic activity using NH_3-TPD and CO_2-TPD measurements [125]. They pointed out that strong acidic sites were unfavorable to desorption of urea, and the intermediate of methyl carbamate and less acidic sites also resulted in lower activity. DMC yield increased with an increase in the amount of weak basic sites and with a decrease in that of strong basic sites. Facile methanol adsorption and methoxy desorption from weak basic sites may accelerate the reaction. These results suggest that the formation of abundant weak acidic sites and basic sites could promote the methanolysis of urea. Namely, dissociative adsorption of methyl carbamate and methanol occurs on a weak acidic site and a basic site, respectively, and the nucleophilic substitution occurs between these adsorbed species, forming corresponding DMC and NH_3. Both acidity and basicity are indispensable for the adsorption of the substrates, but strong acid–base properties may suppress desorption of intermediate, resulting in lower catalytic activity.

For efficient DMC synthesis, the product selectivity should be improved by preventing some side reactions. DMC formed further reacted with the intermediate of methyl carbamate, forming N-methyl methyl carbamate. Another side reaction is the decomposition of DMC into CO_2 and dimethyl ether at high temperature [126]. Recently, Zhang et al. achieved 34.2 % conversion of urea with 97.4 % DMC selectivity at 180 °C [118], and they mentioned that the reaction conditions such as the amount of catalyst, temperature, and reaction time greatly affected DMC selectivity. Wang et al. reported the importance of isocyanic acid HNCO, which was formed by the decomposition of urea above 135 °C, as an accelerator of DMC synthesis [127]. Unfortunately, HNCO is also highly reactive with either urea or DMC, resulting in the formation of by-products. Therefore, higher reaction temperatures may induce the side reaction with DMC and HNCO formed, decreasing the DMC selectivity.

12.4 Synthesis of Nitrogen-Containing Carbonyl Compounds

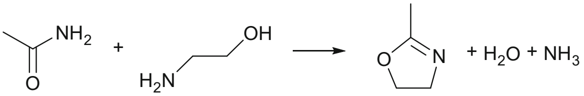
Cyclic and dialkyl ureas and cyclic carbamates, which can be synthesized via the reactions of CO_2 with alkylene diamines, alkyl amines, and amino alcohols, respectively (Scheme 12.12), find extensive applications as intermediates for fine chemicals, pharmaceuticals, cosmetics, pesticides, etc. [4, 5, 11, 128]. Bhanage et al. carried out the reactions of CO_2 with alkylene diamines and amino alcohols without any catalyst [129]. From ethylene diamine, 1,2-propylene diamine and 1,3-propylene diamine, corresponding cyclic ureas were produced with good yields and very high selectivity at 150 °C under 6 MPa CO_2 for 6 h in methanol solvent. However, only a trace amount of cyclic urea was obtained from an aromatic compound of 1,2-phenylene diamine. Under the same reaction conditions, the reactions of CO_2 and amino alcohols producing cyclic carbamates (Scheme 12.12c)



Scheme 12.12 Synthesis of (**a**) cyclic urea, (**b**) dialkyl urea, and (**c**) cyclic carbamates from CO_2

were also investigated. In contrast to the reactions of CO_2 and the diamines, the conversions of amino alcohols and the selectivities to the desired products were low. By-products mainly observed were dimer of the substrates and 1-(hydroxyl alkyl)-2-oxazolidinones. The latter was considered to be produced from the consecutive reaction of the cyclic carbamate produced with another molecule of the amino alcohol. At a higher temperature of 200 °C, a higher conversion was obtained, but the cyclic carbamate yield was still a low value because of the decrease in the selectivity to the desired cyclic product. The same protocol was applied for the synthesis of dialkyl urea (Scheme 12.12b), by Wu et al. [130]. At slightly higher temperature of 180 °C and CO_2 pressure of 10 MPa, dialkyl ureas were obtained from primary alcohols with good yields after the reaction for 24 h without any solvent, while the product yields were low from secondary alcohols. Thus, no use of catalysts makes the reaction procedures simple, and this strategy could effectively be applied for the reactions of CO_2 with various amino compounds, but the applicability largely depends on the type of reactant amino compounds, and, furthermore, the reaction conditions required are rather harsh.

Several groups reported the use of catalysts for these reactions. Kimura et al. used a monomeric tungstate of $[TBA]_2WO_4$ for the reaction of CO_2 and 1,2-phenylene diamine [131], which did not proceed in the absence of catalysts. With this catalyst, the cyclic urea product of 2-benzimidazolone was obtained with an excellent yield at 140 °C in a solvent of NMP for 24 h even under CO_2 at atmospheric pressure. The activities of inorganic and organic strong bases, basic ILs of [TBA]OH and [TBA]Br, and other tungstates of $[TBA]_4W_{10}O_{32}$ and $[TBA]_2W_6O_{19}$ were negligible or very low. Several substituted 1,2-phenylene diamines, 1,8-diaminonaphthalene, and 3,3′-diaminobenzidine could also be converted to corresponding cyclic ureas with good to excellent yields. NMR measurements suggest that WO_4 anion interacts with both CO_2 molecules and the amino groups. Tamura et al. employed CeO_2 for the synthesis of cyclic ureas from CO_2 and aliphatic diamines [132]. CeO_2 could almost quantitatively convert the



Scheme 12.13 The reaction of acetamide and aminoethanol producing 2-methyl-2-oxazoline

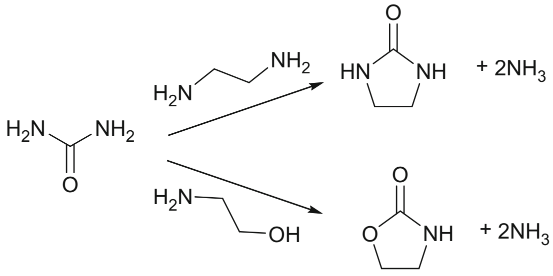
diamines to cyclic ureas at 140 °C and 0.5 MPa CO_2 for 12–36 h in 2-propanol. Thus, these catalysts could lower the CO_2 pressure required for the cyclic urea synthesis.

As mentioned above, cyclic carbamate was produced from CO_2 and amino alcohol with poor yields in the absence of any catalyst. Tamura et al. also applied CeO_2 for this reaction [133]. They showed that various 2-oxazolidinones were quantitatively obtained in acetonitrile at 150 °C and 5 MPa CO_2 for 4 h. Although longer reaction time of 12 or 24 h was required, it was also possible to synthesize 6-membered cyclic carbamates with very high yields from less reactive 3-aminopropanols. Acetonitrile can be a dehydration reagent producing acetamide (Scheme 12.7), which can further react with the reactant of amino alcohol. In the cases of the reaction with aminoethanol, the formation of 2-methyl-2-oxazoline was observed (Scheme 12.13); however, its amount was very small. So the reaction rate of the dehydration would be considerably slower than that of the cyclic carbamate formation.

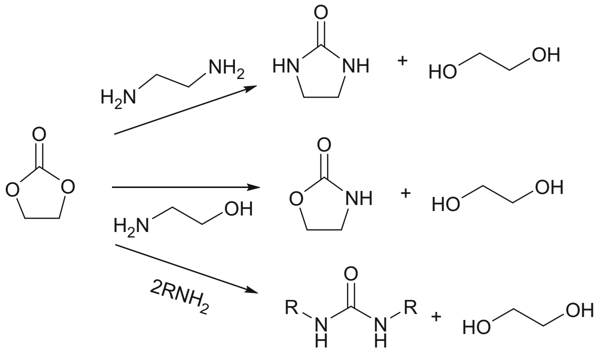
Jiang et al. reported the use of an IL of [BMIm]OH for the reaction of CO_2 producing dialkyl urea [134]. This catalyst system gave good yields of dialkyl ureas at 170 °C under 5.5 MPa CO_2 for 19 h without solvents and dehydration reagents. Shi et al. also carried out the reaction using halogen-containing IL of [BMIm]Cl in combination with CsOH at the same temperature but at a higher CO_2 pressure (6 MPa at room temperature) and with a smaller amine/IL ratio (larger amount of IL [135]). The [BMIm]Cl/CsOH system could give high product yields in shorter reaction time of 4 h. Considering the differences in the CO_2 pressure and the amine/IL ratio, however, the activity of [BMIm]OH would be comparable to that of the combined halogen-containing IL catalyst system. Wu et al. investigated the effectiveness of inorganic and organic base compounds as the catalysts for the reaction [130]. They carried out the synthesis of dibutyl urea in the presence and absence of the catalysts at 180 °C and 10 MPa CO_2 for 4 h. A product yield of 30 % was obtained in the absence of any catalyst, and the yield was increased to only 37 % in the presence of [BMIm]OH. Thus, one can say that the contribution of this IL to the dibutyl urea formation is not so large at least under the reaction conditions employed.

Cyclic urea and cyclic carbamate can also be produced by using urea (Scheme 12.14). These reactions can be indirect utilization of CO_2 for the organic synthesis, because urea is manufactured from CO_2 in industrial scales. Bhanage et al., who investigated the production of these cyclic compounds from CO_2, also carried out the reactions of urea with diamines and amino alcohols under reduced pressure without any catalyst [136]. When an equimolar mixture of urea and 1,2-ethylene diamine was treated at 150 °C for 3 h under a reduced pressure of 80 kPa, 2-imidazolidinone and 1-carbamoyl-2-imidazolidinone were formed with 65 % and 21 % yields, respectively. Similarly, 4-methyl-2-imidazolidinone was obtained from 1,2-propylene diamine in a lower yield of 34 % along with almost

Scheme 12.14 Synthesis of cyclic urea and cyclic carbamate using urea



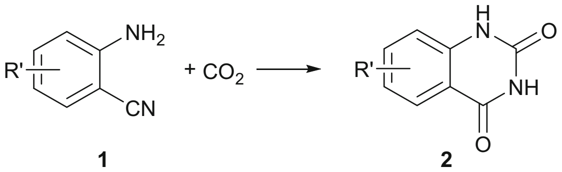
Scheme 12.15 Synthesis of cyclic urea, cyclic carbamate, and dialkyl urea using ethylene carbonate



the same amount of its carbamoyl derivatives. Thus, the synthesis of five-membered cyclic urea using urea is not selective. The carbamoyl imidazolidinones were supposed to be produced from one diamine molecule and two urea molecules. Fortunately, from 1,3-propylene diamine, six-membered cyclic urea was selectively produced with 78 % yield. In contrast to the synthesis of cyclic urea, several aliphatic cyclic carbamates including six-membered one were selectively produced from corresponding amino alcohols with very high yields. Furthermore, 1,2-phenylene diamine and 2-aminophenol were almost quantitatively transformed to aromatic cyclic urea and carbamate, respectively, and 2-aminobenzyl alcohol also selectively afforded corresponding six-membered cyclic carbamate in a high yield. As already described in this section, aliphatic urea was selectively obtained from CO_2 and diamine in high yields. Hence, urea is not attractive for the preparation of aliphatic cyclic urea as compared with CO_2. However, this is not the case for the synthesis of cyclic carbamates and aromatic cyclic urea, whose product yields and selectivities were high. Thus, urea is a useful reagent for the synthesis of cyclic carbamates and aromatic cyclic urea. It should be noted that this protocol does not require any catalyst and ammonia cogenerated can be used for ammonia-oriented products.

Analogous to the DMC synthesis from EC and methanol, synthesis of cyclic urea, cyclic carbamate, and dialkyl urea using EC is also possible (Scheme 12.15). For the former two reactions, MgO and K_2CO_3 were reported as the catalysts [137, 138]. With them, various aliphatic cyclic ureas and carbamates were produced with good to high yields at 80 °C for about 5 h; however, no formation of aromatic cyclic products was observed. For the last reaction, CaO, Cs_2CO_3, and PEG supported KOH catalysts were

Scheme 12.16 Synthesis of quinazoline-2,4(1H,3H)-diones from CO_2 and aminobenzonitriles



found to be effective [139–141]. The reaction was carried out at 90 °C or higher (up to 150 °C) depending on the catalysts employed and the type of amine reactants. Among these catalysts, Cs_2CO_3 could give high conversions within the shortest reaction time. Compared to the direct synthesis of these urea and carbamate compounds from CO_2, the reactions of EC can proceed at lower temperatures.

The reactions of CO_2 and aminobenzonitriles **1** produce rather complex compounds of quinazoline-2,4(1H,3H)-diones **2** (Scheme 12.16), which are a class of important intermediates in the pharmaceutical industry as a key building block for the synthesis of several useful and valuable medicines. For this reaction, CO_2 can replace toxic reagents of phosgene, potassium cyanate, and chrolosulfonyl isocyanate, which have been employed for the conventional synthesis of **2**. Mizuno et al. first reported the use of DBU as the catalyst for the reaction [142, 143]. Following their study, several research groups reported various catalyst systems for the synthesis of **2** by reacting CO_2 with **1**. Those include organic bases of N-methyltetrahydropyrimidine (MTHP) [144] and tetramethylguanidine (TMG) [145], an inorganic base of Cs_2CO_3 [146], ILs of [BMIm]OH, [BMIm]Ac, and tetrabutylphosphonium arginate [TBP] [Arg] [147–149], solid base catalysts of MgO/ZrO_2 and smectite [150, 151], a monomeric tungstate of $[TBA]_2WO_4$ [131], and amine-functionalized MCM-41 [152]. Table 12.2 lists the reaction results obtained with these catalysts. They gave good to excellent product yields at around 120 °C under CO_2 at 10 MPa or below. With a few catalysts, the synthesis was also possible at ambient CO_2 pressure. Most of the catalysts listed were proven to be usable for the reactions with a broad range of substituted aminobenzonitriles. The ILs of [BMIm]OH and [TBP][Arg] could give excellent yields under solvent-less conditions, and the presence of organic solvents showed negative effects on the catalytic performance of the ILs [147, 148]. Interestingly, amine-functionalized MCM-41 showed a higher product yield in water than in DMF, and it gave no product in other less polar organic solvents [152]. Scheme 12.17 represents the proposed reaction mechanism. At first, a carbamate salt is formed. Then, the carbamate species is transformed to quinazoline through intramolecular cyclization and the rearrangement of the resulting cyclic intermediate.

Recently, Han et al. have reported that the reaction of CO_2 and **1** can efficiently proceed in water without any catalyst [153]. In this reaction system, the reactant **1** was almost quantitatively converted to **2** at 160 °C under 14 MPa of CO_2. Several substituted products were also obtained with high yields. No reaction occurred in organic solvents. Scheme 12.18 illustrates the reaction mechanism proposed by the authors. It is well known that CO_2 can form carbonic acid (H_2CO_3) in water. The C and N atoms of the nitrile group of **1** interact with the O atom of C=O group of H_2CO_3 and

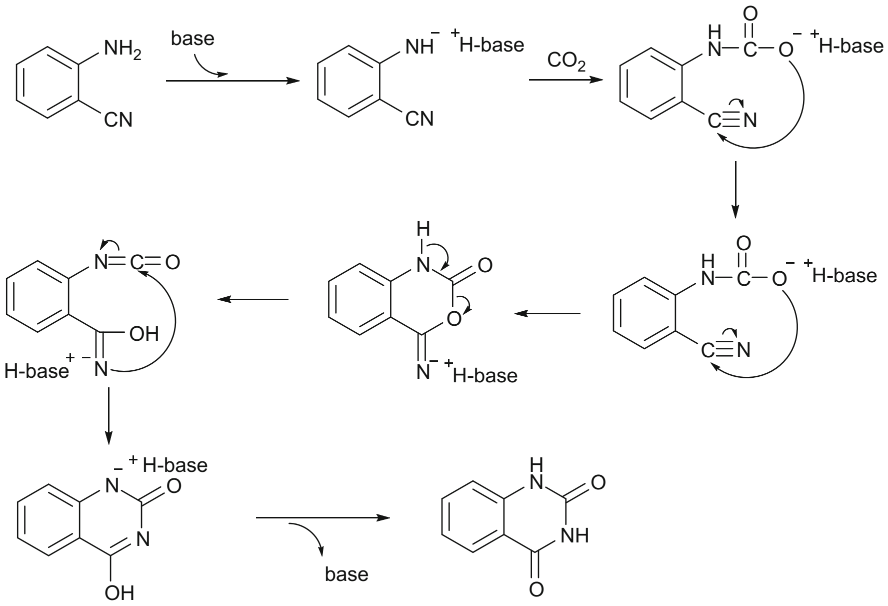
Table 12.2 Comparison of the present catalyst of SM-Na-4 with the earlier reported ones for the synthesis of *2* from *1* and CO_2

Entry	Catalyst[a]	1/Catalyst	Pressure/ MPa	*t*/°C and time/h	Yield/%	Ref.
1	DBU	10/1 mmol	10	80/4	91	[142]
2	DBU	5/1 mmol	0.1	120/4	83	[143]
3	MTHP	10/3 mmol	0.1	100/24	71	[144]
4	TMG	5/0.1 mmol	10	120/4	82	[145]
5	Cs_2CO_3	20/5 mmol	1.3[c]	100/4	94	[146]
6	[BMIm]OH	20/5 mmol	3[c]	120/18	90	[147]
7	[BMIm]Ac	5/5 mmol	0.1	90/10	92	[148]
8	[TBP][Arg]	1/1 mmol	8.5	100/12	91	[149]
9	MgO/ZrO_2	20 mmol/0.24 g	3.7[c]	130/12	92	[150]
10	Smectite	8.5 mmol/0.4 g	4[c]	130/6	67	[151]
11	$TBA_2[WO_4]$	1/0.01 mmol	2	100/24	90	[131]
12	Am-MCM-41[b]	2 mmol/0.03 g	3.5[c]	130/18	91	[152]

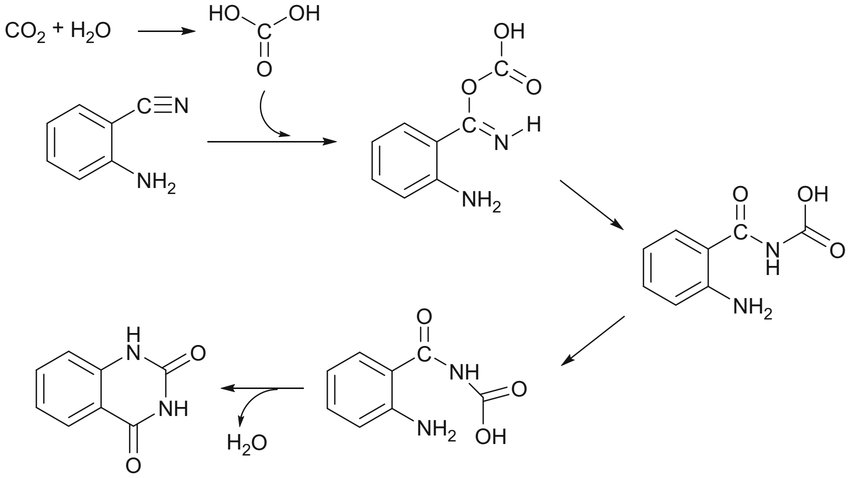
[a] Full names of abbreviations are given in the text

[b] Amine-functionalized MCM-41

[c] Initial pressure at room temperature



Scheme 12.17 A plausible reaction mechanism for the reaction of CO_2 and 2-aminobenzonitrile in the presence of base catalysts



Scheme 12.18 A proposed reaction mechanism for the reaction of CO_2 and 2-aminobenzonitrile in water in the absence of any catalyst

its H atom, respectively, producing a new C–O and N–H bonds. Then, the resulting intermediate is further converted to the product **1** (See Scheme 12.16) via a series of rearrangements and intermolecular dehydration. Although the required reaction temperature and CO_2 pressure were rather high, no use of organic solvent and catalyst would make the post-reaction procedures much easier and the synthesis processes simpler.

12.5 Concluding Remarks

This chapter reviews the current progress in the synthesis of carbonate compounds and nitrogen-containing carbonyl compounds from CO_2 and CO_2-derived materials like urea and EC using different types of halogen-free catalysts. These reactions are benign synthesis ways to avoid the use of toxic chemicals of phosgene, CO, isocyanate, and so on. In addition, the use of halogen-containing catalysts is desirable to be avoided, because halogen species evolved from them are toxic and may cause environmental pollution problems. Therefore, the development of halogen-free catalysts and their use for organic synthesis based on CO_2 would be of significance and interest from the viewpoint of Green Chemistry. A number of different catalyst systems have been reported so far for the target reactions, and some halogen-free catalysts are comparable in the performance to those halogen-containing ones.

For the CO_2 cycloaddition to epoxide, several acid–base bifunctional catalyst systems are known to be highly effective; however, most of them consist of halides. The activities of MgO and ZnHAP are largely improved by the copresence of organic base, and those of some basic halogen-free ILs are comparable to corresponding halogen-containing ILs. Furthermore, protic compounds such as water, phenol, and alcohol may enhance the performance of a phosphonium halide catalyst for the reaction. Taking account of these results, the combination of halogen-free ILs with those inorganic materials and protic compounds may afford highly effective catalyst systems. It is interesting to try such combinations in designing and developing more efficient and environmentally benign processes for the synthesis of cyclic carbonates. Nitrogen-containing carbon materials and bio-resources as cellulose, chitosan, and cyclodextrin would also be candidates for such examinations. For the cyclic carbonate synthesis from CO_2 and glycol, CeO_2–ZrO_2 is selective, but it can give only low product yields because of the reaction equilibrium limitation. In the presence of a dehydration reagent, CeO_2 can selectively produce cyclic carbonates in high yields.

Although many types of halogen-free catalysts have been developed for the direct synthesis of DMC, this reaction does not appear to be very promising because of the reaction equilibrium limitation. Dehydration reagents are required to get high DMC yields. The preferred alternatives would be the transesterification of EC and methanol and the methanolysis of urea, because the synthesis of EC and urea utilizes abundantly available CO_2. A variety of halogen-free catalysts have been employed for these reactions. At present, the transesterification reaction can give higher DMC yields than the methanolysis one.

Diamine and alkyl amine are selectively transformed to cyclic and dialkyl ureas, respectively, under pressurized CO_2 without any catalyst, but the transformation of amino alcohol to cyclic carbamate is not selective. Several halogen-free catalysts may make these reactions more effective. Urea can react with amino alcohol selectively producing cyclic carbamate under reduced pressure in the absence of catalyst. EC can also be used for the synthesis of those nitrogen-containing carbonyl compounds instead of CO_2 and give higher product yields at lower temperatures. Several halogen-free catalysts were found to be effective for the synthesis of quinazoline-2,4(1H,3H)-diones from CO_2 and 2-aminobenzonitriles. This reaction is also possible in water without any catalyst. This system is worth to be further investigated for many reactions, because no use of organic solvent and catalyst would contribute to realize environmentally benign synthetic processes.

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Chapter 13
Research Progress in the Phosgene-Free and Direct Synthesis of Dimethyl Carbonate from CO_2 and Methanol

Zhongwei Fu and Yuezhong Meng

Abstract This chapter contains a short introduction to dimethyl carbonate (DMC) followed by an overview on its phosgene-free synthesis and various applications. DMC is considered as an environmentally benign compound and unique intermediate with versatile chemical reactivity. However, the traditional process of DMC synthesis via phosgene and methanol or methanol exchange is limited owing to the toxic raw material involved. Thus, environmentally friendly phosgene-free processes of DMC have been proposed and developed in the past decades. In this chapter, recent progress in the direct and phosgene-free synthesis of DMC from CO_2 and methanol is reviewed with the focus on the different catalyst systems. Moreover, the application of physical–chemical methods in the direct synthesis of DMC is also introduced. Finally, conventional processes are discussed in order to understand the advantages and disadvantages of direct synthesis of DMC.

Keywords Dimethyl carbonate • Carbon dioxide • Heterogeneous catalytic systems • Support catalysts • Dehydrating agents

13.1 Introduction

DMC is considered as an environmentally benign compound and unique intermediate with versatile chemical reactivity, due to its nontoxicity, good biodegradability, and excellent solubility [1]. It is known as the new material of the organic synthesis for its widely applications in many fields [2]. As nonpolar aprotic solvent, DMC is a viable substitute for some volatile organic solvents, such as the electrolyte of lithium rechargeable batteries [3]. In addition, owing to its outstanding oxygen content (53 wt. %) combined with its good blending properties and low exhaust emissions, DMC is an ideal additive either for gasoline or diesel

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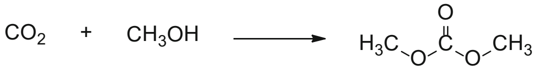


Scheme 13.1 Direct synthesis of DMC from CO_2 and methanol

[4]. Moreover, it is used as an alternative to harmful phosgene for aromatic polycarbonate and isocyanate syntheses as a carbonylation agent, as well as for replacing dimethyl sulfate and methyl halides, because of its great reactivity toward nucleophilic molecules [5].

In spite of the large demand for DMC, the production is still much lower than the industrial needs [6]. Hence, lots of efforts have been made in order to find a sustainable route to produce DMC on a large scale.

Carbon dioxide is a major greenhouse gas that contributes to Earth's global warming. In 2011, global CO_2 emissions were 31.3 Gt, 44 % of which was from coal combustion, 35 % from oil, and 20 % from gas. Regional differences in contributions to global emissions conceal even larger differences among individual countries. Nearly two-thirds of global emissions for 2011 originated from just 10 countries, with the shares of China (25.4 %) and the United States (16.9 %) far surpassing those of all others [7]. For the medium term, in its New Policies Scenario, the World Energy Outlook (WEO 2013) projects that global CO_2 emissions from fuel combustion continue to grow unabated, albeit at a lower rate, reaching 37.2 Gt by 2035 [8].

In light of the concern about energy crisis and global warming, CO_2 has attracted more and more attention, especially as a potential carbon resource which is not widely used yet. Various chemical processes have been tried to convert CO_2 into valuable chemical compounds in recent years. One of the most attractive methods of CO_2 chemical fixation is direct synthesis of DMC from CO_2 and methanol as shown in Scheme 13.1, which is environmentally benign not only for reduction of greenhouse gas emissions but also for development of a new carbon resource.

This chapter attempts to present recent developments in direct synthesis of DMC from CO_2 and methanol. By contrast, conventional processes are also briefly introduced in order to understand the advantages and disadvantages of the direct synthesis of DMC.

13.2 Conventional Synthetic Processes of DMC

Until 1980, DMC was only produced based on the phosgenation of methanol (Scheme 13.2) [6], which involves toxic compounds like chlorine and phosgene, together with other corrosive chemicals to recycle phosgene.

Considering all these shortcomings, it is of desperate importance to find other routes to DMC synthesis.

$$COCl_2 + CH_3OH \longrightarrow CH_3OCOCl + HCl$$

$$CH_3OCOCl + CH_3OH \longrightarrow (CH_3O)_2CO + HCl$$

Scheme 13.2 Phosgenation of methanol

$$2CH_3OH + CO + 1/2O_2 \longrightarrow (CH_3O)_2CO + H_2O$$

Scheme 13.3 Oxidative carbonylation of methanol

$$2CH_3OH + 2NO + 1/2O_2 \longrightarrow 2CH_3ONO + H_2O$$

$$CO + 2CH_3ONO \longrightarrow (CH_3O)_2CO + 2NO$$

Scheme 13.4 Carbonylation of methyl nitrite

13.2.1 Oxidative Carbonylation of Methanol

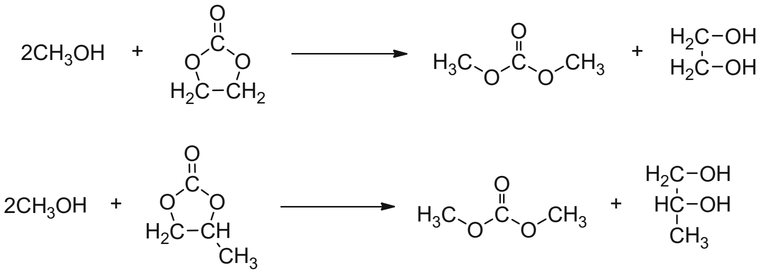
Romano et al. [9] first developed a novel route to produce dimethyl carbonate free of phosgene, namely, the oxidative carbonylation of methanol as shown in Scheme 13.3.

As a mechanism, the authors claimed the process for DMC production from methanol, carbon monoxide, and oxygen is a single redox reaction catalyzed by CuCl [10].

A lot of researches have been carried out in this field, mainly concentrated on the development of new catalysts [11] and understanding of the reaction mechanism [12]. Particularly, Ding et al. [13] proposed a highly efficient catalyst $PdCl_2$–$CuCl_2$–KOAc/AC@Al_2O_3 for gas-phase oxidative carbonylation of methanol, which possessed not only high activity but also favorable stability and selectivity: 98 % of DMC selectivity to methanol, 70 % of DMC selectivity to CO, and space–time yield of DMC ranging from 600 to 700 g L-cat^{-1} h^{-1} for runtime of 40 h.

Furthermore, Nishihira et al. [14] patented the oxidative carbonylation of methanol using NO_x as oxidative agent instead of oxygen (Scheme 13.4), which is also named carbonylation of methyl nitrite.

These two main alternative processes for DMC production, oxidative carbonylation and carbonylation of methyl nitrite, have been replacing the traditional phosgenation of methanol. In spite of improvements achieved by these two routes, they are still quite hazardous [15]. The using of lethal carbon monoxide and oxygen streams increases the risk of explosion. Thus, recent researches focused on electrochemical oxy-carbonylation of methanol to avoid the use of hazardous oxidative agents [16], but the productivity of this route is low and quite far away from industrial implementation.



Scheme 13.5 Transesterification of cyclic carbonate with methanol

$$(NH_2O)_2CO + CH_3OH \longrightarrow NH_2COOCH_3 + NH_3$$

$$NH_2COOCH_3 + CH_3OH \longrightarrow (CH_3O)_2CO + NH_3$$

Scheme 13.6 Methanolysis of urea

13.2.2 Transesterification of Carbonates

In 1985, the transesterification of ethylene carbonate with methanol was claimed by Duranleau et al. [17]. Up to now, it is still a hot spot for DMC synthesis, mainly due to high productivity and selectivity of DMC. In this reaction, EC or PC is usually used as the reactant, which can be synthesized by the reaction of CO_2 with ethylene oxide (EO) or propylene oxide (PO) (Scheme 13.5).

In the past decade, great efforts have been devoted to this attractive process. Numerous homogeneous and heterogeneous catalytic protocols have been developed. More recently, Liu et al. [18] revealed a biocatalyst, *Penicillium expansum* lipase supported over CMC-PVA polymer, with high catalytic performance even under ambient pressure and low temperature (conversion of EC to 94 %, yield of DMC to 93 %, and selectivity of DMC to 99 %).

However, the main drawbacks of this route are high costs of carbonates, considerable thermodynamic limitations, and the fact that carbonates are produced from hazardous reactants, such as ethylene oxide and propylene oxide.

13.2.3 Methanolysis of Urea

Ball et al. [19] first proposed producing carbonates through alcoholysis of urea. This process is performed in two steps, where the first one corresponds to the conversion of urea into methyl carbamate followed by the transesterification of methyl carbamate into DMC (Scheme 13.6).

A lot of catalysts such as organic tin, heteropolyacid, metal oxide, and zinc compounds have been tested toward the reaction of urea and methanol. Wang et al. [20] used ZnO as the catalyst and studied the effects of reaction temperature and time on DMC yield. The results suggested that the highest DMC yield of 30 wt. % was obtained at 443 K for 11 h. Sun et al. [21] tried to use polyphosphoric acid (PPA) to promote the reaction between urea and methanol. A desirable DMC yield of 67.4 % was obtained at 413 K for 4 h with 0.8 MPa CO_2.

Together with wide raw material sources, the product is easy to be separated and purified, as no water generating. For this reason, producing DMC by urea alcoholysis counts as a feasible route in industry and has attracted considerable attention in recent years, although low reactivity of urea requires high reaction temperature (over 423 K), which might lead to the decomposition of DMC.

13.2.4 Comparison of Conventional Routes

As discussed above, all these conventional processes for DMC production possess advantages and disadvantages. As a consequence, we mainly focus on the evaluation of several reaction routes in this section. To keep it fair, all aspects such as economic, environmental, operating, safety, and human health impact should be taken into consideration to condition the choice of the best route.

In view of the economic and environmental factors, Monteiro et al. [22] presented a preliminary screening of eco-technologies for DMC production. The analysis showed that the route of phosgene got the worst results, while the route of CO was much greener without concerning of CO_2 sequestration. Based on the global research results, urea and carbonate routes were eligible for the principle of eco-technologies, since they combine intermediate, sequestration potential and industrial feasibility. Table 13.1 summarizes the main elements of these conventional routes.

Table 13.1 Comparison of conventional routes for the synthesis of DMC [23]

Process	Advantages	Disadvantages
Phosgenation of methanol	High yield	Waste acid formed
		Highly toxic and corrosive
Carbonylation of methanol	No phosgene	Use of CO
	High yield	Risk of explosion and corrosive
Methanolysis of urea	Low toxicity	Low reactivity
	Wide raw material sources	Strict operation condition
Transesterification of carbonates	CO_2 mitigation	High costs of carbonates
		Thermodynamic limitations
		Use of hazardous reactants

13.3 Direct Synthesis of DMC from CO_2 and Methanol

All conventional routes are imperfect with strict operation condition, highly toxic and corrosive, or both. Hence, direct synthesis of DMC from CO_2 and methanol gradually becomes the most attractive method since such an approach is environmentally benign, low costing, as well as mild reactions.

13.3.1 Reaction Mechanism

13.3.1.1 Thermomechanical Analysis

CO_2 is thermodynamically stable, with standard Gibbs energy of -394.4 kJ·mol^{-1}. The molecular structure of CO_2 determines the existence of multiple potential active sites, namely, the carbon atom (Lewis acid) and oxygen atom (Lewis base), which are vulnerable to electrophile and nucleophilic species, respectively. Thus, as an organic compound possessing both nucleophilic and electrophilic centers, methanol can be carbonylated with CO_2 in theory.

As part of mechanism study, the thermodynamical analysis of direct synthesis of DMC from CO_2 and methanol is discussed as follows. Thermodynamics data of various substances involved are listed in Table 13.2. Generally, it is effortless to work out the change of enthalpy and Gibbs free energy with following information.

As shown above, it is an exothermic reaction under standard conditions ($\Delta \mathrm{r} H_{298\mathrm{K}} = -27.90$ kJ·mol$^{-1} < 0$). Meanwhile, the change of Gibbs free energy ($\Delta \mathrm{r} G_{298\mathrm{K}} = 26.21$ kJ·mol$^{-1} > 0$) suggests the reaction non-spontaneous at conditions of normal pressures and 298 K.

$$\Delta r H_{298k} = -613.78 - 285.83 - 2(-239.11) + 393.51 = -27.9\,\mathrm{kJ \cdot mol^{-1}} \quad (13.1)$$

$$\Delta r G_{298k} = -464.23 - 237.14 + 394.38 - 2(-166.60) = 26.21\,\mathrm{kJ \cdot mol^{-1}} \quad (13.2)$$

In addition, if we assume the C_p of all substances is constant within 273~400 K, we can calculate the value of $\Delta \mathrm{r} H$ and $\Delta \mathrm{r} G$ under a higher temperature based on the *Kirchhoff law* (Eq. 13.3).

Table 13.2 Thermodynamic data of various substances

Substances	ΔH_f^{φ}/(kJ·mol^{-1})	ΔG_f^{φ}/(kJ·mol^{-1})	C_p/(J·K·mol^{-1}) for $273 < T/K < 400$
DMC (l)	−613.78	−464.23	109.50
CO_2 (g)	−393.51	−394.38	37.1
H_2O (l)	−285.83	−237.14	75.30
CH_3OH (l)	−239.10	−166.60	81.59
CH_2CH_2O	−78.0	−11.8	88.0
$CH_2CH_2(OH)_2$	−451.5	−319.8	

$$\Delta rH_T = \Delta rH_{298k} + \Delta rCp(T - 298) = -23.29 - 0.0155T \tag{13.3}$$

It reveals that the heat effect decreases with the temperature rises. The changing of Gibbs free energy, a function of temperature, can be written in *Gibbs–Helmholtz* (Eq.13.4):

$$d(\Delta rG/T) = \left[(23.29 + 0.0155T)/T^2\right]dT \tag{13.4}$$

Equation 13.5, the integral of Eq. 13.4, shows that ΔrG_T increases as temperature elevating. Thus, high temperature is thermodynamically unfavorable for direct synthesis of DMC.

$$\Delta rG_T = T\Delta rG_{298k}/298 - 23.29(1/T - 1/298) + 0.0155T\ln[(T/298)] \tag{13.5}$$

Assuming CO_2 is ideal gas, we can write the changing of Gibbs free energy in the equation shown in Eq. 13.6 at a certain temperature (T).

$$d\Delta rG = \Delta VdP = 2VgdP = 2(RT/P)dP \tag{13.6}$$

As the volume of gas is much higher than that of liquid, the volume change (ΔV) of this reaction approximates to $2V$g. Then Eq. 13.7 can be calculated by integrating Eq. 13.6 at certain temperature.

$$\Delta rG_P = \Delta rG_{(T)} - RTln\left(P/P^{\varnothing}\right) = \Delta rG_{(T)} - 2.93\ln\left(P/P^{\varnothing}\right) \tag{13.7}$$

When $T > 298\,K$, $\Delta rG_{(T)} > 0$. Then we can draw a conclusion that raising pressure is profitable when keeping temperature constant.

13.3.1.2 Adsorption of CO_2

The activation of carbon dioxide is the primary focus of the whole reaction. Since the valence state of elemental carbon is the highest and the formation heat of CO_2 is extremely high, it remains intricate to activate the stable molecule without consuming a large amount of energy.

CO_2, with typically symmetrical linear triatomic molecule construction, is determined to be a weak electron donor (with the first ionization energy of 13.79 eV) and strong electron acceptor (with the electron affinity of 38 eV). Compared with losing electrons, it is easy to gain electrons in CO_2. So we can achieve the activation of CO_2 as long as inputting electrons in an appropriate method or capturing electrons from other molecules during the reaction process.

The activation methods of CO_2 are various, including coordination activation, biological activation, pyrolysis activation, photochemical radiation, electrochemical reduction, chemical reduction, chemical adsorption and others. Among all these

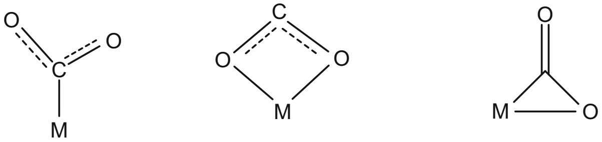


Fig. 13.1 Schematic diagrams of adsorption states of CO_2 on metal surface

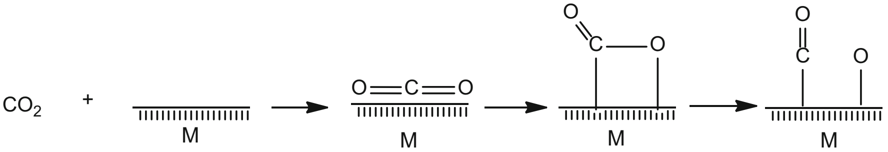


Fig. 13.2 Schematic diagrams of CO_2 chemisorbed on metals

means, chemical adsorption on the surface of metals or metallic oxides is the most probable and effective.

Bartos et al. [23] carried out detailed calculations of free and adsorbed CO_2. Combined with a comprehensive analysis of the compounds formed by CO_2 and transition metals, they came up with three different molecular structures of the intermediates (Fig. 13.1).

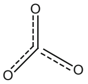
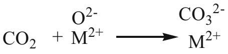
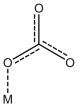
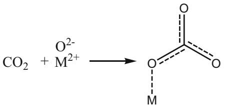
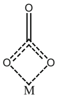
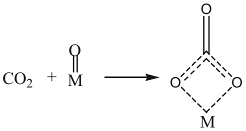
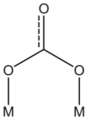
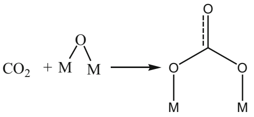
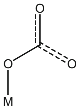
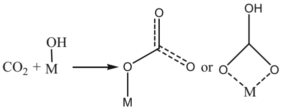
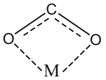
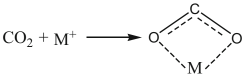
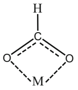
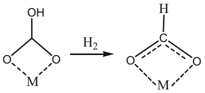
Among these states, the second and the third intermediates are more likely to be formed with due to higher activity. The interaction and electron transfer between CO_2 and metal result in the formation of CO_2^- structure, which leads to the bent of molecular structure, the elongation of C–O bond, and the decrease in C–O symmetric stretching vibratory frequency.

With the solvation of linear molecules, the structure of CO_2^- is fairly stable. It is the most important adsorption intermediate of CO_2 on the surface of single-crystal metal, as well as the precursor of decomposition to CO and O^-. Then, we can get a possible activation path as shown in Fig. 13.2.

Since the acid sites and basic sites exist simultaneously, the adsorbed states of CO_2 on the surface of metallic oxides are multiple. Summarized by the research of Busca et al. [24] and Bianchi et al. [25], several different states of CO_2 exist on the surface, namely, free carbonate, unidentate carbonate, bidentate carbonate, bridge carbonate, supercarbonate, carbonyl, and formate (as shown in Table 13.3).

In conclusion, despite the merits associated to environmental and economic reasons, the route of CO_2 and methanol is still thermodynamically limited. Besides, the water production of the carbonylation of methanol leads to the deactivation of catalysts significantly. As a consequence, the development of novel technologies has captured the world's attention, mainly including the research of high-efficiency catalysts, in situ dehydrants, as well as physical–chemical assistant technologies.

Table 13.3 Adsorption structure and mechanism of CO_2 chemisorbed on metal oxide

Absorptive species	Structure	Mechanism
Free carbonate		 $CO_2 + \overset{O^{2-}}{M^{2+}} \longrightarrow \overset{CO_3^{2-}}{M^{2+}}$
Undentate carbonate		
Bidentate carbonate		
Bridge carbonate		
Supercarbonate		
Carbonyl		
Formiate		

13.3.2 Homogeneous Catalyst Systems

Homogeneous catalysts have been investigated due to its high selectivity for DMC. Up to now, plenty of studies have been devoted to several catalytic systems for this reaction, mainly consisting of metal organic compounds, acetates, and alkali carbonates.

Metal organic compounds were first found to play an important role in the activation of CO_2, in which organotin compound (such as $Bu_2Sn(OEt)_2$, Sn $(OMe)_4$, and $Sn(OBu)_4$ [26]) and titanium alkoxy compounds (such as $Ti(OMe)_4$ and $Ti(OBu)_4$ [27]) are by far the most commonly reported.

Kizlink et al. [28,29] and Kohno et al. [30,31] have conducted many researches on the influence of a series of organotin compounds on direct synthesis of DMC.

$$Bu_2Sn(OMe)_2 + CO_2 \longrightarrow Bu_2Sn(OCOOMe)_2(OMe)$$

$$Bu_2Sn(OCOOMe)_2(OMe) + 2CH_3OH \longrightarrow Bu_2Sn(OMe)_2 + (MeO)_2CO + H_2O$$

Scheme 13.7 Reaction mechanism of $Bu_2Sn(OMe)_2$ for the direct synthesis of DMC

$$CH_3OH \xrightarrow{Base} CH_3O^- + H^+$$

$$CH_3O^- \xrightarrow{CH_3I} CH_3OCH_3 + I^-$$

$$CH_3O^- \xrightarrow{CO_2} [CH_3OCO_2]^-$$

$$[CH_3OCO_2]^- + CH_3I \longrightarrow DMC + I^-$$

$$I^- + H^+ \xrightarrow{Base} HI$$

$$CH_3OH + HI \longrightarrow CH_3I + H_2O$$

Fig. 13.3 Proposed reaction mechanism on various base catalysts

The results indicated that $Bu_2Sn(OR)_2$ (R = Me, Et, Bu) is the most efficient. Besides, the reaction mechanism came up (Scheme 13.7). As generally accepted, CO_2 is activated by the insertion between metal ions and ligands to form the active intermediate, which then reacts with methanol to produce DMC.

Cai et al. [32] first discovered that CH_3OK was an efficient catalyst in the presence of CH_3I, which acted as the promoter. The optimum reaction conditions were 80 °C and 2 MPa, with high yield of 16.2 % and selectivity of 100 %. Compared with metal organic catalyst, the application of acetate and carbonate catalysts are of low toxicity and cost.

Zhao et al. [33] reported the catalytic performance of a series of metal acetates for direct synthesis of DMC. Using nickel acetate as the catalyst, the highest yield of DMC and the minimum production of the by-product (methyl acetate) were obtained. Besides, magnesium acetate, cobalt acetate, and mercury acetate could also bring an acceptable yield, while only methyl acetate formed when sodium acetate or copper acetate was used instead. They proposed that nickel acetate exhibited high activity due to its strong Lewis acid and achieved a DMC yield of 3 % at moderated temperatures (305 K) and 10 MPa. This catalyst showed relatively high activity in the presence of water, although the DMC yield was much lower than that of alkoxy metal compounds.

Fang et al. [34] investigated a series of base catalysts for direct synthesis of DMC and found that the basicity of the catalyst dominated the reaction rather than the carbonate ion, which was elucidated by catalytic activity of some phosphate (K_3PO_4) and organic base $(CH_3)_4NOH$.

Fujita et al. [35] reported a mild catalytic system with all sorts of alkali carbonate catalysts, among which K_2CO_3 exhibited better catalytic performance than any others. However, as the essential promoter in these reactions, CH_3I was deemed to be a reactant according to proposed mechanism researches (Fig. 13.3).

Generally, homogeneous catalytic systems in methanol solvent are active for direct synthesis of DMC from CO_2 and methanol. In these systems, the preparation methods of catalysts are handy and the mechanism is well understood already. However, there are many problems to be solved. For instance, the catalysts decompose themselves in the presence of water, resulting in low efficiency. Moreover, the separation and recycle of catalyst, as well as high cost of methylation agent, remain to be technical barriers.

13.3.3 Heterogeneous Catalytic Systems

Heterogeneous catalysts have numerous nice properties, such as the diversity of types, not easy to deactivation, easy to separate from the product, easy recycling, and environment friendly. Therefore, the development of heterogeneous catalytic systems is preferred, which have attracted much attention nowadays.

As for direct synthesis of DMC from methanol and CO_2, heterogeneous catalysts have been widely used, mainly including metal oxide catalysts, heteropoly acid catalysts, and supported catalysts.

13.3.3.1 Metal Oxide Catalysts

As the most popular object among metal oxide catalysts, ZrO_2 showed a highly catalytic activity in direct synthesis process of DMC. Tomishige et al. [36] first reported catalytic performance of a commercial zirconium hydroxide ($ZrO_2•xH_2O$). They found the activity of catalyst seemed to be related to the acid–base pair sites of the ZrO_2 surface, resulting in a DMC yield of 1 % at 433 K and 5 MPa.

Jung et al. [37] proposed a hypothesis of the adsorption configuration of CO_2, methanol, and DMC over the surface of ZrO_2-based catalysts through Raman spectra. Besides, they made a point that the activity of ZrO_2 is closely related to its crystal structure [38]. It was observed that the formation of CH_3O–Zr species on the surface of monoclinic zirconia (m-ZrO_2) was about two times as much as on the surface of the metastable quartet crystal form (*t*-ZrO_2).

The mechanism for the reaction was clarified in Fig. 13.4 according to Ref. [39]. Methanol binds to Zr^{4+} Lewis acid sites and releases an H atom, which rapidly reacts with a surface OH group to form H_2O. Then CO_2 is inserted into the Zr–O bond of CH_3O–Zr species to produce m-CH_3OCOO–Zr. The interactions of C and O atoms in CO_2 with Lewis acid–base pairs of sites are favorable to this process. Moreover, methyl carbonate species can also be formed by the reaction of CH_3OH with CO_2 adsorbed in the form of bicarbonate species, while this process is slower than that involving the reaction of CO_2 with methoxide species. DMC is formed by transfer of a methyl group to the terminal O atom of methyl carbonate species. The effectiveness of ZrO_2 as a catalyst for the synthesis of DMC from CH_3OH and CO_2 stems from the presence of amphoteric Zr–OH hydroxyl groups and coordinately unsaturated $Zr^{4+}O^{2-}$ sites that act as Lewis acid–base pairs.

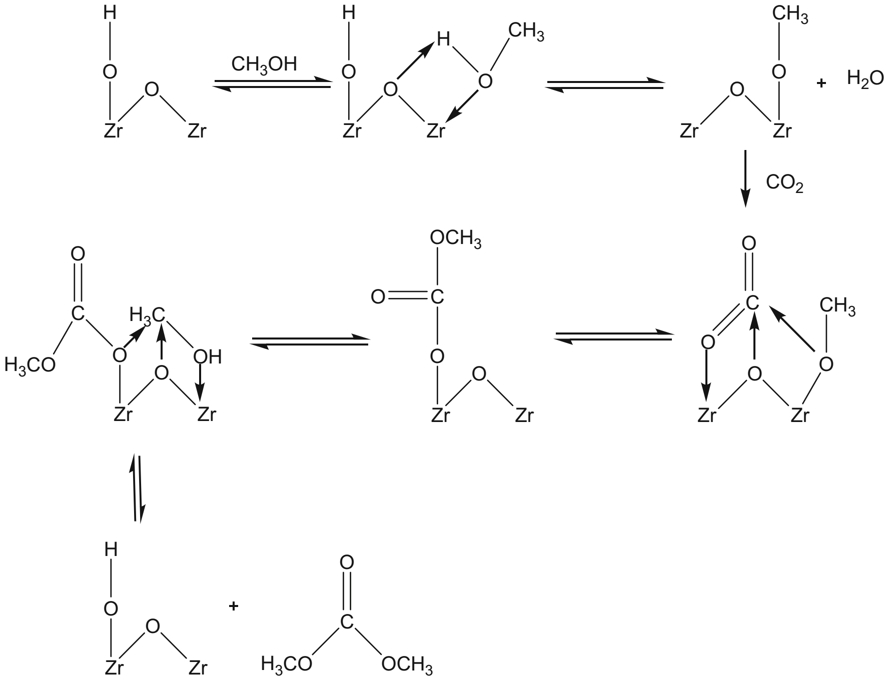


Fig. 13.4 Proposed reaction mechanism on ZrO_2 catalyst

Like ZrO_2, CeO_2 is also a favorable catalyst, showing higher activity than ZrO_2. Yoshida et al. [39] observed that the formation rate of DMC were almost proportional to the specific area above a calcination temperature of 873 K. Tomishige et al. [40] presented a DMC yield of 0.83 % when using a mixture of CeO_2/ZrO_2 at 383 K and 0.6 MPa.

Han et al. [41] obtained $Ce_{1-x}Zr_xO_2$ catalysts by the citric acid complexation method and indicated that the producing rate of DMC was closely related to the content of Zr. Based on the weak Lewis acidity and alkalinity of ZrO_2, Tomishige et al. [42] studied on the catalytic performance of $Ce_{1-x}Zr_xO_2$ with various Ce/Zr value and reached the best activity by $Ce_{0.2}Zr_{0.8}O_2$.

Surface modification of metal oxide catalysts can enhance the surface acidity and promote the reaction activity. Ikeda et al. [43] reported ZrO_2 catalyst modified by H_3PO_4. The weak Brønsted acid sites, which were formed on H_3PO_4/ZrO_2 through the interaction between Zr and P atoms, seemed to be more favorable than that on ZrO_2 for the methanol activation. As a result, the catalyst exhibited higher activity than pure ZrO_2 catalyst at all of the reaction temperatures, with the conversion rate of methanol increased up to about 4.5 %.

In our previous work, the catalytic properties of H_3PO_4-modified V_2O_5 catalysts were investigated, and the bicrystal phase was effective for the DMC synthesis from CO_2 and CH_3OH [44]. The methanol conversion and DMC selectivity increased with the P/V value increasing when H_3PO_4 content was lower (P/V$\leq$ 0.20). Both the DMC yield and selectivity reached a maximum as P/V=0.2, and then the yield and selectivity begin to decrease if the P/V value continued to increase. The direct interaction between V and P was essential to the formation of weak Brønsted acid site, which were more effective for the methanol activation than Lewis acid site on V_2O_5 for the CH_3OH activation on the acid sites.

Besides, we developed a novel synthesis of three different ceria catalysts, CeO_2, CeO_2-SiO_2, and CeO_2-4A, via template-precipitation method [45]. The catalytic results indicated that CeO_2-4A exhibited the highest DMC yield, followed by CeO_2-SiO_2 and CeO_2 catalysts. Under the reaction conditions of 0.6 MPa, 120 °C, and space velocity of 300 h^{-1}, the highest methanol conversion was 3.97 % with DMC selectivity of 81.4 %.

13.3.3.2 Heteropoly Acid Catalysts

Heteropoly acid, as a kind of oxygen bridge-containing acid complexes with Brønsted acid sites, possesses higher acid strength and better oxidation-reduction quality than ordinary inorganic acids. Thus it exhibits higher catalytic activity for direct synthesis of DMC from CO_2 and methanol.

Allaoui et al. [46] compared the catalytic performance of $H_3PMo_{12}O_{40}$ and $Cu_{1.5}PMo_{12}O_{40}$ and discussed the influence of temperature and Brønsted acid site for the catalytic process. When the proton of $H_3PMo_{12}O_{40}$ was replaced by copper ions, the overall activity decreased, while the selectivity of DMC increased slightly. This is mainly because the Brønsted acid site is not in favor of the formation of DMC. Furthermore, low temperature was more conducive to DMC production and the maximum temperature was 328 K.

However, the small surface area of heteropoly acid catalysts limited its application. Therefore, some researchers intended to design active catalyst by loading heteropoly acid on metal oxide.

As both of the acidity and basicity are essential for direct synthesis of DMC, Jiang et al. [47] obtained $H_3PW_{12}O_{40}/ZrO_2$ catalyst and found that it is more active than ZrO_2 for the reaction. This promoting effect was also observed by Kyung et al. [48] on $H_3PW_{12}O_{40}/Ce_xTi_{1-x}O_2$ (as shown in Fig. 13.5). The enhancement of $H_3PW_{12}O_{40}$ is due to the formation of weak Brønsted acid sites, which is similar to the case of H_3PO_4. Its catalytic activity showed a volcano-shaped curve with regard to cerium content, and $H_3PW_{12}O_{40}/Ce_{0.1}Ti_{0.9}O_2$ catalyst showed the best catalytic performance.

13.3.3.3 Supported Catalyst

To develop efficient catalytic systems, more efforts have been devoted to the uses of active species. Owing to the better dispersion and interaction between active species and supports, the introduction of supports can improve the activity of

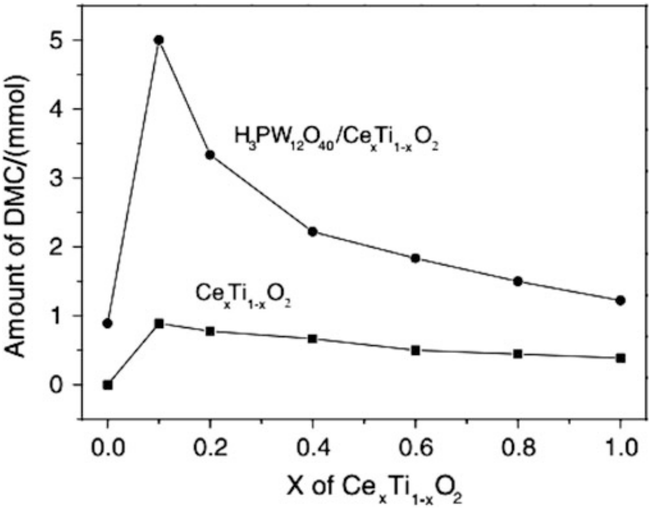


Fig. 13.5 Catalytic activities of $Ce_xTi_{1-x}O_2$ and $H_3PW_{12}O_{40}/Ce_xTi_{1-x}O_2$ at 170 °C after 12 h

catalysts, solving a series of the problems such as separation and regeneration of catalysts. However, the support used in the catalytic system is much less explored. A catalyst support is not merely a carrier, but it may also contribute significantly to the activity of catalyst, since the surface of the support may determine its interaction with the precursor of the active catalytic species. Therefore, the choice of a suitable supporting material is an important factor to be considered, and it may affect the performance of supported catalysts.

Zhong et al. investigated Cu-Ni bimetallic catalysts supported on various composites, such as ZrO_2-SiO_2 [49], V_2O_5-SiO_2 [50], and MoO_3-SiO_2 [51], all of which exhibited higher activity and selectivity to DMC than that of unsupported catalysts. As shown in Fig. 13.6, three active sites including metal site (Cu–Ni alloy, denoted M), Lewis acid site (Zr^{4+}, V^{5+}, or Mo^{6+}), and Lewis basic site (Zr-O^-, V=O, or Mo=O) exist on the surface of supported Cu–Ni bimetallic catalyst. The activation of CO_2 occurred on the metal site in cooperation with the adjacent Lewis acid sites, and methanol could be dissociated with the synergetic effect between Lewis acid site and Lewis basic site. At 140 °C, atmospheric pressure, and space velocity of 1440 h^{-1}, the selectivity to DMC is over 86 % and the total carbon conversion is 15 %.

Besides, they observed the addition of K_2O [52] and KF [53] was beneficial to improve both the conversion rate of methanol and selectivity of DMC in the Cu-Ni/ZrO_2-SiO_2 catalytic system. As a cocatalyst, the introduction of alkali metal increased the charge density of metal atoms, reduced its work function, and enhanced the ability of electron donating, which promoted the absorption of CO_2 and hindered the depth oxidation of methanol.

In the last decade, our laboratory group has carried out many researches on the direct synthesis of DMC from CO_2 and methanol, with the focus on a range of

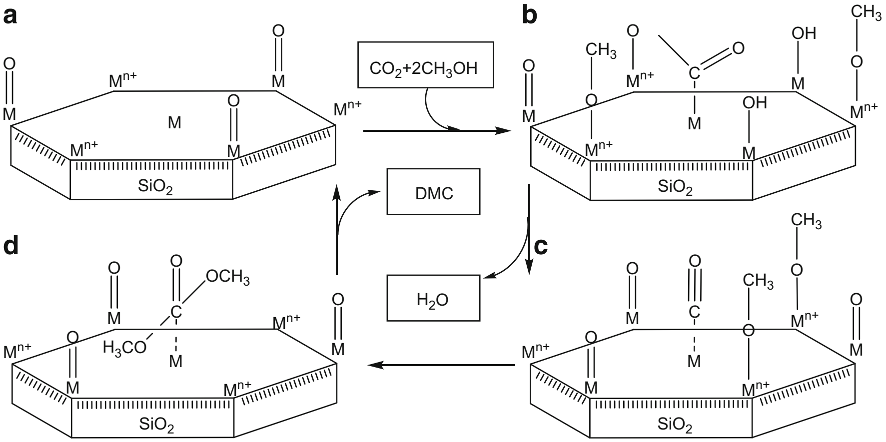


Fig. 13.6 Proposed reaction mechanism on ZrO_2 catalyst

supports. With online Raman test of the synthetic reaction process, we performed the synthesis of DMC using self-prepared Cu-Ni/VSO catalyst and proposed that the crystallinity of the catalyst showed a slight influence on the DMC synthesis and a higher crystallinity resulted in a higher yield of DMC [54].

In addition, our previous works have demonstrated that Cu–Ni bimetallic composite catalysts supported on several different carbonaceous materials (including activated carbon [55], carbon nanotubes [56], natural graphite [57], thermally expanded graphite [58], and graphite oxide [59]) were effective in direct synthesis of DMC.

With multiwalled carbon nanotubes (MWCNTs) as the support, Cu-Ni alloy could be produced partially during the calcination and activation process. Attribute to the well dispersion of metal active particles as well as the interaction between Cu-Ni and MWCNTs, the application of MWCNT support is a practical way to improve DMC yield and accelerate the activation rate of CO_2.

It was also observed that the layered structure of graphite could promote the catalytic activity of Cu–Ni bimetallic catalyst. Metal particles with an average size of 15.8 nm were uniformly dispersed on the support surface. In addition, the graphite has many characteristics such as remarkable ability of electronic transmission and high electrical conductivity, making the electron in graphite release easily and CO_2 activated. Under the optimal reaction condition of 378 K and 1.2 MPa, the highest DMC yield was higher than 9.0 %, and the selectivity of DMC was higher than 88.0 %, which could be attributed to the synergetic effects of metal Cu, Ni, and Cu–Ni alloy in the activation of CH_3OH and CO_2, the unique structure of graphite, and the interaction between the metal particles and the supports.

For Cu-Ni/TEG catalyst, thermally expanded graphite (TEG), with layered structure and multi-pores ranging from 2 to 10 nm, is conducive to the dispersion of metal atoms with the size of about 10–50 nm and centered at approximate 17 nm. Thus, there will be more active metal atoms on the catalyst surface.

Moreover, we immobilized the Cu–Ni nanoparticles in graphite oxide and the Cu–Ni/GO was obtained. As observed, the resulting bimetallic catalysts exhibited extremely high activity for one-step direct synthesis of DMC. Under the optimal catalytic reaction conditions of 105 °C and 1.2 MPa, the highest CH_3OH conversion of 10.12 % and the DMC selectivity of 90.2 % could be achieved.

Natural clays have been often employed as supporting materials because of their low cost and large specific surface area. In our recent research, the alkaline-modified halloysite nanotubes (HNTs) served as efficient and convenient carriers for Cu-Ni bimetals, and the obtained nanocomposites were applied as catalysts for direct DMC formation [60]. The effects of the metal weight loadings on the catalytic performances and surface acid–base properties were also studied. It was found that moderately acid–base balance on the catalyst surface was important for DMC yield. With 21 wt% metal oxides loaded on KHNTs, the highest methanol conversion of 7.85 % and DMC selectivity of 89.0 % could be obtained, in which the acid sites are less than the base sites.

13.3.4 Dehydrating Agents

As mentioned before, water formation leads to the deactivation of catalysts significantly. As a strategy of this issue, Sakakura et al. [61] first introduced a dehydrating agent in this reaction and achieved the formation of DMC by trimethyl orthoacetate, reaching a yield of DMC around 20 % with 93 % of selectivity, and methyl acetate was produced as a secondary product. However, orthoesters are expensive, which makes ketals much more attractive due to the low cost and the easy recycle. Then Sakakura et al. [62] carried the reaction using ketal, which is cheaper and also produces acetone that can be easily recycled into dimethyl phthalate (DMP) by reacting with methanol.

Choi et al. [63] proposed a new dehydration system using molecular sieves. They observed that using molecular sieves to remove the water could reach the same yield of DMC as adding six times more catalyst in the same conditions, which is more attractive compared with the previous reports using orthoesters or acetals as chemical-dehydrating agents since the molecular sieve is easily recyclable and there is no coproduct.

Eta et al. [64] reported a high reaction rate using butylene oxide (BO) as dehydrating agent. A methanol conversion of 10 % and DMC selectivity of 48 % was reached, producing 1,2-butylene carbonate (BC) and methoxybutanol in parallel. Cyclohexene was also used in water removal by Yang et al. [65], producing DMC and 1,2-cyclohexanediol, with 2-methoxycyclohexanol as side product.

Recently, Honda et al. [66] reported using 2-cyanopyridine as dehydrating agent for direct synthesis of DMC from CO_2 and methanol, reaching high DMC yield of around 94 % with 96 % selectivity in the presence of CeO_2. Further study showed that 2-cyanopyridine, which was produced as the hydration of 2-cyanopyridine, could be recovered by dehydration of 2-picolinamide catalyzed by Na_2O/SiO_2.

Besides, as a substitute for the use of a dehydrating agent, the development of novel technology, such as process intensification, coupling reaction, and water separation, would be a potential alternative that might enhance the DMC yield.

13.3.5 Physical–Chemical-Assisted Catalytic Process

Direct synthesis of DMC from CO_2 and methanol is limited by the reaction equilibrium, namely, the thermodynamic constraints and chemical inert of CO_2. Therefore, wide ranges of assisted approaches have been applied in this reaction, such as photo-assisted catalysis, electro-assisted catalysis, membrane separation, as well as supercritical and near-critical assistive technology.

13.3.5.1 Photo-Assisted Catalytic Systems

Due to the introduction of photo-generated carriers, direct formation of DMC can break through the reaction equilibrium limitations and enhance the yield of DMC. For the study of Kong et al. [67], both Cu/NiO-MoO_3/SiO_2 and Cu/NiO-V_2O_5/SiO_2 were active catalysts for the activation of CO_2 and methanol, and the methanol conversion of 13.9 % and high DMC selectivity of 90.1 % could be achieved. As a consequence of the introduction of Cu and NiO, the dispersion of MoO_3 (or V_2O_5) on the SiO_2 surface was improved and the absorption region to visible light was expanded. Moreover, both Cu and NiO dispersed evenly on the surface of MoO_3-SiO_2 (or V_2O_5–SiO_2).

In our previous work, the photocatalytic effect of a copper-modified (Ni, V, O) semiconductor complex catalyst on direct synthesis of DMC was investigated [68]. The results demonstrated that the ultraviolet (UV) irradiation reduced the reaction pressure to 1 atm and DMC yield increased 57 % compared with pure thermal surface catalytic reaction.

13.3.5.2 Electro-Assisted Catalytic Systems

The application of the electro-assisted catalytic system also can overcome the thermodynamic equilibrium of direct synthesis of DMC and lead to the activation of CO_2. Theoretically, direct synthesis of DMC from CO_2 and methanol can be carried on at room temperature and atmosphere pressure by regulating the electrolysis potential.

Yuan et al. [69] studied the electrochemical activation and conversion of CO_2 for the synthesis of DMC, using platinum electrodes in IL–CH_3OK–methanol electrolyte at ambient pressure and 303 K. CH_3OK resulted in a 3.9 % yield of DMC in an ionic liquid with bmimBr as a supporting electrolyte. In this electrochemically catalytic process, the methylation reagent CH_3I and any other organic additives

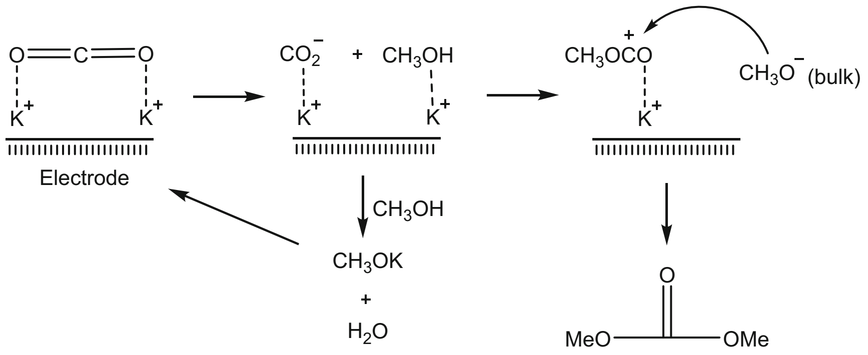


Fig. 13.7 Proposed reaction mechanism of IL-CH_3OK-methanol system

were avoided. Besides, a mechanism was proposed that is very different from those reported in the literature (Fig. 13.7).

Lu et al. [70] synthesized 1-(3-aminopropyl)-3-methylimidazolium bromide (ApmimBr) and used it as electrolyte in the electrochemical activation of CO_2 and synthesis of DMC with graphite electrode at ambient pressure and temperature. In this electrolysis, ApmimBr exhibited best performance for synthesis of DMC with 2.5 % yield and 94.5 % selectivity. This higher activity is likely ascribed to the basicity of functionalized ionic liquid in methanol.

13.3.5.3 Membrane Separation

Membrane catalytic reactor (MCR) enables continuous removal of the generated water from the reaction system, which can promote the equilibrium shift toward DMC production without changing the catalytic mechanism. Moreover, water removal restrains the hydrolysis and deactivation of the catalyst.

Li et al. [71] studied the application of MCR for DMC synthesis. As a result of water removal, the reaction conversion and selectivity was improved. However, it cannot be satisfied because of membrane reactors permeating reactants as well.

Chen et al. [72] prepared STA/CS hybrid membranes by filling silicotungstic acid hydrate (STA) into chitosan (CS) matrix. The results show that separation factor increased with STA content increasing and arrived at a maximum when the STA content is 8 %. The membrane had remarkable separation performance with a flux of 1163 g m^{-2} h^{-1} and separation factor of 67.3 at 50 °C at the feed methanol content, 10 wt.%.

13.3.5.4 Near-Critical and Supercritical Assistive Technology

Due to the extraction of the reaction products, near-critical and supercritical CO_2 reaction system can make the reaction equilibrium moving to break the limitation of the thermodynamic equilibrium and increase the mass transfer efficiency. Thus it plays a promoting effect on the conversion rate, the selectivity of the desired product, and the life of the catalyst. As a consequence, considerable research has been conducted under near-critical or supercritical conditions.

Hong et al. [73] found the maximum yield of DMC could reach 12 %, under the supercritical conditions and in the presence of K_2CO_3/CH_3I together with the dehydrating agent (DMP). Under 305 K and near-supercritical conditions, DMC was the only product, and the yield was 12 times as much as that in the non-supercritical conditions with nickel acetate as the catalyst. As mechanism proposed, the near-supercritical conditions could change the reaction pathway and shift the reaction equilibrium toward the products. The supercritical pressure, the phase composition, and the concentration of methanol could affect the yield and selectivity of DMC.

13.4 Summary

The direct synthesis of DMC from CO_2 and CH_3OH is one of the green routes to CO_2 mitigation or fixation. Besides, as an environmentally benign compound and unique intermediate with versatile chemical reactivity, DMC has been widely used in many fields. Therefore, it is an important research topic with environmentally and friendly characters.

Although much effort has been made to facilitate the technology progress, the synthesis still remains in the laboratory stage and far from the commercialization because of its poor conversions and low yields of DMC, on account of the thermodynamic stability and kinetic inertness of CO_2.

Therefore, intensive research of the catalysts and the process technologies in order to promote the reaction is anticipated. Besides, further work is necessary to solve the problems such as the separation of products and the disruption of equilibrium limitation, as well as fully understanding of the reaction mechanism at the molecular level.

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Chapter 14

Industrial Production of Dimethyl Carbonate from CO_2 in China

Mei-Yan Wang, Hai-Bo Wang, Qiang-Hao Qu, and Liang-Nian He

Abstract This chapter contains a detailed introduction to dimethyl carbonate (DMC) followed by a presentation to the manufacturing process for DMC synthesis. Particularly, we mainly introduce the recent advances on technology of two-step process for DMC production using CO_2 as green carbonyl source in China. Additionally, greener improvement on transesterification technology of cyclic carbonate with methanol is also highlight.

Keywords Carbon dioxide • Dimethyl carbonate • Manufacturing process • Transesterification

Dialkyl carbonates have attracted widespread attention during the last decades owing to their extensive applications in most aspects of daily life such as pharmaceuticals, coatings, and lithium-ion battery electrolytes. Among them, DMC is gaining momentum due to its excellent solubility, negligible toxicity, biodegradability, and low bioaccumulation. As an important organic compound and chemical intermediate with the label of "green-chemical," DMC was completed the registration of nontoxic chemicals in Europe in 1992 [1].

DMC is a colorless, transparent, and flammable liquid with a pleasant odor and a relatively mild toxicology. It can form an azeotrope with water and be fully dissolved in organic solvents (e.g., alcohol, ester, and ketone) and is noncorrosive to metal but irritating to the skin, eye, and mucous membranes (detailed physical and toxicologic properties are listed in Table 14.1) [2–4]. Additionally, due to its

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Table 14.1 Physicochemical and toxicologic properties of DMC

Properties	DMC	Acetone	Trichloroethane	Toluene
Molecular mass	90.08	58.08	133.41	92.1
Melting point/(°C)	4.6	−94.2	−32.6	−94.97
Boiling point/(°C)	90.3	56.1	74.1	110.6
Density/(g cm^{-3})	1.069	0.788	1.338	0.870
Flash point/(°C)	21.7 (open cup)	−18	na[a]	4.4
	18.3 (close cup)	(Close cup)		(Close cup)
Gasoline/water distribution coefficient	2.0	na	na	na
wt% O	53.3	27.6	0	0
Solubility in water/(g L^{-1})	139	Miscibility	Insoluble	Insoluble
Vapor pressure/torr @25 °C	56.0	53.32	99.99	36.68
Viscosity/$\times 10^{-3}$ Pa·s	0.625	0.316	0.903	0.579
Electric constant	2.6	1.01	7.12	2.2
Oral acute toxicity (rats) LD_{50} g kg^{-1}	13.8	na	9.6	7.53
Acute toxicity/LC_{50} mg L^{-1}	140 (4 h, inhalation)	na	17,000	na
Mutagenic properties	None	na	Suspected carcinogen	Suspected carcinogen
Biodegradability	>90 % (28 days)	na	na	na

[a] *na* not available

multifunctional groups including carbonyl, methyl, and ester group, DMC participates in many chemical transformations (methylation, carbonylation, methoxycarbonylation) in place of traditional toxic reagents such as phosgene, methylchloroformate, dimethyl sulfate, and so on.

Moreover, DMC finds wide applications in resin with high performance, solvent, dye intermediates, drugs, spice, and lubricating oil additives, and its application field would be further expanded with deep exploration [5–9].

14.1 DMC Applications

14.1.1 Replacement of Conventional Organic Solvents

DMC has been known as a kind of organic solvents since the 1950s. It offers various advantages in contrast to the conventional organic solvents, such as halogenated organic solvents as well as ketones, ethers, and ester acetates. As listed in Table 14.1, DMC offers a low viscosity and electric constant, high surface tensions, suitable liquid temperature range, and unique solubility property. Meanwhile, its evaporation temperature is high, but its evaporation rate is fast. So as a kind of low toxic, safe, and excellent property solvent, DMC which is spotlighted as a possible alternative to replace VOCs in recent years is used in many fields such as coating and electrochemical and pharmaceutical industries. In China, the half of DMC consumption is on coating, then on medicine which will be introduced in Sect. 14.1.4.

14.1.2 Battery Electrolytes

With the rapid development of electronic technique, more and more batteries with high properties such as lithium-ion batteries are needed. To further improve the property of lithium-ion batteries, the corresponding solvents consisting of organic carbonates have been attracted considerable industrial interest. Among various organic carbonates, propylene carbonate (PC) and ethylene carbonate (EC) allow a good dissolution of lithium salts, but their strong viscosity limits the efficiency of the lithium electrochemical cycle. In this aspect, linear alkyl carbonates such as DMC are usually introduced as cosolvents to increase the conductivity of the electrolyte because of their low viscosity as well as great solvation force toward lithium ions, which leads to diminution of the electrolyte resistance [10]. On the other hand, it has been suggested that the DMC-containing solvent system is one of the best electrolyte systems for the purpose of the formation of a passive film on the surface of the anode, which results in a good electrochemical stability and chemical stability to maintain the total performance of the lithium-ion battery [11, 12]. Generally, in the anode battery with carbon material, electrolyte solvent contains

50–90 % DMC to keep batteries with high current density and conductivity, good resistance to oxidant and reductant, as well as long-term stability.

14.1.3 Fuel Additive

At present, methyl tert-butyl ether (MTBE) is generally used as a kind of gasoline additive. As an octane enhancer, MTBE can improve the octane number of gasoline and reduce the automobile exhaust pollution [13]. However, the use of MTBE has caused serious concern about groundwater and surface water contamination. Out of this, California and other states of America have prohibited the use of MTBE [14, 15]. In Japan, the percentage composition of MTBE in premium unleaded gasoline is limited to less than 7 %. Although the use of MTBE in gasoline has not been limited in China now, with more and more importance that the government attaches to environment, it is a trend to reduce even abolish the addition of MTBE.

Since the 1980s, DMC was patented as an option to meeting oxygenate specifications on gasoline [16–19], due to its excellent blending property, outstanding oxygen content, the more appropriate gasoline/water distribution than C_1–C_3 light alcohols, and, most importantly, its environmental friendliness. On the 2002 ACS conference, the manufacturing technology of DMC as gasoline additive invented by Tianjin University got big attention, which indicates the advantage of DMC than MTBE.

In fact, to obtain the same level of oxygen content in gasoline, the amount of DMC is needed less than 4.5 times than that of MTBE, and therefore the total amount of hydrocarbon, carbon monoxide, and formaldehyde in automobile exhaust reduced. Meanwhile, DMC can also avoid the pollution of groundwater in contrast to water-soluble MTBE. Furthermore, DMC, obtained from the production process by azeotropy with CH_3OH, can be directly used as additive in the gasoline without separation as a result of none effect of the mixed CH_3OH. Therefore, DMC will become one of the most prospective gasoline additives in place of MTBE because of the simplified process and the reduced cost. Moreover, the mixture of several light alkyl carbonates involving DMC have been regarded as a better quality gasoline stock, because of a higher heating value, a lower freeze point and volatility, and slightly less mutual solubility in water.

14.1.4 Organic Synthetic Intermediate

With raising awareness of environmental problems, green and eco-friendly synthesis processes are more attractive and competitive compared with the traditional one, which is identical with the concept of green chemistry. In the past two decades, since the environmentally benign features of DMC have been readily recognized as summarized in Table 14.2, nontoxic, safety, considerable selectivity, and avoidance

Table 14.2 General properties of DMC-, DMS-, MeI-, and phosgene-based reactions

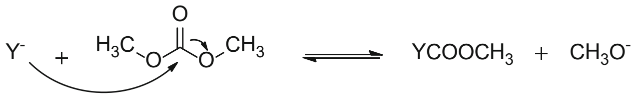
	DMC	DMS	CH_3I	Phosgene
Oral acute toxicity (LD_{50} rats/mg kg^{-1})	13,800	440	76	na[a]
Acute toxicity per contact (LD_{50} cavy/mg kg^{-1})	>2,500	na	110	na
Acute toxicity per inhalation (LC_{50} rats/mg L^{-1}, 4 h)	140	1.5	na	0.016[b]
Mutagenic properties	None	Mutagenic	Possible teratogen	na
Irritating properties (rabbits, eyes, skin)	None	Causes burns	Irritant to skin	Skin corrosion
Hazard identification	Highly flammable	Very toxic and corrosive	Very toxic	Very toxic and corrosive
Solvent	No	Yes	Yes	Yes
Waste water treatment	No	Yes	Yes	Yes
Base consumption	Catalytic amount	Equivalent NaOH	Equivalent NaOH	Two equivalent NaOH
By-products[c]	MeOH, CO_2	$NaCH_3SO_4$	NaI	NaCl
Thermodynamic	Slightly or not exothermic	Exothermic	Exothermic	Exothermic

[a] *na* not available
[b] The time is 1.25 h
[c] By-products defined for methylation processes

or minimization of solvent and derivatization sequences (Fig. 14.1), a great interest has been fuelled toward DMC as an innovative agent for substituting conventional toxic reagents such as phosgene ($COCl_2$), dimethyl sulfate (DMS), and methyl halides (CH_3X, X = I, Br, Cl) in the production of polycarbonate, isocyanate, anisole, and other chemicals [20–22].

DMC molecule possesses two active centers (methyl and carbonyl carbons), whose reactivity can be tuned with the temperature. In particular, two distinct pathways can be recognized in the reaction of DMC with a generic anionic nucleophile (Y^-) (Eqs. 14.1 and 14.2) [23, 24]. At low temperature (T = 90 °C), DMC behaves as an ester, and a methoxycarbonylation reaction takes place through a path A. At a higher temperature (T ≥120 °C), a methylation reaction occurs via the path B.

A



$$Y^- + H_3C{-}O{-}C(=O){-}O{-}CH_3 \rightleftharpoons YCOOCH_3 + CH_3O^- \qquad (14.1)$$

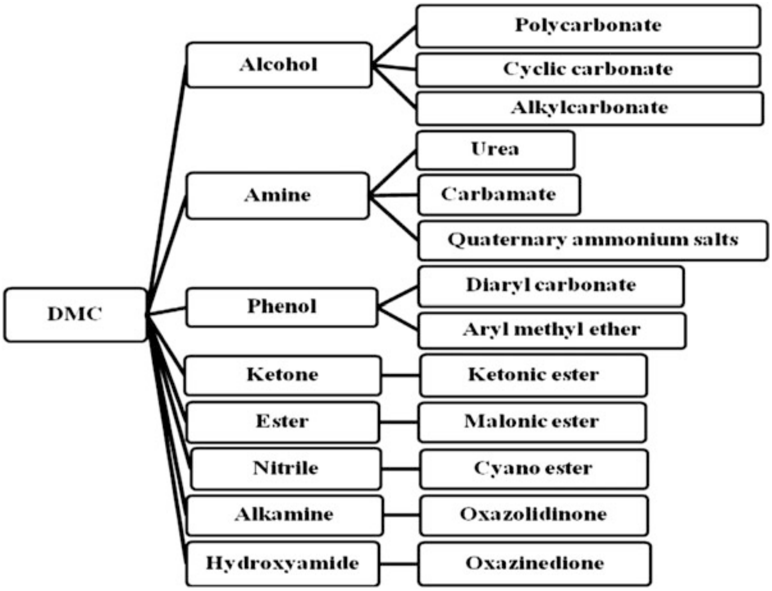
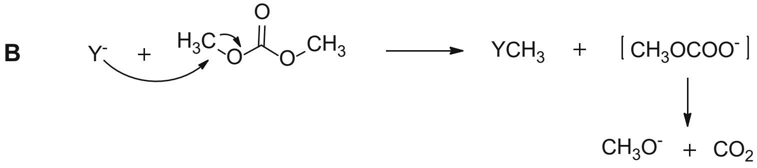
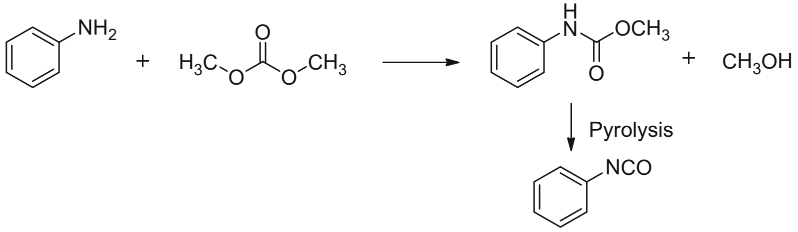


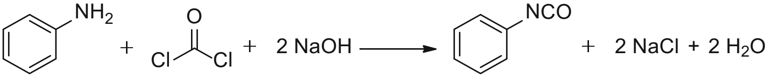
Fig. 14.1 Various chemicals produced by DMC



(14.2)



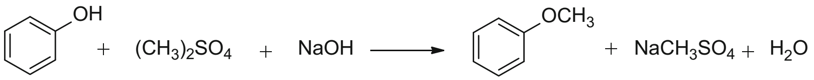
(14.3)



(14.4)

Isocyanate produced through path A has realized industrialization (Eq. 14.3). In the traditional method for isocyanate synthesis, phosgene is used as a feedstock (Eq. 14.4). In this process, not only toxic reagent is used, but also a large amount of base is needed to neutralize the by-product, hydrogen chloride. Obviously, using DMC as reactant can overcome the above disadvantages.

As a methyl agent in path B, the C atom of methyl in DMC is attacked by nuclear reagent Y^-, then the C-O bond breaks and methylate product can be obtained. Traditional methyl agents are methyl halides and DMS (Eqs. 14.5 and 14.6), which are toxic and corrosive. However, using DMC to replace both agents can avoid the usage of hazardous reactants (Eqs. 14.7 and 14.8).



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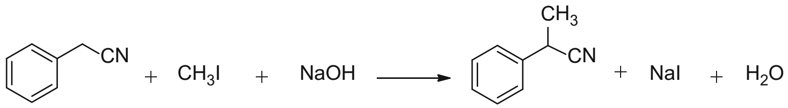
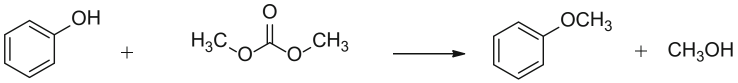


(14.6)



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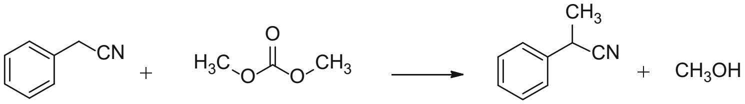


(14.8)

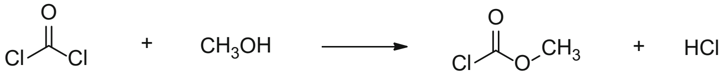
Since both methoxycarbonylation (A) and methylation (B) generate CH_3O^-, both reactions can be carried out in the presence of catalytic amounts of base, which avoids the formation of unwanted inorganic salts as by-products and the related disposal problems. In principle, the only by-products methanol produced can be recycled for the production of DMC. On the contrary, methylation with RX or DMS and carbonylation with phosgene, all generate stoichiometric amounts of inorganic salts. This dual reactivity makes DMC a versatile intermediate for the replacement of dangerous chemicals such as phosgene for carbonylation processes and DMS or methylchloride for methylation reactions.

14.2 Manufacturing Technique of DMC

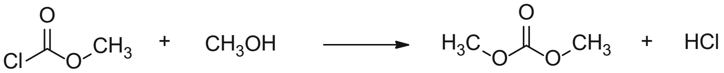
Now, the existing production methods to large-scale product DMC in China and abroad are phosgene process [25], oxidative carbonylation [26], urea alcoholysis [27, 28], and transesterification based on CO_2 [29, 30]. Factually, phosgene route has been out of the production in China as a result of high toxicity of phosgene. For oxidative carbonylation and urea alcoholysis, there are no large-scale production equipments at domestic market. At the present stage, the transesterification process based on two-step synthesis from CO_2, epoxides, and methanol has become the mainstream production technology of DMC in China, and its ratio of production capacity is about 90 % of the total. Delightedly, the urea alcoholysis scale-up experiment in laboratory has been finished in China and has entered into the design stage of industrialization. The mechanisms of the above methods are summarized as follows. We mainly introduce the industrialized transesterification process and, oxidative carbonylation and urea alcoholysis.

14.2.1 DMC Production Using Phosgene

Up to the 1980s, traditional industrial methods for DMC production were carried out via phosgene alcoholysis [31, 32]. In this process, phosgene first reacts with methanol to produce methyl chlorocarbonate. Then methyl chloroformate and methanol are fed continuously into a packed-bed reactor operating with a bottom to top temperature gradient of 72–127 °C. HCl is drawn off the head and DMC (99 %) is withdrawn from the base (Eqs. 14.9 and 14.10) [33]. Catalysis with pyridine is shown to be effective.



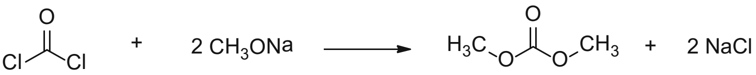
(14.9)



(14.10)

Although this is simple, there are many shortcomings such as complicated process, long operation period, toxic phosgene, enormous amount of HCl, and severe corrosiveness to the device. Despite the high yield, this route has been phased out in view of safety and environmental problems.

Replacing the methanol with sodium methoxide avoids the generation of HCl (Eq. 14.11). However, this method still uses extremely hazardous phosgene as the raw material and requires harsh conditions.



(14.11)

14.2.2 Oxidation of Methanol Carbonylation

With the global phase out of the phosgenation process, the development of phosgene-free processes for DMC synthesis has drawn great attention worldwide to both academic and industrial communities. The oxidative of methanol carbonylation to DMC uses CO, O_2, and CH_3OH as raw materials (Eq. 14.12). It is the

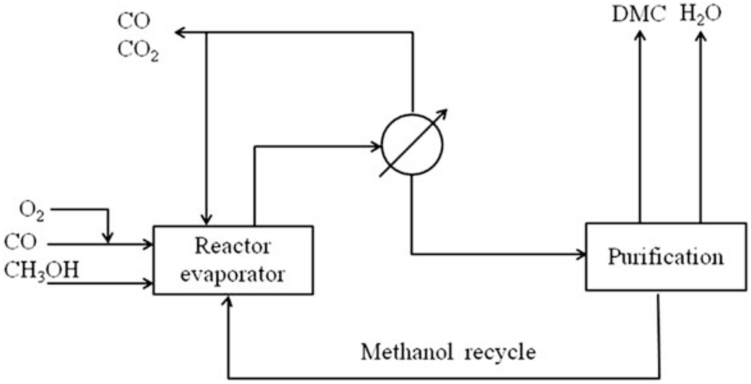
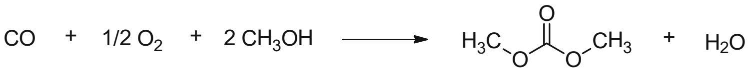


Fig. 14.2 Conceptual scheme of EniChem one-step DMC production process

most favorable route in respect of thermodynamics and relatively moderate operating conditions. Additionally, the formation of water as only by-product is considered a green benefit of the oxidative carbonylation method compared with the phosgenation approach. More importantly, the raw material and CO can be derived from coal, natural gas, shale gas, and biomass. Therefore it will be a competitive synthesis route in China with large reserves of coal and shale gas and the key factor in production is the development of industrial catalysts with not only excellent performance but also long service life. There are three mature processes based on the reaction conditions and reactants: EniChem, Dow, and UBE process.



$$CO + 1/2\,O_2 + 2\,CH_3OH \longrightarrow H_3C{-}O{-}C(=O){-}O{-}CH_3 + H_2O \qquad (14.12)$$

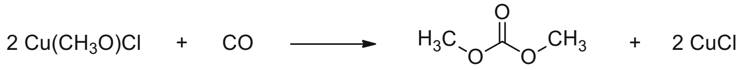
$$\Delta_r G_{298k} = -250.8\ \mathrm{kJ/mol},\ \Delta_r H_{298k} = -311.9\ \mathrm{kJ{\cdot}mol^{-1}}$$

14.2.2.1 EniChem Process

In 1983, Italy EniChem Company first achieved the DMC industrialization of liquid-phase process from CO, O_2, and alcohols under copper catalyst as depicted in Fig. 14.2. In this process, catalyst CuCl and excess methanol which acts as reactant and solvent is added into autoclave before introducing CO and O_2 and then regulated the pressure 1–3 MPa. In catalytic process, some catalytic systems such as copper, selenium, and palladium are generally used, and only CuCl catalytic system provides excellent selectivity and very good reaction rates and has been realized in the industrial production.

It has been proposed that the oxycarbonylation of methanol followed a two-step redox mechanism, through a copper methoxychloride intermediate [34]. In the first step, the CuCl is oxidized by oxygen into copper methoxychloride (Eq. 14.13). Secondly, the copper methoxychloride is reduced by CO, and the DMC is formed (Eq. 14.14). In this step, the CuCl phase is regenerated and a new catalytic cycle is initiated. In the EniChem process, the two steps (oxidation and reduction) proceed simultaneously in the same reactor. The combined reactions lead to a DMC production rate that is fairly insensitive to temperature and pressure near the optimum conditions of 100–130 °C, 2–3 MPa and 1–2 mol·L^{-1} CuCl. The reaction rate is limited by the maximum allowable safe O_2 concentration. The two-step reaction appears to be in the first order in oxygen partial pressure, actually being difficult to abstract a precise reaction order.

$$2\,CH_3OH + 1/2\,O_2 + 2\,CuCl \longrightarrow 2\,Cu(CH_3O)Cl + H_2O \tag{14.13}$$



(14.14)

The oxidative carbonylation of methanol to DMC is highly exothermic (approximately 76 kcal/mol of DMC). This is an important aspect of any process based on the oxidation chemistry. The reaction operates best at relatively modest temperatures (100–130 °C), such that there is a tremendous quantity of low-grade thermal energy that must be removed from the reactor. This contributes to very high utility costs.

Although this method is successfully applied in industrial processes, there are still several shortcomings including high reaction pressure, low single conversion of CH_3OH, strong corrosive to equipment, and short life of catalyst caused by the free chlorine detriment. Additionally, water, produced from the reaction, not only can reduce the catalytic activity but increase the amount of CO_2 by-product and the decomposing of DMC.

14.2.2.2 Dow Process

Gas-phase oxidative carbonylation of alcohols to synthesize carbonates is a promising and competitive method, which was established in 1988 by the Dow Chemical Company [35, 36]. This process initially proceeds in the presence of anhydrous copper chloride compounds ($CuCl_2$ or copper methoxychloride-based pyridine complex) supported on activated carbon (AC) mixed with co-catalysts KCl, $MgCl_2$, or $LaCl_3$ under the conditions of 100–150 °C and 2 MPa. Then the feed gases including methanol, CO, and O_2 push through the solid-bed reactor contained the above catalysts to generate DMC. The reaction mechanism is shown as follows (Eqs. 14.15, 14.16, 14.17 and 14.18):

$$CuCl_2 + 2\,CH_3OH(g) \longrightarrow Cu(CH_3O)Cl + CH_3Cl + H_2O \tag{14.15}$$

$$Cu(CH_3O)Cl + CO \longrightarrow Cu(COOCH_3)Cl \tag{14.16}$$

$$Cu(OCH_3)Cl + Cu(COOCH_3)Cl \longrightarrow H_3C{-}O{-}C({=}O){-}O{-}CH_3 + 2\,CuCl \tag{14.17}$$

$$2\,CuCl + 1/2\,O_2 + 2\,CH_3OH \longrightarrow 2\,Cu(CH_3O)Cl + H_2O \tag{14.18}$$

Chlorine element plays a crucial role in the process and the leaching of Cl^- shortens the life of catalyst. In addition, the selectivity and yield are relatively low. To solve the above problems, many catalytic systems have been investigated and patented. The most valuable ones are Wacker-type catalysts ($CuCl_2$-$PdCl_2$ bimetallic catalysts) and zeolite-based Cu(I) catalysts. However, the key barriers have not been settled. Because drawbacks like low activity of the catalyst and usage of toxic CO still exist, there are no large-scale applications in industry at present.

14.2.2.3 UBE Process

In 1992, UBE developed a DMC synthesis process via the CO and methyl nitrite (MN) over a Pd/C catalyst [37]. Figure 14.3 and Scheme 14.1 show the simplified schematic view of the UBE process, according to a two-step DMC synthesis [8]. The first step involves MN synthesis starting from nitrogen monoxide, methanol, and oxygen (Eq. 14.19). This reaction is generally performed in the liquid phase at 60 °C without any catalyst and with usual contact times ranging from 0.5 to 2 s. There are two consecutive oxidative reactions, such as that of nitrogen monoxide by oxygen into N_2O_3 and that of methanol by N_2O_3 into the final methylnitrite product. At this stage, it is necessary to remove the water in order

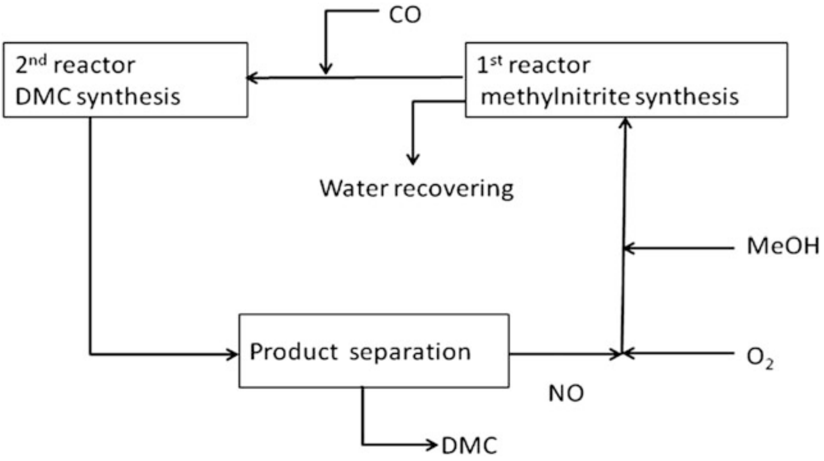
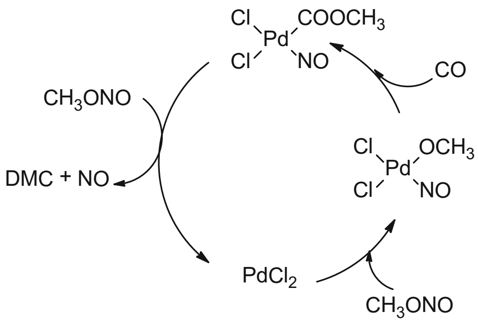


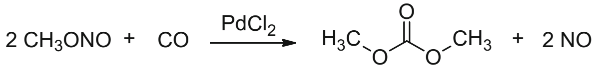
Fig. 14.3 UBE process: DMC synthesis



Scheme 14.1 Catalytic cycle during DMC synthesis by methylnitrite carbonylation

to perform DMC synthesis in a fully anhydrous media and maintain catalyst activity. The second step is the vapor phase catalytic reaction between methylnitrite and carbon monoxide (Eq. 14.20).

$$NO + 1/2\,O_2 + 2\,CH_3OH \longrightarrow 2\,CH_3ONO + H_2O \tag{14.19}$$



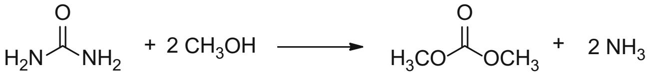
$$2\,CH_3ONO + CO \xrightarrow{PdCl_2} H_3C{-}O{-}C(=O){-}O{-}CH_3 + 2\,NO \tag{14.20}$$

In this route, MN is used as oxidative agent instead of oxygen for reducing the risk of explosion, which is considered as a potential safety problem in direct oxycarbonylation due to the coexistence of CO and O_2. Furthermore, the synthesis of DMC is not accompanied by the formation of H_2O, eliminating the negative effect on catalysts such as the loss of Cl^-. The process also avoids the appearance of ternary azeotrope (CH_3OH–H_2O–DMC), which renders products separation much easier. However, it is also noteworthy that both NO_x and RONO are toxic and corrosive, which could be against the principles of “green chemistry,” and there also are a certain amount of dimethyl oxalate and other by-products.

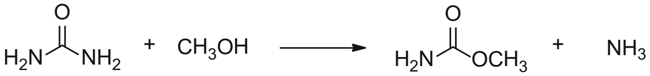
14.2.3 Urea Alcoholysis

As urea production is one of the most mature technologies for CO_2 capture and utilization at present, DMC synthesis from methanol and urea by urea alcoholysis (Eq. 14.21) is an indirect transformation of CO_2. If the liberated ammonia (the sole byproduct) is recycled for the urea production, only CO_2 and alcohols are therefore consumed. Moreover, this method has several extra advantages, such as low-cost raw materials, facile separation and purification, mild reaction conditions, and safe operations. Hence, the process could be sustainable and environmentally friendly. Heitz and coworkers first reported DMC synthesis by alcoholysis of urea in 1980 [38]. However, the reaction is not thermodynamically favorable. Actually, this synthesis is performed in two steps via the methyl-carbamate intermediate

(Eqs. 14.22 and 14.23). The first step proceeds in relatively mild condition (100 °C). Further, the methylcarbamate reacts with methanol to form DMC between 180 and 190 °C. According to the analysis by Amoco, only the LHSV (liquid hourly space velocity) over 0.8 is economically feasible, but 0.02 is the best result to date [8]. Therefore, the method still remains in the stage of lab research, despite the processing shows many advantages.


(14.21)

$$\Delta_r G_{298k} = -12.60\ \mathrm{kJ \cdot mol^{-1}}, \Delta_r H_{298k} = 47.26\ \mathrm{kJ \cdot mol^{-1}}$$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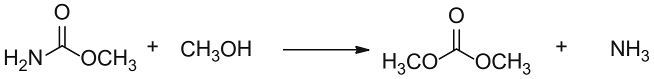
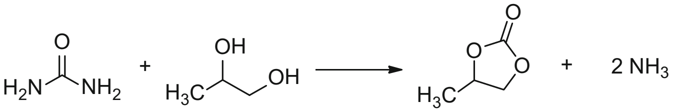

(14.23)

To overcome the barriers in one-step direct urea alcoholysis, the route of two-step alcoholysis has been studied since 1990s and considered a clean DMC process [39]. Xin-Liang Xu et al. have achieved the pilot-scale study in hundreds of tonnes for the synthesis of PC in 99.6 % purity from urea and propylene glycol (PG), which provides indirect synthesis of DMC industrialization in China. This strategy contains two steps, which is in fact a transesterification process. Firstly, urea reacts with PG to produce PC and ammonia (Eq. 14.24). Then, PC reacts with CH_3OH by transesterification to produce PG and DMC (Eq. 14.25). At present, many institutes and enterprises in our country have finished the enlarging production, and industrial apparatus are in the design.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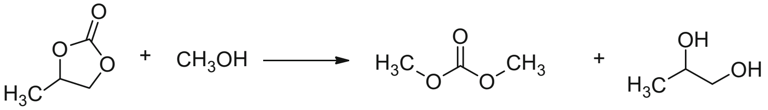

(14.25)

The indirect urea alcoholysis, using available and cheap raw materials with the avoidance of hazardous material, meets the development requirements of clean and "zero emission" technology. What is more, the separation issue can be simplified because of none water formation with economic benefits. Also, it is attractive to explore the downstream products of chemical fertilizer. It is anticipated that the commercialization of DMC production via alcoholysis urea will be realized in the coming years.

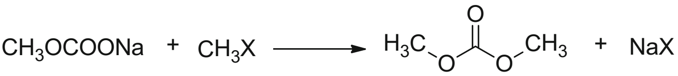
14.2.4 DMC Synthesis from CO_2

CO_2 is considered to be the main greenhouse gas in the aerosphere mainly released from human life and production process. Therefore, CO_2 fixation and conversion hold great promise for recycling CO_2 into value-added products due to the great potential of CO_2 as an abundant, nontoxic, easily accessible, and sustainable C_1 feedstock [40, 41]. The synthesis of DMC using CO_2 as C_1 synthon is a very interesting and significant topic from chemical industry, energy, and environmental protection. In general, there are four main synthetic routes to DMC from CO_2: (1) methylation; (2) direct carbonylation of alcohols; (3) urea alcoholysis, which has already been described in the above; and (4) transesterification of cyclic carbonates with methanol, in which cyclic carbonates are synthesized from epoxides and CO_2 [42, 43].

14.2.4.1 Methylation Method

In 1972, Frevel proposed the methylation route for the synthesis of DMC from CO_2. In this method, sodium methoxide reacts with CO_2 to produce sodium methyl carbonate which then carries on reacting with methyl halide to afford DMC (Eqs. 14.26 and 14.27). But this method stays the stage of laboratory investigation without further development, because large amounts of methyl halide with serious environmental pollution are used.

$$CH_3ONa \quad + \quad CO_2 \longrightarrow CH_3OCOONa \tag{14.26}$$

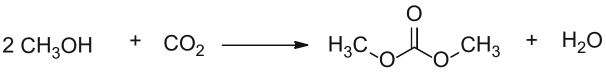


$$CH_3OCOONa + CH_3X \longrightarrow H_3C{-}O{-}C({=}O){-}O{-}CH_3 + NaX \tag{14.27}$$

14.2.4.2 Direct Carbonylation of Alcohols

It should be noted that although DMC is a "green" solvent, this does not hold for its synthesis. The industrial routes to DMC mainly use interesterification method, while cyclic carbonates are synthesized from propylene oxide which is classified as toxic chemical. Therefore, a great deal of research has focused on direct synthesis using alcohols.

This direct synthesis enters in the strategy of using CO_2 as carbon resource targeting simultaneously the environment protection and efficient synthesis chemistry, is usually labeled also as CO_2 valorization. Direct synthesis of DMC by reaction between CO_2 and methanol has been studied since the 1980s (Eq. 14.28) [44].



$$2\,CH_3OH + CO_2 \longrightarrow H_3C{-}O{-}C({=}O){-}O{-}CH_3 + H_2O \tag{14.28}$$

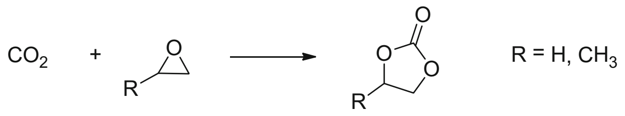
It is one most attractive and challengeable route to feature with many advantages such as simple process, low cost, no issue of “explosive limits,” almost 100 % selectivity and “zero emission,” and beneficial to relieve the carbon crisis. Many studies on the exploring of various catalysts and novel routes have been carried out to promote the reaction. However, most processes still limit to the stage of laboratory study as a result of the thermodynamic stability and kinetic inertness of CO_2 molecule and to the detrimental decomposition of the catalysts and hydrolysis of the carbonate. Further exploration on the green and economic route is carrying on with prospective for industrialization.

14.2.4.3 Transesterification Route

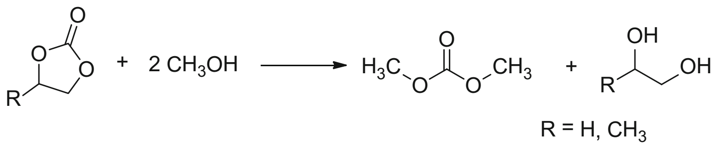
Texaco is the first to exploit the transesterification technology through two-step procedure from ethylene epoxide (EO), CO_2 and methanol with production of ethylene glycol (EG) [45]. In 1992, the technology was applied in industrial with low yield and high cost [46].

The transesterification process is composed of two steps: the reaction of epoxides with CO_2 affords cyclic carbonates first under high temperature and pressure conditions and efficient catalysts [47, 48], e.g., quaternary ammonium salts or alkali halides (Eq. 14.29), and then, cyclic carbonate (e.g., EC, PC) reacts with methanol by transesterification to produce DMC (Eq. 14.30). Various acid and base catalysts have been reported to be effective for transesterification step [49, 50].

EG or PG can be synthesized concomitantly, which enhances the economic efficiency of this route. It is by far the most mature alternative for the synthesis of DMC that have been commercialized. However, major disadvantages of this process are high energy consumption due to the requirement of separation of the intermediate, i.e., cyclic carbonate, and high investment and production costs for epoxides represents a constraint and cost driver in production of the carbonates. In another word, this two-step manipulation is one of the main drawbacks of this process.



(14.29)



(14.30)

To eliminate the separation process of cyclic carbonate in the two-step manufacture, it is very desirable to integrate the cycloaddition of CO_2 with epoxide and the transesterification of cyclic carbonate with methanol into one-pot process. Many efforts have been attempt, but it is still in lab stage [50–52].

14.2.5 Main DMC Synthetic Technologies in China

Recently, DMC synthesis mainly relies on two-step process with CO_2 as C_1 feedstock with the production of PG by-product in China. The total production capacity is about 600,000 tons (0.545 Mt) per year and 50,000 tons (0.0455 Mkg) per year per se. However, the problems in industry become more and more serious with the increase in DMC productivity. For instance, (a) cost of PO is widely fluctuated, (b) requirement for PG cannot match DMC productivity growing, (c) exploration on the downstream market lags behind, and (d) there is increasingly fierce market competition among enterprises.

There are two routes to DMC production in China: urea alcoholysis and two-step process including cycloaddition and transesterification from EO/PO, methanol, and CO_2. Indirect urea alcoholysis avoids the unstable factor of PO price profiting from the stable market of urea and ammonia and supplying PG as coproduct. At present, enlarging production and industrial apparatus design have been achieved. It is mature for transesterification method from EO and methanol.

The indirect urea alcoholysis method requires further industrial trial. Although it is limited to the stage of laboratory study, direct synthesis of DMC from methanol and CO_2 is explored for the hardest as a result of its prospective for industrialization.

14.3 Two-Step Process for DMC Synthesis from CO_2 and PO

In recent years, DMC synthesis from CO_2 and PO gains rapid development in China. The strategy includes two steps: the first one is the synthesis of PC from CO_2 and PO, which gains a high conversion and selectivity, and both could be close to 100 % under moderate conditions [53], and the second is the production of DMC from PC and methanol through interesterification step which is reversible. Therefore, the key point of this route is how to improve the conversion of cyclic carbonates in the second step. To achieve a total conversion of PC, the reactive distillation device is used to remove the azeotrope of DMC and methanol constantly.

14.3.1 The First Step: Synthesis of PC

The reaction of CO_2 and PO is carried out in a tubular reactor with release of heat which is moved out of the system by material circulation in the process. PO and catalyst (generally Bu_4NBr or KI) are introduced into the reactor from the top part and then meet with CO_2 entering in the lower part to afford crude PC. Then pure PC

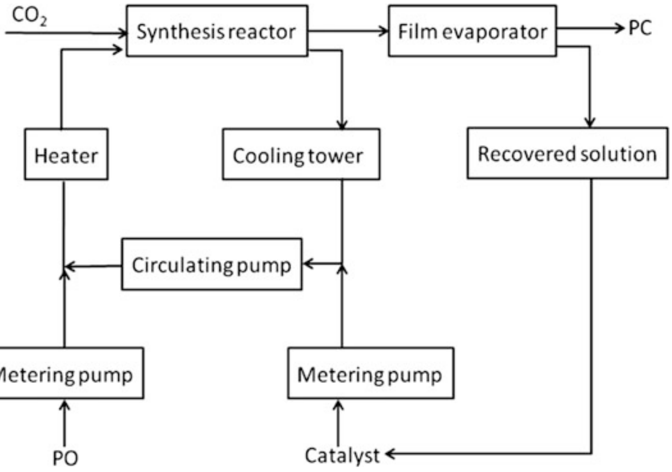


Fig. 14.4 Block diagram of PC process

is obtained from the crude product by distillation through film evaporator. The catalyst in the heavy constituent can be recycled into the reactor. The engineering flow diagram is as follows (Fig. 14.4):

14.3.2 The Second Step: Synthesis of DMC

PC, methanol, and catalyst in appropriate proportion are mixed and introduced into the distillation column in the upper part. Subsequently, the reaction takes place to produce DMC and PG in the stripping section. The azeotrope from DMC and methanol is rectified from the top of tower to shift the equilibrium to the right, resulting in total conversion of PC.

Furthermore, the composition of the azeotrope is changed after the distillation in the appropriate pressure. DMC concentration will reduce with the increase of pressure, and methanol is separated by pressurized distillation, and then crude DMC and methanol are further purified by atmospheric distillation, respectively. The catalyst is recycled after separated by hydrolysis and carbonization treatment from the mixture of PG out of the bottom of the tower.

The technology diagram of transesterification is illuminated in Fig. 14.5. This process can be divided into several parts including reaction distillation section, separation system of the azeotrope, recycle system of methanol, hydrolysis, carbonization and filtration, DMC distillation, PG distillation, and CH_3OH-H_2O separation.

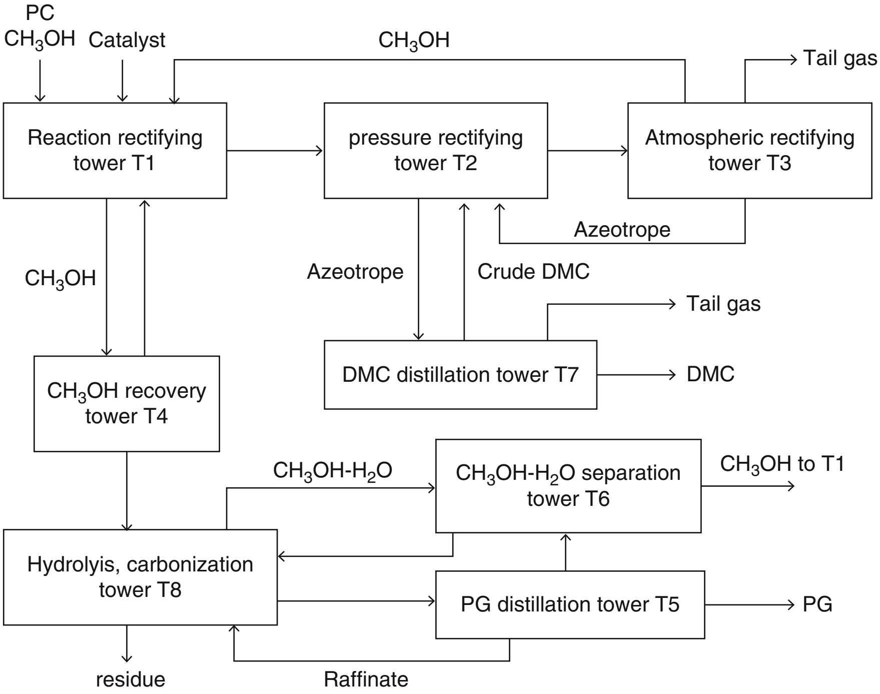


Fig. 14.5 Block diagram of PC process

14.3.2.1 Reaction Distillation Section

Reaction distillation is a separation process combining chemical reaction with physical distillation simultaneously which obeys the dynamic and distillation law. The goal is to improve the reaction and distillation procedure due to obvious effect between reaction and distillation. There are several paramount advantages of distillation: (a) DMC is distilled once a generation, thus breaking the reaction equilibrium and improving the conversion, and (b) the reaction rate can be enhanced through keeping higher concentration of reaction materials than products by removing the product timely.

In this technology, the mixture of PC, methanol, and catalyst is introduced into the top of T1 and then completes the reaction distillation. The azeotrope of DMC and methanol formed in the above process is distilled off from the top of distillation tower, which allows the equivalent shift to right constantly. A negative pressure (−5 to 15 KPa, 54–58 °C) is performed before the azeotrope left the T1 in order to increase the DMC content of azeotrope (up to 32–37 %). Meanwhile, the PG by-product and excess CH_3OH leave from the bottom of the tower and enter into the methanol recovery device, where most of the methanol is recycled through simple distillation to return into the reaction distillation tower and the rest of methanol mixed with PG is transferred into hydrolysis, carbonization, and filtration device.

14.3.2.2 Azeotrope Separation and DMC Distillation Device

There are two methods for the separation of the azeotrope including extraction distillation and variation of pressure distillation, and the latter method is generally used in China.

According to the variable boiling point in different pressure, the azeotrope of DMC and ME is separated in the variation of pressure distillation. The higher the pressure uses, the azeotrope that contained lower content DMC is gained. So the azeotrope from atmospheric pressure can be divided into two sections: one is the pressurized azeotrope that contained superfluous CH_3OH and the other is the crude DMC product. The former enters into the normal pressure distillation tower and the latter is further purified by redistillation in the DMC distillation system to obtain pure DMC.

14.3.2.3 Hydrolysis, Carbonization, and Filtration Device

In fact, PG will be decomposed in the rectification due to the strong basicity of sodium methoxide catalyst in the transesterification. After adding the H_2O and CO_2, sodium methoxide is converted into sodium carbonate as precipitation. Subsequently, sodium carbonate is filtered, and the yield and quality of the PG are also improved. To avoid the decomposition of PG in strong basic condition, sodium methoxide catalyst that fell from the reaction tower must be disposed. In this process, H_2O and CO_2 are added to neutralize the sodium methoxide; then Na_2CO_3 is separated out, and relatively pure PG is input in the PG distillation tower for further purification by distillation to get the commercial PG. The azeotrope of CH_3OH-H_2O is separated and recycled in the CH_3OH-H_2O separation column. Then, methanol is transported to the reaction rectifying column, and water is recycled into hydrolysis, carbonization, and filtration system.

14.4 Improvement of DMC Synthesis by Transesterification

Currently, the two-step transesterification route from PO and CO_2 is still the main technology for DMC synthesis in China. But this two-step manipulation is one of the main drawbacks of this process. To solve the above problem, Tangshan Haoyu Science and Technology Development co., Ltd, who is specialized in the DMC development and manufacturing, has optimized the DMC process according to practice experiences in production process [54, 55].

14.4.1 Energy-Saving Optimization

The major energy consumption in DMC production is in the distillation (rectification) separation process. The cost of energy consumption is 7–14 % comparing with the total proportion. Therefore, energy-saving is significant for the survival and sustainable development of DMC enterprises for it can effectively save resource, reduce environmental pollution, and cut the cost.

Integrated heat transfer system recycles the partial latent and sensible heat released in the interflow of materials to reduce the energy consumption by rational allocation process and grading or comprehensive energy utilization [55]. In the production process of DMC, heat level is different in every tower, taking integrated thermal coupling as an example: 120–130 °C in the top of the pressurized rectification tower, 80 °C in the reaction rectification column, and 65 °C in the atmospheric rectification column. The reaction rectification column and atmospheric rectification column are heated by the material output from the top of the pressurized rectifying column which both make the best of the energy and reduce energy consumption significantly.

14.4.2 Separation Optimization

Currently, the azeotrope of DMC and ME output from the reaction rectifying tower after decompression rectification is separated through dual-tower equipment instead of traditional three-tower equipment. (For the detailed process, see Sects. 14.3.2.1 and 14.3.2.2 [56–58].) By optimization, the device efficiency improves and the total capital investment as well as energy consumption can be reduced.

14.4.3 Productivity Optimization

Metal tube filter is used in the traditional hydrolysis, carbonization, and filtration system, but it is apt to be broken with high cost. Additionally, when the filtrate goes through the surface of the filter tube and filter cone, partial residue adheres to the strainer and mostly precipitates at the bottom. After filtration is completed, the thick residue takes a long time to be dried, and the metal tube filter requires the residue to be cleared away using water.

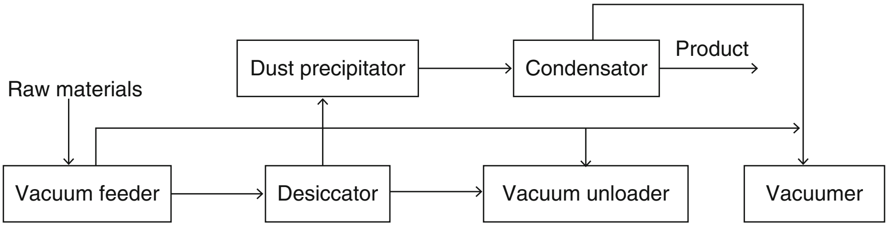


Fig. 14.6 Residue drying technological process

Compared with the metal tube filter, the plate-and-frame-type filter has many apparent superiorities in DMC production [59, 60]. First of all, it has the advantage of less investments. In addition, the filter is more durable and the running costs are much lower. Furthermore, the residue is filtrated by the filtration fabric and distributed among the filter plate in a few centimeter thick. After filtration is finished, the residue is dried by extrusion or blow. Last but not the least, moisture content in residue is cut by 20 % compared with metal tube filter. As a result, the amount of recycled materials is greatly enhanced. Every year, approximately 418.5 tons (380 t) PG is extra-recycled in the device of 30,000 tons (0.027 Mt) per year.

Moisture content in residue is about 35 % after filtration by the plate-and-frame-type filter. Additionally, the left materials in the residue are recovered again by using the residue drying device and the technological process as follows (Fig. 14.6).

Material is introduced into the vacuum feeder and subsequently dried in the desiccator. Then, the liquid materials coming from the top of desiccator enter into the dust precipitator to get rid of the solid dust. The recycled product is obtained after condensation in the condensator. Meanwhile, solid materials continuously pass through the desiccator and vacuum feeder, and then the residue is discharged. Noteworthy, the whole technology is performed in vacuo and the yield of PG was increased by residue drying process.

14.5 Prospective Outlook

DMC industry has got great development since the first transesterification equipment was built in China by Tangshan Chaoyang Chemical Company Limited (the former name is Tangshan Chaoyang Chemical General Factory) in 1996. The actual consumption of DMC in China was about 120,000 tons (0.109 Mt) and exported was about 30,000 tons (0.0272 Mt) in 2008. About half of it is used for the production of coatings and adhesives; and the most of rest is used to produce pesticides and medicines. In the production of coatings, DMC is mainly used to replace solvents like toluene, ethyl acetate, butyl acetate, acetone, or methyl ethyl ketone. In the pharmaceutical industry, DMC is used as a methylation agent to replace dimethyl sulfate. Up to 2014, the total production capacity has been more than 635,000 tons (0.577 Mt) per year, and the production capacity per set increased to 50,000 tons (0.0454 Mt) per year from 300 tons in preliminary stage. What is more, a batch of equipment with 190,000 tons (0.173 Mt) production capacity are under construction and another batch of equipment with 620,000 tons (0.563 Mt) capacity is also planned.

At present, there are two phosgene-free routes for DMC production. One is the oxidative carbonylation of methanol, which is based on the oxidation of carbon monoxide with oxygen in methanol with copper chloride as the catalyst. Another is the two-step process from PO and CO_2, which is the main technology for DMC synthesis in China and whose production capacity is over 90 % of the total. As a result, its development is limited greatly by the price of PO fluctuation, the PG market, and the development lag of downstream product.

To break through the bottleneck, two ways are feasible. One is to reduce the production cost. Improving the existing transesterification process by importing two-step urea alcoholysis method is viable, which avoid the influence of PO price and PG market. In addition, the route to synthesize DMC from methanol and CO_2 is also one clean and promising method. Once the bottleneck of low conversion is broken through, the route will be prospective for industrialization. Another way is to explore the downstream product market. Further exploration on application of DMC in solvent substitute, gasoline additives, synthetic reactant, and so on could extend DMC market.

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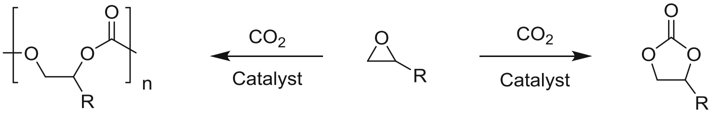
Chapter 15
Halide-Free Synthesis of Cyclic and Polycarbonates

Ian D.V. Ingram, Michael North, and Xiao Wu

Abstract



The 100 % atom-economical reaction between epoxides and carbon dioxide to give either cyclic carbonates or polymers is extremely attractive as part of the process of establishing more sustainable material and chemical industries in the future. Cyclic carbonates are already recognised as non-toxic polar aprotic solvents and chemical intermediates and are widely used as electrolytes for lithium-ion batteries. Polycarbonates prepared via this route have a great deal of potential, both as replacements for conventional polycarbonates and as polyols for the production of polyurethanes. Here, we highlight some of the more sustainable catalytic systems for each reaction, focusing on those with good activity which do not require the use of halides.

Keywords Cyclic carbonate • CO_2 utilisation • Polycarbonate • Halide free • Sustainable catalysis • Epoxide • Polymerisation

15.1 Introduction

Cyclic carbonates **1** and aromatic polycarbonates **2** are both commercial products which traditionally were prepared using phosgene as shown in Scheme 15.1. Cyclic carbonates have numerous applications including as electrolytes in lithium-ion batteries, as polar aprotic solvents and as chemical intermediates in organic synthesis [1, 2]. Aromatic polycarbonates are widely used, due to their mechanical

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P. Tundo et al. (eds.), *Chemistry Beyond Chlorine*,
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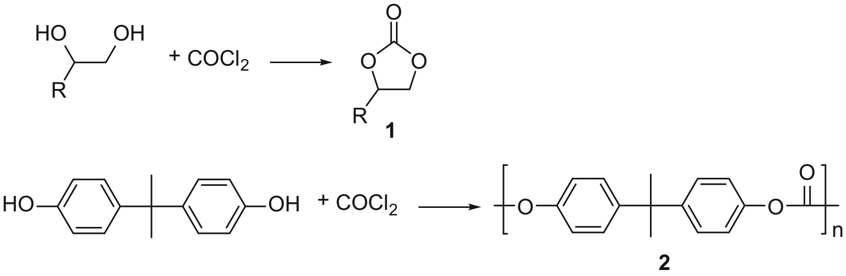
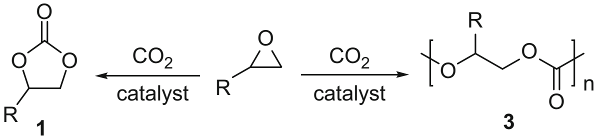


Scheme 15.1 Conventional routes to cyclic and polycarbonates using toxic phosgene

Scheme 15.2 Reaction of epoxides with carbon dioxide to give cyclic or polycarbonates



toughness and optical transparency, for applications such as DVD and blu-ray discs [3] and optical components such as safety glasses and bullet-resistant “glass” [4].

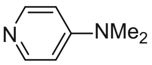
More recently, an alternative route to cyclic and polycarbonates has been developed which involved the reaction of epoxides with carbon dioxide (Scheme 15.2). Depending on the catalyst and reaction conditions, this reaction can be controlled to give either cyclic carbonates **1** or aliphatic polycarbonates **3**. Aliphatic polycarbonates are currently being commercialised as replacements for aromatic polycarbonates. Numerous catalyst systems have been developed for both reactions, and the area has recently been extensively reviewed [5–10].

The vast majority of the catalyst systems developed for the chemistry shown in Scheme 15.2 are themselves halide based, typically metal halide salts, quaternary ammonium halides or quaternary phosphonium halides. Whilst the use of catalytic halide is undoubtedly an improvement on stoichiometric amounts of phosgene, it would be desirable from a life cycle perspective to eliminate the need for halides all together. This chapter highlights the halide-free catalysts that have been developed for the synthesis of cyclic and aliphatic polycarbonates. It should be noted that in some cases, a full life cycle analysis might show that halogen-containing chemicals were required as part of the synthesis of the catalyst, but such an analysis is beyond the scope of the chapter except where the halide is an immediate catalyst precursor. Rather, the intention is to illustrate that halide-free cyclic and polycarbonate synthesis is possible.

15.2 Cyclic Carbonates

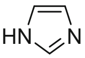
15.2.1 Organocatalysis of Cyclic Carbonate Synthesis

Nitrogen-containing organic bases have been widely used as simple but effective catalysts for the reaction of epoxides and carbon dioxide to produce cyclic carbonates. 4-Dimethylaminopyridine (DMAP) **4** is one of the most studied organic bases for this reaction. Shi and co-workers reported the dual catalytic activity of *p*-methoxyphenol and DMAP for the synthesis of propylene carbonate (**1:** R = Me) from propylene oxide [11, 12]. Generally, the reactions were carried out at 120 °C under 3.57 MPa carbon dioxide pressure for 48 h. DMAP, and an immobilised derivative was also found to be efficient homogeneous [13, 14] and heterogeneous [14] catalysts for the formation of cyclic carbonates from epoxides in the absence of phenols, though higher carbon dioxide pressures were required. At 120 °C and 17.2 MPa carbon dioxide pressure, 85 % conversion of propylene oxide to propylene carbonate was obtained after 4 h. Furthermore, the heterogeneous catalyst exhibits comparable catalytic activity to DMAP, although recyclability has not been extensively investigated. The mechanism of the DMAP-catalysed reaction between epoxides and carbon dioxide has not been elucidated, though it is generally assumed that the reaction is promoted by nucleophilic attack of DMAP to the epoxide with subsequent insertion of carbon dioxide into the resulting alkoxide and ring closure. The role of the *p*-methoxyphenol is then postulated to be that of a hydrogen bond donor (HBD), hydrogen bonding to the epoxide and thus activating it towards ring opening by DMAP.



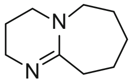
4

4-dimethylaminopyridine
DMAP p*K*a = 9.2

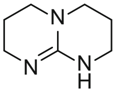


imidazole
p*K*a = 7.0

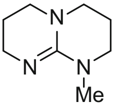
Following on from their early work, Manikandan and co-workers developed an imidazole-based heterogeneous catalyst [15], which exhibits a similar reactivity and selectivity to the DMAP-based heterogeneous catalyst. Organic super bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) **5**, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) **6** and *N*-methyl TBD (MTBD) **7** have also been reported as efficient catalysts for the formation of cyclic carbonates from epoxides and carbon dioxide. For example, Sartori and co-workers described the use of both homogeneous MTBD and heterogeneous TBD in the reaction of epoxides with carbon dioxide [16]. Using 4 mol% of MTBD at 140 °C and 5 MPa carbon dioxide, 98 % conversion of styrene oxide to styrene carbonate (**1:** R = Ph) was achieved after 20 h. As expected, the catalytic activity of heterogeneous catalyst MCM-41-TBD was lower (65 %) than that obtained in the reaction carried out with the homogeneous MTBD. Since the Lewis basicity of DMAP and organic super bases **5–7** are very different, their catalytic roles in the formation of cyclic carbonates from epoxides and carbon dioxide are also thought to be different. It is hypothesised that the catalytic activity of **5–7** is through the direct activation of carbon dioxide. A stable organic super base-carbon dioxide adduct has been isolated and fully characterised [17], thereby providing experimental evidence for the direct interaction of this class of compounds with carbon dioxide.



1,8-diazabicyclo[5.4.0]undec-7-ene
DBU p*K*a = 24.3 in MeCN
5



1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBD p*K*a = 25.9 in MeCN
6

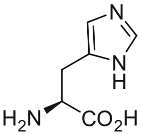


7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
MTBD p*K*a = 25.5 in MeCN
7

Other work on immobilised TBD catalysts has also been reported. Whilst the reaction conditions are similar, using TBD on SiO_2 as a heterogeneous catalyst, both selectivity (99.8 %) and conversions (84–99.5 %) showed significantly higher performance than the MCM-41 system (above) for the synthesis of propylene carbonate from propylene oxide [18]. In order to understand the role of the hydroxyl groups on the surface of the support, they were masked with methyl groups, and the conversion dropped sharply to 0.2 %. This suggested that the SiOH groups were again acting as HBDs towards the epoxide, whilst nucleophilic attack of TBD on the carbon dioxide generates a good nucleophile to ring-open the activated epoxide.

Recently, Zhang and co-workers demonstrated the effectiveness of DBU and cellulose, employed as HBD, in the reaction of epoxides with carbon dioxide [19]. When the reaction was carried out at 120 °C and 2 MPa carbon dioxide pressure for 2 h, 93 % conversion and 99 % selectivity to propylene carbonate from propylene oxide were achieved in the presence of both DBU and cellulose, whilst 80 % conversion and 99 % selectivity were obtained using DBU alone. In contrast, when water was used as the HBD, hydrolysis of propylene oxide to produce propylene glycol took place, and the reaction only gave 50 % conversion to propylene carbonate. The choice of organic base was also very important for the conversion of propylene oxide to propylene carbonate in the presence of cellulose. Although the p*K*a values decrease in the order, TBD > MTBD > DBU, when DBU was replaced with either TDB or MTDB, a dramatic decrease in conversion was observed (8 % and 15 %, respectively). The authors suggested that whilst basicity is one of the important factors to obtain high conversion to cyclic carbonates, the steric properties of the base also play a key role. Finally, to demonstrate the wide applicability of DBU and cellulose as a catalytic system, a range of terminal epoxides as well as internal epoxides were transformed into their corresponding cyclic carbonates in satisfactory yields (75–92 %).

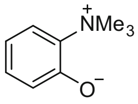
Amino acids are another attractive class of catalysts due to their being readily available and easy to handle. Jing and co-workers investigated the formation of cyclic carbonates from epoxides using naturally occurring α-amino acids as the catalyst in supercritical carbon dioxide [20]. Later, the same authors also developed a solvent-free protocol, and L-histidine **8** was found to be the most efficient catalyst, giving good to excellent yields (75–100 %) at 130 °C under 8 MPa carbon dioxide pressure [21]. This result is in good agreement to those previously reported: [20] that is basic amino acids perform better than acidic amino acids. It was speculated that the epoxide is activated by a cooperative interaction with the ammonium and carboxylate groups within the amino acids.



8

Recently, Park and co-workers demonstrated a very efficient transformation of epoxides into cyclic carbonates in the presence of L-histidine **8** and water under moderate reaction conditions [22]. Again, this demonstrated that the HBD ability of the water molecule plays an important role in activating the epoxide and enhancing the catalytic activity of the system. The reaction conditions are relatively mild compared to those previously reported (120 °C and 1.2 MPa carbon dioxide pressure). Using 0.19 mmol of **8** and 5.5 mmol of water, 90 % conversion with 91 % selectivity to propylene carbonate was achieved after a reaction time of three hours. Amino acids such as threonine and tyrosine have also been anchored onto polystyrene, and their application as heterogeneous catalysts in the synthesis of various cyclic carbonates has been investigated [23]. It was found that both catalysts could be recovered easily and reused five times without significant loss of activity or selectivity.

Similarly, bifunctional organocatalysts featuring an ammonium betaine framework have been developed as a new catalytic motif for the coupling of epoxides and carbon dioxide [24]. Using 1,2-epoxyhexane as substrate, *ortho*-substituted betaine **9** was found to give the best result (76 % yield) at 120 °C and 1 MPa carbon dioxide pressure with a catalyst loading of 3 mol%. To further study the properties of ammonium betaine catalysts, the distance between the two functional groups in the catalysts was tuned to give *meta*-**10** and *para*-isomer **11**. Pleasingly, under the same reaction conditions, both **10** and **11** gave better yields (>99 %) than betaine **9**. At a lower temperature (90 °C) and catalyst loading (2 mol%), the relative catalytic activity of **10** and **11** became more apparent. Betaine **10** afforded butylene carbonate (**1:** R = Et) in 98 % yield, whilst **11** gave just 70 % yield. The higher catalytic efficiency of **10** could be attributed to a higher nucleophilicity of the phenolate anion due to the lack of conjugation stabilisation. Finally, phenyltrimethylammonium phenoxide ($PhN^{+}Me_3$•PhO^{-}) was also tested as a catalyst and found to be much less active than the betaine catalysts. It was speculated that the tight ion pair in $PhN^{+}Me_3{\bullet}PhO^{-}$ reduces its nucleophilicity, whereas the phenolate ion in betaines, such as **10**, is more available to react with carbon dioxide. Furthermore, the proposed betaine-carbon dioxide adduct intermediate was isolated and characterised by both infrared and NMR spectroscopic methods, thus providing experimental proof that ammonium betaine compounds are capable of interacting directly with carbon dioxide.



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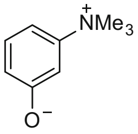

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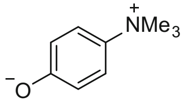
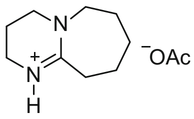
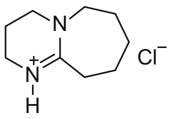


11

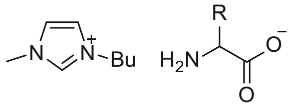
Utilising ionic liquids (ILs) in the synthesis of cyclic carbonates from epoxides and carbon dioxide has attracted much attention [25–27], although catalytic systems containing halides, either as the anion counterpart or as an additive, exhibit the highest activity. Generally, it is assumed that the catalysis occurs through nucleophilic attack on the epoxide by the anionic part of the IL, followed by the stabilisation of resulting alkoxide by the cationic part of the IL. Amongst IL catalyst systems, Lewis basic IL [HDBU]OAc **12** displayed high catalytic activity for the conversion of propylene oxide to propylene carbonate at 140 °C and 1 MPa carbon dioxide pressure, giving both excellent yield (86 %) and selectivity (90 %) after 2 h [28]. This result is comparable to that obtained with [HDBU]Cl **13** (97 % yield and 99 % selectivity).



[HDBU]OAc
12



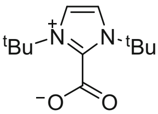
[HDBU]Cl
13



R = Me [bmim][Ala]
R = $(CH_2)_4NH_2$ [bmim][Lys]
14

Simultaneously, He and co-workers developed a class of amino acid-derived ionic liquids **14** consisting of amino acid anions and imidazolium cations and investigated their catalytic activity in the formation of cyclic carbonates [29]. Although in the screening test (130 °C and 4 MPa carbon dioxide pressure for 8 h) [bmim][Lys] gave a higher yield than [bmim][Ala] (40 % and 33 %, respectively), the authors chose [bmim][Ala] as the preferred catalyst due to its excellent fluidity. When the reaction time was extended to 18 h, propylene carbonate was obtained in 96 % yield using 3 mmol% of [bmim][Ala].

In light of Sartori's work using MTBD as a catalyst [11], Lu and co-workers explored the feasibility of using an *N*-heterocyclic carbene (NHC) carbon dioxide adduct as a catalyst system for the synthesis of cyclic carbonates, albeit in dichloromethane as the solvent [30]. Later, Ikariya and co-workers developed a solvent-free protocol, using NHC-CO_2 adduct **15** as the catalyst [31]. The zwitterionic NHC-CO_2 adduct **15** showed excellent catalytic activity at 100 °C and 4.5 MPa carbon dioxide pressure, affording styrene carbonate in 89 % yield after a reaction time of 24 h.



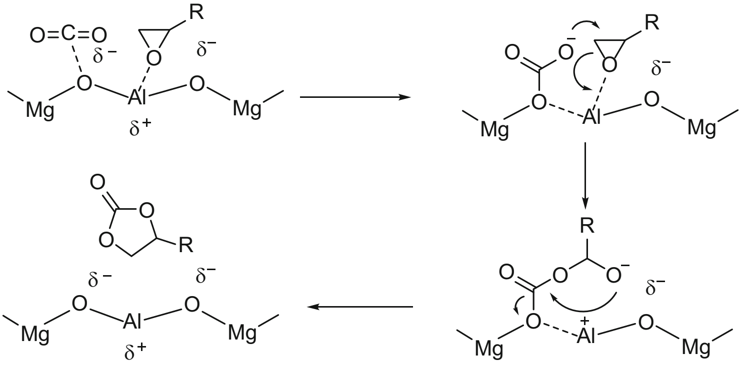
15

Kawanami and co-workers investigated the coupling of epoxides and carbon dioxide in DMF in the absence of any catalysts [32]. When a stoichiometric amount of DMF was used with respect to styrene oxide at 150 °C and 7.9 MPa carbon dioxide pressure for 15 h, an 85 % yield of styrene carbonate was isolated. Building on from this work, a catalytic amount of DMF was also reported to be effective in the synthesis of cyclic carbonates from epoxides [33].

15.2.2 Metal-Catalysed Preparation of Cyclic Carbonates

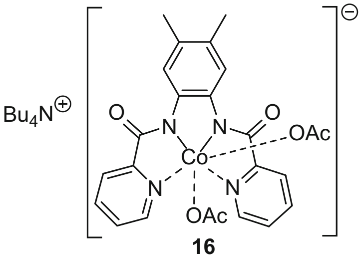
In 1997, Yoshihara and co-workers reported the first example of cyclic carbonate synthesis from epoxides and carbon dioxide using magnesium oxide as the catalyst [34]. When magnesium oxide (calcined at 400 °C) was used at 135 °C and 1.96 MPa of carbon dioxide for 12 h, the authors found that styrene carbonate was isolated in 60 % yield. Further improvement was subsequently reported by Kaneda and co-workers, employing a magnesium-aluminium mixed oxide as a highly active catalyst system [35]. When the reaction was carried out at 100 °C and 0.5 MPa carbon dioxide pressure for 24 h, using a 5:1 magnesium-aluminium mixed oxide (calcined at 400 °C), styrene carbonate was isolated in 90 % yield. When a physical mixture of magnesium oxide and aluminium oxide (magnesium-aluminium ratio of five) was used in place of the calcined magnesium-aluminium mixed oxide, the conversion was significantly reduced to 39 %. The high catalytic activity of the magnesium-aluminium mixed oxide is attributed to dual activation of both epoxides by acidic sites and carbon dioxide by basic sites on the surface of the mixed oxide (Scheme 15.3).

Several examples of metal complex-catalysed synthesis of cyclic carbonates have been reported in the literature [36–40]. In most cases, elevated temperatures and pressures, as well as prolonged reaction times, are required for high conversions of epoxides to cyclic carbonates. As an example, Zevaco and co-workers reported the use of a series of cobalt complexes derived from 2-pyridine-carboxylic acid [41]. In the presence of 3.5 MPa carbon dioxide pressure at 80 °C, 0.5 mol% of complex **16** catalysed the formation of propylene carbonate from propylene oxide



Scheme 15.3 Proposed mechanism for the formation of cyclic carbonates using a magnesium-aluminium mixed oxide catalyst

with 70 % conversion and 100 % selectivity after 20 h. When cyclohexene oxide was used as a substrate under 5 MPa carbon dioxide pressure, polycyclohexene carbonate was obtained in 85 % conversion and 100 % selectivity.



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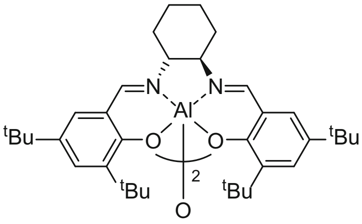
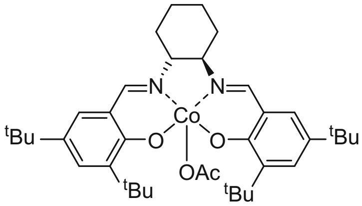


17

Perhaps the most active metal-containing system for the conversions of epoxides into cyclic carbonates is bimetallic aluminium catalyst **17**, reported by North and co-workers [42]. Early work with this catalyst used tetrabutylammonium bromide as a cocatalyst. However, it was subsequently found that the use of 0.5 mol% of catalyst **17** at 50 °C and 5 MPa carbon dioxide pressure, in the absence of any cocatalyst, gave 95 % conversion of styrene oxide to styrene carbonate after a reaction time of 24 h. To demonstrate the utility of catalyst **17**, a range of terminal epoxides were transformed into their corresponding cyclic carbonates in good to excellent yield (50–89 %) under relatively mild reaction conditions (50–100 °C and 1–5 MPa carbon dioxide pressure for 24 h).

The synthesis of enantioenriched cyclic carbonates via kinetic resolution of racemic epoxides is also possible using chiral Co(salen)OAc complex (*R*,*R*-**18**), together with chiral ILs [43]. The highest enantiomeric excess of (*S*)-propylene carbonate is 81 %, which corresponds to a selectivity factor of 10, achieved by using the combination of Co complex (*R*,*R*-**18**) and tetrabutylammonium D-prolinate. However, this required a reaction time of 60 h and gave propylene carbonate in only 3 % yield. More effective catalyst systems were obtained from the combination of complex **18** and ammonium halides, showing that there is still scope for the development of effective halide-free asymmetric catalysts for cyclic carbonate synthesis.



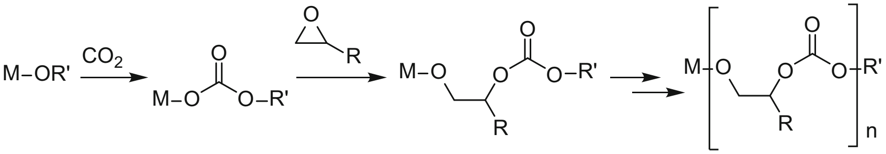
(*R*,*R*)-**18**

15.3 Polycarbonates

15.3.1 Historical Perspective

The copolymerisation of epoxides with carbon dioxide was first described by Inoue et al. in 1969 [44] following their prior work on the copolymerisation of epoxides with anhydrides to form polyesters. Indeed, polycarbonates can be thought of as a special case of polyester with the simplest possible "anhydride" comonomer. The catalyst in this case was diethylzinc in the presence of water, and it may be assumed that the resulting, probably polymeric, zinc alkoxide species promotes the reaction by first forming a metal carbonate which then inserts an epoxide to give a metal alkoxide, a process which then repeats to produce the polymer (Scheme 15.4).

This chemistry is not well controlled, with considerable amounts of chain transfer promoted by the water (or alcohol) present in the system. In the presence of a Lewis acid, epoxides may also form the polyether homopolymer in competition with the copolymerisation with carbon dioxide, so the polymer may have an epoxide to carbon dioxide ratio that is greater than 1:1. This chemistry was reviewed by Coates in 2004 [8], by Inoue and Sugimoto in 2006 [10] and by Rieger et al. in 2011 [9].



Scheme 15.4 Mechanism for polycarbonate formation

15.3.2 Zinc-Based Catalysts

Zinc is now classed as an endangered element, with perhaps only enough ore (primarily zinc sulphide) for 50 years of consumption remaining [45]. Therefore, in order for catalysis with zinc complexes to be considered sustainable, it must carry considerable advantages in terms of performance and recyclability of the catalyst sufficient to justify the use of a limited resource. However, zinc-based catalysts are by far the most mature and well-studied technology for polycarbonate synthesis and are used commercially for the production of polypropylene carbonate (**3:** R = Me).

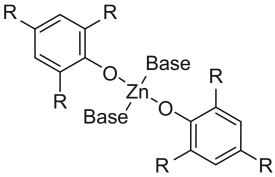
15.3.2.1 Heterogeneous Zinc Catalysts

Diethylzinc in combination with an alcohol, amine or water made up the majority of the early work in this area. The initial work by Inoue [44] was followed by Kuran's systems using phenol additives in place of water or simple alcohols [46]. Whilst the alkylzinc systems in their various forms are halide-free, alkylzinc reagents are produced by the reaction of metallic zinc with alkyl halides. Combined with this, diethylzinc is very pyrophoric, leading to handling and storage issues, which further adds to the undesirability of diethylzinc as a catalyst precursor.

Of greater importance, and greater sustainability, are those catalysts prepared from zinc oxides and hydroxides in combination with dicarboxylic acids. The most important catalyst of this class is zinc glutarate, first prepared by Hattori and co-workers in 1981 from zinc hydroxide and glutaric acid. Under 3 MPa pressure of carbon dioxide at 60 °C, the catalyst gave polypropylene carbonate with an M_n of 12 kDa with a TOF of 1.1 h^{-1} [47]. In 1999, Ree et al. [48] following patent literature by Rokicki and co-workers [49, 50] prepared the same catalyst from zinc oxide; this variant is reported to have much higher activity. Under similar conditions to those used by Hattori for the original work, the system gave polypropylene carbonate with a higher M_n of 210 kDa and much increased TOF of 3.4 h^{-1}. This zinc oxide-derived catalyst has been studied extensively, including the elucidation of the catalyst structure by X-ray crystallography [51, 52] and further optimised for use in supercritical carbon dioxide [53] and under ultrasonication conditions [54]. This last method gave an outstanding TOF of 7.7 h^{-1}. As the polymerisation can only occur at the outer surface of the zinc glutarate particle, TOF values of greater than 10 are effectively out of reach for this type of heterogeneous system. As well as ultrasonication, which remains the gold standard for this type of catalysis, several other strategies have been employed to improve the accessibility of the catalytic surface such as ball milling of the catalyst [51], the introduction of templating additives to alter the morphology of catalyst particles [55] or the dispersion of the zinc glutarate on a high-surface-area substrate such as montmorillonite [56]. The nature of the reaction being catalysed by poorly defined surface species has not only meant that catalyst performance is very dependent upon its method of preparation but also hinders recyclability. It is reported that, likely due to some residues present at the particle surface, recycled catalyst is less active than the freshly prepared zinc glutarate [57].

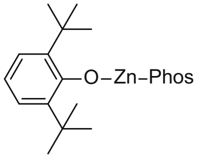
15.3.2.2 Well-Defined Zinc Complexes

Well-defined zinc complexes have also been used to catalyse the synthesis of polycarbonates from epoxides and carbon dioxide. Given the early work by Kuran's group, it is not surprising that homogeneous phenoxide complexes have been investigated for catalysis of this reaction. Darensbourg et al. used a zinc complex **19** with bulky phenoxide ligands to copolymerise cyclohexene oxide with carbon dioxide at 80 °C for 69 h under 5.1 MPa pressure of carbon dioxide [58, 59]. This gave a comparatively high yield of polymer per catalyst, 602:1, and a reasonable TOF of 2.5 h^{-1}. The polymer had a relatively low M_n on the order of 20 kDa but, as might be expected, was reported to be less polydisperse (PDI = 2.5) than the higher molecular weight materials produced using heterogeneous catalysts. The same catalyst without the bulky substituents was found to give the corresponding cyclic carbonate instead of polymer. A number of related structures have been prepared including dimeric species, other oxy ligands alongside phenols and phosphines **20** [60]. These complexes are usually prepared from zinc chloride and so cannot truly be considered to be halide-free even though the reaction mixture itself contains no halogens. It must also be noted that phosphorus is considered to be an endangered element.



R = Ph, tBu, iPr, Me
Base = OEt_2, THF

19

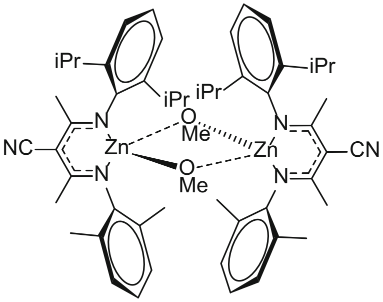


Phos = PPh_2Me or PCy_3

20

These complexes cannot usually successfully copolymerise propylene oxide and carbon dioxide, yielding instead either polymer that contains predominantly polyether linkages or the cyclic carbonate. However, terpolymerisations between carbon dioxide and a mixture incorporating both cyclohexene oxide and propylene oxide are possible [58]. It should be noted that many of the cadmium analogues of these phenoxy complexes were also made; however, the high toxicity of soluble cadmium complexes makes the use of these highly undesirable.

Coates has reported a family of mono- and bimetallic zinc diiminate complexes for the copolymerisation of cyclohexene oxide and carbon dioxide. As for many of the catalysts for this polymerisation, these were also highly active for ring-opening polymerisation of cyclic lactones to give polyesters. The active species for polycarbonate formation is usually considered to be the acetate or alcohol-bridged dimer **21**. The steric bulk of the ortho substituents on the aryl components of the ligand is critical to determining whether, at equilibrium under the reaction conditions, the complex primarily exists as a monomeric or dimeric species and how tightly bound the dimer is. Both monomer and tightly bound dimers are unreactive; therefore, ortho substituents of intermediate bulk, large enough to prevent tight binding yet small enough to allow dimers to form, are necessary for the most active catalysts. Similarly, dilution of the catalyst can reduce the amount of dimer in favour of the monomeric catalyst and decrease catalytic performance. The best performing catalyst **21** gave spectacular performance with a TOF of 2290 h^{-1} and formed polycyclohexene carbonate with $M_n = 22$ kDa and a PDI of 1.1 when reacted with 1000 equivalents of cyclohexene oxide at 50 °C and 0.7 MPa of carbon dioxide pressure for only 10 min [8, 61].

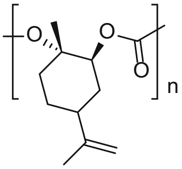


21

More recently, the same authors have developed less symmetrical "second-generation" zinc diiminate catalysts with higher performance. Unfortunately, the best performing of these contains fluorinated substituents [62].

15.3.2.3 Poly(Limonene Carbonate)

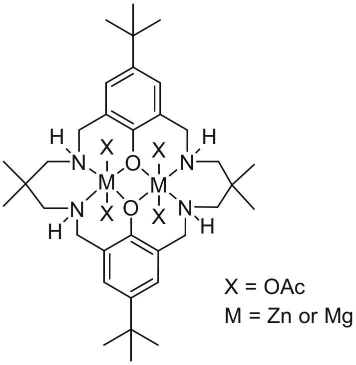
Recently, there has been a surge of interest in the polymerisation of bio-based epoxides and particularly limonene oxide. Coates has used the zinc diiminate catalysts to prepare poly(limonene carbonate) (PLC) **22** [63]. The highest TOFs and molecular weights were achieved using a complex with fluorinated ligands. However, the best performing nonhalogenated complex gave reasonable performance with a TOF of 16 h^{-1} giving an M_n of 4.8 kDa and a PDI of 1.13 in 2 h under 0.7 MPa of carbon dioxide at 25 °C with a catalyst loading of 0.4 mol%. Furthermore, the same group has demonstrated interesting semicrystalline behaviour of 1:1 mixtures of the two enantiopure PLC chains, whereas each isomer alone is amorphous [64]. Koning et al. have developed coatings based on hydroxyl end-capped PLCs cured with isocyanates. The PLC in this work was also prepared using a similar diiminate system to Coates' work.



22

15.3.3 Bimetallic Zinc and Magnesium Catalysts

Amongst the most important recent work in the field of aliphatic polycarbonate synthesis is the work of Williams and co-workers on highly efficient bimetallic catalysts **23** for the copolymerisation of carbon dioxide and cyclohexene oxide. These have featured a variety of metals, including cobalt, iron, zinc and magnesium, and these authors are unusual in commenting upon the sustainability of the metals used. Unfortunately, the di-iron catalyst exists as the tetrachloride complex [65], and so, although iron is the ultimate sustainable metal, these are excluded from the scope of this review. The zinc and magnesium complexes, and the heteronuclear zinc/magnesium complexes, are, however, used as the acetate [66–72].



23

Critically, this class of catalyst is capable of copolymerising cyclohexene oxide with carbon dioxide at atmospheric pressure [67, 71]. This is of great significance for the sustainability of the process as it reduces the energy demands from compressing the gas and simplifies reactor design. Cyclohexene oxide could be copolymerised using the dinuclear zinc catalyst under 0.1 MPa pressure of carbon dioxide at 80 °C in ordinary Schlenk glassware with a catalyst loading of only 0.1 mol% with respect to cyclohexene oxide and gave respectable, given the mild conditions, TOFs of 18 h^{-1} and molecular weights of 6 kDa. The di-magnesium catalyst was somewhat more active under the same conditions, giving a TOF of 35 h^{-1} and an M_n of 13 kDa [73].

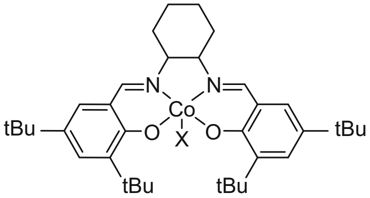
Interestingly, the heterodinuclear zinc-magnesium catalyst has been found to perform better than either of the homonuclear versions or a mixture of the two

[68]. A 0.1 mol% loading of the mixed-metal catalyst in cyclohexene oxide at 0.1 MPa (atmospheric) pressure of carbon dioxide gave a TOF of 79 h^{-1}, whereas the di-zinc and di-magnesium catalysts gave 17 and 52 h^{-1}, respectively, under identical conditions, and a 1:1 mixture gave an overall TOF of 40 h^{-1}. An attempt was made to apply these catalysts to a “greener” substrate, cyclohexadiene oxide derived from the metathesis of fatty acids [70]; however, whilst both the zinc and magnesium bimetallic catalysts were active, they gave only low molecular weight materials (~3 kDa) with low TOF (~5 h^{-1}), so the authors instead focused on the more active cobalt salen systems at higher pressures in this case.

15.3.4 Cobalt Salen Catalysts

Similarly to zinc, cobalt is also considered to be an endangered element. However, the rising use of cobalt in the electrodes of lithium-ion batteries, especially for electric vehicles, may significantly change the demand for and recycling of cobalt in coming years in ways that are difficult to predict at present.

Many cobalt complexes are excluded from this discussion as they exist as the halide salt. One of the exceptions is the cobalt salen acetate complex **24** developed by Coates [74, 75]. This complex has been used to prepare both poly(propylene carbonate) and poly(cyclohexene carbonate); however, in both cases the performance of the halide-free variant of the catalyst was poor compared to those containing either a cobalt halide or pentafluorobenzoate.



X= OAc, Halide, DNP or petafluorobenzoate

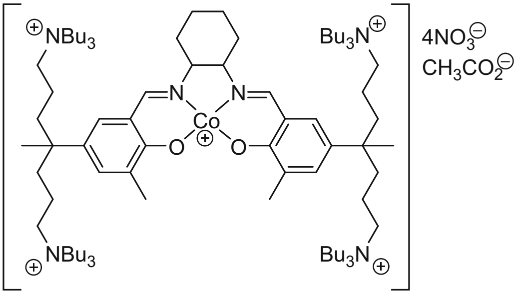
24

The halide-free cobalt acetate salen catalyst gave a modest TOF of 7 h^{-1} for the production of poly(cyclohexene carbonate) in neat cyclohexene oxide (substrate, catalyst = 500:1) under 5.5 MPa pressure of carbon dioxide at 22 °C for 20 h. The yield was only 27 %, and the polymer had a low molecular weight of 9.8 kDa [75]. The performance was slightly better for the corresponding reaction with propylene oxide under the same conditions, giving a yield of 30 % in 2 h with a TOF of 75 h^{-1} when thoroughly degassed. The polymer was similarly low molecular weight ($M_n = 15.5$ kDa) [74].

A highlight of recent work using this class of catalyst is Darensbourg’s work on the production of poly(propylene carbonate) using carbon dioxide released from a

MOF [76]. The catalyst used in this case is a cobalt(salen) complex similar to **24** where the counterion is deprotonated 2,4-dinitrophenol (DNP). A bis-triphenylphosphine iminium dinitrophenolate (PPNDNP) cocatalyst is used. This system is more active than the older Coates systems and under typical reaction conditions of 1.1 MPa of carbon dioxide at ambient temperature was able to produce approximately 50 % conversion with a TOF on the order of 200 h^{-1} and a molecular weight of around 8 kDa. These figures were slightly higher when the same catalyst was used with cylinder-supplied carbon dioxide in place of that released from the MOF, most likely due to traces of moisture in the MOF causing chain transfer. The same group has also used this catalyst to copolymerise butylene oxide and carbon dioxide [77]. Obviously, there are sustainability issues surrounding the use of the PPN cation as phosphorus is an endangered element. PPN salts are also usually made via the PPN chloride, making it debatable whether this type of catalyst is truly halide-free.

Lee et al. have demonstrated the use of an advanced variant on the cobalt(salen) complex **25** which is capable of immortal living polymerisation to give poly (propylene carbonate) of well-controlled molecular weight and architecture, including star polymers grown from tricarboxylic acids [78, 79]. The same catalyst was also used to produce poly(ethylene carbonate) [80], which has the advantage of being biodegradable. Lu demonstrated a similar complex **26** with tethered quaternary ammonium salt “cocatalyst” [81].



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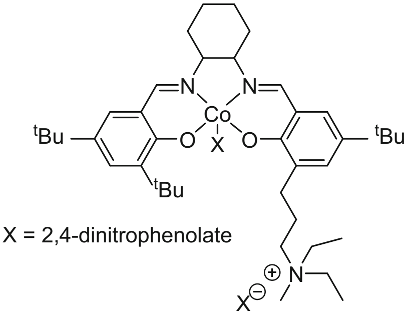

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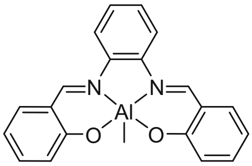
15.3.5 Aluminium Catalysts

Aluminium is not considered to be an endangered element, and as aluminium complexes are well known to be effective Lewis acid catalysts, it is perhaps unsurprising that attempts have been made to use these for the copolymerisation of epoxides and carbon dioxide. Unlike alkylzinc systems, trialkyl aluminium catalysts tend to produce polyethers with only very low incorporation of carbon dioxide, even under high carbon dioxide pressures, though the addition of a Lewis base, such as triphenylphosphine, was shown to improve this [10, 82]. Aluminium alkoxides, phenoxides and aminophenolate complexes also give a large proportion of polyether linkage [83–85].

As for cyclic carbonate formation, discussed in Sect. 15.2.2, and analogously to the cobalt systems, aluminium salen and salophen complexes have been used to produce poly(cyclohexene oxide), usually in conjunction with an onium salt cocatalyst.



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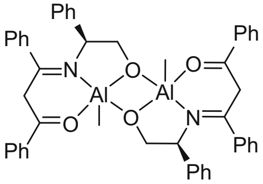
Catalyst **27**, in conjunction with tetraethylammonium acetate as a cocatalyst in a 1:1:250 catalyst-cocatalyst-cyclohexene oxide ratio in dichloromethane under 5 MPa pressure of carbon dioxide at 80 °C, gave 95 % conversion to polycarbonate ($M_n = 10$ kDa, PDI = 1.5) in 24 h [86]. This result is included here despite the use of the chlorinated solvent as it is not likely that the dichloromethane is important to the reaction, and in principle another solvent could be used instead or the reaction carried out “neat” in the monomer.



28

Sugimoto and co-workers also reported a chiral aluminium ketoiminate catalyst **28**, as well as chiral aluminium(salen) complexes that were used for the asymmetric copolymerisation of cyclohexene oxide with carbon dioxide [87]. The best results were obtained using a highly optimised mixture of catalyst **28**, two-site Lewis base and an “epoxide activator” auxiliary Lewis acid with enantiomeric excesses of greater than 60 % being obtained.

15.4 Conclusion and Outlook

The study of the 100 % atom-economical reaction of epoxides with carbon dioxide, either to form polymers or cyclic carbonates, has been underway for almost half a century and today, with the urgency brought about by anthropogenic climate change, is perhaps more relevant, and the subject of more research attention, than ever before.

It can be seen in recent advances in the catalysts used for the production of cyclic carbonates that these molecules are poised to become key intermediates in the emerging more sustainable chemical economy of the future. Several of the examples described in this chapter show that cyclic carbonates can be produced under mild conditions, conducive to the use of waste carbon dioxide without the need for excessive separation and processing of the gas stream. Similarly, catalysts have been developed for the copolymerisation of carbon dioxide with epoxides at atmospheric pressure. Both poly- and cyclic carbonates can be produced using sustainable metals. However, relatively few examples have been demonstrated of catalysts which are effective on highly functionalised or bio-based substrates with perhaps the best existing system being the use of zinc diiminate catalysts to produce poly(limonene carbonate).

The key challenge for this field moving forward is the application of the vast pool of catalytic chemistry experience gained over the past decades to begin to encompass a wider variety of bio-based and sustainable epoxides for both the mitigation of climate change through carbon capture and utilisation and as a key component in the emergent bio-based chemical industry of the future. Vital to this is the transition of the more active and well-defined metal complexes from homogeneous chemistry towards supported catalysts more conducive to flow chemistry and their application on an industrial scale.

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Chapter 16
Heterocyclic Synthesis Through C-N Bond Formation with Carbon Dioxide

Qing-Wen Song and Liang-Nian He

Abstract Carbon dioxide as renewable and environmentally friendly C_1 carbon feedstock, which is in contrast to toxic CO and phosgene, has attracted increasing attention due to its roles as cheap, abundant, and readily available carbon source. Additionally, transition metal-based or organocatalysis capable of activating CO_2 for efficient chemical transformation of CO_2 with chlorine-free process is appealing from a standpoint of green chemistry and sustainable development. The purpose of this article is to demonstrate the versatile use of CO_2 as the alternative carbonyl to phosgene or carbon monoxide in organic synthesis. Herein, we mainly focus on the synthesis of carbonyl-containing value-added chemicals including 2-oxazolidinones and quinazoline-2,4(1H,3H)-diones through C-N bond formation.

Keywords Carbon dioxide • Organocatalysis • Chlorine-free process • Sustainable chemistry • C-N bond formation • Heterocycle

16.1 Reaction of CO_2 with Amino Alcohols

Cyclic urethanes such as 2-oxazolidinones have been known for their wide use in synthetic applications [1–5]. In addition, chiral oxazolidinones known as Evans' auxiliaries [6, 7] have been used as chiral auxiliaries in a broad range of asymmetric syntheses. Oxazolidinones have also been used as a new class of antibacterial agents that are active against pathogenic gram-positive bacteria [8].

There are several conventional methods to the oxazolidone derivatives on the basis of the carbonyl source, i.e., generating from phosgene [9], CO [10, 11], and trichloromethyl chloroformate [12], but the potential of explosion hazard is one of

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the serious limitations of this process. Therefore, exploring new green and environmentally friendly process is of much significance.

Over the past few decades, CO_2 level in the atmosphere has been increasing with the excess use of fossil fuels (coal, petroleum, and natural gas) and the decline of vegetation sharply. On the one hand, CO_2 is one of the most greenhouse gases associated with the climate change. On the other hand, it is potentially used as an abundant and inexpensive C_1 building block in synthetic chemistry to produce value-added chemicals. Much importantly, chemical utilization of CO_2 as green carbonyl source is of great significance as an alternative to conventional phosgene processes in organic synthesis. In particular, catalytic formation of C-N bond involving CO_2 will be important in both industry and academia because such processes offer economical and environmental advantages such as perfect atom efficiency and formation of water as only by-product [13]. In recent years, much attention has been paid to CO_2 chemistry, and many chemicals such as carbonates, polycarbonates, and salicylic acids are produced on an industrial scale. One of the most attractive and effective methods is to use CO_2 as a raw material to afford oxazolidinones due to the great potential of CO_2 as easily available, environmentally friendly, and renewable C_1 building block in organic synthesis.

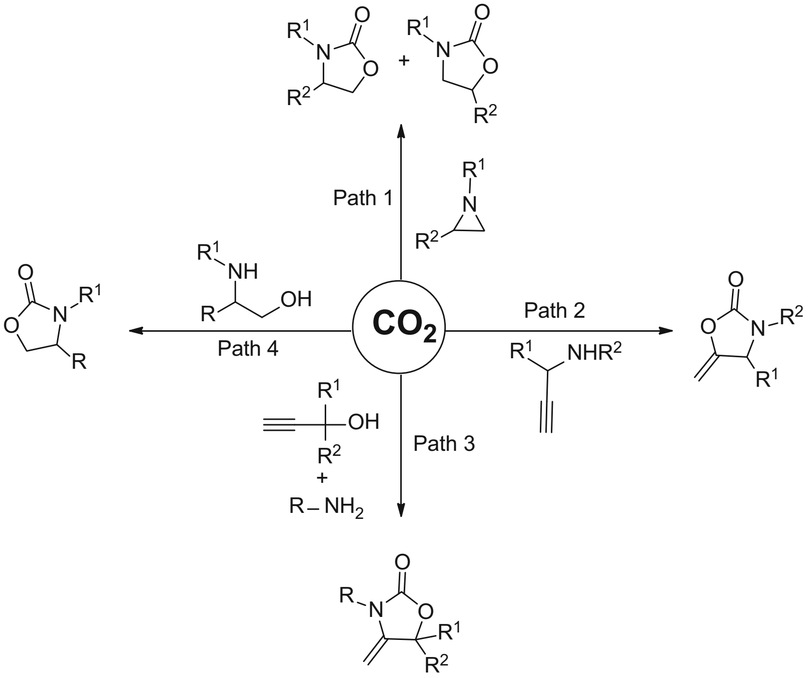
As depicted in Scheme 16.1, there are mainly four effective and straightforward routes to recycle CO_2 into oxazolidinones including (1) cycloaddition of aziridines and CO_2 [14], (2) carboxylative cyclization of propargylic amines and CO_2 [15], (3) three-component reaction of propargylic alcohols, primary amines, and CO_2 [16], and (4) reaction of amino alcohols and CO_2. In the light of the need for a "greener" synthetic process, an environmentally benign direct condensation of 2-amino alcohols with CO_2 will provide a better platform for the synthesis of 2-oxazolidinones in this chapter (Path 4, Scheme 16.1).

Dehydration is the crucial issue for the synthesis of oxazolidinones using amino alcohols and CO_2 as raw materials. There are two strategies of dehydration including indirect dehydration and direct dehydration.

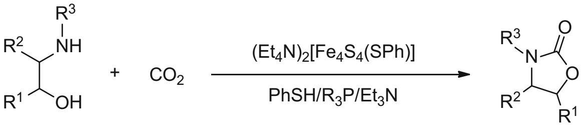
16.1.1 Indirect Dehydration

In 1989, Okuno et al. realized CO_2 fixation into 2-oxazolidone derivatives via 2-ethanolamines [17]. The efficient process was carried out by using tetranuclear ferredoxin analogues $(Et_4N)_2[Fe_4S_4(SPh)_4]$ as the electron mediator together with thiol and phosphine (Scheme 16.2). Up to 88 % yield of 5-phenyl-2-oxazolidone could be obtained for 10 h.

Initially, CO_2 molecule is trapped by 2-amino alcohols to form the carbamate by the aid of Et_3N and thus reacts with the phosphine-diphenyl disulfide adduct in situ generated from diphenyl disulfide and alkyl phosphonic to afford the carbamic ester (Scheme 16.3). Then, intramolecular cyclization followed by interchange esterification produces the 2-oxazolidinone with regeneration of the phosphine oxide and thiol. In the whole procedure, Fe_4S_4 cluster is an excellent catalyst and markedly catalyzes the oxidation of thiol by oxygen for the regeneration of diphenyl disulfide.



Scheme 16.1 Routes to recycle CO_2 into oxazolidinone motifs

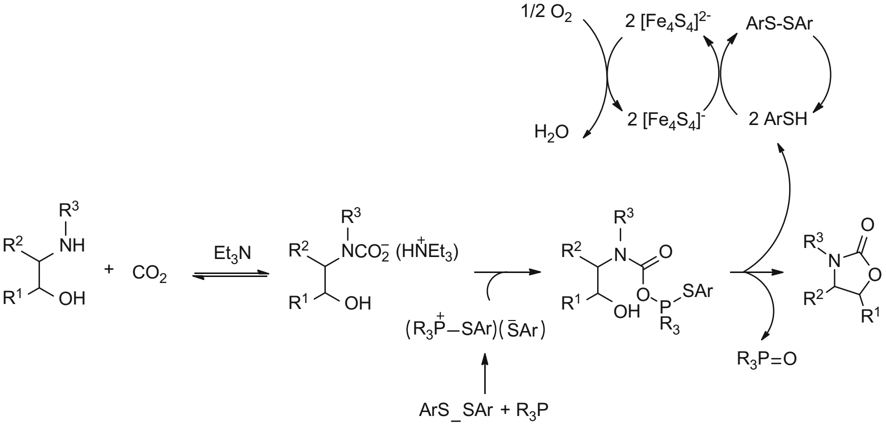


Scheme 16.2 $(Et_4N)_2[Fe_4S_4(SPh)_4]$-promoted 2-oxazolidinones synthesis from 2-amino alcohols and CO_2

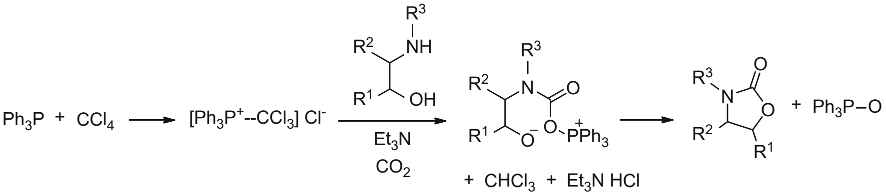
As a result, the redox reaction affords a variety of 2-oxazolidone derivatives, and the process provides an alternative practical protocol for the utilization of CO_2.

Afterwards, Kubota et al. described a successful method for the efficient formation of cyclic urethanes from CO_2 and amino alcohols using phosphorus (III) reagents [Ph_3P, $(PhO)_3P$, etc.] and halogenoalkanes (CCl_4 or CCl_3CCl_3) (Scheme 16.4) [18]. The yield of cyclic urethane was found to be almost proportional to the amount of phosphorus (III) and halogenoalkane reagents.

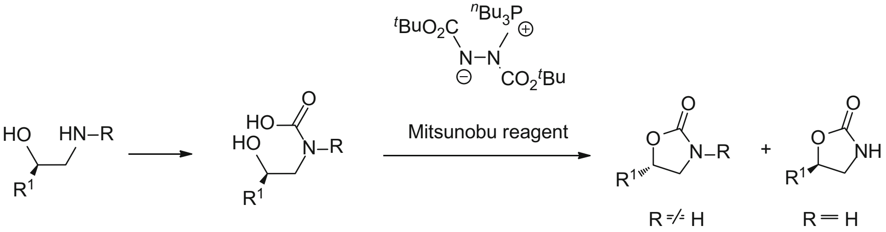
From the viewpoint of reaction mechanism, phosphorus (III) reagents, e.g., PPh_3, initially react with CCl_4 to form an active intermediate $[Ph_3P\text{-}CCl_3]^+Cl^-$ which is quickly transformed into carbamic ester in the presence of 2-amino alcohols, and CO_2. Et_3N is employed to trap the proton and further promote the cyclization with the generation of phosphine oxide, $CHCl_3$, and ammonium salt.



Scheme 16.3 The possible mechanism for CO_2 fixation



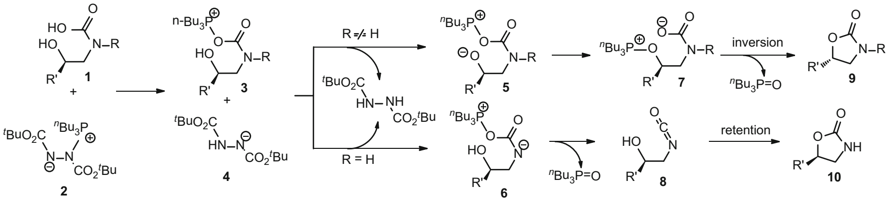
Scheme 16.4 The possible mechanism for CO_2 fixation



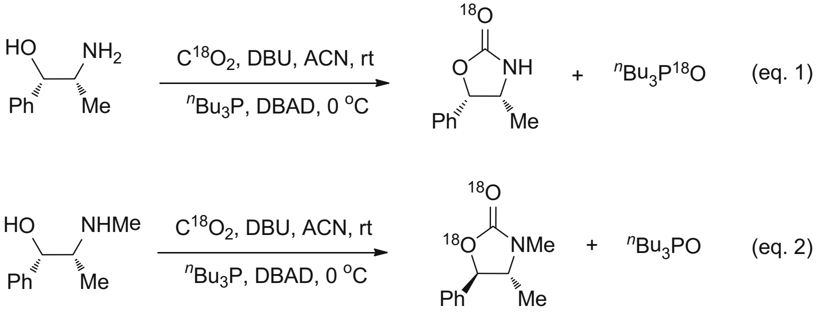
Scheme 16.5 Mitsunobu reagent-promoted synthesis of 2-oxazolidinone

The procedure for the synthesis of 2-oxazolidinones from ethanolamines is effective by in situ N-carboxylation and Mitsunobu cyclodehydration with the retention of configuration. By further investigation, Dinsmore et al. discovered that either inversion or retention of stereochemistry unexpectedly occurs in a manner dictated by the amino alcohol substituents (Scheme 16.5) [19].

Primary amine substrates produce oxazolidinones with retention of configuration at the oxygen-bearing center, while for secondary amines, inversion of configuration in the products is observed, which can be explained by the following proposed reaction mechanism (Scheme 16.6). Generally, 2-amino alcohol easily



Scheme 16.6 Mitsunobu reagent-promoted reaction mechanism

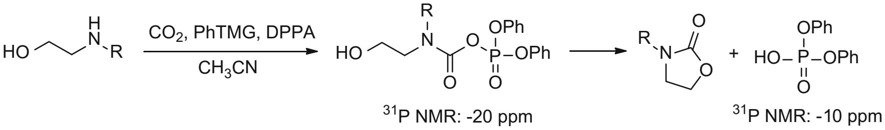


Scheme 16.7 Isotope-labeling experiments

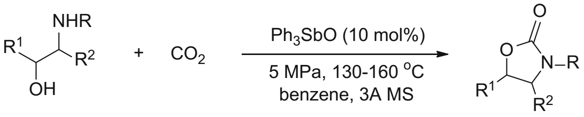
reacts with CO_2 to produce carbamic acid **1**. In the Mitsunobu reaction system, ylide **2** in situ formation from *n*-Bu_3P and di-*tert*-butyl azodicarboxylate (DBAD) reacts with **1** to give carbamic ester **3** together with hydrazide anion **4**. If the nitrogen atom in **3** bears a carbon substituent (R $\neq$ H), deprotonation of the hydroxyl group gives the carbamoyloxyphosphonium alkoxide **5**, which isomerizes to the oxyphosphonium carbamate **7**. Cyclization of **7** with loss of *n*-Bu_3PO can afford the final product **9** with inversion of configuration. If the nitrogen atom of **3** bears a proton (R = H), then N-H deprotonation gives the zwitterion **6**, which collapses with loss of *n*-Bu_3PO to form the isocyanate **8**. Finally, cyclization of a 2-(hydroxyethyl)isocyanate furnishes an oxazolidinone (**10**) with retention of configuration.

Intrigued by the N-substitution-dependent stereochemical divergence, they also undertook isotope-labeling experiments to support the pathways involving either retention or inversion of configuration in the Mitsunobu cyclization as shown in Scheme 16.7. In fact, the results are that primary amine in the presence of $C^{18}O_2$ gave mono-^{18}O-labeled oxazolidinone **10**, along with ^{18}O-tributylphosphine oxide (eq. 1). In contrast, the analogous secondary amine produced doubly labeled **9** with no isotope label in the tributylphosphine oxide (eq. 2). These results are identical to the possible pathways of loss of an OH group from the hydroxyl group (configuration inversion) or the carbamic acid fragment (configuration retention).

Carbamate anion from carbamoyl azide can be eventually transformed into an activated carbonyl species, which in turn could behave as an acylating agent in the



Scheme 16.8 Proposed intermediate detected by ^{31}P NMR spectrum



Scheme 16.9 Triphenylstibine oxide-catalyzed 2-oxazolidinones synthesis from 2-amino alcohols and CO_2

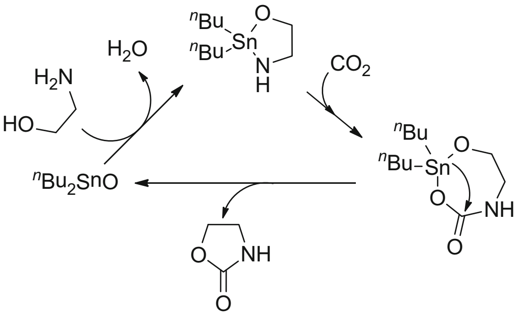
presence of an appropriate nucleophile. This proposal can be applied to synthesize oxazolidinones from 1,2-amino alcohols, CO_2, and a phosphorylating agent under basic conditions [20, 21]. 4-methyl-5-phenyloxazolidinone could be obtained (68–97 % yields) in the presence of various phosphorylating agent such as diphenylphosphoryl azide (DPPA), diphenyl chlorophosphate (DPPCl), and other sulfur and carbon electrophiles ($SOCl_2$, MsCl, TsCl, Tf_2O, AcCl, AcBr, $ClCO_2Et$, etc.), and the base 1,1,3,3-tetramethyl-2-phenyl-guanidine (PhTMG) could be advantageously replaced by 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) or by readily available Et_3N.

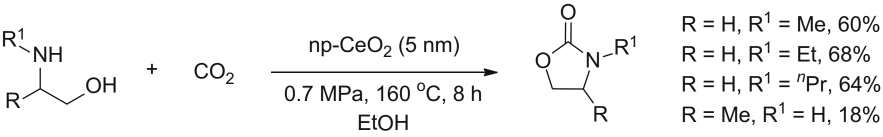
^{31}P NMR spectrum was also applied to investigate the reaction mechanism. A transient signal was observed at around −20 ppm (20×10^{-6}) and disappeared rapidly, while a signal at around −10 ppm (10×10^{-6}) increased in intensity, which is typical for diphenyl hydrogen phosphate (Scheme 16.8).

16.1.2 Direct Dehydration

Although the indirect method is effective, it uses a large amount of bases and electrophiles and meanwhile produced much by-products. With regard to the need for a “greener” synthetic process, an environmentally benign direct condensation of 2-amino alcohols with CO_2 would provide a better platform for the synthesis of 2-oxazolidinones. Synthesis of 2-oxazolidinones from 2-amino alcohols using organometallic complexes was first reported by Matsuda and co-workers [22]. They used organoantimony compounds, especially triphenylstibine oxide, as catalyst to catalyze the cyclocondensation of 2-amino alcohols and CO_2 assisted by molecular sieves 3A in aprotic media (Scheme 16.9). Thus, 3-alkyl-2-oxazolidinones were prepared in 80–94 % yields at 130–160 °C. Although the high efficiency, high temperature and benzene as cosolvent render this process uneconomical and non-ecofriendly.

Scheme 16.10 Dibutyltin oxide-catalyzed reaction of aminoethanol and CO_2





Scheme 16.11 CeO_2-catalyzed carbonylation of ethanolamine

Afterwards, an organotin catalyst, dibutyltin oxide, was reported for the synthesis of 2-oxazolidinones from amino alcohols and CO_2 in the presence of N-methylpyrrolidone as cosolvent [23]. This synthetic process employed relatively high temperature and pressure (180 °C, 5 MPa). Turnover number (TON) and turnover frequencies (TOF) of this catalyst were low (TON, 4–9 and TOF, 0.25–0.53). As for the mechanism, dibutyltin oxide initially reacts with 2-aminoethanol to afford the tin intermediate. Furthermore, a cyclic tin carbamate is formed through the insertion of CO_2 to Sn-N bond. Subsequent intramolecular nucleophilic attack of alkoxy group on the carbonyl carbon atom causes the elimination of 2-oxazolidinone regenerating the starting tin oxide as illustrated in Scheme 16.10.

Recently, the synthesis of 2-oxazolidinones in the presence of 1,3-dichloro-1,1,3,3-tetraalkyldis-tannoxanes was conveyed [24]. One of the advantages is the ability to control Lewis acidity of the catalysts by changing the substituents on the metal center. TON up to 138 can be obtained using the chlorostannoxane catalyst with all butyl substituents on both the metal centers. The catalytic system is applicable to a variety of substrates in moderate yields.

CeO_2 and ZrO_2 are the most widely solid catalysts for various CO_2 fixation reactions [25–28]. The activity of ceria as heterogeneous catalyst for the reaction of CO_2 with primary and N-substituted ω-amino alcohols was investigated (Scheme 16.11) [29]. The catalytic activity of other metal oxides by performing reactions of CO_2 with ethanolamine derivatives ($R = H, R^1 = Me$) decreased in the order of (yield of oxazolidinone): nanoparticle (np)-CeO_2 (5 nm) (60 %) > CeO_2 (40 nm) (43 %) > ZrO_2 (17 %) > Al_2O_3 (7 %). Using np-CeO_2 (5 nm) as catalyst, N-alkyl-1,3-oxazolidin-2-one could be obtained in moderate yields at 160 °C under

0.7 MPa CO_2 within 8 h. Notably, the reaction of CO_2 with amino alcohol could proceed smoothly under 6 MPa CO_2 pressure at 150 °C without any catalyst, but the yields of oxazolidinones are low (<10 %) within 6 h using methanol or ethanol as solvent [30].

16.2 Reaction of 2-Aminobenzonitriles and CO_2

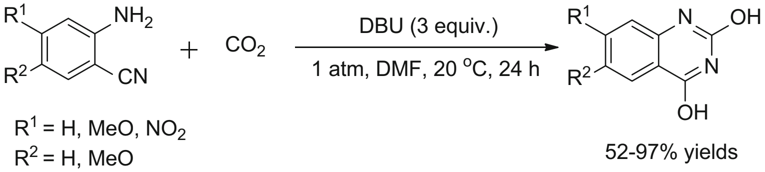
In recent decades, much attention has been paid to the synthesis of quinazoline-2,4 (1H,3H)-diones owing to their various biological activities for usage as anticonvulsants [31], *a*-adrenergic receptor antagonists [32], antibacterial [33], and antihypertensive [34]. Moreover, quinazoline-2,4(1H,3H)-diones are also used as synthetic materials in heterocyclic chemistry [35].

Traditionally, these quinazoline2,4(1H,3H)-diones are synthesized via the reaction of an anthranilic acid with chlorosulfonyl isocyanate [36], anthranilamide with phosgene [37], aromatic amino nitriles with diethylformamide [38], and 2-nitrobenzamide with CO [39]. However, these methods generally require multistep procedures, toxic reagents like phosgene, and time-consuming experimental procedures to realize the effective transformation accompanied by environmental impact like generating a stoichiometric amount of chemical waste. Therefore, a new facile and effective method for the synthesis of quinazoline-2,4 (1H,3H)-diones is urgently needed. Considering these issues, many efforts have been made to replace toxic reagents using incorporation of CO_2 into quinazoline-2,4(1H,3H)-dione derivatives.

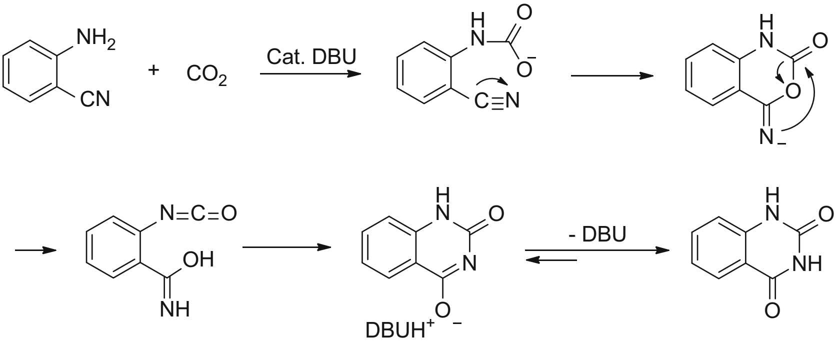
CO_2 is a cheap and abundant natural carbon source, and it can sometimes replace toxic chemicals such as phosgene, isocyanates, or carbon monoxide, leading to greener processes [40, 41]. Hence, CO_2 fixation has attracted much interest in view of sustainable chemistry and "green chemistry" concepts [42, 43]. One of the promising methodologies for CO_2 chemical fixation is the reaction of CO_2 with 2-aminobenzonitriles to form quinazoline-2,4(1H,3H)-diones.

16.2.1 Organic or Inorganic Base-Promoted Cyclization with CO_2

In 2000, Mizuno et al. pioneered a convenient and economical route for the synthesis of quinazoline-2,4(1H,3H)-diones from 2-aminobenzonitriles and CO_2 [44]. As demonstrated, the reaction was performed smoothly under atmospheric pressure of CO_2 at 20 °C assisted by excess amount of 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) to give 2,4-dihydroxyquinazolines in excellent yields as shown in Scheme 16.12.



Scheme 16.12 DBU-promoted reaction of 2-aminobenzonitrile with CO_2



Scheme 16.13 DBU-catalyzed fixation of CO_2 with 2-aminobenzonitriles

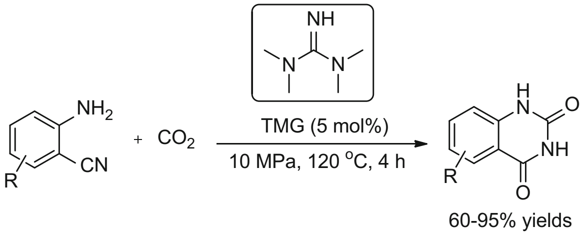
Later, they found that the reaction could be carried out in the presence of a catalytic loading of organic base. For example, using 0.05 equiv. DBU, 7-chloro-1H-quinazoline-2,4-dione was synthesized successfully in 97 % yield under 1.0 MPa at 80 °C in DMF [45].

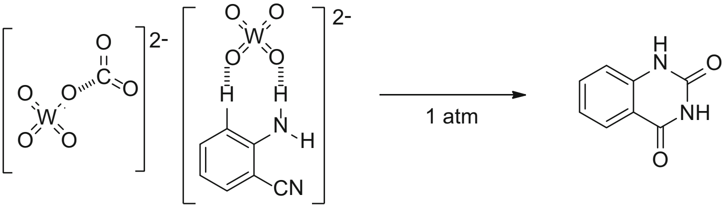
A tentative mechanism for the catalytic amount of DBU-promoted fixation of CO_2 with 2-aminobenzonitriles is illustrated in Scheme 16.13. The carbonylation of 2-aminobenzonitrile with CO_2 initially generates the carbamate salt in the presence of DBU. Then, nucleophilic cyclization of carbamate intermediate, followed by rearrangement through the isocyanate intermediate, gives the final product. In this reaction system, formation of the isocyanate intermediate is crucial.

Supercritical CO_2 ($scCO_2$) is considered to be a green solvent, and thus substantial effort has been devoted to developing chemical processes which $scCO_2$ is used to replace hazardous organic solvent [46–48]. In precious work, the reaction relies on the special organic solvent such as DMF or DMSO to gain the good results. Subsequently, Mizuno group developed a simple organic solvent-free modified synthesis of quinazoline-2,4(1H,3H)-diones from 2-aminobenzonitriles in the presence of catalytic amount of base [DBU, DBN, 1,4-diazabicyclo[2.2.2]octane (DABCO), or Et_3N] under $scCO_2$ conditions [49]. Here, $scCO_2$ acts as both a reactant and a solvent. The process represents a green process for the synthesis of quinazoline-2,4(1H,3H)-diones from the view of green chemistry.

Organic guanidines, which are categorized as organic superbases with ease of structural modification, are efficient organic catalysts for the types of base-induced

Scheme 16.14 TMG-catalyzed reaction of 2-aminobenzonitrile with CO_2



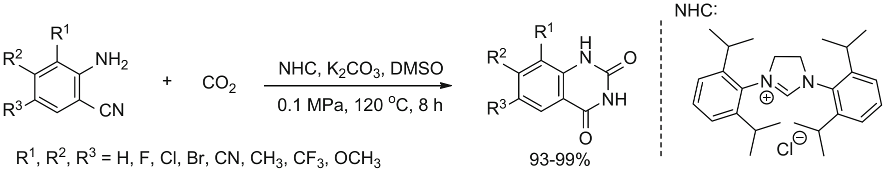


Scheme 16.15 TBA_2WO_4-catalyzed reaction of 2-aminobenzonitrile with CO_2

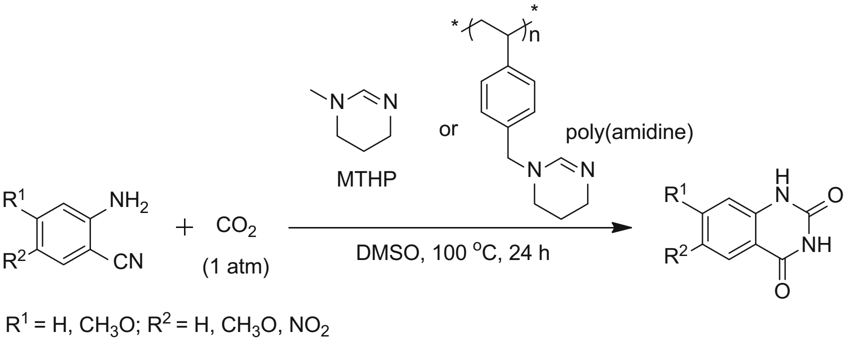
reactions in organic synthesis [50]. Particularly, guanidines could interact with CO_2 through a kinetically reversible way, leading to CO_2 fixation [51]. He et al. developed an efficient guanidine catalytic system for the chemical fixation of CO_2 with 2-aminobenzonitriles under solvent-free conditions (Scheme 16.14) [52]. Notably, the catalysts with low loading worked well for a variety of 2-aminobenzonitriles. TMG might play a dual role in this reaction: (1) activating the substrate by deprotonation to facilitate the attack to CO_2 and (2) activating the CO_2 molecule via forming a CO_2-TMG complex. As a result, quinazoline-2,4 (1H,3H)-diones in present protocol were obtained in good yields under $scCO_2$ conditions. This process represents an alternative method for the greener chemical conversion of CO_2 to value-added products.

Monomeric tungstate, TBA_2WO_4 (TBA = tetra-*n*-butylammonium), could act as an efficient homogeneous catalyst for chemical utilization of CO_2 with 2-aminobenzonitriles to quinazoline-2,4(1H,3H)-diones (Scheme 16.15) [53, 54]. The ^1H and ^{13}C NMR spectra showed the specific interaction of the tungsten-oxo moiety in TBA_2WO_4 with both CO_2 and the substrate. Such simultaneous activation leads to the following advantages: (1) accomplishment of CO_2 transformation at atmospheric pressure, (2) high yields and TON, and (3) applicability to a wide range of substrates. In summary, various kinds of structurally diverse 2-aminobenzonitriles could be converted into the corresponding quinazoline-2,4(1H,3H)-diones in high yields at atmospheric pressure of CO_2. In this case, the TON reached up to 938 and the value was the highest among those reported for base-mediated systems so far.

Under atmospheric pressure of CO_2, quinazoline-2,4(1H,3H)-diones were obtained from 2-aminobenzonitriles with a catalytic amount of N-heterocyclic carbene in DMSO (Scheme 16.16) [55]. It was found that various electron-donating



Scheme 16.16 NHC-catalyzed reaction of 2-aminobenzonitrile with CO_2



Scheme 16.17 Reaction of 2-aminobenzonitriles with CO_2 in the presence of MTHP or poly (amidine)

and electron-withdrawing groups such as −OMe, −F, −Cl, −Br, $-CH_3$, $-CF_3$, and −CN are well tolerated to give the products in almost quantitative yields.

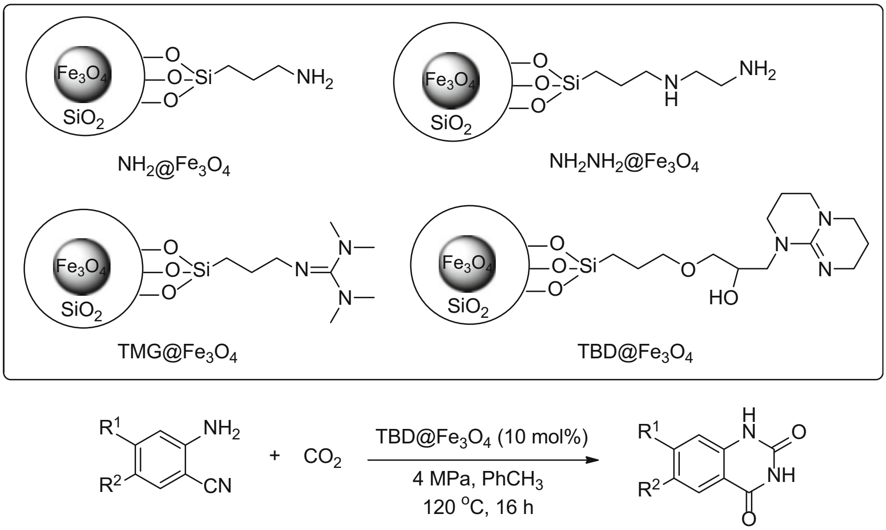
Compared to homogeneous catalysts, heterogeneous catalysts are easy to handle and facilely recovered from the resultants [56]. Thus, designing alternative types of sustainable heterogeneous catalysis in the synthesis of chemicals is gaining increasing importance [57].

The reusability of the catalyst is one of the most important parameters in evaluating catalytic performance. Amidine moiety is supported to the polystyrene derivative and applied to catalyze the reaction of 2-aminobenzonitrile and CO_2 (Scheme 16.17) [58]. Several 1H-quinazoline-2,4-diones are successfully synthesized from the corresponding 2-aminobenzonitriles in the presence of poly (amidine). Notably, the poly(amidine) could easily be separated from the reaction mixture by filtration and reused in new runs.

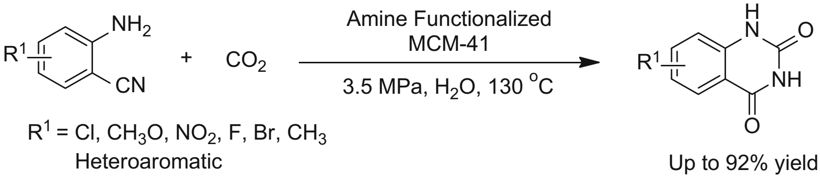
Magnetite is an ideal support, which is easy to prepare, separate, and functionalize, as well as low toxic and inexpensive [59]. These attractive features make magnetic Fe_3O_4 a promising catalyst support alternative to porous and mesoporous materials. Recently, direct use of Fe_3O_4 as a magnetically reusable catalyst has been successfully developed for a variety of fundamental reactions [60].

TBD-functionalized magnetic Fe_3O_4 was demonstrated to be an efficient and recyclable magnetic heterogeneous catalyst for the production of various quinazoline-2,4(1H,3H)-diones in moderate to high yields (Scheme 16.18) [61]. The study revealed that catalytic efficiency decreased in the order TBD@Fe_3O_4 > TMG@Fe_3O_4 > NH_2NH_2@Fe_3O_4 > NH_2@Fe_3O_4, which is probably relative to the basicity of active species. After the reaction, the magnetic heterogeneous catalyst could be recovered using an external magnetic field by an auxiliary magnet. Through the method, heterogeneous catalyst could be recycled three times without significant drop in the catalytic activity.

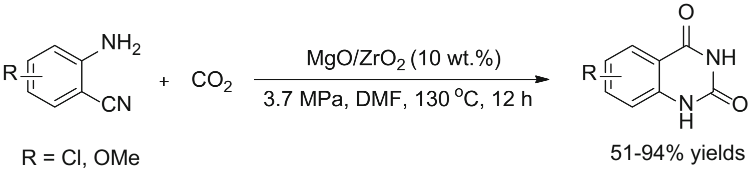
A simple covalently linked amine-functionalized MCM-41 was demonstrated to be a highly efficient, heterogeneous, and recyclable mesoporous catalytic protocol for the synthesis of a variety of quinazoline-2,4(1H,3H)-dione derivatives in aqueous medium (Scheme 16.19) [62]. The developed protocol could be applicable for the synthesis of most important key intermediate 6,7-dimethoxyquinazoline-2,4 (1H,3H)-dione and several biologically active derivatives such as prazosin, bunazosin, and doxazosin. Besides this, the developed catalyst could be reused for five cycles without any significant loss in its catalytic activity.



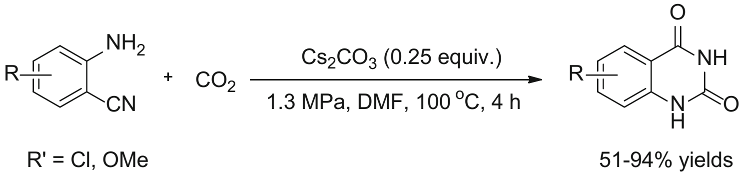
Scheme 16.18 The magnetic catalysts and TBD@Fe_3O_4-catalyzed reaction of 2-aminobenzonitriles and CO_2



Scheme 16.19 Amine-functionalized MCM-41-catalyzed reaction of 2-aminobenzonitriles with CO_2



Scheme 16.20 MgO/ZrO_2-catalyzed reaction of 2-aminobenzonitrile with CO_2



Scheme 16.21 Cs_2CO_3-catalyzed reaction of 2-aminobenzonitrile with CO_2

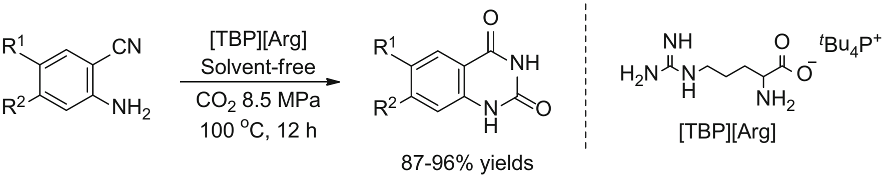
MgO/ZrO_2 as an efficient heterogeneous basic catalyst was also reported for the synthesis of quinazoline-2,4(1H,3H)-diones from 2-aminobenzonitriles and CO_2 (Scheme 16.20) [63]. The synthesized MgO/ZrO_2 catalyst was characterized by XRD and FTIR, and its basic properties were measured using CO_2 temperature-programmed desorption analysis. A wide variety of aromatic aminobenzonitriles and five-membered N-heterocyclic carbonitriles were also synthesized using this protocol.

An efficient protocol for the reaction of 2-aminobenzonitriles with CO_2 using catalytic amount of cesium carbonate had been developed (Scheme 16.21) [64]. Two features are revealed in this study: (1) minimizing the number of unit operations and waste streams (2) with a variety of 2-aminobenzonitriles bearing different steric and electronic groups.

16.2.2 Ionic Liquid-Promoted Cyclization with CO_2

Ionic liquids (ILs) are organic salts with a melting point below 100 °C and very low volatility due to their extremely low vapor pressure. Their structural diversity allows tuning of their properties and thus makes them highly promising candidates for tailored solvent and catalysts [65].

[Bmim]OH was first reported as a homogeneous ionic recyclable catalyst for the synthesis of quinazoline-2,4(1H,3H)-diones from 2-aminobenzonitriles and CO_2 [66]. The reaction was optimized with respect to various electron-rich, electron-deficient aminobenzonitriles and five-/six-membered N-heterocyclic carbonitriles providing good yield of the desired quinazoline-2,4(1H,3H)-diones. This method offers noticeable improvements in operational simplicity, high yields of products, and greenness of the procedure, avoiding hazardous organic solvents and toxic



Scheme 16.22 [TBP][Arg]-catalyzed reaction of 2-aminobenzonitrile with CO_2

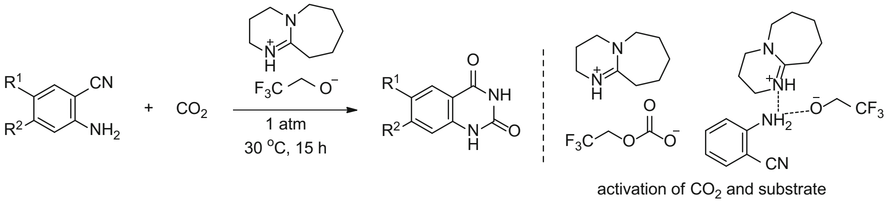
catalysts. Considering the economical value of the quinazoline-2,4(1H,3H)-dione derivatives, the new methodology could minimize the number of unit operations and waste streams. The reusability result showed that the catalyst could be successfully recycled for three times with a slight reduce in the activity. As the mechanism, they proposed it goes through a conventional based-promoted pathway in solvent-free condition.

Later, Han et al. developed a 1-butyl-3-methylimidazolium acetate ([Bmim]Ac)-promoted reaction for the synthesis of quinazoline-2,4(1H,3H)-diones [67]. [Bmim]Ac acting as both solvent and catalyst, the reactions could be carried out efficiently under atmospheric pressure of CO_2, and a high yield of the products was obtained. Moreover, [Bmim]Ac could be reused at least five times without significant decrease in catalytic activity, and the product separation from the IL was very easy. This work provides an additional example that functional ILs have obvious advantages for conducting chemical reactions as catalysts and/or solvents.

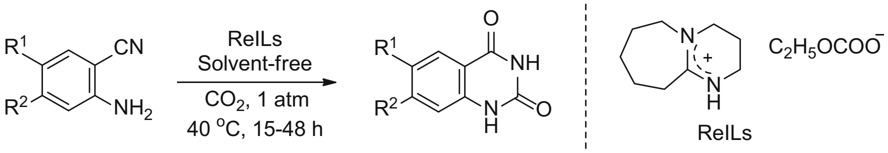
Tetraalkylphosphonium-based amino acid ILs displayed lower viscosities and higher decomposition temperatures than traditional ammonium-based amino acid IL [68]. Amino acid-based IL (AAIL), i.e., [TBP][Arg] comprising a tetrabutylphosphoniumcation and an arginine anion, was found to be an efficient and recyclable catalyst for the synthesis of quinazoline-2,4(1H,3H)-diones from 2-aminobenzonitriles and CO_2 under solvent-free conditions (Scheme 16.22) [69]. Various 2-aminobenzonitriles bearing electron-withdrawing or electron-donating substituents worked well to afford quinazoline-2,4(1H,3H)-diones in excellent yields. Notably, this type of AAIL showed good stability and could be reused five times without significant loss in catalytic activity. This process represents an alternative approach for greener chemical conversion of CO_2 into valuable compounds.

Recently, Liu group reported a bifunctional protic IL (PIL, $[HDBU^+][TFE^-]$) catalyzed CO_2 conversion for the synthesis of quinazoline-2,4-(1H,3H)-diones (Scheme 16.23) [70]. In the system, PIL serves as both the catalyst and solvent. As a bifunctional catalyst for simultaneously activating CO_2 and the substrate, this PIL displayed excellent performance in catalyzing the reactions of CO_2 with 2-aminobenzonitriles at atmospheric pressure and room temperature, thus producing a series of quinazoline-2,4(1H,3H)-diones in high yields.

Reversible ILs (ReILs) generated from superbase and alcohols, as novel, switchable, recyclable solvents, are effective media in organic synthesis [71]. For the first



Scheme 16.23 [HDBU$^+$][TFE$^-$]-catalyzed CO_2 conversion for the synthesis of quinazoline-2,4-(1H,3H)-diones



Scheme 16.24 ReIL-promoted reaction of 2-aminobenzonitrile and CO_2

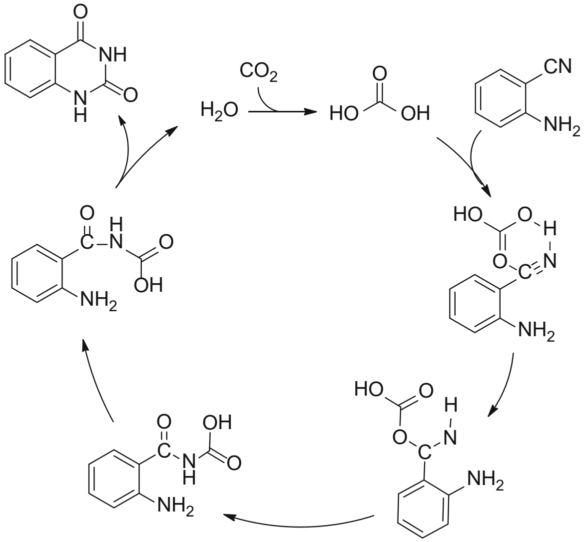
time, the ReILs from DBU and alcohols were used as media for preparing quinazoline derivatives under atmospheric pressure in high yields (up to 90 %) (Scheme 16.24) [72]. By this strategy, the separation of the products was easy from the ReILs which could be reused at least six times without considerable loss in yield. It provides a green efficient protocol for capture CO_2 in ILs to synthesize quinazoline derivatives.

16.2.3 Carbonic Acid-Promoted Cyclization

Water is a well-known green solvent with some unique advantages, such as abundance and cheapness [73, 74]. Very recently, Han group found that quinazoline-2,4(1H,3H)-diones could be synthesized in high yields via the reaction of CO_2 with 2-aminobenzonitriles catalyzed by choline hydroxide in water [75]. In this case, the use of an organic solvent is avoided and the catalyst choline hydroxide is cheap and abundant.

Subsequently, they developed a simple and efficient method to synthesize quinazoline-2,4(1H,3H)-diones in water without any catalyst, and excellent yields were obtained [76]. Using density functional theory (DFT), they conducted the theoretical work to study the mechanism of the reactions in water [77]. It is revealed that CO_2 reacts via carbonic acid (H_2CO_3) with 2-aminobenzonitrile and give the product (Scheme 16.25). Formation of H_2CO_3 from CO_2 and water is the key for the reactions to proceed smoothly in water without a catalyst. The reasons are as follows: (1) H_2CO_3 reacts with 2-aminobenzonitriles more easily than CO_2 itself, and (2) H_2CO_3 can effectively promote the reaction by the synergistic action of its carbonyl O atom and one of the hydroxyl O atoms.

Scheme 16.25 H_2CO_3-promoted conversion of CO_2



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Part VII
Substitutives: *DACs Utilization*

Chapter 17
Beyond Chlorine Reagents: Organic Carbonate Chemistry

Huanwang Jing

Abstract The organic cyclic carbonates, polycarbonates, including their enantiomers, were documented. Their applications in organic synthesis, new material fabrications, industry, agriculture, and medical treatment were described and envisioned. The mechanism of formation of polycarbonates and cyclic carbonated might be discussed.

Keywords Organic carbonates • Cyclic carbonates • Polycarbonates • Production • Utilization • Available compounds • Mechanism

17.1 Introduction

Organic carbonates are widely used in various realms: aprotic polar green solvents, detergents, monomers for polycarbonates and polyurethanes, electrolyte carrier in lithium-ion batteries, organic synthetic intermediates, precursors for biomedical applications, and raw materials for engineering plastics owning to their low vapor pressure, low toxicities, high boiling points, etc. [1], which were conventionally prepared by phosgene and alcohols in industry or by triphosgene and alcohols in laboratory leading hazardous hydrogen chloride [2, 3] (Scheme 17.1). In recent years, in response to the public anxiety about environment issues, many researchers devoted to carbon dioxide chemistry [4–8] that might be reducing the greenhouse effect and build up a new way to realize reutilization of carbon resources in the future, in which systematic investigations about the synthesis of organic carbonates were frequently summarized in recent years. Therefore, the organic carbonate chemistry is merged to be a branch of carbon dioxide chemistry. Nowadays, the organic carbonates have a huge market as solvents, reagents, intermediates for the synthesis of pharmaceuticals and agrochemicals, fuel additives, monomers for polymers [2], etc.

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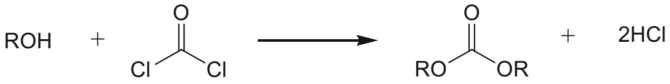
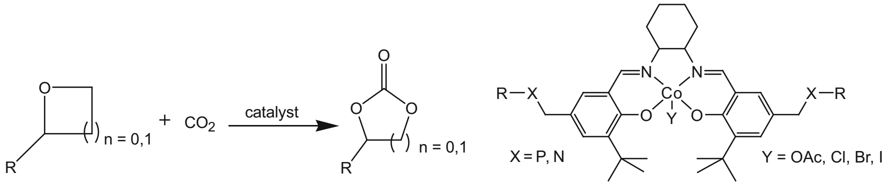


Scheme 17.1 Conventional route to organic carbonates



Scheme 17.2 Green routes to cyclic carbonates and typical bifunctional catalysts

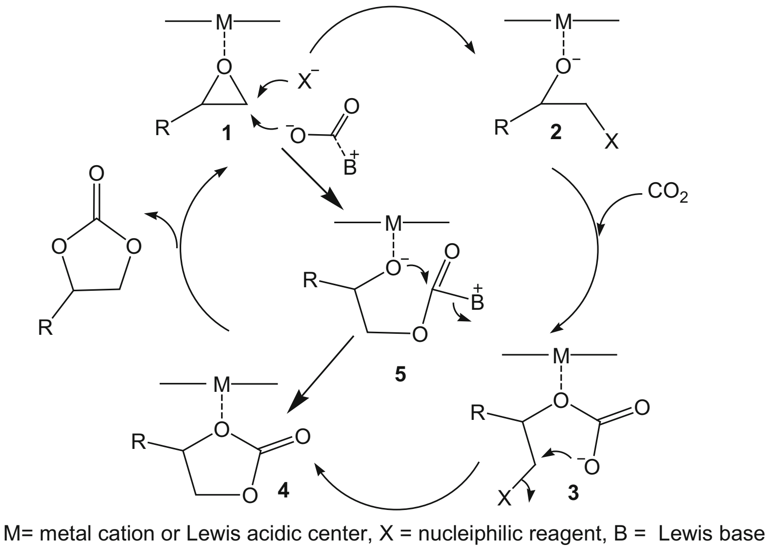
17.2 Synthetic Methods of Organic Carbonates

When the carbon dioxide was used to replace phosgene in the synthesis of organic carbonates [9], many methodologies were developed in literatures, in which, five-member ring cyclic carbonates were the most studied target product and generated by the epoxide and CO_2, while the corresponding six-membered ring derivatives can be produced by oxetanes and CO_2. These approaches are 100 % atom economy and making it a highly desirable transformation [10] (Scheme 17.2).

17.2.1 Coupling of Epoxides and CO_2

Comparing with the synthesis of ethylene carbonate and propylene carbonate which were widely realized in chemical plants, the cyclic carbonates were commonly prepared by terminal epoxide and CO_2 using various catalyst systems (Scheme 17.2). The efficient catalyst systems including the salenM/cocatalyst (M = Co, Cr, Ru, Zn, Mn, Al, Sn, etc.) [6, 10], metalloporphyrin/cocatalyst (metal = Co, Cr, Ru, Zn, Al, Mg, Sn, etc.) [11–13], metal oxides [14, 15], Lewis acid/base [16], and other catalysts were well studied [17]. The Jacobsen catalyst as metallosalen catalyst combining the tetrabutylammonium halogenide is most effective for this cycloaddition reaction producing the relative carbonates in high yields under mild reaction conditions [18]. The ionic liquids were also applied to catalyze this reaction [8, 19]. When the halogen anion was replaced by acidic anion, for example, the amino acidic ionic liquids could act as catalysts or cocatalysts in this reaction [20]. Meanwhile, the coupling of disubstituted epoxides and CO_2 to form five-member ring cyclic carbonates was rarely reported due to their steric hindrance effect [21].

The traditional solvents are ineffective for the reaction between CO_2 and epoxides due to the low solubility of CO_2. This coupling reaction is almost carried out

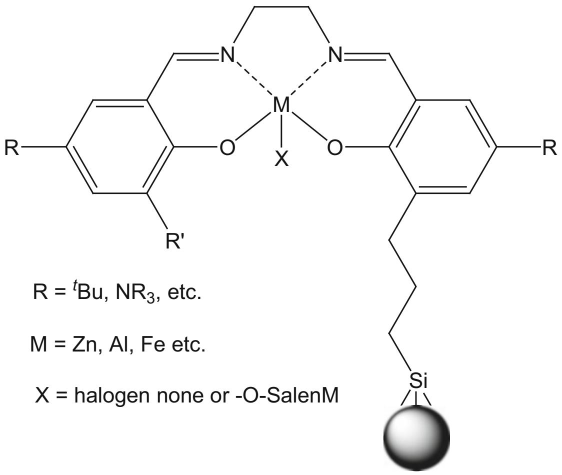


Scheme 17.3 Proposed cycloaddition mechanism of epoxide and CO_2

under solvent-free conditions with the epoxide acting as reactant and solvent. Another solution of ionic liquid as both solvent and catalyst was exploited owning to the high solubility of CO_2. Now, this coupling reaction catalyzed by salenCo(III)Y/TBAX system can be effectively achieved at room temperature under low CO_2 pressure even atmosphere condition. It must be emphasized that the catalyst of salenCo(III)Y, easily oxidized by air in the presence of relative acid, can be dissolved in each common solvent even in toluene compared with the salenCo (II) which precipitates in alcohols.

The mechanism of coupling reaction of epoxide and CO_2 catalyzed by various catalysts is similar to the catalytic cycle of binary catalytic system of salen-type metal complex and TBAX (Scheme 17.3) [22]. The epoxide coordinates firstly to a Lewis acidic center forming intermediate **1** that is attacked by nucleophilic reagent to produce the requisite metal-alkoxide intermediate **2** and that attacks CO_2 to generate intermediate **3**. After intramolecular cyclization of **3**, intermediate **4** is built up and then liberates cyclic carbonate. When the reaction is carried out in a chlorine-free condition, for example, the cocatalyst is just a Lewis base, the intermediate **1** is attacked by a Lewis base-activated CO_2 species to create intermediate **4**. This mechanism insists that both Lewis acidic center and Lewis base center have the same importance when the coupling reaction takes place. The higher activity of these catalytic systems would be attributed to both good nucleophilicity and leaving group except for their appropriate Lewis acidity. The above mechanism was also confirmed by the computational method with some adjustments: in the intermediates **3** and **4**, the coordination oxygen atom switches to the opposite one to overcome the hindrance from substitute R [23, 24].

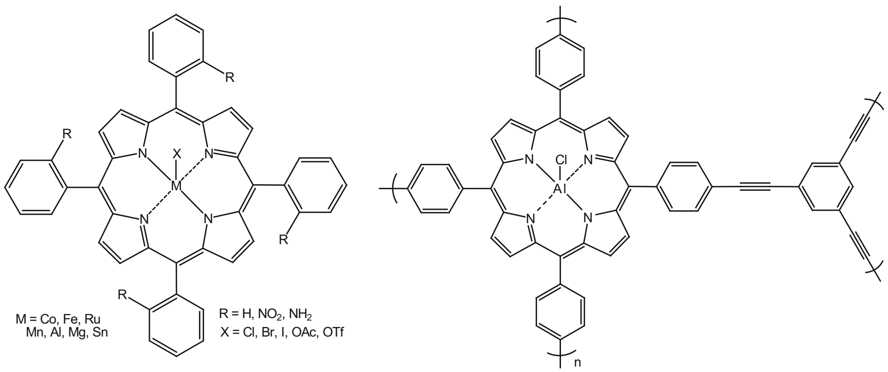
Scheme 17.4 The structural diagram of immobilized catalyst



Based on the understanding about the mechanism of this coupling reaction, many bifunctional catalyst systems (Scheme 17.2) have been developed including ionic liquids [7–9]. Recently, some new type catalyst systems were reported in this cycloaddition of carbon dioxide to epoxides but need harsh reaction conditions [25–29]. Even the C_{60} fullerenol can catalyze this coupling reaction in the presence of potassium iodide [30]. An efficient halogen-free heterogeneous catalyst of carbon material was reported by Hu et al. [31] that was better than the early reported organic base catalysts such as dimethylaminopyridine (DMAP) and 1,5,7-triazabicyclo[4,4,0]-dec-5-ene (TBD) [32–34]. A very simple $ZnBr_2$–EDTANa_2 complex as heterogeneous catalyst can initiate this cycloaddition of CO_2 to epoxide at 150 °C under 2.25 MPa [35].

17.2.1.1 Metal(Salen) Complex Catalysts

Sonbinh T. Nguyen reported some salenCr(III) complexes used as catalysts for the coupling of CO_2 and epoxides at 75 °C under 6.6 atm (0.67 MPa) producing propylene carbonate with 229 of TOF [36], and some salenSn catalysts initiated the coupling reaction under more ambient conditions [5]. Michael North reported a series of bialuminum(salen) complex catalysts that can catalyze this reaction at room temperature and atmosphere pressure [37, 38]. Kleij described some salenZn complex catalysts worked with cocatalyst of TBAI in this coupling reaction using a visual pressure reactor [39, 40]. Recently, some bifunctional metal(salen) complex catalyst and immobilized metal(salen) catalysts were reported by various groups (Scheme 17.4) [41–44].



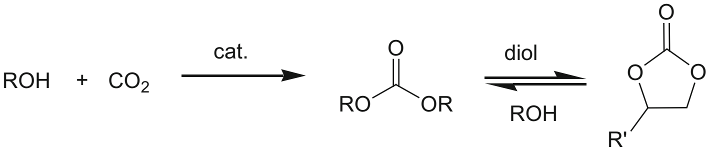
Scheme 17.5 The structural diagram of metalporphyrin and polymeric aluminum-porphyrin catalysts

17.2.1.2 Metalporphyrin Complex Catalysts

In 1995, Krupe et al. reported the first metalporphyrin catalyst of Cr(TPP)Cl used in the synthesis of organic carbonates in the presence of DMAP [13]. Nguyen et al. disclosed Co(TPP)Cl/DMAP catalyst system for this coupling reaction under very mild conditions [45]. A broad series of metalporphyrin complexes (metal = Co, Fe, Ru, Mn, Al, Mg, Sn) were documented by Jing's group (Scheme 17.5) [11, 12]. Recently, a novel conjugated microporous polymer aluminum-porphyrin catalyst, named **Al-CMP**, was reported by Wang and Qin (Scheme 17.5) [46]. Some bifunctional metalporphyrin complex catalysts were reported by Ema [26, 47–49].

17.2.1.3 Ionic Liquid and Heterogeneous Catalysts

Ionic liquids except for their green solvent can also apply as catalysts in the synthesis of organic carbonates [50]. Some immobilized ionic liquids were efficient catalysts in these coupling reactions of epoxides and CO_2 [51, 52]. Various metal–organic framework or MOF-supported ionic liquid catalysts were also developed to this fabrication [53–56]. Magnetic core–shell immobilized salenAl bifunctional catalysts were demonstrated to be a good catalyst system [57]. A simple melamine–ZnI_2 heterogeneous catalyst was also applied for chemical fixation of carbon dioxide to cyclic carbonates [58]. Organic polymeric was revealed to be an efficient catalyst system for this cycloaddition reaction [59]. The fabrication of organic carbonates was also carried out via an electrochemical process using a metal cathode in the presence of TBAX as electrolyte [60].



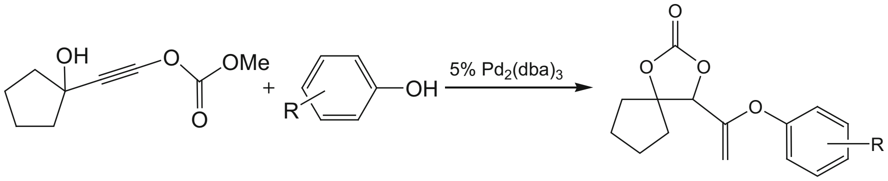
Scheme 17.6 Conversion alcohol to carbonates

17.2.1.4 Halogen-Free Catalysts

In 1997, magnesium oxide was used as catalyst in the cycloaddition of CO_2 to epoxides in DMF at 135 °C. In spite of their lower activity, the catalyst has a good stereoselectivity [61]. A series of quaternary ammonium hydroxides were presented as efficient halogen-free catalysts in the synthesis of organic carbonates from epoxides and carbon dioxide [62].

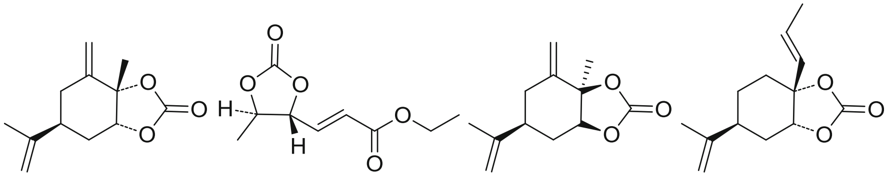
17.2.2 Coupling of Alcohols and CO_2

In fact, the chlorine-free reaction producing the organic carbonates in high yield was early reported by Hoffman in 1982 from the alcohol and carbon dioxide in the presence of triphenylphosphine and diethylazodicarboxylate (DEADC) in tetrahydrofuran: $2ROH + CO_2 + Ph_3P + DEADC \rightarrow ROCO_2R + Ph_3P = O + EtO_2CNHNHCO_2Et$ [63]. The cyclic carbonates were able to be fabricated by diols and carbon dioxide in the presence of catalyst [65, 66]. Sn complexes, known as efficient catalysts for dimethyl carbonate (DMC) preparation from carbon dioxide with methanol or acetals [67], have also been utilized to the synthesis of cyclic carbonate with 99.9 % selectivity [68]. Nowadays, the DMC was commonly synthesized by the exchange reaction of cyclic carbonate, especially the ethyl carbonate (EC) and propylene carbonate (PC), and methanol (Scheme 17.6). Recently, Tomishige et al. reported a new method of direct cyclic carbonate synthesis from CO_2 and diol catalyzed by CeO_2 with 2-cyanopyridine producing five- and six-member ring cyclic carbonates in excellent yield [69]. A special product of 4,4-dimethyl-5-methylene-1,3-dioxolan-2-one was synthesized in 99 % yield at 40 °C and 14 atm (1.4 MPa) pressure by using a solid PS-supported copper iodide catalyst via a carboxylative cyclization of 2-methylbut-3-yn-2-ol in supercritical CO_2 [70]. An interesting palladium-catalyzed CO_2 releasing and refixation from propargylic carbonate and phenols was reported by Yoshida and Ihara in 2003 (Scheme 17.7) [71].



Scheme 17.7 CO_2 releasing and refixation from propargylic carbonate and phenols

Scheme 17.8 Conversion alcohol to carbonates via ammonia



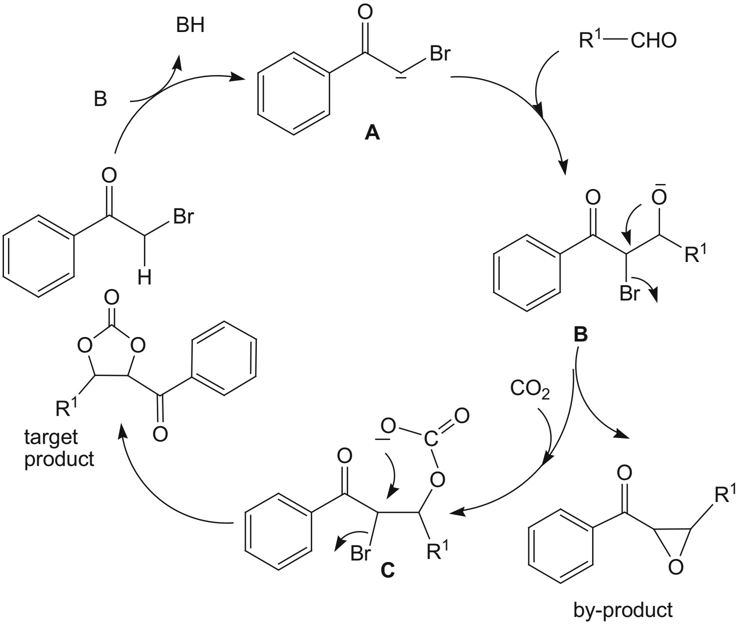
Scheme 17.9 Direct transformation of alkenes to carbonates

17.2.3 Reaction of Alcohols and Urea

In 1946, the reaction of urea with alcohol to yield linear carbonate was firstly reported by Paquin [72] and was carried out in the presence of Ph_3P at 200 °C [73]. Recently, this reaction can be taken place using the metal oxide as catalyst [74] and even in industry reactor [75, 76]. This alcoholysis of urea affords linear carbonates in two steps via an alkyl carbamate intermediate (Scheme 17.8).

17.2.4 Oxidative Carboxylation of Olefins

Oxidative carboxylation of olefins is an alternative single-step pathway for the synthesis of cyclic carbonates (Scheme 17.6). Niobium oxide catalysts reported by Aresta showed modest activity for styrene carbonate synthesis from styrene in the presence of CO_2 and molecular oxygen [77]. This reaction could be carried out in an ionic liquid in the presence of TBAB and *tert*-butyl-hydroperoxide (TBHP) as the oxidizing agent, though pressurized CO_2 to achieve the transformation (10 atm, 80 °C, 6 h, 38 % yield) [78]. The ruthenium porphyrin and SiO_2-supported catalysts can transfer styrene to styrene carbonate in high yield [79–81]. Other procedures were documented in the recent review paper [82, 83]. Recently, an effective transformation of alkenes into cyclic carbonates using $NaHCO_3$ as the C1 source in acetone–water under microwave irradiation conditions has been reported by Hatton et al. (Scheme 17.9) [84].



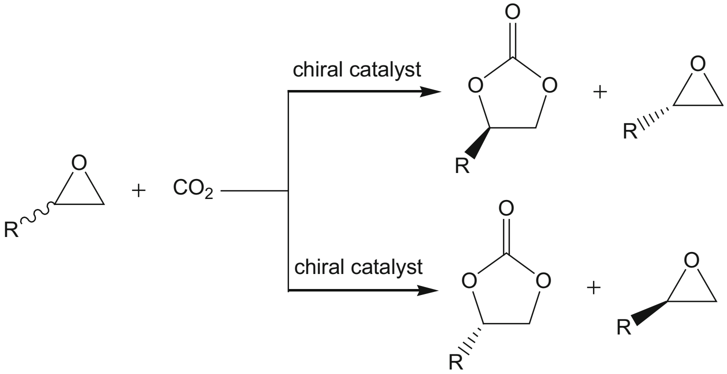
Scheme 17.10 Mechanism for transformation of aldehydes to carbonates

17.2.5 *Conversion of Aldehydes to Cyclic Carbonates*

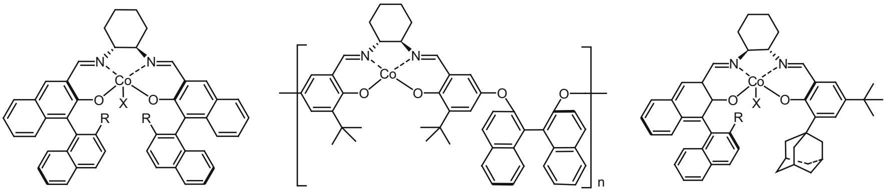
In 2011, Jing et al. reported an extend Darzens reaction of aldehydes, phenacyl bromide, and CO_2 in the presence of lithium diisopropylamide (LDA) [85]. With this strategy, a series of disubstituted cyclic carbonates were successfully obtained from moderate to good yield. The mechanism is depicted in Scheme 17.10, in which the deprotonated phenacyl bromide (**A**) attacks the carbon of aldehyde generating an anion intermediate (**B**). When **B** attacks CO_2-forming intermediate **C**, an intramolecular cyclization occurs and leads the disubstituted cyclic carbonate along with leaving of bromide anion; when an intramolecular cyclization occurs in the intermediate **B**, a by-product of epoxide produces as a typical product of Darzens reaction. Recently, treatment of aldehydes with sulfur ylide ($CH_2 = SOMe_2$ or $CH_2 = SMe_2$) under CO_2 atmosphere at 40 °C in DMSO–THF solution produces cyclic carbonates in high yield [86].

17.3 Synthetic Methods of Chiral Organic Carbonates

Chiral cyclic carbonates are generally fabricated by the cycloaddition of CO_2 to chiral epoxides in the presence of catalysts [43] instead of the reaction of chiral diols with poisonous triphosgene [87]. The chiral cyclic carbonates can be achieved by a catalytic kinetic resolution of racemic epoxides with CO_2 in the presence of



Scheme 17.11 Kinetic resolution of racemic epoxide with CO_2 to chiral cyclic carbonate using

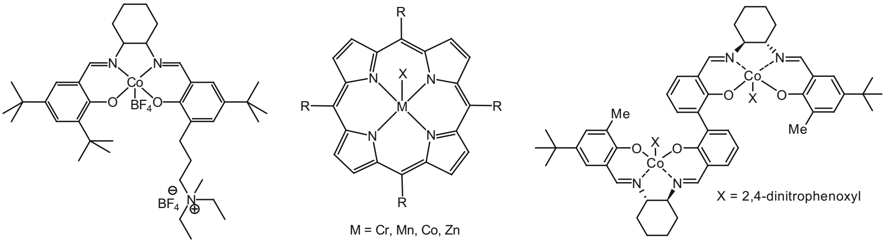


Scheme 17.12 Configurations of common chiral catalysts

chiral catalysts such as Jacobsen catalyst [88, 89] or bifunctional chiral catalyst [90]. New chiral catalysts combing the chirality of BINOL and salen in one molecule can improve the ee value of chiral propylene carbonate up to 95 % under mild reaction conditions [91] and demonstrate a significant synergetic effect from two chiral parts of one molecule [92]. This positive synergetic effect could be observed in a two-component catalyst systems of chiral salenCoX and ionic liquid [20]. Recently, Lu et al. report a structural refined salenCoX catalyst exhibiting good enantioselectivity for the chiral carbonates [93] that has a potential ability to be made suitable pharmaceutical materials. And Hupp and co-workers demonstrated a hafnium-based metal–organic framework catalyst for the regioselective and enantioretentive epoxide activation [57]. The structures of common chiral catalysts are depicted in Schemes 17.11 and 17.12.

17.4 Synthetic Methods of Organic Polycarbonates

The polycarbonate made from the reaction of bisphenol A (BPA) and phosgene in industry are widely used in many purposes such as packaging materials, thermoplastics, digital media (CD, DVD), sport safety equipment, safety glasses, etc. The BPA as a key building block of polycarbonate plastics can be released slowly and come into food and beverage that affect human health confirmed by many research



Scheme 17.13 Typical salenM and metalloporphyrin catalysts for copolymerization of PO and CO_2

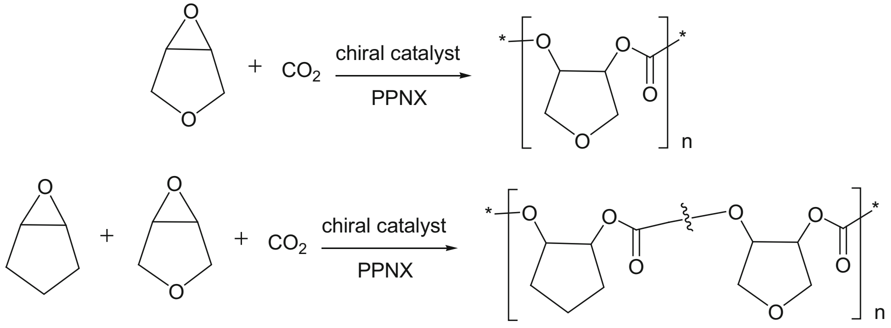
institutes and government agencies including the European Commission's Scientific Committee on Food (SCF). Thus, new-type polycarbonates instead of BPA are really desired in recent years. The metal-catalyzed direct copolymerization of CO_2 and epoxide is a new way to approach polycarbonates [94–96].

In 1969, Inoue and co-workers discovered that a mixture of $ZnEt_2$ and water could catalyze the alternating copolymerization of propylene oxide (PO) and CO_2, marking the advent of epoxide–CO_2 coupling chemistry [97]. The Zn-containing catalysts were good catalysts in the early 2000; a series of them were reported by Coates et al. [98]. The Cr-salen catalyst containing azide N_3^- as counter anion with cocatalyst of $PPN^+N_3^-$ are developed by Darensbourg et al. to catalyze the alternative copolymerization of cyclohexene epoxide and CO_2 under 35 bar (3.5 MPa) to give polycyclohexene carbonate with 1,150 TOF (h^{-1}) [99]. Lu et al. worked on the salenCo catalysts and discovered an efficient of it modified by a linkage of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, Scheme 17.13). This special catalyst (0.01 mol% catalyst loading) can initiate the alternating copolymerization of PO and CO_2 affording poly(propylene carbonate) with excellent selectively and a TOF of 10,880 h^{-1} at 100 °C under 2.5 MPa CO_2 pressure (Scheme 17.13) [100]. The selectivity and the stereoselectivity of catalysts were also discussed. Recently, metalloporphyrin catalysts were also used to catalyze the alternative copolymerization of epoxide and CO_2 [101, 102]. Some investigations about the synthesis of chiral polycarbonates were also reported [103, 104].

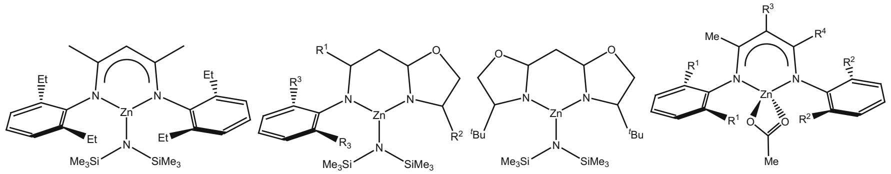
Some functionalized epoxides were copolymerized with CO_2 to produce polycarbonates that can modify further [105, 106]. Terpolymerizations of CO_2, propylene epoxide, and maleic anhydride (MA) could be carried out in a toluene solution using a zinc catalyst [107]. Recently, Lu et al. reported crystalline-gradient chiral polycarbonates using a chiral dinuclear salenCoX catalyst and PPNX ($X = 2$,4-dinitrophenol) (Scheme 17.14). The melting point of chiral polymer could be up to 270 °C [108].

17.4.1 Zinc-Based Complex Catalysts

In 1999, Nozaki et al. discovered that copolymerization of cyclohexene oxide with CO_2 at 40 °C to give poly(cyclohexene carbonate) would be taken placed in the



Scheme 17.14 Crystalline-gradient chiral polycarbonates

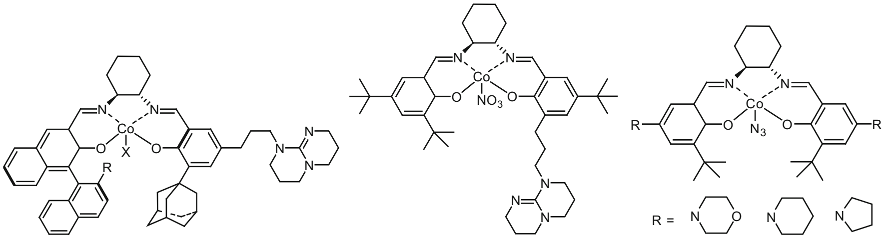


Scheme 17.15 Structures of coates zinc catalysts

presence of a mixture of diphenylpyrrolidine-2-yl-methanol and $ZnEt_2$ [109]. Later, Coates et al. have developed a great variety of Zn complex catalyst that can initiate the alternative copolymerization of a lot of cyclohexene oxide with CO_2 [110–113]. In which, zinc bis(trimethylsilyl)amido complexes that are effective in the stereoselective copolymerization of cyclohexene oxide with CO_2 exhibiting the highest enantioselectivity (72 % ee). The resulting poly(cyclohexene carbonate) is perfectly alternating and has an M_n of 14.7 kDa, a PDI of 1.35, and t_g and t_m of 120 and 220 °C, respectively [110]. The typical zinc complex catalysts were illustrated in Scheme 17.15.

17.4.2 Cobalt-Based Complex Catalysts

Coates and co-workers firstly reported the copolymerization of propylene oxide and CO_2 using salenCo(III)OAc complex catalyst at room temperature under 53 atm (5.4 MPa) generated polypropylene carbonate with 21,700 M_n and 95 % carbonate linkages [114]. Then, Lu and Darensbourg developed many useful and more efficient salen-type cobalt (III) catalysts in this copolymerization that were well reviewed in some literatures [115–121]. With their own devised and synthesized salen-type cobalt catalysts, Lu et al. made a big success in this research area and can get higher selectivity both in carbonate linkage and stereoselectivity and higher molar mass of polymers. These important catalysts are shown in Scheme 17.16.



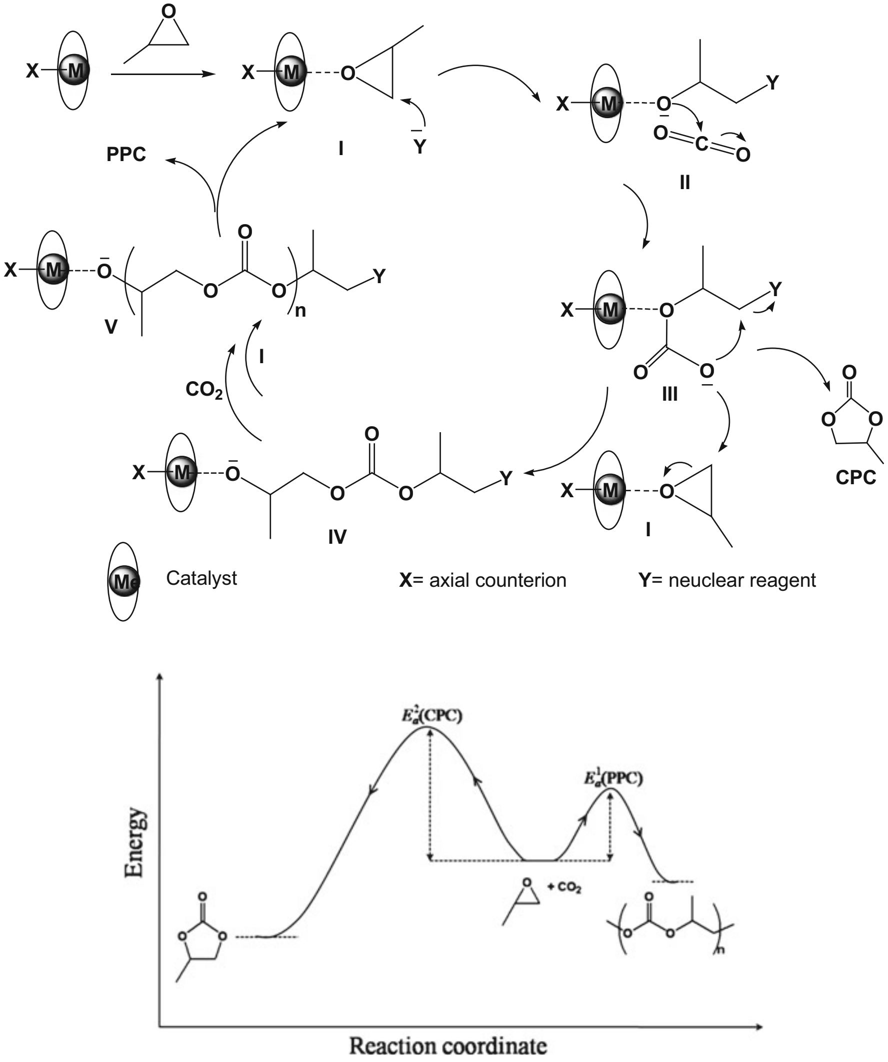
Scheme 17.16 The modified salenCo(III)X catalysts used in the copolymerization

17.4.3 *Other Catalysts*

Aluminum, chromium, and other metal complex catalysts were also used in the copolymerization of epoxides and CO_2 that were documented in different reviews [116, 119]. The iron complex catalyst combined with TBAC can act as efficient catalyst system to generate polycarbonate from the reaction of cyclohexene oxide (CHO) and CO_2 with 1418 M_n in 96 % carbonate linkage [122]. A simple Co(III)–Zn cyanide complex was disclosed as a good catalyst in this reaction [123].

17.5 Mechanism in Synthesis of Organic Polycarbonates

In 2002, Darensbourg and co-workers proposed a dual copolymerization mechanism for the salenCr catalyst system: a bimetallic initiation and monometallic propagation [124]. Later on, Coates and co-workers proposed a bimetallic mechanism for bimetallic catalyst of zinc complexes showing a reaction order of 1.73 of catalyst concentration and a monometallic mechanism for monometallic catalyst showing a reaction order of 1 of catalyst concentration [125]. In 2013, Lu et al. demonstrated that the copolymerization of PO and CO_2 suffers a reaction order of 1.6 for a binary catalyst and 1 for a bifunctional catalyst [126]. Recently, Jing and co-workers suggested a new competition mechanism between the cycloaddition and alternating copolymerization of propylene oxide and carbon dioxide using a C_{2v} cobalt–porphyrin catalyst in terms of their detailed kinetic study [127]. This competition mechanism was not only suitable for the catalyst of metalloporphyrin but also for the catalyst of bifunctional salenCo [128]. A bimetallic initiation and propagation processes were offered and consistent with the second reaction order for catalyst resulted by a detailed kinetic investigations. A monometallic mechanism for the coupling of PO and CO_2 was synchronously proposed. Thus, a unified catalytic cycle for the cycloaddition and alternating copolymerization of propylene oxide and carbon dioxide was revealed and could assist to understand why the activation energy of polymerization is always lower than that of cycloaddition (Scheme 17.17) [126–128]. In fact, large concentration of salenCoX catalyst could yield the polymers too. When the catalyst loading was very small, the product of reaction of PO and CO_2 in the early stage was found to be sole propylene carbonate due to a large probability of intramolecular



Scheme 17.17 Competition mechanism of PO and CO_2 and their schematic reaction process

collision of intermediate III than a low probability of molecular collision between species III and I.

17.6 Properties of Organic Carbonates and Polycarbonates

Organic carbonates have high dipole moment and high dielectric constant. PC has a dipole moment of $\mu = 16.5 \times 10^{-30}$ C·m and an outstanding dielectric constant of $\varepsilon_r = 64.92$. This makes PC particularly well suited for anhydrous, electrochemical applications [129]. The polycyclohexene carbonate (PCHC) typically have higher glass transition temperature ($t_g = 115\ °C$) resulting in materials with properties very similar to polystyrene. PCHC also has a higher decomposition temperature (300 °C), which allows melt processing in industry. In contrast, polypropylene carbonate (PPC) has lower t_g (35–40 °C) and decomposition temperature (<250 °C) allowing applications as adhesives, blinders, additives, pore formers, etc. [96]. The computational investigations about their thermochemical properties are also reported [130, 131]. The depolymerization of polycarbonates was investigated [132]. The important investigations about the reactions of organic carbonates and polycarbonates were summarized below.

Ethylene carbonate is infinitely soluble in water. Propylene carbonate is soluble in 100 g water about 25.0 g (at 25 °C). Butylene carbonate is less soluble (7.0/100 g water at 25 °C). Dimethyl carbonate and diethyl carbonate are only sparingly soluble in water, but soluble in many organic solvents.

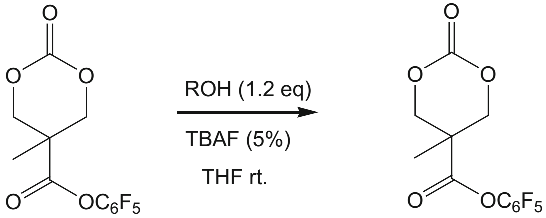
17.7 Reactions of Organic Carbonates and Polycarbonates

Organic carbonates can be used to alkylate active-hydrogen-containing aromatics such as phenol, phenolic resins, thiophenols, etc. The common reagent is a commercially available compound, dimethyl carbonate (DMC).

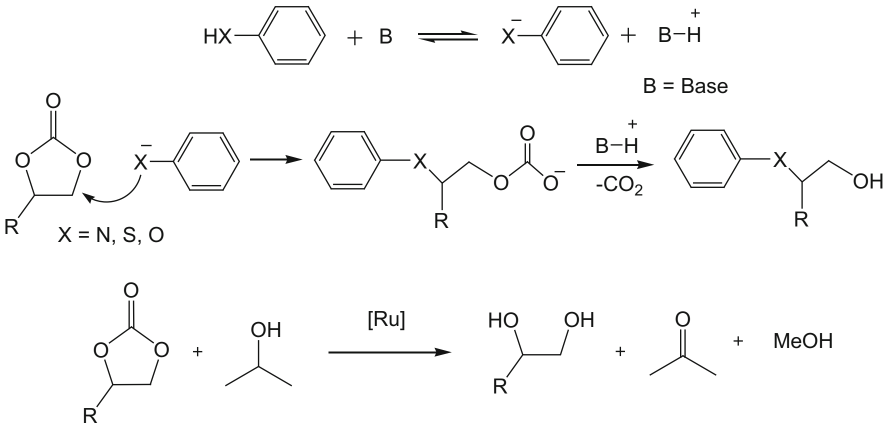
17.7.1 Reactions of Organic Carbonates

As shown in Scheme 17.4, the transetherification of carbonate with alcohol is a commonly used method to transfer the aryl group to carbonate. In 2014, Hederick and co-workers developed a general method for the functionalization of cyclic carbonate monomers via a pentafluorophenyl ester substituent at the 5-position in the presence of TBAF (Scheme 17.18) [133].

Organic carbonates can also react with alcohols, thiophenol, and aniline by heating to afford relative compounds accompanying with the loss of carbon dioxide. The general reaction scheme is illustrated in 17.12. An nucleophilic reagent attacks at either alkylene carbon followed by loss of carbon dioxide to ether/

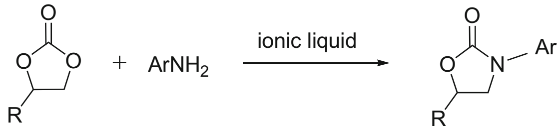


Scheme 17.18 General synthesis of functionalized cyclic carbonates via TBAF-catalyzed transesterification



Scheme 17.19 Reactions with aromatic active-hydrogen-containing moieties and transfer hydrogenation of cyclic carbonates with isopropanol

Scheme 17.20 Carbamates formation from cyclic carbonates



thioether/amine alcohols. Typically, temperatures in the range 100–150 °C are required for alkylation of amines and thiols, whereas higher temperatures in the range of 150–200 °C are required for alkylation of alcohols. In such reactions, the propylene carbonate reacts with BPA giving oligomers in the presence of DBU [134]. A new type reaction of alkylene carbonates and isopropanol results 1,3-diol, methanol, and acetone catalyzed by a ruthenium catalyst is really a good methodology to methanol from CO_2 (Scheme 17.19) [135].

Cyclic carbonates which react with amines to yield hydroxyurethanes catalyzed by organic base, such as DMAP, DBU, DABCO, etc., were investigated [136]. Carbamates could be made from cyclic carbonates in the presence of ionic liquids (Scheme 17.20) [137–139].

Trimethyl carbonate could react with alcohol to produce polymers catalyzed by diphenyl phosphate, which was copolymerized with LLA to generate macrocyclic polycarbonates [140]. Recently, a simple imidazole was introduced to react with diols to form cyclic carbonates that were then polymerized to polycarbonates via a ring-opening reaction in the presence of DBU [141].

17.7.2 Reactions of Organic Polycarbonates

The organic polycarbonates are easy to transfer to organic carbonates in the presence of Lewis acid/Brønsted acid or in the condition of heating [132]. Like organic carbonates, they can react with alcohol and amine in the presence of catalysts. The reactivity of functionalized polycarbonates is different from common polycarbonates, such as propylene carbonate and polycyclohexene carbonate. Researchers have designed and synthesized some functionalized poly carbonates that can further react to form functional groups of sulfonic acid group or carboxylic acid groups [105–107, 142].

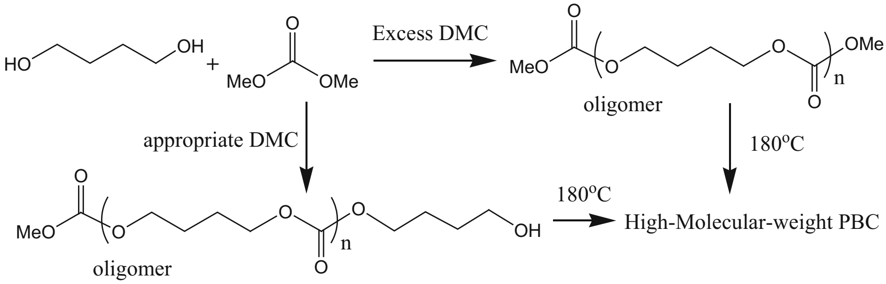
17.8 Applications of Organic Carbonates and Polycarbonates

17.8.1 Organic Carbonates as Solvent in Organic Synthesis

Organic carbonates, particularly cyclic carbonates, have significant benefits as eco-friendly solvents due to their biodegradability, low vapor pressure, odor levels, and toxicities. The organic carbonates can be widely used as solvent except for the electrolyte in lithium battery. It is necessary to be able to predict their behavior in extraction processes in terms of their miscibility with other solvents. Ethylene and propylene carbonate are soluble in water. Butylene carbonate is less soluble. Dimethyl carbonate and diethyl carbonate are only sparingly soluble in water. They are soluble in many organic solvents, particularly polar solvents, such as esters, ketones, ethers, alcohols, and aromatic hydrocarbons. The lower-molecular-weight aliphatic carbonates form azeotropic mixtures with several organic solvents [129, 143]. With excellent polarity, organic carbonates are classified to aprotic highly dipolar solvents like DMSO or DMF. In contrast to these solvents, most organic carbonates show only limited or no miscibility with water. Recently, Hunt et al. demonstrated that ethylene and propylene carbonate are viable greener solvents in Heck reactions, showing a highly effective alternative to traditionally used dipolar aprotic solvents such as NMP, DMF, DMSO, etc. [144].

17.8.2 Organic Carbonates as Protecting Groups in Organic Synthesis

In organic synthesis, especially the total synthesis of useful bioactive compounds or nature products, the strategy of protecting group is very useful and popular. The organic carbonates are used as protecting groups for the functional groups for diols and epoxides in the organic synthesis [145]. This is a catalyzed and greener protecting–deprotecting method to achieve target products.



Scheme 17.21 Two-step strategy of fabricating high-molecular-weight polycarbonate materials

17.8.3 *Organic Polycarbonates as Materials*

Organic polycarbonates as promising biodegradable plastics are responsible for the hope of recovery and the reducing of white pollution of plastics. Hedrick and co-workers have developed some useful polycarbonates for drug delivery [146] and therapeutic method of selective lysis of microbial membranes [147]. Recently, Yang and co-workers have applied polycarbonates onto the surface of PEG to prepare an antifouling PEG, antibacterial cationic polycarbonate, and maleimide-functionalized polycarbonate via organocatalytic ring-opening polymerization as antibacterial and antifouling coating materials [148]. The polymers were grafted onto thiol-functionalized PDMS silicone rubber surfaces via Michael addition. More importantly, the coating was able to resist protein fouling and platelet adhesion and did not cause significant hemolysis. Therefore, this polymer coating holds potential for prevention of bacterial fouling, biofilm formation, and catheter-associated bloodstream infections.

Lee and co-workers develop a new strategy of two steps of polymerization to produce high-molecular-weight aliphatic polycarbonates with molar mass of 100,000–250,000 by using condensation polymerizations of DMC and various diols. In first step, oligomers bearing almost equal numbers of hydroxy and carbonate moieties were prepared via the oligomerization of diols and DMC catalyzed by NaOH 0.1 mol% per diol. And then the polycondensation was carried out by heating at 180 °C under evacuation in second step about 6 h (Scheme 17.21) [149]. The oligomer chains grew mainly by the reaction between −OH and $-OC(O)OCH_3$ end groups releasing methanol. The high-molecular-weight polymers could be gained by simply heating the oligomers by freeing methanol and some of DMC. This new strategy to approach high-molecular-weight polymers shall be applied to the industry in the near future.

17.9 Important Compounds of Cyclic Carbonates

The important cyclic carbonates were illustrated in Table 17.1.

Table 17.1 Important cyclic carbonates

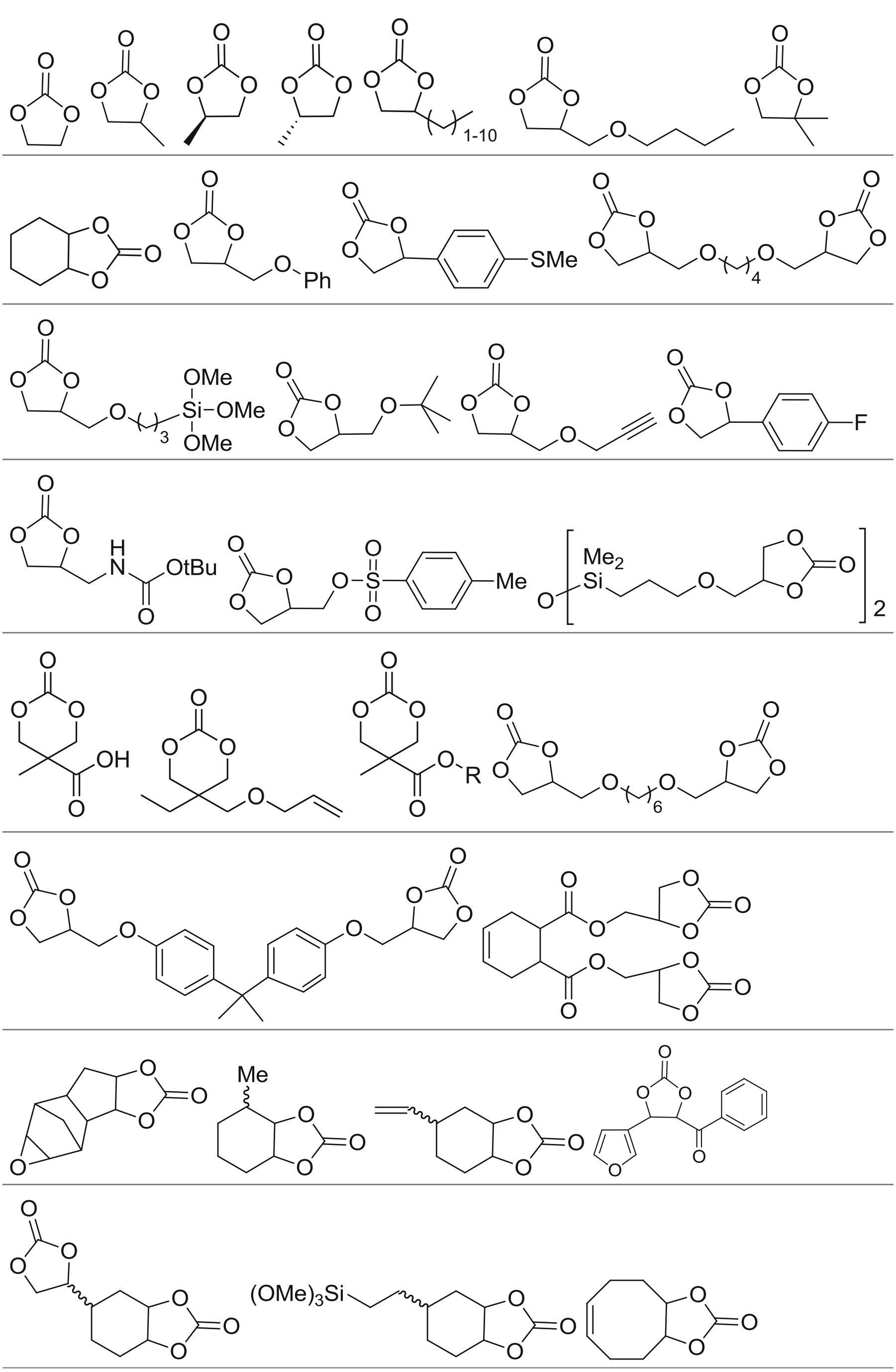


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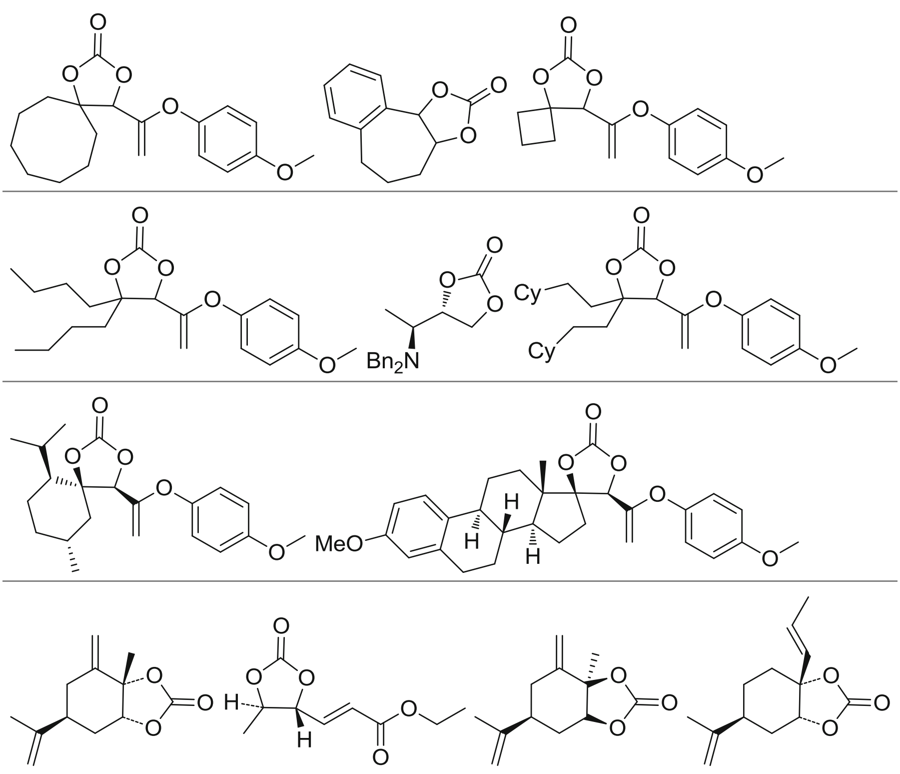
Table 17.1 (continued)



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Chapter 18
Application of Organic Carbonates in Organic Transformation Catalyzed by Ionic Liquids

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Abstract Organic carbonates are renowned for their low toxicity and high biodegradability, which is considered as green reagents and an appropriate alternative to conventional toxic compounds. Additionally, organic carbonates can be produced from CO_2; therefore, the transformation of organic carbonates to other valuable chemicals is an indirect way for CO_2 utilization. The transformation reactions of organic carbonates mainly include alkylation reactions, carbonylation reactions, and transesterification reactions. Ionic liquids, as attractive media, have already exhibited excellent performance on promoting various transformations of organic carbonates. This chapter covers recent applications of organic carbonates in organic transformation reactions catalyzed by ionic liquids.

Keywords Phosgene replacement • Chlorine-free reagent • Organic carbonate • Ionic liquid • Alkylation reaction • Carbonylation reaction • Transesterification reaction

18.1 Introduction

The increasing sustainable awareness, supported by both public opinion and governments, is guiding chemical industries toward eco-friendly directions. To develop greener methodologies, a growing number of efforts have been paid to the replacement of harmful reagents used in organic synthesis. Currently, organic carbonates are regarded as safe, environmentally benign, and versatile substitutes for conventional toxic compounds [1].

Organic carbonates contain several active basic groups such as alkyl, alkoxy, and carbonyl; therefore, they can serve as chlorine-free reagents in alkylation, hydroxyalkylation, and carbonylation reactions in place of dangerous phosgene,

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methyl halides, and dimethyl sulfate [2, 3]. Compared with traditional non-green reagents applied in organic synthesis, organic carbonates produce a minimum amount of waste, exhibiting a low environmental impact. As the main by-products produced from transformations of organic carbonates, alcohols and CO_2 can be recycled to form organic carbonates in principle [4]. Additionally, the production of organic carbonates from renewable carbon resource, e.g., $CO_{2,}$ has been well established, which implies the transformation of organic carbonates to other value-added chemicals is an indirect way for greenhouse gas fixation [5–7]. The transformation of organic carbonates catalyzed by some excellent catalytic systems, such as zeolites, metal oxides, and inorganic bases, has already been reviewed by distinguished scientists [8–10]. In addition, as another powerful catalytic system, ionic liquids are drawing more and more attentions.

Ionic liquids, traditionally defined as special “molten salts” with melting points below 100 °C, are often considered as green solvents [11–13]. The cations in ionic liquids are generally bulk, organic, and low-symmetrical moieties, mostly based on ammonium, phosphonium, imidazolium, pyridinium, pyrrolidinium, or triazolium. The anions in ionic liquids are either organic or inorganic moieties [14, 15]. Although some ionic liquids contain halides, they are still recognized as relatively safe due to their stability and the characteristic of extremely low vapor pressure. Beyond traditional volatile organic solvents (VOCs), ionic liquids provide the potential for developing more eco-friendly catalytic media. Another feature of ionic liquids is potential formation of hydrogen bonds [16, 17]. Both intramolecular and intermolecular hydrogen bonds indicate that ionic liquids are delicate assemblies constituted by hydrogen bond donors and hydrogen bond acceptors, which give them the chance to serve as catalysts. The present investigations have revealed that the cations of ionic liquids can effectively activate electrophiles as hydrogen bond donors, and the anions can activate nucleophiles as hydrogen bond acceptors in organic reaction [18]. Organic carbonates as prominent electrophiles can be activated by cations of ionic liquids through the hydrogen bond interaction and then react with the nucleophile species. The dual activation by the cations and anions makes ionic liquids attract special interests in transformations of organic carbonates.

This chapter will focus on the transformation of organic carbonates catalyzed by ionic liquids, which provides a series of alternative examples for green chemical synthetic methodologies. Particularly, it includes alkylation reactions, carbonylation reactions, and transesterification reactions.

18.2 Alkylation Reaction

Depending on the structural variation, organic carbonates are classified into linear carbonates and cyclic carbonates. In general, linear carbonates can serve as alkylating reagents, and cyclic carbonates can be used as hydroxyalkylating reagents.

Scheme 18.1 O-methylation of phenols with DMC

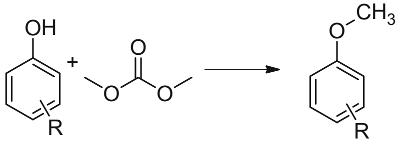


Table 18.1 Reaction of phenol with DMC in the presence of different ionic liquids

Entry	Catalyst	Conversion/%	Selectivity/%	Yield/%
1	BmimCl	99.8	100	99.8
2	BmimBr	62.5	100	62.5
3	$BmimBF_4$	21.6	100	21.6
4	$BmimPF_6$	12.2	100	12.2
5	EmimBr	60.7	100	60.7
6	Bu_4NCl	22.9	86.3	19.8
7	None	0	–	0

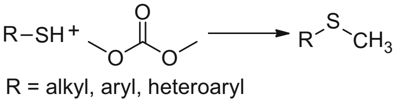
Reaction conditions: phenol 0.10 mol, DMC 0.18 mol, ionic liquid 0.05 mol, 120 °C, 1.5 h

18.2.1 Alkylation Reactions with Linear Dialkyl Carbonates

18.2.1.1 O-Methylation of Phenols with DMC

Aryl methyl ethers are valuable intermediates for the preparation of dyes, agrochemicals, fragrances, and pesticides. They are conventionally produced by O-methylation of the corresponding phenols with methyl halides or dimethyl sulfate. However, these methods require not only harmful reagents but also a stoichiometric amount of strong base to neutralize acidic by-product. To overcome these problems, Thiébaud and coworkers reported O-methylation of phenols with dimethyl carbonate (DMC) in the presence of tetrabutylammonium bromide (TBAB) (Scheme 18.1) [19]. In a semicontinuous process at 130 °C, the 100 mol % TBAB could catalyze the reaction to afford anisole in 100 % yield.

Shen and coworkers studied catalytic activities of different ionic liquids in O-methylation reaction of phenols with DMC (Table 18.1) [20]. The results suggested that the anions in ionic liquids have a strong impact on catalytic activity. Among all investigated ionic liquids, 1-butyl-3-methyl-imidazolium chloride (BmimCl) was the most efficient catalyst, which gave anisole in 99.8 % yield at 120 °C after 1.5 h. When using 1-butyl-3-methyl-imidazolium bromide (BmimBr), 1-butyl-3-methyl-imidazolium tetrafluoroborate ($BmimBF_4$), and 1-butyl-3-methyl-imidazolium hexafluorophosphate ($BmimPF_6$) as catalysts, the yields of product were 62.5 %, 21.6 %, and 12.2 %, respectively. 1-Ethyl-3-methyl-imidazolium bromide (EmimBr) afforded a similar yield as that of BmimBr, indicating that chain length of substituent groups on imidazolium is not a dominating factor on the catalytic reaction. Tetrabutylammonium chloride (Bu_4NCl) provided anisole in only 19.8 % yield and 86.3 % selectivity, much lower than provided by BmimCl. It suggested that the imidazolium cation plays a significant role in the catalysis. Additionally, BmimCl could catalyze O-methylation reactions of substituted phenols with DMC in high yields and 100 % selectivity.



Scheme 18.2 S-methylation of thiols with DMC

To improve the stability of bio-oil, Song et al. investigated O-methylation of the phenolic bio-oil with DMC catalyzed by BmimCl [21]. Under 130 °C for 2 h, phenolic compounds in the bio-oil were methylated efficiently, forming the corresponding aryl methyl ethers. Compared with original phenolic bio-oil, the heating value of the upgraded phenolic bio-oil was greatly elevated more than 30 %.

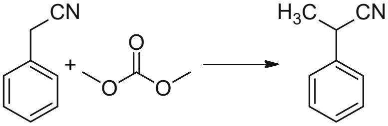
In all these studies of ionic liquid-catalyzed O-methylation of phenols with DMC, ionic liquids were used in the large amount (>50 mol%). The high cost of ionic liquids limits the large-scale industrial application. In the meanwhile, other kinds of high-efficiency catalysts have also been reported. For example, Tundo and coworkers performed the reactions of phenols with DMC under gas-liquid phase-transfer catalysis (GLPTC) conditions in a continuous-flow process at the temperature of 160–180 °C. The desired aryl methyl ethers were produced with high selectivities [22, 23].

18.2.1.2 S-Methylation of Thiols with DMC

Thioether moieties can be found in many pharmaceuticals and biologically active compounds [24]. In 2011, Xie and coworkers reported the synthesis of methyl thioethers from thiols and DMC using ionic liquids as solvents and catalysts (Scheme 18.2) [25]. Different imidazolium- and pyridinium-based ionic liquids were studied, and it was found that the length of substituted groups on cations of ionic liquids did not affect the catalytic activities. BmimCl was the most efficient catalyst, which catalyzed reactions of various alkyl, aryl, and heterocyclic thiols with DMC to produce corresponding products in moderate to high yields at 110 °C. The authors used ^{1}H NMR to investigate the catalytic mechanism. The proton of mercapto group underwent a downfield shift from 13.84 to 14.30 ppm in the presence of BmimCl, which implied that hydrogen bond interaction between BmimCl and the mercapto group might play an important role in the catalysis.

18.2.1.3 C-Methylation of Phenylacetonitrile with DMC

C-methylation of phenylacetonitrile is a model reaction for synthesis of the precursor of the well-known drug ibuprofen [9]. Our group investigated the reaction of phenylacetonitrile with DMC catalyzed by ionic liquids (Scheme 18.3) [18], and the catalytic activities of ionic liquids were listed in Table 18.2. It was found that the C-2 proton of the imidazolium ring is crucial in the catalysis. Ionic liquids containing C-2 proton of the imidazolium ring, such as 1-butyl-3-methyl-imidazolium acetate (BmimOAc), BmimCl, and BmimBr, gave the target product in the yields of 98 %, 96 %, and 70 %, respectively. However, 1,2-dimethyl-3-butyl-imidazolium acetate (BmmimOAc), 1,2-dimethyl-3-butyl-imidazolium chloride

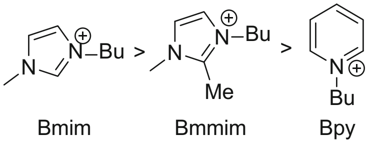


Scheme 18.3 C-methylation of phenylacetonitrile with DMC

Table 18.2 Reaction of phenylacetonitrile and DMC catalyzed by ionic liquids

Entry	Catalyst	Conversion/%	Selectivity/%	Yield/%[a]
1	BmimOAc	98	100	98
2	BmimCl	96	100	96
3	BmimBr	76	92	70
4	BmmimOAc	34	99	34
5	BmmimCl	9	96	9
6	BmmimBr	8	80	6
7	BPyCl	0	0	0
8	$BPyBF_4$	0	0	0

Reaction conditions: phenylacetonitrile 2 mmol, DMC 10 mL, ionic liquid 0.2 mmol, 130 °C, 10 h
[a]GC yield



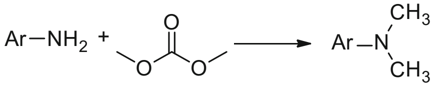
Scheme 18.4 The catalytic activities of different cations

(BmmimCl), and 1,2-dimethyl-3-butyl-imidazolium bromide (BmmimBr), in which the C-2 proton of imidazolium was replaced by a methyl group, only afforded the product in the yields of 34, 9, and 6 % under identical conditions. 1-butyl-pyridinium-based (Bpy) ionic liquids did not give any desired product. The catalytic activities of cations decreased in the order: Bmim > Bmmim > Bpy, consistent with the order of the hydrogen bond donor ability (Scheme 18.4). Meanwhile, the catalytic activities of anions decreased according to the order of OAc > Cl > Br, which is consistent with the order of the hydrogen bond acceptor ability. The cation in BmimOAc that activates electrophile (DMC) as hydrogen bond donor and the anion that activates nucleophile (phenylacetonitrile) as hydrogen bond acceptor catalyze presumably the reaction cooperatively.

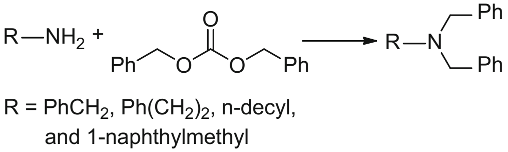
18.2.1.4 N-Alkylation of Amines/Ammonium Salts/Indole

In 2004, Jiang et al. reported N,N-dimethylation of primary aromatic amines with DMC catalyzed by diphenylammonium triflate (Scheme 18.5) [26]. The conversion of aniline and the selectivity to N,N-dimethylaniline were 99.9 % and 99.6 %, respectively, at 180 °C in 160 min, and no by-product N-phenyl carbamate was obtained. Gupte et al. investigated the synthesis of N,N-dimethylaniline derivatives

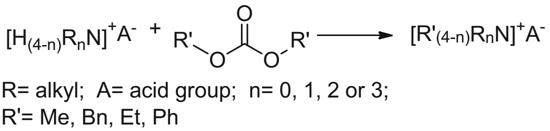
Scheme 18.5 N,N-dimethylation of primary aromatic amines with DMC



Scheme 18.6 N,N-dibenzylation of primary aliphatic amines with DBC



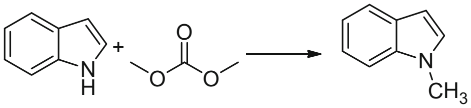
Scheme 18.7 N-alkylation of ammonium salts with dialkyl carbonates



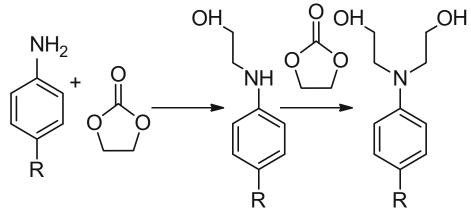
from aromatic amines and DMC catalyzed by ammonium, phosphonium, and guanidinium ionic liquids [27]. They found that a small amount of water is conducive to improve the yield of dialkylated product due to hydrolysis of by-products. In the absence of water, the yield of N,N-dimethylaniline was only 85 %, and appreciable amount of by-product methyl-N-methyl-N-phenylcarbamate was formed (15 % yield). After adding 6 eq. H_2O with respect to aniline, the yield of N,N-dimethylaniline increased to 99.8 %. However, when 35 eq. H_2O was added, the yield of N,N-dimethylaniline decreased to 78 %. For comparison, inorganic solid bases such as MgO, hydrotalcite, zeolites, clay, etc. were also applied to catalyze N-alkylation of aniline with DMC leading to N,N-dimethylaniline in very low selectivity [27]. Selva's group reported N,N-dibenzylation of aliphatic amines with dibenzyl carbonate (DBC) (Scheme 18.6) [28] and N,N-dimethylation of aromatic amines with unsymmetrical methyl alkyl carbonates in the presence of phosphonium-based ionic liquids [29]. In their studies, the phosphonium salt showed higher catalytic activities than ammonium and imidazolium salts.

Wu's group has carried out a series of works on alkylation of ammonium salts with dialkyl carbonates catalyzed by EmimBr (Scheme 18.7) [30–32]. Different anions (A^-) in the starting ammonium salts gave different yields of desired quaternary ammonium salts, which the yields of corresponding products decreased according to the order: Br^-, Cl^-, $NO_3^- > F^-$, $SO_4^{2-} > C_2O_4^{2-}$, CO_3^{2-}, OAc^-. Additionally, the reactivity of the different dialkyl carbonates decreased in the order: DMC > DBC > diethyl carbonate (DEC) > diphenyl carbonate (DPC), which might depend on the steric hindrance of the substituent groups and stability of carbon cations on the carbonates.

Holbrey and coworkers reported methylation of indole with DMC catalyzed by tributylmethylammonium methyl carbonate (Scheme 18.8) [33]. The 100 % conversion and 100 % selectivity to N-methylindole were achieved at 230 °C in 20 min under batch microwave heating conditions. Subsequently, when the reaction was



Scheme 18.8 N-methylation of indole with DMC



Scheme 18.9 N-hydroxyalkylation of aromatic amines with cyclic carbonate

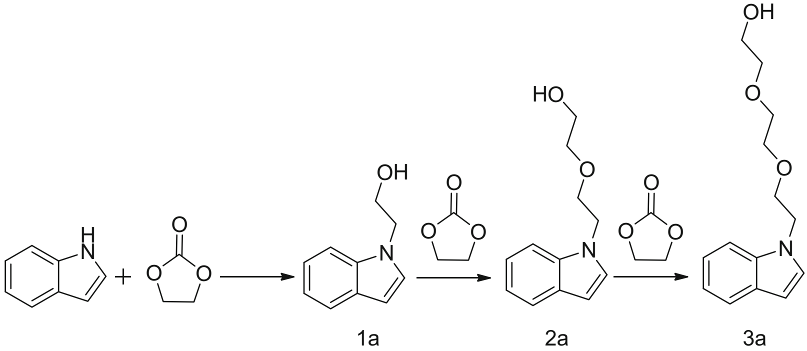
carried out through a high temperature/high pressure (285 °C/150 bar) continuous-flow process, 100 % conversion and 98 % isolated yield were obtained in only 3 min residence time. The efficient continuous-flow process could afford a calculated productivity of ~100 g per day, which has significant potential for industrial application.

18.2.2 Hydroxyalkylation Reaction with Cyclic Carbonate

18.2.2.1 N-Hydroxyalkylation of Aromatic Amines/Indole

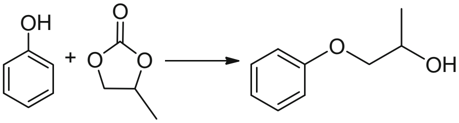
The N-hydroxyalkylation of primary aromatic amines is extensively used, especially in medicinal chemistry, for the synthesis of amino alcohols as intermediates. Selva's group reported selective synthesis of bis-N-(2-hydroxy)alkylanilines from aromatic amines and cyclic carbonates catalyzed by phosphonium-based ionic liquids (Scheme 18.9) [34]. Using tri-isobutylmethylphosphonium tosylate [(*i*-Bu)$_3$PMe]Tos as a catalyst at 170 °C after 2 h, the conversion of aniline was 96 %, and two major products, mono- and bis-N-(2-hydroxy)ethyl aniline, were obtained in the yields of 52 % and 41 %, respectively. When the reaction time was prolonged to 9 h, mono-N-hydroxyalkyl product was totally converted to the bis-N-alkyl product in the yield of 95 %. Additionally, versatile catalytic system can be applied to various substrates. It was found that *p*-anisidine was more reactive than p-toluidine, aniline, and *p*-chloroaniline. However, in the presence of zeolites, such as alkali metal-exchanged faujasites as catalyst, the reaction of anilines and cyclic carbonates afforded mono-N-hydroxyalkyl anilines [34].

Our group developed a simple and eco-friendly procedure for the synthesis of hydroxyalkyl indoles from indole and cyclic carbonates in the presence of catalytic amount of imidazolium-based ionic liquids under solvent-free conditions (Scheme 18.10) [35]. The reaction of indole and ethylene carbonate gave not only 1-(2-hydroxyethyl)indole (**1a**) but also its sequential derivatives



Scheme 18.10 N-hydroxyalkylation of indole with ethylene carbonate

Scheme 18.11 O-hydroxyalkylation of phenol with propylene carbonate



1-(2-(2-hydroxy)ethoxy-ethyl)indole (**2a**) and 1-(2-(2-(2-hydroxy)ethoxy-ethyl) oxy-ethyl)indole (**3a**). The conversion of indole and the yield of **3a** were obviously affected by the anions and followed the order: $OAc^{-} > Cl^{-} > Br^{-} > BF_4^{-}$, which is consistent with the hydrogen bond basicity of the anions. When propylene carbonate was used as the hydroxyalkylating reagent, $BmimBF_4$ could give 1-(2-hydroxypropyl)indole as the sole product in the yield of 35 %. The increase of selectivity in the reaction is attributed to the steric hindrance afforded by the methyl group of the propylene carbonate, which could suppress the tendency toward the sequential hydroxyalkylation of the indole derivatives.

18.2.2.2 O-Hydroxyalkylation of Phenol

Our group reported the O-hydroxyalkylation of phenol with propylene carbonate to synthesize 1-phenoxy-propan-2-ol catalyzed by various imidazolium-based ionic liquids (Scheme 18.11) [36]. The BmimOAc showed the best catalytic activity, which gave the desired product in the yield of 79 % under 120 °C, 9 h. To rationalize the catalytic role of BmimOAc, we used ^{1}H NMR spectroscopy to study the interaction between BmimOAc and substrates (Fig. 18.1). When 1 eq. of propylene carbonate was added to BmimOAc, the C-2 proton of imidazolium cation shifted upfield from 10.20 to 10.17 ppm. It might result from a change of the hydrogen bond donor-acceptor pair. In BmimOAc, besides an electrostatic interaction, the C-2 proton of the imidazolium cation also acts as a hydrogen bond donor to interact with the acetate anion which, in turn, acts as a hydrogen bond acceptor. After addition of propylene carbonate into BmimOAc, the intramolecular hydrogen

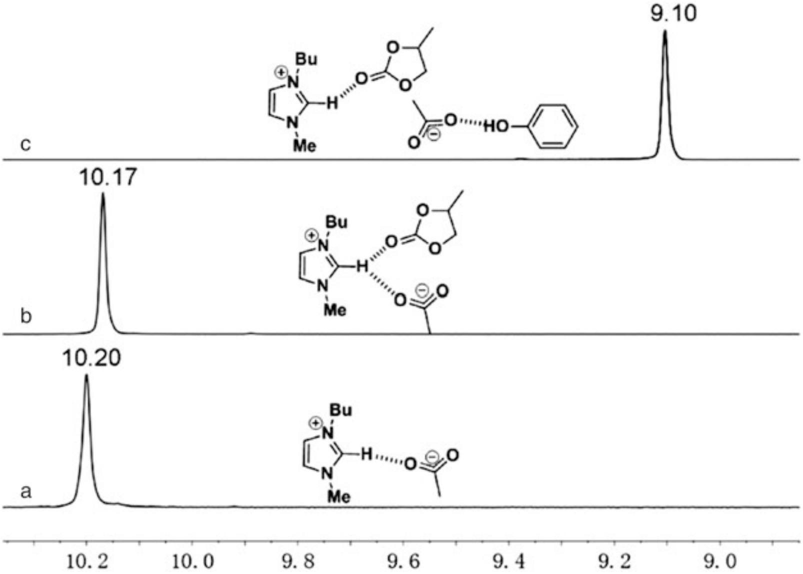
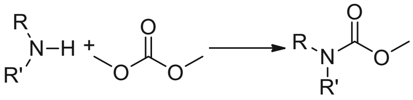


Fig. 18.1 ^{1}H NMR spectra of the C-2 proton of imidazolium in CD_3CN. (**a**) BmimOAc; (**b**) BmimOAc, propylene carbonate = 1:1(mol); (**c**) BmimOAc, propylene carbonate, phenol = 1:1:1 (mol)

bond interaction was weakened, and an intermolecular hydrogen bond interaction between imidazolium and propylene carbonate emerged. These results implied that the carbonyl group of propylene carbonate could be activated by the C-2 proton of imidazolium. After further adding of 1 eq. of phenol, the chemical shift of C-2 proton underwent a significant upfield shift to 9.10×10^{-6}. It might be due to the competition between two hydrogen bond donors (imidazolium and phenol) for the hydrogen bond acceptor (acetate anion), which led to the hydrogen bond interaction between acetate anion and phenol greatly weakening the hydrogen bond interaction between acetate anion and C-2 proton of the imidazolium cation. This demonstrated that phenol could be activated by the acetate through hydrogen bonding. These NMR studies have illustrated that the cation and anion in BmimOAc could cooperatively activate phenol and propylene carbonate by hydrogen bonding to promote the reactions efficiently.

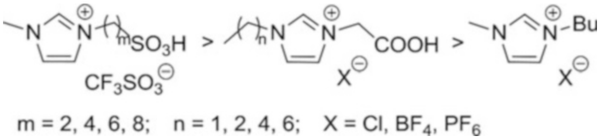
18.3 Carbonylation Reaction

Organic carbonates exhibit versatile and tunable chemical reactivity depending on reaction conditions. Besides being used as alkylating/hydroxyalkylating reagents, organic carbonates can also act as carbonylating reagents when attacked by nucleophiles on carbonyl carbon.



Scheme 18.12 Carbonylation of amines with DMC to synthesize carbamates

Scheme 18.13 The catalytic activities of acid-functionalized ionic liquids

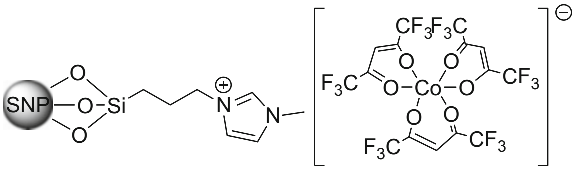


18.3.1 Carbonylation of Amines

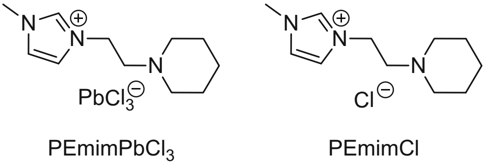
The conventional ways for the synthesis of carbamates and oxazolidinones/oxazines use phosgene or its derivatives, which are neither convenient nor environmentally benign. Among novel eco-friendly methodologies for synthesis of carbamates and oxazolidinones/oxazines, carbonylation of amines with organic carbonates is one of the most attractive routes. In the presence of ionic liquids, carbamates might be obtained by carbonylation with DMC, and oxazolidinones/oxazines might be obtained by carbonylation with either cyclic carbonates or linear dialkyl carbonates.

18.3.1.1 Carbonylation of Amines to Carbamates

Carbamates are important intermediates in the synthesis of pharmaceuticals, pesticides, herbicides, and other fine chemicals. Deng's group reported the synthesis of alkyl carbamates by the reaction of aliphatic amines with DMC using imidazolium-based ionic liquids as solvents and catalysts (Scheme 18.12) [37]. The catalytic activity of ionic liquids was affected by the chain length of substituted groups on imidazolium cations, which followed the order: 1-ethyl-3-methyl-imidazolium tetrafluoroborate ($EmimBF_4$) > $BmimBF_4$ > 1-cetyl-3-methyl-imidazolium tetrafluoroborate ($HmimBF_4$). Subsequently, they used acid-functionalized ionic liquids to catalyze the carbonylation of aliphatic amine with DMC [38]. The -COOH and -SO_3H functionalized ionic liquids showed higher activities, in the following order: -SO_3H functionalized ionic liquids > -COOH functionalized ionic liquids > nonfunctionalized ionic liquids (Scheme 18.13). Catalytic amount (1 wt.%) of 1-methyl-3-(4-sulfobutyl)imidazolium trifluoromethanesulfonate [M$(CH_2)_4SO_3$HimTfO] effectively catalyzed the reaction of 1,6-hexanediamine and DMC to afford the corresponding carbamate in >90 % yield. The ionic liquid could be reused five times without obvious loss of catalytic activity. Unfortunately, these catalytic systems were completely inactive for the carbonylation of aromatic amines.



Scheme 18.14 The nanostarch-functionalized ionic liquid containing cobalt chelate anion



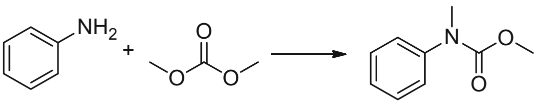
Scheme 18.15 Functional ionic liquids

Zhao and coworkers investigated the synthesis of N-methyl carbamate from aniline and DMC catalyzed by ionic liquid-promoted zinc acetate [39]. In the presence of $BmimPF_6$ and anhydrous zinc acetate (weight ratio = 4:1), the conversion of aniline and selectivity of carbamate were 99.8 % and 99.1 %, respectively, at 170 °C in 4 h. The authors believed that the high catalytic activity of $BmimPF_6$-Zn $(OAc)_2$ was attributed to a structure change of zinc acetate from a bidentate to a unidentate coordination after forming a hydrogen bond between the carbonyl oxygen on zinc acetate and the C-2 proton on imidazolium ring of $BmimPF_6$. The change promoted the coordination of the carbonyl oxygen on DMC with the zinc atom. Then the carbon atom of carbonyl group on the coordinated DMC was attacked by the nitrogen atom on aniline, generating the final product efficiently.

Jain et al. reported synthesis of methyl carbamates by reaction of alkyl, aryl, and alicyclic amines with DMC using a catalytic amount of TBAB in conjunction with L-proline [40]. When using 5 mol% of TBAB or 5 mol% of L-proline alone, the reaction of benzylamine and DMC provided poor yields of the desired carbamate. However, the mixture of 5 mol% of TBAB and 5 mol% of L-proline significantly accelerated the reaction, generating the desired product in 98 % yield at room temperature within 3 h. Because the L-proline was insoluble in DMC, the authors conceived that the improved solubility of L-proline in the presence of the phase-transfer catalyst TBAB might be the reason for the enhanced reaction rate.

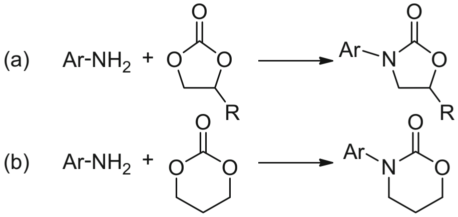
Furthermore, Jain et al. developed a new nanostarch-functionalized ionic liquid containing cobalt chelate anion for the synthesis of carbamates by the reaction of amines with DMC (Scheme 18.14) [41]. The immobilized ionic liquid was prepared through loading of imidazolium to the nanostarch and anion exchange with cobalt salt. At 60 °C, the immobilized catalyst could convert various aromatic and aliphatic amines to the corresponding carbamates in high yields within 6 h. Moreover, the heterogeneous catalyst was facilely separated after reaction and reused six times without any loss in catalytic efficiency.

Our group prepared an acid-base bifunctional ionic liquid, 1-(2-(1′-piperidinyl) ethyl)-3-methyl-imidazolium trichlorolead ($PEmimPbCl_3$), to catalyze one-pot synthesis of methyl-N-methyl-N-phenylcarbamate from aniline and DMC (Schemes 18.15 and 18.16) [42]. Under optimal reaction conditions, the



Scheme 18.16 The synthesis of methyl-N-methyl-N-phenylcarbamate from aniline and DMC

Scheme 18.17 Carbonylation of amines (**a**) with substituted ethylene carbonates to oxazolidinones, (**b**) with trimethylene carbonate to oxazines



bifunctional ionic liquid PEmimPbCl$_3$ afforded the desired product in 72 % yield, which was much higher than the corresponding basic ionic liquid PEmimCl (47 % yield) or acidic PbCl$_2$ (6 % yield). The density functional theory (DFT) calculations illustrated that PEmimPbCl$_3$ increased both the nucleophilicity of aniline by its Lewis basic site piperidine and the electrophilicity of DMC by its Lewis acidic site Pb^{2+}. The unique acid-base cooperative effect of PEmimPbCl$_3$ played a key role in the catalysis.

18.3.1.2 Carbonylation of Amines to Oxazolidinones/Oxazines

The oxazolidinones/oxazines are important heterocyclic compounds, which have attracted much attention in recent decades because of their outstanding biological activity. Our group has carried out a series of work on eco-friendly synthesis of oxazolidinones/oxazines. With the aid of the basic ionic liquid BmimOAc, the reactions of aromatic amines with cyclic carbonates produced various oxazolidinones/oxazines, including 3-aryloxazolidin-2-ones, 3,3′-aryldioxazolidin-2-ones, and 3-aryl[1,3]oxazinan-2-ones, in moderate to high yields at 140 °C within 9 h [18, 43, 44] (Scheme 18.17). DFT calculations were employed to reveal the catalytic role of BmimOAc in the model reaction of aniline and propylene carbonate (Fig. 18.2). The bond C_1-O_1 length of propylene carbonate was elongated from 0.12130 to 0.12584 nm after complexation with BmimOAc, and hydrogen bond O_1 -H_1 was formed with a bond length of 0.13830 nm, which implied that propylene carbonate was activated by a hydrogen bonding interaction between the carbonyl group and the imidazolium. Meanwhile, the length of N_1-H_2 bond of aniline was elongated from 0.10059 to 0.10267 nm after complexation with BmimOAc, and the hydrogen bond H_2-O_2 was formed with a bond length of 0.17967 nm, which demonstrated that aniline was activated by hydrogen bonding with acetate. The DFT calculation results indicated that the cation and anion in BmimOAc cooperatively activated the substrates via formation of hydrogen bonds.

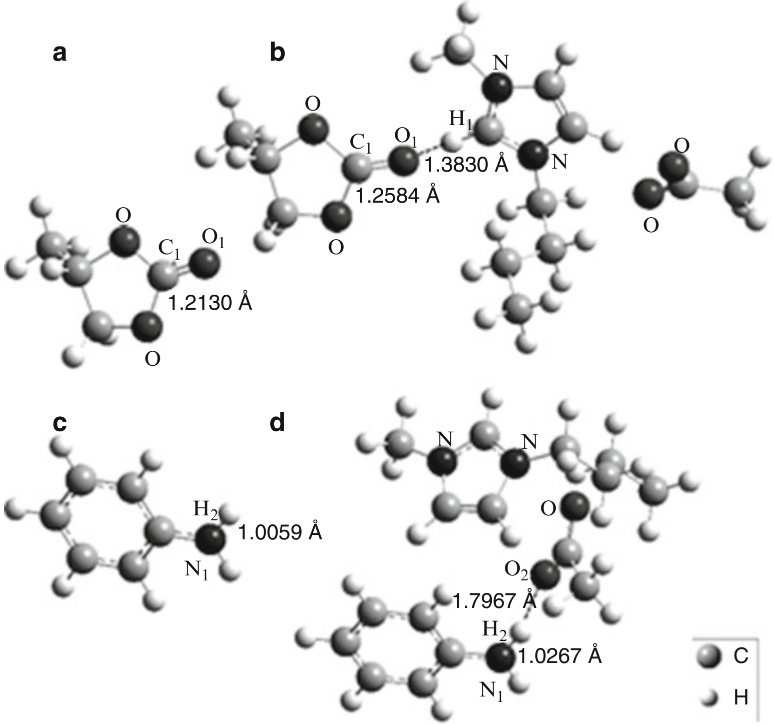
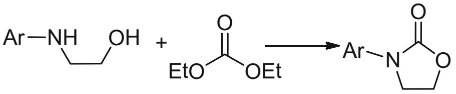


Fig. 18.2 DFT optimized geometry of (**a**) propylene carbonate, (**b**) the complex of propylene carbonate with BmimOAc, (**c**) aniline, and (**d**) the complex of aniline with BmimOAc at the B3LYP/6-31G level implemented in the Gaussian 09 program (1 Angstrom = 0.1 nm)

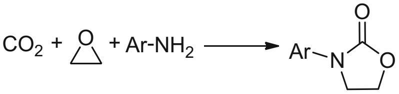


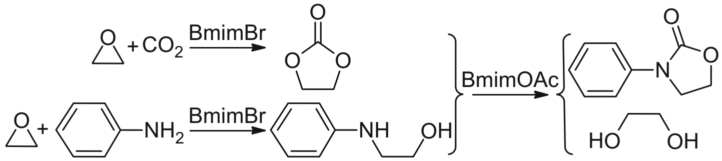
Scheme 18.18 Carbonylation of 2-(arylamino) alcohols with DEC to 3-aryloxazolidin-2-ones

Our group also investigated the synthesis of 3-aryloxazolidin-2-ones by direct carbonylation of 2-(arylamino) alcohols with DEC (Scheme 18.18) [45]. At 130 °C within 1 h, 2-(arylamino) alcohols with either electron-donating substituents (such as alkoxy) or electron-withdrawing substituents (such as halides) were converted to corresponding products in >99 % yields catalyzed by 5 mol% BmimOAc. In the reaction, ethyl 2-(arylamino) ethyl carbonate was considered as the key intermediate, which was proved by reacting with DEC to afford 3-phenyloxazolidin-2-one in quantitative yield under identical reaction conditions.

We found one-pot conversion of CO_2, ethylene oxide, and aromatic amines to 3-aryloxazolidin-2-ones catalyzed by binary ionic liquids of BmimBr and BmimOAc (Scheme 18.19) [46]. This one-pot method consisted of two parallel

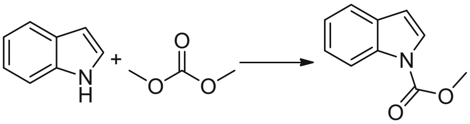
Scheme 18.19 One-pot conversion of CO_2 to 3-aryloxazolidin-2-ones





Scheme 18.20 Reaction mechanism of the one-pot conversion

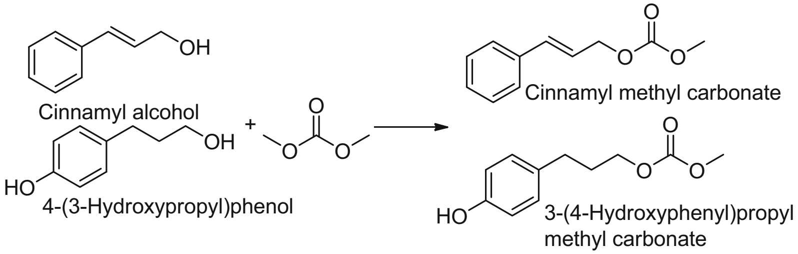
Scheme 18.21 Carbonylation of indole with DMC



reactions and a subsequent cascade reaction (Scheme 18.20). Firstly ethylene oxide was used to fix CO_2 to ethylene carbonate. At the same time, ethylene oxide reacted with aniline to form the intermediate 2-(phenylamino)ethanol. Then, 2-(phenylamino)ethanol reacted with ethylene carbonate to give 3-phenyloxazolidin-2-one and by-product ethylene glycol. The binary ionic liquids demonstrated a synergistic catalytic effect on the transformation of CO_2 to 3-aryloxazolidin-2-ones. BmimBr was essential to two parallel reactions owing to the good nucleophilicity and leaving ability of bromide, and BmimOAc played a dominant role in subsequent cascade reaction owing to the strong basicity of acetate.

18.3.2 Carbonylation of Indole

Our group reported an environment-friendly process for the synthesis of indole-1-carboxylic acid methyl ester from indole and DMC catalyzed by imidazolium-based ionic liquids (Scheme 18.21) [47]. 1-Butyl-3-methyl-imidazolium (Bmim)-based ionic liquids gave the target product in relatively high yields of $>83\,\%$ regardless of anion types (BF_4^-, Br^-, Cl^-, OAc^-, and OH^-), which indicated that the anions in ionic liquids did not play a dominating role in catalyzing the reaction. In contrast, 1,2-dimethyl-3-butyl-imidazolium (Bmmim)-based ionic liquids provided poor yields of $<13\,\%$, which exhibited the importance of C-2 proton of imidazolium in catalysis. It was believed that C-2 proton of imidazolium could activate DMC by the hydrogen bond interaction with carbonyl group of DMC. This efficient protocol could be applied to convert other N-heterocycles, such as pyrrole,



Scheme 18.22 Carbonylation of cinnamyl alcohol and 4-(3-hydroxypropyl)phenol with DMC

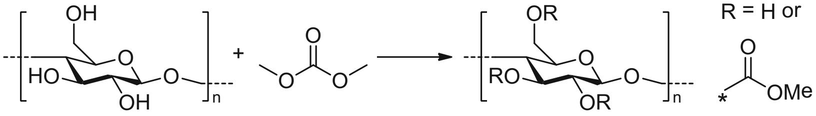
carbazole, and phthalimide, into the corresponding N-heterocyclic carbamates in >84 % yield.

18.3.3 Carbonylation of p-Coumaryl Alcohol Model Compounds

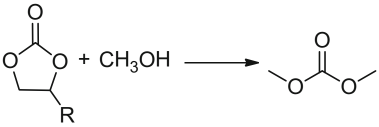
In a study of upgrading phenolic streams derived from lignin into higher value bio-based chemicals, Perosa et al. used cinnamyl alcohol and 4-(3-hydroxypropyl) phenol as model compounds of p-coumaryl alcohol to react with DMC in the presence of trioctylmethylphosphonium methyl carbonate ($P_{8881}CH_3OCOO$) ionic liquid (Scheme 18.22) [48]. Cinnamyl methyl carbonate could be obtain by carbonylation of cinnamyl alcohol in 80 % yield at 90 °C, 5.5 h, and only traces of by-product cinnamyl methyl ether (4 % yield) was generated. When using 4-(3-hydroxypropyl)phenol as the substrate, carbonylation of the aliphatic hydroxyl with DMC was the main reaction, which produced 3-(4-hydroxyphenyl)propyl methyl carbonate in 74 % yield at 90 °C within 49 h. The aromatic hydroxyl group remained relatively inert, and the by-product 3-(4-methoxyphenyl)propyl methyl carbonate was generated in 16 % yield. The results showed the possibility for straightforward and efficiently catalytic upgrading of lignin-derived chemical building blocks. Moreover, $P_{8881}CH_3OCOO$ showed higher activity and selectivity than other inorganic catalysts such as K_2CO_3, $CsF/\alpha Al_2O_3$, NaX, and NaY [48].

18.3.4 Carbonylation of Cellulose

Cellulose is the most abundant renewable and biodegradable natural polymer, which can be chemically converted to a number of polymeric derivatives with remarkable properties. As one of cellulose derivatives, cellulose carbonate has been found applications as intermediates in the synthesis of aminopolysaccharides via aminolysis, supports for the delivery of therapeutics, and imaging agents. King and coworkers investigated the synthesis of cellulose methylcarbonate using DMC in



Scheme 18.23 Carbonylation of cellulose with DMC



Scheme 18.24 Transesterification of cyclic carbonates to dialkyl carbonate

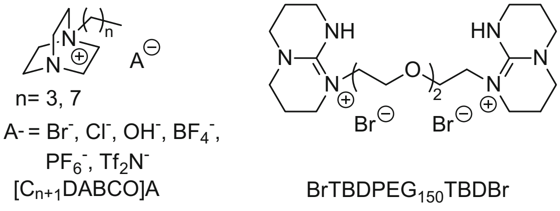
the presence of ionic liquids (Scheme 18.23) [49]. Employing trioctylphosphonium acetate (P_{8881}OAc)/DMSO (90:10 wt.%) or single 1-ethyl-3-methyl-imidazolium acetate (EmimOAc) as solvent, the reaction of microcrystalline cellulose and DMC afforded cellulose carbonate with a moderate degree of substitution (DS~1) in 87 % yield at 60 °C within 1 h. After the film formation, the mechanical properties of product were comparable to commercial cellulose acetate films. Hence it has the potential application in packaging film.

18.4 Transesterification Reaction

In recent years, the growing demand for eco-friendly organic carbonates has triggered a massive research on transesterification. The transesterification is a process of exchanging the organic group between carbonate and alcohol to produce a new carbonate. Mainly, the transesterification reactions contain transesterification of cyclic carbonates to linear carbonates, transesterification of linear carbonates to cyclic carbonates, transesterification between cyclic carbonates, and transesterification between linear carbonates.

18.4.1 *Transesterification of Cyclic Carbonates to Linear Carbonate*

Since the manufacturing techniques of cyclic carbonates from CO_2 have been well developed, the transesterification of cyclic carbonates with methanol is considered to be a sustainable pathway for the preparation of linear dialkyl carbonates (Scheme 18.24). Both homogeneous ionic liquids and heterogeneous immobilized ionic liquids have been applied to catalyze the transesterification reactions.



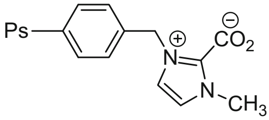
Scheme 18.25 Lewis basic ionic liquids

18.4.1.1 Transesterification Catalyzed by Homogeneous Ionic Liquids

Park's group used quaternary ammonium and 1-alkyl-3-methyl-imidazolium ionic liquids to catalyze the synthesis of DMC by transesterification of cyclic carbonates with methanol [50–52]. It was found that ionic liquids containing more nucleophilic anions exhibited higher activities in the reaction. The most efficient chloride ionic liquids could provide DMC in a moderate yield at 140–180 °C within 6 h. In addition, an extra high pressure of CO_2 was needed to stabilize cyclic carbonates from decomposition under reaction conditions. Subsequently, they employed energy-efficient microwave heating for transesterification of ethylene carbonate to DMC in the presence of ionic liquids [53]. Compared with classical heating modes, the microwave heating gave target product in higher yields within much shorter reaction time (only 15 min). Under microwave irradiation, ionic liquids were regarded as not only catalysts but also heat-generating additives, which were helpful to increase the temperature of reaction mixture.

He's group ingeniously developed DABCO-derived (1,4-diazobicyclo[2.2.2] octane) Lewis basic ionic liquids for transesterification of ethylene carbonate with methanol (Scheme 18.25) [54]. Among all investigated ionic liquids containing different alkyl length of the cations and anions, $[C_4DABCO]OH$ exhibited the highest catalytic activity which gave 81 % yield of DMC and 90 % conversion of ethylene carbonate at 70 °C. The reason for high activity of $[C_4DABCO]OH$ was that methanol could be activated by cage-like tertiary nitrogen in the cation of the ionic liquid in combination with hydroxide anion. Later, they developed another novel polyethylene glycol (PEG)-functionalized Lewis basic ionic liquid $BrTBDPEG_{150}TBDBr$ for transesterification of ethylene carbonate (Scheme 18.25) [55]. DMC could be obtained in 85 % yield from ethylene carbonate at 70 °C within 4 h. This result was attributed to the activation of methanol assisted by the secondary and tertiary nitrogen in the cation of ionic liquid. Especially, $BrTBDPEG_{150}TBDBr$ was also an efficient catalyst for synthesis of cyclic carbonates by cycloaddition reaction of CO_2 and epoxides, which could integrate the "one-pot two-stage" process to afford DMC from CO_2 directly in 83 % yield without separation of ethylene carbonate.

Scheme 18.26 The PS-supported DMIC



18.4.1.2 Transesterification Catalyzed by Heterogeneous Immobilized Ionic Liquids

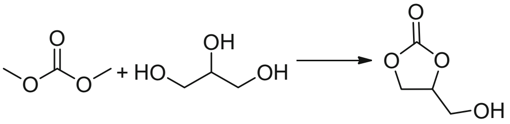
Compared with homogeneous ionic liquids, heterogeneous immobilized ionic liquids show additional advantages such as easy separation and recovery from the reaction mixture. Generally, the separation of heterogeneous catalysts only needs simple filtration without other tedious processes. Hence, immobilized ionic liquids have attracted considerable attentions as catalyst for the transesterification of cyclic carbonates to DMC.

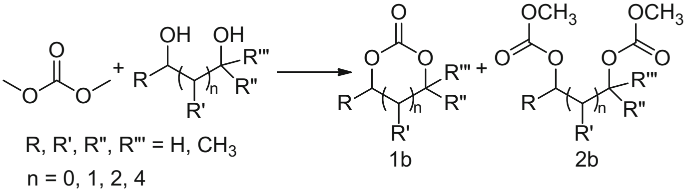
In continuation of their studies on transesterification of cyclic carbonates, Park's group immobilized ionic liquids on the commercial silica, amorphous silica, and ordered mesoporous silica MCM-41, respectively [56–58]. All of these immobilized ionic liquids showed moderate catalytic activities in the transesterification of ethylene carbonate with methanol, which could give DMC in >70 % yield at 160–180 °C, 4–6 h. And the catalysts could be reused at least three times with only a slight loss of yield and selectivity. Notably, the immobilized ionic liquids even provided higher yields of DMC than using the same amount of homogeneous ionic liquids under identical reaction conditions. The authors thought the reason was that immobilized ionic liquids have a good distribution of active sites due to high surface area of the supporters, which provided a better accessibility than homogeneous system. The synergistic effect of organic and inorganic moieties was another advantage of immobilized ionic liquids on silica.

Li and coworkers successfully immobilized basic 1-(triethoxysilyl) propyl-3-methyl-imidazolium hydroxide (SmimOH) on the mesocellular silica foams (MCF) and then applied it to DMC synthesis via transesterification of ethylene carbonate with methanol [59]. The immobilized MCF-SmimOH possessed 3D mesoporosity and ultra-large pore size, which favored immobilizing more amount of ionic liquid as well as mass transfer, consequently enhancing its catalytic performance. Under mild 65 °C within 5 h, heterogeneous catalyst efficiently afforded DMC in yield as much as 83 %.

Zhang's group covalently anchored the carboxylic functionalized 1,3-dimethyl-imidazolium-2-carboxylate (DMIC) onto a highly cross-linked polystyrene resin (PS) as a heterogeneous catalyst for DMC synthesis (Scheme 18.26) [60]. The catalytic activity and stability of the PS-supported DMIC for the transesterification were evaluated in a continuous-flow fixed-bed catalytic reactor at 110 °C. During continuous performance for 200 h, 67 % conversion of ethylene carbonate and 95 % selectivity of DMC were always maintained without obvious loss, which showed its potential application in industry.

Scheme 18.27 Transesterification of DMC to glycerolcarbonate





Scheme 18.28 Transesterification of DMC with various diols

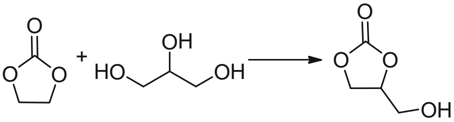
18.4.2 Transesterification of Linear Carbonate to Cyclic Carbonates

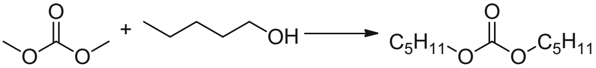
Due to reversible nature of transesterification, it provides a thermodynamic possibility for transformation of linear carbonate to cyclic carbonates, which has also attracted many investigations in the organic synthesis.

To effectively utilize glycerol that formed in large amounts during the production of biodiesel, Plasseraud and coworkers reported transesterification of DMC with glycerol to prepare glycerol carbonate catalyzed by 1-butyl-3-methylimidazolium-2-carboxylate (Bmim-2-CO_2) (Scheme 18.27) [61]. In the presence of 5 mol% catalyst, quantitative glycerol carbonate could be obtained within 30 min at 74 °C. It was worth mentioning that Bmim-2-CO_2 catalyst was still efficient on raw glycerol directly from a biodiesel production plant with 88 wt.% purity and contamination of water, which gave glycerol carbonate in 93 % yield after 5 h. This character strongly contrasted with K_2CO_3 catalytic system which required pure glycerol containing less than 2 % water.

Selva's group systematically investigated the transesterification of DMC with various diols catalyzed by phosphonium-based ionic liquids (Scheme 18.28) [62]. Diols with different chain lengths and substituent groups afforded different types of carbonates when using $P_{8881}CH_3OCOO$ as catalyst. For example, cyclic carbonates (**1b**) were obtained as a main product when 1,2-propanediol and ethylene glycol were employed, which propylene carbonate and ethylene carbonate were obtained in 95 % and 94 % yield, respectively. However, the reaction of DMC with 1,3-butanediol, 2-methyl-1,3-propanediol, 1,3-propanediol, 2,2-dimethyl-1,3-propanediol, 1,4-butanediol, and 1,6-hexanediol produced corresponding linear di-carbonates (**2b**) as main products in yields of >80 %. Notably, the formation of polycarbonates, which occurred preferentially over traditional base catalysts, could be avoided in all cases.

Scheme 18.29 Transesterification of ethylene carbonate to glycerol carbonate





Scheme 18.30 Transesterification of DMC to dipentyl carbonate

18.4.3 Transesterification Between Cyclic Carbonates

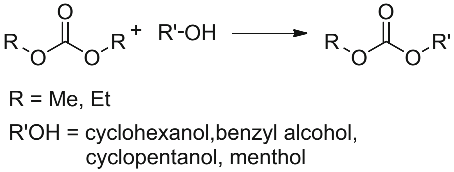
Park's group reported transesterification of ethylene carbonate with glycerol to synthesize glycerol carbonate catalyzed by immobilized ionic liquids (Scheme 18.29) [63]. The catalysts were prepared by immobilizing different trialkylamines on chloropropyl-functionalized MCM-41. Compared with immobilized triethylamine, tri-*n*-propylamine, and tri-*n*-hexylamine, the immobilized tri-*n*-butylamine ionic liquid showed a slightly higher catalytic activity, which afforded the 94 % conversion of glycerol and 84 % selectivity to glycerol carbonate at 80 °C, 60 min. And it was noted that the transesterification reaction proceeded very rapidly, giving 86 % conversion of glycerol after only 5 min of reaction.

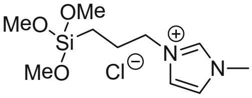
18.4.4 Transesterification Between Linear Carbonates

Long-chain alkyl carbonates are excellent environmental protection lubricant base materials because of their good lubricity, wear ability, self-cleaning ability, corrosion resistance, high-thermal oxidative stability, good biodegradability, and good solubility in hydrocarbon oils. Han's group reported the synthesis of dipentyl carbonate by transesterification of DMC with 1-pentanol using ionic liquid BmimOH as catalyst (Scheme 18.30) [64]. During the reaction methanol was distilled off, which made the reaction to produce dipentyl carbonate continuously. Under 110 °C, dipentyl carbonate was obtained in yield of 76 % employing 2 % amount of catalyst within 1 h.

Different from symmetrical organic carbonates, the unsymmetrical organic carbonates have unique applications in various fields. Using their excellent phosphonium salt ionic liquids as catalysts, Selva's group investigated the transesterification of DMC/DEC with alcohols to produce unsymmetrical dialkyl carbonates (Scheme 18.31) [65]. In the reaction of DMC with cyclohexanol, the ionic liquid exhibited much higher catalytic activity than conventional catalysts (including K_2CO_3, DBU, and DMAP), which 1 mol% of P_{8881}OAc provided the

Scheme 18.31 Transesterification of DMC/DEC to unsymmetrical dialkyl carbonates





Scheme 18.32 1-(3-Trimethoxysilylpropyl)-3-methyl-imidazolium chloride (TmimCl)

product in 93 % yield at 200 °C, 3 h. The phosphonium ionic liquid could also efficiently catalyze the transesterification of DMC/DEC with other primary and secondary alcohols, such as benzyl alcohol, cyclopentanol, and menthol, to the corresponding unsymmetrical dialkyl carbonates in high yields (>90 %) and high selectivity (>99 %). Furthermore, the phosphonium ionic liquid was stable enough under relatively high reaction temperature, and no trace of thermal degradation was detected.

Jain et al. reported an efficient synthesis of unsymmetrical dialkyl carbonates by transesterification of DMC with alcohols promoted by 1-(3-trimethoxysilylpropyl)-3-methyl-imidazolium chloride (TmimCl) ionic liquid (Scheme 18.32) [66]. Using TmimCl as solvent and catalyst, the reaction of DMC and 1-butanol produced butyl methyl carbonate in 99 % yield at 80 °C, 4 h. The siloxyl-containing ionic liquid TmimCl exhibited a higher efficiency than corresponding BmimCl, which illustrated that synergistic effect of the trimethoxysilyl moiety accelerated the reaction, probably by the formation of a reaction center within the ionic liquid via interaction of the silicon atom with reactants.

18.5 Conclusions

Organic carbonates with low toxicity and environmentally benign properties have widely opened the field of phosgene replacement as well as halogen-free synthesis. They have been used as alkylating/hydroxyalkylating reagents, carbonylating reagents, and transesterificating reagents in both laboratories and industrial applications. Ionic liquids have the characteristic to cooperatively activate substrates through hydrogen bonding. They can serve as hydrogen bond donors and acceptors to promote reactions between electrophiles and nucleophiles. The dual activation of ionic liquids makes them catalyze the transformation of organic carbonates smoothly. The combination of green organic carbonates with powerful ionic liquids' catalytic mediums is helping us pursue intrinsically safe, clean, energy-efficient, and chlorine-free synthetic processes.

Acknowledgments We sincerely thank the National Natural Science Foundation of China (grant number 21273078) and Shanghai Leading Academic Discipline Project (project number B409) for their financial support.

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Chapter 19
Linear and Cyclic Carbamates via Dialkyl Carbonate Chemistry

Fabio Aricò, Alexander Aldoshin, and Pietro Tundo

Abstract Dialkyl carbonates (DACs) as reagents have found recent application in phosgene-free synthesis of both linear and cyclic carbamates. Different types of catalysts have been investigated for the carbamoylation of aniline via dimethyl carbonate (DMC) in batch. The possibility of conducting this reaction in a fixed-bed continuously fed reactor has been investigated.

DACs have also been employed in a novel green approach to six-membered cyclic carbonates (1,3-oxazolidin-2-ones). Reaction of primary amines or hydrazines with bis(methyl carbonate) derivatives of 1,3-propanediols in the presence of potassium *tert*-butoxide resulted in the synthesis of several 1,3-oxazolidin-2-ones in good yield. These compounds can also be prepared by a one-step intermolecular cyclization where the 1,3-bis(methyl carbonate) intermediate is formed in situ.

Keywords Carbamates • 1,3-oxazinan-2-ones • Cyclization • Dialkyl carbonates • Dimethyl carbonate

19.1 Introduction

Nowadays chlorine is employed to prepare many intermediates and solvents, used in the production of numerous everyday goods. However, chlorinated molecules have both a direct (greenhouse gases) and indirect (energy consumption) impact on climate change. Moreover, halogen chemistry does not obey the principles of atom economy and waste minimization since chloride anions, by-products of chlorine-based reactions, are formed as waste.

An option currently receiving increased focus is the use of CO_2 either as a direct substitute for phosgene ($COCl_2$) or via its derivatives, organic carbonates.

Short chain DACs and in particular DMC are renowned for possessing properties of low toxicity and high biodegradability, which make them true green solvents and

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reagents. More than 90 % of DMC is nowadays produced by insertion of CO_2 into epoxides followed by transeterification reaction with an alcohol [1, 2].

DMC has been used as an efficient eco-sustainable substitute of the most common methoxycarbonylating and methylating agents such as phosgene, methyl halides, or dimethyl sulfate [3, 4] showing high selectivity with different monodentate and bidentate nucleophiles [5–8]. The reactivity of the two electrophilic centers of DMC can be selectively tuned, temperature being the key factor. In fact, usually at reflux temperature ($T = 90\ ^\circ C$), DMC acts as methoxycarbonylation agent by $B_{Ac}2$ mechanism, while, at higher temperature ($T \geq 150\ ^\circ C$), the methylation reaction occurs via a $B_{Al}2$ mechanism [9–11]. Reactions produce as by-product only methanol and eventually CO_2. This peculiar reactivity of DMC can be explained through the hard-soft acid-base (HSAB) theory of Pearson [12].

DACs as reagents have found recent application in phosgene-free synthesis of carbamates [13]. Noteworthy, organic carbonates have been demonstrated to be efficiently employed in the preparation of both linear and cyclic carbamates.

19.2 DMC-Mediated Synthesis of Methyl N-Phenylcarbamate

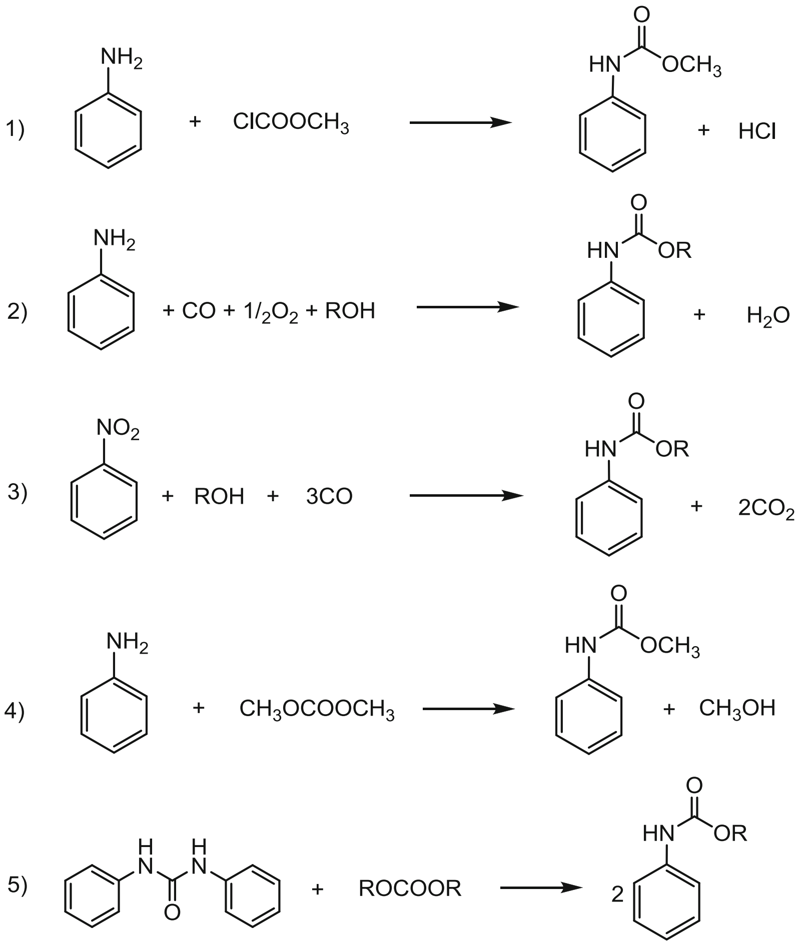
Linear carbamates are industrial relevant compounds that over the last 30 years have found numerous applications as pesticides, fungicides, herbicides, dyes, pharmaceuticals, and cosmetics, as well as protecting groups [14–16] and intermediates for polyurethane synthesis [17, 18].

Scheme 19.1 reports, as an example, the most common synthetic approaches used for the preparation of methyl *N*-phenylcarbamate.

Industrially, this compound is synthesized predominantly *via* phosgene routes, i.e., by reacting the parent amine with chloroformate (Eq. 1, Scheme 19.1) [19–22].

Due to the toxicity of this process, in recent years, many environmentally benign and alternative pathways have been investigated, i.e., oxidative carbonylation of amines (Eq. 2, Scheme 19.1), reductive carbonylation of aromatic nitro compounds [23, 24] (Eq. 3, Scheme 19.1), and carbonylation of amines or urea derivatives *via* carbonate chemistry (Eq. 4–5, Scheme 19.1) [25–29]. Noteworthy, carbonylation process of urea derivatives is very efficient only when the two components (urea and carbonate) are either both aliphatic and aromatic, limiting the possible number of accessible products.

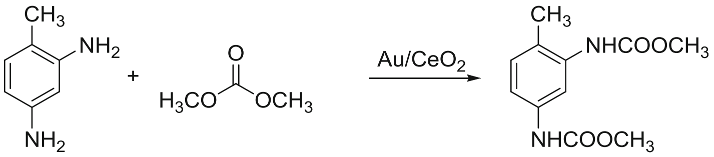
If we consider the abovementioned reactions, the carbamoylation of primary amines *via* DMC/DAC chemistry is probably the most promising phosgene-free route to carbamates. DMC and its derivatives have been shown to effectively react with aliphatic [30, 31] and aromatic [32–34] amines and hydrazines [7]. In fact, over the last 15 years, reactions between amines and symmetrical DACs have been investigated resulting in the highly selective synthesis of monoalkyl, dialkyl derivatives, and in some cases of the related carbamate [35–40].



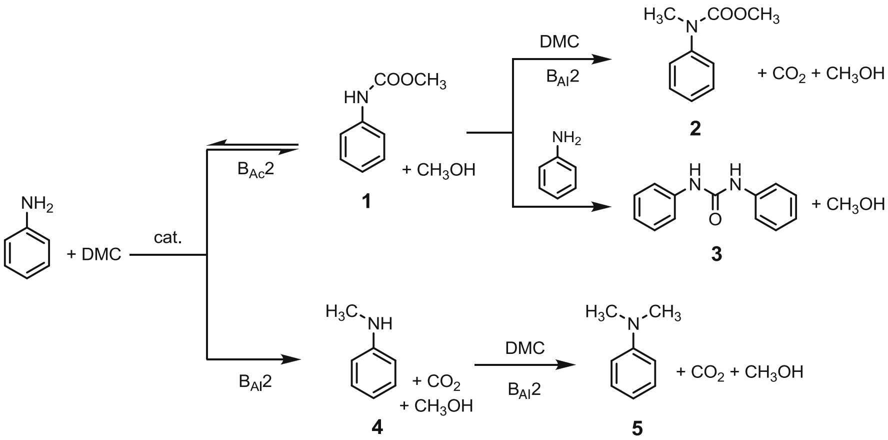
Scheme 19.1 Synthetic approaches to methyl *N*-phenylcarbamate

Several examples of carbamoylation of aniline [41–44], 4,4′-methylenedibenzenamine [45] (for the synthesis of methylene diphenyl diisocyanate, MDI) and 2,4-diaminotoluene [46] (for the synthesis of toluene diisocyanate TDI), have been reported by DMC chemistry in the presence of either homogeneous or supported catalysts. An example is the efficient carbamoylation of 2,4-diaminotoluene (DAT) by gold-catalyzed phosgene-free synthesis (Scheme 19.2). This approach is particularly interesting as it can be extended to a one-pot process which starting from 2,4-dinitrotoluene leads directly to the polyurethane precursor TDI [47].

Recently the carbamoylation reaction of aniline via DMC chemistry has also been investigated. The reaction, as reported in the Scheme 19.3, led to the formation of methyl *N*-phenylcarbamate **1**, as well as, to several by-products such as *N*-methyl



Scheme 19.2 carbamoylation of 2,4-diaminotoluene by gold-catalyzed phosgene-free synthesis



Scheme 19.3 Synthesis of the methyl *N*-phenylcarbamate **1** by reaction of aniline with DMC. The synthetic pathways leading to the by-products **2**-**5** are also shown

aniline **4** and *N*,*N*-dimethyl aniline **5**. Besides, the methyl carbamate **1** can further react either with DMC to give the methyl *N*-phenylcarbamate **2** or with aniline to form the diphenylurea **3**. Noteworthy, the reactions leading to the formation of carbamate **1** and urea **3** are equilibrium reactions ($B_{Ac}2$ mechanism), meanwhile the reactions leading to the methyl derivatives **2**, **4** and **5** are not equilibrium reactions ($B_{Al}2$).

In a first set of experiments, a selection of homogenous catalysts has been studied and their reactivity compared to zinc acetate – the most investigated homogeneous catalyst [42, 45, 46] for DMC-based carbamate synthesis (entries 1–6, Table 19.1). Then the best homogenous catalysts have been supported on silica or alumina. In a typical procedure, the metal salts were dissolved in water and the chosen support was added to the mixture. The resulting supported heterogeneous catalysts were recovered by solvent removal and were calcinated at 500 °C overnight. The final concentration of the metal on the support depended on the solubility of the salt and on the absorption capability of the support. The heterogeneous supported catalysts were then tested for the carbamoylation of aniline (entries 7–17, Table 19.1). Finally, also several heterogeneous catalysts were investigated (entries 18–22, Table 19.1). Results are collected in Table 19.1.

In a typical experiment, the carbamoylation of aniline by DMC was carried out in an autoclave at 160–180 °C in the presence of the selected catalyst.

Table 19.1 Reaction of aniline with DMC (10 mol. eq.) in the presence of different types of catalysts in autoclave

#	Catalyst		Time	Conv.	Me *N*-phenyl carbamate (%)^{b}	Other products (%)^{b}			
	(% mol)^{a}		h	(%)^{b}	**1**	**2**	**3**	**4**	**5**
Homogeneous at 160 °C									
1.	$Zn(AcO)_2.2H_2O$	(1.0)	6	97	96	0	2	2	0
2.	$Ti(BuO)_4$ (0.5)		6	22	60	0	0	37	3
3.	Dibutyltin dilaurate (DBTDL)	(1.0)	2	11 (84)^{c}	55 (76)^{c}	0 (0)^{c}	19 (4)^{c}	26 (14)^{c}	0 (5)^{c}
4.	Cs_2CO_3	(1.6)	7	94	10	73	0	13	3
5.	Pb_3O_4	(1.6)	5	99	99	0	0	1	0
6.	$Yb(CF_3SO_3)_3\cdot xH_2O$	(1.0)	5	97	39	0	0	9	51
Supported catalysts at 160 °C									
7.	Bi 18 % on $Al_2O_3\ \alpha^{d}$	(1.8)	6	48	48	0	34	16	2
8.	Zn 10 % on $Al_2O_3\ \alpha^{e}$	(1.9)	5	36	36	0	20	37	7
9.	Pb Het. 8.5 % on SiO_2	(1.0)	7	60	68	0	10	19	2
10.	Pb on basic $Al_2O_3{}^{e}$	(1.6)	7	54	54	0	21	21	4
11.	Pb 8.4 % on $Al_2O_3\ \gamma^{f}$	(1.6)	6	98	99	0	0	1	0
12.	Pb 9 % on $Al_2O_3\ \alpha$	(1.6)	4	99	97	1	0	1	1
Supported catalysts at 180 °C									
13.	Bi/Act. Carbon	(1.8)	2.5	82	61	0	9	20	10
14.	Sn 6.7 % on $Al_2O_3\ \alpha^{d}$	(1.6)	3.3	18	11	0	11	65	13
15.	Zn Het. 7.5 % on SiO_2	(3.2)	2.3	83	55	0	2	27	15
16.	Pb 10 % on $Al_2O_3\ \gamma$	(1.6)	3	51	59	0	10	24	7
17.	Pb 5.4 % on $Al_2O_3\ \alpha^{d}$	(1.0)	3.5	99	94	2	0	1	2
Heterogeneous catalysts at 160 °C									
18.	$[ZnCO_3]_2\,[Zn(OH)_2]_3$		5	96	94	0	3	3	1
19.	$(PbCO_3)_2\cdot Pb(OH)_2$	(1.6)	4	99	99	0	0	1	0
20.	$(BiO)_2CO_3$	(1.6)	2	11	45	0	31	24	0

(continued)

Table 19.1 (continued)

	Catalyst		Time	Conv.	Me *N*-phenyl carbamate (%)[b]	Other products (%)[b]			
#	(% mol)[a]		h	(%)[b]	**1**	**2**	**3**	**4**	**5**
21.	$Zn_3(PO_4)_2$	(1.6)	1	2	13	0	0	87	0
22.	$CuCO_3 \cdot Cu(OH)_2$	(3.2)	3	12	53	0	17	30	0

[a] % mol on aniline concentration

[b] Conversion and selectivity calculated by HPLC measurements using nitrobenzene as internal standard

[c] Raising the temperature at 180 °C for 3 h

[d] Fused alumina

[e] Alumina brockman activity I, basic

[f] Nanopowder alumina

Among the homogenous catalysts investigated, only lead oxide (entry 5, Table 19.1) was as effective as the commercially used zinc acetate (entry 1, Table 19.1). In both experiments, aniline was quantitatively converted into the methyl *N*-phenylcarbamate **1**.

Insoluble supported and heterogeneous catalysts are more advantageous as they can be easily recovered at the end of the reaction without using any time-wasting separation and/or purification needed for the homogeneous catalysts. Among the heterogeneous catalysts studied for this reaction, both zinc and lead carbonate basic (entries 18–19, Table 19.1) gave good results in terms of selectivity and conversion. However, due to its toxicity, commercially available zinc carbonate basic (entry 18, Table 19.1) resulted more advisable as catalyst.

Further reaction optimization in presence of zinc carbonate basic showed that optimal reaction conditions were the following: 180 °C, 1/10 of aniline/DMC molar ratio, and 3.2 mol. % of catalyst amount.

Since zinc carbonate basic is nearly insoluble in the reaction mixture, it can be easily separated by filtration and reused. Therefore in order to study the recycling of the catalyst, zinc carbonate was recovered at the end of the reaction, dried, and tested again. The recycled zinc carbonate basic resulted almost as efficient as the fresh one. However, after two cycles, both conversion and selectivity moderately decreased.

Most of the carbamoylation reactions reported in the literature have been carried out in batch conditions. Few examples have been reported using a continuous-flow (CF) apparatus, i.e., a semicontinuous process for the synthesis of methyl carbamate from urea and methanol [48] and a gas-solid oxidative carbonylation reaction of aniline in a semibatched fixed-bed reactor [49]. The latter process employed a NaI-Pd/C catalyst and the synthesis proceeded in only 2 h with 80 % of aniline conversion and 74 % carbamate yield. An example of high yielding carbamoylation of aromatic anilines employing a tetranuclear cluster $Zn_4O(OAc)_6$ as catalyst has been reported. However, also in this case, all the reactions have been performed in autoclave and the use of a CF apparatus has only been mentioned [50].

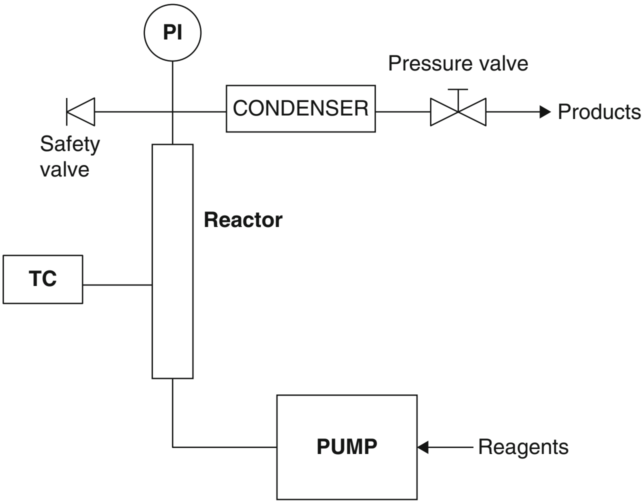


Fig. 19.1 Fixed-bed continuous-flow reactor

According to the best results achieved by DMC-mediated carbamoylation of aniline, basic zinc carbonate was also investigated as catalyst in a fixed-bed continuously fed reactor (Fig. 19.1). The fixed-bed CF reactor, used for the reactions, consisted of a stainless steel tube (4.15 mL capacity, 4.6 mm id, length 250 mm) thermostated with a coiled heating band. Several variables have been investigated, i.e., molar ratio of the reagents, flow rate, reaction temperature, volume of the reactor, and catalysis stability to optimize the operating conditions of the system [51].

In a typical experiment, zinc carbonate was charged into the reactor and packed manually. The aniline/DMC solution was fed by a Jasco 880 PU HPLC pump. Products were formed, were cooled by a condenser, and were collected via a proportional relief valve, set at $p = 15$ bar (1.5 MPa).

Considering the economical aspect of an eventual industrial process, i.e., lowest amount of reagents possible and best conversion and selectivity, the optimal reaction conditions were found at 200 °C, 1/10 of aniline/DMC molar ratio and (0.10 $\text{mL}\cdot\text{min}^{-1}$) of flow rate. In this case, 98 % conversion of the substrate and 97 % selectivity of the carbamate were achieved. Although diphenyl urea was formed as the main by-product, it can be easily converted into the methyl phenylcarbamate by transesterification reaction with methanol or DMC [52, 53].

The efficiency of the catalyst over time (180 h) showed that catalyst retained its activity unaltered for the entire duration of the trial as the carbamoylation of aniline proceeded in high conversion and selectivity (above 90 %).

Furthermore the amount of zinc carbonate present in the product mixture was measured using atomic absorption spectroscopy analysis. Results indicated that only (0.8 mg $\text{Zn}\cdot\text{L}^{-1}$) were present in the solution. This demonstrated the catalyst was stable and suitable for use in a long-term continuous process.

Variation of reactor volume from 4.15 to 10.73 mL taking into account the maintenance the same residence time showed that both conversion and selectivity remained the same value. This experiment proved that the reaction can be easily scaled-up without loss of its efficiency.

19.3 DAC-Mediated Synthesis of Cyclic Carbamates

Similarly to linear carbamates, also most of the synthetic routes to cyclic carbamates involve the use of phosgene or its derivatives. Five- and six-membered cyclic carbamates are widely used as intermediates of agrichemical, pesticide, herbicide and pharmaceutical agents, solvents, and chiral auxiliaries [54–61].

Six-membered cyclic carbamates or 1,3-oxazinan-2-ones (Fig. 19.2) are, in particular, compounds of great interest due to their biological activity. In fact, recently, they have appeared in numerous patents as intermediates in the synthesis of pharmaceutical drugs used in the treatment of Alzheimer's [62–64] diseases mediated by the activation of β3-adrenoceptorother [65], diseases related to kinases activity [66], and for the regulation of cholesterol [67]. They are also used as herbicides with excellent crop-weed selectivity [68]. 1,3-Oxazinan-2-ones have also been employed as monomers for the preparation of hyperbranched polyamines [69–71] or polyurethane by cationic ring-opening polymerization [72].

There are many synthetic routes to 1,3-oxazinan-2-ones; however, most of them involve phosgene or its derivatives [73, 74] (Eq. 1, Scheme 19.4) and alkyl halide chemistry [75–78] (Eq. 2, Scheme 19.4). Another common synthetic approach encompasses the use of isocyanate compounds [79–82] in the presence of hexamethylphosphoramide (HMPA) (Eq. 3, Scheme 19.4).

Other procedures require complex starting materials such as allylic amines and allylic carbamates [83–86] (Eq. 4, Scheme 19.4) or multiple steps to give the final product [87, 88].

More recently, oxazinanones and oxazolidinones have been prepared utilizing CO_2 as carbonylating agent and amino alcohols as starting material. However, some reactions (Eq. 5, Scheme 19.4) involve stoichiometric or greater amount of phosphorylating agents such as diphenylphosphoryl azide (DPPA) and diphenyl chlorophosphate (DPPCl) or halogen-based electrophiles ($SOCl_2$, TsCl, or AcCl) [89].

A greener synthetic route to cyclic carbamates (Eq. 6, Scheme 19.4) employs cerium oxide, but it also requires high pressure over a long time period and results in only moderate yields of the products [90]. Other green routes to oxazinanones

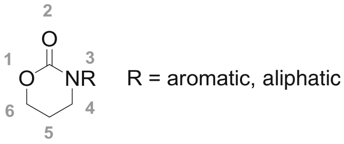
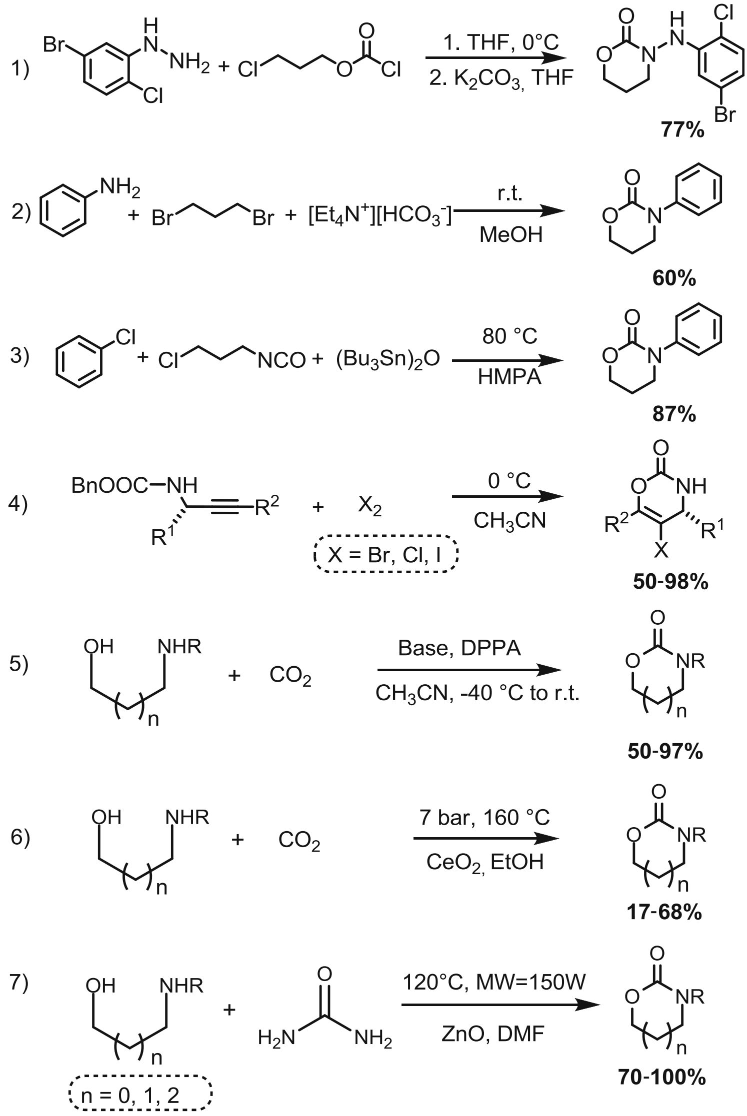


Fig. 19.2 1,3-oxazinan-2-one motif



Scheme 19.4 Synthetic approaches to cyclic carbamates via: (Eq. 1) phosgene; (Eq. 2) halide chemistry; (Eq. 3) isocyanate compounds; (Eq. 4) allylic carbamates; (Eq. 5) CO_2 chemistry; (Eq. 6) cerium oxide; (Eq. 7) urea

employ microwave-assisted coupling reactions between amino alcohols and urea (Eq. 7, Scheme 19.4), which occur in good yields [87, 91]. But all these routes are limited by the availability/ease of synthesis of the starting 1,3-amino alcohols [92].

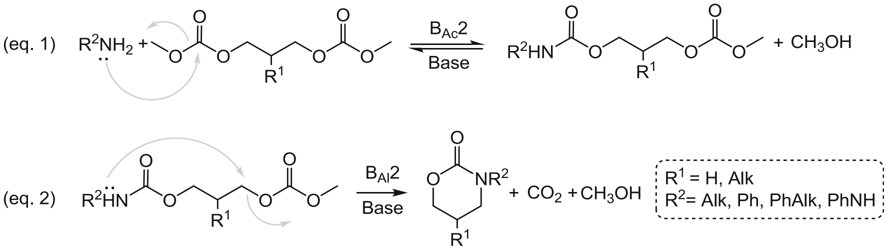
New green DAC-based routes to 1,3-oxazinan-2-ones in good yield have also been reported. Synthesis of 6-membered carbamates was conducted by reaction of primary amines or hydrazines with bis(methyl carbonate) derivatives of 1,3-propanediols in the presence of potassium *tert*-butoxide (Schemes 19.5 and 19.6) [93].

The cyclization reaction proceeds in two steps as depicted in Scheme 19.5.

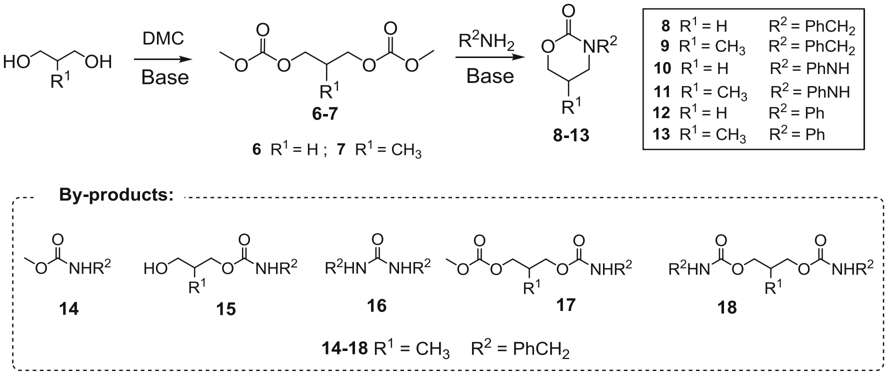
According to the HSAB theory, in the first step (Eq. 1, Scheme 19.5), the amine behaves as a hard nucleophile and proceeds through a $B_{Ac}2$ pathway leading to the formation of the linear carbamate intermediate. In the second step (Eq. 2, Scheme 19.5), the formedintermediate undergoes nucleophilic displacement of the carbonate group through a $B_{Al}2$ intramolecular cyclization pathway leading to the cyclic carbamate.

Benzylamine was chosen as starting material and reacted with dicarbonates **6** and **7** to synthesize 3-benzyl-1,3-oxazinan-2-one **8** and 3-benzyl-5-methyl-1,3-oxazinan-2-one **9**, respectively (Scheme 19.6).

Study of the reaction benzylamine with dimethyl 2-methylpropane-1,3-diyl dicarbonate **7** showed that several by-products formed as a result of numerous concurrent reactions (Scheme 19.5). In particular, they include methyl *N*-benzylcarbamate **14**, 3-hydroxy-2-methylpropyl *N*-benzylcarbamate **15**,



Scheme 19.5 Proposed reaction mechanism of *intermolecular* formation of a cyclic carbamate *via intramolecular* cyclization



Scheme 19.6 Synthetic pathway to 1,3-oxazinan-2-ones via DMC and major by-products of reaction of benzylamine with dicarbonate 7

Table 19.2 Reactions of benzylamine (1. eq. mol) with dicarbonate **7** (1. eq. mol) using different bases

#	Base (Eq.)	*t*/°C	Conv./%	Selectivity/%						
				1,3-Oxazin-2-one **9**	**14**	**15**	**16**	**17**	**18**	**Others**
1.	None[a]	90	78	0	21	30	0	10	2	15
2.	K_2CO_3 (1)[a]	90	82	1	19	31	0	11	0	20
3.	Cs_2CO_3(1)[a]	90	89	3	22	40	1	4	5	15
4.	NaOMe (1)[b]	90	99	24	39	20	4	1	3	7
5.	*tert*-BuOK (1)[b]	90	99	64	17	12	2	0	3	1

[a] 18 h reaction time

[b] 2 h reaction time

1,3-dibenzylurea **16**, methyl 2-methyl-3-(benzylcarbamoyl)propyl carbonate **17**, and 2-methylpropane-1,3-dibenzylcarbamate **18**.

Table 19.2 shows the results observed for the reaction of benzylamine with the dicarbonate **7** using different bases. Results collected showed that without base or in the presence of weak bases the cyclic product formed in negligible amounts and numerous by-products were present in the reaction mixture (entries 1–3, Table 19.2).

The best results were observed employing potassium *tert*-butoxide. In this case, benzylamine was quantitatively converted and the cyclic carbamate **9** was obtained with good selectivity (64 %) in only 2 h reaction time (entry 5, Table 19.2). Sodium methoxide showed to be less effective as the methoxy anion can partake in a competitive reaction with the methyl carbonate giving DMC, which in turn reacts readily with the amine to give methyl *N*-benzyl carbamate **14**. Noteworthy, potassium *tert*-butoxide owing to the bulky nature of its related anion inhibits such parasitic reactions [94]. It probably behaves primarily as a base, extracting a proton from the tetrahedral intermediate, which ultimately results in the formation of the cyclic product. The more hindered nature of the base limits its activity as a nucleophile and thus it might partake in the $B_{Ac}2$ transesterification reactions at a lower rate, so improving the yield of the cyclic carbamate.

The linear carbamate **14** can also be formed by reaction of benzylamine reacting with the dicarbonate **7** giving the 3-hydroxy-2-methylpropyl methyl carbonate as leaving group instead of methanol.

The monofunctional 3-hydroxy-2-methylpropyl methyl carbonate promoted the formation of many unwanted by-products. In fact, the linear carbamate **15** is formed through the reaction of benzylamine with 3-hydroxy-2-methylpropyl methyl carbonate giving methanol as the leaving group.

Both the compounds **16** and **18** are formed through the reaction of benzylamine with a by-product already incorporating an aromatic group (**14** and **17**, respectively).

It is noteworthy that similar cyclization reactions involving benzylamine, aniline, and phenylhydrazine with bis(methyl carbonate)s derived from butan-1,4-diol

Table 19.3 Reaction of primary amines and phenyl hydrazine with dicarbonates **6** or **7**

#	Amine	DAC	Conv./%	Product	Yield/%[a]
1.	$PhCH_2NH_2$	**6**	99	**8**	44[b] (40[c])
2.	$PhCH_2NH_2$	**7**	99	**9**	64[b] (53[c])
3.	$PhNHNH_2$	**6**	100	**10**	65[d] (30[e])
4.	$PhNHNH_2$	**7**	100	**11**	68[d] (35[e])
5.	$PhNH_2$	**6**	91	**12**	52[d] (27[e])
6.	$PhNH_2$	**7**	94	**13**	68[d] (42[e])

[a] By-products are consistent with those observed in Scheme 5

[b] Determined *via* HPLC analysis

[c] Isolated yield through column chromatography

[d] Determined *via* GCMS

[e] Isolated yield through recystalization

and pentan-1,5-diol do not yield cyclic products. This indicates that the $B_{Al}2$ nucleophilic displacement shown in Scheme 19.5 (Eq. 2) is most likely the reaction-determining step for the formation of the cyclic compound and is evidently controlled by entropic effects.

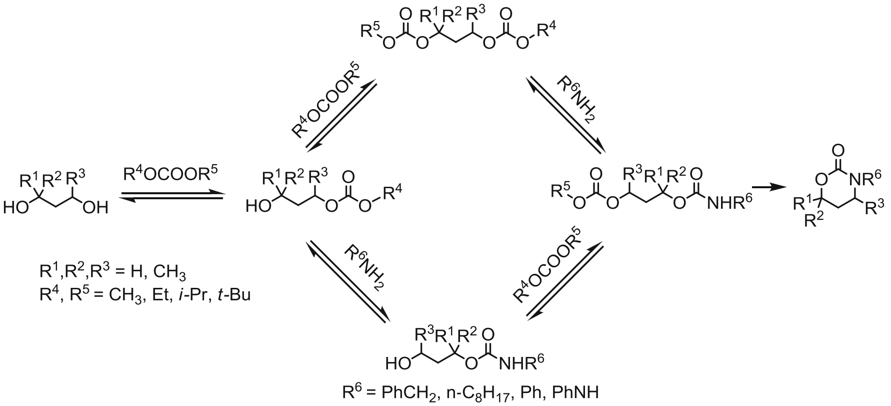
Further optimization of cyclization reaction demonstrated that the best conditions for 1,3-oxazinan-2-ones synthesis were 1:1:1 ratio of amine/bis(methyl carbonate)/potassium *tert*-butoxide reacted at 90 °C.

This investigation was then extended to different starting compounds. Table 19.3 shows results of 1,3-oxazinan-2-ones synthesis from aniline, benzyl amine, and phenyl hydrazine utilizing bis(methyl carbonate)s **6** and **7**.

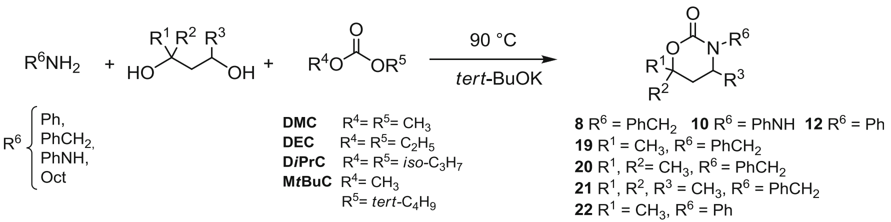
Under such conditions, the terminal amine of hydrazine reacts selectively, while the other nitrogen remains unreacted. The formation of both unsubstituted and substituted cyclic carbamates was achieved also in this case in appreciable yield. The observed conversion of aniline into its cyclic derivative (entries 5–6, Table 19.3) was lower than that of hydrazine or benzylamine as usually the aromatic amines are weaker nucleophiles than aliphatic ones and as such do not react as readily [32]. It should be noted that although the yields obtained are comparable to those already reported in the literature, the proposed synthetic pathway is greener, simpler, and faster, and it utilizes cheap, readily available starting materials [79, 81, 95].

A synthetic approach to 1,3-oxazin-2-ones was also performed in a one-step synthesis without the preliminary preparation of bis(methyl carbonate) derivative. In this case, an amine (or phenylhydrazine), 1,3-diols, and dialkyl carbonate have been reacted in the presence of a stoichiometric amount potassium *tert*-butoxide at 90 °C. The formation of bis(dialkyl)-propane-1,3-diyl-dicarbonates takes place in situ and the cyclization reaction to form 1,3-oxazinan-2-one proceeds through a cascade reaction (Scheme 19.6).

The general application of this methodology and the influence on the yield of differently substituted 1,3-diols and DACs have been investigated. The synthesis was also carried out on different nucleophiles, i.e., aliphatic and aromatic amines and phenylhydrazine (Scheme 19.7).



Scheme 19.7 The cascade reaction to 1,3-oxazinan-2-one. All reactions are equilibriums with exception of the final cyclization step



8 R^6 = $PhCH_2$ **10** R^6 = PhNH **12** R^6 = Ph
19 R^1 = CH_3, R^6 = $PhCH_2$
20 R^1, R^2= CH_3, R^6 = $PhCH_2$
21 R^1, R^2, R^3 = CH_3, R^6 = $PhCH_2$
22 R^1 = CH_3, R^6 = Ph
23 R^1, R^2 = CH_3, R^6 = Ph
24 R^1 = CH_3, R^6 = PhNH
25 R^1, R^2 = CH_3, R^6 = PhNH
26 R^6 = Oct **27** R^1 = CH_3, R^6 = Oct

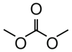
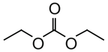
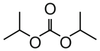
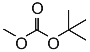
Scheme 19.8 Synthesis of 1,3-oxazinan-2-ones synthesis *via* DAC chemistry in one-step process (R = H when not specified)

In order to observe the effect of the steric factor influence of the substrate on the 1,3-oxazinan-2-one synthesis, differently substituted 1,3-diols were employed (Scheme 19.8). DACs selected for this study were DMC, diethyl carbonate (DEC), diprop-2-yl carbonate (DiPrC), and *tert*-butyl methyl carbonate (M*t*BuC). The unsymmetrical carbonate M*t*BuC was used instead of the di-*tert*-butyl carbonate as the latter is too sterically hindered for any reaction to occur. It is noteworthy that the reactions do not require the presence of a solvent.

In a first set of experiments, benzylamine was selected as substrate and reacted with 1,3-propandiol, 1,3-butandiol, and 3-methyl-1,3-butandiol in the presence of different DACs to give 1,3-oxazinan-2-ones **8**, **19**, and **20**, respectively. The results are reported in Table 19.4.

Table 19.4 shows a significant trend in selectivity and isolated yield with the increasing steric hindrance of the selected DAC from entries 1 to 4 for each

Table 19.4 One-pot synthesis of 1,3-oxazinan-2-ones via DACs chemistry

	Diol	1,3-Propandiol			1,3-Butandiol			3-Methyl-1,3-butandiol		
			Yield **8**/%			Yield **19**/%			Yield **20**/%	
#	DAC ↓	Conv./%	HPLC	Isolated[a]	Conv./%	HPLC	Isolated[a]	Conv./%	HPLC	Isolated[a]
1.		98	29	21	98	28	14	97	28	16
2.		96	38	36	98	39	27	96	39	21
3.		95	43	47	98	46	44	94	46	29
4.		96	50	57	96	51	45	94	51	32

[a] Reactions of benzylamine (1 eq. mol) with different diols (1 eq. mol) in the presence of DAC (3 eq. mol) and potassium tert-butoxide (2 eq. mol) at 90 °C for 2 h to yield 1,3-oxazinan-2-one isolated by column chromatography

oxazinanone. The resulting scale of carbonate reactivity in the cyclization reaction is:

$$^{t}\mathrm{BuOCOOMe} > i\mathrm{PrOCOO}i\mathrm{Pr} > \mathrm{EtOCOOEt} > \mathrm{MeOCOOMe}$$

It is already known when reacting an amine with a DAC in the presence of a base, the more hindered the DAC, the easier the formation of a carbamate, as more hindered alkoxides are better leaving groups [94]. Conversely, when an alcohol is reacted with a DAC in basic conditions, the trend of leaving group is almost the reverse of that observed with an amine [96].

Despite the large number of equilibrium reactions taking place, results shown here seemed to be in good agreement with previous observations.

Significantly, proton NMR analysis of 3-benzyl-6-methyl-1,3-oxazinan-2-one **19** and 3-benzyl-6,6-dimethyl-1,3-oxazinan-2-one **20** confirmed the methyl group is exclusively located in the 6 position of the oxazinanone ring.

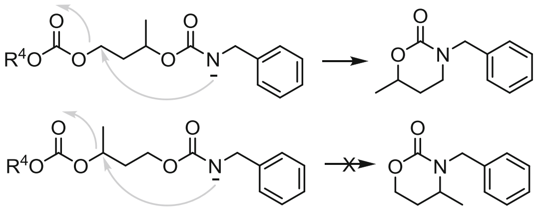
Additionally, when reacting 2-methylpentan-2,4-diol with benzylamine and M*t*BuC in the presence of potassium *tert*-butoxide, only a negligible selectivity of 3-benzyl-4,6,6-trimethyl-1,3-oxazinan-2-one **21** was detected (0.3 %). In this case, analysis of the reaction by GCMS indicated that the major product was methyl *N*-benzylcarbamate, most likely as a result of the steric hindrance both of the diol and of the α carbon in the *intramolecular* cyclization step. This suggests that *intramolecular* attack on the soft electrophilic center of the carbonate functionality ($B_{Al}2$ pathway) preferentially occurs on a sterically unhindered CH_2 group (Scheme 19.9). As a consequence, such cyclization reaction results in high selectivity toward substituents in the 6 and not in the 4 position of the oxazinanone ring.

The general applicability of the one-pot synthesis to 1,3-oxazinan-2-ones was then investigated employing several nucleophiles, i.e., aniline, phenylhydrazine and *n*-octylamine. These substrates were reacted with differently substituted 1,3-diols in the presence of the preferred DAC, M*t*BuC (Scheme 19.7).

Table 19.5 shows that this cascade synthetic approach to 1,3-oxazinan-2-ones can be employed efficiently to several amines and also to phenylhydrazine, giving adequate to good yields.

In all cases, proton NMR analysis of the 1,3-oxazinan-2-ones confirmed that methyl substituent(s) were also found solely in the 6 position.

Table 19.5 shows a disparity between the observed and isolated yields since the products were mostly isolated by crystallization (Entries 1–6); thus, it is expected that a certain amount of the compounds remain within the liquor. Also, in the case



Scheme 19.9 Selectivity toward 6-methyl 1,3-oxazinan-2-ones

Table 19.5 Cascade synthetic approach to 1,3-oxazinan-2-ones[a]

#	Nucleophile	Diol	Product	GCMS yield/%	Isolated yield/%
1.	Aniline	1,3-Propandiol	**12**	46	34[b]
2.	Aniline	1,3-Butandiol	**22**	62	41[b]
3.	Aniline	3-Methyl-1,3-butandiol	**23**	34	32[b]
4.	Phenylhydrazine	1,3-Propandiol	**10**	61	24[b]
5.	Phenylhydrazine	1,3-Butandiol	**24**	76	53[b]
6.	Phenylhydrazine	3-Methyl-1,3-butandiol	**25**	52	18[b]
7.	n-Octylamine	1,3-Propandiol	**26**	51	25[c]
8.	n-Octylamine	1,3-Butandiol	**27**	32	17[c]

[a] Reaction of amines or phenylhydrazine (1 eq. mol) with different 1,3-diols (1 eq. mol) in the presence of methyl *tert*-butyl carbonate (3 eq. mol) with potassium *tert*-butoxide (1 eq. mol) at 90 °C for 2 h

[b] Isolated by recrystallization in propan-2-ol

[c] Isolated by column chromatography

of the other 1,3-oxazinan-2-ones (Entries 7–8), the large hydrophobic chain present in the compound made its separation from other by-products via column chromatography somewhat difficult.

19.4 Conclusions

Several synthetic pathways have been so far reported in the literature for the preparation of linear (aromatic) and cyclic carbamates. With the intent of pursuing phosgene-free synthetic approach, DACs have demonstrated to be green and efficient reagents for the efficient of both these type of carbamate molecules. For the synthesis of methyl *N*-phenylcarbamate, reactions have been conducted in batch and in CF conditions.

In batch conditions, several homogeneous, heterogenized, and heterogeneous catalysts have been investigated. Zinc carbonate basic showed to be among the best catalyst giving quantitative conversion and selectivity for the wanted product. Its reactivity was comparable with the extensively investigated zinc acetate with the advantage to be a heterogeneous catalyst and thus easier to separate from the reaction mixture. However, zinc acetate led also to unwanted side products such as methyl acetate that is not formed in the case of zinc carbonate. Furthermore the latter catalyst was easily recovered at the end of the reaction, and after calcination, it can be efficiently reused. Noteworthy, the carbamate **1** can be recovered by evaporation of the solvent without any time-wasting and/or expensive purification.

The direct carbamoylation of aniline in a fixed-bed continuously fed reactor charged with basic zinc carbonate reactor has been also investigated. Results collected demonstrated that, in this CF system, zinc carbonate performs efficiently for the DMC-mediated synthesis of methyl phenylcarbamate. The optimal conditions have been found for a reactor with a capacity of 4.15 mL were an aniline/DMC *ratio* of 1/10, temperature of 200 °C, and a flow rate of 0.10 mL·min^{-1}, resulting in 98 % conversion and 97 % selectivity. The carbamoylation reaction was also conducted on a larger scale employing a reactor with the capacity (10.73 mL), achieving similar results in terms of conversion and selectivity. Investigation on the stability of the catalyst showed efficient conversion and selectivity throughout without showing any loss of activity. Furthermore, negligible leaching of the zinc carbonate was observed.

DACs have been also employed for a new green route to 1,3-oxazinan-2-ones. This *intermolecular* cyclization was carried out using a primary amine and a bis (methyl carbonate) derivatives of 1,3-propanediols synthesized from DMC and 1,3-diols. Potassium *tert*-butoxide showed to be the most efficient base for such process. The optimal conditions found include a 1:1:1 ratio of amine/dicarbonate/potassium *tert*-butoxide and 90 °C.

Besides a one-pot synthesis of 1,3-oxazinan-2-ones from amines or phenyl hydrazine, 1,3-diols, and DAC through a cascade reaction in the presence of a base and without any solvent has been described. The role of the DAC in the cascade cyclization reaction is multifunctional. They act as leaving groups, entering groups, and sacrificed molecule. The more hindered the DAC, the greater the yield of oxazinanones observed. A very high level of selectivity is found when reacting a 1,3-diol with both primary functionality and a substituent α to the other OH group. For cyclization to occur through nucleophilic displacement, primary CH_2 functionality α to the carbonate must be present, as substituents on the 1,3-oxazinan-2-ones ring are found in the 6, never in the 4 position. Synthesizing the 1,3-dicarbonate in situ removes a lengthy step from the production of the oxazinanone, requires far less equivalents of DACs, and reduces the energy consumption for the process.

In conclusion the use of DACs represents a step forward in halogen-free chemistry, presenting intrinsically clean, solvent-free approaches for the synthesis of both linear and cyclic carbamates. The low-cost and easily available starting materials, coupled with the green reaction pathway, could allow to a wider applications of this class of compounds in several research areas.

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Part VIII

Chlorine Derivatives Utilization and Recycle: *Utilization*

Chapter 20
State of the Art and Problems of Organochlorine Synthesis

Yury Treger and Mark Flid

Abstract The chemical industry consumes up to 70 % of the chlorine produced; up to 60 % is used for the production of organochlorine compounds. It is demonstrated that modern industry needs a good few of organochlorine products including epichlorohydrin used to produce the epoxy resins; chloroprene, which is the intermediate for manufacturing of special rubber; methyl chloride and chloroform, which are necessary for the production of organosilicon and organofluorine compounds; PVC, which is widely used in many industries; etc. The technologies of production and application of these products should be designed in such a way that they have a minimum influence on the environment and people's health. The technologies of organochlorine compounds production with the emphasis on environmental impact are discussed in the article. It is demonstrated that indexes of ecological safety of organochlorine plants largely comply with governmental regulations, but unsolved problems (e.g., the need for environmentally benign catalyst for vinyl chloride monomer production) are also addressed. The advantages of balanced schemes that prevent environment pollution by the waste hydrochloric acid itself or the products of its neutralization are shown. The main regularities about the treatment of wastes formed during organochlorine compounds production as well as the necessity of chlorine-containing xenobiotics removal from industrial use are discussed in the article.

Keywords Balanced scheme • Chlorination • Chloromethanes • Epichlorohydrin • Industrial organochlorine synthesis • Hydrocarbon feedstock • Hydrochlorination • Montreal protocol • Oxidative chlorination • Ozone layer • Polyvinyl chloride (PVC) • Stockholm convention • Treatment of organochlorine wastes • Vinyl chloride monomer (VCM)

Organochlorine synthesis originates from the late eighteenth century. The first known organochlorine compound is 1,2-dichloroethane. It was synthesized in 1795 by Dutchmen Deimann, Van Troostwyk, Bondt, and Louwreburgh. Henceforth it was known as

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"oil of Dutch chemists." In 1830s, Liebig, Dumas, and Regnault opened such compounds as chloroform, chloral, methyl chloride, and vinyl chloride.

Organochlorine synthesis began rapidly developing in industrial scale in 1920s–1930s. As a result of this development, the chlorinated hydrocarbons play now an important role in the chemical industry and provide the principle routes by which chlorine reaches the heavy chemical market.

Thus, the chlorinated derivatives of the hydrocarbons are by far the most important link between the inorganic and organic chemical industries. Their development had its beginnings in the early 1900s and was considerably accelerated in the years following World War I by the emergence of liquefied chlorine as the principal commercial chlorine commodity, held for almost a century by bleaching powder. During and after World War II, chlorinated hydrocarbon production rapidly rose to a dominant position in the chemical industry, along with the postwar development of the organic chemical industry; such rise was promoted, in particular, by the great expansion of the petroleum chemical sector.

By 2015, the world production of chlorine reached 55 million tons (49.9 Mt) per year. Accordingly, output volume of the second product of electrolysis, namely, NaOH, achieved approximately 63 million tons (57.2 Mt) per year. No alternative to caustic soda in a variety of industries dictates the necessity of a qualified use of the entire amount of chlorine generated. The chemical industry consumes up to 70 % of the chlorine produced; up to 60 % is used for the production of organochlorine compounds. The high demand for these compounds originates from the 1950s and does not reduce up to now. This fact points at the very important role of chlorine and its derivatives in contemporary life. The scope of caustic soda and

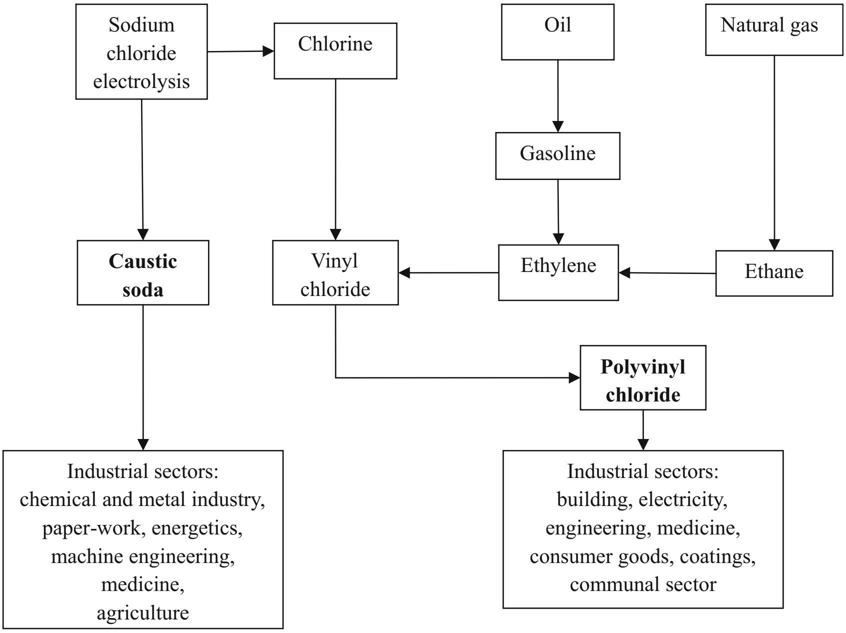


Fig. 20.1 The flow diagram of caustic soda and polyvinyl chloride production and use

polyvinyl chloride (PVC), as an example of organochlorine compound, is outlined in Fig. 20.1.

Many branches of industry consume organochlorine products; between them are the industry of plastics, synthetic resins and fibers, machinery, electronics, petroleum, pharmaceutical industry, household chemical production, communal sector, etc. The most demanded organochlorine products include chlorinated monomers like vinyl chloride, which is designated for polymerization to form PVC; vinylidene chloride which is used in combination with vinyl chloride, acrylonitrile, butadiene, and other monomers for thermoplastic copolymer production; and chloroprene which is used for elastomers (e.g., chloroprene rubber) production. The main raw material for the epoxy resins, fiberglass, and ion-exchange resins is epichlorohydrin produced from allyl chloride or glycerol.

Chloromethanes also find widespread application. Methyl chloride is used as a monomer in the organosilicon compounds production. Methylene chloride is consumed mainly for the production of non-combustible triacetylcellulose films. Chloroform is the starting compound for the production of ozone-safe freons and (poly) tetrafluoroethylene (PTFE). It is also used as an effective solvent.

Perchloroethylene and trichloroethylene are effective solvents as well. They are used in dry cleaning as oil, fat, wax, and resin-removing agents. Ozone-safe freons are also produced from these compounds.

Many different kinds of organochlorine compounds were developed until now. Depending on the type of compound, reactivity of functional groups, presence of extra elements in the molecule, etc., they can be used as vulcanization agents (hexachloro-p-xylene, hexachloroethane, derivatives of chlorinated phenols, and others), plasticizers (liquid chlorinated paraffin and polyphenols), the flame retardants (solid chlorinated paraffin wax), and inhibitors (chlorophenols). The polymer modification is realized by the use of chloranhydrides of carbonic acids, in particular, dichloranhydride of terephthalic acid, organochlorine ketones, and other compounds. Such (poly)functional compounds also find widespread application.

The technologies of organochlorine compounds production have been continuously improved, and currently they are characterized by the reduced emissions into the environment. The efficiency of feedstock use is typically more than 96–97 %. The indexes of ecological safety of organochlorine plants largely comply with governmental regulations.

The processes of organochlorine compounds production usually include the stages of chlorination, oxidative chlorination (oxychlorination), hydrochlorination, dehydrochlorination, oxidation, hydrogenation, and others in various combinations. The recycle schemes are often implemented in the processes which allow high-performance achievement. Considerable efforts and resources are invested in the modern technologies of waste recovery. The tough environmental and economic approach to these processes dictates the following main requirements for processing of wastes:

- High conversion of wastes
- Absence of toxic compounds in effluents
- Low values of energy consumption and cost of processing

- Maximum recycle of raw materials which were not consumed in the process to prevent waste formation
- Possibility of qualified use of the ultimate products of waste processing

The manufacturing routes for some C_1-C_2 chlorinated carbons and hydrocarbons and some C_3, C_4, and C_6 chlorinated hydrocarbons are presented on Figs. 20.2 and 20.3, respectively.

The total annual world output of chlorinated organic products is about 60 million ton. Some of the manufactures of these products are in good progress, some are in a stable state, and some ceased operation due to economic or environmental reasons.

The products of the industrial organochlorine synthesis can be divided into four groups on the basis of their application scopes:

1. The first group comprises products widely used in industry such as epichlorohydrin, perchloroethylene, and chloroform, chlorobenzene which is used as semi-product for manufacture of chemical filaments, monochloroacetic acid which is used for manufacture of carboxymethylcellulose, and others. There is no adequate replacement for these products at the moment. The world production of these compounds is stable ranging from 0.27 to 1.82 Mt.
2. The second group comprises chloropolymers such as chloroprene rubber, polyvinylidene chloride, chlorinated and sulfochlorinated polyethylene, and chlorinated polyvinyl chloride; but the major member of this group is actually polyvinyl chloride (PVC) which is unique and most widely produced compound in organochlorine industry. It is the only organochlorine product having world

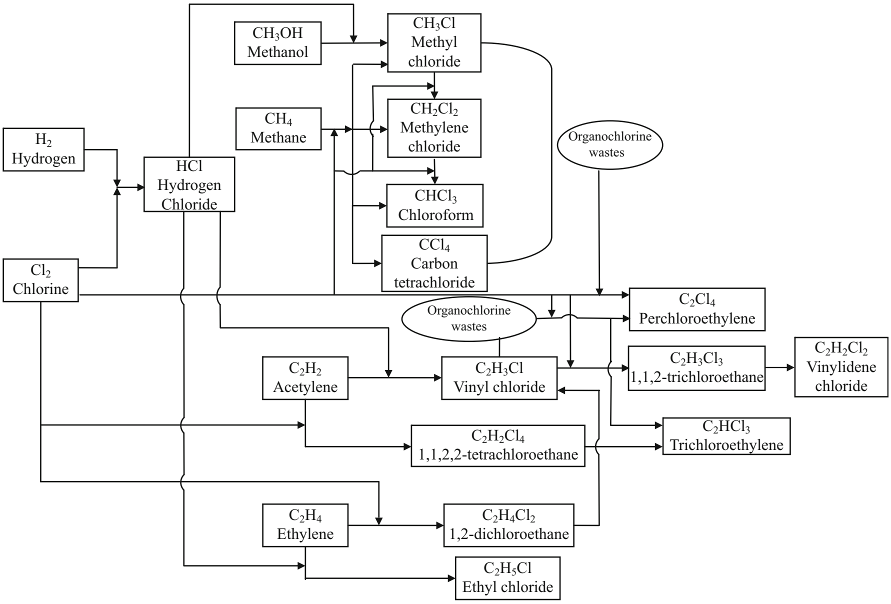


Fig. 20.2 Manufacturing routes for some C_1 and C_2 chlorinated carbons and hydrocarbons

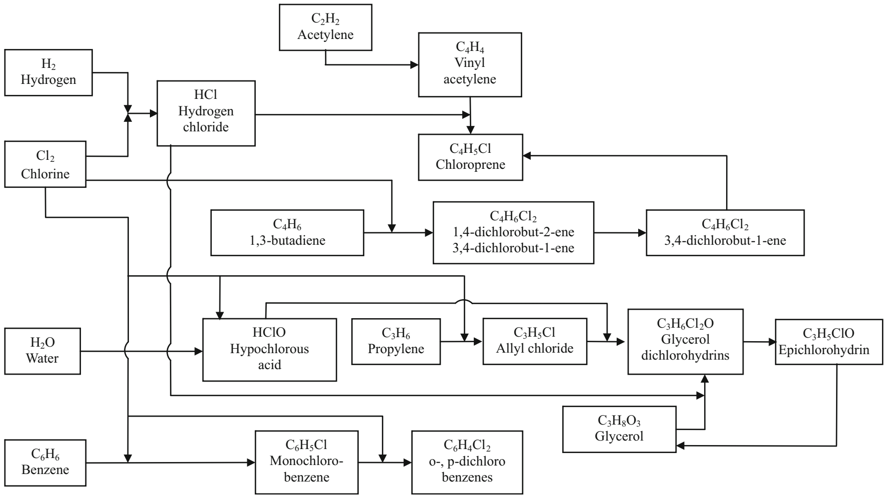


Fig. 20.3 Manufacturing routes for some C_3, C_4, C_6 chlorinated hydrocarbons

output which increases by 4–5 % per year; now it reaches near 40 million tons per year. PVC production correlates with the gross domestic product in the world and consumes up to 40 % of the chlorine produced worldwide. Till now no alternative to PVC was found so it is irreplaceable in the manufacture of cables, window frames, linoleum, and pipes.

3. The third group includes compounds commercially available in the past and directly affecting human health, such as mustard gas, lewisite, persistent pesticides, and polychlorinated biphenyls (PCBs). Production and use of these compounds are prohibited by various international agreements such as Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction (Chemical Weapons Convention, CWC), entered into force in 1997; Stockholm Convention on Persistent Organic Pollutants, signed in 2001 and effective from 2004: and others. Stockholm Convention is the most significant international agreement. PCBs, 1,1,1-trichloro-2,2-di(p-chlorophenyl)ethane (DDT), polychlorinated dibenzo-p*ara*-dioxins (PCDD$_s$), and polychlorinated dibenzofurans (PCDF$_s$), which is known under the group name dioxins, have been included in the original list of contaminants prohibited by this convention. Later this list was widened by the inclusion of a number of chloro-, bromo-, and fluoroorganic compounds. The correctness and efficiency of these international decisions for environmental safety is indubitable.
4. The fourth group comprises chlorinated compounds destroying the ozone layer, such as chlorofluorocarbons, as well as tetrachloromethane and 1,1,1-trichloroethane. The production and use of these compounds are prohibited by Montreal Protocol, 1987.

A wide range of chemical substances, which do not contain chlorine themselves, are synthesized via the intermediate formation of chlorinated products [1]. The synthesis of chlorinated derivatives of organic molecules provides the ways of the different group ($-OH$, $-SH$, $-NO_2$, $-F$, $-CN$) introductions, as well as alkylation and acylation of aromatic compounds through Friedel-Crafts reactions, opening the route to the organometallic chemistry. Chlorinated organics are used in the manufacture of industrial isocyanates which are necessary raw materials for the polyurethanes production and in the synthesis of (poly)carbonates using phosgene route. Chlorine is playing a role of a chemical intermediate, and it is eliminated at the end of a process as an inert inorganic chloride, but more frequently it is recycled [1].

More detailed consideration of the technological processes in organochlorine compounds production will be presented below.

20.1 The Manufacture of Methyl Chloride

Methyl chloride is produced on an industrial scale by the interaction of hydrogen chloride and methanol in the gas phase over $ZnCl_2$/support catalyst, according to Reaction (20.1):

$$CH_3OH + HCl \rightarrow CH_3Cl + H_2O \tag{20.1}$$

The process is carried out in tubular reactor at 200–250 °C. Molar ratio of HCl: CH_3OH in the range of 1.2–1.5:1 is used. The excess of hydrogen chloride in the initial mixture is required for the suppression of the side reaction giving dimethyl ether. The yield of target methyl chloride is more than 95 % based on methanol. The resulting hydrochloric acid (from 1362 to 1816 kg per 908 kg of methyl chloride) is directed to the purification and then is used as the commercial product.

Methyl chloride can be also produced in the liquid phase by interaction of hydrogen chloride and methanol over the catalyst or without it, or in the process of gas-phase methane chlorination, according to Reaction (20.2):

$$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl \tag{20.2}$$

20.2 The Manufacture of Chloroform

Chloroform can be produced by chlorination of either methane or methyl chloride or by reduction of carbon tetrachloride (Reactions (20.3, 20.4, and 20.5), respectively):

$$CH_4 + 3Cl_2 \rightarrow CHCl_3 + 3HCl \quad (20.3)$$

$$CH_3Cl + 2Cl_2 \rightarrow CHCl_3 + 2HCl \quad (20.4)$$

$$CCl_4 + H_2 \rightarrow CHCl_3 + HCl \quad (20.5)$$

Industrial manufacturing processes are based on the chlorination route. When methane or methyl chloride is used as starting materials, all chlorinated methanes are formed as by-products together with the desired chloroform. Their relative proportions depend on the process operating conditions. It is impossible to find reaction conditions where chloroform is formed as a single product. However various industrial processes for methane chlorination have been developed to produce desired particular chloromethane as a major product. It is advantageous to use chlorination of methyl chloride according to Reaction (20.4). In this case, by-product hydrogen chloride formed during subsequent chlorination steps can be recycled to react with methanol and produce methyl chloride for further chlorination.

A typical methane chlorination process for the production of chloroform together with chloromethanes as by-products is as follows. A preheated mixture of methane and chlorine is injected into the reactor. The temperature in the reactor needs to be maintained at about 500 °C. At this temperature, chlorine is totally consumed in reaction with methane. The yield of chloroform depends on CH_4:Cl_2 molar ratio and reaches 30 %; the molar excess of chlorine is about 1.25–1.50. The chlorination reactions are highly exothermic (105 kJ/mol Cl_2 is generated), so the dilution by inert gas is necessary for the reaction heat removal. Then the mixture of chloromethanes and hydrogen chloride is directed to the distillation unit. The amounts of methylene chloride and carbon tetrachloride by-products formed in chlorination process are 0.9 and 0.5 ton, respectively, per 1 ton of chloroform. Methylene chloride is used as the commercial product; carbon tetrachloride is returned to further processing. The heavy ends (10 kg per 908 kg of chloroform) are burned.

20.3 The Manufacture of Perchloroethylene

The industrial production of perchloroethylene is realized as the high-temperature chlorination of C_1–C_3 hydrocarbons and their chlorine-containing derivatives such as organochlorine plant wastes (Reaction 20.6):

$$C_2H_4Cl_2(\text{as an example}) + 3Cl_2 \rightarrow C_2Cl_4 + 4HCl \quad (20.6)$$

The wastes are evaporated before feeding into the reactor. Chlorination is carried out in the hollow lined reactor at approximately 600 °C. The heat of the reaction is removed by recirculation of the liquid products such as carbon tetrachloride and perchloroethylene. The process is realized at the excess of chlorine up to 10–15 %

in the exhaust gases. Further the reaction gases are directed to the quench column where the temperature decreases to 145 °C. The reaction products are separated in this column as well, whereas unreacted chlorine is returned to the reactor. The main by-product which is carbon tetrachloride is also returned to the reactor where it is dechlorinated to form perchloroethylene. This decision is necessary because the use of carbon tetrachloride is prohibited by the Montreal Protocol (1987). Hydrogen chloride after purifying can be used in industrial processes of hydrochlorination or oxychlorination.

The consumption of raw materials per 1 ton of perchloroethylene produced is as follows: 1.9 ton (1725 kg) of chlorine (evaporated) and 0.5–0.7 ton (454–636 kg) of organochlorine products (depending on the composition of the feedstock). The heavy ends (up to 200 kg per 1 ton (per 908 kg) of perchloroethylene) are burned. The sewage (11–12 ton per 1 ton of perchloroethylene) after purifying is directed to the sanitation system.

20.4 The Manufacture of Epichlorohydrin

The production of epichlorohydrin is a multistage process characterized by significant amount of waste production. Epichlorohydrin can be produced both from the petroleum-based (propylene) and the biomass-based (glycerol) raw materials.

20.4.1 Epichlorohydrin Production from Propylene

The process includes three main stages:

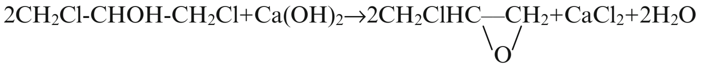
1. Synthesis of allyl chloride by high-temperature chlorination of propylene (Reaction 20.7):

$$CH_3 - CH = CH_2 + Cl_2 \rightarrow CH_2Cl - CH = CH_2 + HCl \tag{20.7}$$

2. Synthesis of glycerol dichlorohydrins by chlorohydrination of allyl chloride (Reaction 20.8):

$$CH_2Cl - CH = CH_2 + HOCl \begin{array}{l} \rightarrow CH_2Cl - CHOH - CH_2Cl \\ \rightarrow CH_2OH - CHCl - CH_2Cl \end{array} \tag{20.8}$$

3. Synthesis of epichlorohydrin by dehydrochlorination of glycerol dichlorohydrins (Reaction 20.9):



$$2CH_2Cl\text{-}CHOH\text{-}CH_2Cl + Ca(OH)_2 \rightarrow 2CH_2ClHC\underset{\diagdown O \diagup}{—}CH_2 + CaCl_2 + 2H_2O \tag{20.9}$$

Stage (1). Allyl chloride is synthesized directly by chlorination of propylene under conditions favoring to substitution of a hydrogen atom which is bonded with saturated carbon atom by chlorine atom. The double bond keeps unchanged, and hydrogen chloride is produced as by-product. The reaction is exothermic; the heat effect is 112 kJ/mol (112 kJ·mol^{-1}). The chlorination process is carried out at 500 °C. The maximum yield of allyl chloride is achieved using the adiabatic reactor designed to provide rapid and intimate mixing of a reaction mixture. Before feeding to the reactor, propylene is heated up to 340–370 °C; chlorine is directed to the reactor without heating. Propylene is fed to the reactor in a five-hold excess relative to chlorine to remove the reaction heat. The complete conversion of chlorine is achieved within 1 s.

A number of side reactions can proceed in this process, between them the addition of chlorine and hydrogen chloride to the double bond of hydrocarbons, substitutive chlorination of the products, condensation, dehydrochlorination, and others. The process effluent contains about 80 % of allyl chloride; the remaining 20 % of effluent comprise a number of various by-products. The amount of these by-products can be as high as up to 280 kg per 1 ton (per 908 kg) of allyl chloride.

The by-products are used as raw material in perchloroethylene production. The coproduced hydrogen chloride is directed to the production of commercial hydrochloric acid having concentration up to 30–31 wt.%.

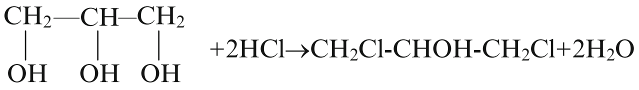
Stage (2). Glycerol dichlorohydrins are produced in industry in the form of 4–5 wt.% water solution. They are synthesized by the interaction between hypochlorous acid and allyl chloride. Two isomers of dichlorohydrins are formed at alpha/beta forms ratio equal to 1/2.3. The increase of dichlorohydrins concentration leads to the decrease of yield. The optimal process temperature is 20–25 °C. To increase the yield of dichlorohydrins, it is necessary to distribute allyl chloride quickly and evenly in the reaction medium. It can be realized by intensive mixing or by decreasing of reagent concentration using the solution recycle. In the optimal conditions, the yield of glycerol dichlorohydrins achieves 90–92 %. The wastes which are formed in the amount from 30 to 50 kg per 1 ton (per 908 kg) of dichlorohydrins are burned.

Stage (3). Epichlorohydrin is produced by dehydrochlorination of glycerol dichlorohydrins under the influence of lime milk or caustic soda. The temperature at the reaction zone is 95–100 °C. The yield of target epichlorohydrin achieves 92–93 %. Epichlorohydrin is removed from the reaction mixture by distillation. Ample amount of sewage is formed in the process. After purifying, they are sent to the sanitation system.

20.4.2 Epichlorohydrin Production from Glycerol

There are two stages in this process. The first stage comprises an interaction between glycerol and hydrochloric acid to produce glycerol dichlorohydrins

(Reaction 20.10). The second stage is saponification of dichlorohydrins similar to the stage (3) of the process described above.



$$\underset{\displaystyle OH}{CH_2}\text{—}\underset{\displaystyle OH}{CH}\text{–}\underset{\displaystyle OH}{CH_2} + 2HCl \rightarrow CH_2Cl\text{-}CHOH\text{-}CH_2Cl + 2H_2O \tag{20.10}$$

To produce the dichlorohydrins, excess hydrogen chloride and acetic acid which is used as the catalyst are used. The reaction may be run at 130 °C to distill out water by-product; the dichlorohydrin is obtained at 90 % yield. A major side reaction of polyglyceride formation may be reduced by decreasing the reaction temperature to 100 °C. The utilization of hydrochloric acid is not complete at this temperature. At 160 °C, the dichlorohydrin formed may be continuously removed from the reaction mixture. Another type of process by-products is acetates, which are produced mainly during the distillation.

Depending on market conditions, it is possible to realize the reverse process of synthetic glycerol production from epichlorohydrin.

20.5 The Manufacture of Chlorobenzene

The chlorobenzene is produced by continuous chlorination of benzene (Reaction 20.11) which is carried out in the column reactors. Ferric chloride is used as the catalyst in this process, which is realized at 80–85 °C, corresponding to the boiling point of the reaction mixture. The process is carried out until the content of benzene in the system fall down to the level of 40 wt.%; benzene to chlorine molar ratio is equal to 3.5:1. The reaction heat is used for the evaporation of benzene and chlorobenzene. The products of chlorination are directed to the stage of ferric chloride and hydrogen chloride removal from reaction solution by washing; then they are directed to the distillation stage to recover commodity chlorobenzene.

$$C_6H_6 \rightarrow C_6H_5Cl + HCl \tag{20.11}$$

The by-products of the process include polychlorinated benzenes, between them 1,4- and 1,2-dichlorobenzenes are desired products. The hydrochloric acid with the concentration up to 31 % is used as the commercial product.

20.6 The Manufacture of Monochloroacetic Acid

In industry monochloroacetic acid is produced by the continuous chlorination of acetic acid (Reaction 20.12):

$$CH_3COOH \rightarrow Cl_2 \rightarrow CH_2ClCOOH + HCl \tag{20.12}$$

Acetic anhydride is used as the catalyst. The chlorination process is carried out at 100–120 °C in the medium of the ultimate chlorination product containing near 75 % of monochloroacetic acid, as well as acetic and dichloroacetic acids. This composition of the reaction mixture is maintained by altering the molar ratio of acetic acid and chlorine in the feedstock used in the chlorination stage. This ratio may change in the range of 1:(0.65–0.7). The heat of the chlorination process is consumed on a partial evaporation of the products. These products are removed from the reactor together with effluent gases. The reaction mixture after condensation and purifying is sent to the stages of crystallization and separation of target product. Monochloroacetic acid is used commercially in two forms, as free crystalline acid or as dry powdered sodium salt. The by-product is 31 % hydrochloric acid which is a commodity chemical. It is possible to transform side dichloroacetic acid to the target product by hydrogenation.

20.7 The Manufacture of Chloroprene

On an industrial scale, chloroprene may be obtained by two main methods: (1) from acetylene through intermediate formation of monovinylacetylene or (2) from n-C_4-hydrocarbons or butadiene through intermediate formation of 3,4-dichlorobut-1-ene.

20.7.1 Chloroprene Production from Acetylene

This process consists of four stages: (1) synthesis of monovinylacetylene, (2) purification of monovinylacetylene, (3) synthesis of crude chloroprene, and (4) distillation of crude chloroprene.

Monovinylacetylene is produced by acetylene dimerization in a liquid phase (Reaction 20.13):

$$2CH{\equiv}CH \rightarrow CH_2 = CH - C{\equiv}CH \tag{20.13}$$

The process is carried out at the temperature of about 60 °C in a horizontal copper reactor which is equipped with a horizontal agitator. The reactor is half filled with catalyst solution, prepared from highly concentrated water solution of cuprous chloride, solid ammonium chloride, finely divided copper powder, and hydrochloric acid. The contact time is about 16 s. The acetylene conversion is about 16 % per pass. Unreacted acetylene is recycled to the reactor. The yield of monovinylacetylene is reached 85–90 % on the base of reacted acetylene.

The reaction gases are directed to the stage of washing from acid. Washed gases are transferred to the acetylene removal unit and monovinylacetylene distillation from by-products such as divinylacetylene and acetaldehyde. The purification of monovinylacetylene can be also realized in the absorption unit.

Then monovinylacetylene is directed on the hydrochlorination stage for the production of chloroprene (Reaction 20.14):

$$CH_2 = CH - C{\equiv}CH + HCl \rightarrow CH_2 = CH - CCl = CH_2 \qquad (20.14)$$

The process is carried out in the 30 % water solution of ferric and cupric chlorides in the temperature range 30–50 °C. Short contact time of about 5 s is applied. The conversion of acetylene is low, about 15–25 %; but the chloroprene yield from the reacted monovinylacetylene approaches 96 %. After purification of reaction mixture, the target product comprises no less than 99.95 % of chloroprene.

20.7.2 *Chloroprene Production from 1,3-Butadiene*

The process consists of four stages: (1) gas-phase chlorination of 1,3-butadiene to form dichlorobutenes (Reaction 20.15a, b), (2) isomerization of dichlorobutenes (Reaction 20.16), (3) dehydrochlorination of 3,4-dichlorobut-1-ene in the liquid phase (Reaction 20.17), and (4) distillation of crude chloroprene:

$$CH_2 = CH - CH = CH_2 + Cl_2 \rightarrow CH_2Cl - CH = CH - CH_2Cl \qquad (20.15a)$$

$$\rightarrow CH_2 = CH - CHCl - CH_2Cl \qquad (20.15b)$$

$$CH_2Cl - CH = CH - CH_2Cl \rightarrow CH_2 = CH - CHCl - CH_2Cl \qquad (20.16)$$

$$\begin{aligned} CH_2 = CH - CHCl - CH_2Cl + NaOH \rightarrow CH_2 = CH - CCl \\ = CH_2 + NaCl + H_2O \end{aligned} \qquad (20.17)$$

Chlorination of 1,3-butadiene is carried out in a gas phase at 290–330 °C. The initial reagents should be thoroughly drained, and oxygen content in a feedstock must be strictly limited. It is necessary to use the excess of butadiene to avoid side reactions. The conversion of 1,3-butadiene is usually 10–25 %; total yield of dichlorobutenes is 85–95 %; the ratio of 3,4-dichlorobut-1-ene : 1,4-dichlorobut-2-ene in the reaction products comes up to about 40:60. The excess of 1,3-butadiene after distillation is recycled to reactor.

Isomerization of 1,4-dichlorobut-2-ene to 3,4-dichlorobut-1-ene is realized in a tubular reactor in the liquid phase at 100 °C under vacuum. Various salts of copper, iron, and manganese can be used as the catalysts.

Dehydrochlorination of 3,4-dichlorobut-1-ene is realized in the column partitioned reactor using 5–15 % water solution of caustic soda at 80–110 °C and 0.25 MPa pressure. The yield of chloroprene achieves more than 95 %, and purity is also very high, no less than 98.5 %.

The organochlorine wastes can be directed to the perchloroethylene production by high-temperature chlorination process.

20.8 The Manufacture of Polyvinyl Chloride (PVC)

The problem of PVC production and use should be considered separately. High market demands for PVC and products of its further processing is due to their durability, resistance to environmental conditions, low flammability, and easy handling. PVC is a polymer material with the very attractive environmental and energy balance and optimal parameters for sustainable growth. The best price/quality ratio is characteristic for PVC in comparison with other polymers. Actually the energy capacity for PVC manufacturing is one-third less than that necessary for polyolefins production. No carbon dioxide emission proceeds during chlorine manufacture process itself, such emissions are characteristic only for the production of energy, which is necessary in this process. However due to lower gross energy demands in PVC production, total carbon dioxide emission value can be even lower than during polyolefin manufacturing. As for depletion of natural resources, no more than 4 % of world's petroleum production is consumed in PVC manufacturing processes that is less than for chlorine-free polymer production. Indeed, this process demands ample amount of sodium chloride; however, natural resources of this salt are virtually unlimited [2].

PVC is the cheapest of the large-scale polymers. This statement can be confirmed, for example, by the comparison of market prices for polyethylene and PVC. According to [3], average European price for polyethylene in 2015 is 1400 Euro per 908 kg; at the same time, the price for PVC is only 800–1000 Euro per 908 kg. This significant difference can be explained in terms of ethylene consumption during polymer production: PVC comprises only 43 % of ethylene and 57 % of chlorine. Although the chlorine manufacture is quite energy intensive – for membrane electrolysis (about this process, see [4]), the electricity expenditure is 1800–2000 kWt-h per 908 kg of chlorine [5] – the contribution of this component to the PVC production costs is relatively low. Even at the average price of electricity in Europe equal to 15 Euro cents for 1 kilowatt-hour [6], the cost for 908 kg of chlorine (allowed for the cost of caustic soda) will be no more than 200 Euro. Meanwhile the average price of ethylene in Europe is 1000 Euro per 908 kg [3]. Significant difference in the price of mineral and organic raw materials leads to lower prices on PVC compared with polyethylene.

The presence of chlorine in the PVC structure makes it easy to mix it with technological and functional additives and to get a wide range of products with diverse properties, shapes, and colors. PVC is a recyclable polymer. The options for the PVC mechanical recycling are described in detail, for example, in [7, 8]. As a result, more rapid growth of PVC consumption in comparison with the growth of world gross product is observed.

An intermediate product in the PVC manufacturing is vinyl chloride monomer~~,~~ which is obtained by the processing of chlorine and hydrocarbon feedstock such as ethylene or acetylene. The type of the raw material is an important aspect affecting the economical indexes of PVC manufacture in whole.

20.8.1 The Manufacture of Vinyl Chloride Monomer (VCM)

In 2015 vinyl chloride monomer (VCM) is produced all over the world using the following industrial technologies:

- Acetylene hydrochlorination
- So-called balanced method based on ethylene and chlorine

20.8.2 Production of Vinyl Chloride Monomer by Hydrochlorination of Acetylene

The process of acetylene hydrochlorination was the first commercially implemented technology of VCM production. The first plant started has been launched in Germany in 1929. The process proceeds in a gas phase at 130–180 °C using $HgCl_2$/active carbon catalyst (Reaction 20.18); it is characterized by high conversion (more than 99 %) of acetylene and hydrogen chloride in combination with high VCM selectivity (no less than 99 %):

$$C_2H_2 + HCl \rightarrow C_2H_3Cl \tag{20.18}$$

Undoubted advantage of the process is the simplicity of the technology and the relatively small amount of the liquid organochlorine wastes formed. These wastes are disposed by incineration method. Specific consumptions of feedstock components (kg per 908 kg VCM) are presented below: acetylene, 425 (theoretical, 416); hydrogen chloride, 610 (theoretical, 584); and catalyst, 1.0.

The durability of the catalyst typically ranges from 12 to 18 months. The catalyst activity gradually decreases due to the removal of mercuric chloride. The mercuric chloride usually is recovered from exhaust gases by absorption using hydrochloric acid, but some problems arise during its purification. The waste catalyst containing 2.5–3 % of mercury chloride is directed to the mercury plants for processing and production of metallic mercury.

The main disadvantages of the technology are listed below:

- The use of expensive acetylene as a hydrocarbon raw material
- Low unit productivity of the reactor (maximum 8–10 Mt per year) because of the restrictions on heat removal
- High toxicity of the mercury catalyst which falls under Minamata Convention on Mercury (2013)

The most important drawback of this process is the use of mercury-containing catalyst. Numerous attempts to elaborate mercury-free catalyst were made using Pd, Au, Rh, and other metals. Recently ternary Au1Co(III)3Cu(II)1 catalyst supported on spherical activated carbon demonstrated 99.7 % acetylene conversion, 99.9 % selectivity to vinyl chloride, and an estimated lifetime exceeding 6513 h [9] that is comparable with mercury catalyst lifetime. It seems that such catalyst has good potential for industrial application. The progress in catalysis science and many efforts devoted to the development of new catalysts for this process provide hope that once environmentally benign effective catalyst will be implemented, but at the moment mercury catalyst is the only choice for industry.

The poor ecological performances of the acetylene and further VCM production led to the fact that in developed countries almost all systems for the VCM manufacture from acetylene were decommissioned. The additional factor in favor of this decision was the sharp increase in demand for PVC which the technology based on acetylene could not meet.

Regrowth of interest to VCM production from acetylene dates back to the early 2000s. In the years from 2000 to 2014, more than 100(!) VCM plants using acetylene as feedstock were created in China. Currently the total annual capacity of these plants is more than 20 million tons (18.2 Mt). The output of VCM and PVC is near 15 million tons (13.6 Mt) per year; that is close to 40 % of world industrial production. The reason of that is the large reserve of coal which is the main source of hydrocarbon feedstock. However, the use of coal led to the formation of significant quantities of wastes forming serious environmental problem.

Lately the situation has changed and China is gradually reoriented to ethylene as the main hydrocarbon raw material which can also be produced from coal, for example, through methanol-to-olefins (MTO) process. This strategy should ultimately lead to the decrease of the number of VCM plants based on acetylene, and their replacement by the ethylene based plants.

20.8.3 VCM Production by Balanced Method

The so-called balanced processes in organochlorine synthesis are realized in the case when hydrogen chloride formed during chlorination and/or dehydrochlorination stages is used at the hydrochlorination and/or oxidative chlorination (oxychlorination) units to form target products. Realization of balanced schemes prevents environment pollution by the waste hydrochloric acid itself or the products of its neutralization. The balanced processes contribute to the implementation of the objectives of green chemistry.

The design of VCM plants by balanced scheme became possible due to industrial scale implementation of ethylene oxychlorination process to produce 1,2-dichloroethane (EDC). This process nearly completely consumes the hydrogen chloride that is formed on the stage of VCM direct production by EDC pyrolysis. The first industrial implementation of a balanced cycle was carried out by B. F. Goodrich Company in 1964.

Figure 20.4 shows a simplified flow diagram of the balanced process of VCM production. The process involves three main reaction stages [10, 11]:

- Direct chlorination of ethylene in a liquid phase with the production of EDC (Reaction 20.19):

$$C_2H_4 + Cl_2 \rightarrow C_2H_4Cl_2 \tag{20.19}$$

  The process takes place at temperatures of 50–120 °C, and the catalyst comprises ferric chloride as main component.
- Oxychlorination of ethylene (Reaction 20.20) is the gas-phase catalytic process; it is performed in the temperature range from 210 to 260 °C on cupric chloride/carrier catalyst, often promoted with chlorides of alkali or alkali-earth metals. The process can be carried out using fixed or fluidized catalyst bed.

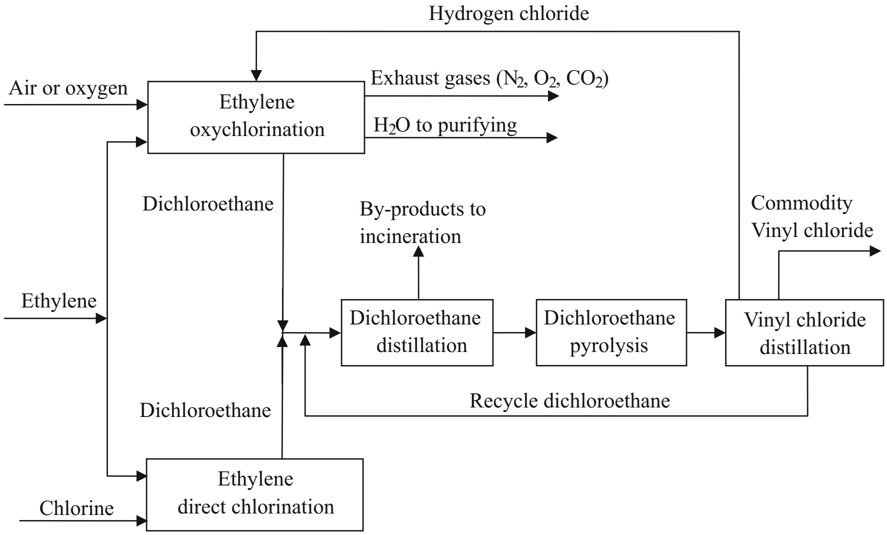


Fig. 20.4 The simplified flow diagram of VCM production by balanced process

$$C_2H_4 + 2HCl + 0.5O_2 \rightarrow C_2H_4Cl_2 + H_2O \tag{20.20}$$

- Target VCM and by-product hydrogen chloride are formed by pyrolysis of EDC (Reaction 20.20) that is the gas-phase process at 470–520 °C. HCl is recycled to the oxychlorination stage:

$$C_2H_4Cl_2 \rightarrow C_2H_3Cl + HCl \tag{20.21}$$

The processes of direct chlorination and oxychlorination of ethylene are characterized by the conversion of initial reagents exceeding 98 % and 96–99 % selectivity of EDC formation. Selectivity of VCM formation on the pyrolysis stage exceeds 98 %.

An essential advantage of the balanced method of VCM production is the ability to create large complex plants with the annual capacity of 300–500 thousand ton and more. This approach is economically viable. In the United States, Western Europe, South-East Asia, and Middle East, VCM is produced only by balanced method. Obviously upon construction and during the operation of such large complexes, the solution of environmental problems is the overriding task. Generally, the modern VCM plants are characterized by small contaminants emissions into the environment. This is a consequence of high degree of the main and auxiliary raw materials' beneficial use, skilled purifying, and disposal of wastes.

20.8.4 Waste Treatment of Vinyl Chloride Manufacture

Four types of wastes are formed during VCM production, between them (1) solid waste including the coke and polymers, (2) liquid organochlorine wastes, (3) sewage, and (4) exhaust gases. The common basic principles of waste treatment are applied on various organochlorine producing plants, and some considerations on the subject are presented below.

1. The amount of the solid waste products of VCM producing plants usually does not exceed 0.02–0.10 kg per 1 ton of product. However, net amount is valuable: particularly for the VCM plant with the annual capacity of 250 Mt, the amount of solid wastes can achieve 20–25 t per year. The solid wastes are usually directed for disposal on the landfills specially equipped for these purposes.
2. The liquid organochlorine waste products (~30 kg per 1 ton VCM) as a rule are sent to incineration or to a processing by chemical methods.

   Although the technology of VCM production by balanced scheme belongs to the category of low-waste (useful use of raw material is more than 97 %), the absolute amount of wastes is considerable. For the plant capacity of 300,000 tons per year, the total amount of wastes can achieve from 8 to 10 thousand ton per year; therefore, special unit for waste processing is required. Many different methods including oxidation, chlorination, pyrolysis, hydrogenation, and others

[10] have been proposed for processing of organochlorine wastes. To our opinion, incineration is the most attractive method of waste destruction, because it provides 99.99 % waste conversion. The average content of chemically linked chlorine in wastes is 65–70 %, and therefore no addition of combustible compounds to the system is needed.

The products of combustion are carbon dioxide and hydrochloric acid, the concentration of which may vary widely, from 3–4 to 31–33 % depending on the requirements. To prevent highly toxic dioxins formation, the process of incineration should be carried out at temperatures not lower than 1200 °C, at residence time of gases in the reactor in the range 2–3 s, and air excess should not be less than 8–10 %. According to regulations, the maximum content of dioxins in the exhaust gases should be no more than 10^{-10} g/m^3 [10]. The modern plants for waste incineration fully satisfy these requirements; however, strict everyday monitoring needs to be performed.

When hydrogen chloride concentration in the effluent gases of the incineration plants is low, it is neutralized and discharged to the sewerage; at high concentration (30–33 %), it is used as a commercial product or may be subjected to stripping with subsequent recycle of gaseous hydrogen chloride to the technological cycle.

The productivity of the incineration units is usually from 1.5 to 3 ton wastes per hour. More detailed information on technological and engineering solutions of this process is given in [10].

3. The technological sewage is formed at the stages of oxychlorination, direct chlorination of ethylene, and EDC drying, and it is directed to the purifying stage. The total amount of wastewater sent to the treatment plant is 600–700 kg per 1 ton of VCM. The wastewater contains EDC; inorganic salts such as NaCl, NaClO, Na_2CO_3, and NaCOOH; and copper, iron, and aluminum compounds.

   The treatment of wastewater is a multistage process. At first EDC is removed from the water by steam treatment. Then the sodium hypochlorite is destroyed by the treatment with sodium sulfite. After that the heavy metals such as copper, iron, and aluminum are precipitated by changing pH of the reaction medium. The back-osmotic membranes can be used in the process. The content of impurities in the purified water fully complies with the environmental standards.
4. Exhaust gases. The problem of the gas emissions is important when the ethylene oxychlorination process is operated using air as an oxidizing agent. The volume of the gas emission on this stage reaches 800 m^3 per 1 ton of VCM produced. Therefore, for the plant having production capacity of 250,000 tons per year, hourly volume of gas emissions will be 25,000 m^3. EDC which is entrapped with the gases is removed at the absorption unit; however, due to incomplete absorption, its emissions would still achieve several tens of kilograms per hour. Modern VCM plants use the concentrated oxygen as the oxidizing agent. The volume flow of the vent gases in such processes is no more 300–500 m^3 per hour. The exhaust gases are directed to incineration. This variant of the technological scheme significantly reduces the popping of the ethylene oxychlorination process emission products into the atmosphere (in this case vent gas volume is about

2–5 % of that for air-based operation) [11]. Small fugitive emissions are also possible at VCM plants, about 0.1–0.5 g VCM per 1 kg of the product depending on output [10]. Environmental conditions such as ambient temperature or the temperature of cooling water does not influence vinyl chloride emissions [12].

Thus the modern VCM plants designed according to balanced scheme are characterized by the relatively low level of the waste formation; herewith the qualified processing of these wastes with strict monitoring of effluent streams ensures the minimum negative impact on the environment.

Taking into account that VCM is one of the largest-scale products in the chemical industry, its maximum permissible concentrations in the environment and influence on human health are the subject of numerous studies. Detailed information on this issue is presented in [10].

20.8.5 PVC Production

In industry PVC is produced mainly by three methods of VCM polymerization, namely, suspension polymerization, which accounts for about 80 % of total production, emulsion polymerization (about 15 %), and micro suspension polymerization (about 5 %). Suspension PVC is widely used for manufacture of molding products; emulsion and microsuspension PVC are used for the production of plastisols, linoleum, and coverings.

The process of suspension polymerization is carried out in the droplets of the emulsion obtained by dispersion of VCM in water in the presence of high molar mass stabilizers of emulsion and initiator which is soluble in monomer. The typical composition for the suspension polymerization reaction medium comprises 33.3 wt.% of VCM, 66.6 wt.% of water, 0.015 wt.% of initiator (e.g., organic peroxide), and 0.005 wt.% of stabilizer (e.g., polyvinyl alcohol). The process is realized in batch-type mode at 45–65 °C in the big reactors having the volume from 50 to 200 m^3.

The process is exothermic (106 kJ/mol), so highly efficient heat removal is provided with special reactor design [13].

Emulsion and micro suspension VCM polymerization are carried out in continuous or batch-type reactors. In the polymerization process PVC particles from 0.02 to 2 μm in size are formed. This is achieved using dissolved ionic surfactants and water-soluble initiators (emulsion polymerization) or by preliminary dispersion of VCM – water emulsion using monomer soluble initiator (micro suspension polymerization). Emulsion polymerization is carried out in autoclaves at 40 to 55 °C and 7–8 atm pressure. The drawback of this method is the relatively high residual content of emulsifier, electrolytes, and other impurities in a product polymer, which can adversely influence performance characteristics.

The technological scheme of PVC production in addition to polymerization unit includes the units for PVC decontamination, separation, and drying. Residual VCM in the exhaust gases is destroyed by thermal or catalytic oxidation. The VCM content in the exhaust gases after purifying is no more than 3 ppm [14]. However, sewage and solid wastes are formed during PVC production as well.

20.8.6 Waste Treatment of PVC Manufacture

Below some considerations about the treatment of wastes formed during PVC production are presented:

1. Sewage. The largest volume of sewage, up to 5 m^3 per 908 kg PVC, is formed during the suspension polymerization. It is lower for emulsion PVC production, near 2–3 m^3 per 908 kg PVC. The wastewater is contaminated by suspended polymer particles (up to 0.8 g/l) and dissolved organic (up to 0.4 g/l) and inorganic (up to 0.1 g/l) substances. The average size of suspended particles falls in the interval from 50 to 100 μm. The large particles are easily sedimented; the fine particles form the dispersion which can be characterized by kinetic and aggregative stability. Coagulants are usually used for the precipitation of such fine particles. Ultrafiltration and ozone treatment can be used to remove surfactants. In particular, emulsifying agents are destroyed during ozone treatment. Their concentration is decreased from 400 to 14–15 $mg \cdot L^{-1}$. The treated water can be reused in a polymerization process [14].
2. The solid wastes are formed at the different process stages: polymerization (peel, grit), drying (peel, sifting), and wastewater purifying (slurries). The total amount of solid wastes in the PVC production is up to 20 mg per 908 kg of product. The solid wastes are ecologically safe and can be used in the manufacture of the construction materials and asphalt for pavements providing an increase of its operational characteristics such as strength and durability. A small part of solid wastes is transported to the landfill [8].

In the whole disposal technologies applied for the wastes of modern industrial VCM and PVC production complexes make possible minimization of their environmental impact [8].

20.9 The Use of PVC and Its Disposal

Great importance of ecological safety of PVC-based product use in everyday life from economic and social viewpoints is stipulated by large-scale PVC production. There is a fairly widespread concern in society connected with possible evolution of vinyl chloride monomer and highly toxic dioxins from PVC during its use and subsequent disposal. The anxiety is caused by well-known ability of these compounds to cause serious damage to human health and environment [2].

In reality, the anthropogenic impact of PVC and its products on the environment under normal conditions is rather weak. For example, there is no emission of vinyl chloride from PVC and PVC-containing consumer goods at a wide temperature range. During the thermal decomposition or aging of PVC, depolymerization does not occur [15]. All organic polymers are combustible when sufficient heating is applied. However, PVC is among the polymers that tend to have superior fire performance [16].

Thermal decomposition of PVC occurs mostly by chain stripping, whereby hydrogen chloride species are released, but that is often followed by cross-linking in some extent. This process enhances char formation. At high temperatures, cross-linking between polymer chains results in a fully carbonized residue. This is the excellent means of polymer flammability decrease [17].

PVC compositions contain plasticizers, fillers, stabilizers, and other additives. However, migration of these components into the environment is negligible. PVC does not degrade in the ground, which is essential in terms of its disposal. According to [15], the emission of vinyl chloride under these conditions also does not occur.

There is a risk of dioxins emission during uncontrolled combustion of PVC. Some results presented in literature describe this risk as overestimated. Thus in [15, 18], it was shown that the amount of such emissions into the environment does not exceed the value characteristic for the firewood burning (6–7 and 3–28 micrograms per 908 kg, respectively). The investigation of clean waste incineration with the heat recovery demonstrates that PVC has no negative effect on emissions to the air [7]. The amount of dioxins formed during incineration is primarily the function of the furnace design and operational characteristics of the process but not the presence or absence of PVC in the burned material. According to [17], the emission of dioxins associated with VCM-PVC production did not exceed 1 % of the total dioxins emissions in 1995. Nonetheless careful monitoring of dioxins' presence or absence in exhaust gases is necessary during PVC-containing waste incineration.

20.10 Organochlorine Products and Ozone Layer

The debates on the problem of ozone layer depletion by the anthropogenic activity have run for a long time. It is believed that one of the main reasons of ozone layer depletion is the use of chlorofluorocarbons (CFC) as refrigerants, in aerosol spray cans and fire extinguishers. The ozone layer allegedly destroyed by the actions of chlorine atoms which are formed as a result of the impact of solar radiation on freons. This phenomenon is associated with the formation of "ozone holes." To solve this problem, the Montreal Protocol on Substances that Deplete the Ozone Layer was signed in 1987, and the number of amendments has been signed in the subsequent years. Some data on the subject are presented, for example, in [19]. To prevent ozone layer destruction, chlorofluorocarbons have to be substituted with the hydrofluoroalkanes as the more inert compounds relative to ozone [1].

It cannot be excluded, however, that the appearance and disappearance of the ozone holes is caused by natural processes, and the human impact is very small. Nevertheless, in the last 25 years, a significant amount of industrial plants oriented on CFC and some other chlorinated hydrocarbon productions have been closed.

20.11 Conclusion

It is pertinent to remember the words of former IUPAC President Albert E. Fischli [20]: “Are organo-chlorines harmless or harmful? The question seems as irrelevant as asking if natural compounds are harmless and anthropogenic ones toxic.”

To conclude it has to be underlined that modern industry needs a good few of organochlorine products which at present have no alternative. They include epichlorohydrin used to produce the epoxy resins; chloroprene, which is the intermediate for manufacturing of special rubber; methyl chloride and chloroform, which are necessary for the production of organosilicon and organofluorine compounds; PVC, which is widely used in many industries; and some other products. The technologies of production and application of these products should be designed in such a way that they have a minimum influence on the environment and people’s health.

Some organochlorine compounds, for example, and certain solvents need to be replaced by chlorine-free analogs. In some cases, there is a great need for new processes which could make this possible to avoid the use of chlorinated organic compounds. For example, benzoic acid, which was earlier obtained in some countries by hydrolysis of trichloromethylbenzene, currently is produced by direct oxidation of toluene.

Finally, chlorine-containing xenobiotics which are the subject of the Stockholm Convention and other internationally accepted agreements must be completely removed from the sphere of circulation.

As regards to existing facilities, it is necessary to understand that the presence of chlorine in industrial processes requires serious industrial safety precautions.

The growth of the organochlorine industry in the twentieth century provided a big share for industrial progress. This industry is still playing a significant role in satisfying the global needs and will play it in the foreseen future.

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Part IX

Chlorine Derivatives Utilization and Recycle: *Recycle*

Chapter 21
Disposal of Chlorine-Containing Wastes

Ekaterina Lokteva, Elena Golubina, Vladimir Likholobov, and Valery Lunin

Abstract In this chapter the survey is presented about the scale of chlorine-containing organic wastes including commonly used consumables, persistent chlorinated pollutants, and polymers (PVC). The routine and novel methods of treatment such as landfill, disposal, and recycle have been compared. In accordance with the principles of green chemistry, the emphasis has been given to the methods excluding formation of more toxic products and producing useful feedstock from wastes, such as catalytic hydrodechlorination (HDC) and other reductive techniques. Characteristic features of the use of such methods for different types of wastes and reaction media have been analyzed. The basic principles of design of effective catalysts for chlorinated wastes HDC have been elucidated. Main strategies of chlorinated polymer processing involving recycle and transformation to form adsorbents or other demanded materials have been overviewed.

Keywords Chlorinated wastes • Catalyst • Hydrodechlorination • Chlorinated polymer • Disposal methods

21.1 Introduction

Ever since electrolysis has been developed as the method of alkalies production from sodium chloride, huge branch of chlorine industry grew to use by-product chlorine as a source of organic chlorinated substances. Due to promising properties, they found applications in many directions, such as solvents, electrotechnical fluids,

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herbicides, pesticides, intermediates in organic synthesis, monomers in polymer industry, etc. Inevitably huge amounts of chlorinated organic wastes were formed and disseminated in the environment. Unfortunately chlorinated organics are extraneous substances for human and other mammals. They can cause various harms to human health, from skin diseases (chloracne) to serious carcinogenic and teratogenic effects. Chlorinated organics form the main part of the so-called Dirty Dozen – the group of very dangerous persistent organic pollutants (POPs), banned for production, import, or export by developed countries. Between them till now hexachlorobenzene and polychlorinated biphenyls (PCBs) are still in use in some countries, and polychlorinated dioxins/furanes (PCDD/F) are unintentionally produced during most forms of combustion, including a burning of municipal and medical wastes, backyard burning of trash, and industrial processes including deep oxidation of chlorinated organic substances. The history of some chlorinated POPs widely accepted in industry in previous century can serve as examples of the commercial use of substances before their influence on human health and environment was properly investigated. Such mistakes should be avoided in the future according to the principles of "green" chemistry. Several international laws were adopted to prevent the dissemination of harmful and persistent chemicals in the environment, between them the Stockholm Convention on Persistent Organic Pollutants, which was adopted in 2001 and entered into force in 2004, and Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and Their Disposal (1989) that focuses on improving controls on the movement of wastes, including some POP wastes, preventing illegal traffic, and ensuring that waste is disposed as close as possible to its source.

In spite of international efforts, intended to prevent the influence of the chlorinated wastes on the environment, the production of hazardous chlorinated products continues in some countries. Furthermore, large amounts of chlorinated wastes were accumulated in the past and need to be disposed. Historical global production of PCBs was estimated at about 1.3 million tons, and almost 97 % of the global historical use of PCBs have occurred in the Northern Hemisphere [1]. In Russia the Stockholm Convention was adopted only in 2011 by the Federal Law 164 of Russian Federation "About Ratification of The Stockholm Convention on Persistent Organic Pollutants." According to this Law the operation of the equipment containing PCBs will be stopped until 2025, but not completely, because continuing the use of such equipment if some conditions ascertained by statute are met is covered by this Federal Law. The inventory of PCBs in Russia was estimated at 20–30 thousand tons.

Between commercially produced chlorinated organics, some are relatively harmless such as chlorinated polymers; the others are very toxic (hexachlorobenzene (HCB), polychlorinated dibenzo-p-dioxines and furanes etc.). Significant amounts of chlorinated organics end up in soils and water (chlorophenols, chloroalkanes, chloroalkenes, etc.). The development of the optimal disposal methods includes careful analysis of physical, chemical, and toxic properties, as well as production scales of chlorinated wastes, the amount of inventory, and the hazard level. Especially promising are those methods which completely exclude the production of PCDD/F. Such substances have an influence on the endocrine system and increase the hazard of cancer of various types [2, 3]. Additional benefits provide those disposal techniques, which make it possible to transform chlorinated wastes to useful products, e.g., extract hydrocarbon moiety of chlorinated molecules for reuse, produce carbonaceous adsorbents, or recycle polymers for further use.

Analysis of the literature demonstrates that disposal of some chlorinated substances dwindles in time due to phaseout of their production and use, whereas the disposal of others takes on new significance because of production scaling up. For example, the recycle and disposal of PVC-containing wastes becomes increasingly important.

About 500 bln tons of PVCs were produced worldwide since the 1960s [4]. In Russia since 2014, annual production is 900 kt PVCs, and this amount does not cover the needs of Russian industry [5]. Annual world demand in PVCs is more than 36 bln tons and is inferior only to polyethylene production [6, 7]. In spite of long service life of many PVC goods, such as window frames and pipes, large amount of PVC-containing articles is removed of service annually and this amount will grow significantly in coming years. Other PVC products, e.g., medicine equipment, need to be disposed immediately after use.

Another challenging task is the water pollution with the chlorinated wastes. Between them serious concern is caused by volatile chlorinated organics such as chlorinated light alkanes and alkenes [8]. Another type of widespread chlorinated environmental pollutants is highly toxic and bioaccumulative chlorinated phenols (CPs) which are extensively used in the production of pesticides, leather, and dyes. CPs have been classified as priority pollutants by the US Environmental Protection Agency [9]. Hydrodechlorination is the attractive way for CPs' disposal, because this reaction provides the production of phenols and, in combination with further hydrogenation, even more the desired product cyclohexanone, which serves as an intermediate in the manufacture of nylons (6 and 66).

Up to now huge array of literature data about dechlorination methods was accumulated [10–13]. The majority of widely accepted techniques appropriate for the disposal of organic chlorinated wastes could be divided on the following main groups:

- Oxidative methods including combustion [14, 15] and catalytic oxidation [16–19]
- Reductive methods using H_2 or other reducing agents, e.g., alcohols, acids, $LiAlH_4$, and $NaBH_4$ [12, 20–23], in the presence of homogeneous [12, 24] or heterogeneous catalysts [10, 21, 22]
- Transformation assisted by high-energy influence: photo- [25, 26], plasma- [27–29], and electrochemical [25, 26, 30] methods and sonification [31–34]
- Biological dechlorination [35, 36] alone or coupled with chemical or electrochemical [13] methods.

It is clear that disposal strategy will differ significantly depending on the nature of chlorinated wastes, the media of their accumulation (water, soil, landfill site, industrial waste dump yard, etc.), and the extent of purity (the disposal of mixed wastes, e.g., plastics, is much more challenging task than pure ones; further, PVCs after medical uses need to be disposed rather than recycled).

Each method has its own advantages and drawbacks. Thus biological methods are slow; the transformation by high-energy treatment is energy demanding and often unselective.

The first choice methods for the disposal of polychlorinated organics usually include oxidative ones because of the apparent simplicity and ready availability of the air as oxidant. However oxidation techniques have several disadvantages, both evident and disguised. Polychlorinated wastes are inflammable and need the addition of superior amounts of fuel to be combusted. The products of partial oxidation can include PCDD/Fs. In addition PCDD/Fs can be formed in exhaust pipelines [37] due to catalytic action of some metals (e.g., steel components) [38]. The monitoring of these hazardous products is very difficult and expensive. Besides PCDD/Fs will be concentrated in fly ash which in turn needs to be disposed. Some methods were developed for decontamination of fly ash: the treatment with aqueous mixture of calcium hydroxide and sulfur [39] and oxidation with H_2O_2 under supercritical water that is much more effective in oxidation of PCDDs than PCDFs [40] etc.

The two main positive features of reductive methods are the exclusion of PCDD/Fs formation and possibility of recycle of hydrocarbon moiety being a part of chlorinated organic molecules or formation of useful chlorinated products (chlorinated monomers, $CHCl_3$, etc.).

Therefore the most attractive ways of heavy chlorinated organic waste processing include reductive dehydrochlorination (DHC) (HCl elimination to produce unsaturated hydrocarbons) and hydrodechlorination (HDC) (substitution of Cl with H atom to produce saturated hydrocarbons). The first technique produces alkenes or alkynes that can be used as monomers for polymerization. The second method is more general because it could be applied to a wider group of chlorinated molecules, e.g., for hydrogen-free ones such as hexachlorobenzene (HCB). Catalytic reduction provides high yields of reusable hydrocarbons and good selectivity which can be tuned depending on desired products; furthermore, reaction conditions are usually not severe.

It was found that the decrease of the number of chlorine atoms in the molecules of polychlorinated benzenes causes a sharp decrease of toxicity [41]. Thus, even a partial hydrodechlorination of HCB leads to a significant detoxification of contaminated sites. This additional advantage makes hydrodechlorination even more attractive remediation technique.

HDC reactions are very sensitive to the nature of the catalyst and reaction conditions. They can be performed in a numerous arrangements of reaction systems. That is why ample amount of investigations was performed in this field.

However, there are several problems connected with the use of these methods, between them the most important are insufficient stability and high cost of catalytic systems for HDC (noble metals) as well as the need of hydrogen use (HDC) which is strongly demanded in different industrial applications and therefore shortened in supply.

In this chapter the analysis of some approaches for the development of effective catalysts of chlorinated wastes of HDC will be presented, as well as some results obtained in this field by the authors. Also some information will be given about possible methods of chlorinated polymer disposal and recycle.

21.2 Catalytic Reduction of Chlorinated Organic Molecules

21.2.1 The Active Component of the Catalyst

The most active in catalytic reduction of chlorinated organics are catalysts on the base of the transition metals of Group VIII of the periodic table: noble, Pd, Pt, Ru, or Rh [10, 42, 43], or non-precious, Ni, Co, and Fe [44–46].

Between noble metals the most effective one is Pd. Comparison of carbon-supported Pd, Ru, Rh, Pt, and Ni catalysts [47], having similar metal concentration and dispersion, in CCl_4 hydrodechlorination to form preferable product $CHCl_3$, demonstrated the decrease of activity in the raw Pd/C $>>$ Pt/C $>$ Rh/C $>$ Ni/C. However Pt/C showed stable work in HDC of dichloromethane (DCM) and chloroform (TCM), while Pd/C deactivated after 90 h of operation, particularly during HDC of DCM [48]. The deactivation of Pd/C catalyst can be attributed to a lower proportion of zero-valent species and a larger metal particle size, which hinder hydrogen activation and provoke both the formation of carbonaceous deposits as the last stage of coupling reactions and the formation of a new inactive PdC_x phase.

The oxidation state of the active metal is one of the key factors defining the efficiency of the catalysts. It was reported that an optimal ratio of Me(0) to Me(δ+) species is important for the best performance of the active component. Such observations were first described in the works of M. Gomez-Sainero with coauthors [47, 49] for HDC of CCl_4, where Pd^0 to Pd^{n+} (1:1) ratio provided high efficiency of the catalysts due to the balance of H_2 activation on Pd^0 and C–Cl bond activation on Pd^{n+}. Later this approach was successively used to prepare highly active Pd/TiO_2 [50] or Pd/ZrO_2 where strong influence of active metal with support was achieved due to precipitation of $Pd(OH)_2$ instead of Pd salts. Such strong influence allows the presence of Pd^{n+} species along with Pd^0 even after reduction of the catalyst [51]. Similar effect was found for Pd/ZrO_2 catalysts prepared using biotemplates to modify a texture [52]. PdO/ZrO_2 catalyst precursors were prepared by deposition–precipitation (PdO/ZrO_2 DP), using two biotemplates – pine sawdust (PdO/ZrO_2 SD) or cellulose (PdO/ZrO_2 CL). Temperature-programmed reduction (TPR) profiles were different for these samples. The peaks connected with the reduction of PdO strongly bonded with the surface of zirconia were more intensive and shifted to a higher temperature (more than 400 °C) in the TPR profiles of

PdO/ZrO_2 SD and PdO/ZrO_2 CL in comparison with PdO/ZrO_2 DP. The temperature of a peak maximum of the slightly bonded PdO reduction grows in the raw Pd/ZrO_2 DP < $PdO–ZrO_2$ SD < $PdO–ZrO_2$CL. Stronger interaction between PdO and zirconia in biomorphic systems is connected with simultaneous formation of both phases. That is why such catalysts comprise mixed oxides or solid solutions alongside with individual oxides. As a result the Pd^0 to Pd^{n+} ratio after reduction will be lower for biomorphic samples and higher for DP sample. This fact together with some other factors (the difference in porous structure and in Pd particle size distributions) provided the difference in catalytic properties. Thus, on Pd/ZrO_2 DP 100 % conversion of chlorobenzene to cyclohexane in H_2 atm was achieved in flow-type fixed-bed catalytic system at 150–300 °C, whereas on $PdO–ZrO_2$SD and $PdO–ZrO_2$CL, benzene and cyclohexane were formed in various amounts depending on the reaction temperature, again at 100 % CB conversion. All three samples were stable during 27 h operation at 100–250 °C. During these experiments 2.6 kg CB/1 g Pd was transformed to hydrocarbons.

The structural sensitivity of HDC reaction, i.e., the dependence of catalytic properties on the particle size of the active component, was found in many researches, both for carbon-supported Pd [53] and for alumina-supported Pt [54]. The use of various carbon supports provides catalysts having different metal dispersion: in [55] Pd/activated coal (AC) with Pd particle size of 5–10 nm and Pd/graphitized carbon fiber (GCF) (4–15 nm) were more active than Pd/graphite (2–5 nm). The metal–support interaction was stronger on the carbon supports with higher structure organization (GCF and graphite) that was manifested in better crystallinity of the metal particles.

The particle size of the active component influences the selectivity as well. Thus small Pd particles (less than 4 nm) transform CCl_4 to methane [54], whereas larger ones provide more desired $CHCl_3$ formation due to different adsorption properties.

Less attention was given in the literature to the effects of the extent of surface coverage with active metal nanoparticles, the distance between particles, space environment, and charge effects in supported metal catalysts, albeit there is a growing interest to the influence of these issues on catalytic properties that was analyzed, e.g., in the review [56]. The main reason of such ignorance is the difficulties of synthesis of appropriate model systems comprising the particles of equal nanosize. Such model systems can provide the tool to divide the influence of metal particle size and effects of particle arrangement on the surface of a support. But recently some methods such as laser electrodispersion (LED) and supporting from colloid dispersions of metal nanoparticles give the platform of such researches.

The main feature that differs LED technique [57] from the known laser ablation methods of nanostructure production is the formation of nanoparticles not from atomic fraction of a vaporized metal (bottom-up strategy) but as a result of dividing metal microdrops knocked out of a melted surface of a metal target during irradiation with a laser (top-down strategy). Microdrops are charging in the plasma of a laser torch that forces the partition until the certain drop size will be achieved. This size (1.5–5 nm) depends only on the work function of a metal and does not depend on the support nature or supporting time. For each metal the width of a particle size distribution is usually narrow, often not more than 1 nm. Using planar or granulated supports, layered or core–shell-supported systems comprising amorphous metal nanoparticles can be produced, in which metal nanoparticles are stable and do not coagulate even at high coverage, more than one monolayer. LED method is universal; a wide range of catalytic systems were produced using noble and base metals (Cu, Ni, Co, Au, Pd, Pt) on flat or granulated supports (Si, C, SiO_2, Al_2O_3) [58–60]. An additional advantage is its environmental friendliness because the use of metal salts, e.g., chlorides and nitrates with subsequent disposal to form chlorinated volatile substances or NOx, in LED method is totally excluded [60].

Such produced catalysts can include separate nanoparticles or ensembles of nanoparticles; the ratio between them depends on the preparation conditions. It was demonstrated that ensembles of nanoparticles in LED catalysts provide unusually high activity values in such structure-sensitive reactions as HDC, which is superior in comparison with small clusters, separated nanoparticles, and compact films that can be found in supported catalytic systems prepared by LED or other known supporting techniques. In most cases for LED catalysts, the extreme dependence of specific catalytic activity (SCA) values on the surface coverage was also found. Such dependence can be connected with the electrical conductivity of surface metal shell. It was found that the change in SCA values of Cu catalysts produced by LED in chlorinated organic transformations correlates with the increase of Cu films' conductivity.

Such approach provides a possibility to produce very efficient hydrodechlorination catalysts with extremely low loading of a metal, which is important for cost saving. The most active and stable are Pd-containing LED catalysts. Thus, LED catalysts containing low loadings of Pd supported on a surface-oxidized Si plate (model system) or on a commercially available granulated carbon support Sibunit [61] provide thousand times higher SCA values and higher CB conversions in gas-phase CB transformation to benzene in a flow-type system with fixed-bed catalyst [62] in comparison with Pd, supported on detonation nanodiamonds (DND) with much higher Pd loading (0.5 %) (Table 21.1). As it

Table 21.1 Results of comparative tests of palladium catalysts prepared by LED technique and impregnation method in gas-phase chlorobenzene HDC [62]

Catalyst (preparation method)	Pd/ mass %	t/°C	CB conversion/%	SCA/ (mol·(mol Pd′h)$^{-1}$
Pd/Sibunit (LED), granule size of (2.5–3.0 mm)	0.0004	200	86	610.000
Pd/SiO_2/Si (LED)	0.0002	200	29	410.000
	0.0004	200	92	650.000
	0.0008	150	100	140.000
Pd/nanodiamonds (impregnation)	0.5	200	100	570
Ni/Sibunit (LED)	0.0013	150	12	7.500
		250	30	18.900
Ni/nanodiamonds (impregnation)	5	150	19	60

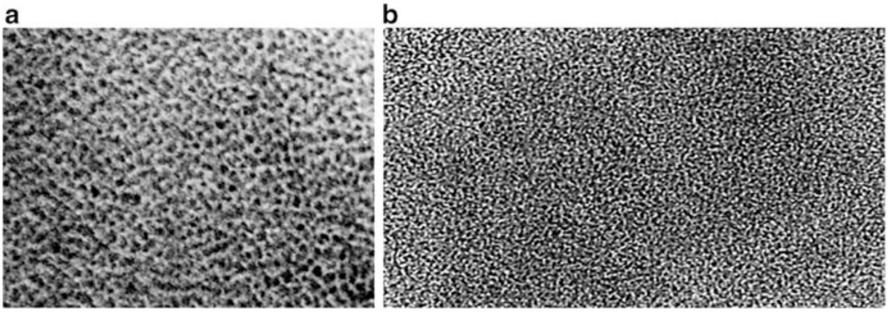

Fig. 21.1 TEM images of Pd (A) and Ni (B) nanoparticles deposited on thermally oxidized silicon by LED

will be demonstrated below, DND-supported catalysts are much more effective in HDC reactions in comparison with AC-supported analogs due to mesoporosity and some other features.

Another significant advantage of LED catalysts is a high stability to HCl poisoning. In the laboratory experiments, Pd/Sibunit was stable during time on stream for several days. The best properties were found at incomplete (<30 %) surface coverage of a support. Making use of this effect allows the amount of metal on the support to be reduced by three orders of magnitude.

Ni/Sibunit catalysts prepared by LED method are less active than Pd, but again in comparison with Ni supported by impregnation on DND, LED catalysts provide the improvement of SCA values in the orders of magnitude (see Table 21.1).

Supported Pd catalysts prepared by LED method were active also in HDC of polychlorinated benzenes, e.g., 1,4-dichlorobenzene (Fig. 21.1).

The approach, found using such model systems as LED catalysts, can be applied to improve the activity of less exotic catalysts [63]. Stabilization of metal particles of uniform size in a colloidal dispersion (CD) with subsequent support onto the catalytic carrier leads to the catalytic systems having also very narrow particle size distributions, but the size of a supported metal particle can be tuned in this method, in contrast with LED method. Magnetic properties of Ni metal makes possible separation of the catalyst from reaction mixture after use [64]. Besides this "wet" method has a better perspective for a commercial use.

In [63] Ni/Al_2O_3 catalysts with a very low nickel content (<0.1 %) prepared using LED or CD methods were compared in chlorobenzene HDC. When used without reduction, 0.03Ni(LED) provided higher conversion of CB in flow-type gas-phase HDC reaction (32 % CB conversion to benzene during steady-state operation) than 0.1Ni(CD) (only 10 % CB conversion). However, after reduction with H_2, the CB conversion on 0.1Ni(CD) increased up to 50 % and remained at this level during long-time (about 10 h) catalytic run, whereas 0.03Ni(LED) after short-time improvement of conversion to 80 % returned during steady-state operation to the former low conversion value.

Using X-ray photoelectron spectroscopy (XPS), the presence of Ni^0 species was proved in the catalysts with relatively high Ni content, prepared by both methods (0.03Ni(LED) and 0.1Ni(CD)). This observation is highly unusual, because at very low loadings on alumina Ni is very prone to oxidation to form oxides or spinels. The share of Ni^0 was lower for CD catalyst (5 %) and significantly higher in LED analog (17 %). Nearly the same Ni^0 content was found earlier in Ni/Sibunit LED catalyst, in which spinel formation is excluded. The increase in the stability of the 0.1Ni (CD) sample after reducing treatment was caused by the increase of Ni^0 content. Furthermore, the larger size of nickel particles in Ni(CD) (mainly 4–8 nm), found by TEM, as compared to that in Ni(LED) (1–2 nm), enables to avoid deactivation upon thermal treatment and under reaction conditions.

The results provided using model systems with very narrow and uniform distribution of the active metal particles give reliable instrument for the improvement of catalytic performance of common HDC catalysts by careful tuning of the particle size and the oxidation state of the active metal.

21.2.2 Modification of the Active Metal

The main challenges for the large-scale application of catalytic reduction for the disposal of chlorinated wastes are deactivation of active component under the influence of reaction conditions (HCl, reaction temperature, solvents) due to sintering and oxidation of metal nanoparticles, destruction of a support, and carbonaceous deposit formation; difficulties in the achievement of total dechlorination in the case of polychlorinated waste processing; and the achievement of high selectivity to a desired product, because often it is difficult to find further application for a products' mixture. Therefore activity, stability, and selectivity of the catalysts need to be controlled.

It is common in catalysis to provide a stabilization of catalytically active metal nanoparticles by surface oxidation with O_2 diluted with inert gas to form surface oxide shell which can be easily reduced in reaction conditions. Recently it was found that surface coverage of Ni or Fe nanoparticles with some layers of graphene-like carbon also can be used to save them from sintering [65]. Using TEM, XPS, Raman spectroscopy, TPR, and some other methods, it was found that Ni@C and Fe@C nanocomposites, prepared in the group of A. Yermakov by a variant of chemical vapor deposition method, consist of the core of Me^0 (Me = Ni or Fe) about 3–4 nm in diameter and onion-like carbon shell formed by some layers of the defected graphene. The nanoparticles of such nanocomposites are unusually stable to oxidation: after the shelf storage in air during 4 years, not more than 15 % of the metal was oxidized to form Ni or Fe oxides. Surprisingly it was found that such systems are very active and stable in HDC of chlorobenzene and other chlorinated benzenes [66, 67]. During three consecutive cycles of reaction temperature increase and decrease in the range from 150 to 350 °C, no decline of stable-state conversion at each reaction temperature in HDC of chlorobenzene to benzene in flow-type fixed-bed system was observed for Ni@C nanocomposite [66]. 50 % CB conversion was achieved approximately at 150 °C and 90 % conversion at about 200 °C. Carbon shell was intact during such prolonged catalytic tests, as was shown by HRTEM and XPS. Later in [65], it was demonstrated, both experimentally and using DFT calculations, that H_2 activation is possible on the surface of graphene thin layer activated by the presence of defects and transition metal in subsurface layers. An activation of chlorine-containing molecules on the surface of carbon supports was described earlier in many publications.

Generally the improvements of several properties of HDC catalysts can be achieved by the addition of modifiers to the active component [68–72] or to the support [73–76], base addition [77], pretreatment [78, 79], optimization of reaction conditions using membranes [80], interphase catalysis [81, 82], the use of optimized arrangement of the reactor systems, etc. Especially effective for the disposal of polychlorinated organics is HDC in multiphase conditions [83–86], elaborated in Ca'Foscari University of Venice, Italy, by P. Tundo and his group.

The modification of a noble metal with a second metal can lead to the changes in electronic state, providing the pair Me^0/Me^{n+} [50]. Often the dilution with base metal makes possible significant depreciation of the noble metal catalysts without deterioration of the catalytic properties. V. Simagina with coauthors [87] found no changes of catalytic efficiency after the replacement of 95 % Pd in Sibunit-supported catalyst with cheaper Ni.

Often synergistic effect was achieved on bimetallic HDC catalysts. Such effect was observed for PdFe/C catalysts in HDC of chlorobenzene [88], HCB and 2,4,8-trichlorodibenzofuran [72], PdNi/C catalysts in HDC of HCB [87], AuPd/Sibunit in HDC of dichlorodifluoromethane [89], and 2-chlorophenol [90]. The formation of bimetallic alloys, prevention of Pd carbide formation, optimization of the active site structure, and obviation of Pd oxidation were proposed to elucidate the synergistic effects in bimetallic catalysts.

In some cases the sequence of metal supporting influences on the catalytic activity. Au/Al_2O_3, Ni/Al_2O_3, and $Au\text{-}Ni/Al_2O_3$ catalysts prepared by LED technique described above were compared in HDC of chlorobenzene. Two different orders of Au and Ni supporting were used: to prepare $Au/Ni/Al_2O_3$ alumina was first covered with Ni and then Au; during $Ni/Au/Al_2O_3$ inverse sequence was used [60]. The loadings of metals were determined by atomic-adsorption spectroscopy. Au:Ni ratio was about 10:1 at 10^{-2} mas.% Au loading. Mean Ni particle size was about 1–2 nm, but Au particle size distribution was much boarder (1–5 nm), and also the presence of an atomic fraction of Au was proposed on the basis of TEM results; these facts distinguish Au from other LED-prepared metal systems. By the small-angle diffraction analysis of different areas during TEM investigation, no areas were found in bimetallic catalysts where only one metal was presented, confirming close interaction between Ni and Au. Note that strong interaction between nickel and alumina leads to the oxidation of Ni in alumina-supported Ni and NiAu catalysts, whereas Au is presented only in a metal state, as it was demonstrated by XPS. However, SCA of the catalysts in chlorobenzene HDC decreased in the raw $Ni/Al_2O_3 > Au/Ni/Al_2O_3 > Au/Al_2O_3 > Ni/Au/Al_2O_3$. Low activity of Au/$Al_2O_3$ is caused by the deviation of Au particle sizes in this sample from the optimal range characteristic for catalytic activity of Au nanoparticles. Specific activity of Au/Al_2O_3 has approximately mean value in comparison with two bimetallic samples. It seems that deposition of Au on Ni/Al_2O_3 leads to the partial enclosure of active Ni particles by gold; this process causes the decrease of SCA in comparison with Ni/Al_2O_3. On the other hand, it was found by TEM and confirmed by XPS that Ni is presented on the alumina surface mostly in oxidized state, probably as oxide or spinel. If gold particles fall on such modified surface, their properties can change significantly leading to the changes in catalytic activity.

PdFe bimetallic catalysts on different supports demonstrate good catalytic performance and provide high selectivity, e.g., in HDC of 2,4-dichlorophenol [91]. In our work the 2, 5, and 8 mas. % Pd/C catalysts and corresponding bimetallic systems of Pd–Fe/C (total metal content 10 mas. %, molar ratio Pd:Fe = 1:0.5, 1:7.7, and 1:2) were tested in multiphase HDC of 1,3,5-trichlorobenzene (TCB) and HCB. Conversion of the substrates after 100 min of the reaction in the presence of monometallic and bimetallic catalysts is shown in Fig. 21.2. Monometallic Fe/C catalyst demonstrated no catalytic activity for both substrates. Conversion of TCB and HCB was lower than 20 % on 8 % Pd/C. It is clearly seen from Fig. 21.2 that Fe addition leads to a significant increase of catalytic activity. Maximum activity was observed at the molar ratio of Pd:Fe = 1:0.5 (molar concentration of Pd is 67 %). In the presence of this catalyst, about 100 % conversion was achieved after 100 min of reaction both for TCB and HCB [72, 92]. Magnetic measurements performed for Pd–Fe/C show the presence of newly formed phase having Curie temperature,

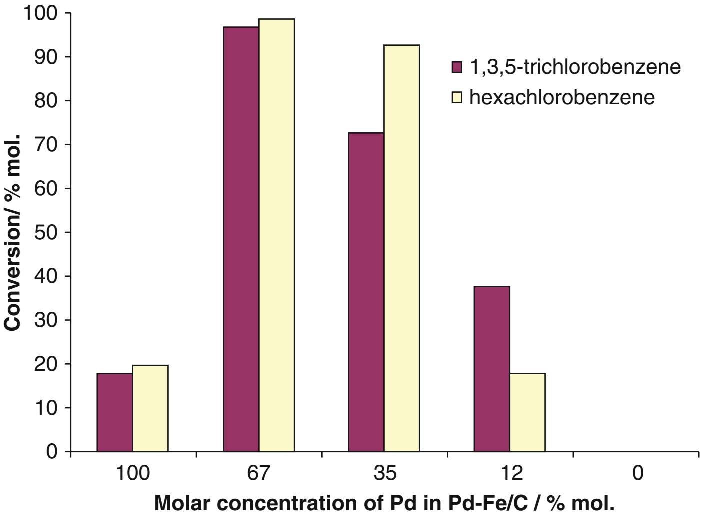

Fig. 21.2 Conversion of 1,3,5-trichlorobenzene and hexachlorobenzene after 100 min of the reaction in the presence of monometallic 8 % Pd/C and bimetallic catalysts with different Pd/Fe ratio (total metal content 10 mas.%) (multiphase conditions, batch system, 50 °C). The data are taken from [72]

corresponding to Pd–Fe alloy enriched with Pd. Asymmetry of Pd 3d line in XPS spectrum of Pd–Fe/C indicates the close interaction of Fe and Pd in this specimen. XPS data demonstrate the presence of Fe_2O_3 in the surface layer of bimetallic catalysts, even after reduction with H_2 at 500 °C. It was proposed that Fe_2O_3 protects the active sites from poisoning by chlorine. Formation of $FeCl_3$ on the surface of the bimetallic Pd–Fe/C particle is thermodynamically favored with respect to $PdCl_2$ [70]. Therefore Fe addition to Pd/C provides synergistic effect due to two reasons: (1) buildup of a new type of active sites as a consequence of PdFe alloy formation and (2) prevention of catalyst poisoning. However, the increase of Fe content above optimal concentration leads to surface coverage with $FeCl_3$ and shielding of the active sites.

In [88] the decrease of particle size was mentioned between the reasons of a positive influence of Fe addition on catalytic performance of Pd/C in chlorobenzene HDC. Indeed the addition of 2 % Fe to 2 % Pd/C leads to a formation of FePd bimetallic particles of a smaller size (15 nm) instead of large Pd clusters (55 nm) found in 2% Pd/C. Thus, bimetallic catalyst provided CB conversion more than 80 %, in contrast to 2% Pd/C (less than 5 %).

Surface coverage of Ni nanoparticles with Pd with subsequent immobilization of Ni@Pd on fibrous nano-silica with dandelion structure performed in [93] provided high accessibility of the Pd-active sites with simultaneous decrease of Pd loading and the possibility of easy magnetic separation of the catalysts from reaction medium for recycle due to the presence of Ni cores. Such original catalyst was very active in 4-chlorophenol HDC.

The choice of the metals for bimetallic catalysts provides the means for selectivity control. We have found that modification of Pd with Co promotes fast benzene formation at HCB hydrodechlorination with nearly no intermediate partially chlorinated benzene formation. Thus, the presence of PdCo/DND catalyst (0.1 g) provides nearly 100 % HCB (0.5 mmol) conversion to benzene during 0.5 h under multiphase conditions (10 % KOH in water, Aliquat 336, isooctane, H_2, 50°). Due to a reasonable price of DND and low Pd loading due to dilution with Co, such catalyst could be very promising for heavy chlorinated POP processing.

The addition of Cu to Pt/C [94, 95], Pd/C [96], Pd/MCM-41 [75], Ni/SiO_2 [97], or Ni/BEA zeolite [98] leads to the predominant formation of unsaturated hydrocarbons during HDC of chlorinated alkanes. The investigation by medium-energy ion scattering [99] was performed to elucidate the composition of chemically pure surface of $Cu_{50}Pd_{50}$ (110). It was demonstrated that it is enriched with Cu, but adsorption of chlorinated alkanes (1,1- or 1,2-dichloroethane, trichloroethane) increases surface Cu loading from 65 to 100 %, whereas hydrocarbon adsorption leads to a decrease of surface Cu content to 47 %. Probably this effect is valid for bimetallic catalysts containing Pd and other base metals and defines the common property of bimetallic catalysts to provide selectivity more characteristically for modifier rather than for Pd.

Pt/C modified with Co, which is known as Fischer–Tropsch reaction catalyst, performed transformation of CF_2Cl_2 mainly to C_2–C_3 hydrocarbons (50 % selectivity) [70]. Fe or Ag as modifiers for Pt/C provided methane formation, whereas the presence of Cu as the second component leads to a coupling reaction producing tetrafluoroethylene.

The addition of Fe to Pd/Sibunit at 4:1 ratio shifted a selectivity of CCl_4 transformation to a formation of C_2–C_4 hydrocarbons that are more valuable products than methane [100]. Partially oxidized state of metals proved by magnetic measurements and TPR is responsible for such changes.

Surely the literature data about modifying action of a second metal addition in catalytic reduction of chlorinated organic molecules go beyond short description provided in this chapter. However, even this concise review demonstrates main features that can cause the improvement of activity and stability, as well as change in selectivity of bimetallic catalysts in comparison with monometallic analogs: the formation of new bimetallic active sites; changes in charge state and size of metal particles, as well as of their interaction with support; prevention of the poisoning of more active metal due to chlorination of base metal component; etc.

21.2.3 The Nature of Catalytic Support

Between catalytic supports the most attractive for HDC catalysts are those on the base of carbon due to inertness to HCl by-product [101–103], but oxide supports such as SiO_2 [104, 105], Al_2O_3 [106], ZrO_2 [76], TiO_2 [77], zeolites [98] or oxide mesoporous materials [75], polymers [68], as well as mixed supports were also successfully used.

The progress in a synthesis of the new carbon materials provides effective and stable types of carbon supports for dechlorination catalysts, such as Sibunit [100, 107, 108], detonation nanodiamonds (DNDs) [109, 110], carbon nanotubes [111], reduced graphene oxide [112], etc.

It is believed that mesoporous supports (e.g., DNDs) allow better transport of large polychlorinated molecules to the active sites and therefore are advantageous in comparison with microporous ones [109]. Using TEM method, good distribution of Pd particles (average size 5 nm) on the DND support was found, whereas distribution of Pd particles on AC is broader (5–40 nm). Besides DNDs provide the formation of both reduced and oxidized Pd forms that were confirmed by FTIR investigation after CO adsorption on Pd/DND catalysts [109, 113–115]. All three reasons explain improved activity of Pd/DND in comparison with Pd/AC in polychlorinated benzene hydrodechlorination. Thus very effective 1,3,5-trichlorobenzene (TCB) hydrodechlorination was performed in multiphase system (including 1,3,5-TCB, 5% KOH in water, isooctane, Aliquat 336, and H_2 gas) to produce benzene as a final product. On 5% Pd/DND after 30 min at 50 °C, 100 % conversion of TCB was achieved. Comparative catalyst 5 % Pd/AC (Fluka) provided only 10 % conversion during this period at the same conditions [115].

5 % Pd/DND demonstrated better performance also in HCB transformations in comparison with commercially available 5 % Pd/AC (Fluka) catalyst with the same Pd loading. After 20 min of reaction, HCB conversion was 92 % on 5 % Pd/DND

and only 70 % on 5% Pd/AC(Fluka); benzene content in the corresponding reaction mixtures was 52 and 23 %, and SCA values were 10.2 and 2.4 h^{-1}, respectively.

Mesoporous systems can be produced by template method, using both organic and biotemplates. The waste of some branches of industry such as sawdust, nut shell, etc., can serve as a source for both microporous (activated carbon) and mesoporous supports. In the latter case special measures can be undertaken to save anisotropic mesoporous structure characteristic for biotemplates in the catalysts.

Recently it was found in our work that promising carbon-supported Pd catalysts can be obtained by pyrolysis of chemically activated sawdust at 400 °C [116]. Chemical activation was performed by impregnation of sawdust with metal salts, e.g., Pd nitrate. By XPS and Raman spectroscopy, it was demonstrated that pyrolysis in inert gas leads to the formation of carbon material similar to AC. SEM investigation shows that the material has a texture similar to that of sawdust template with characteristic porous system. The generation of reducing gases (CO, H_2) during biomass pyrolysis provides total Pd reduction proved by XPS. In addition, optimal for catalysis narrow Pd^0 particle size distribution with the maximum at about 4 nm was shown by TEM. Due to a presence of Pd^0 and optimal sizes of Pd nanoparticles, such catalytic system 2 % Pd/C demonstrates very good catalytic performance in HDC of both chlorobenzene in gas phase and polychlorinated organic molecules (e.g., hexachlorobenzene) in batch system using toluene as a solvent. It needs to be stressed that 88 % HCB transformation to benzene at 50 °C proceeds during 5 h with nearly no intermediate chlorinated benzene formation (Fig. 21.3).

The disadvantage of such produced catalysts is low BET-specific surface value (about 7 m^2/g), but special treatment provides the means to improve this value up to 250 m^2/g.

Nevertheless Pd on activated carbon (AC) remains a very attractive system due to low cost and a wide range of the commercially available grades, as well as

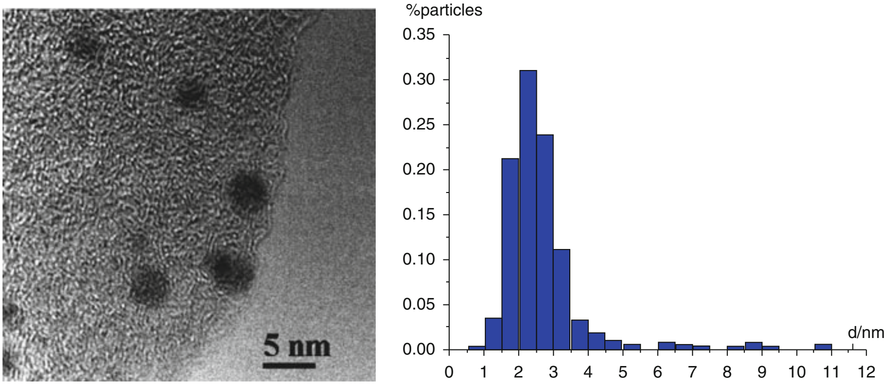

Fig. 21.3 TEM and Pd particle size distribution of 2 % Pd/C catalyst prepared by pyrolysis in Ar at 400 °C (4 h) of birch sawdust impregnated with palladium nitrate

appropriate catalytic efficiency. No deactivation of Pd/AC was found during processing at mild conditions (30 °C, 1 atm) of chlorinated organic herbicides 4-chloro-2-methylphenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, and 2,4-dichlorophenol, that is used as a precursor in the synthesis of the later [117].

The processing of polychlorinated benzenes, biphenyls, and technical liquids on the base of PCBs in batch-type system (7.6 atm, 100–180 °C) in the presence of NaOH water solution (up to 22 mas.%) was effectively performed on Pd/C (C = Sibunit) catalyst by the group of Russian researchers [118, 119].

An improvement of a substrate adsorption can be achieved by the right choice of a reaction medium. The addition of water to alcohol (isopropanol/water = 6:4) used as a solvent increased the rate of PCBs containing transformer oil processing [120] due to NaCl product removal from the surface of Pd/AC, used as a catalyst. Such cleaning of the catalytic surface leads to a high stability, so the catalyst can be reused in at least ten consecutive reaction runs.

21.2.4 *Characteristic Feature of Catalytic Reduction in Water Medium*

Reductive methods are very appropriate for the removal of chlorinated wastes from water and soil. This topic attracts significant interest, but it will be only shortly overviewed here. It could be mentioned that methods of groundwater and soil remediation from Cl-VOCs were reviewed recently in [8]. The authors mentioned reductive methods, hydrodechlorination (HDC) and reduction by zero-valent metals, predominantly Fe^0, as a separate group, where the other two include absorption and oxidative methods (combustion, ozonation, photocatalytic oxidation). Both HDC and reduction by zero-valent metals (Fe alone or with a second metal addition) are thermodynamically favorable and lead to relatively low-toxic products (hydrocarbons, HCl). Two drawbacks of this method are low rate of reduction processes using zero-valent Fe as reducing agent and its possible passivation.

During dechlorination by Fe^0 nanoparticles in water, no hydrogen addition is needed because H_2 which replaces Cl atoms in the chlorinated molecules is produced as a result of iron oxidation. The addition of a second metal, e.g., Pd, improves significantly the efficiency of chlorinated waste decomposition. The possible mechanism of a catalytic action is presented below [121].

$$
\begin{aligned}
&(\mathrm{I})\mathrm{Fe} + 2\mathrm{H}^+ \rightarrow \mathrm{Fe}^{2+} + \mathrm{H}_2\\
&\mathrm{Fe} + 2\mathrm{H}_2\mathrm{O} \rightarrow \mathrm{Fe}^{2+} + \mathrm{H}_2 + 2\mathrm{OH}^-\\
&\mathrm{Fe} + \mathrm{RC1} + \mathrm{H}^+ \rightarrow \mathrm{RH} + \mathrm{Fe}^{2+} + \mathrm{C1}^-\\
&(\mathrm{II})\mathrm{Pd} + \mathrm{H}_2 \rightarrow \mathrm{Pd}\cdot\mathrm{H}_2\\
&\mathrm{Pd} + \mathrm{RC1} \rightarrow \mathrm{Pd}\cdots\mathrm{C1}\cdots\mathrm{R}\\
&(\mathrm{III})\mathrm{Pd.H}_2 + \mathrm{Pd}\cdots\mathrm{C1}\cdots\mathrm{R} \rightarrow \mathrm{RH} + \mathrm{H}^+ + \mathrm{C1}^- + 2\mathrm{Pd}
\end{aligned}
$$

Pd is very prone to absorption of hydrogen produced in the process of Fe^0 corrosion in the water medium, to form PdH_2. In addition coordination of chlorinated molecule easily proceeds on free orbitals of Pd leading to Pd-Cl-R intermediate. The presence of an excess of hydrogen provides fast hydrodechlorination of such intermediate. As it is clear from the scheme above, low pH improves the catalytic action of Fe-based catalytic systems. The other metals that can provide H_2 activation such as less expensive Ni [122], Co, and Cu [123] can be used instead of Pd to modify Fe^0.

The coupling of different remediation approaches is a very attractive strategy. For instance, a complex method comprising adsorption and the use of nanosized particles of metals which are catalytically active in dehydrochlorination or hydrodechlorination of Cl-VOCs was effectively used for the removal of aromatic and aliphatic halogenated compounds from water and soil. Nanocomposites including metal nanoparticles (Pd, Fe) in the matrixes of silica microspheres, organo-bentonite, organo-smectite, alumina, or carbon keep a high efficiency in dechlorination of polychloroethylenes and polychlorophenoles after several adsorption–regeneration cycles [124].

Therefore reductive methods constitute a huge group of disposal technologies appropriate for the processing of chlorinated wastes in various media, and recent development of catalytic systems provides new perspectives for cost saving and improvement of the efficiency.

Taking into account the growing amount of chlorine-containing polymer wastes, some information about the strategies for its disposal and recycle will be presented in the next section.

21.3 Disposal of PVC and Other Chlorine-Containing Polymers

Disposal of chlorine-containing polymers is difficult because of nonuniform composition and structure of PVC, which is produced as a set of grades (emulsion, suspension PVCs, block-PVC, and microemulsion PVCs, as well as copolymers of various compositions). In addition, many processing aids are included into final articles, such as window frames, pipes, siding, cable trays, etc. The most common processing aids are thermal stabilizers (Ca, Ba, Zn, Pd, or Cd compounds), pigments (titania, iron oxides, etc.), plasticizing agents (mainly phthalates of different carbon chain length), as well as some other substances. The methods and aspects of PVCs and mixed PVCs containing waste recycle are reviewed in [125].

Landfill of PVC wastes demands large areas. Combustion of PVCs is not easy to perform due to high chlorine content; the temperature about 1400 °C is needed that increases the cost of such disposal [125]. In optimal condition the PCDD/F formation is low, but in the presence of catalytically active metals, primary Cu, as at combustion of the braid of Cu-containing cables, the exhaust of dioxins grows significantly [126].

Clearly the first choice for PVC disposal is a recycle to produce secondary plastics or energy. However, till now only a small fraction of all PVC wastes are recycled. In Europe special programs were launched to stimulate recycling (e.g., voluntary program "Vinyl 2010") [127], but only a few percent of such wastes are involved into a recycle. Important challenges at PVC recycle are (1) improvement of the compatibility of PVC wastes with other polymers and fresh PVCs, (2) development of separation techniques, (3) improvement of the properties of recycled PVCs, and (4) development of repeated recycle methods.

Recycle of PVCs could be performed chemically or mechanically. First strategy includes thermal or chemical destruction of polymer (thermal cracking), often in the presence of catalysts, to produce monomers or other non-polymer substances, processed downstream to form the same or other polymers [127, 128]. Chemical recycle makes it possible to process polymer mixtures, but this method includes two energy demanding stages: thermal/catalytic destruction and new polymer formation.

Many variants of chemical recycle are proposed in the literature. Thus, pyrolysis at high temperatures (1150–1250 K) in the presence of catalytically active materials such as alumina can provide syngas [129] that can be used as a raw material to produce hydrocarbons, alcohols, and other important commodities, e.g., using Fischer–Tropsch synthesis. Thermal cracking of chlorine-containing polymers leads to a polyene structure, which could be transformed, depending on the reaction conditions, to a wide range of products [129]. Carbonaceous materials and hydrocarbons, as well as HCl, are main products of the pyrolysis in inert atmosphere [130].

Interesting method of chemical recycle was proposed by Kryazhev et al. in [131]. Dehydrochlorination of the carbon-chain halogenated polymers (e.g., polyvinyl chloride–polyvinylidene chloride system) under the action of a strong base followed by thermal treatments (carbonation in an inert atmosphere and activation in an oxidative medium) provides strongly disordered turbostratic carbonaceous materials with a developed porous structure including micro-, meso-, and macropores [132]. The synthesis of porous carbon was performed in three stages, including the low-temperature treatment of the polymeric precursor with alkali metal (Li or K) hydroxides or alkoxides in polar organic solvents, thermal treatment in an inert atmosphere at temperatures up to 400–600 °C (carbonation), and activation at temperatures up to 950 °C in the presence of water steam or CO_2. First dehydrochlorination stage leads to a chlorinated polyene structure, stabilized by the presence of alkali. This material has developed porous structure including micro-, meso-, and macropores [133] and can be used as very efficient recyclable adsorbent of benzene or phenol both from air and from water. Carbonaceous material produced on the second pyrolysis stage also has high adsorption ability. It is important that relatively low pyrolysis temperature (less than 300 °C) can be used on the second stage making the process more economically feasible. Modification of carbonaceous material by the addition of carbon structures of various types (nanotubes, nanoglobules, nanofibers), or nanoparticles of metals during synthesis, could provide a wide range of materials having interesting properties, which can be found useful in supercapacitors, as adsorbents, catalytic materials, etc.

Transformation of waste PVC pipes to carbonaceous material in two-stage process after extraction of processing aids with solvent was described in [134]. The tar, produced on the first stage, was then stabilized and carbonized to produce carbon fibers. Further activation of carbon fibers in CO_2 atm provides material with high specific surface and low oxygen concentration that can find commercial use.

Hydrogen chloride evolving at PVC disposal after cleaning can be used for downstream processes. Another way to prevent HCl exhaust to the atmosphere is to absorb it by bases. Instead of strong bases, various metal oxides can be used to improve the efficiency of PVCs' dehydrochlorination [135]. Similar action can be achieved by polyethylene glycol (PEG) addition [136]. In contrast to metal oxides, the use of PEG does not lead to metal salt formation; therefore, possible recycle of PEG makes this alternative more attractive [137].

A trapping of HCl by base oxides is widely used during PVCs' chemical recycle. Due to low price the use of CaO [138] and CaO-containing wastes, e.g., shells of scallops [139], for HCl bonding becomes a very popular approach.

Layered double metal hydroxides can be effectively used to absorb HCl. Thus, MgZnAl systems such as $Mg_3ZnAl_2(OH)_{12}(C_{17}H_{35}COO)_{24} \cdot H_2O$ absorb 13 M HCl [140]. $CaCO_3$ can be transformed to commercial $CaCl_2$ in two-stage NKT–Watech pyrolysis [141]; simultaneously organic part of PVCs is transformed to solid coke. Nitrogen-containing compounds and the waste materials, containing such compounds, also are appropriate for HCl bonding to decrease corrosion effect. Pyrolysis of PVC together with cattle manure (1:5) provides good HCl removal, especially at low heating rate and high pyrolysis temperature (450°C) [142].

The coupling of PVCs' waste processing with a disposal of other wastes attracts significant interest in recent years. For instance, the milling of PVCs together with waste metal alloys leads to metal chlorides, which are soluble in water, and can be easily separated from hydrocarbon products of PVC dechlorination [143]. Similar approach was used in [144] where PVC milling together with $LiCoO_2$ (e.g., from lithium–ion secondary batteries) in planetary mill with subsequent dispersion of the product in water makes it possible to separate lithium (100 %) and cobalt (90 %) as chlorides. Simultaneously up to 90 % of Cl is deleted from PVC wastes.

PVC interaction with nucleophilic agents such as sulfonyl group [145] or I-, OH-, and CNS- in ethylene glycol [146] to produce substituted PVCs and HCl is the other way of chemical PVC processing.

Original approach to PVC disposal includes the use of plastic during steel production instead of coke to reduce iron ore [147]. Coke economy and shortening of greenhouse gas production constitute the advantages of this method.

Especially challenging, as it was mentioned above, is the processing of PVCs containing mixtures. In recent review [148] about industrial methods of municipal solid waste pyrolysis, it is recommended to separate PVC before the processing of other wastes to prevent corrosion of the equipment and toxic product formation.

A limited volume of the chapter prevents us from giving additional information concerning mixed chlorine-containing polymer waste processing, but the details can be found in [125].

The data found in the literature demonstrate that between ample amounts of recycle techniques proposed for chlorinated polymers, there is the lack of industrially appropriate methods. Taking into account the fast increase of the chlorinated polymer production, the development of new industrial disposal and recycle processes is the urgent need of mankind.

21.4 Conclusion

Chlorine-containing organic products still are produced in ample amounts worldwide and end up in the environment; therefore, more attention has to be given to a disposal of such waste types including those which are now treated as relatively safe (e.g., chlorinated polymers). Various methods have been developed, so appropriate technique can be chosen for nearly all existing types of individual waste, its concentration, and wasted medium. The problems are connected with industrial application of some methods, especially for the recycle and disposal of the mixed wastes.

Economical considerations in many cases impede the right handling with chlorinated wastes. Very promising approach includes coupled processing of chlorinated wastes together with the other waste types. As for other issues connected with environment protection, governmental efforts and public information are needed to improve the situation.

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Part X
Metrics

Chapter 22
Application of Green Metrics Analysis to the Synthesis of Dicyclohexylcarbodiimide (DCC) – Comparison of Chlorine Versus Non-chlorine-Based Routes

John Andraos

Abstract Green metrics at four levels of analysis are determined for various synthesis plans for dicyclohexylcarbodiimide (DCC) covering material efficiency, environmental impact, safety-hazard impact, and energy input demands to identify the greenest plan available to make this important dehydrating reagent. Chlorine-based routes using phosgene chemistry are juxtaposed against non-chlorine-based routes.

Keywords Atom Economy (AE) • Benign Index (BI) • Dicyclohexylcarbodiimide (DCC) • Dicyclohexylurea (DCU) • E-factor • Energy input • Environmental impact • Green metrics • Process Mass Intensity (PMI) • Reaction Mass Efficiency (RME) • Reaction Yield (RY) • Safety-Hazard Index (SHI) • Synthesis network

22.1 Introduction

Dicyclohexylcarbodiimide (DCC), first made in 1938 [1] from dicyclohexylthiourea and silver oxide in carbon disulfide solvent, is a well-known dehydrating agent used in peptide amide bond syntheses since its initial application by Sheehan and Hess in 1955 for the preparation of carbobenzoxyglycyl-L-phenylalanylglycine ethyl ester, phthaloyl-L-phenylalanylglycine ethyl ester, phthaloyl-L-alanyl-L-proline benzyl ester, carbobenzoxy-L-seryl glycine ethyl ester, and phthaloyl-L-phenylalanyl-L-leucine ethyl ester [2]. Its use in automated solid phase syntheses of polypeptides and proteins under mild conditions has been well documented [3–13]. The byproduct of its reaction with carboxylic acid and amino substrates is dicyclohexylurea (DCU), which is operationally easily removed by filtration. In this chapter, we investigate the syntheses of DCC by chlorine-based

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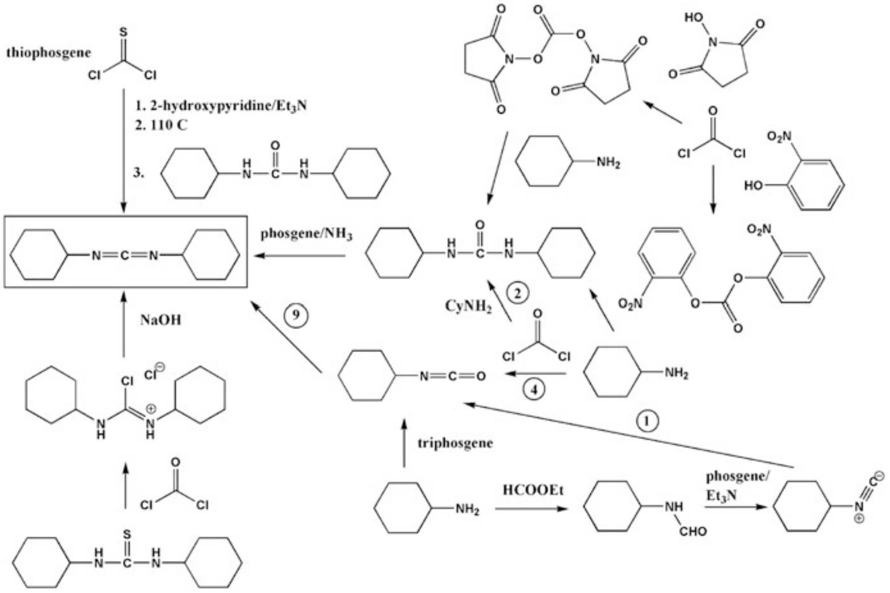
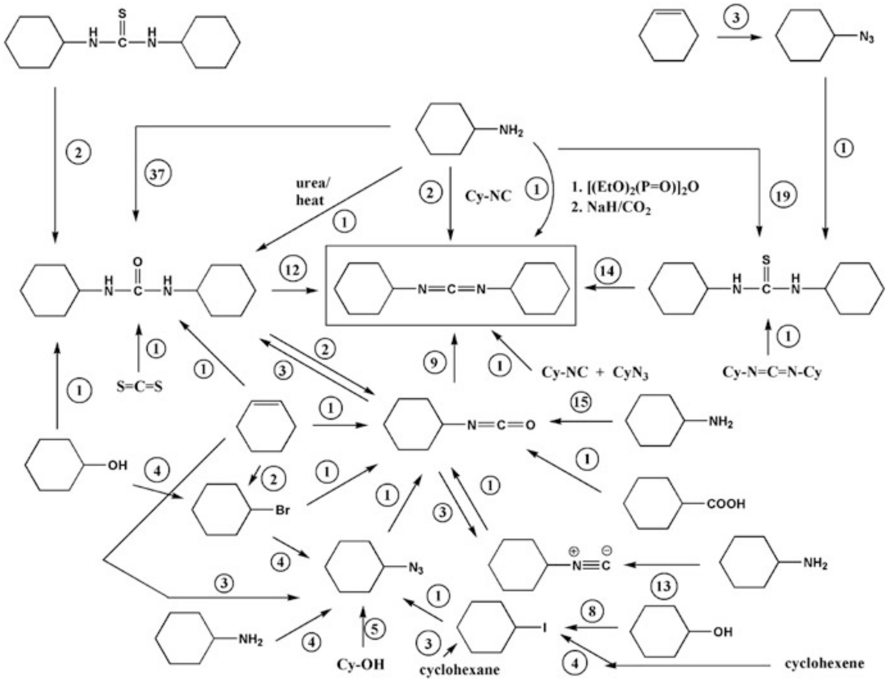
and non-chlorine-based methods with a view to ascertain their merits of greenness with respect to material efficiency, environmental and safety-impacts, and input energy demands. Specifically, we analyze synthesis performance by determining green metrics in each of these categories using algorithms recently developed by Andraos [14–16], which were first applied to the determination of material efficiencies of synthesis plans for oseltamivir phosphate, a neuraminidase inhibitor used to treat the H5N1 influenza virus. The application of this algorithm was then expanded to create an extensive database of green metrics analyses of synthesis plans for various natural products, pharmaceuticals, agrichemicals, fragrances, sweeteners, dyestuffs, industrial commodity chemicals, and miscellaneous compounds of theoretical interest [17, 18]. The chlorine-based methods described herein involve phosgene chemistry which has been previously investigated by materials efficiency green metrics analysis for syntheses of industrially important commodity chemicals such as carbonates, carbamates, ureas, and isocyanates [19]. The structure of the chapter is as follows. Synthesis networks for chlorine-based and non-chlorine-based plans to DCC are first introduced and analyzed to determine the total number of possible routes and strategies employed to date based on an extensive literature search. Next, the best performing subset routes in each of the two networks are determined based on material efficiency performance using the metrics: reaction yield (RY), atom economy (AE) [20], reaction mass efficiency (RME) [21–23], E-factor (E) [24], and process mass intensity (PMI) [25, 26]. These routes are then further subjected to analysis according to environmental and safety-hazard impact for both input and waste materials using benign index (BI) [27] and safety-hazard index (SHI) [28]. Finally, the last assessment involves the determination of total input energy required based on enthalpic contributions at the reaction conditions of temperature and pressure employed for each reaction in each synthesis plan. All metrics calculations are determined with respect to a common basis scale of 1 t of DCC manufactured. For each level of analysis, the pros and cons of the best performing methods are discussed. The chapter is to be interpreted as a practical hands-on approach to carry out green metrics assessments that can be applied to any synthesis network representing a set of plans to a given target molecule.

22.2 Synthesis Network

The Reaxys database [29] was used to conduct a thorough literature search for all documented methods to make DCC from journal articles and patents covering the period 1907 up to 2013. Schemes 22.1 and 22.2 show the resulting synthesis networks for chlorine-based and non-chlorine based strategies, respectively. The circled numbers above the reaction arrows indicate the number of different reactions connecting intermediates. From these networks, or graphs, we may determine the total number of routes and strategies to DCC from various starting materials by



Scheme 22.1 Synthesis network for phosgene-based routes to DCC. *Circled* numbers represent the number of documented routes between pairs of intermediates



Scheme 22.2 Synthesis network for non-phosgene-based routes to DCC. *Circled* numbers represent the number of documented routes between pairs of intermediates

Table 22.1 Summary of enumeration data for the chlorine-based routes to DCC

Starting material	Number of routes	Number of strategies
Cyclohexylamine	56	2
Phosgene	1	1
Thiophosgene	3	1
TOTAL	60	4

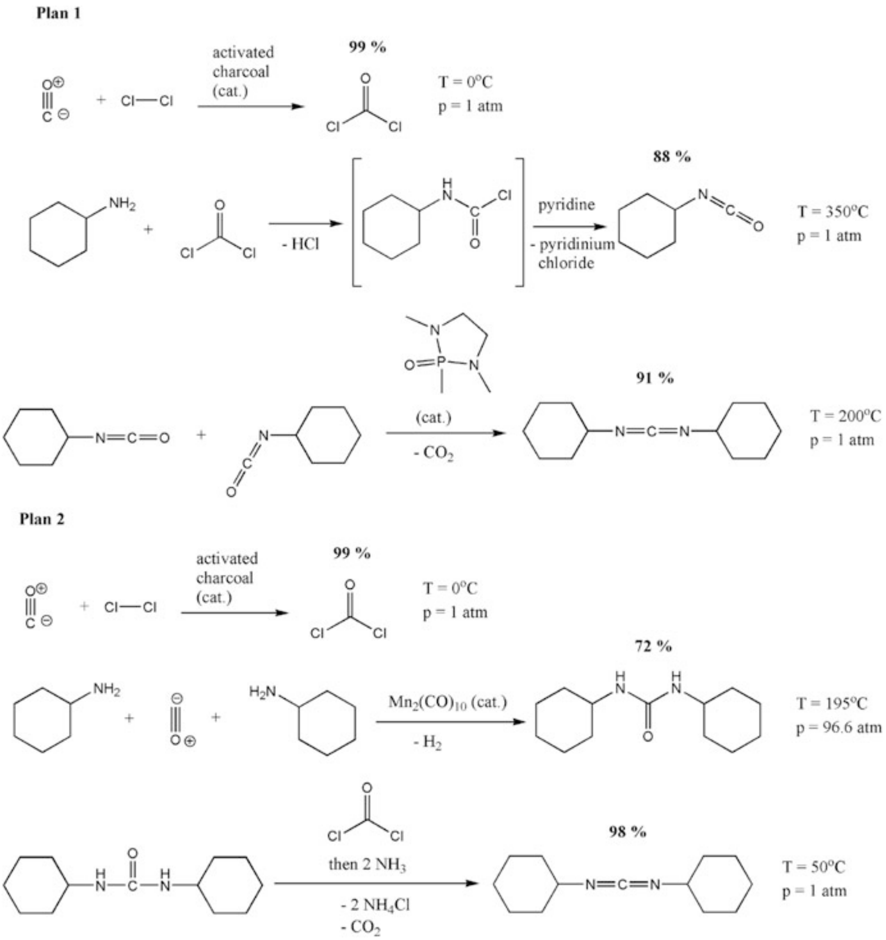
Table 22.2 Summary of enumeration data for the non-chlorine-based routes to DCC

Starting material	Number of routes	Number of strategies
Cyclohexylamine	3457	15
Cyclohexanol	2617	16
Cyclohexene	1410	18
Cyclohexane	249	4
Cyclohexylcarboxylic acid	45	2
Carbon disulfide	30	2
Cyclohexylazide + cyclohexylisocyanide	52	1
TOTAL	7860	57

drawing out synthesis mapping trees that explicitly allow enumeration of the routes. The results are summarized in Tables 22.1 and 22.2.

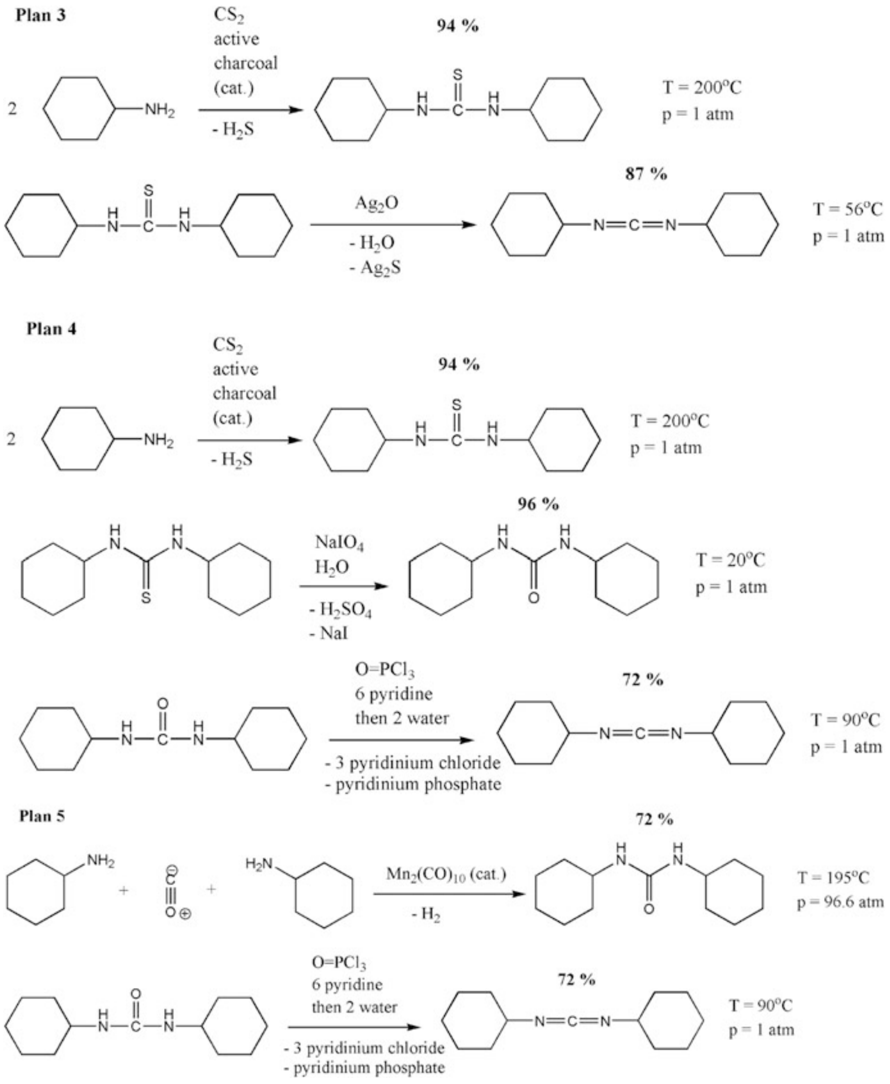
Though there are less than 8000 routes in total to consider, there are only 4 documented strategies to make DCC by chlorine-based methods versus 57 by non-chlorine-based methods. In order to identify the most promising candidate green routes from both networks, we can make the problem more tractable by first determining the most material efficient route for a given transformation based on least PMI scores. Specifically, for each arrow shown in a network, we determine the lowest PMI transformation. PMI refers to the mass ratio of total input materials used in a plan from all sources (reagents, reaction solvents, catalysts, ligands, additives, and other auxiliary materials used in work-up and purification procedures) to DCC product generated. Essentially, we are using material efficiency as the primary hierarchical sifting criterion for the entire suite of metrics used. This simple algorithm reduces the number of routes to match the number of strategies so that each reaction arrow appearing in a synthesis network is matched to a specific reaction with the lowest PMI. For brevity, we will focus on the top two chlorine-based routes and the top five non-chlorine based routes to DCC. The corresponding set of plans in each category is shown in Schemes 22.3 and 22.4. All plans begin with cyclohexylamine as a common starting material.

Plan 1 [30–32] is a three-step route involving the synthesis of phosgene from carbon monoxide and chlorine gas, followed by amidation with cyclohexylamine and subsequent elimination to yield cyclohexylisocyanate, and followed by catalytic decarboxylative dimerization to DCC. Plan 2 [30, 33–35] is a three-step convergent plan that begins with the same preparation of phosgene as for plan 1. Then, dicyclohexylurea is prepared in a parallel step from cyclohexylamine and



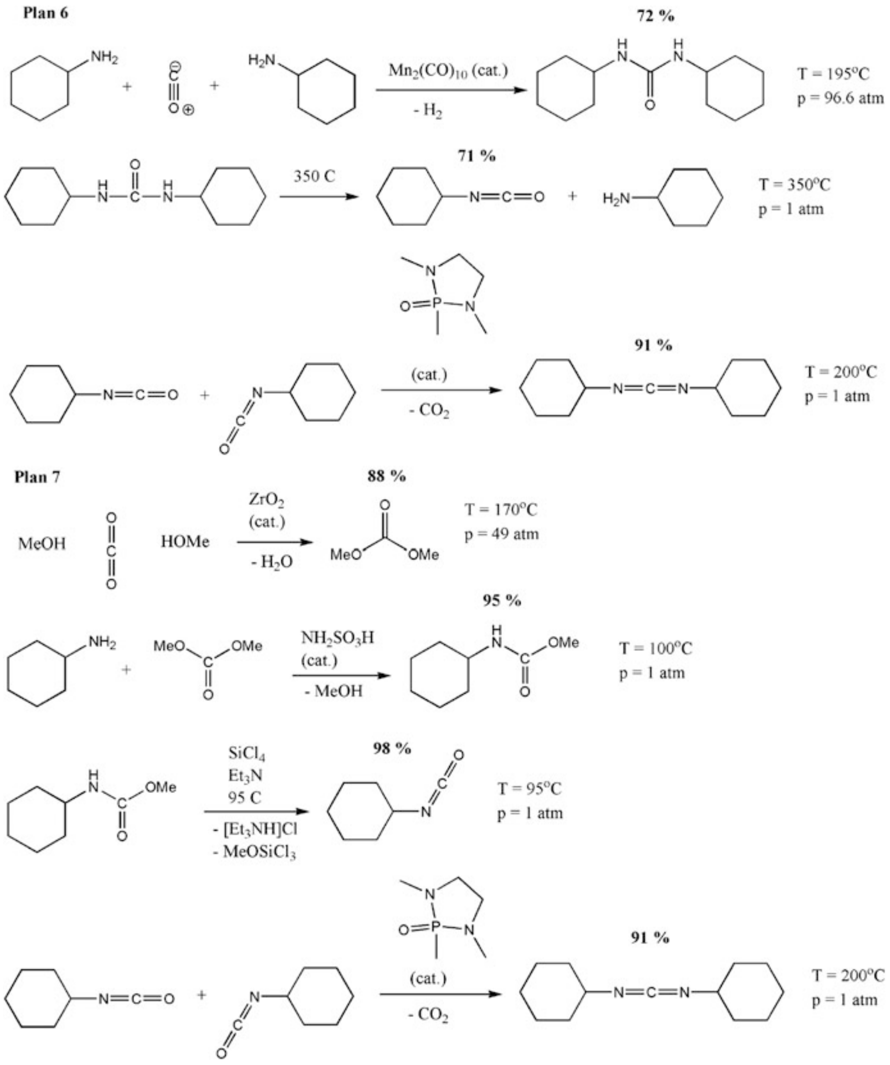
Scheme 22.3 Synthesis plans for best material efficient phosgene-based routes to DCC

carbon monoxide. The two intermediates are then combined to produce DCC via dehydration. Plan 3 [36, 37] is a two-step route that involves the preparation of dicyclohexylthiourea from cyclohexylamine and carbon disulfide followed by hydrogen sulfide elimination. Plan 4 [36, 38, 39] is a three-step route that begins with the same preparation of dicyclohexylthiourea as in plan 3, followed by oxidative sulfur to oxygen exchange with sodium periodate, and followed by dehydration with phosphorus oxychloride. Plan 5 [33, 39] is a two-step route that involves the preparation of dicyclohexylurea as in step two of plan 2 followed by dehydration as in step 4. Plan 6 [32, 33, 40] is a three-step route that involves the preparation of dicyclohexylurea as in step 1 of plan 5, followed by thermal elimination to yield cyclohexylisocyanate and cyclohexylamine, and followed by



Scheme 22.4 Synthesis plans for best material efficient non-phosgene-based routes to DCC

catalytic dimerization of the cyclohexylisocyanate intermediate as in step three of plan 1. The final plan, plan 7 [32, 41–43], is a four-step route that begins with the preparation of dimethyl carbonate from methanol and carbon dioxide, followed by amidation to make methyl cyclohexylcarbamate, followed by elimination of methanol yielding cyclohexylisocyanate, and followed by catalytic dimerization to DCC as in step three of plan 1.



Scheme 22.4 (continued)

22.3 Material Efficiency

Having identified the most promising candidate routes from both synthesis networks based on PMI, the next task is to elaborate on their material performance by dissecting their AE, RY, and E-factor metrics. Tables 22.3 and 22.4 summarize these parameters as well as the individual E-factor components E-kernel, E-excess, and E-aux, which correspond to waste from reaction byproducts and unreacted stoichiometric reagents, excess reagents, and all auxiliary materials. Figure 22.1 shows a visual depiction of the E-factor profiles for all seven DCC plans. Plan 1 is

Table 22.3 Summary of material efficiency metrics for best phosgene-based plans to DCC as shown in Scheme 22.3

Plan	No. steps	AE/%	RY/%	E-kernel	E-excess	E-aux	E-total	PMI	SM[a]
1	3	37.2	80	2.4	0.5	1.1	4.0	5.0	Cy-NH_2
2	3	57.4	71	1.2	1.0	7.3	9.6	10.6	Cy-NH_2

[a] SM = starting material

Table 22.4 Summary of material efficiency metrics for best non-phosgene-based plans to DCC as shown in Scheme 22.4

Plan	No. steps	AE/%	RY/%	E-kernel	E-excess	E-aux	E-total	PMI	SM[a]
3	2	40.7	82	1.9	1.5	9.0	12.5	13.5	Cy-NH_2
4	3	17.6	65	7.1	10.1	2.1	19.4	20.4	Cy-NH_2
5	2	23.2	52	5.6	4.4	2.5	12.5	13.5	Cy-NH_2
6	3	45.6	47	3.7	2.5	1.5	7.8	8.8	Cy-NH_2
7	4	21.6	75	4.5	4.3	18.1	26.9	27.9	Cy-NH_2

[a] SM starting material

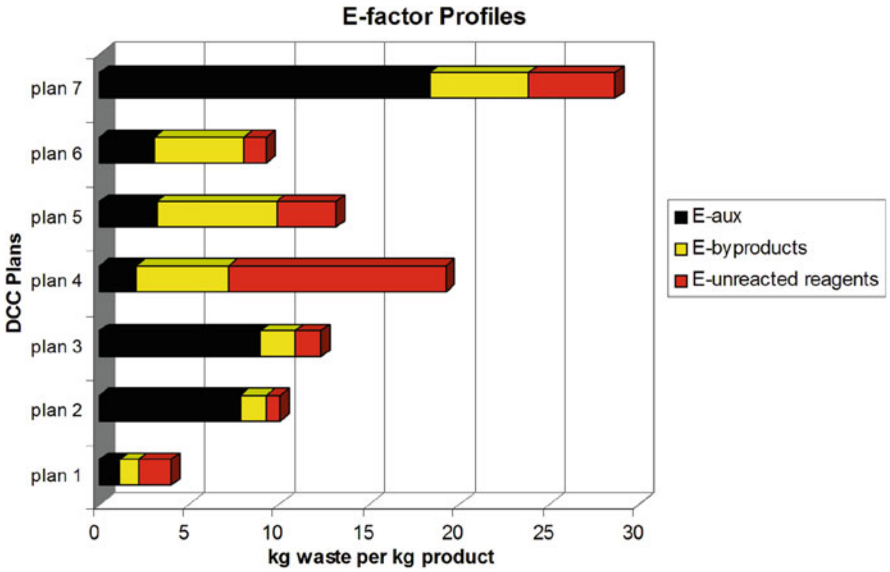


Fig. 22.1 E-factor profiles for the seven DCC plans shown in Schemes 22.3 and 22.4

the leading chlorine-based route following a linear three-step strategy that involves the generation of phosgene from carbon monoxide and chlorine gas followed by reaction with cyclohexylamine to make cyclohexylisocyanate followed by catalytic decarboxylative dimerization to DCC. Plan 6 is the leading non-chlorine-based route also following a linear three-step strategy involving the generation of dicyclohexylurea in a catalytic multicomponent fashion from cyclohexylamine and carbon monoxide followed by thermal decomposition to cyclohexylisocyanate followed by catalytic dimerization as in plan 1. This route allows for the recovery of cyclohexylamine in step 2 that can be used as a reagent in step 1. Plan 1 outperforms plan 6 with respect to material efficiency in all material efficiency metrics parameters. Among the non-chlorine-based routes, plan 3 has the highest overall yield and lowest E-kernel and E-excess values, and plan 6 has the highest AE and lowest E-aux value.

22.4 Environmental and Safety-Hazard Impact

The environmental impact of waste materials generated in all seven DCC plans was evaluated using the benign index (BI) methodology [27] given by Eq. (22.1).

$$BI = 1 - \frac{\sum_j f_j \left(\frac{\text{impact potential for compound j}}{\text{impact potential for reference compound}} \right)_j}{\sum_j \left(\frac{\text{impact potential for compound j}}{\text{impact potential for reference compound}} \right)_j} \tag{22.1}$$

where f_j represents the fractional mass contribution to total waste. This parameter is determined on the basis of the following eight impact potentials: acidification-basification (AB), ozone depletion (OD), smog formation (SF), global warming (GW), inhalation toxicity (INHT), ingestion toxicity (INGT), bioaccumulation (BA), and abiotic resource depletion (ARD). Each waste chemical generated in a chemical reaction in turn requires eight parameters to determine its BI: number of carbon atoms, pK_a of acidic hydrogen atoms, ozone depletion, smog formation, LD_{50}(oral), LC_{50}(inhalation), Henry law constant, and log K_{ow} (octanol-water partition coefficient). It is important to note from Eq. (22.1) that BI is a mass weighted quantity so that the impact potential of any one waste chemical component in a synthesis plan is proportionally weighted according to its percent mass contribution to the total mass of waste generated. Values of BI closer to 1 indicate low environmental impact and are interpreted to be relatively greener than values closer to 0. Figure 22.2 shows the resulting profile for environmental impact for the seven DCC plans. The greatest contributing potential to environmental impact over all plans is ingestion toxicity arising from LD_{50}(oral) data.

In an analogous manner, the safety-hazard impact of input and waste materials were evaluated using the safety-hazard index (SHI) methodology [28]. This parameter is determined on the basis of the following 11 impact potentials: corrosive properties of gases, liquids, or solids (CG and CL); flammability (F); oxygen

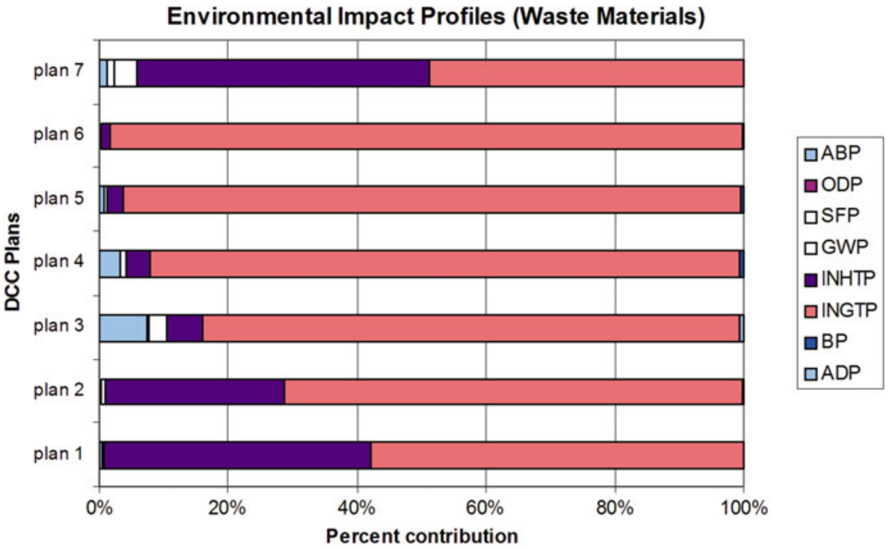


Fig. 22.2 Environmental impact profiles for waste materials profiles for the seven DCC plans shown in Schemes 22.3 and 22.4 by percent contribution for each potential

balance (OB); hydrogen gas generation (HG); explosive vapour (XV); explosive strength (XS); impact sensitivity (IS); occupational exposure limit (OEL); skin dose (SD); and risk phrases (RP). Each input chemical used or waste chemical generated in a chemical reaction requires 11 parameters to determine its SHI: number of oxygen atoms required to oxidize substance, LD_{50}(dermal), flash point, LC_{50}(inhalation), number of moles of hydrogen gas generated, lower explosion limit, impact sensitivity, Trauzl lead block test, occupational exposure limit, skin dose, and risk R-phrases. Figure 22.3 shows the resulting safety-hazard profiles for input and waste chemicals for the seven DCC plans. Occupational exposure limit and skin dose potential are the dominant impact parameters for SHI.

A detailed compilation of best available reliable database sources for all necessary parameters to evaluate BI and SHI has been published [27, 28]. However, there were instances encountered where not all parameters were known. In such cases, a percent uncertainty may be associated with the BI and SHI determinations according to the expression given in Eq. (22.2) [44]

$$\%\ \text{Uncertainty} = \left(\frac{x}{nC}\right)100 \tag{22.2}$$

where x is the number of missing parameters for all the substances used in a given reaction, n is the number of parameters needed to estimate EI ($n = 8$) or SHZI ($n = 11$) for each substance, and C is the total number of chemicals required for carrying out a given reaction, including reagents, catalysts, additives, ligands, reaction solvents, workup materials, and purification materials.

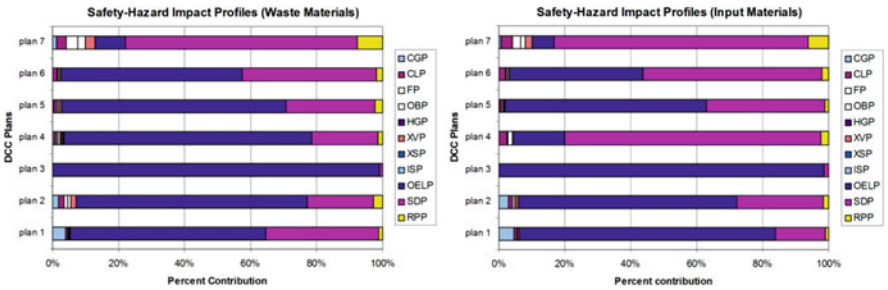
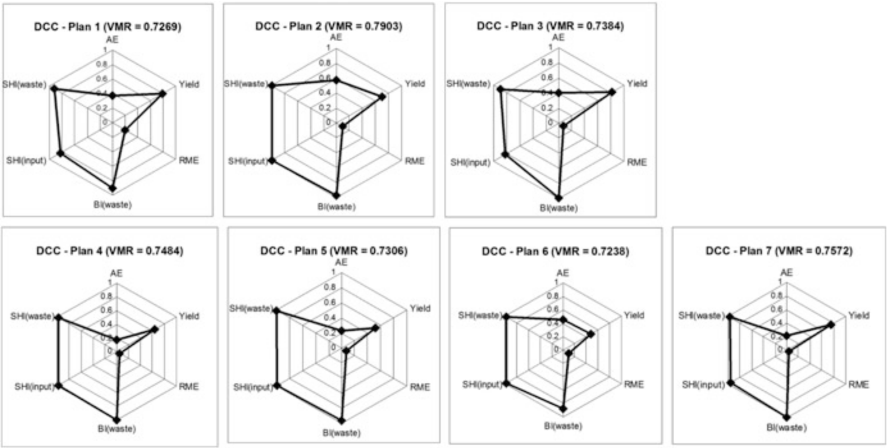


Fig. 22.3 Safety-hazard impact profiles for waste and input materials for the seven DCC plans shown in Schemes 22.3 and 22.4 by percent contribution for each potential

It is possible to depict the performances of all seven plans visually using radial polygon diagrams [45], which are constructed from the six metrics parameters RY, AE, RME, BI(waste), SHI(waste), and SHI(input) that are all quantities ranging between 0 and 1. From these diagrams, the vector magnitude ratio (VMR) for each plan is determined, given by Eq. (22.3), which estimates an unbiased overall score of green performance covering material efficiency, environmental impact, and safety-hazard impact relative to the ideal score of unity.

$$VMR = \frac{1}{\sqrt{6}}\left[(AE)^2 + (RY)^2 + (RME)^2 + (BI_w)^2 + (SHI_w)^2 + (SHI_{in})^2\right]^{1/2} \tag{22.3}$$

A vector quantity was chosen over an area quantity because the latter depends on the order of the parameters drawn in the radial polygon diagram, whereas the former does not. Figure 22.4 shows the respective radial polygons and corresponding VMR scores for the seven DCC syntheses shown in Schemes 22.3 and 22.4, and Table 22.5 summarizes all BI, SHI, associated uncertainties, and VMR data. From these data, we find that plan 2, which is the only one of the seven following a convergent strategy, is also the one with the highest overall VMR. The four-step plan 7 involving dimethyl carbonate chemistry is the best performing non-chlorine-based route when material efficiency, environmental and safety-hazard impact are considered; albeit, it has the highest associated uncertainties in BI and SHI determinations. Plan 4 has the highest BI(waste) value, plan 2 has the highest SHI(input) value, and plans 2 and 5 have the highest SHI(waste) values. Though plan 2 utilizes phosgene chemistry, its high SHI scores are reflective of the low mass proportion of this chemical with respect to all input materials used (5 % of total) or all waste materials generated (1.5 % of total) in this plan. The bulk of the waste generated in this plan, about 68 %, comes from methyl t-butyl ether used in step 2 as reaction and work-up solvent. As an input material, this chemical represents 53 % of the total mass of ingredients needed to carry out this plan.



DCC - Plan 1 (VMR = 0.7269)

DCC - Plan 2 (VMR = 0.7903)

DCC - Plan 3 (VMR = 0.7384)

DCC - Plan 4 (VMR = 0.7484)

DCC - Plan 5 (VMR = 0.7306)

DCC - Plan 6 (VMR = 0.7238)

DCC - Plan 7 (VMR = 0.7572)

Fig. 22.4 Radial polygon diagrams showing VMR scores for the seven DCC plans shown in Schemes 22.3 and 22.4

Table 22.5 Summary of BI, SHI, and VMR metrics for the seven DCC plans shown in Schemes 22.3 and 22.4

Plan	BI(waste)	% U	SHI(input)	% U	SHI(waste)	% U	VMR	Rank
1	0.908	8	0.831	8	0.921	7	0.7269	6
2	0.975	5	0.987	5	0.993	5	0.7903	1
3	0.991	1	0.813	6	0.886	5	0.7384	4
4	0.996	5	0.977	5	0.979	8	0.7484	3
5	0.962	9	0.982	5	0.992	8	0.7306	5
6	0.880	8	0.983	12	0.982	9	0.7238	7
7	0.992	10	0.951	13	0.970	13	0.7572	2

Plan 1 which was the most material efficient ranks sixth overall by its VMR score. In this plan, ingestion toxicity due to pyridine and inhalation toxicity due to phosgene were the main sources of environmental impact; and occupational exposure due to phosgene and skin dose potential due to hydrochloric acid byproduct were the main sources of safety-hazard impact.

22.5 Input Energy

The final layer of metrics analysis that can be applied is the determination of total energy consumption required to carry out all reaction steps in a synthesis plan. Specifically, the total energy required to heat, cool, and pressurize all input materials in a synthesis plan at the appropriate reaction conditions is determined. In this analysis, we focus on the heating and cooling contributions only since the magnitude of the pressure contribution is negligible for reaction pressures below 100 atm which is the case for reaction conditions shown in Schemes 22.3 and 22.4 [46, 47]. For all calculations presented here, the efficiencies of all apparatuses used in reaction procedures are neglected and so the results represent theoretical values. We first set a basis scale of 1 t for DCC for all plans. Next, we determine the corresponding mole scales and masses of all input materials required to produce a final mass of 1 t of DCC. For each input material in a plan, the enthalpy change in kJ for heating that substance from 298 K to the reaction temperature is determined on a per mole basis and is given by the parameter q. Processes involving heating have $q > 0$ and those involving cooling have $q < 0$. The q value of a given substance is then multiplied by its corresponding mole scale as prescribed in the synthesis plan in which that substance appears. The procedure is repeated for all input materials in a plan and the overall input energy sum is determined for a 1 t synthesis of DCC, which can then be converted back to units of kJ/mol. The enthalpic contribution due to heating a substance depends on the phase transitions it can undergo from standard state conditions (298 K and 1 atm) to reaction conditions. The following cases given by Eqs. (22.4), (22.5), (22.6), (22.7), (22.8), (22.9), (22.10), (22.11), (22.12) illustrate the possible calculation scenarios for determining the temperature change contribution to enthalpy. All thermodynamic data were obtained from the DIPPR (Design Institute for Physical Property Data) database [48] and Yaws [49].

Case I Heating a liquid at 298 K from 298 K to T_{rxn} (T_{rxn} is above boiling point, T_b) where the liquid undergoes a phase transition from liquid to gas:

$$q = \int_{298}^{T_b} C_{p,\mathrm{liq}}(T)dT + \int_{T_b}^{T_{rxn}} C_{p,\mathrm{gas}}(T)dT + \Delta H_{\mathrm{vap}} \tag{22.4}$$

$$C_{p,\mathrm{liq}}(T) = A + BT + CT^2 + DT^3 + ET^4 \tag{22.5}$$

$$C_{p,\mathrm{gas}}(T) = A + B\left[\frac{C/T}{\sinh(C/T)}\right]^2 + D\left[\frac{E/T}{\cosh(E/T)}\right]^2 \tag{22.6}$$

where ΔH_{vap} is the heat of vaporization, the functions $C_p(T)$ represent the temperature dependent heat capacity functions at constant pressure for liquids and gases, and the parameters A, B, C, D, and E are constants specific to a given substance.

Case II Heating a liquid at 298 K from 298 K to T_{rxn} (T_{rxn} is below boiling point, T_b) where the liquid does not undergo a phase transition:

$$q = \int_{298}^{T_{rxn}} C_{p,\mathrm{liq}}(T)dT \tag{22.7}$$

Case III Heating a gas at 298 K from 298 K to T_{rxn}:

$$q = \int_{298}^{T_{rxn}} C_{p,gas}(T)dT \tag{22.8}$$

Case IV Heating a solid at 298 K from 298 K to T_{rxn} (T_{rxn} is above both the boiling point, T_b, and the melting point, T_m) where the solid undergoes phase transitions from solid to liquid and from liquid to gas:

$$q = \int_{298}^{T_m} C_{p,sol}(T)dT + \int_{T_m}^{T_b} C_{p,liq}(T)dT + \int_{T_b}^{T_{rxn}} C_{p,gas}(T)dT + \Delta H_{\mathrm{fus}} + \Delta H_{\mathrm{vap}} \tag{22.9}$$

$$C_{p,sol}(T) = A + BT + CT^2 + DT^3 + ET^4 \tag{22.10}$$

where ΔH_{fus} is the heat of fusion and $C_{p,\mathrm{sol}}(T)$ is the temperature dependent heat capacity function at constant pressure for solids.

Case V Heating a solid at 298 K from 298 K to T_{rxn} (T_{rxn} is above melting point, T_{m}) where the solid undergoes a phase transition from solid to liquid:

$$q = \int_{298}^{T_m} C_{p,sol}(T)dT + \int_{T_m}^{T_{\mathrm{rxn}}} C_{p,liq}(T)dT + \Delta H_{\mathrm{fus}} \tag{22.11}$$

Case VI Heating a solid at 298 K from 298 K to T_{rxn} (T_{rxn} is below melting point, T_m) where the solid does not undergo a phase transition:

$$q = \int_{298}^{T_{\mathrm{rxn}}} C_{p,sol}(T)dT \tag{22.12}$$

Table 22.6 summarizes the overall energy consumption results for the seven DCC syntheses based on the reaction conditions given in Scheme 22.3 and 22.4. Figure 22.5 shows the histograms of total input energy for the production of 1 t of DCC illustrating the relative contributions from each reaction step in each plan. In all plans, except for plan 4, lower limits for energy consumption could be determined since thermodynamic data for specialized reagents and catalysts, such as 1,2,3-trimethyl-2-oxo-1,3,2-diazaphospholidine (plans 1, 6, and 7), $Mn_2(CO)_{10}$ (plans 2, 5, and 6), and ZrO_2 (plan 7), were not available. Despite this shortcoming,

Table 22.6 Summary of energy consumption data for the seven DCC plans shown in Schemes 22.3 and 22.4

Plan	Energy consumption to heat input materials/(kJ·mol^{-1} DCC produced)	Rank
1	>469	4
2	>344	3
3	>168	1
4	196	2
5	>579	5
6	>1455	6
7	>1620	7

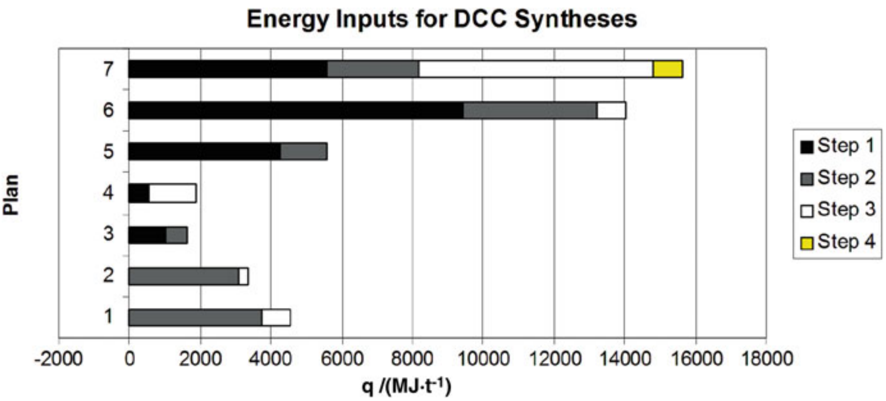


Fig. 22.5 Histograms showing energy input contributions for each step in each of the seven synthesis plans producing 1 t of DCC

we observe that plans 3 and 4 are the least energy demanding (168 and 196 kJ·mol^{-1} DCC produced, respectively) compared to plans 6 and 7 (1455 and 1620 kJ·mol^{-1} DCC produced, respectively). Plans 1 and 2 required cooling to 0 C for the first step and the convergent step, respectively. However, this cooling energy is negligible (21 and 9 MJ/t DCC produced, respectively) compared to the heating requirements in the second step of both plans (3732 and 3102 MJ·t^{-1} DCC produced, respectively). In plan 4, the second step required no input energy since it was run under ambient conditions, a key reason why this plan was ranked high in this category. It is also the most reliably determined since all thermodynamic data were available for all substances used in that plan which underwent heating. In plans 5 and 6, the first steps contribute 76 and 67 %, respectively, to the total energy demand. In plan 7, the most energetically demanding, steps 1 and 3 contribute 36 and 42 %, respectively, to the total energy demand. These steps represent the synthesis of dimethyl carbonate and the elimination of methanol from methyl cyclohexylcarbamate. From all of these data, we may conclude that plans 3 and 4, based on dicyclohexylthiourea chemistry, are the most competitive with respect to energy input metrics. Both of these plans outperform the phosgene-based routes (plans 1 and 2).

22.6 Concluding Remarks

In this chapter, we have examined in detail several literature plans to produce the dehydrating reagent DCC with respect to green metrics in the following categories: material efficiency, environmental impact, safety-hazard impact, and energy input demands. The analysis is based on an examination of best material efficient methods distilled from a synthesis network comprising about 8000 routes and 61 strategies. Best material efficient chlorine versus non-chlorine routes were examined with a view to determine which synthesis had the best overall green profile. We have found that the four-step plan 7 involving dimethyl carbonate chemistry is the best performing non-chlorine-based route when material efficiency, environmental and safety-hazard impact are considered; however, it is the worst with respect to energy input demands. Plan 4 involving dicyclohexylthiourea chemistry is the winning plan with respect to least energy consumption, but ranks third with respect to the other three categories of analysis, very close behind the dimethyl carbonate route. It is hoped that the kinds of analyses described herein may serve as a template for the examination of greenness of any set of synthesis plans to any specified target molecule. The greatest limitations to implementing the described algorithms are the availability of disclosed material consumption data in experimental procedures, and toxicological parameters and thermodynamic data for all substances used in each reaction.

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