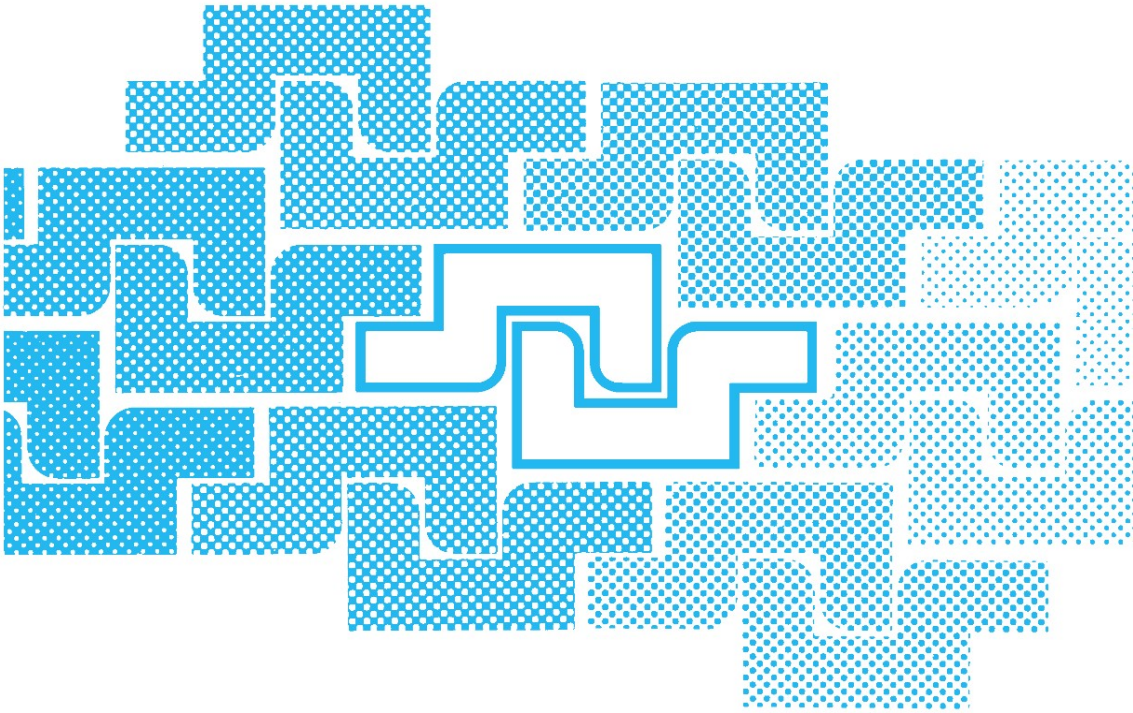

New Methodologies and Techniques for a Sustainable Organic Chemistry

Edited by

Alessandro Mordini
and Ferenc Faigl

NATO Science Series

II. Mathematics, Physics and Chemistry – Vol. 246

New Methodologies and Techniques for a Sustainable Organic Chemistry

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Series II: Mathematics, Physics and Chemistry – Vol. 246

New Methodologies and Techniques for a Sustainable Organic Chemistry

Edited by

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PREFACE

The NATO–ASI NeMeTOC was proposed and organized with the aim of upgrading the participants on the new methods and techniques in organic chemistry which are presently available to achieve the goal of production of chemicals in a secure environment. This is an ambitious task that we decided to undertake being absolutely convinced that it is necessary to give to the young generations of chemists all those new tools which will allow them to make their research work in the most efficient and, at the same time, least environmentally demanding way.

It is indeed nowadays widely acknowledged that there is a growing need for more sustainable processes in the chemical industry, and organic chemists have to face such need finding new solutions to avoid, or minimize, waste in chemical processes and the use of toxic and/or hazardous substances, to reduce the energy required for carrying chemical transformations, to increase as much as possible efficiency and yields. All these targets seem very difficult to reach at present, but there are already some useful methods and techniques we can use to overcome these problems, at least partially. In this NATO – ASI, we have tried to deeply discuss on all these topics taking advantage of the experience of the most prominent scientists working in the field nowadays and pushing all participants to reflect upon, and eject ideas and own experiences into open debates on this topics and in spaces dedicated to the presentation of their own research activities (short and flash presentations, poster sessions).

During the intense ten days of activities, four main themes have been addressed in a deliberate potpourri fashion.

• *New efficient and selective catalytic processes*

All the most important aspects of catalysis have been covered: the search for new chiral ligands, transition metals and catalysts, the application of catalysis in different reactions (Ojima, Echavarren) and particularly in industrially relevant processes (Cabri, Westerduin), the use of non-usual media such as water (Genet) or non-usual activation techniques such as microwaves, the choice of homogeneous or heterogeneous phase catalysis (Lipshutz), the most recent advances on organocatalysis (Barbas III). All these aspects have been also discussed in a "Panel discussion" entitled *Why is asymmetric catalysis not being used more in industry*? (moderator: Bolm) by all participants.

• *Use of non-usual media or environmentally benign reagents*

The change from organic solvents or reagents to more benign ones reduces at the same time the impact on the environment and hazards. These

important topics have been extensively developed in the school. A general description of the concepts associated with these aspects of organic synthesis has been first presented (Sheldon, Tundo) and then the most important items such as the use of water as a solvent (Genet), the technology involved in the use of supercritical fluids (Licence), the advantages of employing biphasic systems (Horvath) and solventless processes (Ricci), and the use of solid phase-supported reagents (Taddei) have been all fully developed. The topics have been also the subject of a "Panel discussion" entitled *Non-conventional reagents and media* (moderator: Sheldon).

• *New selective and efficient synthetic methods*

New processes characterized by a high degree of efficiency (chemical yields), a reduced amount of required chemicals (high atom economy) and reduced waste of materials are essential in order to achieve the goal of a sustainable development coupled with an effective protection of the environment. These topics have been the subject of lectures which have covered several different aspects in the field of organometallic chemistry, separation technologies and "click chemistry" (Sharpless, Faigl, Mordini). In addition, the development of a new technology based on microreactors has been also illustrated (Wahl).

• *New techniques based on alternative energy sources*

Important recent progresses have been made by the scientific community on the use of alternative energy sources characterized by high efficiency together with the use of milder and safer conditions. This has been deeply developed at the ASI in the course of lectures mainly dealing with the use of microwaves in organic synthesis (Kappe, Ricci, Lipshutz) and photoirradiation (Albini), and has been also treated in a "Panel discussion" entitled *Microwave effects* (moderator: Kappe).

The understanding of all the above-mentioned topics has been greatly improved by the exhibition of all the most updated technical equipments to perform such sustainable processes in a laboratory scale. Participants have had the opportunities to see and try all the newest microwave, parallel synthesis and programmable reactors, and the most efficient apparatus for fast and efficient separations and purifications.

We do hope that this book which contains the contributions of most of the lecturers who participated the ASI will reflect all the aspects mentioned above providing a report on the current status of the art in diversified fields having in common the target of answering to virtually any question which may arise during the development of a new environmentally benign organic synthesis.

All these intense and exciting activities have been carried out in a wonderful, secluded but very comfortable and cosy old monastery in the mar-

vellous countryside of Siena. Such a peaceful and enchanting surrounding has certainly helped in inspiring high-level scientific interactions while the delicious food and the wonderful wine have been the catalysts for creating a very nice and confidential atmosphere among all participants. People coming from more than twenty different countries have had the opportunity to discuss and exchange different experiences, cultures and ideas in a relaxing and very friendly atmosphere. The long time spent together has been responsible for establishing new friendships and to allow interactions between lecturers and students. Evening spent together have shown either simply people talking and discussing while drinking wine or even very young students and less young but equally enthusiastic lecturers dancing together.

I think all those who have spent with us the ten days at Certosa di Pontignano would agree with us saying that it has been a wonderful, pleasant experience that we will remember for very long time.

For this event we like to warmly thank many people, the lecturers for having given us outstanding and comprehensive lectures, the chairmen and the exhibitors for their availability and willingness in promoting discussions and most of all the participants who have attentively followed all the activities of the ASI making our tasks easy and pleasant.

The success of the ASI is of course due to many people. We are really in debt with them and we wish to warmly thank them for having shared with us such a beautiful adventure. First of all Gianna Reginato who has been the real engine for moving everything. She has participated the whole preparation process with always perfect scientific and practical suggestions and she has then faced with us all the problems that inevitably rise when you organize such an event. Besides Gianna all the Florence group (Alice, Assunta, Barbara, Chiara, Daniela, Francesco, Gabriella, Lorenzo, Maria Pia, Massimo) deserves our best gratitude. They have not only helped taking care of transportation of lecturers and students, projection of lectures, preparation of lecture notes, helping in all social events, but also with their enthusiasm they have catalyzed the establishment of a friendly and relaxing atmosphere among all people. Warm thanks are due also to the Congress Office of the University of Siena and particularly to Roberta Corsi who has organized almost everything concerning the practical aspects of the school and to the staff at Certosa di Pontignano who have been always very kind and helpful.

The Organizing Committee (C. Bolm, J. P. Genet, B. Lipshutz, A. Ricci, M. Taddei) not only took part in establishing the scientific content of the school, but also took part in developing the scientific and the social activities at Certosa di Pontignano. They have chaired oral and flash communication sessions creating a very relaxing but also stimulating atmosphere among the students, they have promoted discussions during the panel sessions, and they

have been always available and very helpful. Maurizio Taddei deserves our special thanks as being also the local organizer, he has taken on his shoulder most of the practical and financial problems.

Thanks are due to the Ministero della Ricerca Scientifica e Tecnologica for financial support, to the Società Chimica Italiana, Divisione di Chimica Organica, to the Consiglio Nazionale delle Ricerche and to Regione Toscana for their highly appreciated patronage.

Last but not least we warmly thank NATO – Science for Peace and Security (SPS). They have first of all given us the opportunity to organize this beautiful event and they have been always very helpful and patient trying to answer always to our numerous and sometimes difficult questions and to solve all our problems. We are particularly grateful to Fausto Pedrazzini and Alison Trapp for their continuous assistance.

CONTENTS

REACTIONS IN NON-CONVENTIONAL MEDIA FOR SUSTAINABLE ORGANIC SYNTHESIS

ROGER A. SHELDON*

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Abstract: The growing awareness of the pressing need for greener, more sustainable technologies has focused attention on the use of atom efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. Another aspect which is receiving increasing attention is the use of alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents. The use of nonconventional reaction media also provides opportunities for facilitating the recovery and recycling of the catalyst. Liquid–liquid biphasic catalysis provides an industrially attractive method for the recovery and recycling of catalysts as an alternative to the more traditional solid heterogeneous catalysts. Various approaches to liquid–liquid biphasic catalysis.– aqueous biphasic, fluorous biphasic, supercritical carbon dioxide, ionic liquids, and various combinations thereof – are presented and compared.

"The best solvent is no solvent" but if a solvent is needed then water has a lot to recommend it and catalysis in aqueous biphasic systems is has found broad application in an industrial setting. Similarly, supercritical carbon dioxide is an interesting reaction medium in the context of green chemistry and catalysis in various mono- and biphasic systems involving this solvent are presented. Fluorous biphasic systems and ionic liquids also have advantages in certain situations and the advantages and limitations of these media are compared. The ultimate in clean catalytic technologies is to telescope multistep syntheses into one pot in the form of catalytic cascade processes. Examples of such catalytic cascades involving both chemo- and biocatalytic conversions are presented. Biocatalysis has a distinct advantage in this

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context in that the reactions all take place at or close to ambient temperature and pressure. A problem encountered in the design of catalytic cascade processes is the incompatibility of the various catalysts. The solution to this problem is compartmentalization which is achieved by immobilization of the various catalysts. In this context, a novel and effective method for the immobilisation of enzymes as cross-linked enzyme aggregates (CLEAs) is presented and the use of a combi CLEA, containing two enzymes, for the one-pot conversion of benzaldehyde to *S*-mandelic acid is reported.

Keywords: Green Chemistry, catalysis, alternative reaction media, cascade reactions, immobilization

1. Introduction

Sustainability can be defined as 'meeting the needs of the present generation without compromising the rights of future generations to meet their own needs'.[1] It is widely acknowledged that there is a growing need for more sustainable processes in the chemical industry. This trend towards 'Sustainable Technologies' necessitates a paradigm shift from traditional concepts of process efficiency, that focus largely on chemical yield, to one that assigns economic value to eliminating waste at source and avoiding the use of toxic and/or hazardous substances. The means to achieving this lofty goal is via the application of the principles of Green Chemistry which can be summarized as follows:

Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.

A useful measure of the potential environmental acceptability of chemical processes is the E factor,[2] defined as kilograms of waste per kilogram of desired product formed. The sheer magnitude of the waste problem in chemicals manufacture is readily apparent from a consideration of typical E factors in various segments of the chemical industry as shown in Table 1. The

TABLE 1. E Factors in the Chemical Industry

	Tonnage	*E* = kg waste/kg product
Bulk chemicals	10^4–10^6	<1–5
Fine chemical Industry	10^2–10^4	5–>50
Pharmaceutical Industry	10–10^3	25–>100

E factor takes the chemical yield into account and includes reagents, solvent losses, all process aids and, in principle, even energy. There is one exception: (process) water is generally not taken into account as this would generate E factors which are not very meaningful.

The waste generated in the manufacture of organic compounds consists primarily of inorganic salts. This is a direct consequence of the use of stoichiometric inorganic reagents in organic synthesis. Fine chemicals and pharmaceuticals manufacture, for example, are rampant with antiquated 'stoichiometric' technologies. Organic chemistry textbooks are resplendent with pertinent examples: stoichiometric reductions with metals (Na, Mg, Zn, Fe) and metal hydride reagents ($LiAlH_4$ and $NaBH_4$), oxidations with permanganate, manganese dioxide, and chromium (VI) reagents and a wide variety of reactions, e.g. sulfonations, nitrations, halogenations, diazotizations, and Friedel–Crafts acylations, employing stoichiometric amounts of mineral acids (H_2SO_4, HF, H_3PO_4) and Lewis acids ($AlCl_3$, $ZnCl_2$, BF_3).

2. Catalysis: The Key to Sustainability

The solution to the waste problem is evident: substitution of classical stoichiometric methodologies with cleaner catalytic alternatives. Indeed, a major challenge in (fine) chemicals manufacture is to develop processes based on H_2, O_2, H_2O_2, CO, CO_2, and NH_3 as the direct source of H, O, C, and

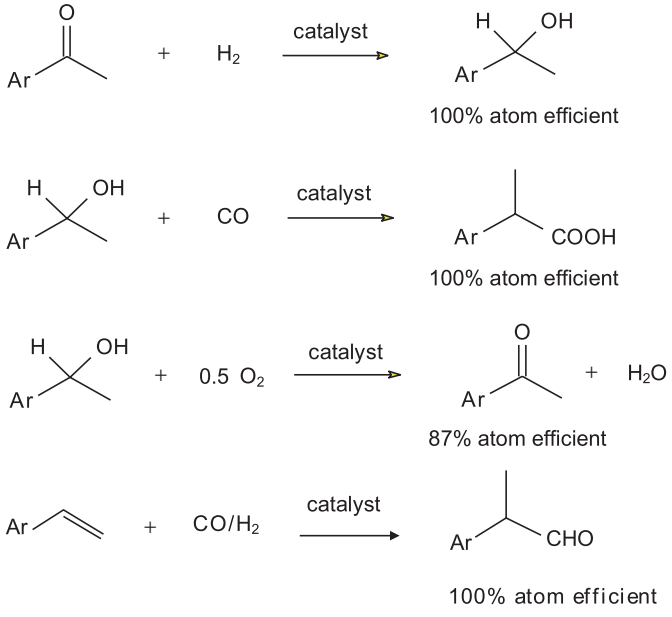


Figure 1. Atom-efficient catalytic processes.

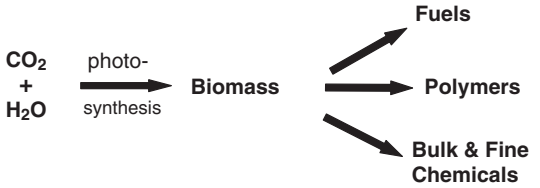


Figure 2. Renewable raw materials.

N. Catalytic hydrogenation, oxidation, carbonylation, and hydroformylation are good examples of highly atom efficient, low-salt processes (Figure 1).

Currently, much attention is focused on the use of renewable raw materials (biomass) as a source of energy, polymers and bulk and fine chemicals (Figure 2).[3] The biomass is ultimately derived from carbon dioxide and water, with the aid of solar energy, via photosynthesis. Hence, the basic raw materials of the future will be carbon dioxide, water, oxygen, and nitrogen, with conversion of biomass in biorefineries replacing the conversion of fossil fuels in conventional oil refineries.

3. Alternative Reaction Media

Another important issue in the context of sustainability is the use of organic solvents. Glaxo Smith Kline scientists[4] have estimated that ~85% of the total mass of chemicals involved in pharmaceutical manufacture comprises solvents, and recovery efficiencies are typically 50–80%. In the context of Green Chemistry there are several issues which influence the choice of solvent. Preferably, it should have a minimum environmental footprint, that is it should be biodegradable and relatively non-toxic and non-hazardous, e.g. not inflammable or corrosive. Ideally, it should be contained, that is it should not be released to the environment. Furthermore, it should be readily separated from the product and the catalyst and readily recycled.

Pfizer, for example, received a Presidential Green Chemistry Challenge Award in 2002 for the redesign of the sertraline manufacturing process.[5] Among other improvements, a three step sequence, involving the use of a different solvent in each step, was streamlined to one employing ethanol as the sole solvent (Figure 3). This eliminated the need to use, distil and recover four solvents (methylene chloride, tetrahydrofuran, toluene, and hexane) employed in the original process. Similarly, Pfizer scientists have recently reported[6] that the optimized manufacturing process for sildenafil citrate afforded a reduction in solvent use of two orders of magnitude compared with the original medicinal chemistry recipe. The currently optimized manufacturing process has an E Factor of 6 which is excellent for a pharmaceutical (see Table 1).

Removal of residual solvent from products usually involves evaporation or distillation and the most popular solvents are, therefore, highly volatile.

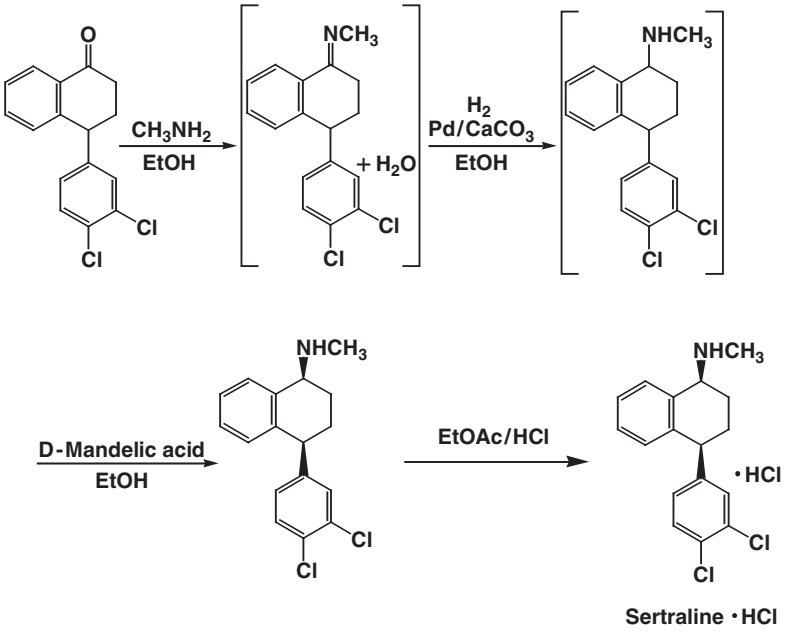


Figure 3. Improved process for sertraline manufacture.

However, spillage and evaporation inevitably lead to atmospheric pollution. Moreover, worker exposure to volatile organic compounds (VOCs) is a serious health issue. Consequently, many chlorinated hydrocarbon solvents have already been banned or are likely to be in the near future. Unfortunately, many of these solvents are exactly those that have otherwise desirable properties and are, therefore, widely popular with organic chemists. Another class of solvents which presents environmental problems comprises the polar aprotic solvents, such as dimethylformamide and dimethyl sulfoxide, that are the solvents of choice for, e.g. many nucleophilic substitutions. They are high boiling and not easily removed by distillation. They are also water-miscible which enables their facile separation by washing with water. Unfortunately, this also leads to contaminated aqueous effluent.

These issues surrounding a wide range of volatile and non-volatile, polar aprotic solvents have stimulated a quest for more benign alternatives. Among conventional organic solvents, there is a marked trend away from hydrocarbons and chlorinated hydrocarbons towards lower alcohols, esters and some ethers such as methyl *tert*-butyl ether and methyl tetrahydrofuran. The latter solvent is available from renewable raw materials. Inexpensive natural products such as ethanol have the added advantage of being readily biodegradable and ethyl lactate, produced by combining two innocuous natural products, is currently being promoted as a solvent for chemical reactions.

In this context, it is also worth mentioning that the polyols, polyethylene glycol (PEG) and polypropylene glycol (PPG), are potentially interesting solvents for performing (catalytic) organic reactions.[7] They are readily available and inexpensive, non-toxic and biodegradable (they are used in beverages), non-volatile and thermally robust and, depending on the molecular weight, can be water miscible or immiscible.

The conclusion is evident: the problem with solvents is not so much their use but the seemingly inherent inefficiencies associated with their containment, recovery and reuse. Alternative solvents should, therefore provide for their efficient removal from the product and reuse. Recovery and reuse of the catalyst is desirable from both an environmental and an economic viewpoint (many of the catalysts used in fine chemicals manufacture contain highly expensive noble metals and/or chiral ligands). If a catalyst is an insoluble solid, that is, a heterogeneous catalyst, it can easily be separated by centrifugation or filtration. In contrast, if it is a homogeneous catalyst, dissolved in the reaction medium, recycling presents more of a problem: separation of the (expensive) catalyst from reaction products and its quantitative recovery in an active form is cumbersome and offsets the major advantages of homogeneous catalysts, such as high activities and selectivities (see Table 2).

Separation by distillation of reaction products from catalyst generally leads to heavy ends which remain in the catalyst phase and eventually deactivate it. Moreover, in the manufacture of pharmaceuticals quantitative separation of the catalyst is important in order to avoid contamination of the product. Consequently, there have been many attempts to heterogenize homogeneous catalysts by attachment to organic or inorganic supports. However, these approaches have, with few exceptions, not resulted in commercially viable processes, for a number of reasons, such as leaching of the metal, poor catalyst productivities, irreproducible activities and selectivities and degradation of the support.

TABLE 2. Heterogeneous vs homogeneous catalysis.

	Homogeneous	Heterogeneous
Advantages	Mild reaction conditions	Facile separation of catalyst and products
	High activity and selectivity	Continuous processing
	Efficient heat transfer	Heat transfer problems
		Low activity and selectivity
Disadvantages	Cumbersome separation and recycling of catalyst	
	Product contamination	
	Not readily adapted to continuous processing	

3.1. HETEROGENIZATION OF CATALYSTS AND LIQUID–LIQUID BIPHASIC CATALYSIS

This need for efficient separation of product and catalyst, while maintaining the advantages of a homogeneous catalyst, has led to the concept of *liquid–liquid biphasic catalysis*, whereby the catalyst is dissolved in one phase and the reactants and product(s) in the second liquid phase. The catalyst is recovered and recycled by simple phase separation. Preferably, the catalyst solution remains in the reactor and is reused with a fresh batch of reactants without further treatment or, ideally, it is adapted to continuous operation. Obviously, the solvents used for both phases are subject to the same restrictions as discussed above for monophasic systems.

An early example of the application of liquid–lquid biphasic catalysis in an industrial process was in the nickel catalyzed oligomerization of ethylene, a key step in the SHOP process for higher olefins manufacture, commercialized by Shell in the 1970s (Figure 4). The homogeneous nickel catalyst and the ethylene reactant are dissolved in 1,4-butane diol, whereas the liquid oligomeric products are immiscible and can be recovered by simple phase separation while the catalyst remains in the butane diol phase and can be recycled.[8]

Several different combinations have been intensely studied in recent years, including *water (aqueous biphasic), supercritical CO_2, ionic liquids, and fluorous biphasic systems*. The use of water and supercritical carbon dioxide as reaction media would seem to be particularly attractive in the context of sustainability.

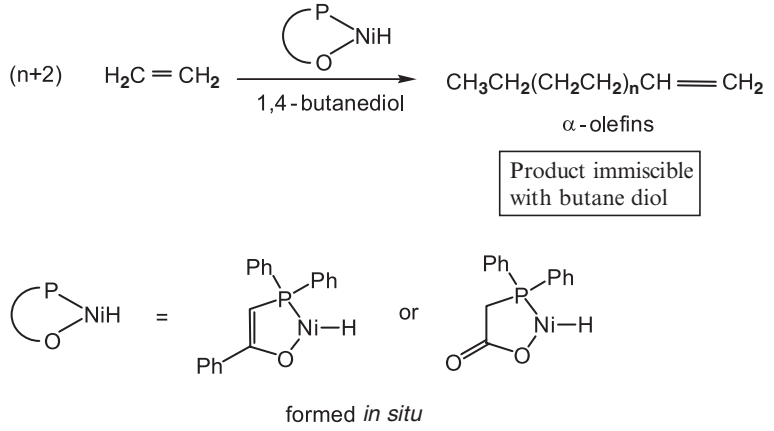


Figure 4. Biphasic catalysis in the SHOP process.

3.2. AQUEOUS BIPHASIC CATALYSIS

The best solvent is no solvent and if a solvent (diluent) is needed then water is preferred. Water is non-toxic, non-inflammable, abundantly available, and inexpensive. Moreover, owing to its highly polar character one can expect novel reactivities and selectivities for organometallic catalysis in water. Furthermore, by performing the reaction in an aqueous biphasic system, whereby the catalyst resides in the water phase and the product is dissolved in, or forms the organic phase,[9] the catalyst can be recovered by simple phase separation and recycled.

In order to perform organometallic catalysis in water the catalyst has to be rendered water soluble, by employing water soluble ligands resulting from the introduction of hydrophilic moieties, e.g. sulfonate groups, into conventional lipophilic ligands such as organophosphines.[9] An example of a large-scale application of this concept is the Ruhrchemie/Rhône Poulenc process for the hydroformylation of propylene to *n*-butanal (Figure 5), which employs a water-soluble rhodium(I) complex of trisulfonated triphenylphosphine (tppts) as the catalyst.[10] The tppts ligand has a solubility in water at ambient temperature of 1,100 g/L. In the traditional process separation of the catalyst from the heavy ends (high boiling byproducts), in an active form, is problematical. In contrats,catalyst recovery in the RPRC process is extremely efficient : rhodium losses amount to ~1 kg/10^9 kg of product.

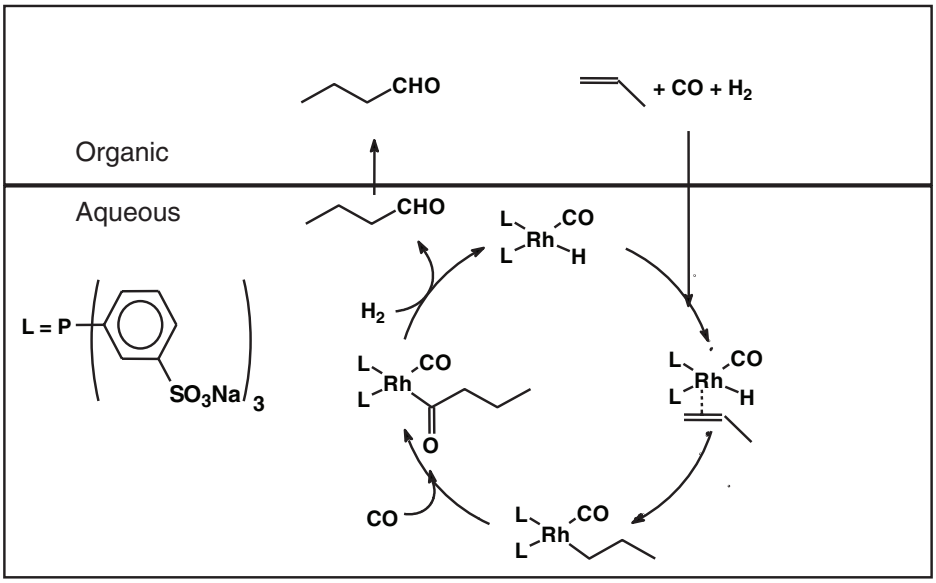


Figure 5. Rhone Poulenc/RuhrChemie process for aqueous biphasic hydroformylation.

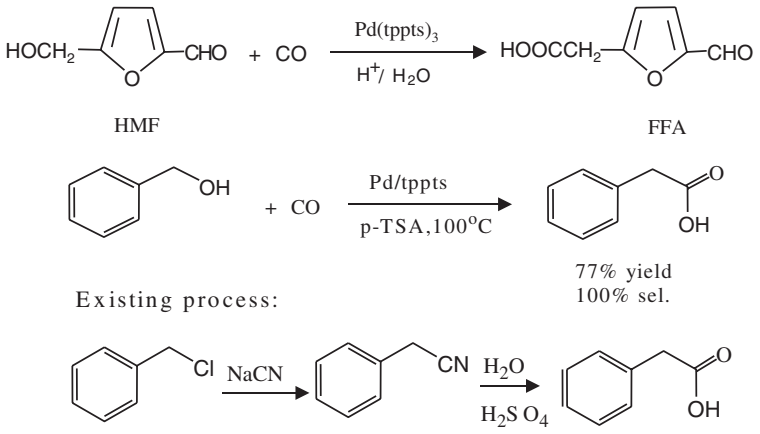


Figure 6. Aqueous biphasic carbonylation.

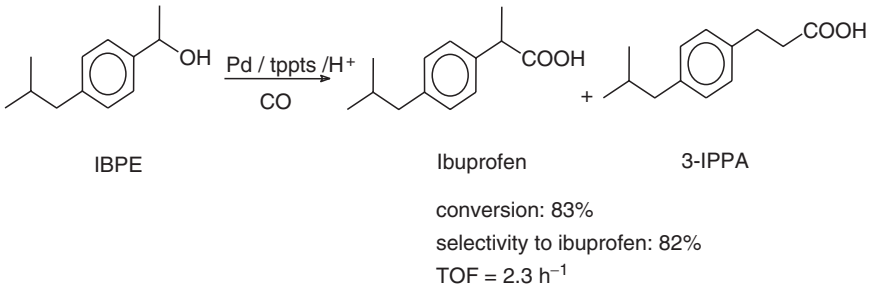


Figure 7. Ibuprofen via aqueous biphasic carbonylation.

Similarly, we showed that Pd/tppts, in the presence of a Bronsted acid cocatalyst, catalyzes the carbonylation of alcohols in aqueous mono- or biphasic media.[10] Examples of the former are the carbonylation of the water miscible alcohols, hydroxymethyl furfural (HMF) and benzyl alcohol (Figure 6).HMF is of interest as a renewable raw material derived from biomass and the carbonylation of benzyl alcohol represents a green alternative the classical manufacture of phenyl acetic acid via reaction of benzyl chloride with sodium cyanide (Figure 6).

An example of an aqueous biphasic system is the synthesis of ibuprofen by biphasic carbonylation of 1-(4-isobutylphenyl) ethanol (Figure 7).[11]

We also applied the methodology to the biphasic hydrocarboxylation of olefins (Figure 8).[12] These reactions are proposed to involve the formation of an intermediate carbenium ion (hence the need for an acid cocatalyst) which reacts with the Pd(0) complex to afford an alkylpalladium (II) species.[13]

When a sulfonated diphosphine is used as the ligand the complex formed with palladium(0) catalyzes the alternating copolymerization of ethylene and CO to give the engineering thermoplastic polyketone, Carilon.[14,15] Indeed,

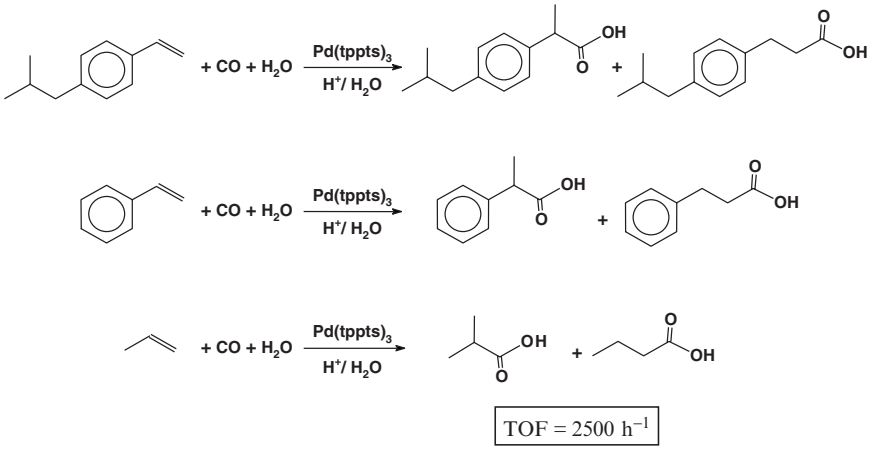


Figure 8. Aqueous biphasic hydrocarboxylation of olefins.

when a well-defined complex was used exceptionally high activities were observed,[16] with turnover frequencies (TOFs) higher than the conventional catalyst in methanol as solvent.

We next turned our attention to palladium catalyzed oxidations with molecular oxygen in water. A major problem in palladium catalyzed oxidations in general is that the reactions proceed via the Pd(II)/Pd(0) redox couple and, because reoxidation of Pd(0) to Pd(II) is rather sluggish, Pd(0) agglomerates to form palladium metal (palladium black) resulting in catalyst deactivation. By analogy with the use of sulfonated (di)phosphine complexes of palladium (II) as catalysts for carbonylations in aqueous media, we reasoned that sulfonated dinitrogen ligands could stabilize transient Pd(0) species in water and, thus, prevent agglomeration to palladium black. Indeed,the palladium(II) complex of sulfonated bathophenanthroline proved to be a highly effective catalyst for the aqueous biphasic aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes or carboxylic acids and ketones, respectively (Figure 9).[17] No organic solvent was necessary, unless the substrate is a solid, and turnover frequencies of the order of $100\,h^{-1}$ were observed. The catalyst could be recovered and recycled by simple phase separation (the aqueous phase is the bottom layer and can be left in the reactor for the next batch). The method constitutes an excellent example of a green catalytic oxidation using oxygen (air) as the oxidant, no organic solvent and a stable recyclable catalyst. The only disadvantage of the use of water as a solvent for aerobic oxidations is the low solubility of oxygen in water. Combined with the necessity

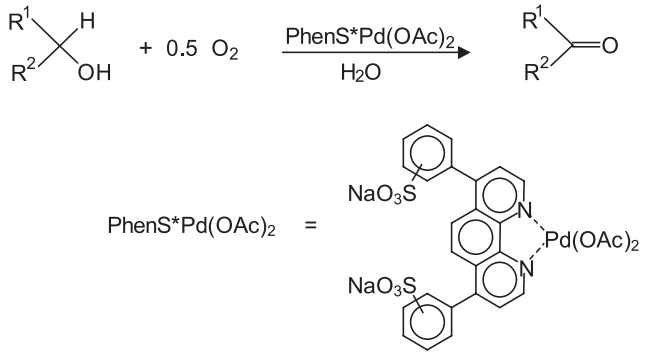
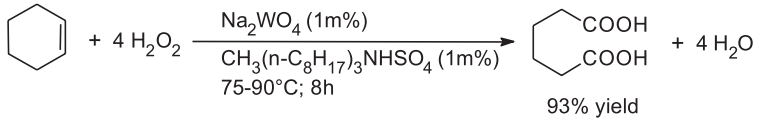


Figure 9. Aqueous biphasic Pd-catalyzed aerobic oxidation of alcohols.



redo

Figure 10. Green oxidation of cyclohexene to adipic acid.

(for safety reasons) for diluting the oxygen with nitrogen this means that a pressure of 10–30 bar is needed to provide for a sufficient concentration of oxygen in the aqueous phase.

Alternatively, the use of hydrogen peroxide as the terminal oxidant is eminently compatible with the use of water as the reaction medium and hydrogen peroxide has been used, in aqueous biphasic systems, for the oxidation of alcohols to aldehydes or ketones, the epoxidation of olefins and the oxidative cleavage of olefins or ketones to carboxylic acids, e.g. cyclohexene to adipic acid (Figure 10).[18]

3.3. BIOCATALYSIS

Biocatalysis has many attractive features in the context of green chemistry: mild reaction conditions (physiological pH and temperature), an environmentally compatible catalyst (an enzyme) and solvent (often water) combined with high activities and chemo-, regio- and stereoselectivities in multifunctional molecules. Furthermore, the use of enzymes generally circumvents the need for functional group activation and avoids protection and deprotection steps required in traditional organic syntheses. This affords processes which are shorter, generate less waste and are, therefore, both environmentally and economically more attractive than conventional routes.

The time is ripe for the widespread application of biocatalysis in industrial organic synthesis and according to a recent estimate[19] more than 130 processes have been commercialized. Advances in recombinant DNA techniques have made it, in principle, possible to produce virtually any enzyme for a commercially acceptable price. And advances in protein engineering have made it possible, using techniques such as site directed mutagenesis and in vitro evolution, to manipulate enzymes such that they exhibit the desired substrate specificity, activity, stability, pH profile, etc.[20] Furthermore, the development of effective immobilization techniques has paved the way for optimizing the performance and recovery and recycling of enzymes.

An illustrative example of the benefits to be gained by replacing conventional chemistry by biocatalysis is provided by the manufacture of 6-aminopenicillanic acid (6-APA), a key raw material for semi-synthetic penicillin and cephalosporin antibiotics, by hydrolysis of penicillin G.[21] Up until the mid-1980s a chemical procedure was used for this hydrolysis (Figure 11). It involved the use of environmentally unattractive reagents, a chlorinated hydrocarbon solvent (CH_2Cl_2) and a reaction temperature of −40°C. Thus, 0.6-kg Me_3SiCl, 1.2-kg PCl_5, 1.6-kg $PhNMe_2$, 0.2-kg NH_3, 8.4-L *n*-BuOH and 8.4-L CH_2Cl_2 were required to produce 1-kg 6-APA. In contrast, enzymatic cleavage of penicillin G is performed in water at 37°C and the only reagent used is NH_3 (0.9 kg/kg of 6-APA), to adjust the pH. The enzymatic process currently accounts for the majority of the several thousand tons of 6-APA produced annually on a worldwide basis.

DuPont has developed a process for the manufacture of glyoxylic acid, a large volume fine chemical, by aerobic oxidation of glycolic acid (Figure 12), mediated by resting whole cells of a recombinant methylotrophic yeast.[22] The glycolic acid is readily available from acid-catalysed carbonylation of formaldehyde. Traditionally, glyoxylic acid was produced by nitric acid oxidation of acetaldehyde or glyoxal, processes with high E factors. The key enzyme in the biocatalytic process is an oxidase which utilizes dioxygen as the oxidant, producing one equivalent of hydrogen peroxide, without the need for cofactor regeneration.

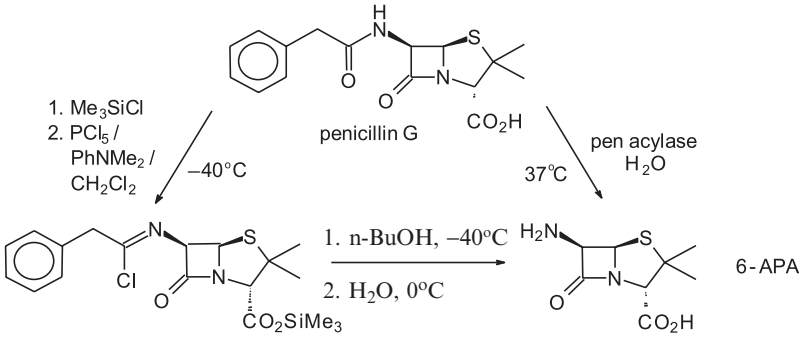
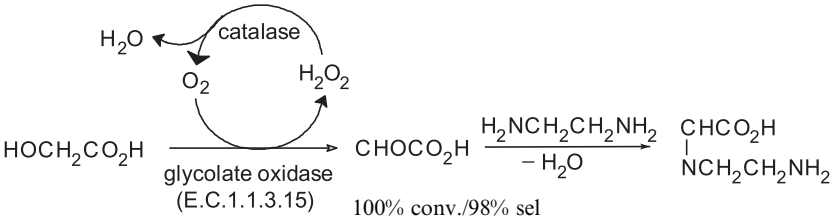


Figure 11. Enzymatic versus chemical deacylation of penicillin G.



Existing Processes:

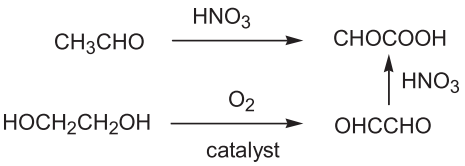


Figure 12. Biocatalytic vs chemical production of glyoxylic acid.

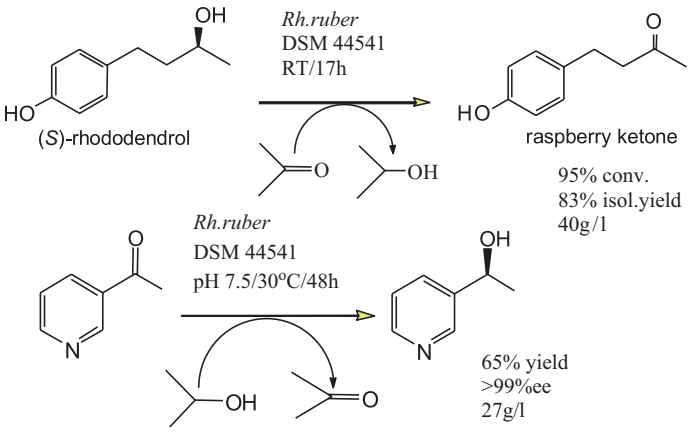


Figure 13. Biocatalytic Oppenauer oxidations and MPV reductions.

Another class of enzymes which catalyze the oxidation of alcohols comprises the alcohol dehydrogenases. However, in this case cofactor regeneration is required, which is an impediment to commercialization. Recently, a highly enantioselective alcohol dehydrogenase, showing broad substrate specificity and exceptionally high tolerance for organic solvents, was isolated from *Rhodococcus ruber* DSM 4451.[23] The enzyme maintains a high activity at concentrations of up to 20% (v/v) acetone and 50% (v/v) 2-propanol. This enables the use of the enzyme, conveniently as whole microbial cells, as a catalyst for (enantioselective) Oppenauer oxidation of a broad range of alcohols, using acetone (20% v/v in phosphate buffer at pH 8) as the oxidant (Figure 13), with substrate concentrations up to 1.8 mol L^{-1} (237 g L^{-1} for octan-2-ol). Alternatively, the reaction

could be performed in a reduction mode, using the ketone as substrate and up to 50% v/v isopropanol as the reductant, affording the corresponding (*S*)-alcohol in 99% ee at conversions ranging from 65% to 92%.

4. Supercritical Carbon Dioxide as a Reaction Medium

Other non-classical reaction media have, in recent years, attracted increasing attention from the viewpoint of avoiding environmentally unattractive solvents and/or facilitating catalyst recovery and recycling.[24] For example, supercritical carbon dioxide has been receiving increasing attention as an alternative reaction medium in recent years.[25] Several features of $scCO_2$ make it an interesting solvent in the context of green chemistry and catalysis. For carbon dioxide the critical pressure and temperature are moderate: 74 bar and 31°C, respectively. Hence, the amount of energy required to generate supercritical carbon dioxide is relatively small. In addition, carbon dioxide is non-toxic chemically inert towards many substances, non-flammable, and simple depressurization results in its removal. It is miscible with, e.g. hydrogen, making it an interesting solvent for hydrogenation and hydroformylation (see below). Although it is a greenhouse gas its use involves no net addition to the atmosphere; it is borrowed as it were. Its main uses are as a replacement for VOCs in extraction processes. For example it is widely used for the decaffeination of coffee where it replaced the use of a chlorinated hydrocarbon. The pre-existence of an established SCF extraction industry meant that the necessary equipment was already available.

The use of $scCO_2$ as a solvent for catalytic hydrogenation was pioneered by Poliakoff and has been commercialized by Thomas Swan and Co for the manufacture of trimethyl cyclohexanone by Pd-catalyzed hydrogenation of isophorone (Figure 14).[26] The miscibility of $scCO_2$ with hydrogen results in high diffusion rates, and provides the basis for achieving much higher reaction rates than in conventional solvents. The high reaction rates allow for the use of exceptionally small flow reactors. Chemoselectivities with multifunctional compounds could be adjusted by minor variations in reaction parameters. Similarly, $scCO_2$ has been used for olefin hydroformylation using an immobilized rhodium catalyst.[27]

Just as with water, $scCO_2$ is also an ideal inert solvent for performing catalytic aerobic oxidations; it is inflammable and completely miscible with oxygen. Recently, much interest has also been focused on catalytic oxidations

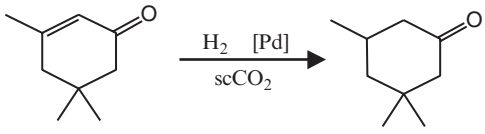


Figure 14. Catalytic hydrogenation of isophorone in $scCO_2$.

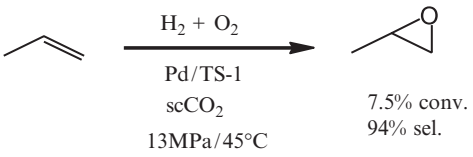


Figure 15. Epoxidation of propylene with H_2/O_2 in $scCO_2$.

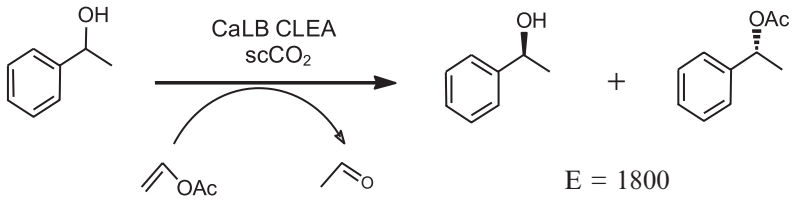


Figure 16. Kinetic resolution of secondary alcohols with Novozyme 435 in $scCO_2$.

with hydrogen peroxide, generated in situ by Pd-catalyzed reaction of hydrogen with oxygen, in $scCO_2$/water mixtures.[28] The system was used effectively for the direct epoxidation of propylene to propylene oxide over a Pd/TS-1 catalyst.[29] These reactions probably involve the intermediate formation of peroxycarbonic acid by reaction of H_2O_2 with CO_2 (Figure 15).

$scCO_2$ is also an interesting solvent for performing bioconversions. The first reports of biocatalysis in $scCO_2$ date back to 1985[30] and in the intervening two decades the subject has been extensively studied.[31] Enzymes are generally more stable in $scCO_2$ than in water and the *Candida antarctica* lipase (Novozym 435)-catalyzed resolution of 1-phenylethanol was successfully performed at temperatures exceeding 100°C in this solvent.[32] Matsuda et al., found that the enantioselectivity of alcohol acylations catalyzed by Novozyme 435 in $scCO_2$ could be controlled by adjusting the pressure and temperature.[33] The same group recently reported a continuous flow system in $scCO_2$ for the enzymatic resolution of chiral secondary alcohols via Novozyme 435 catalyzed acylation with vinyl acetate (Figure 16).[34] For example, the kinetic resolution of 1-phenyl ethanol at 9 MPA CO_2 and 40°C afforded the (*R*)-acetate in 99.8% ee and the (*S*)-alcohol in 90.6% ee at 48% conversion (E = 1,800). More recently, cross-linked enzyme aggregates (CLEAs, see later) of CaLB have been shown[35] to be more effective than Novozyme 435 for the resolution of chiral alcohols in $scCO_2$.

Similarly, the enantioselective reduction of prochiral ketones catalyzed by whole cells of *Geotrichum candidum* proceeded smoothly in $scCO_2$ in a semi-continuous flow system.[36] The use of $scCO_2$ as a solvent for biotransformations clearly has considerable potential and we expect that it will find more applications in the future.

5. Fluorous Biphasic Systems

Fluorous biphasic catalysis was pioneered by Horvath and Rabai[37] who coined the term 'fluorous, by analogy with 'aqueous', to describe highly fluorinated alkanes, ethers and tertiary amines. Such fluorous compounds differ markedly from the corresponding hydrocarbon molecules and are, consequently, immiscible with many common organic solvents at ambient temperature although they can become miscible at elevated temperatures. Hence, this provides a basis for performing biphasic catalysis or, alternatively, monophasic catalysis at elevated temperatures with biphasic product/catalyst separation at lower temperatures. A variety of fluorous solvents are commercially available, albeit rather expensive compared with common organic solvents (or water). Barthel-Rosa and Gladysz have published an extensive 'user's guide' to the application of fluorous catalysts and reagents.[38]

In order to perform fluorous biphasic catalysis the (organometallic) catalyst needs to be solubilized in the fluorous phase by deploying "fluorophilic" ligands, analogous to the hydrophilic ligands used in aqueous biphasic catalysis. This is accomplished by incorporating so-called "fluorous ponytails".

Hydroformylation of higher olefins in an aqueous biphasic system is problematic owing to the lack of solubility of the substrate in the aqueous phase. On the other hand, hydroformylation in an organic medium presents the problem of separating the long-chain aldehydes from the catalyst. In contrast, this is not a problem with a fluorous biphasic system where at the elevated reaction temperature the mixture becomes a single phase. Cooling the reaction mixture to room temperature results in a separation into a fluorous phase, containing the catalyst, and an organic phase, containing the aldehyde products. This concept was applied by Horvath and Rabai, to the hydroformylation of 1-decene in a 1:1 mixture of $C_6F_{11}CF_3$ and toluene.[37] The catalyst was prepared in situ from $Rh(CO)_2$ (acac) and $P[CH_2CH_2(CF_2)_5CF_3]_3$, (P/Rh = 40). Upon completion of the reaction the reactor was cooled to room temperature phase separation occurred. When the upper, organic phase was returned to the reactor, with fresh reactants, negligible reaction was observed, demonstrating that catalytically active rhodium species are not leached into the organic phase. It was subsequently shown[39,40] that recycling of the catalyst phase, in nine consecutive runs, afforded a total turnover number (TON) of more than 35,000. The rhodium losses amounted to 4.2%, which constitutes ~1 ppm/mol of aldehyde. Unfortunately there was some leaching of the free ligand into the organic phase, resulting in a slight decrease in (n/i) selectivity (from ~92/8 to 89/11), which is dependent on the ligand/Rh ratio. The three different concepts for olefin hydroformylation – organic solvent, aqueous biphasic and fluorous biphasic – are compared in Figure 17.

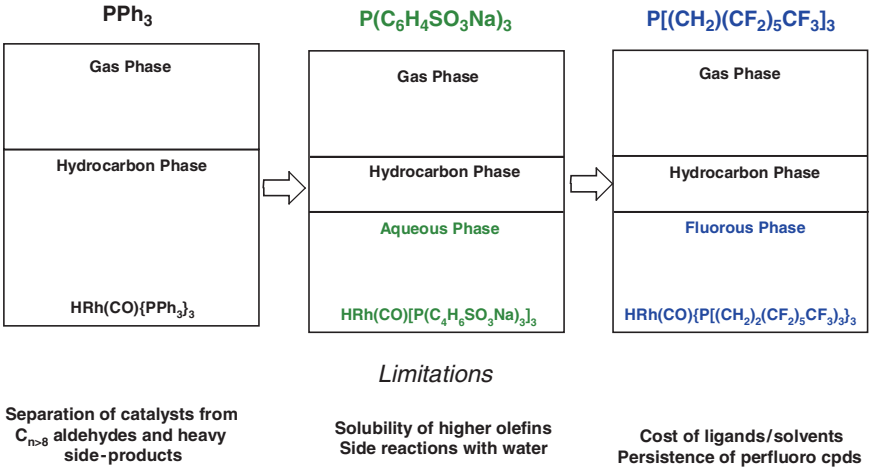
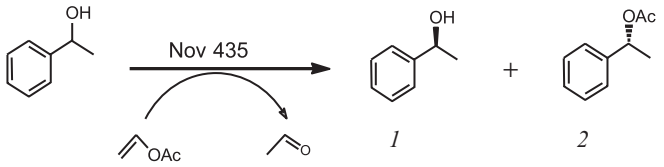


Figure 17. Different concepts for olefin hydroformylation.



Solvent	time (h)	conv.(%)	ee *1* (%)	ee *2* (%)
CH_2F_2	5	50	>99	>99
CH_2FCF_3	3.5	49	96	>99
CF_3CHFCF_3	4	49	96	>99
Hexane	8	46	85	>99
MTBE	35	49	96	>99

Figure 18. Biocatalysis in HCFCs.

The successful demonstration of the fluorous biphasic concept for performing organometallic catalysis sparked extensive interest in the methodology and it has subsequently been applied to a wide variety of catalytic reactions. Fluorous media are particularly suitable for performing aerobic oxidations based on the high solubility of oxygen in fluorocarbons. A few examples of catalytic oxidations in fluorous media have been reported.[41,42]

In an interesting recent development, it was shown[43] that readily available, inexpensive hydrofluorocarbons (HCFCs), are excellent solvents for biocatalytic transformations (see Figure 18) giving superior results to conventional organic solvents. HCFCs are non-inflammable, essentially nontoxic and, in contrast to their cousins the CFCs, are not ozone depleters.

5.1. IONIC LIQUIDS

Ionic liquids are quite simply liquids that are composed entirely of ions.[44] They are generally salts of organic cations, e.g. tetraalkylammonium, alkylpyridinium, 1,3-dialkylimidazolium, and tetraalkyl phosphonium (Figure 19). Room temperature ionic liquids exhibit certain properties which make them attractive media for performing green catalytic reactions. They have essentially no vapour pressure and are thermally robust with liquid ranges of e.g. 300°C, compared to 100°C for water. Polarity and hydrophilicity/hydrophobicity can be tuned by a suitable combination of cation and anion, which has earned them the accolade, "designer solvents".

Ionic liquids have been extensively studied in the last few years as media for organic synthesis and catalysis in particular.[45] For example, the hydroformylation of higher olefins, such as 1-octene, was performed in ionic liquids.[46] Good activities were observed with rhodium in combination with the water-soluble ligand, tppts, described above but the selectivity was low (n/iso ratio = 2.6). In order to achieve both high activities and selectivities special ligands had to be designed (Figure 20). No detectable (less than 0.07%) Rh leaching was observed and the IL phase containing the catalyst could be recycled after separating the product which formed a separate phase. However, the need for rather exotic ligands will presumably translate to higher costs for this process.

Many catalytic reactions have now been successfully performed in ionic liquid media[45] including Friedel–Crafts acylations and Heck reactions.[47,48]

In recent years increasing attention has also been devoted to conducting biocatalytic transformations in ionic liquids.[49] The first report of enzyme (lipase) catalyzed reactions in water-free ionic liquids dates from 2000 and involved transesterification, ammoniolysis and perhydrolysis reactions catalyzed by *Candida Antarctica* lipase B (Figure 21).[50]

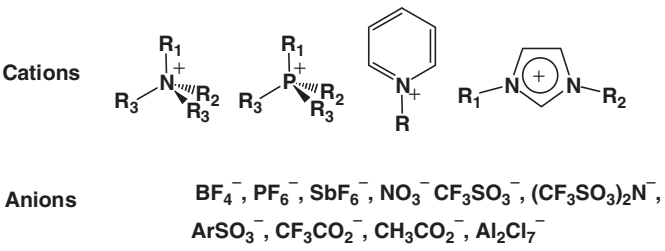


Figure 19. Examples of ionic liquids.

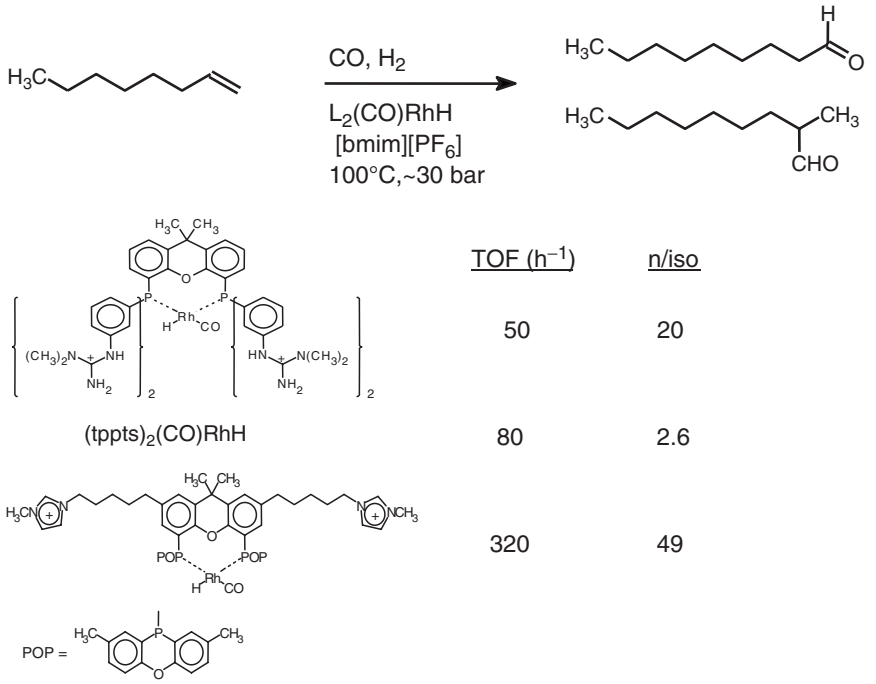


Figure 20. Hydroformylation of 1-octene in [bmim][PF_6] at 100°C and 30 bar.

The use of ionic liquids as reaction media for biotransformations has several potential benefits compared to conventional organic solvents, e.g. higher operational stabilities and enantioselectivities[49] and activities are generally at least as high as those observed in organic solvents. They are particularly attractive for performing bioconversions with substrates which are very sparingly soluble in conventional organic solvents, e.g. carbohydrates and nucleosides.

Notwithstanding the advantages of ionic liquids as reaction media for catalytic processes, they have not yet been applied in industry. The reasons for this are probably related to their high prices and the paucity of data with regard to their toxicity and biodegradability. The replacement of conventional VOCs with ionic liquids is an obvious improvement with regard to atmospheric emissions but small amounts of ionic liquids will inevitably end up in the environment, e.g. in ground water. Consequently, it is important to establish their effect on the environment. Indeed, the current trend in ionic liquid research is towards the development of non-toxic, biodegradable ionic liquids, e.g. based on renewable raw materials.[51]

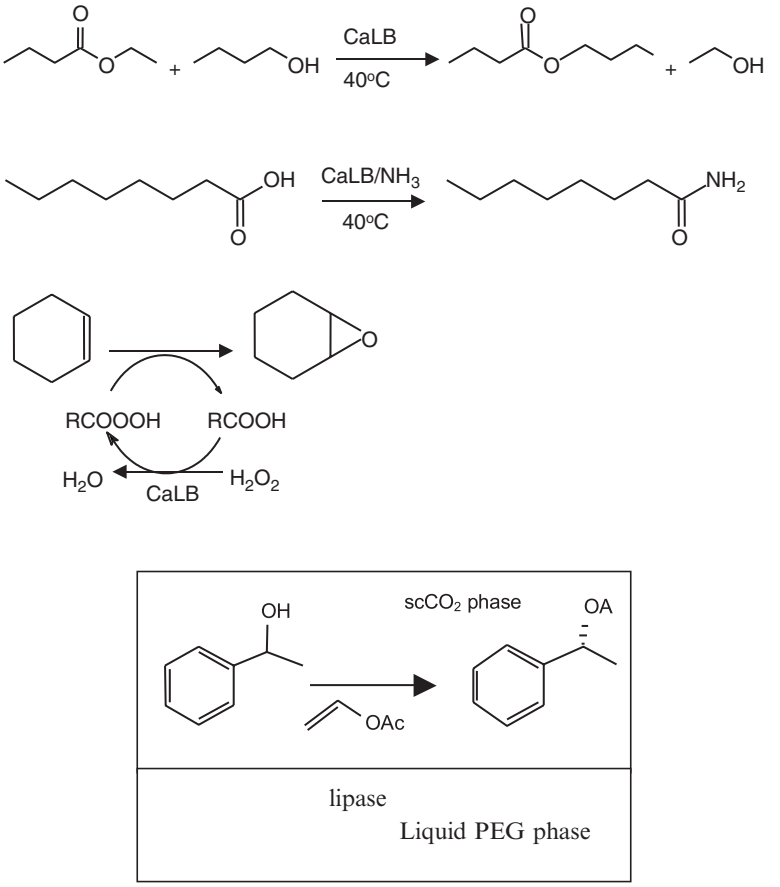


Figure 21. Candida Antarctica lipase B-catalyzed transformations in water-free ionic liquids.[50]

5.2. BIPHASIC SYSTEMS WITH SUPERCRITICAL CARBON DIOXIDE

One problem associated with the use of ILs is recovery of the product and recycling of the catalyst. If this is achieved by extraction with a volatile organic solvent then it is questionable what the overall gain is. An attractive alternative is to use $scCO_2$ as the second phase, whereby the catalyst remains in the IL phase and the product is extracted into the $scCO_2$ phase. This concept has been successfully applied to both homogeneous metal catalysis[52] and biocatalytic conversions.[53] We have recently applied the concept of using a 'miscibility switch', for performing catalytic reactions in IL/$scCO_2$ mixtures.[54] In this concept the reaction is performed at a pressure where there is one phase. Subsequently the pressure is reduced to afford two phases which

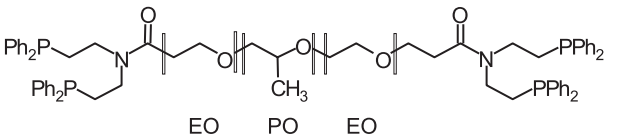
can easily be separated. The catalyst remains in the ionic liquid phase while the products and unreacted starting material is in the CO_2 phase.

Other combinations with $scCO_2$ have also been considered which dispense with the need for an ionic liquid altogether. For example, a biphasic water/$scCO_2$ system, whereby the catalyst, e.g. a metal complex of tppts, resides in the water phase and the product is removed in the $scCO_2$ phase.[55] The system has its limitations: the catalyst needs to be water soluble and all reaction components must be stable towards the acidic pH (3) of carbonic acid. More recently, an attractive system comprising a biphasic mixture of poly (ethylene glycol) (PEG) to dissolve the catalyst and $scCO_2$ as the extractive phase was used for the RhCl $(Ph_3P)_3$-catalyzed hydrogenation of styrene.[56] PEGs have the advantage over ILs that they are much less expensive and are non-toxic (analogous to CO_2, they are approved for use in foods and beverages). They are, moreover, miscible with common organic ligands and in the above example the catalyst was stable and recyclable in the PEG phase.

The same concept has also been applied to an enzymatic transformation. Lipase catalyzed enantioselective acylation of 1-phenylethanol was performed in a biphasic PEG/$scCO_2$ system whereby the lipase resided in the stationary PEG phase and the product was continuously removed in the $scCO_2$ phase (Figure 22).[57]

5.3. THERMOREGULATED BIPHASIC CATALYSIS

Another approach to facilitating catalyst separation while maintaining the benefits of homogeneous catalysis involves the use of thermoregulated biphasic catalysis,[58] whereby the catalyst is dissolved in a particular solvent at one temperature and insoluble at another. For example, a diphosphine ligand attached to an ethylene oxide/propylene oxide block copolymer (Figure 23) afforded rhodium complexes that are soluble in water at room temperature but precipitate on warming to 40°C. The driving force for this inverted temperature dependence on solubility is dehydration of the ligand on heating. Hence, a rhodium catalyzed reaction, such as hydrogenation or hydroformylation can be performed at room temperature in a single phase



$M_W = 1100 - 4400$

Figure 22. Lipase-catalyzed tranesterification in PEG/$scCO_2$.

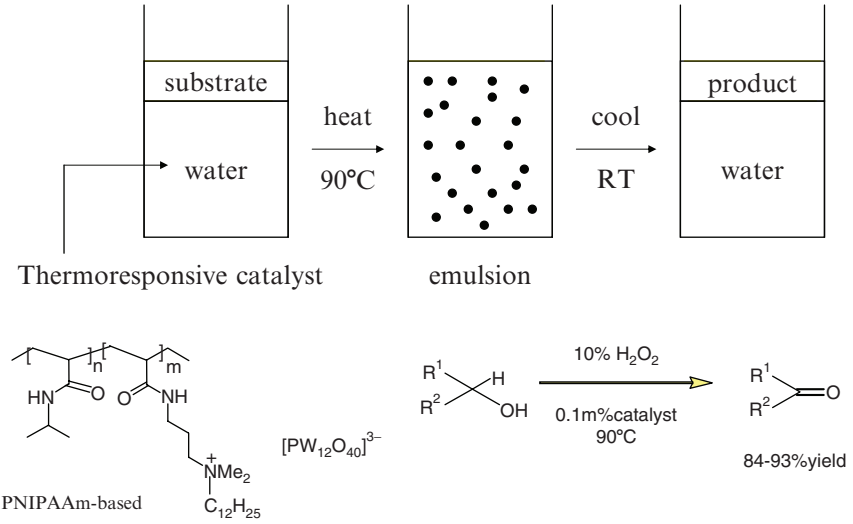


Figure 23. Ligand for thermoregulated biphasic catalysis.

and the catalyst separated by precipitation at a higher temperature. An added advantage is that runaway conditions are never achieved since the catalyst precipitates and the reaction stops on raising the temperature. This principle has also been applied to biotransformations by covalent attachment of an enzyme, e.g. penicillin acylase to poly-*N*-isopropylacrylamide (PNIPAM).[59]

An interesting example of the use of a recyclable, thermoresponsive catalyst in a micellar-type system was recently reported by Ikegami et al.[60] A PNIPAM-based copolymer containing pendant tetraalkylammonium cations and a polyoxometalate, $PW_{12}O_{40}^{3-}$, as the counter anion was used as a catalyst for the oxidation of alcohols with hydrogen peroxide in water (Figure 24). At room temperature the substrate and the aqueous hydrogen peroxide, containing the catalyst, formed distinct separate phases. When the mixture was heated to 90°C a stable emulsion was formed, in which the reaction took place with as little as 0.1mol% catalyst. Subsequent cooling of the reaction mixture to room temperature resulted in precipitation of the catalyst which could be removed by filtration and recycled.

6. Catalytic Cascade Processes and Combi-CLEAs

The widespread application of chemo- and biocatalytic methodologies in the manufacture of fine chemicals is resulting in a gradual disappearance of the traditional barriers between the subdisciplines of homogeneous and heterogeneous catalysis and biocatalysis. The key to successful implementation of catalytic methodologies is integration of catalytic steps in multistep

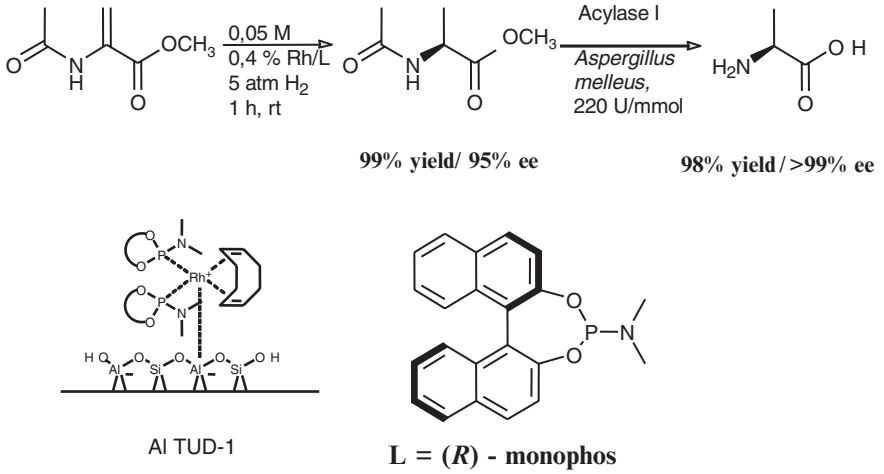


Figure 24. Oxidation of alcohols with hydrogen peroxide using a thermoresponsive catalyst in a micellar system.

organic syntheses and downstream processing. The ultimate in integration is to combine several catalytic steps into a one-pot, multi-step catalytic cascade process.[61] This is truly emulating Nature where metabolic pathways conducted in living cells involve an elegant orchestration of a series of biocatalytic steps into an exquisite multicatalyst cascade, without the need for separation of intermediates. Such 'telescoping' of multi-step syntheses into a one-pot catalytic cascade has several advantages – fewer unit operations, less solvent, and reactor volume, shorter cycle times, higher volumetric and space time yields and less waste (lower E factor) – which translates to substantial economic and environmental benefits. Furthermore, coupling of reactions together can be used to drive equilibria towards product thus avoiding the need for excess reagents. On the other hand, there are several problems associated with the construction of catalytic cascades: catalysts are often incompatible with each other (e.g. an enzyme and a metal catalyst), rates are very different and it is difficult to find optimum conditions of pH, temperature, solvent, etc. Catalyst recovery and recycle is complicated and downstream processing is difficult. Nature solves this problem by compartmentalization of the various biocatalysts. Hence, compartmentalization via immobilization is conceivably a way of solving these problems in cascade processes. It is also worth noting that biocatalytic processes generally proceed under roughly the same conditions – in water at around ambient temperature and pressure – which facilitates the cascading process.

For example, we have recently combined an asymmetric hydrogenation, using a supported chiral Rh catalyst, with enzymatic hydrolysis of the

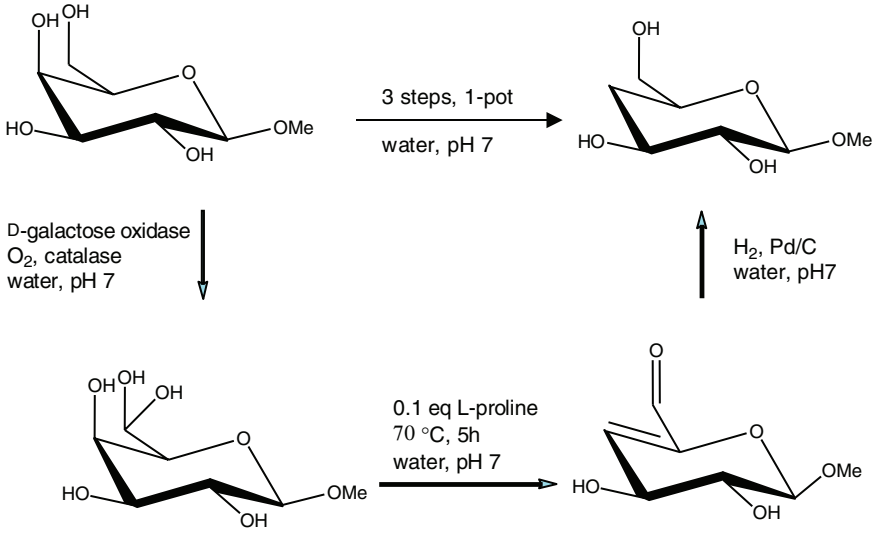


Figure 25. Chemoenzymatic, one-pot synthesis of an amino acid.

product, affording a one-pot cascade process in water as the only solvent (Figure 25).[62] An additional benefit is that the enantiomeric purity of the product of the asymmetric hydrogenation is upgraded in the subsequent enzymatic hydrolysis which is highly selective for the desired enantiomer.

An example of a one-pot, three-step cascade involving an enzyme, a metal catalyst and an organocatalyst is shown in Figure 26. In the first step galactose oxidase catalyzes the selective oxidation of the primary alcohol group of galactose to the corresponding aldehyde. This is followed by L-proline-catalysed elimination of water and catalytic hydrogenation, affording the deoxy sugar.[63]

We have recently developed an extremely effective method for immobilizing enzymes as so-called Cross-Linked Enzyme Aggregates (CLEAs).[64] They exhibit high activity retention and stability and can be readily recovered and recycled without any loss of activity. Furthermore, the method is exquisitely simple-precipitation from aqueous buffer followed by cross-linking with, for example, glutaraldehyde and is applicable to a broad range of enzymes. It does not require highly pure enzyme preparations and it actually constitutes a combination of purification and immobilization into one step. The methodology can also be applied to the co-immobilization of two or more enzymes to give 'combi CLEAs' which are more effective than mixtures of the individual CLEAs. These are ideally suited to conducting enzymatic cascade reactions in water, where an equilibrium can be shifted by removing the product in a consecutive biotransformation. For example, we have used a combi CLEA containing an *S* – selective nitrilase (from *Manihot esculenta*)

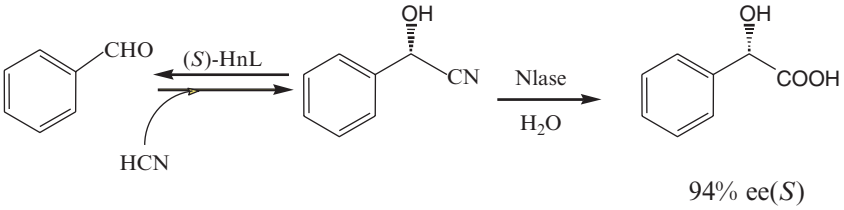


Figure 26. One-pot, three-step synthesis of a deoxy sugar.

and a non-selective nitrilase, in DIPE/Water (9:10) at pH 5.5, 1 h, for the one-pot conversion of benzaldehyde to *S*-mandelic acid (Figure 27) in high yield and enantioselectivity.[65]

7. Conclusions and Prospects

The employment of catalytic methodologies – homogeneous, heterogeneous and enzymatic – in water or supercritical carbon dioxide as the reaction medium holds much promise for the development of a sustainable chemical manufacturing industry. Water is cheap, abundantly available, non-toxic and non-inflammable and the use of aqueous biphasic catalysis provides an ideal basis for recovery and recycling of the (water-soluble) catalyst. Water is also the ideal solvent for many processes catalyzed by Nature's catalysts, enzymes. Hence, the use of water as a reaction medium meshes well with the current trend towards a sustainable chemical industry based on the utilization of renewable raw materials rather than fossil fuels as the basic feedstock.

Supercritical carbon dioxide also has many potential benefits in the context of sustainability. In common with water, it is cheap, abundantly available, non-toxic, and non-inflammable. It is also an eminently suitable solvent for a homogeneous, heterogeneous and biocatalytic processes and is readily separated from the catalyst and products by simple release of pressure. Reaction rates are very high in $scCO_2$, owing to its intermediate properties, between a gas and a liquid. Biphasic systems involving $scCO_2$ with, for example, an ionic liquid or polyethylene glycol, also hold promise as reaction media for a variety of catalytic processes integrated with product separation and catalyst recycling.

The ultimate in sustainable catalytic processes is the integration of chemocatalytic and/or biocatalytic steps into catalytic cascade processes that emulate the metabolic pathways of the cell factory. We believe that one-pot syntheses via catalytic cascade processes, involving chemo- and biocatalysis, and based on water and carbon dioxide as basic raw materials and reaction media, will provide the basis for a sustainable chemical industry.

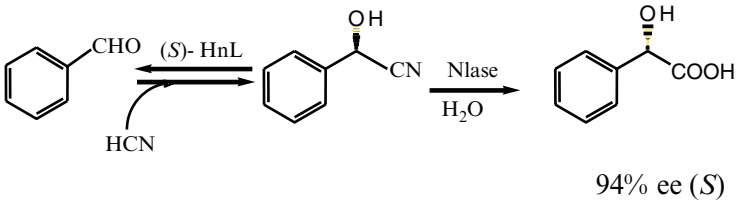


Figure 27. One-pot conversion of benzaldehyde to *S*-mandelic acid with a combi CLEA.

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CATALYTIC ASYMMETRIC SYNTHESIS WITH NOVEL MONODENTATE PHOSPHORUS LIGANDS

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Abstract: A library of new fine-tunable monodentate phosphite and phosphoramidite ligands based on chiral biphenol has been designed and developed. These monodentate phosphorus ligands have exhibited excellent enantioselectivity in the Pd-catalyzed asymmetric allylic alkylation, Rh-catalyzed asymmetric hydrogenation and hydroformylation, and Cu-catalyzed conjugate addition reactions.

Keywords: biphenol-based, monodentate, phosphorus, phosphoramidite asymmetric, catalysis, hydrogenation, allylic-alkylation, hydroformylation, conjugate-addition, enantioselectivity, regioselectivity, rhodium, palladium, copper

1. Introduction

Recently chiral monodentate phosphorus ligands have been attracting considerable interest because of their structural simplicity as well as excellent efficiency in a variety of catalytic asymmetric transformations. It is literally a regain of interest that takes place after three decades of predominance of diphosphine ligands with C_2 symmetry, which was often considered as a prerequisite for efficient asymmetric induction. This new wave of designing simple and readily modifiable chiral structures fits very well to the trendy and highly practical combinatorial approach to the development of the most suitable chiral ligands for a particular catalytic asymmetric process of commercial value or academic interest. This approach is currently considered the

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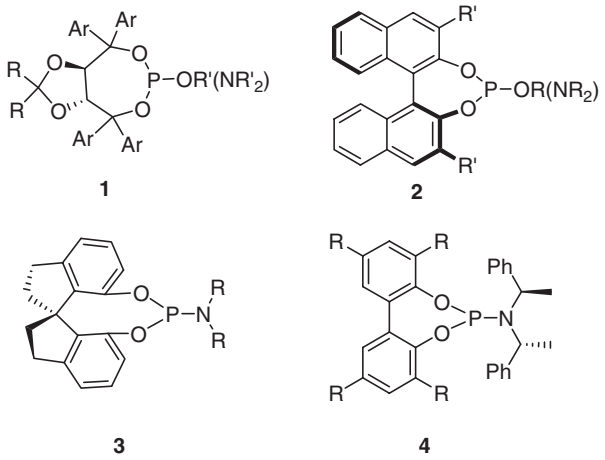


Figure 1. Structure of known chiral monodentate phosphite and phosphoramidite ligands.

most practical rather than trying to develop a universal and almighty ligand for different types of catalytic asymmetric transformations.

Prior to our research on monodentate phosphorus ligands based on axially chiral 2,2′-dihydroxy-6,6′-dimethylbiphenyls (Figure 2), the vast majority of such ligands were based on TADDOL (**1**),[1] BINOL (**2**),[2–4] spiroindanol (**3**)[5] or achiral biphenol (**4**)[6] bearing a chiral or achiral secondary alcohol or amine (Figure 1).

These ligands have found a wide range of applications in metal-catalyzed asymmetric transformations such as hydrogenation,[7–15] 1,4-addition of diethyl zinc[16–22] or boronic acid[23,24] to conjugated systems, hydrovinylation,[25,26] hydrosilylation,[27] hydroformylation,[19,28] intramolecular Heck reaction,[29,30] allylic alkylation,[31–34] amination[35–37] and etherification.[38,39]

We have been developing a previously uninvestigated class of monophosphite and monophosphoramidite ligands based on readily accessible axially chiral biphenol units (Figure 2).[9,19] One of the salient and practical features of these ligands is the fine-tuning capability through modifications of the R^1, R^2 and R^3 groups in the formula **5** and **6** (Figure 2). This feature is of critical importance as it allows the design of a combinatorial approach to find the most suitable chiral ligand for a specific catalytic process.

We describe here the applications of these novel monodentate phosphorus ligands to various transition metal-catalyzed asymmetric transformations, which demonstrate the clear advantages that their fine-tuning capability can offer for achieving high catalyst efficiency and enantioselectivity. The catalytic reactions discussed here include the Rh-catalyzed hydrogenation of dimethyl itaconate, the Pd-catalyzed

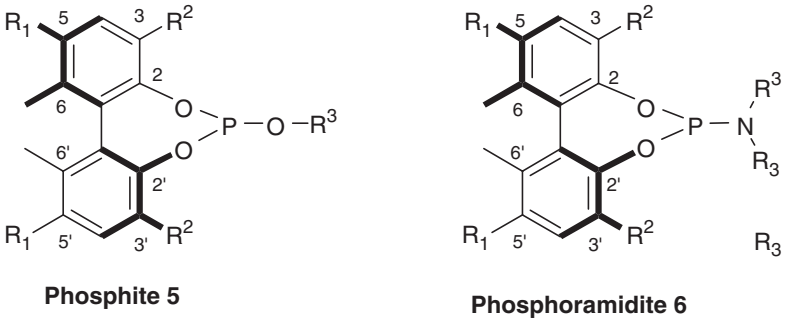


Figure 2. General structure of fine-tunable biphenol-based ligands.

allylic alkylation, the Rh-catalyzed hydroformylation of allyl cyanide and the Cu-catalyzed conjugate addition of diethylzinc to α,β-unsaturated ketones and nitroalkenes.[9,19,40]

2. Synthesis of Monodentate Ligands

A library of chiral monophosphite and monophosphoramidite ligands has been designed and synthesized. These monodentate phosphorous ligands are comprised of various substituents at the 3,3′-positions of the enantiopure 5,5′,6,6′-tetramethylbiphenol moiety as well as different alkoxy-, aryloxy- and dialkylamine moieties on the phosphorous (Figure 3).

(*R*)- and (*S*)-5,5′,6,6′-tetramethylbiphenols were efficiently prepared through oxidative coupling followed by separation of the corresponding (−)-menthoxyphosphate diastereomers.[41] Substituents at the 3,3′-positions were introduced through electrophilic substitutions and Suzuki coupling.[9,19] Thus, up to five different substituents, i.e. H, Me, Br, *t*-Bu, and Ph, have been introduced to the 3,3′-positions of the biphenol skeleton. For the synthesis of the corresponding chiral phosphorus ligands, a biphenol is reacted with an alkoxyphosphorous dichloride or a *N,N*-dialkylaminophosphorous dichloride in the presence of Et_3N in THF at room temperature for 12 h (Scheme 1). The alcohols or amines used are commercially available with the exception of chiral *N,N*-bis(1-arylethyl)amines.[42]

3. Rhodium-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate

Chiral monodentate phosphorus ligands have recently shown high efficiency in the asymmetric hydrogenation of prochiral olefins.[3,4,7] Since the early work of Claver[3], Reetz[4] or Feringa[7], a variety of monodentate phosphorus

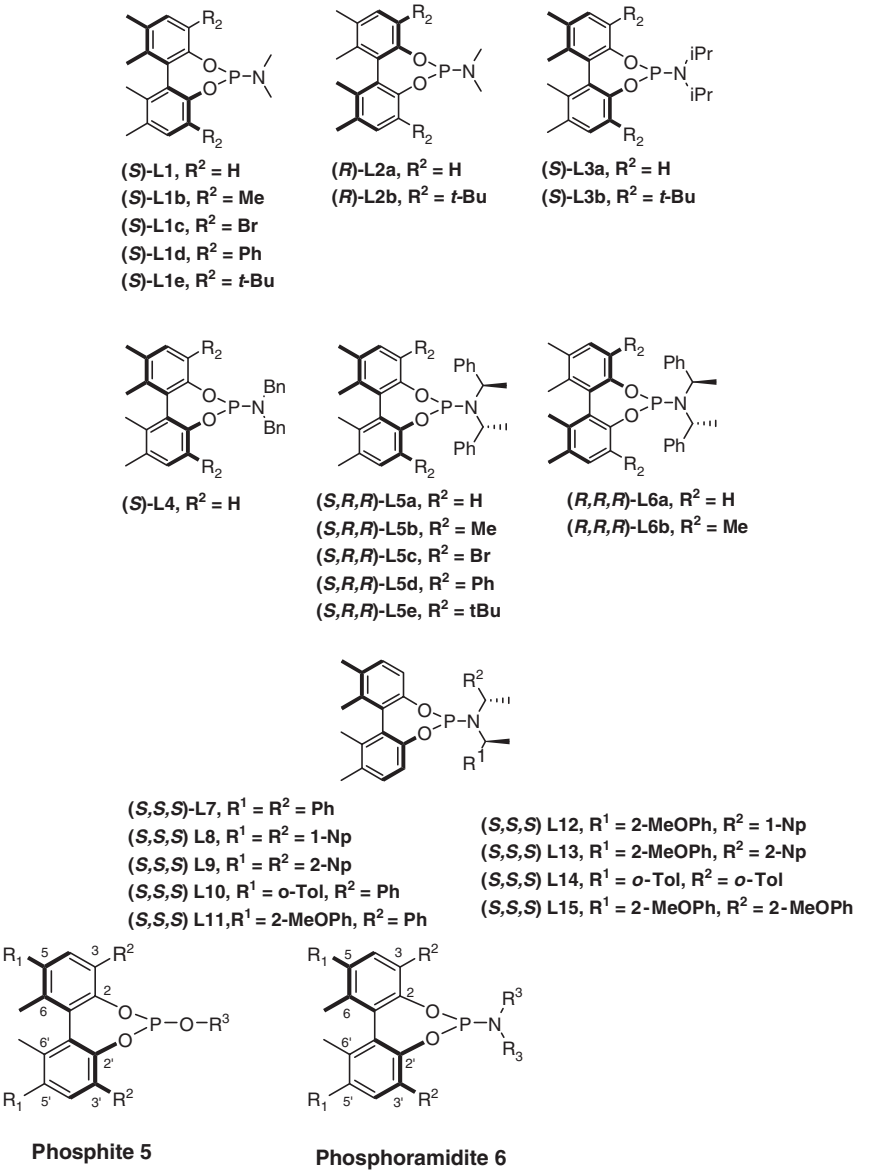


Figure 3. Library of phosphoramidite and phosphite ligands.

ligands has been developed. However, more efficient chiral ligands along this line are clearly needed to achieve excellent enantiopurity and high catalyst efficiency. We describe here the successful application of a library of biphenol-based monophosphite ligands[9] (Figure 3) to the Rh(I)-catalyzed

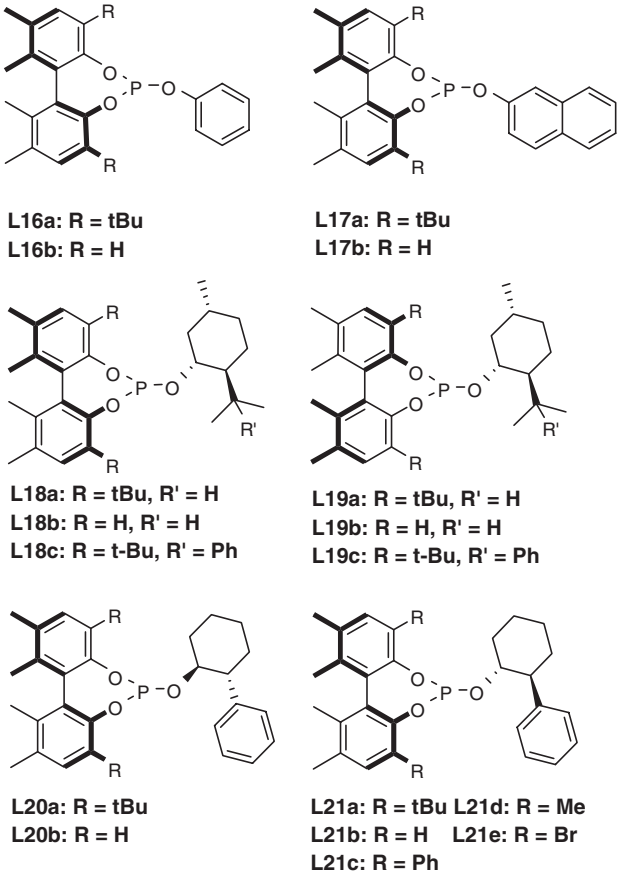
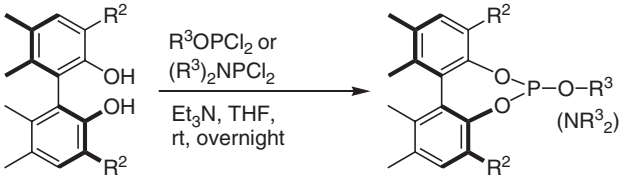


Figure 3. (continued)



Scheme 1. Synthesis of chiral monodentate phosphorus ligands.

asymmetric hydrogenation of dimethyl itaconate, which has achieved excellent enantioselectivity up to 99.6% ee.

First, reactions were carried out using ligands **L16a**–**L21a** and $[Rh(COD)_2]BF_4$ in CH_2Cl_2 at ambient temperature under 6.8 atm of H_2. The catalyst was preformed by stirring 2 equivalents of a chiral ligand with the

TABLE 1. Asymmetric hydrogenation of dimethyl itaconate using $[Rh(COD)_2]BF_4$ with monodentate phosphite ligands[a]

Entry	Ligand	Conv. (%)[b]	% ee[b,c]
1	**L16a**	90	14.0 (*R*)
2	**L16b**	100	96.5 (*S*)
3	**L17a**	97	19.0 (*R*)
4	**L17b**	100	96.4 (*S*)
5	**L18a**	100	25.0 (*R*)
6	**L18b**	100	92.0 (*S*)
7	**L19a**	100	44.0 (*S*)
8	**L19b**	100	93.0 (*R*)
9	**L18c**	3.5	24.3 (*R*)
10	**L19c**	4.3	32.0 (*S*)
11	**L20a**	<1	–
12	**L20b**	<1	–
13	**L21a**	<1	–

[a]The reactions were performed in CH_2Cl_2 at 23°C and 6.8 atm of H_2 for 20 h, [substrate (0.5 mmol, 0.1 M)/$[Rh(COD)_2]BF_4$/ligand = 200:1:2].
[b]Conversion and enantiopurity were determined by chiral GC analysis.
[c]The absolute configuration was determined by comparing the chiral GC spectra with those of authentic samples.

Rh(I) complex in CH_2Cl_2 at ambient temperature under nitrogen. Results are summarized in Table 1.

As Table 1 shows, the Rh-catalysts with ligands **L16b–L19b** (R^2 = H) exhibited excellent enantioselectivity (92–96.5% ee) along with complete conversion (entries 2, 4, 6, and 8). In contrast, Rh-catalyst with ligands bearing a *tert*-butyl group at the 3,3′-positions of the biphenol (**L16a**–**L21a**, **L18c** and **L19c**) exhibited poor to excellent catalytic activity and low to moderate enantioselectivity (entries 1, 3, 5, 7, 9–11 and 13). The introduction of a (−)-menthol as a chiral alkoxy moiety (**L18b** and **L19b**) did not improve the enantioselectivity as compared to that achieved by the use of **L16b** and **L17b**, which contain achiral aryloxy moiety (entries 6 and 8 vs entries 2 and 4). Moreover the diastereoisomeric ligands **L18b** [(*S*)-biphenol] and **L19b** [(*R*)-biphenol] bearing the same (−)-menthol moiety virtually gave the same level of enantioselectivity (entries 6 and 8). Accordingly, it appears that the chiral alkoxy moiety has a little effect on the enantioselectivity of the reaction. In contrast, the substitutions at the 3,3′-positions of the biphenol moiety appear to exert a critical influence on the direction and the extent of the asymmetric induction. Ligands bearing a hydrogen at the 3,3′-positions of the biphenol gave complete conversion of the substrate to the (*S*)-methylsuccinate [(*R*) for **L19b**] with excellent enanti-

oselectivity (92.0–96.5% ee) (entries 2, 4, 6, and 8). The ligands containing *tert*-butyl groups at the 3,3′-positions of the biphenol (**L16a**, **L17a**, **L18a** and **L19a**) showed a reversal in the direction of the asymmetric induction and afforded the (*R*)-methylsuccinate with low to moderate enantioselectivity (14–44% ee) [(*S*) for **L19a**] (entries 1, 3, 5, and 7). Ligands **L18c** and **L19c**, bearing a phenylmenthyloxy group exhibited low conversion and enantioselectivity (entries 9 and 10). Ligands bearing a bulky 2-phenylcyclohexyloxy group (**L20a**, **L20b** and **L21a**) did not show any appreciable activity under the same conditions (entries 11–13).

Next, we switched the Rh-catalyst precursor from $[Rh(COD)_2]BF_4$ to $[Rh(COD)_2]SbF_6$ and carried out the reactions at 50°C under 6.8 atm of H_2 in CH_2Cl_2. The results are summarized in Table 2. As Table 2 shows, under these conditions, the bulky ligands **L18c, L19c, L20a** and **L21a**, that gave poor enantioselectivity and almost no catalytic activities under the previous conditions (Table 1), now achieved complete conversion and excellent enantioselectivity (up to 99.6% ee) (entry 5–12). A remarkable effect of the counter anion of the catalyst on the catalytic activity as well as enantioselectivity was observed. Other Rh(I) catalyst precursors such as $[Rh(COD)_2]ClO_4$ and $[Rh(COD)_2]OTf$, gave a total conversion but with lower enantioselectivity.

However, the remarkable improvement was observed only for the ligands bearing very bulky alkoxy moieties (**L18c, L19c, L20a** and **L21a**). Thus, ligands bearing aryloxy moiety (**L16a** and **L17a**) (entries 1 and 2) or (−)-menthyloxy moiety (**L18a** and **L19a**) did not show any improvements. Nevertheless, the catalytic activity was greatly improved, affording the product in quantitative yield in all cases. The configuration of the resulting product depends solely on the configuration of the biphenol moiety, i.e. (*S*)-biphenol-based ligands yield (*R*)-methylsuccinate while (*R*)-biphenol-based ligands give (*S*)-methylsuccinate. Additionally, ligands **L20a** and **L21a**, both synthesized from the (*S*)-biphenol achieved almost the same enantioselectivity despite the reversed chirality in their 2-phenyl-cyclohexyloxy moiety.

It is also worth mentioning the critical effect of the solvent on the enantioselectivity of the reaction. Reactions in other solvents such as MeOH, THF, EtOAc and $CHCl_3$, gave the desired product in quantitative yield, but with no enantioselectivity. It appears that CH_2Cl_2 and $ClCH_2CH_2Cl$ are appropriate solvents for this asymmetric hydrogenation and the use of $ClCH_2CH_2Cl$ has achieved the best enantioselectivity in all cases examined. A similar observation was reported for the reaction with BINOL-based phosphoramidite ligands.[3]

In order to further examine the effect of substituents at the 3,3′-positions on enantioselectivity, we introduced different substituents other than *tert*-butyl group (**L21a**) at these positions in the **L21** ligand series (Table 2, entries 13–16). Thus, bromine, methyl and phenyl groups were introduced at the

TABLE 2. Asymmetric hydrogenation of dimethyl itaconate using $[Rh(COD)_2]SbF_6$ with monodentate phosphite ligands.[a]

Entry	Ligand	Solvent	Conv[b] (%)	% ee [b,c]
1	**L16a**	CH_2Cl_2	100	16.4 (*R*)
2	**L17a**	CH_2Cl_2	100	22.5 (*R*)
3	**L18a**	CH_2Cl_2	100	14.5 (*R*)
4	**L19a**	CH_2Cl_2	100	9.3 (*S*)
5	**L18c**	CH_2Cl_2	100	94.4 (*R*)
6	**L18c**	$ClCH_2CH_2Cl$	100	98.9 (*R*)
7	**L19c**	CH_2Cl_2	100	97.6 (*S*)
8	**L19c**	$ClCH_2CH_2Cl$	100	98.7 (*S*)
9	**L20a**	CH_2Cl_2	100	97.8 (*R*)
10	**L20a**	$ClCH_2CH_2Cl$	100	99.6 (*R*)
11	**L21a**	CH_2Cl_2	100	99.0 (*R*)
12	**L21a**	$ClCH_2CH_2Cl$	100	99.1 (*R*)
13	**L21b**	CH_2Cl_2	81	2.7 (*S*)
14	**L21c**	CH_2Cl_2	100	97.8 (*R*)
15	**L21d**	CH_2Cl_2	100	76.9 (*R*)
16	**L21e**	CH_2Cl_2	100	97.1 (*R*)

[a]The reaction was performed at 50°C and 6.8 atm of H_2 for 20 h [substrate (0.5 mmol, 0.1 M)/$[Rh(COD)_2]SbF_6$/ligand = 200:1:2]. [b]Conversion and enantiopurity were determined by GC on a Supelco Beta Dex-225 column. The absolute configuration was determined by comparing chiral GC spectra with those of authentic samples.

3,3′-positions of the biphenol moiety of **L21** to give ligands **L21c–e**. Results are listed in Table 2 (entries 13–16). As Table 2 shows, the size of the R^2 substituent has a critical effect on the selectivity of the reaction. Thus, the enantioselectivity decreases in the order *t*-Bu > Ph > Br > Me > H, which is in accordance with the decrease in the size of this substituent. In the case of ligand **L21b** (R^2 = H), a marked decrease in enantioselectivity was observed and the opposite enantiomer was obtained with only 2.7% ee.

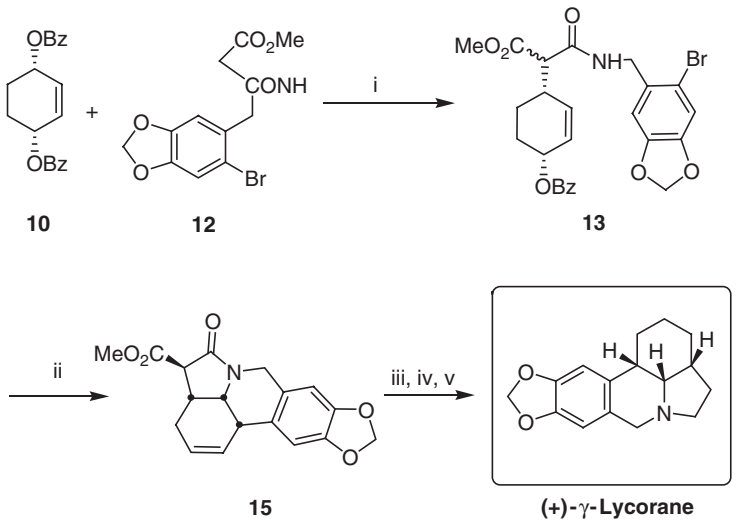
4. Total Synthesis of Enantiopure (+)-γ-Lycorane Using Palladium-Catalyzed Asymmetric Allylic Alkylation

Catalytic asymmetric allylic substitution provides one of the most powerful methods for the stereo-controlled formation of carbon–carbon bonds and carbon-heteroatom bonds. This reaction now serves as a reliable method for the synthesis of enantiopure natural and unnatural products.[43,44] Extensive studies have been performed to address mechanistic issues relevant to the regio- and stereoselectivity of this reaction.[43–47] Trost et al. pioneered the asymmetric allylic alkylation with unique C_2-symmetric chiral diphosphine

ligands bearing two bis(diarylphosphino)benzoic acid units that allowed to achieve excellent enantioselectivity in various systems.[45,46,48] Catalytic asymmetric allylic substitution reactions have found a wide range of applications in organic syntheses, to date, along with the design and development of a variety of chiral ligands for these reactions.

Application of chiral monodentate phosphorus ligands to the Ir-catalyzed allylic substitution, which generally leads to branched products with excellent regioselectivity, is well documented.[49] However, the corresponding Pd-catalyzed reaction with chiral monodentate phosphorus ligands has only been poorly explored in spite of the fact that palladium is generally the metal of choice for asymmetric allylic substitution reactions.[34,50,51] Accordingly, we set out to explore the use of novel monodentate phosphoramidite ligands in the Pd-catalyzed asymmetric allylic alkylation, especially for the asymmetric synthesis of pentacyclic alkaloid (+)-γ-lycorane.

(+)-γ-Lycorane isolated from the plants of *Amaryllidacae* family belongs to a class of alkaloids that exhibit a variety of biological activities.[52] Due to its unique pentacyclic structure (+)-γ-lycorane has inspired many synthetic chemists to develop a number of innovative approaches towards its total synthesis.[53–58] In 1995, Mori and coworkers reported the first asymmetric total synthesis of this alkaloid (Scheme 2).[59]



Scheme 2. Mori's Synthesis of (+)-γ-lycorane. Reagents and conditions: (i) Pd(OAc)2 (5 mol%), (S)-BINAPO (10 mol%), 12 (2.6 eq.), LDA (2.6 eq.), THF/CH3CN, 0°C, 1 h; (ii) Pd(OAc)/2/dppb, NaH, DMF, 50°C, 3 h then EtiPr2N, 100°C, 5 h; (iii) NaCl (1 eq.), DMSO/H_2O; (iv) Pd/C, H_2, MeOH; (v). LAH, reflux, 1 h.

This synthesis featured a Pd-catalyzed asymmetric allylic alkylation as the key step wherein sequential allylic amination and intramolecular Heck reaction led to the pentacyclic system **15** (Scheme 2). However, the best enantioselectivity achieved in the key step using (*S*)-BINAPO and 2.6 equivalent of **12** and LDA was 54% ee, giving **13** in 30% yield. The yield and enantiopurity of **13** were dependent on the amount of **12** and LDA used. Thus, 1.1 equivalents of **12** and LDA provided **13** with 40% ee in 66% yield. Compound **13** (40% ee) was then used to complete the five-step total synthesis of (+)-γ-lycorane in 23% overall yield.

Since this short total synthesis appeared to have a plenty of room for improvements, we revisited this process by applying our library of monophosphoramidite ligands for optimization of enantioselectivity and chemical yields. First, a preliminary study was performed on the desymmetrization of *meso*-diester **10** with dimethyl malonate (Table 3).[60]

As Table 3 shows, a clear increase in enantioselectivity is observed as the size of the amine moiety of the ligand increases (entries 1–4). Thus, **L2a** afforded **11** with 28.7% ee while 81.3% ee was obtained with **L6a**. It is noteworthy that ligands bearing a (*S*)-biphenol moiety gave the (+)-enantiomer of **11** as the major product, while (*R*)-biphenol-based ligands afforded (−)-**11** as the major product, i.e. the axial chirality of the biphenol moiety controls the direction of enantiodiscrimination of the two benzoate leaving groups. Introduction of methyl groups at the 3,3′-positions of the biphenyl moiety of **L6b** has a detrimental effect on the enantioselectivity as well as the conversion of the reaction (50% conv., 10.8% ee, entry 5). These results served as the starting point for application of our ligands to the key step of the total synthesis of (+)-γ-lycorane.

Since ligand **L6a** gave the most promising results in the model study (Table 3) the efficacy of this ligand was evaluated in the asymmetric allylic

TABLE 3. Pd-catalyzed asymmetric allylic alkylation – desymmetrization of meso-diester **10** with dimethyl malonate[60]

Entry	Ligand	Conv[a] (%)	% ee[b]
1	**L2a**	80	28.7 (−)
2	**L3a**	82	48.1 (+)
3	**L5a**	70	68.4 (+)
4	**L6a**	82	81.3 (−)
5	**L6b**	50	10.8 (−)

[a]Determined by ^{1}H NMR. [b]Determined by HPLC using a Daicel Chiralpak AD column.

TABLE 4. Pd-catalyzed asymmetric allylic alkylation – desymmetrization of **10** with **12**[a]

(i) $[Pd(allyl)Cl]_2$, dppb, LDA, CH_3CN-THF, −50°C ~ rt, 2.5 h. (ii) NaCl, DMSO-H_2O, 175°C, 2.5 h.

Entry	Ligand	**13** (%)[b]	**15** (%)[b]	% ee[c]
1	**L6a**	93	6	86.2
2	**L6a**[d]	27	–	92.6
3	**L7**[e]	63	31	89.5
4	**L8**	Conv. <5%	–	–
5	**L9**	92	7	85.5
6	**L10**	85	13	83.0
7	**L11**[f]	76	19	99.7
8	**L12**	Conv. <5%	–	–
9	**L13**[f]	83	16	99.4
10	**L14**	Conv. 0%	–	–
11	**L15**	Conv. <5%	–	–

[a] Reactions were run with 100 mg (0.31 mmol) of **10**, $[Pd(allyl)Cl]_2$ (2 mol%), a ligand (8 mol%), **12** (1.2 equivalents), LDA (1.2 equivalents) in THF at −60°C for 15 h unless otherwise noted. [b]Isolated yield. [c]Estimated based on enantiopurity of **10** determined by chiral HPLC analysis using Daicel Chiralpak AD-RH column. [d]Reaction run with 2.6 equivalents of **12**, reaction completed in 20 min. [e]Reaction run with 2 equivalents of **12**. [f]Reaction time was 8 h.

alkylation/desymmetrization of **10** with nucleophile **12** for the synthesis of enantiopure (+)-γ-lycorane. Results are summarized in Table 4.

Enantioselectivity of the reaction was determined by converting **13** to **14**. We also examined the effects of the amount of **12** and LDA on the reaction. The reaction with 2.0 and 2.6 equiv. of **12** and LDA gave **13** with 89.5% ee (63% yield) and 92.6% ee (27 % yield), respectively (entries 2 and 3). [Note: **L7** is the enantiomer of **L6a**.] The results indicate that the use of excess amounts of **12** and LDA increases the enantioselectivity of the reaction. However this increase is accompanied by a significant decrease in the yield of **13**.

We found that the observed decrease in the yield of **13** was associated with the formation of dialkylated product **15**. This side product is obviously coming from the second allylic alkylation reaction of **13** with **12** and its amount naturally increases on using excess of **12** and LDA. We believe that enantiomer-selective kinetic resolution by the chiral Pd-catalyst is taking place in the second allylic alkylation of **13** with **12**, giving **15**. A proposed mechanism is shown in Figure 4.

It is reasonable to hypothesize that the minor enantiomer of **13** that results from the first asymmetric allylic alkylation, *ent*-**13** reacts with the chiral Pd complex much faster than **13** to form the corresponding π-allylic

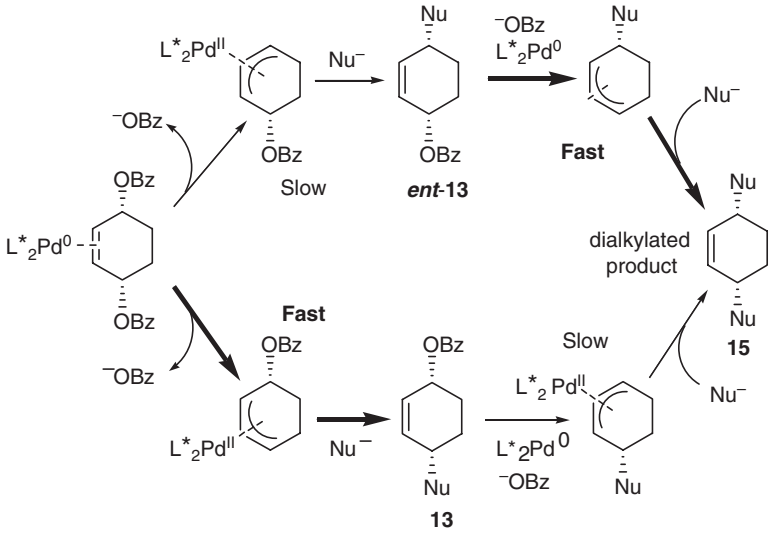


Figure 4. Proposed mechanism for the formation of the dialkylated product **15**.

Pd-complex, which reacts with **13** to afford the dialkylated product **15**. This is because the remaining benzoate group in *ent*-**13** is the preferred leaving group for the chiral Pd-catalyst. Accordingly, enrichment of **13** may occur through selective conversion of *ent*-**13** to **15**, but a decrease in the yield of **13** would be inevitably accompanied.

Although it was already a remarkable improvement that **13** was obtained in 93% yield and 86.2% ee as compared with Mori's original work (40% ee in 66% yield, or 54% ee in 30% yield), we strongly felt that more improvements could be done through the systematic optimization of ligand **L7** (*S,S,S*), which provides (+)-**13**, i.e. the key intermediate for the total synthesis of (+)-γ-lycorane. Since the amine moiety was shown to have a substantial effect on the enantioselectivity (see Table 4), similar ligands bearing different C_2-symmetric, *pseudo*-C_2-symmetric and non-symmetrical chiral *N,N*-bis(1-arylethyl)amines were synthesized and evaluated (Figure 3).

Alexakis and co-workers recently reported the markedly favorable effects of chiral *N,N*-bis(1-arylethyl)amine substituents on the enantioselectivity as well as reaction rate in their Ir-catalyzed asymmetric allylic substitution.[61] Thus, we set out to examine the effect of the *ortho* substitution on our biphenol-based ligands/Pd system. We synthesized a series of chiral *N,N*-bis(1-arylethyl)amines based on a combination of different aryl groups, i.e. phenyl, *o*-tolyl, *o*-methoxyphenyl, 1-naphtyl and 2-naphtyl groups. These (*S,S,S*) ligands were then applied to the reaction using 1.2 equivalents of LDA in THF at −60°C for 15 h. Results are summarized in Table 4.

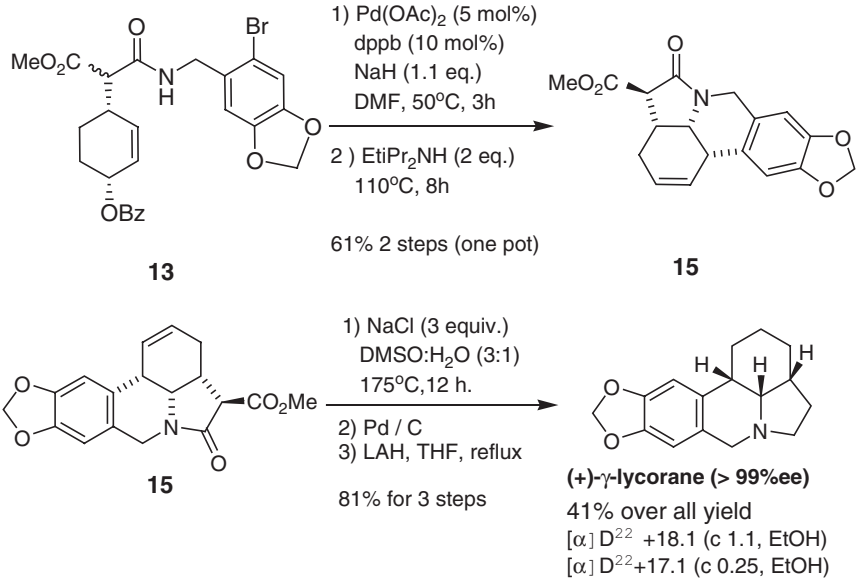
As Table 4 shows, a very interesting and rather unanticipated substituent effect of the aryl groups of the amine moiety on the enantioselectivity as well as catalytic activity is observed. First of all, the markedly contrasting results for the use of **L8** ($R^1 = R^2$ = 1-Np) and **L9** ($R^1 = R^2$ = 2-Np) is worth mentioning (entries 4 and 5). The result of **L9** (85.5% ee) is similar to that for **L7** (entry 3), while the reaction with **L8** almost did not proceed under the same conditions and no improvement was observed even when forcing the reaction at room temperature. The use of 1-naphthyl group seems to be detrimental for the Pd-catalyst activity. Thus, the reaction using **L12** (R^1 = 1-Np, R^2 = 2-MeO-Ph) virtually failed (entry 10). To our surprise, ligands **L14** and **L15** bearing C_2-symmetric *N,N*-bis(1-arylethyl)amine moieties behaved very poorly resulting in no or <5% conversion (entries 8 and 9, respectively), while **L10** (R^1 = Ph, R^2 = 2-tolyl) gave 83.0% ee (entry 6). Thus, this reaction was found to be very sensitive to the bulkiness and arrangements of the aryl moiety at the coordination site.

A breakthrough in the enantioselectivity was achieved with ligands **L11** (R^1 = Ph, R^2 = 2-MeO-Ph) and **L13** (R^1 = 2-Np, R^2 = 2-MeO-Ph), bearing non-symmetrical *N,N*-bis(1-arylethyl)amine moieties wherein one of the aryl groups is a 2-MeO-Ph. The reactions using **L11** and **L13** gave (+)-**13** with 99.7% ee (76% yield) and 99.4% ee (83% yield), respectively (entries 7 and 11). Both reactions had 100% conversion in 8 h. It appears that 2-methoxyphenyl group in the non-symmetrical *N,N*-bis(1-arylethyl)amine moiety exerts a profound effect on the enantioselectivity and the reaction rate. It is possible to hypothesize that the oxygen of the 2-methoxyphenyl moiety in ligands **L11** and **L13** interacts with the Pd metal to fix the orientation of the phenyl ring, which has a crucial effect on the enantio-discrimination (desymmetrization) of the two benzoate groups in *meso*-**10**.

Since the use of **L13** gave **13** in good yield and excellent enantioselectivity, the synthesis of enantiopure (+)-γ-lycorane was carried out to its completion. A tandem allylic amination – intramolecular Heck reaction afforded the pentacyclic oxo-lycorane **16** in 61% yield. **16** was then subjected to sequential demethoxycarbonylation, hydrogenation and reduction with $LiAlH_4$ to give the target (+)-γ-lycorane (>99% ee) in 41% overall yield (six steps) from **10** (Scheme 3).

5. Rhodium-Catalyzed Hydroformylation of Allyl Cyanide

Hydroformylation of terminal olefins has been extensively investigated with a particular attention on addressing the issues of the chemo-, regio- and stereoselectivity associated with this reaction. The selective formation of linear aldehydes from terminal olefins can be carried out with very high efficiency by virtue of well-defined metal catalysts/ligands systems. However,



Scheme 3. Completion of the total synthesis of (+)-γ-lycorane.

the selective formation of the branched aldehydes, except for styrene and 1-alkenes bearing an electron-withdrawing substituent, still remains a challenge, especially in the case of aliphatic olefins as it faces the regio- and stereoselectivity issues.

The asymmetric hydroformylation of allyl cyanide **17** offers an attractive route for obtaining chiral 2-methyl-4-aminobutanol. This intermediate is a key building block for the synthesis of TAK-637, a drug candidate for the treatment of urinary incontinence. de Vries and co-workers reported the asymmetric hydroformylation of allyl cyanide using (*R,S*)-BINAPHOS as the ligand, which afforded the aldehyde **b-18** with 66% ee in a 72:28 branched-to-linear ratio.[28] BINOL-based phosphoramidite ligands have also been used in this reaction, but the best result was to give **b-18** in a 76:24 branched-to-linear ratio and only 18% ee.[28] Moreover, the reaction rate was low with only 31–45% conversion when the reaction was carried out in toluene at 60°C under 30 atm of CO and H_2 (1:1). Accordingly, it is apparent that this process is useful but quite demanding and it is necessary to improve the regioselectivity and enantioselectivity of this process to be practical. Thus, we selected allyl cyanide as the substrate to evaluate the efficacy of our phosphoramidite ligands.

First, the evaluation of the efficacy of the phosphoramidite ligands was conducted at 60°C in benzene under 40 atm of CO and H_2 (1:1) for 5 h.

Results are summarized in Table 5. In sharp contrast with the BINOL-based ligands, the biphenol-based ligands completely converted allyl cyanide to aldehyde **18** within 5 h as shown in Table 5. It is also worth mentioning that no hydrogenated product was formed. The best result under these conditions was obtained with ligand **L2b** bearing bulky *tert*-butyl groups at the 3,3′-positions, which gave aldehyde **18** in a 92:8 branched-to-linear ratio and 69% ee (entry 5). Results shown in Table 5 also indicate dramatic substituent effects on the regio- and enantioselectivity of the reaction. Thus, ligands bearing smaller substituents, i.e. H, Me, Br or Ph at the 3,3′-positions of the biphenol, gave lower branched-to-linear ratio (80:20–84:16) and significantly lower enantioselectivity (2–14% ee) (entries 1–4). In addition, introduction of a large amino group (i.e. diisopropylamino) to the phosphorus (**L3b**) is detrimental to the enantioselectivity (entry 6).

After initial screening to select the most efficient ligand **L2b** from our library, reaction variables were investigated. To our surprise, only minor difference was observed when the ligand/Rh ratio was changed from 1:1

TABLE 5. Rh(I)-catalyzed asymmetric hydroformylation of allyl cyanide

Entry	Ligand	L/Rh	Solvent	Temp (°C)	Time (h)	Conv. (%)[a]	b/l[b]	% ee[c]
1	**L2a**	3	C_6H_6	60	5	100	80:20	5 (*S*)
2	**L1b**	3	C_6H_6	60	5	100	85:15	14 (*R*)
3	**L1c**	3	C_6H_6	60	5	100	83:13	2 (*R*)
4	**L1d**	3	C_6H_6	60	5	100	84:16	10 (*R*)
5	**L2b**	3	C_6H_6	60	5	100	92:8	69 (*S*)
6	**L3b**	3	C_6H_6	60	5	100	81:19	0
7	**L2b**	1	C_6H_6	60	5	100	90:10	61 (*S*)
8	**L2b**	2	C_6H_6	60	5	100	91:9	65 (*S*)
9	**L2b**	3	C_6H_6	60	5	100	92:8	68 (*S*)
10	**L2b**	4	C_6H_6	60	5	100	93:7	65 (*S*)
11	**L2b**	3	Toluene	60	5	100	90:10	67 (*S*)
12	**L2b**	3	THF	60	5	100	86:14	58 (*S*)
13	**L2b**	3	CH_2Cl_2	60	5	100	89:11	60 (*S*)
14	**L2b**	3	CH_3OH	60	5	100	91:9	49 (*S*)
15	**L2b**	3	Toluene	50	5	100	92:8	76 (*S*)
16	**L2b**	3	Toluene	40	5	89	93:7	78 (*S*)
17	**L2b**	3	Toluene	40	23	100	93:7	78 (*S*)
18	**L2b**	3	Toluene	30	47	100	95:5	79 (*S*)
19	**L2b**	3	Toluene	25	74	100	96:4	80 (*S*)

Reactions were performed in a 1 mmol scale with [Rh(acac)CO_2] (0.5 mol%) and the indicated amounts of ligand in a degassed solvent (5 mL). [a] The conversion was determined by ^{1}H NMR analysis. [b] The branched-to-linear ratio was determined by ^{1}H NMR analysis. [c]Enantiopurity was determined by converting the aldehyde to the corresponding aldimine of (*S*)-methylbenzylamine and subjected to ^{1}H NMR analysis. Absolute configuration was determined by converting **b-17** to 4-dihydrofuran-2-one, followed by the measurement of its specific optical rotation.

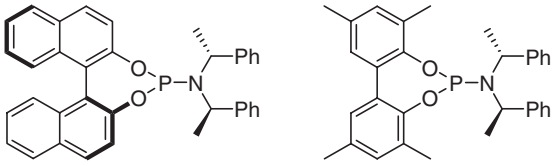
to 4:1. The best enantioselectivity was achieved with a 3:1 ratio. Thus, keeping the 3:1 ligand to Rh ratio, we examined the effect of the solvent on the selectivity (entry 11–14). All reactions performed in THF, CH_2Cl_2, MeOH or toluene gave the aldehydes **18** in 100% conversion with no traces of hydrogenated product. The use of THF and CH_2Cl_2 afforded **18** with lower region- and enantioselectivity, while the reaction in toluene gave similar regio-, and stereoselectivity as that in benzene (90:10 b:l, 67% ee). Thus, toluene was selected as the solvent for further optimization. Finally, the effect of reaction temperature on the regio- and enantioselectivity was examined. As anticipated, the lower temperature exhibited a favorable effect on the selectivity (entries 11 vs 15–19). The best result was obtained when the reaction was performed at 25°C, giving **18** with a 96:4 branched: to:linear ratio and 80% ee (entry 18). This clearly demonstrates substantial improvements from those attained by using (*R,S*)-BINAPHOS and BINOL-based ligands.

6. Copper-Catalyzed Conjugate Addition of Diethylzinc to Cycloalkenones

Asymmetric conjugate addition of organometallic reagents to α,β-unsaturated carbonyl is an attractive process for the enantioselective formation of carbon-carbon bonds. Conjugate addition of dialkylzinc reagents to α,β-unsaturated ketones has been extensively studied in the last several years. Feringa and coworkers developed an efficient chiral BINOL-based phosphoramidite ligand bearing (*R,R*)-bis(1-phenylethyl)amine moiety on the phosphorus (**L22**, Figure 4).[62] Alexakis et al. developed a phosphoramidite ligand **L23** derived from racemic atropisomeric biphenol and (*R,R*)-bis(1-phenylethyl)amine.[6,63]

We evaluated the efficacy of our phosphoramidite ligands (Figure 2) in the $Cu(OTf)_2$-catalyzed conjugate addition of diethylzinc to cyclohexenone (**19**), cycloheptenone (**21**) and cyclopentenone (**23**).

First, Cu-catalyzed conjugate addition (Figure 5) of diethylzinc to 2-cyclohexanone was investigated. Results are summarized in Table 6. As Table 6 shows, significant influence of the substituents (R^2) at the 3,3′-positions of the biphenol moiety on the enantioselectivity is observed. Thus, in the case of ligands bearing a dimethylamine moiety (**L2a** and **L1b–e**), the enantioselectivity decreases as the bulkiness of the R^2 substituent increases in the order H, Me, Br, Ph, and *t*-Bu (entries 1–5). When a diisopropylamine moiety is introduced to the phosphorus, the substituent effect at the 3,3′-positions becomes more drastic, i.e. ligand **L3a** (R^2 = H) gave **20** with 57.7% ee (entry 6) while ligand **L3b** (R^2 = *t*-Bu) afforded **20** with only 7.9% ee (entry 7). In addition, the use of (*R,R*)-bis(1-phenylethyl)amine (**L5** series), brings about a dramatic increase in the enantioselectivity of the



L22 **L23**

Figure 5. Representative phosphoramidite ligands used for Cu-catalyzed conjugate addition of R_2Zn.

TABLE 6. Cu-catalyzed addition of diethylzinc to 2-cyclohexenone **19**[a]

Entry	Ligand	Solvent	Temp. (°C)	% ee[b,c]
1	**L2a**	Toluene	23	52.7 (*R*)
2	**L1b**	Toluene	23	46.0 (*S*)
3	**L1c**	Toluene	23	27.4 (*S*)
4	**L1d**	Toluene	23	30.4 (*S*)
5	**L1e**	Toluene	23	23.5 (*R*)
6	**L3a**	Toluene	23	57.7 (*S*)
7	**L3b**	Toluene	23	7.9 (*S*)
8	**L5a**	Toluene	23	94.2 (*S*)
9	**L5b**	Toluene	23	97.3 (*S*)
10	**L5c**	Toluene	23	93.2 (*S*)
11	**L5d**	Toluene	23	68.7 (*S*)
12	**L22**	Toluene	23	95.5 (*S*)
13	**L5b**	Toluene	−30	98.4 (*S*)
14	**L5b**	Et_2O	−30	98.8 (*S*)

[a]The reactions were carried out in 1 mmol scale in a solvent (5 mL) under nitrogen using Miniblock XT reactor (reactions at room temperature). Conversion was determined by ^{1}H NMR and GC analysis. All reactions gave complete conversion in 4 h. [b]The enantiopurity was determined by GC analysis using a Supelco Beta Dex-225 column. [c]The absolute configuration was determined by GC analysis in comparison with authentic samples.

reaction (93.2–97.3% ee) (entries 8–10). However, when R^2 is a phenyl group (**L5d**), the enantioselectivity drops to 68.7% ee (entry 11.)

Further optimization of the reaction conditions was carried out using the best ligand **L5b**. For comparison purposes, the reaction using BINOL-based ligand **L22** was also carried out under the same reaction conditions, which gave **20** with 95.5% ee (entry 12). Decreasing the reaction temperature to −30°C improved the enantioselectivity (98.4% ee, entry 13) and at last,

TABLE 7. Cu-catalyzed addition of diethylzinc to 2-cycloheptenone **21**[a]

Entry	Ligand	Temp.(°C)	Conv. (%)	% ee[b,c]
1	**L5a**	23	100	91.9 (*S*)
2	**L5b**	23	100	89.4 (*S*)
3	**L5c**	23	99	81.5 (*S*)
4	**L5d**	23	48	59.6 (*S*)
5	**L5a**	−30	100	95.3 (*S*)
6	**L5b**	−30	100	97.5 (*S*)
7	**L22**	−30	100	95.4 (*S*)

[a,b,c] See footnote of Table 6

changing the solvent to Et_2O further increased the enantioselectivity to 98.8% ee (entry 14).

In a similar manner, the Cu-catalyzed conjugate addition of diethylzinc to cycloheptenone **21** was performed with the same set of ligands, i.e. **L5a–d**. Results are summarized in Table 7.

As Table 7 shows, the substituent R^2 at the 3,3′-positions of the biphenol also exerts a dramatic effect on the enantioselectivity and the reaction rate (entries 1–4). The enantioselectivity decreases from 91.9% ee to 59.6% ee (entries 1–4) as the size of R^2 increases (from H to Ph). Interestingly, the most efficient ligand for this reaction at 23°C is **L5a**, while the best ligand for 2-cyclohexanone is **L5b**. The conversion of the reaction is also dependent on the R^2 substituent since it drops from 100% in most cases to only 48% with ligand **L5d** (entry 4). When the reaction was performed at −30°C with ligands **L5a** and **b**, the enantioselectivity increased to 95.3% and 97.5% ee, respectively (entries 5 and 6). However, a crossover in ligand efficiency is observed at this temperature, i.e. **L5b** gives higher enantioselectivity (97.5% ee) than **L5a** (95.3% ee). This observation suggests a larger entropic term for ligand **L5b** as compared to ligand **L5a** in the enantioselectivity-determining step of the reaction. As a comparison, the reaction with BINOL-based ligand **L22** gave **22** with 95.4% ee under the same reaction conditions.

The same set of ligands was evaluated for their efficacy in the reaction of cyclopentenone **23** with diethylzinc. It has been shown that this substrate is challenging for achieving high enantioselectivity as compared to 2-cyclohexenone with a few exceptions.[16,64] We carried out the $Cu(OTf)_2$-catalyzed reaction under the optimized conditions found for the reaction of 2-cyclohexenone. Results are shown in Table 8.

As Table 8 shows, enantioselectivity achieved in this reaction is significantly lower than that obtained with cyclohexenone (**19**) and cycloheptenone (**21**). The best result so far obtained is with ligand **L5b** (52% ee, entry 2). The ligand bearing a phenyl group as R^2, gave 46% ee (entry 4). In comparison,

TABLE 8. Cu-catalyzed addition of diethylzinc to 2-cyclopentenone **23**[a]

Entry	Ligand	Temp (°C)	Conv (%)	% ee[b,c]
1	**L5a**	−30	100	29 (*S*)
2	**L5b**	−30	100	52 (*S*)
3	**L5c**	−30	100	8 (*S*)
4	**L5d**	−30	100	46 (*S*)
5	**L22**	−30	100	15 (*S*)

[a,b,c] See footnote of Table 6.

the BINOL-based ligand **L22** could only achieve a moderate 15% ee under the same reaction conditions. Although the enantioselectivity attained to date is far from satisfactory, we believe that these results demonstrate again the merit of the fine-tuning capability of the biphenol-based phosphoramidite ligands to obtain clues for achieving high enantioselectivity in this reaction.

7. Asymmetric Conjugate Addition of Diethylzinc to Nitroalkenes

Copper-catalyzed dialkylzinc addition to nitroalkenes provides a useful method for the synthesis of a variety of optically active synthetic building blocks bearing nitrogen-functional groups, e.g. amines, amino alcohols, amino ethers, β-amino acids, etc.[65,66] Accordingly, this reaction has been extensively studied in recent years with the development of chiral mono dentate phosphorus ligands.[16,18,21,67–72] Most notably, Feringa[2,66,73] and Alexakis[63] have developed chiral monodentate phosphoramidite ligands for this reaction, and their best ligands are **L22** and **L23**, respectively.

However, the scope of this reaction is still very limited in terms of substrate structures and dialkylzinc species. The enantioselectivity of this reaction has been modest to fairly good except for only a few particular types of substrates.[16,63,73] In particular, the reaction of dialkylzinc with aromatic nitroalkenes still remains challenging, even using **L22** (up to 69% ee) or **L23** (82% ee).[63,68,72,73]

Thus, we have evaluated the efficacy of our monophosphoramidite ligands in the Cu-catalyzed conjugate addition of diethylzinc to *trans*-β-nitrostyrene and its derivatives. First, a preliminary screening of effective ligands was performed using *trans*-β-nitrostyrene as the substrate in order to establish a possible structure-efficiency relationship. Reactions of *trans*-β-nitrostyrene were carried out using $Cu(OTf)_2$ with a ligand (**L5a–d** or **L6b**) as the catalyst at −45°C in toluene, which give **26a** as the product. Results are summarized in Table 9.

TABLE 9. Conjugate addition of diethyzinc to **25**[a]

Entry	Temp (°C)	Ligand	Conv (%)	% ee[b]
1	−45	**L5a**	50	0
2	−45	**L5b**	100	47 (*R*)
3	−45	**L5c**	100	15 (*R*)
4	−45	**L5d**	100	31 (*R*)
5	−55	**L5b**	100	67 (*R*)
6	−65	**L5b**	100	94 (*R*)
7	−65	**L6b**	61	70 (*R*)

[a]The reaction was performed with 0.5 mmol of **24**, $Cu(OTf)_2$ (1 mol%), and a ligand (2 mol%) in 5 mL of toluene. All reactions were run for 6 h unless otherwise noted. All reactions completed in 6 h except for entries 1 and 7.
[b]Determined by Chiral GC.

As Table 9 shows, ligand **L5b**, bearing methyl groups at the 3,3′-positions, provided the best enantioselectivity (47% ee, 100% conv.) (entry 2). The use of ligands with groups bulkier than methyl as R^2, i.e. **L5c** and **d**, resulted in lower enantioselectivity (entries 3 and 4). The $Cu(OTf)_2$/ligand **L5a** complex gave a moderate conversion and no enantioselectivity (50% conv., 0% ee). On the basis of the screening results, ligand **L5b** was selected for further optimization.

Next, the effect of reaction temperature on the catalyst activity and enantioselectivity was examined. Then, a significant increase in enantioselectivity was observed as the reaction temperature was lowered to −55°C (67% ee, entry 5) and to −65°C (94% ee, entry 6). In both cases, the reactions reached complete conversion. However, the reaction at −75°C slowed considerably and the enantioselectivity did not improve. Thus, the optimum temperature for this reaction appears to be −65°C.

It has been shown that the optimal reaction temperature for **L22**-$Cu(OTf)_2$ catalyst is −45°C and that for **L23**-$Cu(OTf)_2$ catalyst is −30°C (both in toluene).[63,73] Also, the enantioselectivity did not increase and the reaction rate dropped significantly at lower temperatures.[63,73]

Accordingly, **L5b**-$Cu(OTf)_2$ clearly exhibits a higher catalytic activity than those reported by Feringa (**L22**) and Alexakis (**L23**) since the reaction can be carried out at lower temperatures to increase the enantioselectivity to 94% ee. It is worth mentioning that that there is a clear matching/mismatching of the axial chirality and the center chirality in these ligands. For example, **L5b** (*S,R,R*) gave better enantioselectivity than its (*R,R,R*) counterpart **L6b** (entries 6 and 7).

In order to see the scope of the reaction catalyzed by **L5b**-$Cu(OTf)_2$, the reactions of several aromatic and heteroaromatic substrates were carried out under the same reaction conditions as those shown in Table 9 (−65°C,

toluene, 6 h). Results are summarized in Table 10. It should be noted that previously reported enantioselectivity obtained with these substrates using a variety of chiral ligands, were only ranging from 1% to 75% ee.[68,73]

As Table 10 shows, these reactions have achieved much higher enantioselectivity to give **26** with up to 99% ee. Results show a clear electronic effect of the aryl substitution on the enantioselectivity. An electron-donating group at the *para* position of the phenyl moiety (**25b** and **c**) increases enantioselectivity (98% ee, entry 1; 99% ee, entry 2) as compared to 94% ee obtained for parent *trans*-β-nitrostyrene **25a**. However, electron-withdrawing groups such as *para*-fluoro and *para*-trifluoromethyl groups (**25f** and **i**) decrease enantio selectivity (91% ee, entry 5; 77% ee, entry 8).

In addition, the steric effect on the enantioselectivity is clearly observed. Enantioselectivity decreases in the order *para* > *meta* > *ortho* substitution as a substituent of the phenyl group is placed in those positions, regardless of its electronic nature. With *ortho*-substituted phenyl moieties, the enantioselectivity is substantially lower (entries 2–4 and 5–7). An exception to these results is the *trans-β-ortho*-CF_3-styrene (**25j**), which gave a higher selectivity (88% ee, entry 9) than the *para*-isomer **25i** (77% ee, entry 8). A possible explanation for this result is the non-coplanar structure of the substrate **25j** due to the bulkiness of the CF_3 group, which cancels the electron-withdrawing effect of this group. The observed electronic and steric effects provide significant information for the mechanism of this process.

TABLE 10. Conjugate addition of diethyzinc to nitroalkenes[a]

Entry	**Substrate 14**	Ligand	Conv (%)	**25**	% ee
1	**25b** (R = *p*–Me–C_6H_4)	**L5b**	100	26b	98
2	**25c** (R = *p*–MeO–C_6H_4)	**L5b**	100	26c	99
3	**25d** (R = *m*–MeO–C_6H_4)	**L5b**	100	26d	84
4	**25e** (R = *o*–MeO–C_6H_4)	**L5b**	100	26e	67
5	**25f** (R = *p*–F–C_6H_4)	**L5b**	100	26f	91
6	**25g** (R = *m*–F–C_6H_4)	**L5b**	100	26g	88
7	**25h** (R = *o*–F–C_6H_4)	**L5b**	100	26h	74
8	**25i** (R = *p*–CF_3–C_6H_4)	**L5b**	100	26i	77
9	**25j** (R = *o*–CF_3–C_6H_4)	**L5b**	100	26j	88
10	**25k** (R = furyl)	**L5b**	100	26k	92
11	**25l** (R = thienyl)	**L5b**	100	26l	96
12	**25m** (R = $((MeO)_2CH)$)	**L5b**	100	26m	96
13	**25m** (R = $((MeO)_2CH)$)	**L6b**	100	26m	97

[a] The reaction was performed with 0.5 mmol of nitroalkene, $Cu(OTf)_2$ (1 mol%), and ligand (2 mol%) in 5 mL of toluene. All reactions completed in 6h. [b] In 15 mL of toluene. [c] Determined by Chiral GC or HPLC. Absolute configuration of **26b**, **26d**, and **26l** is known to be R, others are unknown. Nevertheless it is reasonable to assign R configuration to all products.

Reactions of heteroaromatic nitroalkenes **25k** and **l** smoothly proceeded to give **26k** (92% ee, entry 10) and **26l** (96% ee, entry 11), respectively. for comparison purpose, 1-nitroprop-1-ene dimethylacetal (**25m**) was also employed as substrate. The reaction afforded **26m** with 96% ee (entry 12). It was reported that **L22**-Cu(OTf)$_2$ achieved the same enantioselectivity for this reaction. It is worth mentioning that, unlike the reaction of **25a**, the reaction catalyzed by **L6b**-Cu(OTf)$_2$ achieved excellent enantioselectivity, giving **26m** with 97% ee (entry 13).

8. Conclusion

A series of novel monodentate phosphite and phosphoramidite ligands based on axially chiral biphenols has been developed and applied to various asymmetric catalytic reactions. The salient features of these ligands are their easy preparation and structural modifications that enable de facto the fine-tuning capabilities of these systems. The advantages of the fine-tuning capability have been demonstrated in a series of asymmetric transformations, i.e. a rational design and optimization of a lead ligand through fine-tuning allowed us to find the best-fit ligand for a particular reaction. It is noteworthy that the 3,3′-positions of the biphenol moiety exert a critical influence on the enantioselectivity as well as catalytic activity of a reaction. Alcohols and amines moieties for phosphites and phosphoramidites, respectively, also proved to be of critical importance for the efficacy of the chiral ligand. For instance, a slight modification of the *N,N*-bis(1-arylethyl)amine moiety of the phosphoramidite ligand had a profound effects on the enantioselectivity of the Pd-catalyzed allylic alkylation reaction. These studies have also provided useful insights into the nature of the catalyst specie as well as the mechanism of the reactions. Further investigations into the expansion of our ligand library as well as its applications to a variety of catalytic asymmetric transformations are actively underway in our laboratory.

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NEW CYCLIZATION AND CYCLOADDITION REACTIONS IN ORGANIC SYNTHESIS

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Abstract: An account of our recent studies on the rhodium-catalyzed carbocyclizations, cycloadditions and cyclohydrocarbonylations is presented. Silicon-initiated cascade carbocyclizations, including carbonylative carbocyclizations, provide powerful methods for the rapid construction of heterocyclic as well as carbocyclic compounds in one step. Efficient [2 + 2 + 2 + 1] cycloaddition process also furnishes an easy access to fused tricyclic systems. Cyclohydrocarbonylation reactions provide useful and efficient methods for the synthesis of a variety of nitrogen-heterocycles of medicinal interests.

Keywords: carbocyclization, carbobicyclization, carbotricyclization, [2 + 2 + 2 + 1] cycloaddition, cyclohydrocarbonylation, carbonylative, silicon-initiated, rhodium-catalyzed, heterocycle, carbocycle

1. Introduction

Design and development of highly efficient and catalytic processes for the syntheses of biologically active compounds is a central scheme in modern organic synthesis. One attractive approach along this line is to apply catalytic processes for the transformations of simple starting materials into cyclic scaffolds that can be further elaborated into specific targets.[1–3] The transition metal-catalyzed carbocyclization[4–6] and cycloadditions[7–13] are among the most synthetically useful processes for rapidly increasing molecular complexity. In the course of our investigation into the silicon-initiated cyclization reactions catalyzed by rhodium complexes, we have discovered intramolecular silylformylation of siloxyalkynes,[14–19] silylcyclocarbonylation (SiCCa) of silylaminoalkynes,[20] silylcarbocyclizations (SiCaC and CO-SiCaC) of enynes,[21–25] silylcarbobicyclization (SiCaB) of diynes,[26,27] silylcarbotricyclizations (SiCaT and CO-SiCaT) of enediynes,[28–30] and [2 + 2 + 2 + 1] cycloaddition of enediynes.[30,31] These new reactions make it possible to construct a variety

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of cyclic and fused-ring systems from readily available starting materials. In general, these catalytic processes proceed under mild conditions with high efficiency.

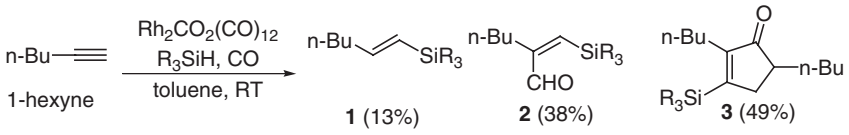
On the other hand, the hydroformylation of 1-alkenes is not only an important industrial process[32] but also a powerful method in modern organic synthesis.[32–35] We have been developing unique hydrocarbonylation processes of functionalized alkenes, involving cyclization subsequent to hydroformylation, which are termed "cyclohydrocarbonylation" reactions.[36–43] Thus, the adroit introduction of certain functional groups to the hydroformylation substrate will lead to the construction of a cascade cyclization process or a one-pot multi-step cyclization process. These cyclohydrocarbonylation reactions find a host of applications in organic synthesis.[32,34,35]

2. Carbocyclization Reactions

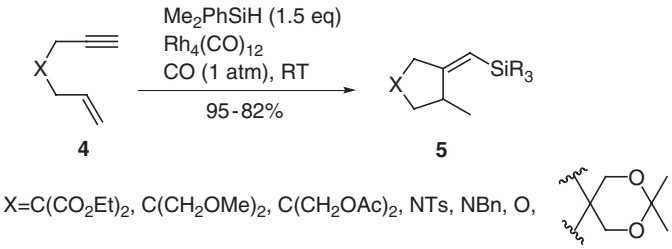
2.1. SILICON-INITIATED CARBOCYCLIZATIONS (SICACS)

The first example of silylcarbocyclization (SiCaC) was found during our detailed product analysis for the silylformylation of 1-hexyne catalyzed by rhodium and rhodium–cobalt carbonyl clusters.[21] Besides the expected silylformation product **2** and hydrosilylation product **1**, dibutylcyclopentenone **3** was isolated. The formation of unexpected product **3** was attributed to an intramolecular silicon-initiated carbonylative carbocyclization process (CO-SiCaC) involving two molecules of 1-hexyne, one molecule of CO and one molecule of hydrosilane (Scheme 1).[21]

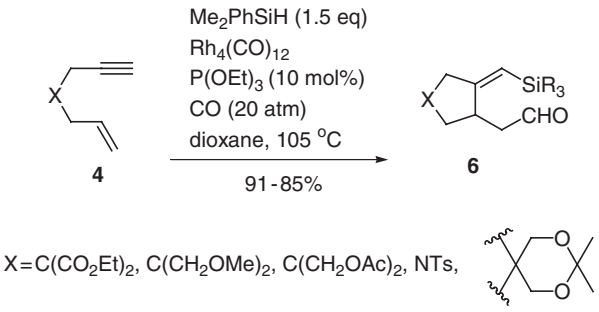
Following up this discovery, the intramolecular version of this reaction was investigated using a variety of 1,6-enynes **4** (Scheme 2).[21,24] For the SiCaC reactions, $Rh_4(CO)_{12}$ and $Rh_2Co_2(CO)_{12}$ were found to be very efficient catalysts, which can promote the reaction to completion within a minute under ambient CO pressure. Although CO is not incorporated into the SiCaC products, CO atmosphere is required to stabilize the active catalyst species. This process apparently includes the efficient intramolecular carbometalation of the alkene moiety with the β-silylvinyl-[M] intermediate formed through insertion of the alkyne moiety to the Si-[M] species.



Scheme 1. Silylcarbocyclization (SiCaC) of 1-hexyne.



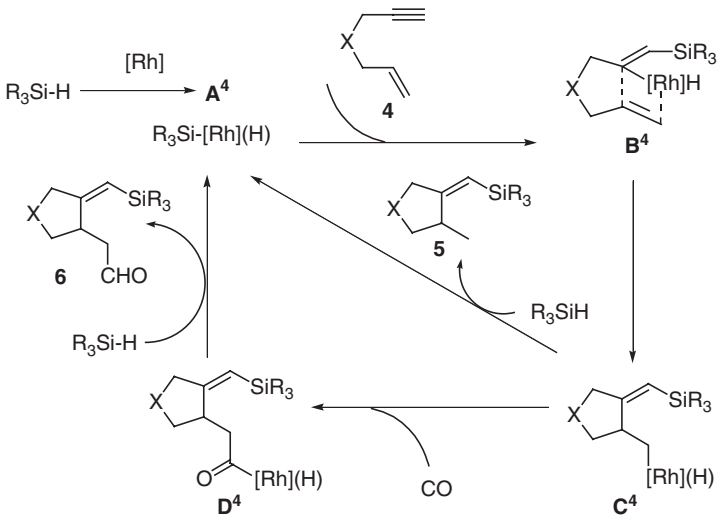
Scheme 2. SiCaC reaction of enynes.



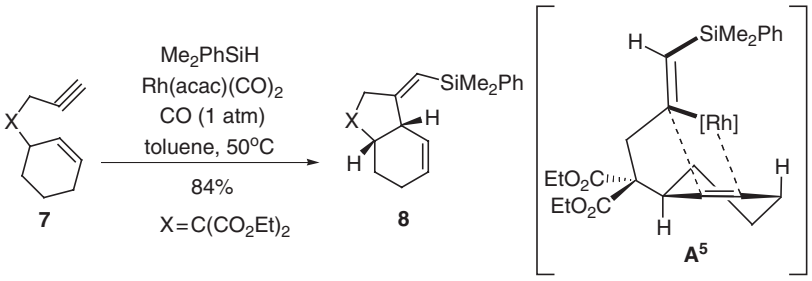
Scheme 3. CO-SiCaC reactions of enynes.

When the reactions of 1,6-enynes **4** with hydrosilane were carried out under higher CO pressure (20 atm) and dilute conditions in the presence of a phosphite ligand, the CO-SiCaC products, aldehydes **6**, were obtained virtually exclusively (Scheme 3).[24]

A plausible mechanism accommodating the formation of SiCaC product **5** and CO-SiCaC product **6** is illustrated in Scheme 4.[24] The reaction commences with the formation of the active species, Si–[Rh]H complex **A**[4] through the oxidative addition of a hydrosilane to a metal complex. Subsequent insertion of the acetylene moiety of enyne **4** into Si–[Rh]H generates β-silylvinyl-[M] intermediate **B**[4]. Coordination of the olefin moiety followed by intramolecular carbometalation leads to the formation of [Rh] complex **C**[4]. At higher CO concentration, CO insertion followed by subsequent hydrosilane-promoted reductive elimination affords CO-SiCaC product **6** via acyl–[Rh] complex **D**[4] and regenerates the active species **A**[4]. At low CO concentration, reductive elimination of **C**[4] takes place prior to CO insertion to give SiCaC product **5** and regenerates the catalyst species **A**[4].



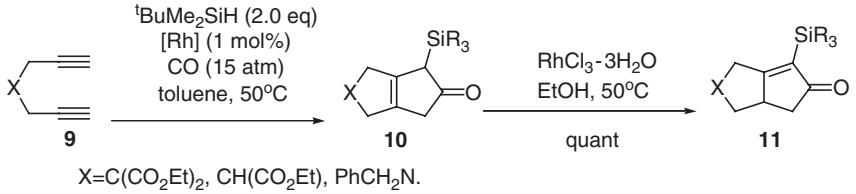
Scheme 4. Proposed mechanism of SiCaC and CO-SiCaC reactions.



Scheme 5. SiCaC of cyclic olefines.

In the presence of excess hydrosilane under the SiCaC conditions, silylcarbonylation-hydrosilylation (SiCaC-HS) of 1,6-diynes takes place to give the corresponding 1,2-bis(silylmethyl)cyclopentenes or their heterocyclic congeners with *exo* and/or *endo* double bond in good yields.[24]

Another SiCaC pathway, ending in the formation of diene **8**, was found in the reaction of enyne **7**, wherein the olefin moiety is a part of a ring structure. The SiCaC reaction under the standard conditions at 50°C gave bicycle[4.3.0] product **8** in 84% isolated yield.[24] As Scheme 5 illustrates, the approach of the β-silylvinyl-[Rh] intermediate to the cyclohexenyl moiety is possible only from one direction as shown, introducing the *cis* juncture exclusively in the product. Subsequent β-hydride elimination leads to the formation of the diene product **8**.



Scheme 6. SiCaB reaction of diynes.

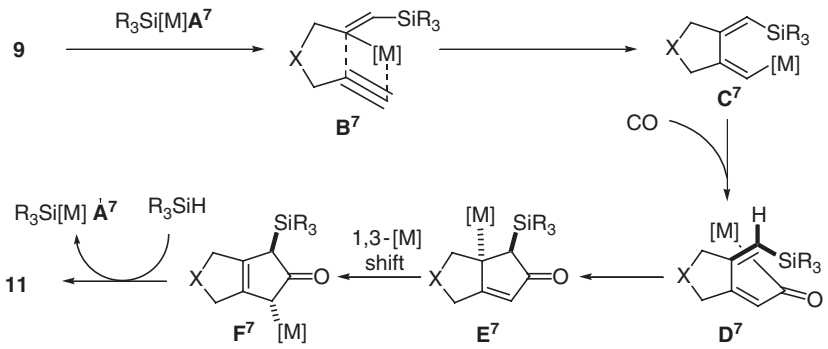
The successful intramolecular trapping of β-silylvinyl-[M] species with the olefin moiety of enynes prompted us to investigate the trapping of the same species with the acetylene moiety of a diyne. This investigation led to the discovery of the silylcarbobicyclization reaction (SiCaB) of 1,6-diynes.[23,26] As Scheme 6 shows, the reaction of diyne **9** with *t*-$BuMe_2SiH$ catalyzed by $Rh(acac)(CO)_2$ or $Rh_2Co_2(CO)_{12}$ at 50°C in toluene under CO atmosphere (15 atm) afforded bicyclo[3.3.0]octenones **10** in 93% yield. Bicyclo[3.3.0]octenones are very useful intermediates for the synthesis of a variety of biologically active cyclopenanoids and other natural products.[11] Compound **10** was isomerized quantitatively to the thermodynamically more stable enone **11** by treating with a catalytic amount of $RhCl_3$ in ethanol.

A proposed mechanism is shown in Scheme 7.[23,26] The active catalyst species **A**[7] is formed through oxidative addition of a hydrosilane to metal complex. Subsequent insertion of an alkyne group, followed by intramolecular carbometallation and CO insertion, gives acyl–[Rh] complex **D**[7]. Carbocyclization of acyl–[Rh] complex **D**[7] leads to the formation of bicyclic intermediate **E**[7], which can undergo the 1,3-[M] shift to the intermediate **F**[7]. Subsequent reductive elimination produces bicyclo[3.3.0] product **11** and regenerates active catalyst **A**[7].

When 4,4-(hydroxymethyl)-1,6-heptadiyne and its derivatives were used as substrates under more forced conditions (120°C), another type of SiCaB reaction was found to proceed to give bicyclo[3.3.0]octa-1,5-dien-3-ones, which are a unique class of compounds, possessing a highly strained ring system whose properties remain to be explored. This SiCaB process provides a highly efficient and convenient access to this unique class of compounds from readily available 1,6-diynes.[23,26]

2.2. SILICON-INITIATED CARBOTRICYCLIZATION (SICAT)

The SiCaC processes have been further extended to cascade SiCaC processes, which provide powerful methods for the construction of bicyclic and polycyclic



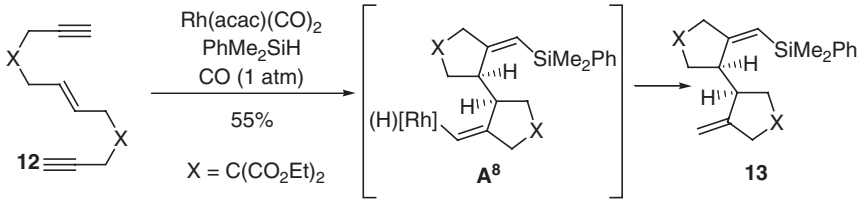
Scheme 7. Proposed mechanism of SiCaB reaction.

ring systems, especially those relevant to biologically active natural and unnatural products. The incorporation of additional alkene or alkyne functional group(s) into an enyne or diyne substrate should allow the trapping of intermediary metal species in a cascade manner to form bicyclic and polycyclic ring systems.

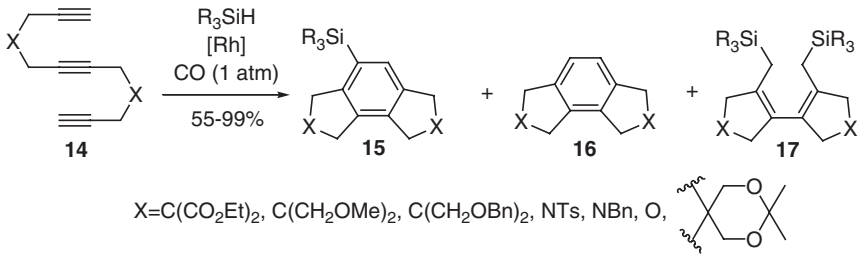
The first successful cascade SiCaC reaction was observed when (*E*)- or (*Z*)-enediyne **12** was employed as the substrate for the reaction with PhMe2SiH catalyzed by $Rh(acac)(CO)_2$ in toluene at 50°C under ambient pressure of CO. The reaction gave the corresponding bis(*exo*-methylenecyclopentene) **13** with complete stereospecificity (Scheme 8; only *Z*-**12** is shown).[25]

As Scheme 8 implies, after cascade biscyclization, an intramolecular carbometalation of the vinylsilane moiety of the intermediate $\mathbf{A^8}$ with the [Rh]-vinyl moiety to form the corresponding tricyclic framework is conceptually possible. However, such process did not occur. This result may well be attributed to the rotational freedom of the σ-bond connecting the two cyclopentyl units, which makes the reductive elimination much more favorable than the carbocyclization process.

Accordingly, it was anticipated that restriction of the rotational freedom of the carbon-carbon bond connecting two cyclopentyl rings by incorporating a double bond, locking the [Rh] moiety *syn* to the vinylsilane group in the intermediate $\mathbf{A^8}$, would make the third cyclization possible.[28] Such an intermediate could be generated if a 1,6,11-triyne is used. In fact, the reaction of triyne **14** (X = $C(CO_2Et)_2$) with $PhMe_2SiH$ catalyzed by $Rh(acac)(CO)_2$ at 70°C in toluene under ambient pressure of CO gave a 2:2:1 mixture of **15**, **16** and **17** (X = $C(CO_2Et)_2$) (Scheme 9). Thus, the first silylcarbotricyclization (SiCaT) via three consecutive carbocyclizations was achieved. The symmetrical bis(silylmethylpentyl) **17** is a side product and formed only when a hydrosilane is used in excess. Several Rh complexes



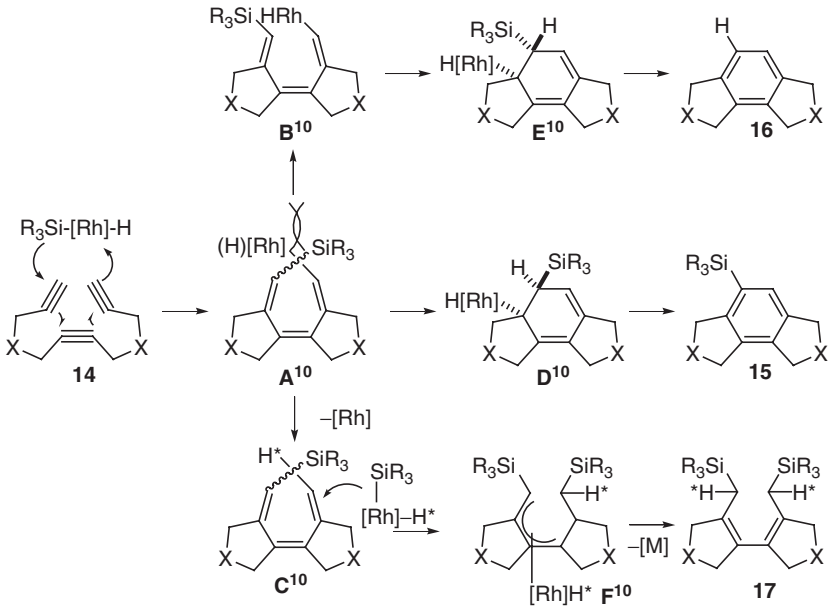
Scheme 8. First cascade SiCaC reaction.



Scheme 9. SiCaT reaction of triynes.

such as $Rh(acac)(CO)_2$, $[Rh(NBD)_2Cl]_2$, $[Rh(COD)_2Cl]_2$, $Rh_4(CO)_{12}$, and $Rh_2Co_2(CO)_{12}$ are effective in the SiCaT reaction. A variety of hydrosilanes such as $PhMe_2SiH$, Ph_2MeSiH, Ph_3SiH, Et_3SiH, *t*-$BuMe_2SiH$, $(EtO)_3SiH$, $(EtO)_2MeSiH$, can be used in this reaction. Various 1,6,11-triynes, including those with oxygen and/or nitrogen atoms in the backbone, are good substrates for this process as well. Under the optimized conditions using $Rh_4(CO)_{12}$ as the catalyst and 2 equivalents of a hydrosilane at room temperature, fused tricyclic silylbenzene **15** was obtained in an excellent yield with 84–93% selectively. The use of exactly one equivalent of a hydrosilane led exclusively to the formation of fused tricyclic benzene **16**.

A proposed mechanism for the SiCaT process is illustrated in Scheme 10.[28] The reaction commences with an insertion of an alkyne moiety into the Si-[Rh] bond of the hydrosilane–Rh oxidative adduct (active catalyst species), followed by three consecutive carbometalations to give common intermediate **A**[10]. Subsequent carbocyclization followed by β-hydride elimination affords the normal silylated SiCaT product **15**. It should be noted that deuterium labeling experiment confirmed the cascade process and eliminated the involvement of any common metallacycle in the catalytic cycle. If *Z–E* isomerization of intermediate **A**[10] takes place prior to carbocyclization to generate intermediate **B**[10], the subsequent carbocyclization followed by syn β-silyl elimination yields non-silyl product **16**.

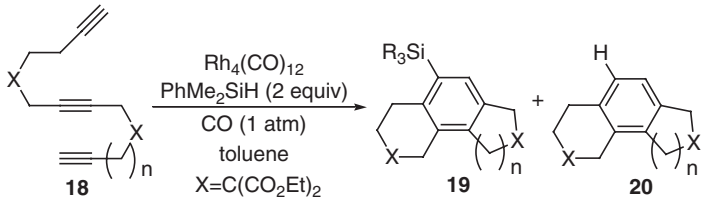


Scheme 10. Proposed mechanism of SiCaT reaction.

The SiCaT reaction is also applicable to the construction of 6-6-5 and 6-6-6 fused tricyclic frameworks such as **19** and **20**,[28] which find many applications to the syntheses of medicinally active compounds (Scheme 11). Since the formation of six-membered ring other than benzene ring by catalytic carbocyclization is demanding in general, the ability to construct such ring systems adds more significance and advantage to the SiCaT process as synthetic method.

2.3. SILICON-INITIATED CARBONYLATIVE CARBOTRICYCLIZATION (CO-SICAT)

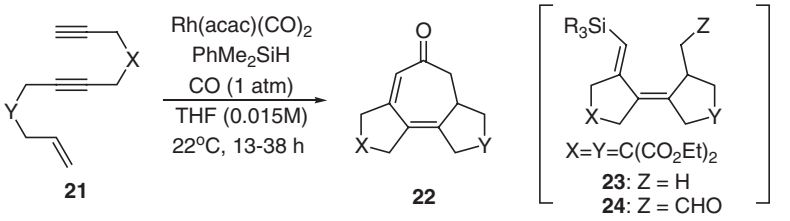
As an extension of the SiCaT reaction or triynes discussed above, the reaction of enediyne **21a** (X = $C(CO_2Et)_2$) with $PhMe_2SiH$ catalyzed by $Rh(acac)(CO)_2$ at 70°C under ambient pressure of CO. Naturally, the-anticipation was the formation of the corresponding 5-6-5 fused tricyclic product. To our surprise, however, a novel and synthetically very attractive carbonylative carbotricyclization process (CO-SiCaT), forming 5-7-5 fused ring system was serendipitously discovered. Thus, the reaction gave cyclopenta[e]azulene **22a** (X = $C(CO_2Et)_2$) and bis(cyclopentylidene) **23** as major products and aldehyde **24** as minor product in 70% overall yield



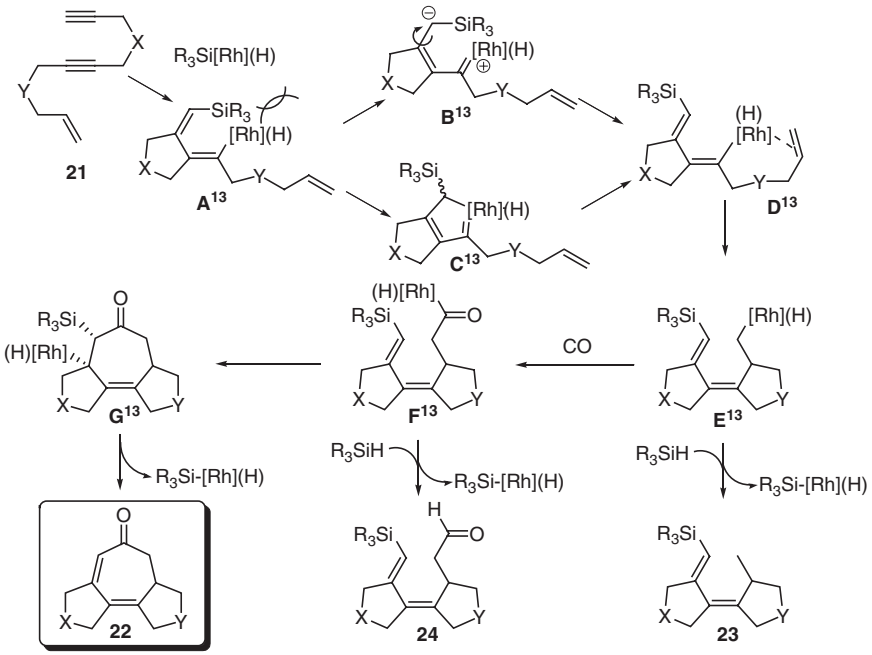
Scheme 11. SiCaT reactions of triynes forming 6-6-5 and 6-6-6 fused cyclic systems.

(**22a**:**23**:**24** = 36:43:21) (Scheme 12).[29] Although no silyl group is incorporated into **22a**, the reaction does not proceed in the absence of $PhMe_2SiH$, which clearly indicates that the hydrosilane is necessary for this novel reaction. On the basis of the analysis of possible mechanisms it was concluded that only a catalytic amount of a hydrosilane should be necessary for the formation of **22a** since the catalytically active Si-[Rh] species should be regenerated in the reaction system (see Scheme 13). In fact, the use of a catalytic amount (10 or 50 mol%) of $PhMe_2SiH$ brought about the exclusive formation of **22a** by completely suppressing the formations of **23** and **24**. Under the optimized conditions (0.5 equivalents of $PhMe_2SiH$) at high dilution (0.015 M) in THF, **22a** was exclusively obtained in 92% isolated yield (Scheme 12). For the catalyst, $Rh(acac)(CO)_2$, $Rh_4(CO)_{12}$ and $[Rh(CO)_2Cl]_2$ show similar activity. For hydrosilane, $PhMe_2SiH$ is the best, but Ph_2MeSiH, $(EtO)_3SiH$, and Et_3SiH can be used in this process as well. A variety of functional groups, e.g. ether, ester, hydroxyl, and sulfonamide, and heteroatoms in the backbone of enediynes **21** are well tolerated in this reaction to afford the corresponding fused 5-7-5 tricyclic products **22** in good to excellent isolated yields (Scheme 12).[29]

A proposed mechanism for the CO-SiCaT process is illustrated in Scheme 13.[29] The reaction begins with an insertion of the terminal alkyne moiety into the Si–[Rh] bond of the active catalyst species, similar to that in the SiCaT process. Carbocyclization proceeds to form intermediate **A**[13]. Because of the steric hindrance between the silyl moiety and the vinyl-Rh moiety, inermediate **A**[13] isomerizes to **D**[13] via either **B**[13] or **C**[13] through the "Ojima–Crabtree" mechanism.[44,45] Subsequent carbocyclization of intermediate **D**[13] generates intermediate **E**[13], which undergoes either reductive elimination to yield **23** or CO insertion to give intermediate **F**[13]. Reductive elimination of intermediate **F**[13] should yield **24**. Carbocyclization of **F**[13] produces tricyclic intermediate **G**[13], which has the silicon and the [Rh] moieties in syn positions. Subsequent β-silyl elimination affords fused tricyclic 5-7-5 product **22** and regenerates the active catalyst species. This mechanism accommodates the observed three



Scheme 12. CO-SiCaT reaction of enediyes.



Scheme 13. Proposed mechanism of CO–SiCaT reaction.

products at non-optimized, dilution effect and the fact that employment of only sub-stoichiometric amount of hydrosilane is necessary for the formation of **22**.

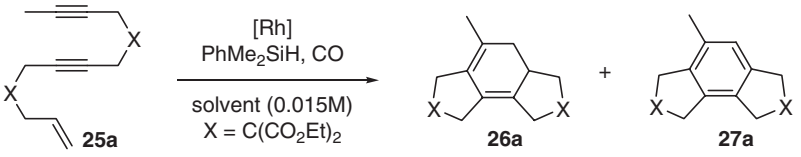
3. Cycloaddition Reactions

In the last two decades, considerable advances have been made in the development of higher-order cycloaddition reactions such as [4 + 3],[46–49] [5 + 2],[50–54] [6 + 2],[55] [4 + 2 + 2],[56,57] and [5 + 2 + 1][58] processes. Thus, transition-metal-catalyzed carbocyclization and higher-order cycloaddition reactions[59–61] provide powerful methods for the construction of complex polycyclic systems.[6,62,63] During our studies on the scope and limitation of the CO-SiCaT reaction, we found a closely related [2 + 2 + 2] cycloaddition reaction of enediyne **25a**, involving metallacycles as key intermediates, i.e. this reaction is mechanistically distinct from the cascade carbometalation process discussed above. Then, we serendipitously discovered that the reaction of 1-substituted dodec-11-ene-1,6-diynes **25** catalyzed by $[Rh(COD)Cl]_2$ in the absence of a hydrosilane gave carbonylative tricyclization products **28** in good to excellent yields.[31] This marked the first example of a [2 + 2 + 2 + 1] cycloaddition reaction, which is a new addition to higher-order cycloaddition processes.

3.1. [2 + 2 + 2] CYCLOADDITION OF ENEDIYNE

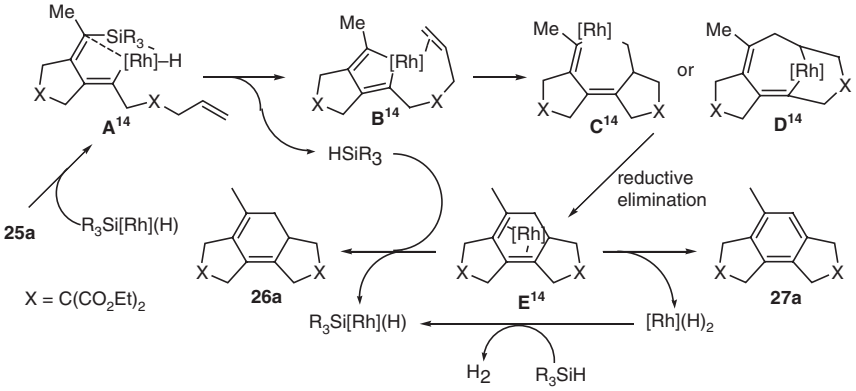
As a part of the scope and limitation study on the CO-SiCaC reaction, we investigated the reaction of enediyne **25a**, in which a methyl group was introduced to the terminal acetylene moiety of enediyne **21a**. To our surprise, this small modification exerted a dramatic effect on the outcome of the reaction as shown in Table 1.[29] Thus, the attempted CO-SiCaT reaction of **25a** did not take place under the optimized CO-SiCaT conditions (Entry 1). However, when

TABLE 1. Tricyclization of endiyne **25a** via intramolecular [2 + 2 + 2] cycloaddition.



entry	catalyst	$PhMe_2SiH$ (eq.)	solvent	temp (°C)	CO (atm)	time (h)	yield (%)[a]	product ratio[b] 26	27
1	$Rh(acac)(CO)_2$	1.0	THF	22	1	24	No reaction		
2	$Rh_4(CO)_{12}$	1.0	toluene	70	1	3	50	67	34
3	$Rh(acac)(CO)_2$	0.3	toluene	70	1	3	96	100	0
4	$Rh(acac)(CO)_2$	0.1	toluene	70	1	24	90	50	50
5	$Rh(acac)(CO)_2$	0.3	toluene	70	25	24	Low conversion		
6	$Rh(acac)(CO)_2$	none	toluene	70	1	72	No reaction		

a: Isolated yield. b: NMR ratio



Scheme 14. Proposed mechanism of silicon-initiated [2 + 2 + 2] cycloaddition.

the reaction was carried out in toluene at 70°C, SiCaT products **36a** and **37a** (X = $C(CO_2Et)_2$) were obtained (Entries 2 and 4). The reaction catalyzed by $Rh(acac)(CO)_2$ with 0.3 equivalents of $PhMe_2SiH$ for 3 h gave **26** exclusively in 96% yield (Entry 3). The use of higher CO pressure suppressed the reaction (Entry 5). Reaction did not proceed in the absence of hydrosilane (Entry 6). The observed results are best accommodated by a unique silicon-initiated intramolecular [2.+.2.+.2] cycloaddition process shown in Scheme 14.[29]

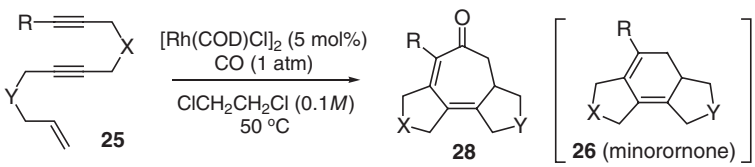
We believe that the reaction begins in the same manner as that of CO-SiCaT, generating $\mathbf{A}^{14}$ after the first silylcarbocyclization. Because of the methyl substituent, however, the *Z–E* isomerization does not take place. Since the Si–C bond and the Rh–H bond are very close, a σ-bond metathesis occurs to form metallacycle $\mathbf{B}^{14}$ and regenerates hydrosilane. This makes a sharp contrast with the CO-SiCaT mechanism. There are two possible routes for the subsequent olefin insertion into the Rh–C bond of metallacycle $\mathbf{B}^{14}$, affording 5-7-5 tricyclic metallacycle $\mathbf{C}^{14}$ or 5-7-6 tricyclic metallacycle $\mathbf{D}^{14}$. Reductive elimination of $\mathbf{C}^{14}$ or $\mathbf{D}^{14}$ yields fused 5-6-5 tricyclic diene–[Rh] complex $\mathbf{E}^{14}$, which reacts with a hydrosilane to give **26a** and regenerates the active catalyst species $R_3Si[Rh](H)$. In the absence of sufficient hydrosilane, diene–[Rh] complex $\mathbf{E}^{14}$ aromatizes via dehydrogenation to give **27a** and dihydrido-Rh species. The latter reacts with a hydrosilane to liberate molecular hydrogen and regenerates the active catalyst species.

3.2. [2 + 2 + 2 + 1] CYCLOADDITION OF ENEDIYNE AND CARBON MONOXIDE

A possible intermediacy of metallacycle $\mathbf{C}^{14}$ shown in Scheme 14 encouraged us to explore hitherto an unknown [2 + 2 + 2 + 1] cycloaddition of endiyne

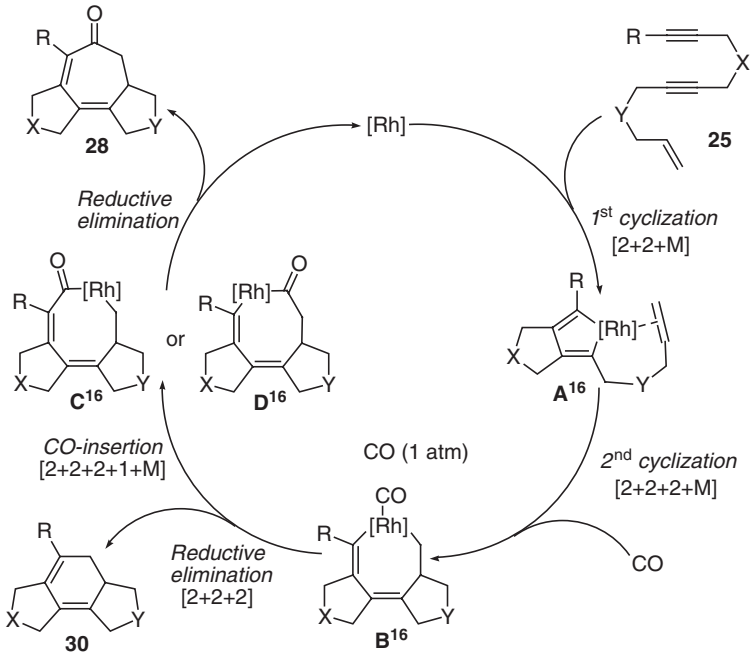
with CO, forming the corresponding fused 5-7-5 tricyclic system in one step.[31] The formation of metallacycles such as **B**[14] from 1,6-diynes is common in carbocyclizations.[4–6] Accordingly, the reaction conditions and variables, which might promote the novel [2 + 2 + 2 + 1] cycloaddition process, were investigated using **25a** as the substrate. Fortunately, it was serendipitously found that the desired fused 5-7-5 tricyclic product **28a** (X = $C(CO_2Et)_2$) was formed through [2 + 2 + 2 + 1] cycloaddition *in the absence of hydrosilane*, although the reaction was accompanied by intramolecular [2 + 2 + 2] cycloaddition product **26a** (X = $C(CO_2Et)_2$) when using $Rh(acac)(CO_2)_2$ as catalyst.[31] Optimization of the reaction revealed that $[Rh(COD)Cl]_2$ and dichloroethane were the best catalyst and solvent, respectively, and ambient pressure of CO gave the best result. It has been shown that $[Rh(COD)Cl]_2$ is an efficient catalyst for the catalytic Pauson–Khand reactions of enynes.[64–67] Under the optimized conditions, **28a** was obtained almost exclusively in 88% yield (Scheme 15).[31] In order to examine the scope of this reaction, especially for its functional group tolerance, a variety of 1-substituted dodec-11-ene-1,6-diynes **25**, containing ether, sulfonamide, carbamate, ester, and ketal groups, were employed. In addition, enediynes **25** bearing a methyl, phenyl, or TMS as the substituent of the terminal acetylene moiety were employed as well. These functional groups and heteroatoms are generally well tolerated in this process, affording the corresponding **28** in good to excellent yields (Scheme 15).[31]

A proposed mechanism of the novel [2 + 2 + 2 + 1] cycloaddition is illustrated in Scheme 16. This reaction proceeds through a series of metalla cycles, including (1) coordination of the diyne moiety of **25** to the active [Rh] species, leading to the formation of rhodacycle **A**[16] ([2 + 2 + M]), (2) insertion of the olefin moiety of **25** into the [Rh]–C bond to form 5-7-5 fused tricyclic rhodacycle **B**[16] (2 + 2 + 2 + M), (3) coordination of CO to the [Rh] metal followed by migratory insertion into the Rh–C bond to give a 5-8-5 tricyclic rhodacycle **C**[16] or **D**[16] ([2 + 2 + 2 + M + 1]), (4) reductive elimination to yield cycloadduct **28**. If reductive elimination from **B**[16] occurs before the CO insertion, [2 + 2 + 2] cycloadduct **26** is formed.[31]



X,Y=$C(CO_2Et)_2$, $C(CH_2OMe)_2$, $C(CH_2OBn)_2$, $C(CH_2OAc)_2$, $C(CH_2O)_2CMe_2$, O, NTs, N-Boc^t
R = Me, Ph, TMS

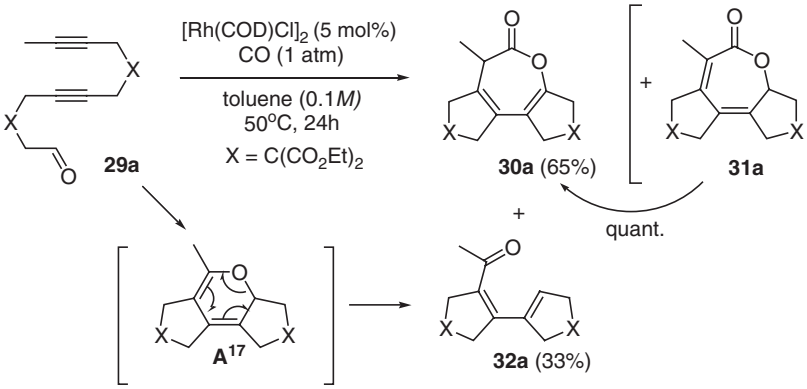
Scheme 15. [2 + 2 + 2 + 1] cycloaddition reaction of enediynes and CO.



Scheme 16. Proposed mechanism of [2 + 2 + 2 + 1] cycloaddition.

At this point, it would be useful to summarize the characteristics of two different reactions, i.e. CO-SiCaC and [2 + 2 + 2 +1] cycloaddition that give 5-7-5 fused tricyclic products incorporating CO. The mechanisms of these two processes are fundamentally different although the same type of products is obtained (Schemes 13 and 16). These two reactions are complementary each other. The CO-SiCaT reaction proceeds only with 1-terminal free 1,6,11-endiynes through silicon-initiated cascade carbocyclization process. On the other hand, the [2 + 2 + 2 +1] cycloaddition reaction occurs with 1-substituted and unsubstituted endiynes through sequential metallacycle formations.

Diynals can be used as substrates for the [2 + 2 + 2 +1] cycloaddition. For example, the reaction of dodeca-5,10-diyn-1-al (**29a**, R = Me) under the standard conditions gave 5-7-5 fused tricyclic lactones **30a** and **31a** (65% combined yield), as well as the acetylbis(cyclopentenyl) **32a** (33%) in nearly quantitative overall yield (Scheme 17). It was found that lactone **31a** was a kinetic product. Thus, clean and complete isomerization of **31a** to **30a** was observed in $CDCl_3$. The formation of **32a** can be attributed to the electrocyclic ring opening of the central pyrane moiety of

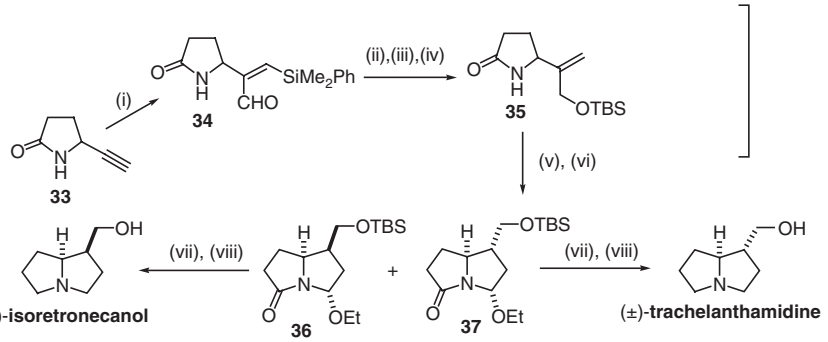


Scheme 17. [2 + 2 + 2 + 1] reaction of diynal and CO.

the initially formed intramolecular [2 + 2 + 2] cycloadduct **A**[17] to the bicyclic dienone structure. The reaction of undeca-5,10-diyn-1-al (**29b**, R = H) under the same conditions gave only **30b** (52%) and **32b** (18%). Although this is the first example of the [2 + 2 + 2 + 1] cycloaddition of diynal with CO, the [2 + 2 + 2 + 1](major) and [2 + 2 + 2] (minor) cycloaddition processes are competing. Thus, further optimization of the [2 + 2 + 2 + 1] cycloaddition process is necessary for this reaction to be synthetically useful. Nevertheless, it is encouraging that unique fused 5-7-5 tricyclic lactones can be obtained in fairly good isolated yields even at this discovery stage.

4. Cyclohydrocarbonylation

Cyclohydrocarbonylation is an intramolecular cascade process, consisting of a hydroformylation of a functionalized alkene to form an aldehyde intermediate, followed by the addition of a nucleophile in the same molecule to the aldehyde, leading to the formation of the corresponding cyclization product(s). As a variant, the cyclohydrocarbonylation also includes an intramolecular cascade process involving the hydrocarbonylation of a functional alkene, generating an acyl-metal intermediate, which undergoes intramolecular nucleophilic substitution to give the corresponding cyclic carbonyl compounds. The functional groups such as amide, amine, hydroxyl, and carbon-nucleophiles in the alkene substrates are representative functional groups in these processes. In fact, the cyclohydrocarbonylation reaction has been incorporated to more sophisticated cascade processes, forming bicyclic and polycyclic compounds in one-pot.



(i) $HSiMe_2Ph$, CO(20 atm), $Rh(acac)(CO)_2$RT, 98%, (ii) $NaBH_4$,0°C,100%, (iii) TsH, MeCN (2%H_2O), 75%, (iv) TBS-Cl, imidazole, 98%, (v) CO, H_2, $HRh(CO)(PPh_3)_3$, $HC(OEt)_3$, 72% (*syn*/*anti* = 2/1), (vi) SiO_2 column, (vii) n-Bu_4NF, RT, 96%, (viii) $LiAlH_4$, 65-70%

Scheme 18. Synthesis of isoretronecanol and tranchelanthamimidine.

4.1. CYCLOHYDROCARBONYLATION INVOLVING AMIDES AND AMINES

A combination of intermolecular silylformylation and cyclohydrocarbonylation provides an efficient route to pyrrolizidine alkaloids (Scheme 18).[17,18]

The regio- and diastereoselective Rh-catalyzed silylformylation of 5-ethynyl-2-pyrrolidinone **33** afforded (*Z*)-**34** in an excellent yield. Subsequent reduction and desilylation, followed by protection of the resulting hydroxyl group as tert-butyldimethylsilyl (TBS) ether gave **35**. Cyclohydrocarbonylation of **35** catalyzed by $HRh(CO)(PPh_3)_3$ afforded a diastereoisomeric mixture (*syn*/*anti* = 2/1) of bicyclic products **36** and **37**, which were readily separable by flash chromatography. Removal of the silyl protecting group and reduction of both the amidal and amido group gave (±)-isoretronecanol and (±)-trachelanthamidine, respectively (Scheme 18).[17,18]

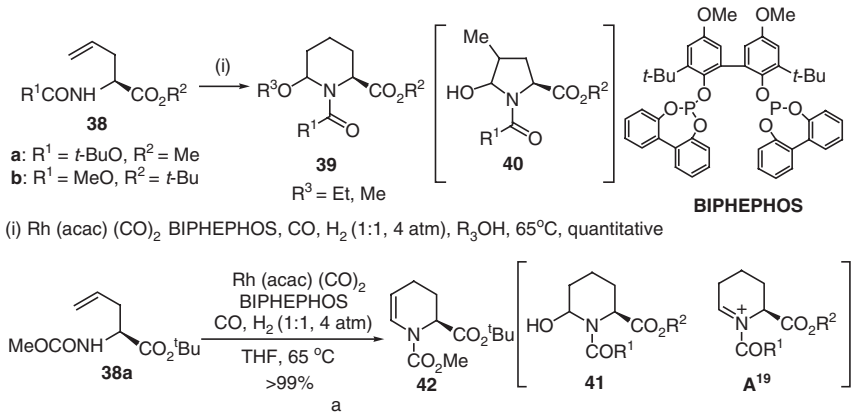
The combination of $Rh(acac)(CO)_2$ and BIPHEPHOS,[68] is an excellent catalyst system for the linear-selective hydroformylation of a wide range of alkenes.[17,32–34,68] This catalyst system has been successfully applied to the cyclohydrocarbonylation reactions of alkenamides and alkenylamines, which serve as key intermediates for the syntheses of piperidine,[37,38] indolizidine, and pyrrolizidine alkaloids.[34]

Cyclohydrocarbonylation of N-carbalkoxyallylglycinate **38** catalyzed by $Rh(acac)(CO)_2$-BIPHEPHOS in an alcohol solvent gave 1-carbalkoxy-6-alkoxypipecolate **39** in quantitative yield (Scheme 19).[38] In this reaction, the use of BIPHEPHOS ligand was essential for the exclusive formation of piperidine ring via a linear aldehyde intermediate. When the same reaction was

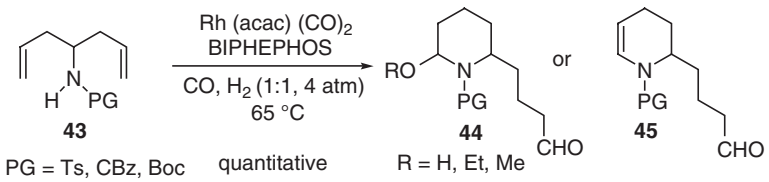
carried out using a classical catalyst, such as $HRh(CO)(PPh_3)_3$ in the presence of a large excess of PPh_3 (20 equivalents), a 1:1 mixture of regioisomers **39** and **40** was formed.

This process includes the extremely linear-selective hydroformylation of an olefin moiety, generating the corresponding terminal aldehyde, followed by the formation of hemiamidal **41** and then the dehydration to the acyliminium ion intermediate **A**[19]. Addition of an alcohol to the acyliminium ion intermediate **A**[19] gives **39**. When the reaction of **38a** was performed in an aprotic solvent such as THF, toluene, hexane, ethyl acetate, etc., 5,6-didehydropipecolate **42** was obtained in 99% yield via deprotonation and double bond migration of the common acyliminium ion intermediate **A**[19] (Scheme 19).[38]

Cyclohydrocarbonylation of 4-tosylamino-1,6-heptadiene **43** catalyzed by $Rh(acac)(CO)_2$-BIPHEPHOS in THF gave *N*-tosyl-2-hydroxypiperidine **44** (R = H) and/or *N*-tosyl-5,6-didehydropiperidine **45**, depending on the duration of the reaction (Scheme 20).[37] When the reaction was stopped after 2 h, **44** was quantitatively formed as the sole product, but a prolonged reaction time (18 h) gave **45** exclusively in quantitative yield. This strongly



Scheme 19. Cyclohydrocarbonylation of *N*-carbalkoxyallylglycinate **38**.

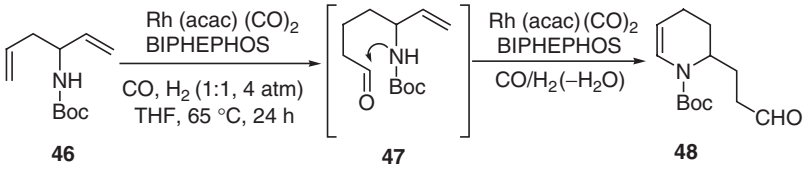


Scheme 20. Cyclohydrocarbonylation of 4-tosylamino-1,6-heptadiene **43**.

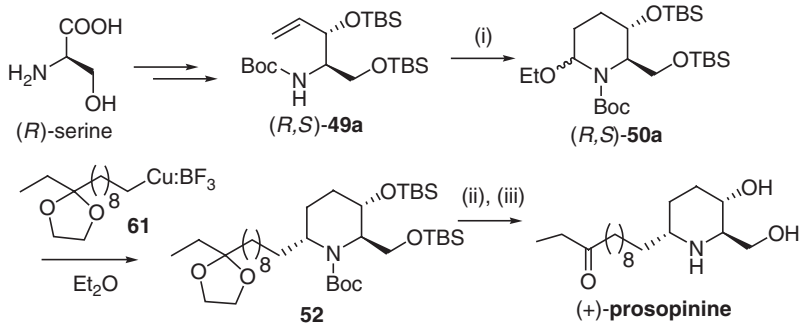
indicated that the hemiamidal **44** was the precursor of the acyliminium ion intermediate similar to **A**[19]. When the reaction was carried out in ethanol or methanol, *N*-tosyl-2-ethoxylpiperidine-aldehyde **44** (R = Et or Me) was obtained in quantitative yield. As protecting groups for the amine moiety, the Cbz and *t*-Boc groups were employed in addition to the tosyl group. 2-Alkoxypiperidine-aldehyde **44** (R = Et, Me) and 5,6-didehydropiperidine-aldehyde **45** serve as useful precursors for the syntheses of various piperidine and indolizine alkaloids.

The reaction of unsymmetrical amidodiene **46** catalyzed by Rh–BIPHEPHOS complex gave dehydropiperidine-aldehyde **48** as the sole product, i.e. no pyrroline was formed (Scheme 21).[37] The fact that no pyrroline is formed indicates that this reaction is extremely site- and regioselective in that the hydroformylation takes place at the homoallylic olefin moiety exclusively, only yielding the linear aldehyde **48**.

A short total synthesis of (+)-prosopinine from (*R*)-serine was achieved via cyclohydrocarbonylation catalyzed by Rh–BIPHEPHOS complex for the construction of the key piperidine (2*R*,3*S*)-**50a** (Scheme 22).[39] The resulting

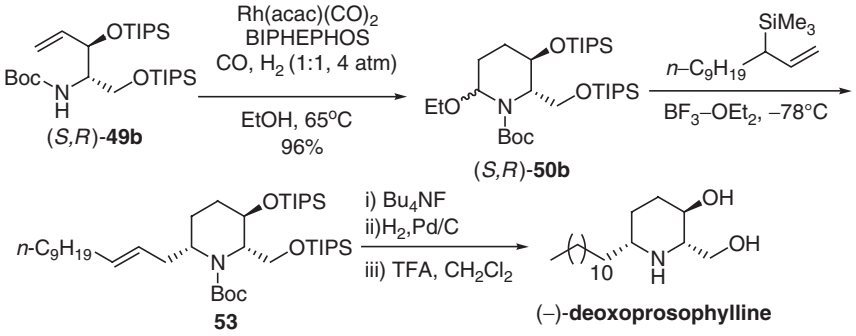


Scheme 21. The reaction of unsymmetrical amidodiene **46**.

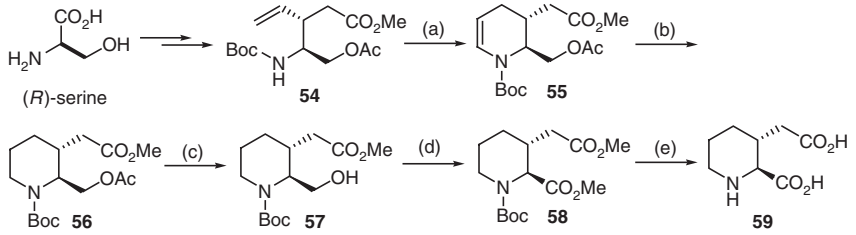


(i) Rh (acac) $(CO)_2$ (1 mol%), BIPHEPHOS (2 mol%), CO, H_2 (1:1, 4 atm), 92%
(ii) *n*-Bu_4NF, THF (iii) TFA, CH_2Cl_2

Scheme 22. Total synthesis of (+)-prosopinine.



Scheme 23. Total synthesis of (−)-deoxoprosophylline.



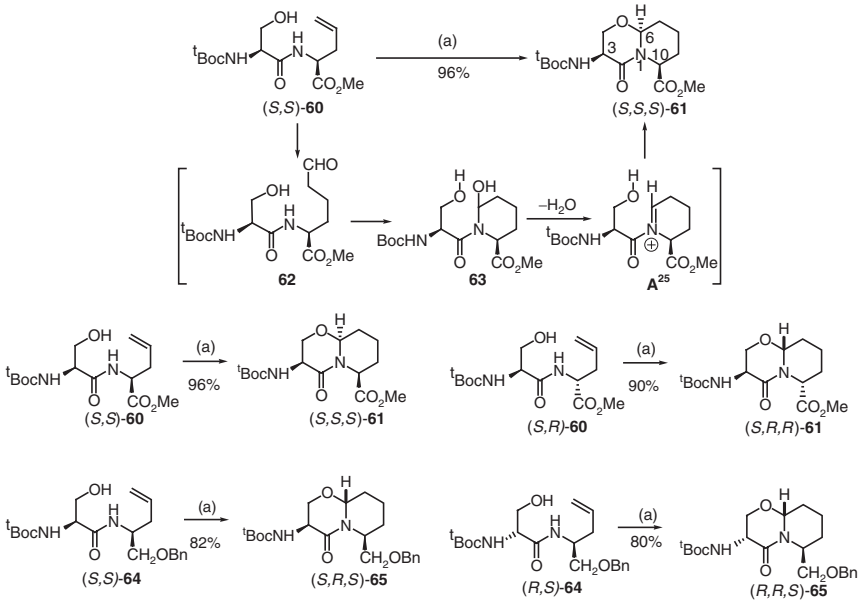
(a) Rh(acac)$(CO)_2$ (0.25 mol %), BIPHEPHOS (0.50 mol %), toluene, H_2 (2 atm) ,CO (2 atm), 75 °C, (99%) (b) 5% Rh-C, H_2 (10 atm), MeOH, RT, (95%) (c) DBU, LiBr, MeOH, RT (d) (i) TEMPO, KBr, NaOCl, acetone-$NaHCO_{3(aq)}$, 4° C (ii) CH_2N_2, MeOH, 92% overall yield from **68** (e) (i) 6N $HCl_{(aq)}$, reflux, (ii) propylene oxide-EtOH, reflux 83%.

Scheme 24. Synthesis of 3-pipecolinoglutamic acid (**59**).

(2*R*,3*S*)-**50a** was converted to (+)-prosopinine via the nucleophilic displacement of the ethoxy group with organocopper reagent **51**.

A similar strategy was used for the total synthesis of (−)-deoxoprosophylline, featuring the cyclohydrocarbonylation of (2*S*,3*R*)-**50b** derived from (*S*)-serine in the key-step. The C-6 side chain was introduced by a Lewis acid-promoted allylsilane addition to (2*S*,3*R*)-**50b** via acyliminium ion intermediate to secure the required 2,6-*cis* stereochemistry of the target molecule (Scheme 23).

This method has also provided an excellent route to 3-pipecolinoglutamic acid (**59**), which is a potential antagonist for the glutamate receptors (GluRs) (Scheme 24).[40] Cyclohydrocarbonylation of olefin **54**, derived from (*R*)-serine, afforded enecarbamate **55** as a key intermediate. Hydrogenation of **55** over Rh/C under ambient pressure furnished piperidine **56**, which was subsequently



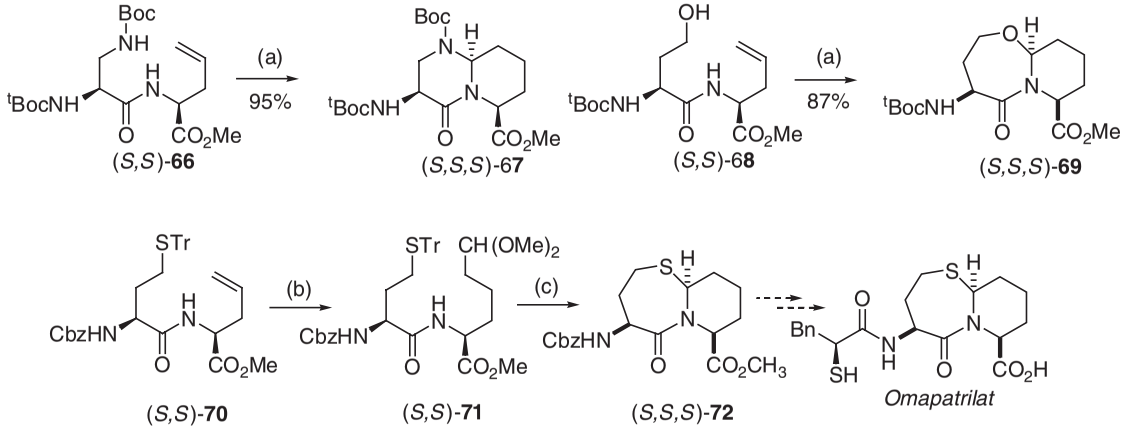
(a) Rh (acac)$(CO)_2$, (2 mol%); BIPHEPHOS (4 mol%), CO, H_2 (1:1, 4 atm), PTSA (10 mol%), toluene, 65° C, 20 h

Scheme 25. Synthesis of 1-azabicyclo[X.Y.0]alkane amino acids.

deprotected, oxidized and then methylated to afford pipecolinoglutamate **58**. Hydrolysis and neutralization of **58** gave free amino acid **59**.

The Rh-BIPHEPHOS–catalyzed cyclohydrocarbonylation has also been successfully applied to the rapid synthesis of a variety of 1-azabicyclo [X.Y.0]alkane amino acids, which are known as conformationally restricted dipeptide surrogates for enzyme inhibitors and receptor antagonists, directly from dehydrodipeptide substrates (Scheme 25).[41]

Reaction of (*S,S*)-*N*-^{t}Boc-serinylallylglycinate (*S,S*)-**60** under the standard cyclohydrocarbonylation conditions gave 5-oxa-1-azabicyclo[4.4.0]-decanecarboxylate (*S,S,S*)-**61** in an excellent yield. This reaction includes an extremely selective hydroformylation to form linear aldehyde **62**, followed by the formation of hemiamidal **63**. Subsequent generation of acyliminium ion **A**[25] and intramolecular nucleophilic addition of the hydroxyl group of the serine moiety yields (*S,S,S*)-**61** with excellent diastereoselectivity at C-6 (Scheme 28). The reaction of the other diasteromer, (*S,R*)-**60**, gives (*S,R,R*)-**61** as the sole product in 90% yield. Thus, the C-10 position appears to be the stereogenic center in these reactions. The stereochemistry at the C-6 position, however, is also dependent on the nature of the C-10 substituent. For example, the reaction of (*S,S*)-**64**, bearing a CH_2OBn group instead of a



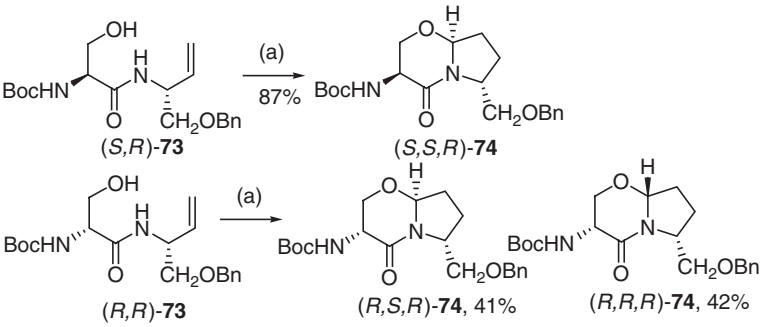
(a) $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), CO, H_2 (1:1, 4 atm), PTSA (10 mol%), toluene, 65°C, 20h.
(b) $Rh(acac)(CO)_2$, (2 mol%), BIPHEPHOS (4 mol%), CO, H_2 (1:1, 4 atm), MeOH, 65°C, 20 h.
(c) TFA (cat), CH_2Cl_2.

Scheme 26. Synthesis of (*S,S,S*)-**72**.

CO_2Me group at C-10, gave (*S,R,S*)-**65**, in which the absolute configuration at C-6 is *R*. In the same manner, the reaction of (*R,S*)-**64**, gives (*R,R,S*)-**65**, i.e. the absolute configuration at C-6 is *R* as well. The results confirm that the C-10 position is the stereogenic center in this process, but also indicate that the stereoelectronic nature of the C-10 substituent governs the diastereoface selection in the cyclization step.[42]

In a similar manner, the reaction of (*S,S*)-**66** bearing a β-aminoalanine residue instead of the serine residue, proceeded efficiently in the presence of p-toluenesulfonic acid (PTSA) to give (*S,S,S*)-**67** exclusively in 95% yield (Scheme 26).[41] It should be noted that no 1-azabicyclo[4.3.0] product was formed in spite of the fact that either ^{t}Boc-amino group in the β-aminoalanine residue could react with the acyliminium intermediate. The reaction is readily applicable for the construction of 1-azabicyclo[5.4.0] system. Thus, the reaction of (*S,S*)-**68** under the standard conditions afforded (*S,S,S*)-**69** in 87% yield.[43] The stereoselectivity for the C-6 bridgehead is controlled by the C-10 ester group in accordance with the general mechanism for this cascade process discussed above. In the case of a dipeptide substrate bearing a cysteine residue, an *S*-trityl derivative (*S,S*)-**70** has been used. Since the thiol group was protected, a spontaneous cyclization could not take place. Thus, the reaction of (*S,S*)-**70** was carried out in MeOH to trap the resulting aldehyde moiety by converting it to the corresponding acetal (*S,S*)-**71** in situ. The subsequent deprotection-cyclization with catalytic amount of TFA afforded (*S,S,S*)-**72** in 84% isolated yield for two steps in one-pot. Compound (*S,S,S*)-**72** is the key precursor of *Omapatrilat*,[69] a powerful ACE inhibitor (Scheme 26).

However, cyclohydrocarbonylation of amide **73** bearing a vinylglycinol moiety showed that the product distribution was dependent on the relative



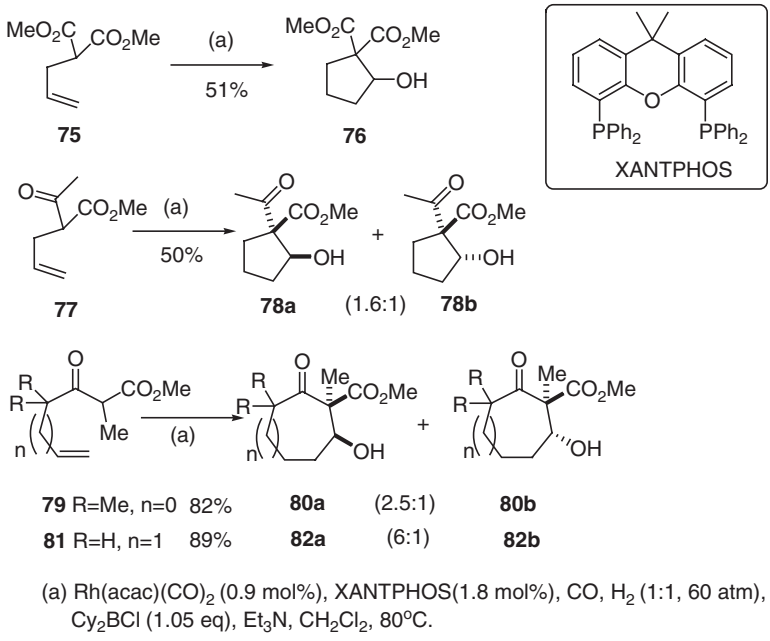
(a) $Rh(acac)(CO)_2$ (2 mol%), BIPHEPHOS (4 mol%), CO, H_2 (1:1, 4 atm), PTSA (10 mol%), toluene, 65 °C, 20 h

Scheme 27. Cyclohydrocarbonylation of amide **73**.

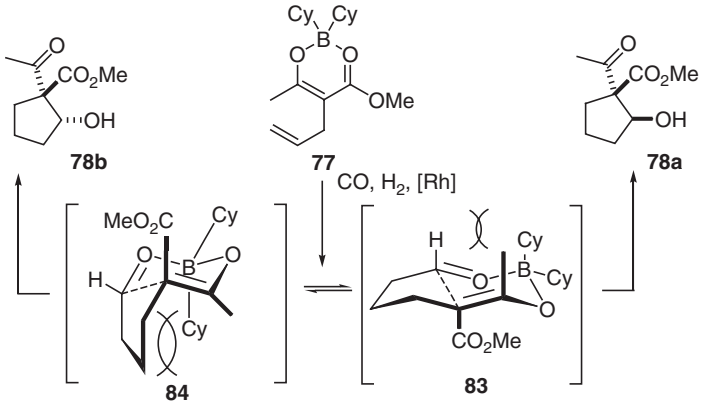
configurations of two chiral centers. For example, the reaction of (*S,R*)-**73** with a matching pair of configurations led to the formation of (*S,S,R*)-**74** as the sole product, whereas the reaction of (*R,R*)-**73** with a mismatching pair of configurations yielded a nearly 1:1 mixture of two diastereomeric products, (*R,S,R*)-**74** and (*R,R,R*)-**74** (Scheme 27).[43]

4.2. CYCLOHYDROCARBONYLATION INVOLVING CARBON NUCLEOPHILES

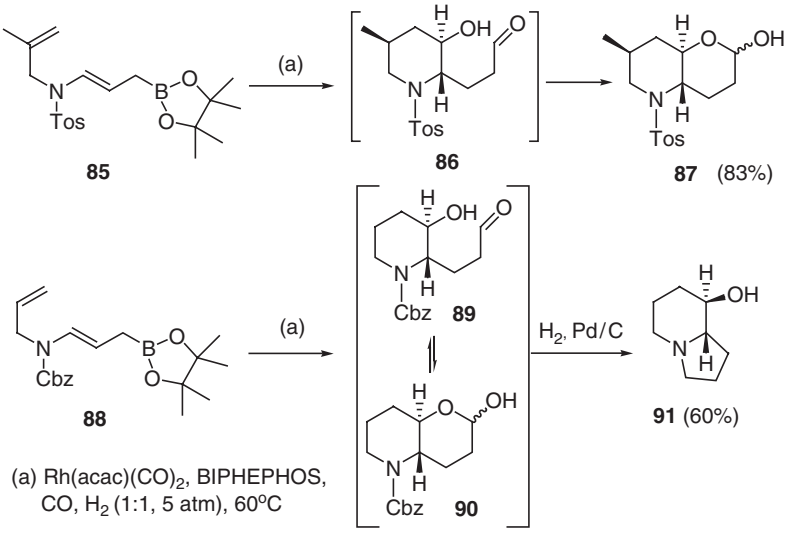
In relation to the cyclohydrocarbonylation reactions developed in our laboratories, other research groups have reported the reactions involving carbon nucleophiles in place of hetroatom nucleophiles. For example, the Rh-XANPHOS-catalyzed hydroformylation reactions of allylmalonate **75**, 2-allylacetoacetate **77**, 2-(3-butenoyl)propanoate **79**, and 2-(4-pentenoyl)propanoate **81** in the presence of Cy_2BCl and triethylamine gave the corresponding cycloalkanols, **76, 78, 80**, and **82**, in fairly good to high yields (Scheme 28).[70] Cycloalkanols, **76, 78, 80**, and **82**, thus formed, possess a quaternary carbon center next to the hydroxyl group in a molecule,



Scheme 28. Rh-XANPHOS-catalyzed hydroformylation reactions of allylmalonate **75, 77, 79**, and **81**.



Scheme 29. Synthesis of **78a**.



Scheme 30. Synthesis of indazolidine **91**.

and would serve as useful polyfunctionalized synthetic intermediates in organic synthesis. The observed diastereoselectivity in these reactions can be accommodated by taking into account the relative extent of 1,3-diaxial interactions in the bicyclic transition states, involving a chair structure of **83** rather than **84**, for the preferential formation of **78a** (Scheme 29).[70]

Another example is the cascade hydroformylation-allylboration-hydroformylation of (*E*)-aminoallylborate **85**. The reaction catalyzed by Rh(acac)$(CO)_2$-BIPHEPHOS afforded oxazabicyclic lactol **87** via linear aldehyde **86** in 83% yield (Scheme 30).[71] The chemoselective hydroformylation of γ-amidoallylboronate **88** gave linear aldehyde **89** which spontaneously cyclized to give an equilibrium mixture of aldehyde **89** and lactol **90**. Removal of the Cbz group by hydrogenolysis initiates another cascade process, i.e. enamination-hydrogenation, affording indolizidine **91** in 60% overall yield (Scheme 30).[71–73]

5. Conclusion

In summary, an account of the Rh-catalyzed silicon-initiated carbocyclizations of enynes, diynes, and enediynes, i.e. SiCaCs, SiCaC-hydrosilylation, SiCaBs, and SiCaT, as well as carbonylative carbotricyclization (CO-SiCaT), which have discovered and developed in our laboratory, is presented. A novel higher order [2 + 2 + 2 + 1] cycloaddition reaction of enediynes with CO is also discussed. These reactions provide powerful methods in constructing mono-, bi- and fused tricyclic systems from linear starting materials in one step with high tolerance with various functional groups. Thus, these reactions have quite high potential in organic synthesis.

A variety of cyclohydrocarbonylation processes provides efficient and versatile methods for the construction of monocyclic, bicyclic and polycyclic heterocycles as well as carbocycles, starting from readily accessible materials. It is noteworthy that many of cyclohydrocarbonylation reactions can be performed under mild conditions and low pressure of "syngas", which may add more values to these processes as useful synthetic methods. Cyclohydrocarbonylations have already found many applications in organic synthesis, but further creative applications of these processes will surely emerge in the near future.

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NEW CHIRAL CATALYSTS FOR C–C-BOND FORMATIONS

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Abstract: This overview is mainly focused on the use of chiral catalysts for asymmetric reactions in organic synthesis. Recently, a new ligand type having sulfur as the sole stereogenic element has been introduced, and use of such, sulfoximines' leads to products with excellent enantioselectivities in asymmetric C–C-bond forming reactions and imine hydrogenations. For large-scale applications, the synthetic access of sulfoximines had to be improved. In addition, metal-free asymmetric anhydride openings with alkaloids as reaction mediators will be presented.

Keywords: aldol reactions, alkaloids, anhydride openings, asymmetric sulfoxidations, hetero-Diels–Alder reactions, iminations, imine hydrogenations, sulfoximines

1. Introduction

Asymmetric catalysis has been recognized as one of the most efficient methods for the synthesis of optically active molecules.[1] Significant progress has been made in recent years, and the area was highlighted by the awardings of the Nobel Prizes in chemistry to Professors Noyori, Sharpless, and Knowles in 2001.[2] Over the years many new catalysts have been developed, which now allow to convert a variety of achiral starting materials into optically active products with excellent enantioselectivities. The most significant progress has been achieved in asymmetric hydrogenations, whereas enantioselective oxidations and, in particular, C–C-bond forming reactions appear highly challenging. Whereas initially, most chiral catalysts were metal-based, an alternative research area, called, asymmetric organocatalysis', has recently emerged. This overview will report on progress in these two directions related to asymmetric catalysis.

A. Mordini and F. Faigl (eds.), New Methodologies and Techniques for a Sustainable Organic Chemistry, 85–98.

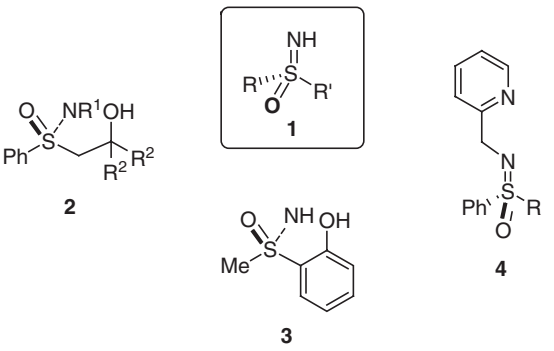
2. Topic 1: New Catalysts for Enantioselective C–c-bond Formations

2.1. SULFOXIMINES AS CHIRAL LIGANDS

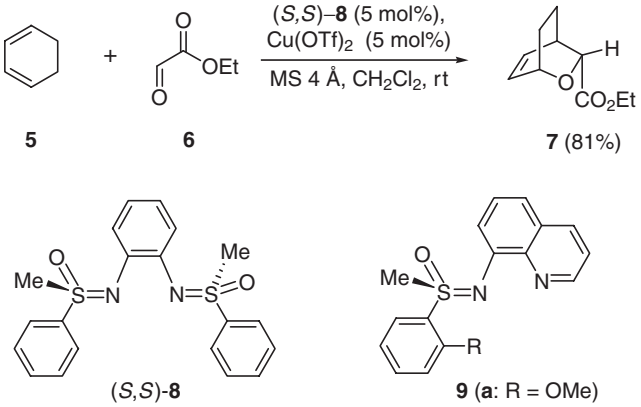
After their discovery in the 1940s, sulfoximines **1** have intensively been investigated by Johnson and co-workers, who utilized these mono-aza analoges of sulfones as (stoichiometric) auxiliaries in organic synthesis.[3] In the early 1990s we initiated a program focussing on attempts to make use of such sulfur reagents as *chiral ligands in asymmetric metal catalysis*.[4] The long-term goal was clearly defined: Sulfoximines were to be found, which could be applied in small (substoichiometric) quantities and which were capable of interacting with metals converting them into efficient chiral catalysts. In the subsequent years, various compounds were identified, which – at least in part – fulfilled the expectations. For example, β-hydroxy sulfoximine **2** proved applicable in catalyzed enantioselective diethylzinc additions to aldehydes,[5] and sulfoximines **3** and **4** could be applied as chirality inducers in titanium-mediated additions of trimethylsilylcyanide to aldehydes[6] and palladium-catalyzed allylic alkylation reactions,[7] respectively. In all case, the enantioselectivities were remarkable (up to >90% ee) demonstrating proof-of-principle (Scheme 1).

A major breakthrough was achieved in 2001, when C_2-symmetric bis-sulfoximine **8** was demonstrated to be applicable in copper-catalyzed hetero-Diels–Alder reactions affording products with up to 98% ee (Scheme 2).[8]

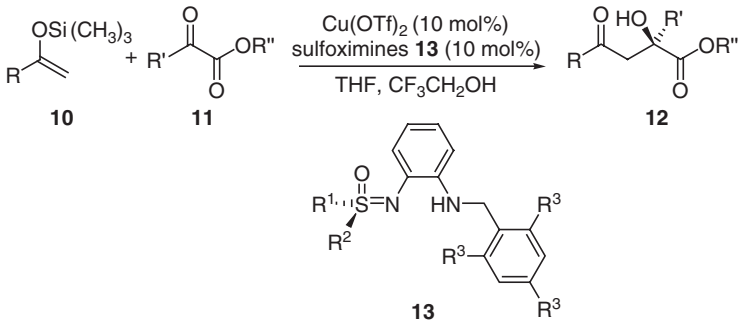
EPR studies of possible intermediates suggested that C_1-symmetric monosulfoximines **9** could be excellent ligands as well.[9] This assumption was confirmed by the application of **9a**, which gave hetero-Diels–Alder products with >90% ee.[10]



Scheme 1. Sulfoximines initially applied in catalyzed C–C-bond formations.



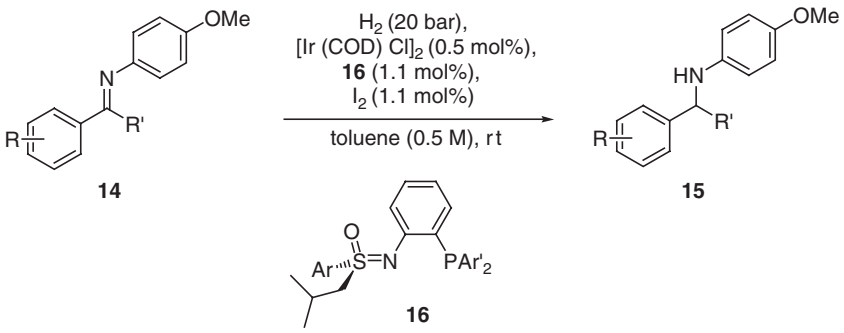
Scheme 2. Asymmetric hetero-Diels–Alder reaction catalyzed by a copper complex bearing C_2-symmetric bissulfoximine **8**.



Scheme 3. Enantioselective Mukaiyama-type aldol reaction catalyzed by a copper complex with C_1-symmetric monosulfoximine 13.

In subsequent work it was demonstrated that copper complexes with C_1-symmetric monosulfoximines **13** catalyzed Mukaiyama-type aldol reactions leading to products with quarternary stereogenic carbon centers with up to 98% ee (Scheme 3).[11] The same ligand type proved also useful in the vinylogous version of this reaction[12] and in ene reactions.[13]

Up to this stage, only *O,N*- and *N,N*-chelates had been investigated as chiral ligands in asymmetric catalyses. The situation changed in 2004, when a new (copper-mediated) *N*-arylation protocol was developed,[14] which allowed – for the first time – the preparation of sulfoximine-based *P,N*-ligands. This discovery proved particularly useful for iridium-catalyzed imine hydrogenations (Scheme 4). With diarylphosphino-substituted sulfoximines **16** excellent enantioselectivities were achieved in asymmetric hydrogenations of imines of type **14** leading to amines **15** with commonly > 90% ee.[15]



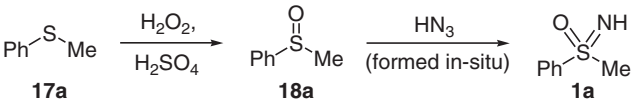
Scheme 4. Asymmetric imine hydrogenations with iridium catalysts bearing diarylphosphino-substituted sulfoximine **16**.

2.2. SULFOXIMINES BY NEW IMINATION REACTIONS

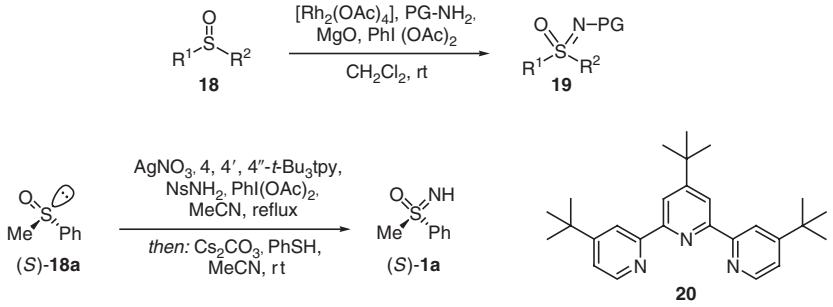
Most commonly, sulfoximines are prepared by oxidation of a sulfide followed by imination of the resulting sulfoxide. In this manner a wide variety of chiral sulfoximine derivatives became accessible, and even large-scale reactions have been well established.[3] In particular, methylphenyl sulfoximine (**1a**) was identified as attractive intermediate since it can easily be prepared in multigram quantities starting from sulfide **17a** in a matter of days.[16] A straightforward resolutions gives access to both enantiomers of **1a**, which can then serve as valuable intermediates for the preparation of more elaborate sulfoximines (Scheme 5).

In the reaction sequence illustrated in Scheme 5, the imination process to give methylphenyl sulfoximine (**1a**) from sulfoxide **18a** plays a critical role. Commonly, mixtures of sodium azide and sulfuric acid are used for this NH-transfer reaction. Noteworthy, however, this protocol involves the (in situ) formation of hydazoic acid (HN_3), which is known to be a highly toxic, explosive gas. In order to avoid this dangerous chemical, we initiated a search for alternative imination methods with the goal to use non-toxic reagents under mild reaction conditions. The first success along these lines was the discovery of an imination reaction catalyzed by rhodium acetate.[17] It proceeds at room temperature and allows the application of various amides including trifluoroacetic amide. In this manner *N*-protected sulfoximines **19** are formed, which can easily be hydrolyzed to give the synthetically important, free' *NH*-sulfoximines **1**. Since the reaction is stereospecific, enantiopure products become readily available (Scheme 6).

Although the rhodium catalysis represented a major advance in the sulfoximine synthesis, the high cost of the metal salt hampers large-scale applications of this protocol. After an intensive metal screening it was found that simple silver nitrate (which is ~100 times less expensive than rhodium



Scheme 5. Synthesis of sulfoximine methylphenyl sulfoximine (**1a**).



Scheme 6. Metal-catalyzed iminations of sulfoxides.

acetate) could also be used as catalyst.[18] In this case, the presence of chelating ligand **20** was essential and (the preparatively convenient) trifluoroacetic amide had to be substituted by nosyl amide as nitrogen source. Again, the imination occurred stereospecifically and various sulfoximines **19** (with PG = Ns) became accessible (Scheme 6). Finally it was discovered that under certain conditions (at elevated temperature) the imination even proceeded in the absence of a metal catalyst.[19] This result is remarkable and appears promising, although at the present stage the substrate scope seems rather limited.

3. Topic 2: Asymmetric Catalysis With and Without Metal

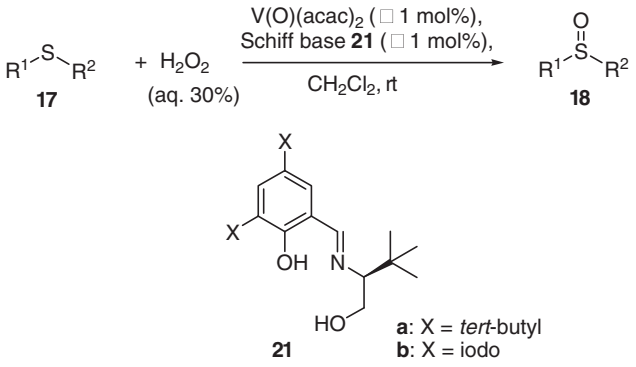
3.1 METAL-CATALYZED ASYMMETRIC SULFOXIDATIONS WITH H_2O_2

Oxygen transfer onto a prochiral sulfide provides a sulfoxide with a stereogenic center at the sulfur atom (e.g. see the conversion of sulfide **17a** into sulfoxide **18a** as shown in Scheme 5). This transformation becomes particularly challenging, when the procedure shall be catalytic and proceed with full stereochemical control. Due to the large number of synthetically interesting sulfoxides (which, for example, have been used as stereochemical directors in asymmetric synthesis[20] and key fragments in biologically active substrates[21]), much effort has been devoted the development of truly catalytic enantioselective sulfide-to-sulfoxide ('cess') oxidations.[22] Most catalytic systems involve chiral titanium complexes and hydroperoxides as oxidants,[23]

and in fact it is this approach, which has most widely been used in the industrial syntheses of optically active sulfoxides.[21] In 1995, we reported an alternative asymmetric sulfide oxidation utilizing a chirally modified vanadium complex as the central catalytic element.[24,25] The results were remarkable in several respect. For example, 1 mol% of the catalyst (or even 0.01 mol%) was sufficient to give optically active sulfoxides (with up to 85% ee). The ligand was an easy-to-prepare Schiff base (**21a**) derived by a one-step condensation of a salicylic aldehyde and *tert*-leucinol. Furthermore, the reaction conditions were simple allowing to perform the catalysis in open vessels with safe and inexpensive hydrogen peroxide as oxidant (Scheme 7).

Soon after our initial publication, Ellman and co-workers applied the chiral vanadium catalyst for the monooxidation of di-*tert*-butyl disulfide yielding synthetically important *tert*-butyl *tert*-butanethiosulfinate with >90% ee.[26] Following the involvement of several other research groups (all around the world), a protocol was recently reported by Jackson and co-workers, which now allows to prepare optically active sulfoxides with >99.5% ee.[27] Interestingly, Schiff base **21b** yielded the most selective vanadium catalyst in this case.

On the basis of the positive results with the chiral vanadium catalysts, we decided to screen other metals on their catalytic behavior in this important sulfide oxidation reaction. To our surprise we found that simple iron salts in combination with Schiff bases **21** were also capable of catalyzing asymmetric sulfoxidations and that hydrogen peroxide was applicable as oxidant in these reactions as well.[28] Albeit the enantiomeric excesses of the resulting optically active products were satisfying (moderate to good), the chemical yield (with 42% at best) was initially the most problematic issue. Taking into account the importance of additives in asymmetric catalysis,[29] the effect of the presence of various carboxylic acids was investigated. Most rapid progress was achieved by using commercially available substituted benzoic acid derivatives, which



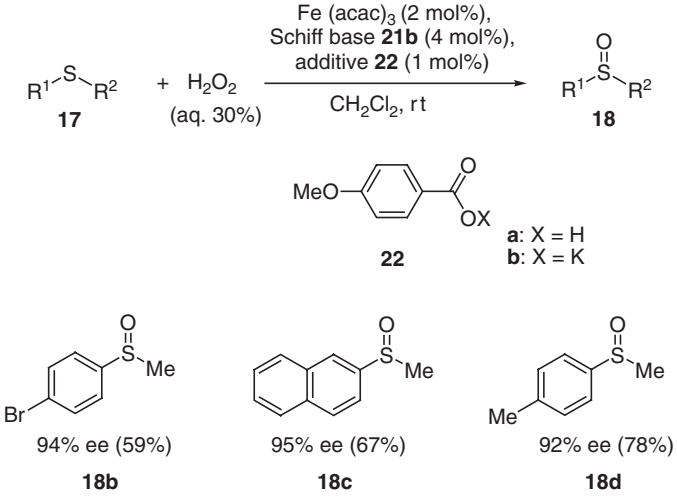
Scheme 7. Vanadium-catalyzed asymmetric sulfoxidation with hydrogen peroxide.

allowed to rapidly test the impact of the electronic and steric properties of the additive. Finally, *para*-methoxy benzoic acid (**22a**), and, in particular, its lithium salt **22b** were identified as the most effective additives in terms of both enantioselectivity and yield.[30] With only 1 mol% of **22**, sulfoxides **18** with up to 96% ee (for *para*-nitrophenylmethyl sulfide as substrate; not shown) were formed (Scheme 8).

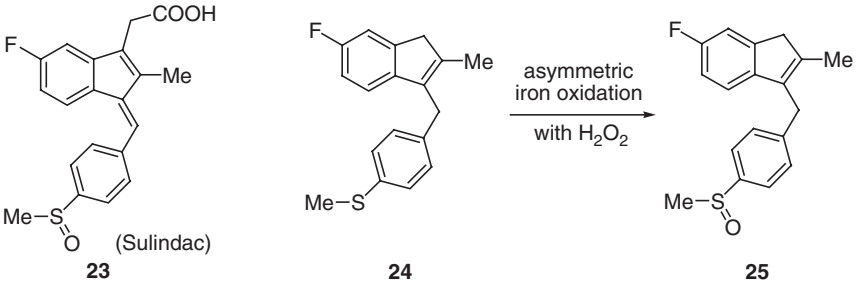
Subsequently, it was demonstrated that this novel asymmetric iron catalysis[31] was applicable in the synthesis of Sulindac (**23**), an efficient nonsteroidal anti-inflammatory drug (NSAID), which was introduced to the market as a racemate by Merck. In this case, the key conversion of sulfide **24** into sulfoxide **25** was studied, and delightfully we found that **25** was formed with up to 92% ee (in 71% yield) using the standard reaction conditions involving 2 mol% of $Fe(acac)_3$, 4 mol% of ligand **21b** and 1 mol% of acid **22a** (Scheme 9). In this case, use of lithium salt **22b** as additive did not improve the catalysis and almost identical results (92% ee, 69% yield) were obtained.[32] Subsequently, sulfoxide **25** was converted into Sulindac (**23**) by a known epimerization-free route.[33]

3.2. ALKALOID-MEDIATED ASYMMETRIC ANHYDRIDE OPENINGS

As highlighted in the previous chapter, one of the most impressive characteristics of the vanadium-catalyzed asymmetric sulfide oxidation is its required minimal catalyst loading, which can be as low as 0.01 mol%. In comparison



Scheme 8. Iron-catalyzed asymmetric sulfoxidation with hydrogen peroxide.

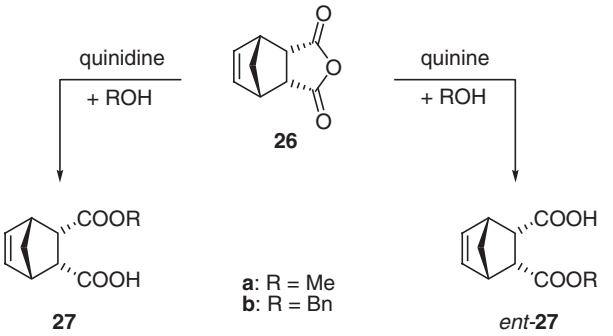


Scheme 9. Iron-catalyzed asymmetric synthesis of Sulindac.

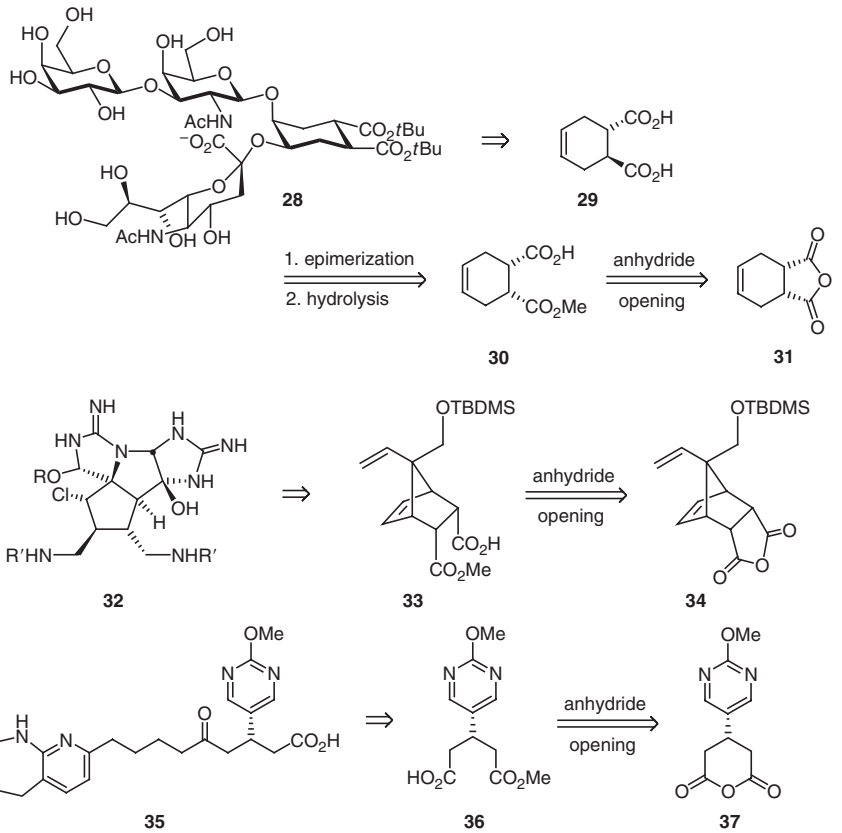
to other asymmetric oxidations this is remarkable, and in conjunction with the use of the environmentally friendly oxidant, hydrogen peroxide, this attribute renders this asymmetric sulfoxidation reaction synthetically particularly attractive.[34] At this level of catalyst loading, traces of remaining metal should be easy to remove, which might become relevant in the preparation of pharmaceutically important products. *A subsequent advance in an asymmetric catalysis could be the avoidance of any metal in a synthetic organic transformation*. Recently, this, non-metallic' approach towards catalytic reactions has been termed "Asymmetric Organocatalysis".[35] Despite the fact that metal-free catalysts have been in the focus of a large number of investigations for almost a century by now,[36] the field recently attracted significant visibility and became a high-priority research area all around the world.

Our group has been investigating metal-free transformations since the late 1990s, and the first published contribution stems from 1999.[37] Based on initial studies by Oda and Aitken,[38] we reported the use of alkaloids in asymmetric openings of *meso*-anhydrides with methanol yielding hemiesters with up to 98% ee. By the selection of the alkaloid (either quinidine or quinine), both enantiomers of the products became available.[37] One single example illustrating this strategy is shown in Scheme 10. In an analogous manner a wide variety of substrates reacted affording products with generally >90% ee.[39,40] Furthermore it is noteworthy that selected epimerization at the ester-bearing carbon allowed to convert the *cis*- into the *trans*-isomeric hemiesters.

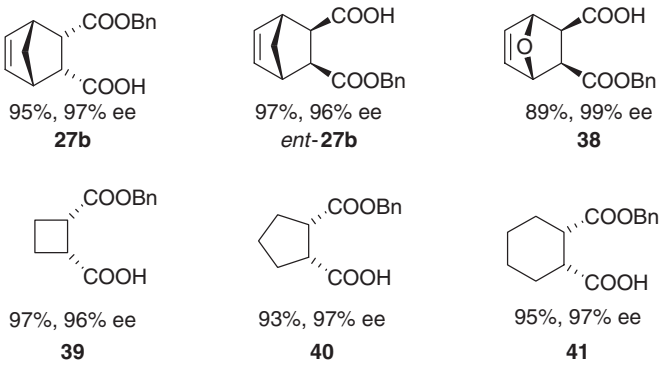
Products such as **27** were then demonstrated to be excellent intermediates for a variety of synthetically important substrates such as β-amino acid derivatives,[41] ROM-oligomers thereof,[42] unsymmetrical norbornane scaffolds as inducers for hydrogen bond interactions in peptides,[43] bicyclic diamines,[44] and backbones for unsymmetric bisoxazolines.[45]



Scheme 10. Example of a metal-free asymmetric opening of a *meso*-anhydride.



Scheme 11. Complex products obtained by using the alkaloid-mediated anhydride opening as starting point.



Scheme 12. Products obtained by asymmetric *meso*-anhydride opening using benzyl alcohol as nucleophile.

Particularly pleasing was the acceptance of this protocol by the community revealing its importance hemiester **30** with a six-membered carbocyclic backbone (obtained by the alkaloid-mediated asymmetric anhydride opening of **31** with methanol) was a highly useful intermediate in the synthesis of a cholera toxin **28**.[46] Carreira showed that the same process was applicable as starting point (from *meso*-anhydride **34**) for the synthesis of marine alkaloid **32**.[47] A related version of the anhydride opening was used by Merck in their synthesis of $\alpha_v\beta_3$-antagonist **35** starting from anhydride **37** (Scheme 11).[48]

The most recent improvement in this asymmetric organocatalysis involves the use of benzyl alcohol as nucleophilc reagent.[49] The process was optimized and on a 10 mmol scale (in toluene as solvent) consistently products with both excellent ee-values and high yields have been obtained. A few examples are shown in Scheme 12.

Currently, other amino alcohols, which can be obtained by efficient enantiomer resolutions,[50] are being investigated as chiral catalysts.

Acknowledgments

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INTRAMOLECULAR REACTIONS OF ALKYNES WITH ALKENES CATALYZED BY PLATINUM AND GOLD

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Abstract: Two major pathways are followed in the reaction of alkenes with alkynes catalyzed by electrophilic transition metals. If the metal coordinates the alkyne and the alkene, an oxidative cyclometallation can ensue to give a metallacyclopentene, which usually evolves by β-hydrogen elimination (Alder-ene cycloisomerization). Alternatively, the selective coordination of the metal to the alkyne promotes an attack of the alkene (usually *anti*) to give cyclopropyl metal carbenes.

Keywords: gold, platinum, enynes, cyclizations, rearrangements, atom-economical reactions

1. Introduction

Reactions of α,ω-enynes **1** catalyzed by a wide variety of electrophilic transition metal complexes or halides MX_n give carbo- or heterocycles **2–5** in atom-economical processes (Scheme 1).[1]

The first examples of this chemistry were reported by Trost using palladacyclopentadiene complexes formed in situ, which usually favor formation of 1,4-dienes of type **3** (Alder-ene cycloisomerization).[1,2,3] Later on, cationic Ru(II) complexes such as $[CpRu(MeCN)_3]^+PF_6^-$ were found to catalyze the Alder-ene-type cycloisomerization of enynes to give selectively dienes of type **3** under mild conditions.[4] Cationic Rh(I) complexes have been also shown to be excellent catalysts for the formation of cycloisomerization products **3**.[5]

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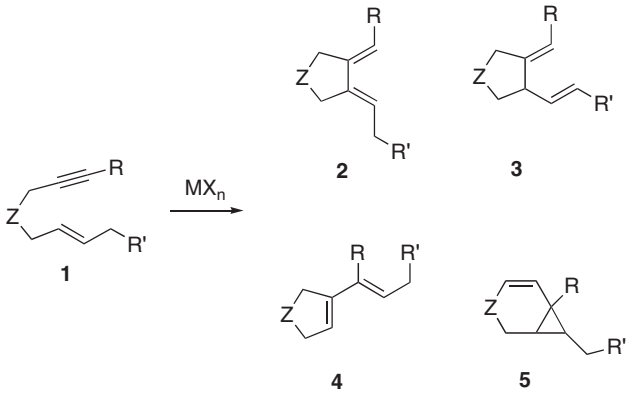
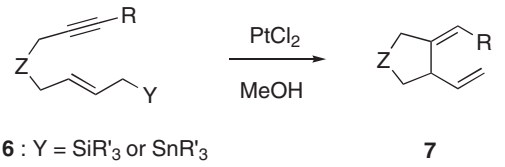
Skeletal rearrangement products **4** are also formed in reactions catalyzed by Pd(II) complexes by an apparent metathesis reaction.[2,4] In addition, several electrophilic Ru(II) and Pt complexes catalyze the formation of dienes of type **4** from enynes **1**.[6,7,8,9] Ir(I) complexes also catalyze the cycloisomerization or rearrangement of enynes depending on the reaction conditions.[6c] Interestingly, the non-transition metal catalyst $GaCl_3$ has been shown to be particularly active in the skeletal rearrangement of enynes.[6d] Another type of cyclization has been observed for enynes tethered by heteroatoms (Z = O or NR), which give cyclopropanes of type **5** with $PtCl_2$[7] or $PtCl_4$[10] as catalysts.

Transition metals also catalyze the transformation of allylsilanes or allylstannanes **6** into dienes **7** (Scheme 2).[11] This reaction leads to five- and six-membered ring carbo- and heterocycles and is catalyzed by several electrophilic metal halides, although more general results are usually obtained with $PtCl_2$ in MeOH. In this reaction, the transition metal probably coordinates the alkyne to form an electrophilic (η^2-alkyne)metal complex, which is attacked intramolecularly by the allyl nucleophile in an *anti* manner. Although this cyclization appears to be similar to the Alder-ene cycloisomerization process (Scheme 1), the contabfiguration of the exocyclic alkene in **7** is the opposite of that displayed in products **3**.



Scheme 1. Transition metal catalyzed cyclization of enynes.



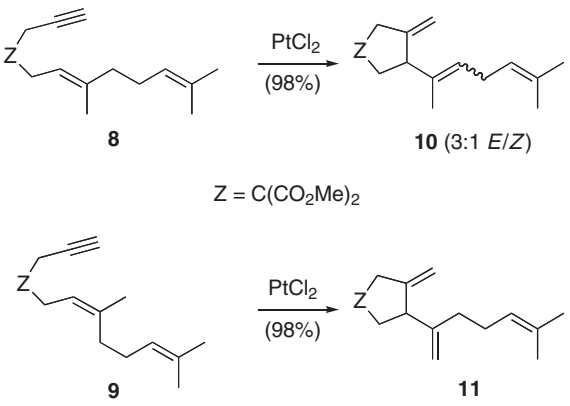
Scheme 2. Transition metal catalyzed cyclization of allylsilanes or stannanes.

In the processes summarized in Schemes 1 and 2, the metal can selectively coordinate the alkyne and then trigger the attack of the alkene or, alternatively, could coordinate simultaneously the alkyne and the alkene. In this review we present the most important reactions catalyzed by transition Pt and Au that follow these two alternative reaction pathways.

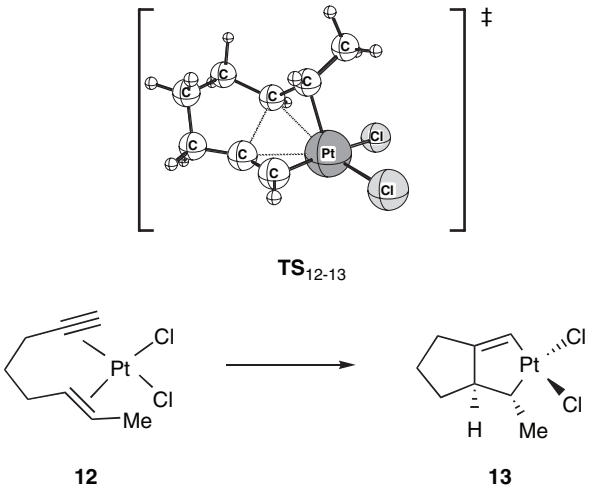
2. Alder-ene cycloisomerization

When the reactions of enynes catalyzed by $PtCl_2$ are performed in acetone or 1,4-dioxane as solvents, cycloisomerization products are selectively obtained in good yields.[12,13] These reactions are fully atom-economical processes that proceed under relatively mild conditions. Yields are usually high, and work-up procedures are very simple. The process results in the formal migration of a hydrogen from the alkyl chain *trans* to the alkene. Thus, derivatives **8** and **9** give stereospecifically trienes **10** and **11**, respectively (Scheme 3). Similar cycloisomerizations also proceed with $RuCl_3$ or $Ru(L)_2Cl_2$ as the catalysts.[12]

Deuteration studies demonstrate that the Alder-ene cycloisomerization is an intramolecular process. According to DFT calculations carried out on (*E*)-2-octen-1-yne complexed to $PtCl_2$ (**12**), the reaction gives platinacycle **13** by an oxidative cyclometalation (Scheme 4). This transformation is exothermic (25.7 kcal·mol^{-1}), although it proceeds with a significantly high activation energy (E_a = 29.6 kcal·mol^{-1}). It is important top note that mechanistically related processes take place in other important organometallic transformations. Thus, an oxidative cyclometallation is one of the key steps in the synthetically useful Pauson–Khand synthesis of cyclopentenones with $Co_2(CO)_8$[14] or other transition metals.[15]



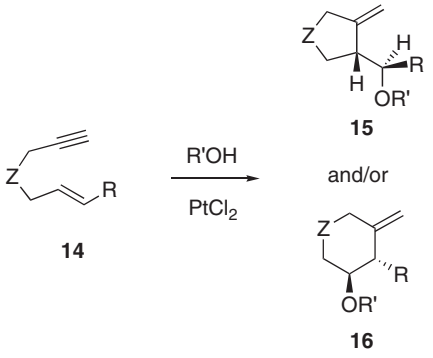
Scheme 3. Alder-ene cycloisomerization.



Scheme 4. DFT calculation in the Alder-ene cycloisomerization.

3. Alkoxy- and hydroxycyclizations

The reaction of simple enynes **14** with $PtCl_2$ as catalyst in the presence of alcohols or water gives carbo- or heterocycles **15** and **16** by *5-exo-trig* or *6-endo-trig* cyclizations (Scheme 5).[12,13] In this context, terms *5-exo-trig* and *6-endo-trig* are only meant to describe the overall cyclization with regards to the C–C bond formation on the alkene. As discussed bellow, this is a stepwise process, where the formation of **15** or **16** depends on the regioselective cleavage of one of the cyclopropane bonds of the intermediate.

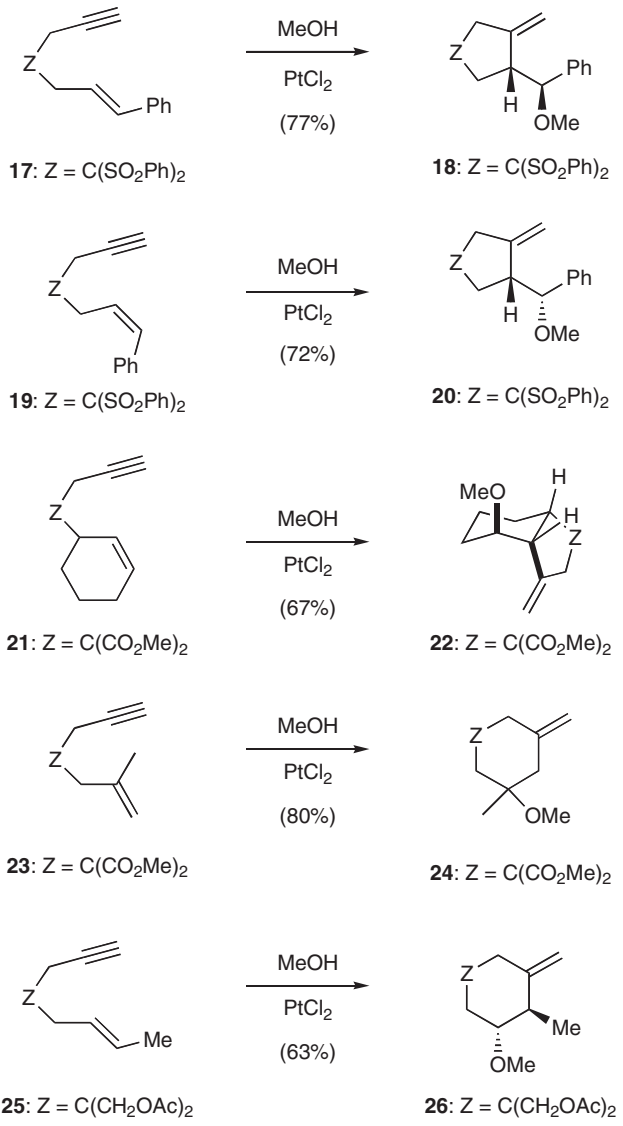


Scheme 5. *5-Exo-trig* or *6-endo-trig* cyclizations of enynes.

Although more limited in scope, the alkoxy- and hydroxycyclization Scheme 5 would stay better here after the first paragraph of chapter 3 can also be promoted by Ru(II), Au(III),[12] and Pd(II) complexes as catalysts.[13a]

The hydroxycyclization reaction has also been found to be catalyzed by highly electrophilic $Hg(OTf)_2$.[16]

Representative cyclization examples carried out in MeOH are shown in Scheme 6. The reaction is stereospecific, as shown in the transformation of *E*-enyne **17–18** and *Z*-enyne **19–20**. The reactions proceed, formally, by the *anti*-addition of the alkyne and ROH to the alkene, as demonstrated in the transformation of **21** into **22** (Scheme 6).

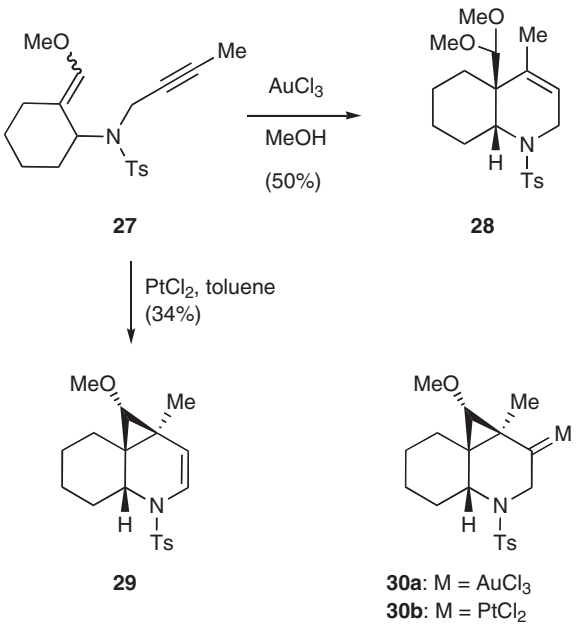


Scheme 6. Representative cyclization examples.

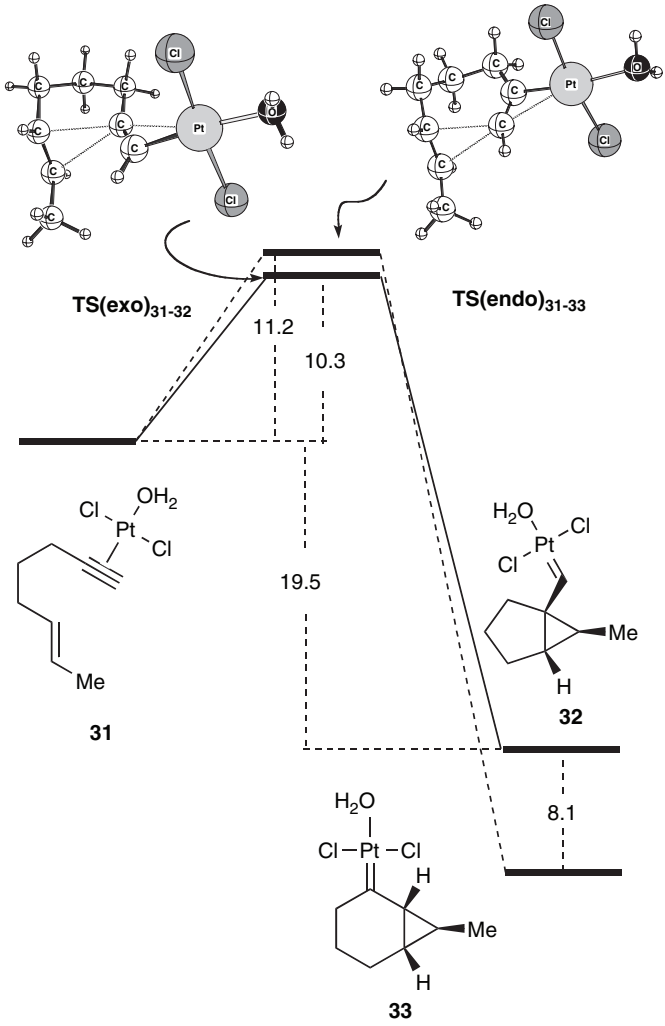
The *6-endo-trig* cyclization is favored in the cyclization of enyne **23**, with a 2,2-disubstituted alkene, which gives cyclohexane derivative **24**. Substrate **25**, with a 1,2-disubstituted alkene, also reacts by a *6-endo-trig* pathway to give exclusively **26**. Interestingly, a substrate similar to **25**, but with $C(CO_2Me)_2$ reacts to give a 1.5:1 mixture of *6-endo-trig* and *5-exo-trig* products, whereas the corresponding disulfone ($Z = C(SO_2Ph)_2$) cyclizes by the *5-exo-trig* pathway.

The *6-endo-dig* cyclization is also possible.[17] Thus, enol ether **27** reacts in MeOH to give heterocycle **28** as the only isolated product (Scheme 7). In this case, best results were obtained with $AuCl_3$ as the catalyst. When the reaction was carried out in a non-nucleophilic solvent, cyclopropane **29** was obtained. Formation of **28** and **29** can be rationalized by evolution of intermediates **30a** or **30b** by nucleophilic attack by MeOH or β-hydrogen elimination, respectively.

To analyze the competitive *5-exo-dig* and *6-endo-dig* cyclization modes, DFT calculations were performed on (*E*)-6-octen-1-yne complexed to $PtCl_2(H_2O)$ (**31**) (Scheme 8).[17] Evolution of complex **31** was found to provide bicyclic complexes **32** and **33**, which can be described as cyclopropyl Pt carbenes or cyclopropyl methyl cations[18,19] stabilized by the $PtCl_2(H_2O)$ fragment. Both reactions are exothermic (−19.5 and −27.6 kcal·mol^{-1}),



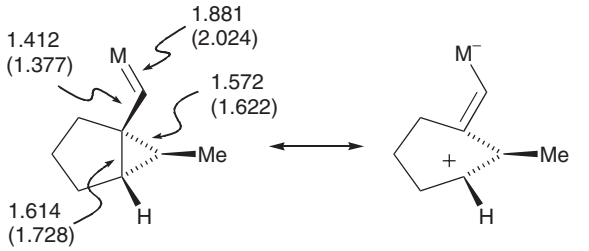
Scheme 7. *6-Endo-dig* cyclization.



Scheme 8. DFT calculation for competitive *5-exo-dig* and *6-endo-dig* cyclization modes.

although the six-membered product **33** is the most stable intermediate. For related cases, but with an oxygen at the tether, the *6-endo-dig* pathway was found to be both kinetically and thermodynamically the most favored process. Similar results were obtained for analogous enyne-$AuCl_3$ complexes.[17]

Calculations of (*E*)-6-octen-1-yne complexed to $[Au(PH_3)]^+$ indicate that a highly polarized complex **34** similar to **31** is formed, which shows a substantial electron-deficiency at C-2.[20] This complex reacts by an *exo* cyclization with a very small activation energy (E_a ~0.1 kcal·mol^{-1}) to give cyclopropyl gold(I) carbene **34** (Scheme 9).



Scheme 9. Bond distances (Å) for the calculated (DFT) structures of the *exo-dig* intermediates. Values in parentheses correspond to the Au(I) intermediate **34**.

Complex **34** shows a very distorted cyclopropyl structure in which the cyclopropane C–C bonds conjugated with the carbene are particularly long. The structure of this intermediate actually resembles canonical form **34b**, which can be envisioned as a Au(I)-stabilized homoallylic carbocation. The activation energy for the *6-endo-dig* process to give a carbene similar to **33** (Scheme 8) is 6.1 kcal·mol^{-1}, which indicates that the *exo* cyclization is favored with Au(I) catalysts, at least for substrates related to (*E*)-6-octen-1-yne.

Accordingly, cationic Au(I) catalysts formed by the activation of [Au(PPh_3)Me] with protic acids catalyze the methoxycyclization of enynes (**14** → **15**) under much milder conditions than those required using $PtCl_2$ or any other metal catalyst.[20] With this cationic Au(I) catalyst, most enynes are efficiently cyclized at room temperature, whereas reaction catalyzed by Pt(II) require longer times and higher temperatures (60–65°C). Better results were achieved by generating the Au(I) catalysts by chloride abstraction from [Au(L)Cl] complexes with Ag(I) salts.[20b] Related Au(I) complexes also promote a variety of reactions of 1,5-enynes.[21] Importantly, Alder-ene type products have not been observed in Au(I)-catalyzed reactions, which is consistent with the selective coordination of cationic complexes $[Au(L)]^+$ to the alkyne.

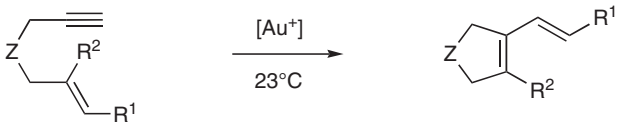
4. Skeletal rearrangement

Skeletal rearrangement products **4** (Scheme 1) are also obtained by metathesis reactions of **1** catalyzed by Grubbs Ru(II) carbenes.[22] However, the reactions of **1** catalyzed by electrophilic metal complexes MX_n proceed by fully intramolecular processes and are mechanistically different from metathesis reactions.[20]

Some of the most active catalysts for these transformations are Au(I) complexes formed in situ from $[Au(PPh_3)Cl]/AgX$ (X = BF_4 or SbF_6).[20] With these catalysts, the rearrangements of α,ω-enynes **35–38** are completed in most cases in less than 15 min at room temperature to give products **39–42** in good to excellent yields (Scheme 10).

Importantly, skeletal rearrangement by an *endo-dig* pathway was also observed for the first time with Au(I) catalysts.[20] Thus, enyne **43** gives cleanly heterocycle **44**, while enyne **45** affords a 7:1 mixture of *endo* (**46**) and *exo* (**47**) rearrangement products (Scheme 11).

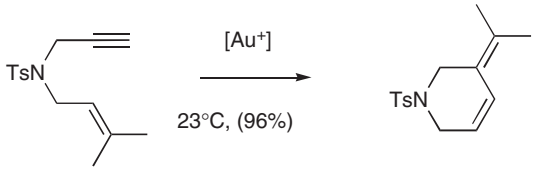
Recently, we have found that Au(I) species formed from complexes **48a–c** and $AgSbF_6$,[20,23] or cationic complexes **49a–b**[24] (Scheme 12) are particularly



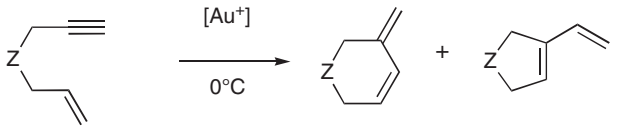
35: Z = $C(SO_2Ph)_2$, $R^1 = R^2 = H$ — **39** (100%)
36: Z = $C(CO_2Me)_2$, R^1 = Me, R^2 = H — **40** (96%)
37: Z = $C(SO_2Ph)_2$, R^1 = Me, R^2 = H — **41** (100%)
38: Z = $C(CO_2Me)_2$, R^1 = H, R^2 = Me — **42** (76%)

$[Au^+] = [Au(PPh_3)Cl]/AgSbF_6$

Scheme 10. *Exo-dig* rearrangements of α,ω-enynes.



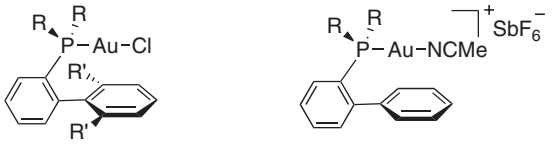
43 **44**



45: Z = $C(CO_2Me)_2$ **46** (67%) **47** (10%)

$[Au^+] = [Au(PPh_3)Cl]/AgSbF_6$

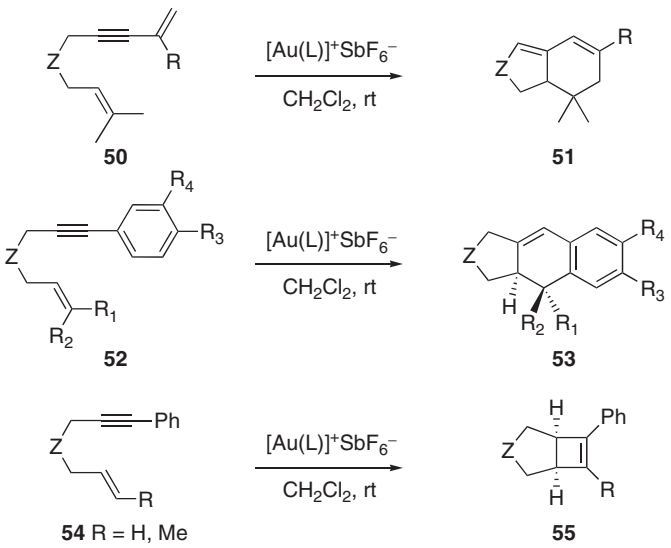
Scheme 11. *End-dig* rearrangements of α,ω-enynes.



48a R = Cy, R' = H
48b R = *t*Bu, R' = H
48c R = Cy, R' = OMe

49a R = Cy
49b R = *t*Bu

Scheme 12. Cationic complexes for enynes cyclization.



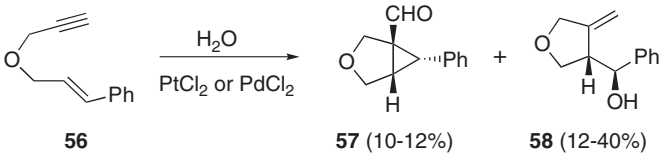
Scheme 13. Examples of enynes cyclizations with cationic Au complexes.

active for the cyclization of a variety of enynes. In these complexes, the sterically hindered biphenylphosphine presumably stabilizes the highly reactive Au(I) center.

Thus, dienynes **50** react with cationic Au(I) catalysts bearing biphenyl-based phosphines leading to products **51** as a result of a formal intramolecular [4 + 2] cycloaddition (Scheme 13).[24] The analogous thermal cycloadditions (dehydro-Diels-Alder reactions) of dienynes such as 2-methylnona-1,8-dien-3-yne only take place at temperatures as high as 600°C.[25] Similarly, enynes **52** substituted at the alkyne with an aryl group led to products **53** resulting from a formal intramolecular [4 + 2] cycloaddition occurring also at unusually low temperatures.[23] On the other hand, substrates **54** with R = H or Me gave cyclobutenes **55** with Au(I) catalysts.[26,27]

5. Cyclopropyl Carbenes as Intermediates

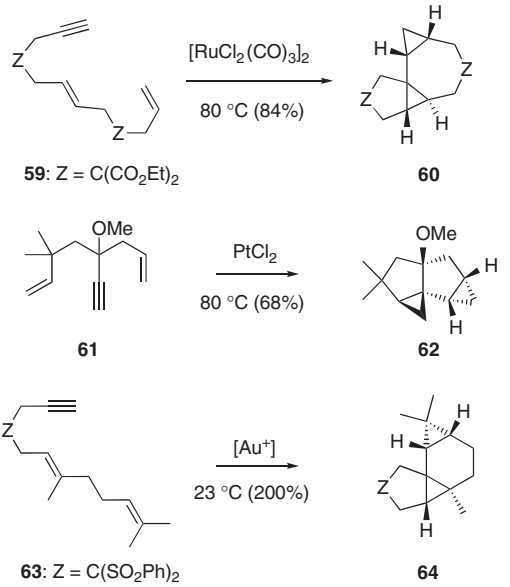
Products of intramolecular cyclopropanation **5** (Scheme 1) are obtained for enynes where Z = O or NTs.[7,10] An example of cyclopropanation catalyzed by $PtCl_2$ was shown in Scheme 7 (**27** → **29**). Cyclopropyl derivatives were occasionally obtained as secondary products in hydroxycyclization reactions of enynes. Thus, reaction of substrate **56** using $PtCl_2$ or $PdCl_2$ as catalysts, lead to cyclopropane **57**, in addition to the expected alcohol **58** (Scheme 14).[12,13]



Scheme 14. Cyclopropanation of enynes.

These results support the involvement of **32–34** as the actual intermediates in the intramolecular reactions of alkenes with alkynes catalyzed by electrophilic MX_n.

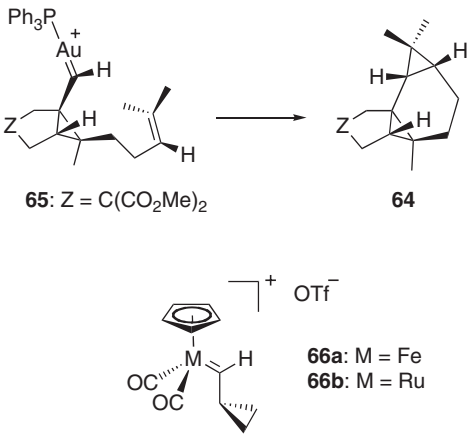
The involvement of metal carbenes was strongly suggested by the results disclosed by the group of Murai in the cyclization of **59** to give tetracycle **60**, in which a Ru(II) carbene is intramolecularly trapped by the terminal



Scheme 15. Cyclopropanes by polyciclization of enynes.

alkene[28] (Scheme 15). Related cyclizations of substrates **61** and **63** are catalyzed by Pt(II),[29] and Au(I)[20,30] complexes, respectively.[31] Other Rh(I) carbenes, formed by intramolecular reactions of carbonyl compounds or imines with alkynes, have been trapped intermolecularly with alkenes.[32]

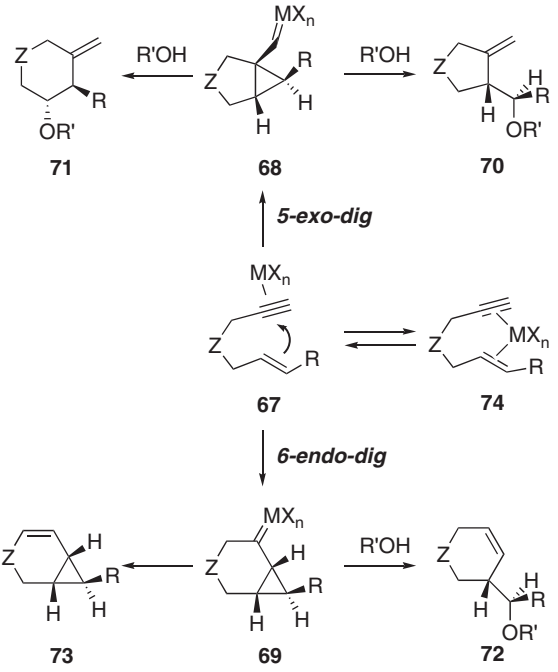
The polycyclizations shown in Scheme 15 provide tetracycles **60**, **62**, and **64** stereoselectively. The stereochemistry of the second cyclopropanation can be rationalized by assuming an antiperiplanar arrangement of the cyclopropane and



Scheme 16. Antiperiplanar arrangement of the cyclopropane and the metal carbene in the cyclopropanation reactions.

the metal carbene (i.e. **65**, Scheme 16), which is in full agreement with the results of the calculations.[12,17,20] This arrangement is also in accord with the results of Brookhart et al.,[33] which show a preferred *s-trans*-anticlinal (antiperiplanar) conformation for cyclopropyl carbene iron (**66a**) and ruthenium (**66b**) complexes.

Calculations and experimental results of the alkoxy and hydroxy cyclizations are in accord with the general mechanistic interpretation summarized in Scheme 17. Thus, coordination of MX_n to the alkyne forms a (η^2-alkyne)metal complex **67**. In addition to the *5-exo-dig* cyclization via complex **68**, a *6-endo-dig* process gives complexes like **69**. Attack of R′OH at the electrophilic cyclopropyl carbons of **68** leads to **70** or **71**. On the other hand, intermediate **69** could suffer nucleophilic attack to give **72** or by hydrogen elimination (probably via a base-catalyzed process) to give **73** in the case of Z = O or NR. The alternative nucleophilic attack at the other electrophilic cyclopropyl centre of **69** would give seven-membered ring compounds, although this process has not yet been observed. The regioselectivity in the nucleophilic attack is controlled by the substitution pattern of the alkene and the electronegativity of the substituent Z. Accordingly, attack at the more substituted site of the alkene is usually observed. Strong

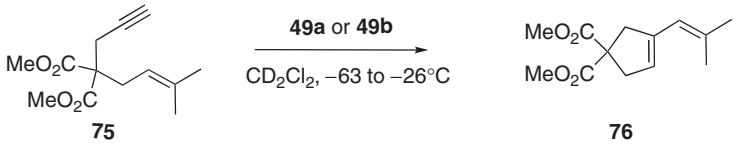


Scheme 17. Mechanistic interpretation of the alkoxy and hydroxy cyclizations.

electron-withdrawing substituents at the tether Z favor the formation of five-membered ring derivatives **70**, while less electron-withdrawing substituents at the tether favor formation of six-membered ring derivatives **71**.

Although the Alder-ene cycloisomerization and alkoxy- and hydroxy cyclization processes are mechanistically different, they are related by an equilibrium between species in which the metal coordinates the alkyne **67** and species **74** where the enyne coordinates to the metal through both the alkyne and the alkene. Calculations show that the equilibrium is shifted towards **67** for $MX_n = PtCl_2$ by the addition of H_2O, which is a better ligand for Pt(II) than the alkene.[12]

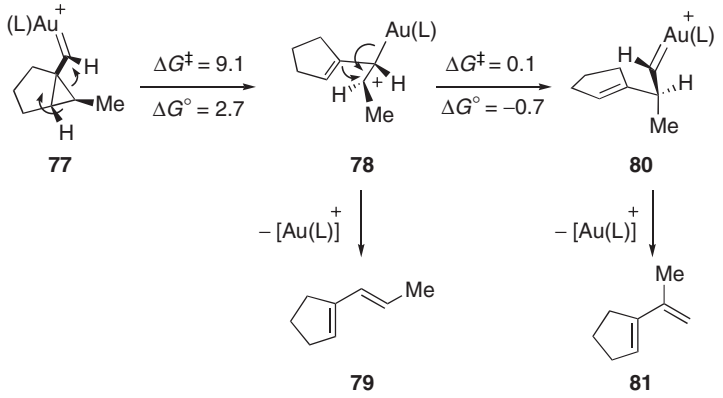
Single cleavage rearrangement of enyne **75** to form quantitatively **76** could be carried at a temperature as low as −63°C with catalysts **49a–b** (Scheme 18). Importantly, no intermediate was observed during clean formation of diene **76** from **75** by ^{1}H NMR in CD_2Cl_2. The rearrangement was found to be pseudo-first order in **75**, which led to the determination the thermodynamic parameters shown in Scheme 18. These results indicate that the reaction proceeds with a low enthalpic barrier and that the process is a entropically controlled. The large and negative activation entropies suggest that an associative ligand substitution[34] is the rate-determining step of the process. Most probably this corresponds to the last step in the catalytic cycle, namely the substitution of diene **76** coordinated to Au(I) by the incoming enyne **75**.



	$\Delta G^{\ddagger}_{298}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
49a	21.7 ± 1.1	3.7 ± 0.3	–60.6 ± 1.2
49b	21.2 ± 2.1	6.2 ± 0.5	–50.3 ± 2.0

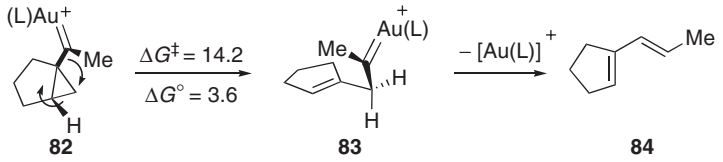
Scheme 18. Single cleavage rearrangement of enynes. $\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}.

DFT calculations[35] support pathways for the skeletal rearrangement summarized in Schemes 19 and 20. Thus, complex **77** evolves to form cation **78**, which would furnish dienes **79** by elimination of [Au(L)]$^+$ (Scheme 19).[24] Alternatively, a 1,2-alkenyl shift gives gold carbene **80** through an almost flat potential surface. Dienes **81** would result from **80** by β-hydrogen elimination and demetalation. This β-hydrogen elimination probably involves a base-promoted elimination of the hydrogen α to the carbene, followed by a proto-demetalation of the resulting alkenyl–metal complex.



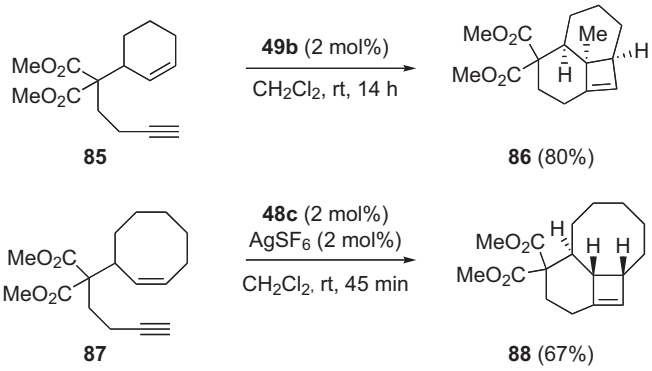
Scheme 19. Suggested pathway for the skeletal rearrangement. $\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}.

Intermediate **82** would be formed in the cyclization of 1-hepten-6-yne, a model for enynes substituted at the alkyne (Scheme 20). In this case, the double cleavage rearrangement was found to give directly intermediate **83**. This process is mechanistically quite remarkable as it involves a 1,2-shift of a metal carbene with concomitant cleavage of the distal C–C bond of the cyclopropane and formation of a double bond.



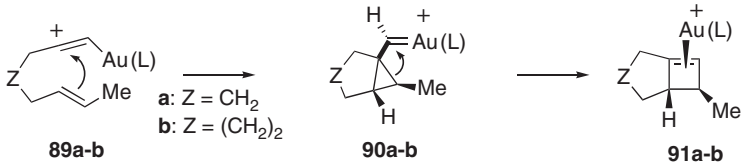
Scheme 20. Mechanistic pathway of the cyclization of 1-hepten-6-yne $\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}.

Cyclobutenes are observed in some reactions of α,ω-enynes catalyzed by Pd(II),[2,36] Pt(II)[7], and $GaCl_3$.[6d] We have found that Au(I) species formed from complexes **48a–c** and $AgSbF_6$, or cationic complexes **49a–b** are particularly active catalysts for the cyclization of enynes.[20,23,24,30] Thus, enyne **85** reacts with catalyst **49b** to give cleanly **86** at room temperature (Scheme 21). Similarly, reaction of enyne **87** with a cationic Au(I) catalyst generated from **48c** gave **88**. Tricycles **86** and **88** did not undergo ring opening at 120–150°C to form 1,3-dienes.



Scheme 21. Cyclobutanes formation in α,ω-enynes rearrangement.

Schemes 19 and 20 provide explanations for the single and double cleavage rearrangements that do not involve the intermediacy of any cyclobutene. Indeed, a direct pathway for the formation of a cyclobutene from **77** was not found. Similar results were obtained with the platinum analogue of **77**. In contrast, *syn*-**89** forms **90** (Scheme 22). This ring expansion is more favorable for the formation of bicyclo[3.2.0]oct-6-enes from 1,7-enynes (**89b–91b**) in accordance to experiments (see Scheme 6). Importantly, complexes *syn*-**90a–b** are formed by a *syn*-type attack of the alkene to the (alkyne)gold moiety of complexes **89a–b**.



89a-b **90a-b** **91a-b**

	$\Delta G^{\ddagger}$	ΔG		$\Delta G^{\ddagger}$	ΔG
89a → **90a**	9.4	–8.8	**90a** → **91a**	7.8	–5.4
89b → **90b**	10.8	–5.2	**90b** → **91b**	5.7	–17.9

Scheme 22. Formation of cyclobutanes in the rearrangement of enynes $\Delta G^{\ddagger}_{298}$ and $\Delta H^{\ddagger}$ in kcal mol^{-1}, $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}.

The *anti* to *syn* isomerization from **77** (Scheme 19) to **90a** (ΔG = 3.1 kcal mol^{-1}) requires a relatively high activation energy of 24.7 kcal mol^{-1}, which can be attributed to the loss of conjugation between the gold carbene and the cyclopropane. This isomerization process is then rather unlikely under the reaction conditions, as the initially formed anti **77** would suffer a more facile rearrangement via **78** ($\Delta G^{\ddagger}$ = 9.1 kcal mol^{-1}, Scheme 19).

6. Summary and Outlook

Following the pioneer work of Trost's and Murai's groups, more recent work with Pt(II) and Au(I) catalysts has allowed to establish a clearer picture of the mechanisms followed in the intramolecular reactions of alkynes with alkenes catalyzed by late-transition metal complexes. Thus, alkynes react with (η^2-alkyne)metal complexes to form cyclopropyl metal carbenes **92** (Scheme 23) as intermediates. This reaction mode corresponds to an electrophilic addition to an alkene, in which the electrophile is a (η^2-alkyne)metal complex.

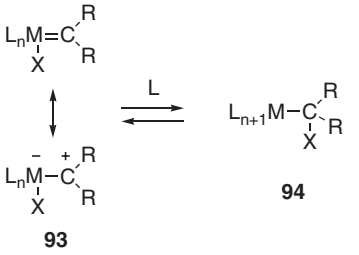
The similarities between this chemistry and the carbocationic rearrangements of the cyclopropylmethyl-cyclobutyl manifold, first pointed out by Fürstner,[7] is remarkable. However, differences clearly exist due to the metal stabilization of the reactive species. Significant progress has also been done

92

Scheme 23. Cyclopropyl metal carbenes.

in broadening the scope of these synthetically useful transformations. At present, Au(I) [20,23,24,30] complexes are the most reactive (alkynophilic) catalysts for the activation of α,ω-enynes, allowing for the selective activation of a variety of substituted substrates under very mild conditions.

Although all experimental and theoretical studies point to distorted cyclopropyl metal carbenes as the likely intermediates in these transformations, it should be stressed that no such carbene has been isolated in any reaction from an enyne and MX_n.[37] Possible alternatives to metal carbenes complexes **93** (Fisher-type) are metal carbenoids[38] **94** (Scheme 24), which could be in equilibrium with the carbene species.



Scheme 24. Intermediates which could be involved in the rearrangements of enynes.

Other aspects of this chemistry also require clarification. Thus, the factors that control the *exo*/*endo*-*dig* selectivity in the attack of the alkene to the alkyne as well as the single–double selectivity in the skeletal rearrangements are not completely understood. Additional mechanistic work is also required to clarify the mechanism of the *endo* rearrangements.

Furans have also been shown to react like alkenes (similarly to enol ethers)[17] in their intramolecular reactions with alkynes catalyzed by Pt(II)[39] and Au(III).[40] Whether or not similar pathways are followed in the Friedel–Crafts-type reactions of arenes[41,42] and other heteroarenes[43] with alkynes catalyzed by electrophilic MX_n complexes remains to be established.

Acknowledgments

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INDUSTRIAL SYNTHESIS DESIGN WITH LOW ENVIRONMENTAL IMPACT IN THE PHARMA INDUSTRY

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Abstract: The key concepts of industrial process design are discussed. Two industrial synthesis of 7ACA and Erlotinib hydrochloride centred on the use of enzymatic and organometallic catalysis are described.

Keywords: catalysis, fermentation, synthesis, cephalosporin, anticancer

1. Introduction

Nowadays, medicinal chemists can design any kind of structure based on the paramount of chemical reaction and technologies available. The most important and spectacular characteristics of modern drugs are complexity and sophistication of their architecture. However, in addition to this challenge, Process Development Groups must design processes that comply with other basis requirements define by several external entities: EH&S, quality, IPO.[1]

NATO countries can sustain these challenges in competition with emerging countries only with the development of chemical synthesis with an extraordinary technical and scientific efforts to get a very low impact of variable costs: raw materials, energy and labour. In fact, the cost structure in India and China is completely different, being in these countries raw materials and energy 90–95% of the full cost.

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2. Process design

European and US chemical companies must apply the 12 principles of green chemistry.[2] European laws in terms of EH&S changed completely after two dramatic accident in the 1970s, Seveso (Italy, 1976) and Flixborough (UK, 1974).[3] The Sheldon E-factors range for pharmaceutical products is between 25 and 100. This number clearly shows that, what is going into a reactor (reagents, solvents, gas, and energy), is coming out mainly as a waste (Figure 1). Process Development Groups must design processes that comply with Green Chemistry principles not only to have a low environmental impact, but mainly to have low production costs.

The synthesis of complex chemical structures is generally approached, when possible, taking advantage of nature. In Figure 2, there are few examples: camptothecin **1**, that is the starting material for the anticancer Irinotecan **2**, is extracted from the plant *Camptothecia Acuminata*.[5] Daunomycin **3**,[6] Cephalosporin C **5**[7] and Lysergic acid **7**,[8] that are all obtained by fermentation, are the starting material for the synthesis of Idarubicin 4, 7ACA 6, Pergolide **8**, respectively.

Catalysis plays a major role in modifying these complex and sensitive scaffolds fulfilling the green chemistry principles. For this reason, organometallic and enzymatic catalysis are the main technologies investigated by industrial research groups.[9]

The examples discussed in the following paragraphs cover two different class of product, antibacterial antibiotics and anticancer. The main difference

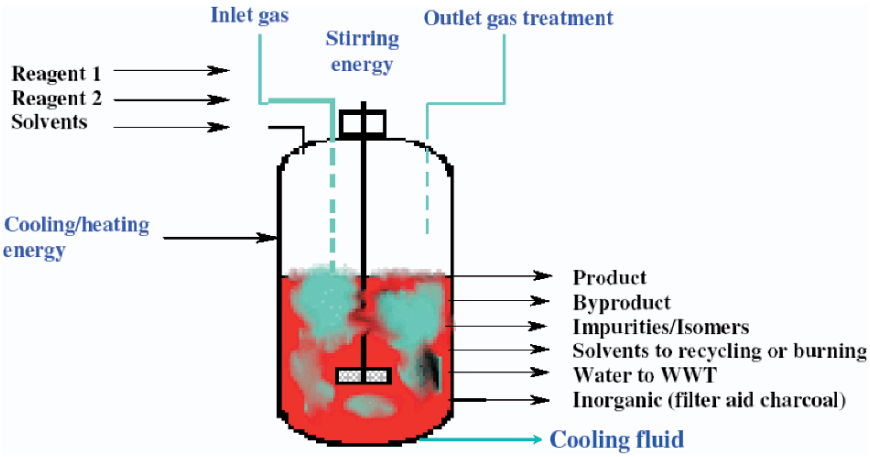


Figure 1. Chemical reactor: in and out.

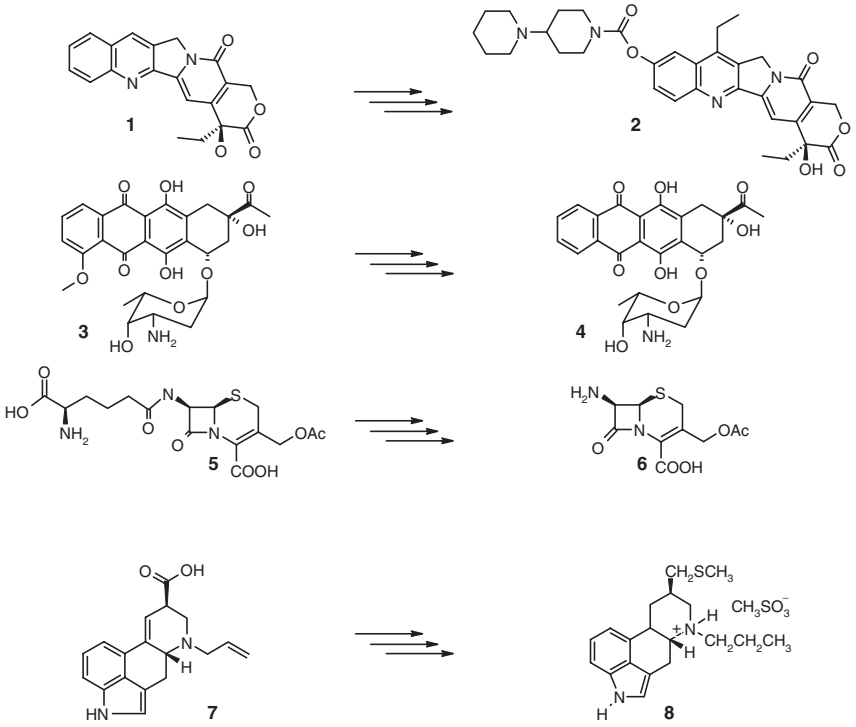
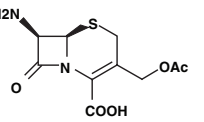


Figure 2. Examples of complex chemical structures.

between the two products is the production volumes involved: hundreds tons for 7ACA and few hundred kilograms for erlotinib hydrochloride.

2.1. ENZYMATIC CATALYSIS: THE PRODUCTION OF 7AMINO-CEPHALOSPORANIC ACID, 50 YEARS OF COMPETITION

7ACA



Companies	Antibioticos, Sandoz, China, Korea
CAS	33069-62-4
MW	272.28
Biosynthetic class	β-lactams
Source	Semysinthesis Morin 1962 (Eli Lilly)
Discovery	1955 (Abraham&Newton)

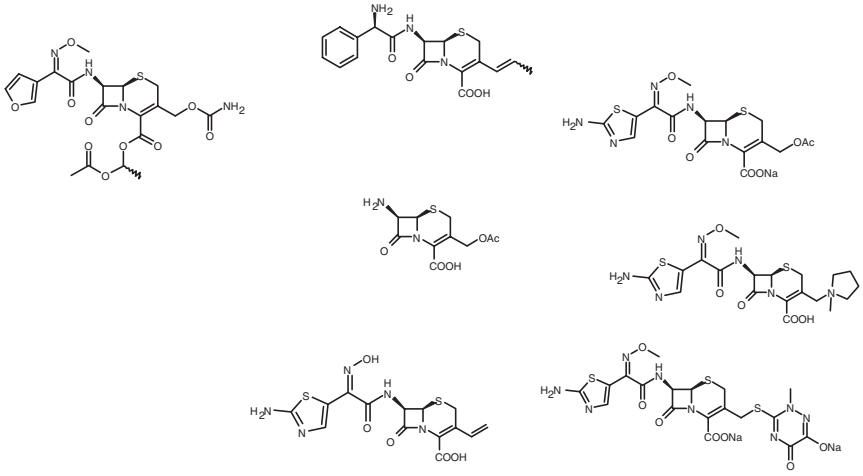
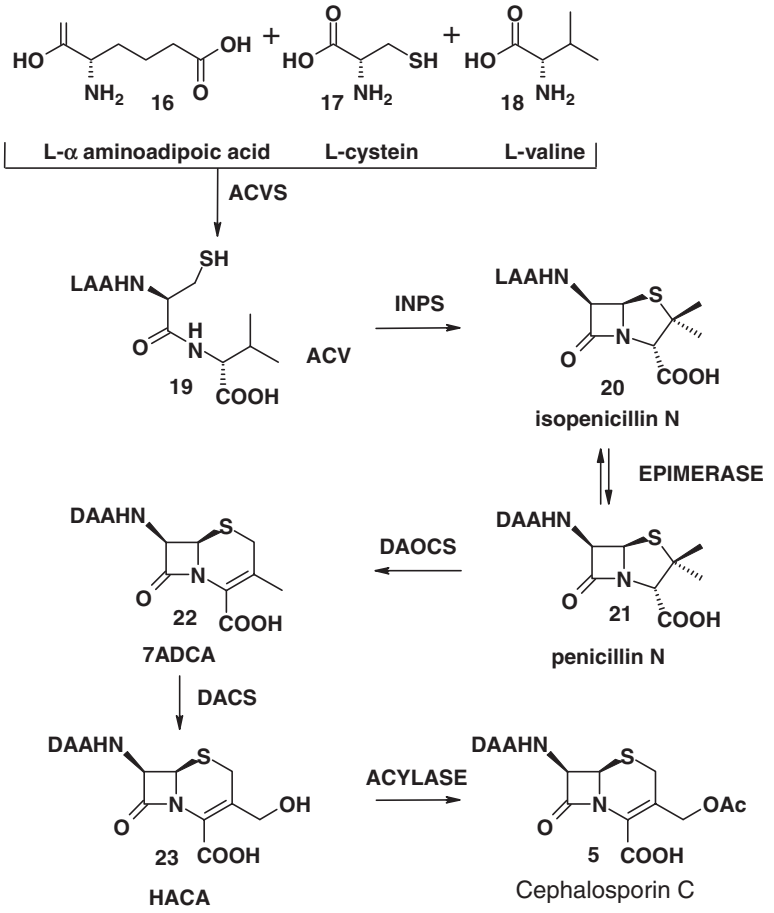


Figure 3. Semisynthetic cephalosporins.

The history of the production of 7ACA **6** is strictly related with the evolution of modern drug discovery. *Cephalosporium acremonium* was first isolated by an Italian Medical Doctor, Giuseppe Brotzu at the end of the Second World War[10] and later the microorganism was transferred in England. The National Research Development Corporation took over the development of the new antibiotic. Clavedon Research Laboratories (already involved in the development of the penicillin), Oxford and Glaxo were part of NRDC. The original microorganism discovered by Brotzu was developed by Clavedon researchers. Oxford scientist (Newton&Abraham) isolated the new antibiotic named cephalosporin C. Glaxo was responsible of the scaling up.[11] Cephalosporins antibiotics are one of the most important weapons of antibacterial therapy. The examples described in Figure 3 showed the evolution of the structures from the 1980s: Cefprozil **15**, Cefotaxime **9**, Ceftriaxone **11**, Cefuroxime sodium or axetil **14**, Cefepime **10** with the one from the 1990s Cefdinir **12** or Ceftobibrole medocaril **13**. Cefotaxime **9**, for example, is synthetized by a simple acylation followed by formation of the sodium salt, on the other hand Ceftobiprole medocaril **13**, that shows a consistent increases of chemical complexity, is synthetized 8 through chemical steps.

2.1.1. Cephalosporin C fermentation

The microorganisms used by industrial producers are coming from the Brotzu's *C. acremonium*; in fact, the discovery of NRDC was later licensed worldwide. The original microorganism had been completely modified by the producers to increase potency and quality of cephalosporin C **5**. The biosynthetic intermediate of the cephalosporin C **5** are described in Scheme 1.

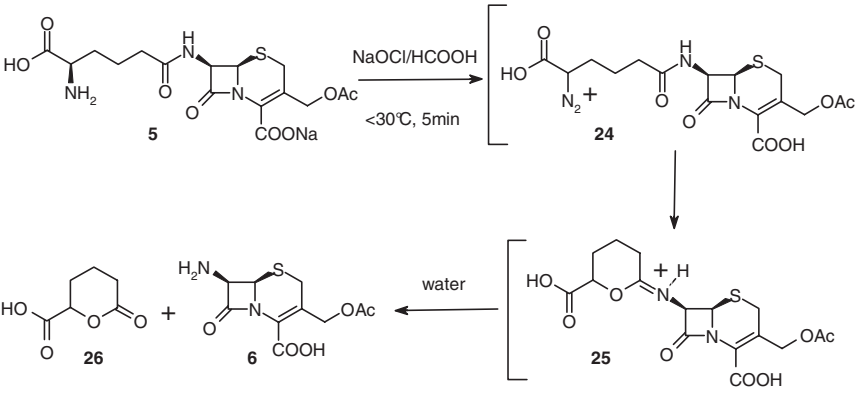


Scheme 1. Cephalosporin C biosynthesis.

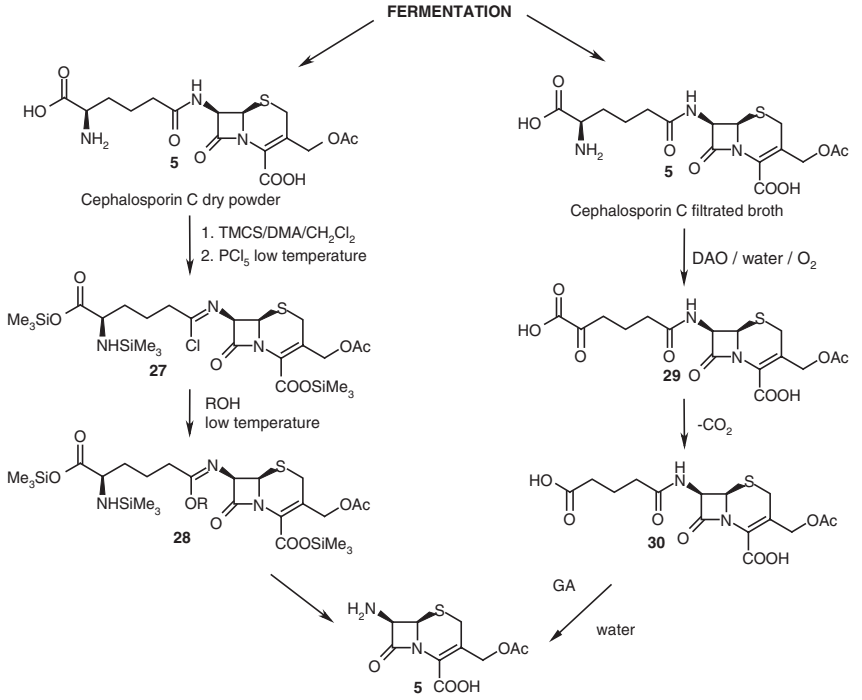
2.1.2. 7ACA from Cephalosporin C

Abraham and Newton discovered cephalosporin C and also described the first synthesis of 7ACA in 1% yield with diluted aqueous HCl.[12] Few years later, Morin from Eli Lilly discovered a high yield synthesis of 7ACA (Scheme 2).[13]

Morin generated with an oxidation the diazonium salt of the side chain that by cyclization followed by hydrolysis afforded 7ACA in 40% yield. Modern chemical 7ACA **7** synthesis are based on temporary protective groups, but the side chain hydrolysis goes always through the iminium salt (Scheme 3). Cephalosporin C sodium salt can be isolated after fermentation.



Scheme 2. Morin approach to 7ACA production.



Scheme 3. 7ACA Modern approaches.

This step is necessary to have an almost dry powder ready for silylation with trimethylchlorosilane (TMCS) and dimethylaniline (DMA) in dichloromethane. After chlorination and methanolysis 7ACA is isolated by crystallisation in 85% molar yield. This synthesis has a very high environmental impact that can be decreased only by recycling of dichloromethane, methanol, HMDSO, and DMA. The water coming from this synthesis is contaminated by phosphates that must be removed prior water waste treatment.[7]

Antibioticos developed a two step enzymatic process for the production of 700 t per year of 7ACA **6**. The cephalosporin C **5** coming from the fermentation broth is directly oxidised by a D aminoacid oxidase (DAO). The aminoacid fragment is transformed into the corresponding ketoacid **29** with concomitant generation of hydrogen peroxide. Hydrogen peroxide promotes the oxidative decarboxylation affording glutaryl-7ACA **30**. Intermediate **30** is then enzymatically hydrolysed to get 7ACA **6** using a genetically modified glutaryl acilase (GA) (Scheme 3). The overall yields of the chemical and enzymatic approaches are almost identical. However, the enzymatic synthesis does not use chemicals and the sensitive beta-lactam ring is always manipulated under almost neutral conditions in a safe 10–20°C temperature range.

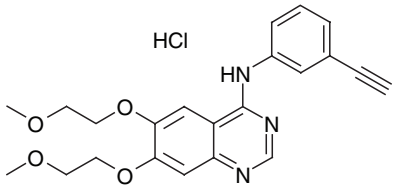
Summing up, the enzymatic approach has a low environmental impact and a very high productivity because the cephalosporin C **5** coming from the fermentation broth is directly oxidised by DAO. The comparison of the two processes is described in Table 1.

TABLE 1. 7ACA process comparison

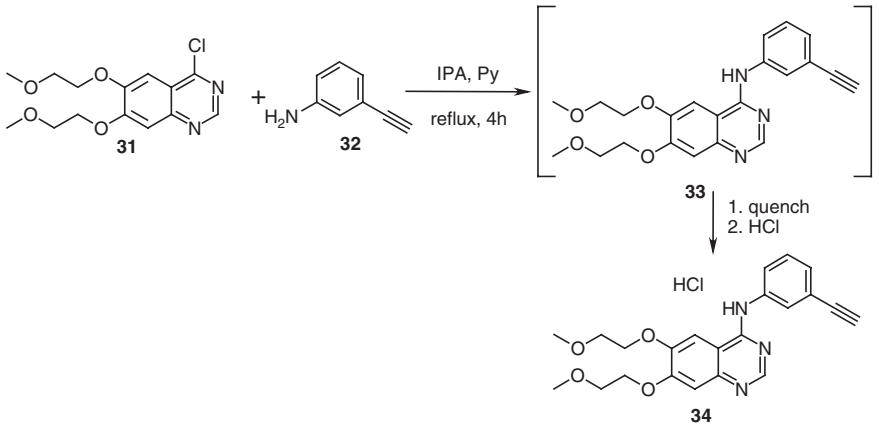
Enzymatic	Chemical
Continuous process from fermentation. High productivity	Cephalosporin C sodium must be isolated in a dry form to be subjected to the silylation step. Batch process with low productivity
Temperature range 20–25°C	Temperature range –50–30°C
pH range 7–8	pH range 0–4
One isolation step	Two isolation steps
One solvent for drying of 7ACA	Methanol, dichloromethane
No chemicals	DMA, TMCS, PCl_5
> 98% potency	95–97% potency
> 99.5% purity	> 98% purity
Open β-lactams impurities absent	1% of open β-lactam impurities
Mild reaction conditions	Severe reaction conditions

2.2. ORGANOMETALLIC CATALYSIS: ERLOTINIB HYDROCHLORIDE SYNTHESIS, THE SONOGASHIRA REACTION.

ERLOTINIB HYDROCHLORIDE

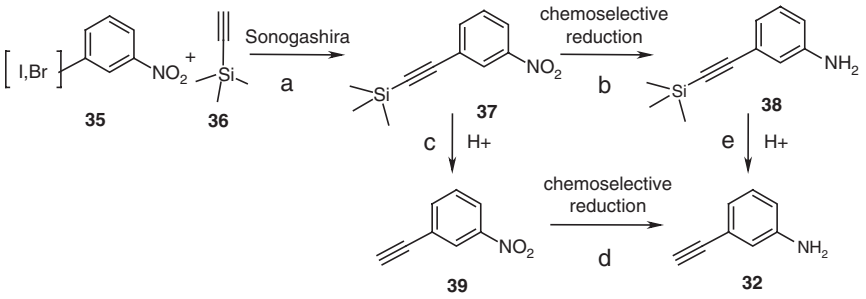


Originator	OSI
Status	Launched 22.11.2004 non-small-cell lung cancer second line
CAS	HCl salt 183319-69-9; Free base 183321-74-6
MW	429.90
MF	$C_{22}H_{23}N_3O_4$. HCl
Chemical class	Anilinoquinazoline
Therapeutic area	Epidermal Growth Factor Receptor Tyrosine Kinase inhibitor
FDA	NDA 21–743
Source	Synthetic
Trademark	Tarceva



Scheme 4. Erlotinib synthesis.

Erlotinib hydrochloride is an oral anti-cancer drug under development by OSI Pharmaceuticals, Genentech and Roche. It is a member of the epidermal growth factor receptor (EGFR) inhibitor class and it is on the market (2004 USA, 2005 Europe) as a second line therapy of non-small-cell lung cancer (NSCLC). On the back of successful phase III trials in pancreatic cancer, Tarceva (the drug product) has now secured FDA approval for treatment of advanced pancreatic cancer in combination with gemcitabine in chemo-



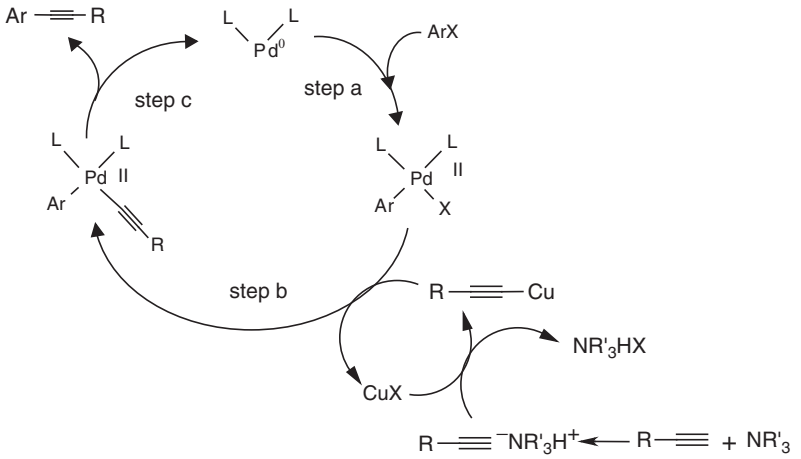
a. $Pd(OAc)_2/PPh_3$ in Et_3N. b.Several reductions procedures have been stuied $FeSO_4$; Zn/NH_4OH; $NaHSO_3$; $RuCl_3/Al_2O_3/H_2$; orRuS_2/H_2;c/e. HCI treatment 40-50°C gave almost a quantitative reaction.

Scheme 5. 3-Aminophenyl acetylene synthesis.

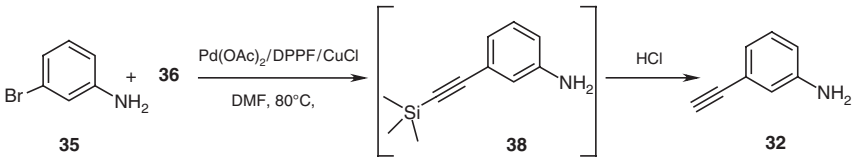
therapy-naïve patients. The original synthesis of Erlotinib hydrochloride **34**, described in Scheme 4, was based on the coupling between 4-chloro-6,7-bis-(2-methoxy-ethoxy)-quinazoline **31** and 3-amino-phenyl acetylene **32** in isopropanol using pyridine to trap hydrochloridric acid. The treatment with HCl afforded the target product in 70–74% molar yield.[15]

The quality of Erlotinib hydrochloride **34** was directly related to the purity of 3-aminophenyl acetylene **32**. Compounds similar to **32** had been investigated as herbicides during the 1970s. This simple molecule was synthetised by a Sonogashira type reaction[16] followed by reduction of the nitro group (Scheme 5).[17–19] The protocol published by Lau and coworkers was the first copper-free Sonogashira type reaction reported in literature.[16] The authors simply applied the Heck protocol to an alkyne. The next step was the chemoselective reduction of the nitro group. Several reduction processes uses using stoichiometric amounts of reactants like $FeSO_4/Zn/NaHSO_3$,[18] therefore the most appealing process appears to be the catalytic hydrogenation.[19] However, in spite of all efforts, hydrogenation was not completely chemoselective and unfortunately, the quality of the final **32** did not improve determining the necessity of extensive purifications.

The easy way to avoid this problem was the elimination of the chemoselective reduction step from the synthetic route. In fact, the Sonogashira type reaction could be in principle carried out using commercially available 3-bromo-aniline **35** and trimethylsilyl acetylene **36**. Lau and coworkers reported that this reaction failed.[16] We observed, in presence of copper under standard Sonogashira conditions [$Pd(OAc)_2/PPh_3$ in Et_3N], a very low conversion. The use of bidentate phospine ligands can in principle favour oxidative addition (step a) and reductive elimination (step c, Scheme 6). The catalyst generated in situ with bis(diphenylphospine)ferrocene (DPPF) as palladium ligand and $Pd(OAc)_2$ increased the reaction performances but



Scheme 6. Sonogashira type reactions a simplified mechanism.



Scheme 7. 3-Aminophenyl acetylene synthesis. An alternative approach.

the complete conversion was achieved only changing the organic base and the reaction solvent. It appears that the generation of the organo-copper species was the less-efficient reaction step. The best reaction conditions were obtained using 1,1,3,3-tetramethyl guanidine (TMG) in DMF at 80°C with 0.6% of $Pd(OAc)_2$, 1.2 mol% of DPPF and 0.3 mol% of CuCl. 3-amino-phenyl acetylene **32** was isolated after acidic work up in 85% yield and >99% purity by HPLC.[20]

Conclusions

Scientific excellence is the only choice for pharmaceutical companies to suceed in the globalization era. In other words, the design of efficient low environmental impact and low cost processes based on the green chemistry principles is a must. Our experience is that fermentation, catalysis, low energy consumption reactions, and high productivity (continuous or telescoped processes) are the key factors to compete in the worldwide market.

Acknowledgments

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NEW EFFICIENT CATALYTIC PROCESSES IN WATER: AN ENVIRONMENTAL BENING SOLVENT

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Abstract: Water has attracted significant attention as an alternative solvent for transition metal-catalyzed reactions because it is non-toxic, non flammable solvent. The use of water as solvent allows simplified procedures for separation of the catalyst from the products and recycling the catalyst. This type of catalysis contributes to the concept of green chemistry. This chapter will focus on old and recent developments in the design and applications of some aqueous phase palladium, rhodium, platinum, and ruthenium reactions which have a great academic and industrial interest.

Keywords: catalysis, water-soluble phosphines, aqueous phase, recycling

1. Introduction

Over the past few years, significant research has been directed toward the development of new technologies for environmentally benign processes. The use of water as solvent in homogeneous metal-catalyzed reactions has gain increasing attention because of the potential environmental and economic benefits of replacing organic solvent with water. Indeed, water is an attractive solvent because it is inexpensive, non flammable, non-toxic and the most attractive feature being its utility in the development of green and environmentally safe processes.[1,2,3,4] Another reason that water has received significant

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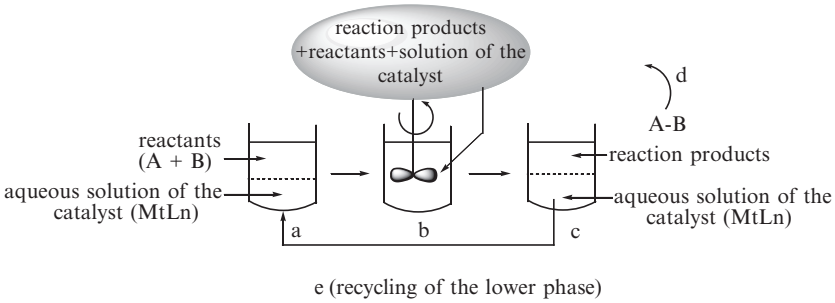
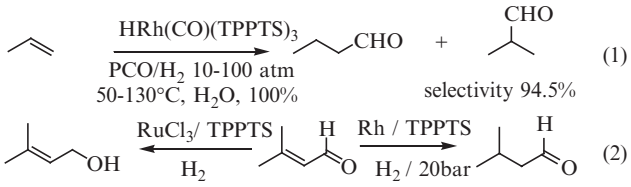


Figure 1. Process of biphasic catalytic reactions. Catalyst recycling.

attention as solvent for homogeneous catalyzed reaction is the potential to simplify separation of catalysts from the organic products. Separation often requires solvent and/or energy intensive protocols and can lead to degradation both of the product and the catalysts used. However in the use of water and water-soluble catalyst (MtLn), the complex applied as catalyst gains its water solubility by incorporation of L, a strongly hydrophilic phosphine ligand. Thus, water can simplify catalyst separation by creating a biphasic system and reaction may be performed as shown in Figure. 1. This type of approach was first used commercially with a nickel complex for the polymerization of ethylene, the Shell Higher Olefin Process (SHOP).

2. History

The first water-soluble phosphine, mono m-sulfonated phosphine (TPPMS) was reported in 1958 by Ahrland et al.[5] In the late 1970s, Kuntz reported the m-trisulfonated triphosphine (TPPTS).[6] This highly soluble phosphine has been used for a wide variety of chemical processes under biphasic conditions. The development of the hydroformylation of propene by Ruhrchemie/Rhone-Poulenc,[7] the reduction of saturated and unsaturated aldehydes catalyzed by metal-sulfonated phophines complexes (Rh or Ru), Eqs. (1) and (2) are some examples.[8]



Coupling reactions have been achieved in such biphasic systems with rhodium catalyst including telomerization of dienes. The pioneering work of Beletskaya has shown that Heck-coupling can be conducted in water[9] using Pd $(OAc)_2$, however this system precludes simple catalyst recovery. Casalnuovo et al. were the first to apply water-soluble ligand, preformed Pd $(TPPMS)_3$[10] for Suzuki, Heck, and Sonogashira coupling of aryl iodides in a water/acetonitrile solvent. In 1992, Genet et al. reported palladium coupling reactions: Heck, Suzuki-Miyaura, Tsuji-Trost, Sonogashira[11] catalyzed by water-soluble palladium (0) complex produced in situ from Pd $(OAc)_2$ with TPPTS. They have shown for the first time that Sonogashira coupling can be achieved without copper additive in aqueous medium.

At that time, only a few dozen references existed in the literature on this subject. A growing number of academic and industrial groups have worked to develop effective, aqueous phase-catalyzed reactions since these early reports. Now, organic reactions in water have become the most exciting research endeavors. In one decade several books and reviews have been published in this field.[12,13]

3. Some palladium- and platinum-catalyzed reactions

Palladium-catalyzed cross-coupling reactions, such as the Heck, Tsuji–Trost, Sonogashira, Suzuki, Stille, and Buchwald–Hartwig coupling have become powerful method for C–C or C–X bonds formation. These reactions are widely used in the pharmaceutical, agrochemical, and fine chemical industries.[14]

3.1. ACHIRAL WATER-SOLUBLE PHOSPHINES

Since the discovery of TPPMS[5] **1** and TPPTS[6] **2** several groups including ours have worked intensively preparing new water-soluble phosphines. The use of ligands providing the ability to fine-tune the reactivity, selectivity, and solubility characteristic of the catalyst system is of great interest. For these reasons a wide range of hydrophilic ligands **1, 2, 3**[15a], **4**[16], **5**[17], **6**[18], **7**[19], **8**[20], **9**[21], **10**[22], **11**[23] (Figure 2) bearing anionic and cationic groups have been applied to aqueous phase-catalyzed reaction. These ligands have shown interesting properties in palladium-catalyzed reactions.

Recently, we have reported a versatile preparation of the water-soluble m-TPPTC **3** functionalized by carboxylated moieties, which presents a very high solubility (1,100 g/L).[15a] We also have investigated steric and electronic properties of this new ligand and we have shown that m-TPPTC phosphane is more basic than the sulfonated analphogue inducing different selectivities compared to TPPTS.[15b]

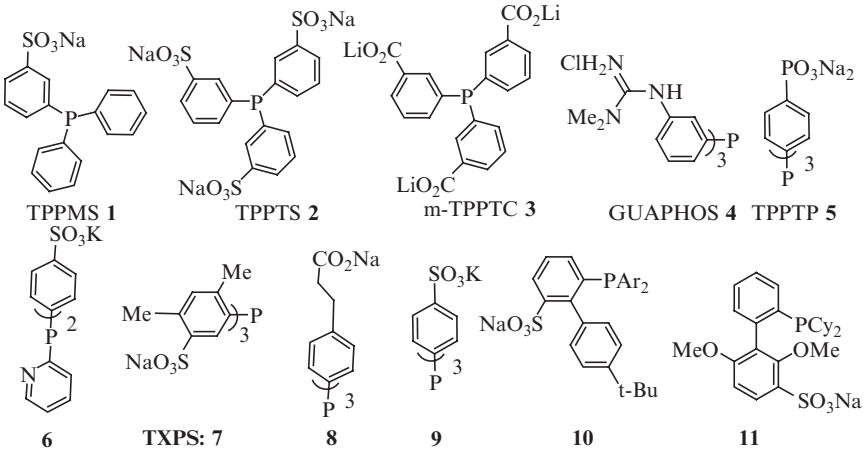


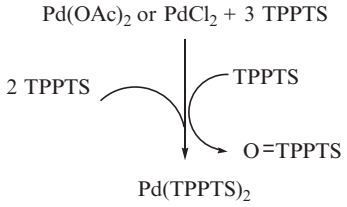
Figure 2. Selected achiral water-soluble ligands.

3.2. HECK REACTIONS WITH SULPHONATED AND CARBOXYLATED PHOSPHINES

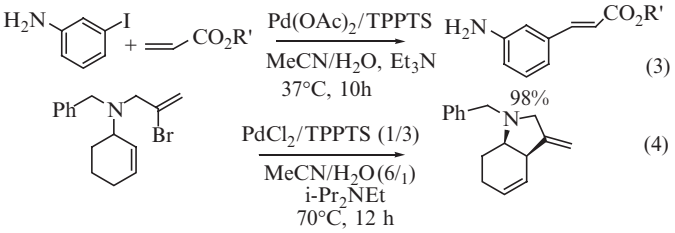
Casalnuovo et al. have reported[10] the Heck reaction of aryl iodides with α, β-unsaturated esters in the presence of preformed [Pd (TPPMS)$_3$]; the reaction proceeds at 80°C in acetonitrile-water. TPPMS is moderately soluble in water (80 g/L). TPPTS is significantly more soluble (1.1 kg/L) and cannot be extracted from water by organic solvents.

Genet et al. have demonstrated, through a series of kinetic and ^{31}P NMR experiments, that a mixture of Pd (OAc)$_2$ and TPPTS affords spontaneously a palladium zero valent complex[24] as shown Scheme 1.

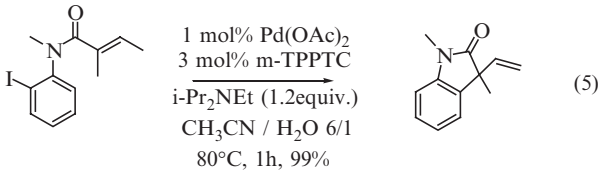
This in situ generated catalyst has been applied successfully to intra and intermolecular Heck reactions. The reaction proceeds under mild conditions, as illustrated in Eqs. (3) and (4).[25]



Scheme 1. In situ preparation of Pd (TPPTS)$_2$ catalyst.

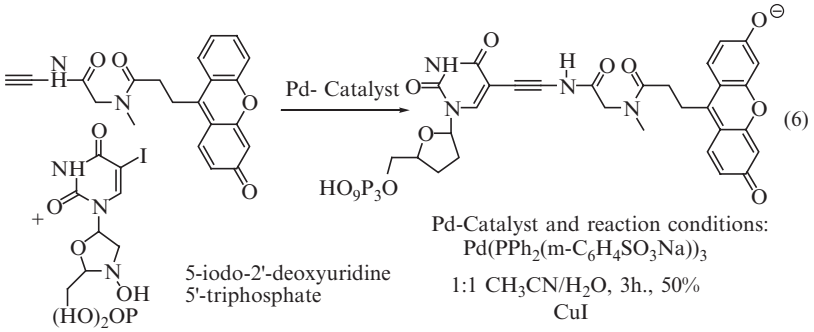


The scope of Pd $(OAc)_2$ m-TPPTC catalyst was explored using substrate derived from iodo-anilines. The formation of the cyclized product is quantitative after simple removal of the water-soluble catalyst; the crude product is very clean, and no purification is necessary[14a], Eq. (5).



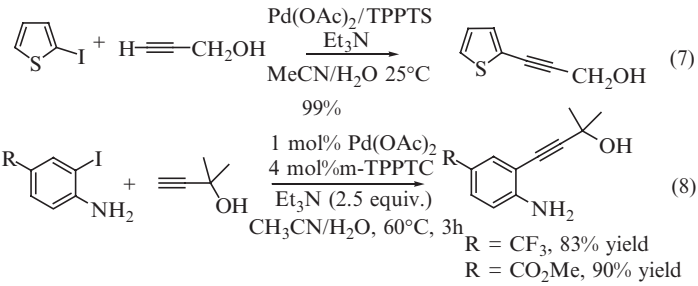
3.3. SONOGASHIRA AND ALKYNE OXIDATIVE DIMERIZATION

A demonstration of the synthetic utility of the palladium cross-coupling in aqueous medium is illustrated in an alternative synthesis of T-505, of member a family of chain terminating nucleotide reagents used in DNA sequencing and labeling. In the commercial syntheses of these reagents, the acetylene coupling is carried out prior to the hydrophilic phosphate formation due to the insolubility of Pd $(PPh_3)_4$. The convergent route, Eq. (6), developed by Dupont can be conducted in the final step using the water-soluble Pd $(TPPMS)_3$.[10]

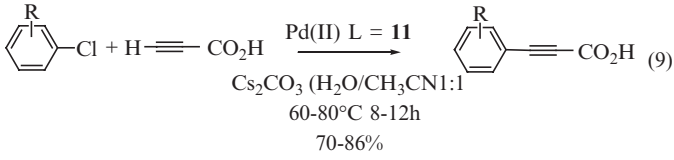


The Pd/TPPTS catalyst efficiently promotes the coupling of iodo-aromatics and vinyl halides with a variety of terminal alkynes at 25°C in a few hours without the need for Cu (I) promoter. High yields are observed and the catalyst is tolerant to a wide range of functionalities.[11]

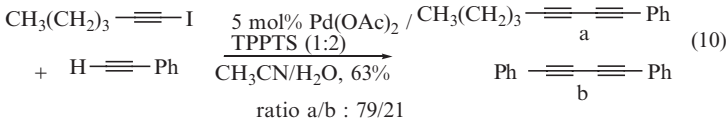
Copper-free Sonogashira-coupling was also achieved using Pd (II) TPPTC catalyst.[14b] The reaction with 2-iodo-anilines proceeds with high selectivity, Eqs. (7) and (8).



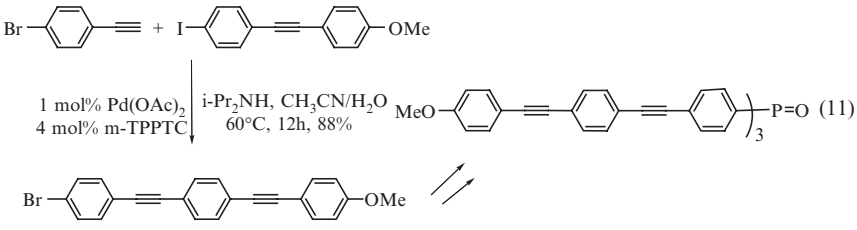
Very recently Buchwald et al. have reported a Sonogashira-coupling with aryl chlorides using the combination of Pd (II) salts and the sulphonated ligand and **11**. The reaction takes place in H_2O/CH_3CN (1:1) at 60–80°C giving the corresponding alkynes with good yields, Eq. (9).[23]



The water-soluble Pd-TPPTS catalyst has also proved its efficiency in alkynes oxidative dimerization the afford diynes in good yields again without any Cu (I) promoter, Eq. (10).

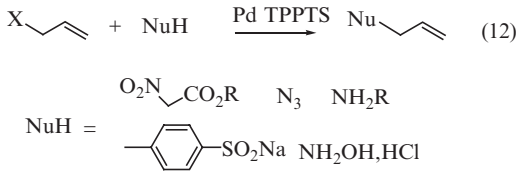


An interesting application of Sonogashira-coupling using Pd (II) hydrophilic TPPTC **3** is the preparation of novel fluorophores as shown in Eq. (11).[26]



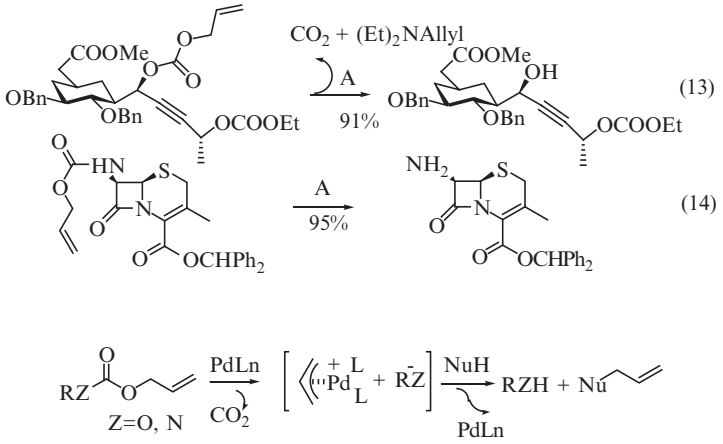
3.4. ALLYLIC SUBSTITUTION REACTIONS

Allylic substitutions, well known as Tsuji–Trost reaction, is probably the most widely used palladium reaction in organic syntheses.[14] Various water-soluble catalysts formed in situ from Pd $(OAc)_2$ or Pd_2 $(dba)_3$ and TPPTS are efficient catalyst for substitution of allylic substrates with acyclic and cyclic carbon-centered nucleophile and hetero nucleophile under mild condition, Eq. (12).[11–27]



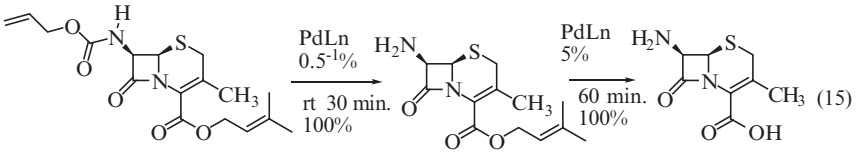
An interesting application of this palladium-catalyzed alkylation in homogeneous ($MeCN/H_2O$) or biphasic media (n-$PrCN/H_2O$) is the removal of the allyl and alkyloxycarbonyl group (Alloc) form allylic ester carbamates in the presence of Et_2NH as an allyl scavenger (Scheme 2).[28]

Fast and chemo selective deprotections of primary and secondary alcohols and amines occur smoothly as shown in Eqs. (13) and (14). The major practical advantage of this procedure using water-soluble palladium catalyst is the easy separation of the deprotected alcohol and amines from the catalyst in pure form thus, no purification is necessary. Interestingly, the catalyst can be recycled ten times without loss of efficiency.



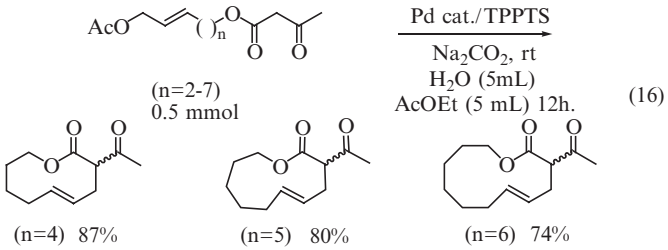
Scheme 2. Deprotection of alloc protecting group with Pd (0) catalyst.

A very interesting chemo selective deprotection has been found using Pd-TPPTS catalyst and diethyl amine as allyl scavenger, Eq. (15).[29] This methodology has been applied using biphasic conditions to the synthesis of tetra peptides.[30]



(15)

Very recently an efficient synthesis of medium and large-sized lactones in aqueous organic biphasic system using Pd (TPPTS) catalyst has been reported by Oshima et al., Eq. (16).[31]

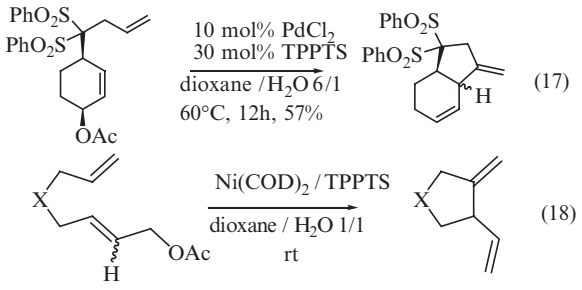


(16)

3.5. METALLO-CATALYZED CYCLIZATIONS OF POLYFUNCTIONAL UNSATURATED DERIVATIVES

3.5.1. Ene-reactions

The development of routes for the synthesis of functionalized five or six membered rings has also attracted attention via organic/aqueous metal-catalyzed reactions. Efficient metallo-ene reactions are reported using the water-soluble Pd $(TPPTS)_3$ (Eq. (17)), RhCl $(TPPTS)_3$ and Ni $(TPPTS)_3$ (Eq. (18)) catalysts. The latter is particularly attractive as the cyclization proceeds at room temperature for a wide range of substrates.[32]

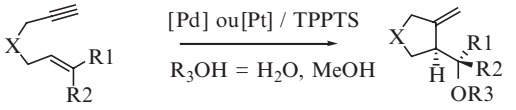


(17)

(18)

3.5.2. Enynes Cyclization Reactions

Genet et al. discovered a new reaction when propargylic enynes were subjected to $PdCl_2$/TPPTS[33] and $PtCl_2$/TPPTS system in homogeneous medium. The cyclization proceeds diastereoselectively with simultaneous formation of C–O bond via hydroxy or methoxy functionalization, Eq. (19).

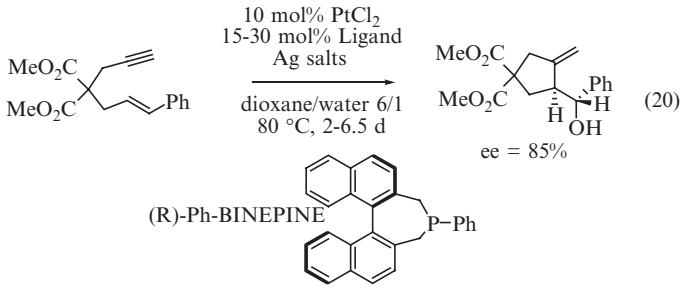


(19)

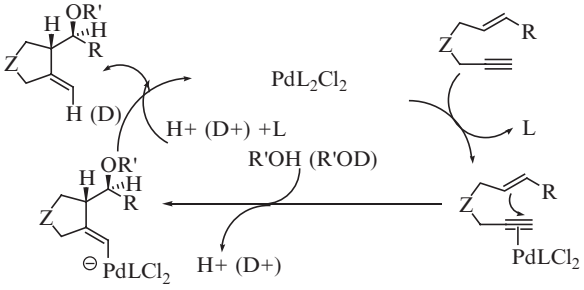
X = O, NTs, $C(CO_2Me)_2$;R_1 = Ar, Me, R_2 = H, Me...

Several mechanisms have been proposed. Apparently the reactions are catalyzed by small amount of unreduced Pt (II)-TPPTS complex: complexation of the enyne by palladium may promote intramolecular anti addition followed by concomitant attack of water or alcohol similar to Wacker process[34] as shown in Scheme 3.

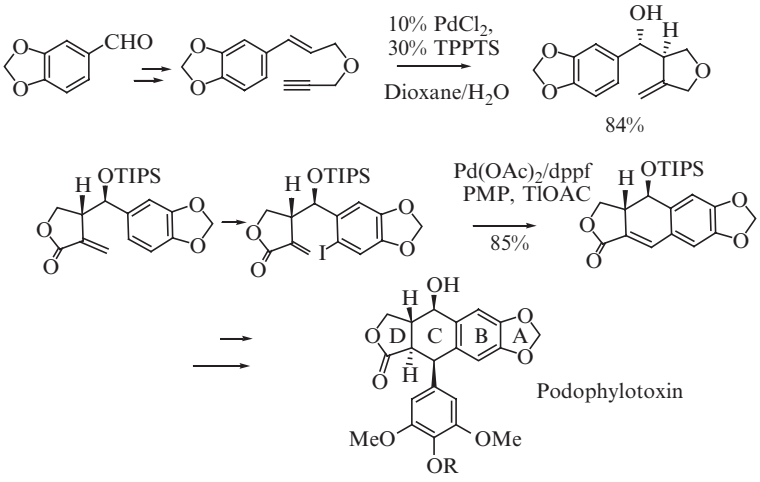
The hydroxy and alkoxyclization reactions were developed with various 1,6-enynes in the presence of palladium and platinum catalysts.[34] In view of its utilization in the synthesis of natural product of biological interest, we investigated the asymmetric version of this novel and ideal reaction in term of atom economy. As shown in Eq. (20), we have developed the first enantioselective



(20)



Scheme 3. Mechanism of Pt and Pd hydroxy and alkoxy cyclization.



Scheme 4. Synthesis of a podophylotoxin intermediate.

Pt-promoted enyne carbo-alkoxycyclization. The use of silver salts combined with (R)-Ph-BINEPINE, a monophosphane atropisomeric ligand, was found to be the best combination giving enantioselectivity up to 85% ee.[35]

This atom-economical reaction has been applied to the synthesis of anti-tumor podophylotoxin precursors[36] as shown in Scheme 4.

3.6. SUZUKI–MIYAURA REACTION (S–M)

Among metal-mediated cross-couplings, the Suzuki–Miyaura (S–M) reaction between different type of organoboron compounds and various electrophiles such as halides, triflates in the presence a base, provides a powerful and general methodology for the formation of C–C bond, Eq. (21).[37]

$$R{\cdot}X + R'{-}B(OR')_2 \xrightarrow[\text{Base}]{\text{[Pd] cat.}} R{-}R' \quad (21)$$

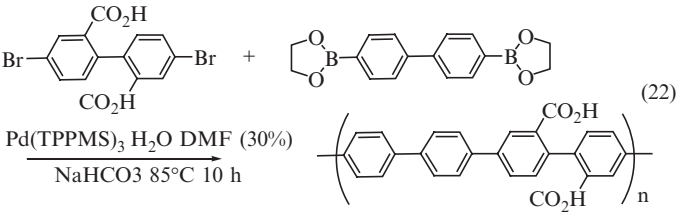
The coupling offers several advantages such as a broad tolerance of wide range of functional groups and has been applied to many interesting biologically active compounds, for example, losartan,[38] palytoxin.[39]

The (S–M) reaction requires the presence of bases. Therefore, a standard technique of performing the Suzuki–Miyaura reaction is the use of aqueous solvents to increase solubility of the inorganic salts. The presence of water is an important factor, which has led to the development of aqueous phosphine-free and biphasic phosphine assisted techniques. The (S–M) reaction with phosphine-free palladium catalysis allows catalyst efficiency to be dramatically increased and the yields are in most cases quantitative.[40] An

interesting phosphine-free (S–M) has been reported using Pd/C; this catalyst can be recycled several times.[41]

3.6.1. Palladium-Catalyzed Reactions

The Suzuki–Miyaura reaction in the presence of TPPMS ligand has been successfully applied to the preparation of water-soluble phosphenylenes containing carboxylic groups, Eq. (22).[42]

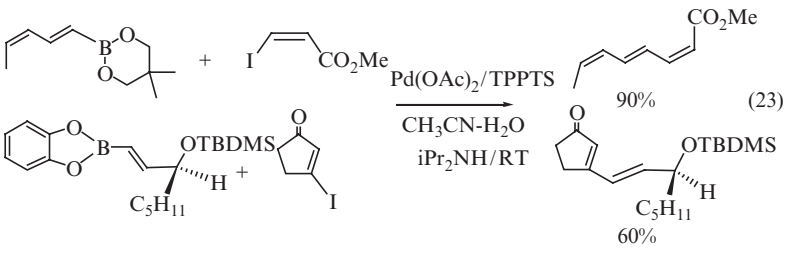


(22)

The basic (S–M) reaction using the hydrophilic phosphine assisted method has been recently improved with aryl bromides in aqueous medium (CH_3CN/H_2O), low catalyst loading with sterically demanding water-soluble alkyl phosphine as well as recycling the catalyst using a polystyrene-supported *N*-heterocyclic Pd catalyst in DMF/water (1:1).[43]

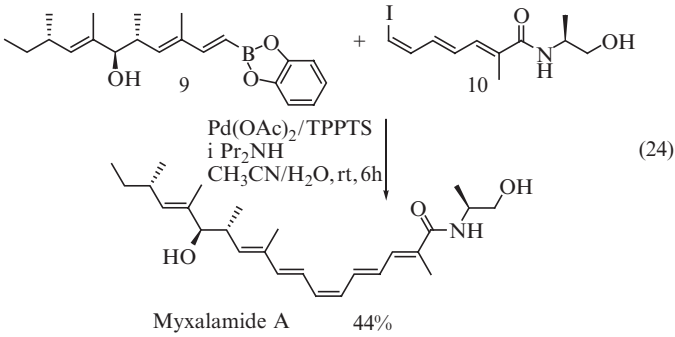
The method in which palladium complexes with hydrophilic phosphines are used in a biphasic system of water-organic solvent, can be considered complementary to the standard protocol. Recycling is possible but is hampered by the accumulation of inorganic borate salts in the aqueous layer. Casalnuovo et al. reported the first reaction with the assistance of hydrophilic phosphine with TPPMS ligand in acetonitrile or neat water. The reaction required prolonged heating at 80°C, thus doing no specific advantages over the standard protocol.[10]

Genet et al. have shown that the use of TPPTS[11] ligand offers a new and mild selective method suitable both for common needs[44] and for complex reaction with fragile substrates. The reaction can be run at room temperature with amine as bases, which are generally ineffective in the classical methods, Eq. (23).[45]



(23)

Heathcok et al. have used this system in the last step of the synthesis of myxalamide A, a polyene antibiotic, Eq. (24).[46] It has been shown that the addition of surfactants increase the efficiency of this hydrophilic phosphine assisted protocol.[47]

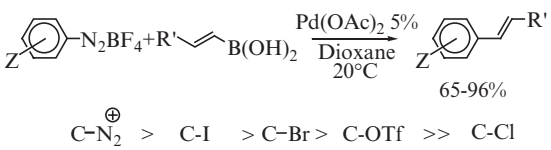


(24)

In addition to aryl halides and triflates, it has been shown that the highly stable and non-explosive arene diazonium tetrafluoroborates are good partners in the Suzuki–Miyaura reaction. The reaction takes place under mild condition at 20°C in dioxane using Pd $(OAc)_2$ without additions of phosphine.[48] Later it was shown that this phosphine-free catalysis could be applied in aqueous medium, though in this case this procedure gave no distinct advantages over anhydrous organic solvents.[49]

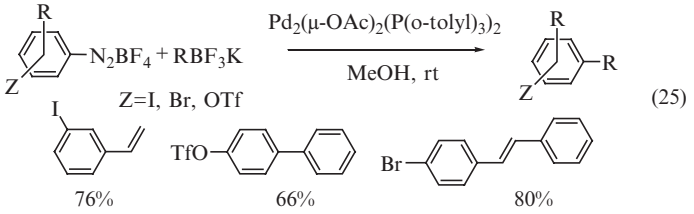
The order of reactivity of aryl halides and pseudo-halides for the (S–M) cross-coupling reaction of organoboronic acids or esters is shown in Scheme 5.

For a long time, an important limitation of Suzuki–Miyaura reaction was the inefficiency of aryl chlorides. However, in view of the increased availability and decreased expense of aryl chlorides relative to aryl bromides and iodides, an efficient procedure for cross-coupling of aryl chlorides was highly desirable. Fu et al. have reported that the use of Pd_2dba_3 in the presence of electron-rich phosphane such as PCy_3 or $PtBu_3$, the reaction takes place in dioxane and Cs_2CO_3 as base at 80°C with excellent yields up to 90%.[50] Very recently Buchwald et al. have shown that water-soluble aryl chlorides and heterocyclic halides react in organic aqueous medium or neat water in the presence of Pd $(OAc)_2$ containing water-soluble electron-rich phosphine **11** with good yields.[23]



Scheme 5. Reactivity order of aryl halides and pseudo halides in S–M reaction.

It was reported by Darses, Genet et al. that potassium organoborates readily react with aryl diazonium salts.[51] This palladium phosphine-free cross-coupling reaction is very efficient in methanol and without addition of base as used in the original protocol of Suzuki–Miyaura reaction, Eq. (25).



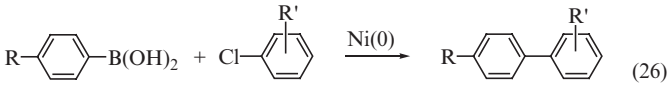
(25)

In 2000, Roche described the introduction of avinyl substituent on a 3-bromo-pyridine derivative using potassium vinyl trifluoroborate in the presence of palladium in water. As a base in the original procedure, is required in this cross-coupling reaction.[52] Batey, Molander, and Buchwald have used similar catalytic systems in the Pd cross-coupling of a wide range of potassium organo trifluoroborates with aryl halides and pseudo halides in alcoholic solvent or DME/water.[53]

3.6.2. Nickel-Catalyzed Reactions

The synthesis of biarylic compounds based on Suzuki–Miyaura is very often based on palladium-catalyzed coupling between aryl-electrophiles (diazonium salts, triflates, and aryl halides) and boronic acids.

Again, the use of more accessible aryl chlorides remains challenging since they are generally less reactive towards oxidative addition of palladium zero valent catalysts. Interestingly Ni (0)-catalyzed cross-coupling of aryl chlorides and aryl boronic acids have been reported using hydrophobic phosphine–nickel catalysis[54] and hydrophilic phosphine (TPPTS) biphasic assisted technology, Eq. (26).[55]



(26)

$NiCl_2$dppf, Buli, K_3PO_4,70-80°□C
$NiCl_2$dppf, K_3PO_4,dioxane, 95°□C
$NiCl_2$, dppe, TPPTS, Zn powder

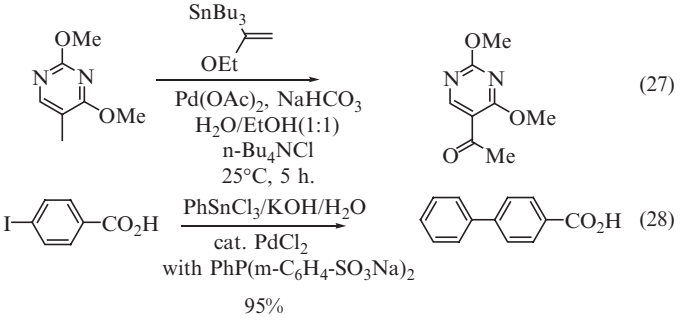
3.7. STILLE REACTION

The organostannes have also emerged as the reagents of choice in various transition metal-catalyzed reactions.[14] Organo tin reagents tolerate a variety of functional groups that many other reactive organometallic do not, except

organoboranes. Thus, organic chemists can easily handle them but with special care because of their toxicity. The basic technique for carrying out the Stille reaction requires palladium complexes with phosphines ligands in anhydrous organic solvents, often at elevated temperatures.

However, there is nothing in the Stille reaction that cannot tolerate water. The addition of small amounts of water in the system, help to increase the selectivity and yields.[56]

The main drawback in Stille reaction is the utilization of only one of the four organic radical, which leads to the formation of highly toxic waste R_3SnX. The best solution would be the use of mono substituted $RSnX_3$, which are less volatile and toxic. However these compounds are less reactive, to overcome this difficulty, the cross-coupling of trichloro organo stannanes may be conducted with water-soluble aryl and vinyl halides in the presence of palladium catalysts in water, Eqs. (27) and (28).[57,58]



4. Rhodium-Catalyzed Reactions with Trivalent Organoboron and Potassium Trifluoroborate Compounds

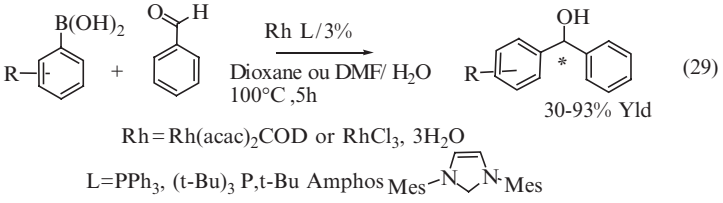
The 1,2- and 1,4- additions of organometallic reagents to unsaturated compounds are some of the most versatile reactions in organic synthesis. In that context, it has been shown that trivalent organoboronic acids add efficiently to unsaturated substrates in the presence of rhodium catalyst.[59] It has also been shown that potassium trifluoro(organo)borates participate in rhodium-catalyzed addition reactions.[60]

4.1. ACHIRAL ADDITION TO UNSATURATED COMPOUNDS

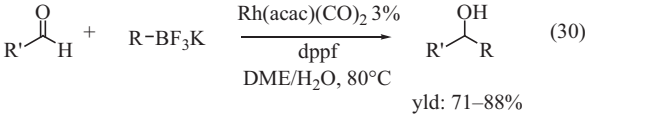
4.1.1. 1,2- Addition to keto groups

The 1,2- additions of boronic acids are facilitated by the presence of electro withdrawing group on the aldehyde and electron donating on the boronic acid. The reaction is accelerated by the use of electron rich phosphines and

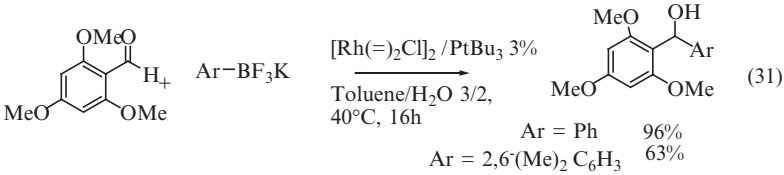
proceeds in dioxane or DMF/H_2O at 100°C using $Rh(acac)_2COD$ catalyst. It has been recently reported that carbene ligand with nitrogen donor atom are highly efficient as shown in Eq. (29).[61] The combination of t-Bu-Amphos and $RhCl_3$ gave a recyclable catalyst.

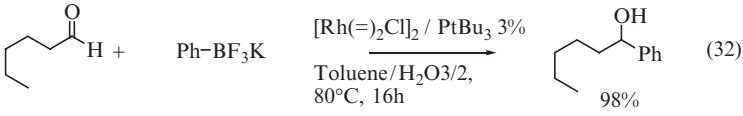


The potassium trifluoro(organo)borates also participated in the rhodium 1,2- addition to aldehydes using $Rh(acac)_2CO_2$ with dppf ligand in DMF/H_2O giving carbinol in good to excellent yields, Eq. (30).



This system is limited to electro-deficient aldehydes.[62] A more efficient system has been reported using rhodium catalyst in the presence of an electron-rich phosphine such as PBu_3. The reaction proved to be general, allowing the production of highly hindered diaryl carbinols and aliphatic aldehydes were also reactive under these conditions, Eqs. (31) and (32).[63]

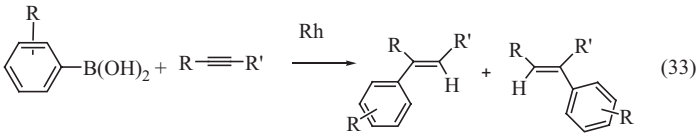




4.1.2. Hydroarylation of alkynes

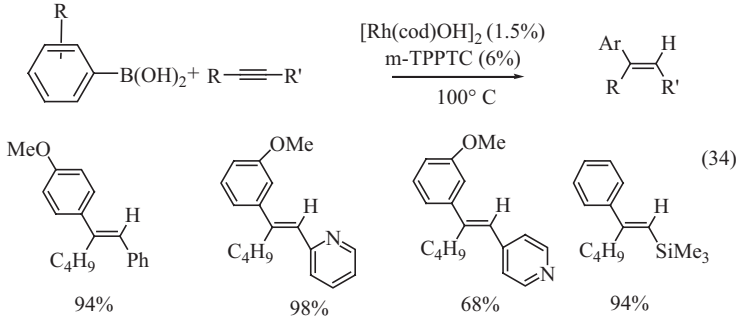
Hayashi's group has reported Rh-catalyzed addition of boronic acids to alkynes in dioxane water using rhodium/diphenyl phosphane system for the first time, Eq. (33).[64]

There was one system described in water requiring basic conditions and the presence of a surfactant. This latter being very specific limited to 2-alkynyl pyridyl substrates.[65] Moreover, the use of the well-known hydrophilic



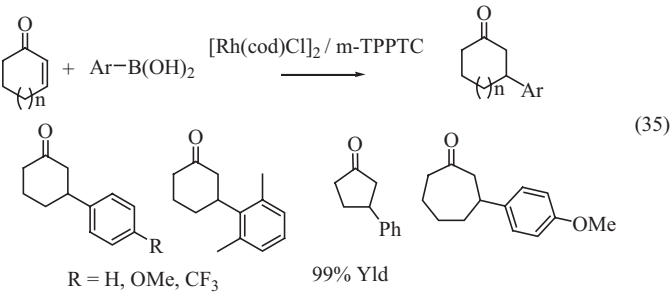
sulfonated phosphane TPPTS, was ineffective. However it has been found that alkynyl hetero aromatic compounds react with aryl boronic acids to give trisubstituted olefins in the presence of $[Rh(COD)Cl]_2$ with pyridine substituted water-soluble ligand **6**.

Michelet, Genet et al. have found that the use of $[Rh(COD)OH]_2$ associated with the water-soluble TPPTC **3**, Eq. (34) was highly efficient for hydroarylation of alkynes. The scope of the reaction is wide and totally regioselective for alkyl aryl alkynes.[66] This procedure in aqueous medium has significant advantages compared to the classical procedure using TPPTS. In addition the Rh/m-TPPTC system was for the first time recycled without loss of the activity and with excellent purity of the trisubstituted alkenes.



4.1.3. 1,4- Addition of organoboron compounds to α, β unsaturated enones

We have reported that enones reacted with arylboronic acids to give β arylated ketones in the presence of Rh-TPPTC catalyst, Eq. (35).[67] This system is more efficient than Rh-TPPTS,[68] probably due to the higher basicity of TPPTC vs TPPTS.[15c]

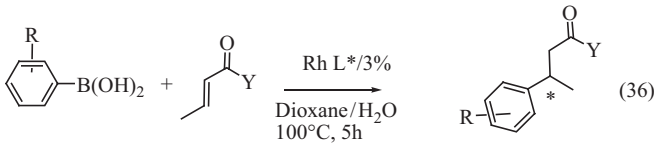


The reaction proceeds with very high yields and the biphasic phosphine assisted technique allows recycling of the expensive rhodium catalyst (four cycles without loss of activity).

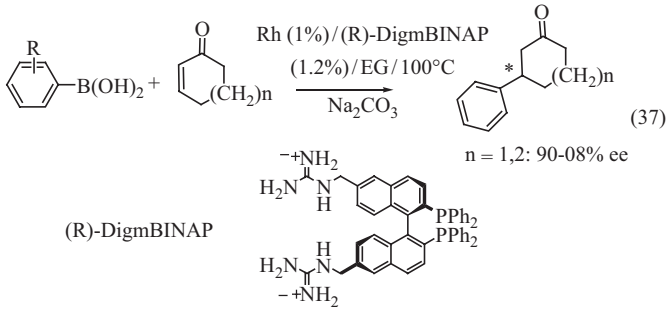
4.2. ASYMMETRIC 1,4- ADDITION OF ORGANOBORON COMPOUNDS

4.2.1. Trivalent organoborane compounds

Hayashi and Miyaura have independently reported 1,4- addition of boronic acids to Michael acceptors using $Rh(acac)_2C_2H_4$ in the presence of BINAP. The scope of this reaction is wide and proceeds in dioxane-water at 100°C, 5 h. with high selectivity up to 98% ee, Eq. (36).[69]



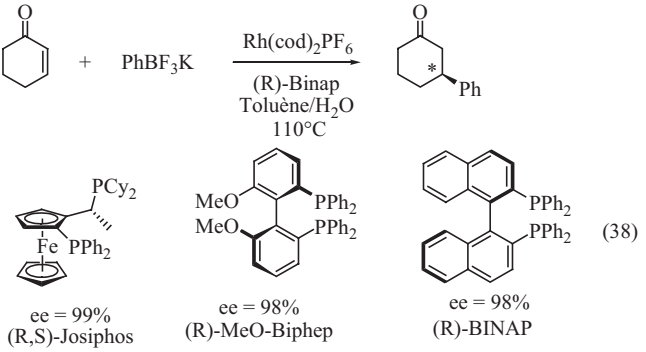
This reaction is complementary to copper-catalyzed 1,4- addition. A new synthetic method for the synthesis of chiral organosilicon compounds has been developed by employing (R,R)-Bnbod chiral catalyst. Michelet, Genet et al. have found that using Rh diguanidinum-BINAP in ethylene glycol the reaction proceeds with high selectivity, Eq. (37). In this particular example a significant decrease of selectivity is observed using water as co-solvent.[70]

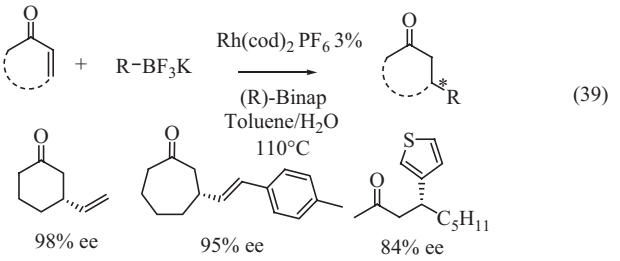


4.2.2. Potassium trifluoro(organo)borates

Batey et al. have reported the first achiral conjugate addition of potassium trifluoro(organo)borates to enones.[63] However the asymmetric 1,4- addition turned out to be more tricky than the racemic version. Most rhodium catalysts described earlier by Batey, Miyaura, and Hayashi underwent poor conversions

and/or low enantiomeric excesses. It has been reported, by Darses, Genet et al. that, after careful optimization of the reaction system including ligand, solvent, temperature, potassium trifluoro(organo)borates react efficiently and selectively with enones in the presence of $[Rh(cod)_2]PF_6$ associated to chiral phosphine BINAP, JOSIPHOS and MeO-BIPHEP in a biphasic toluene-water mixture (10:1), Eqs. (38) and (39).[71] The reaction has been applied to α, β unsaturated amides, ester and lactones.[72]





5. Other Selected Reactions in Aqueous Medium

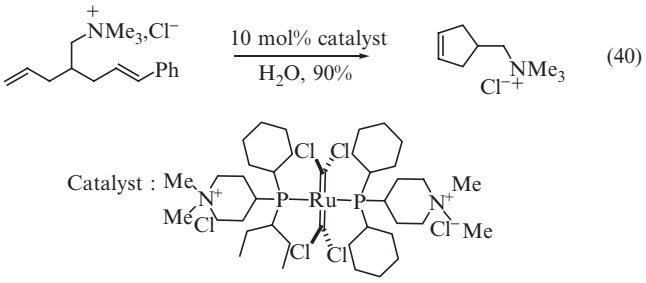
5.1. ASYMMETRIC HYDROGENATION REACTIONS

Asymmetric hydrogenation of prochiral substrates such as α-amido acrylic acids, α, β-unsaturated acids, β-keto esters and imines in water or in a two-phase system is one of the most studied reaction. Over the last three decades, a number of new methodologies and concepts have been developed for recycling the catalyst, in particular in organic aqueous medium. Several excellent and recent reviews have been devoted to this important field of research.[73]

5.2. OLEFIN METATHESIS

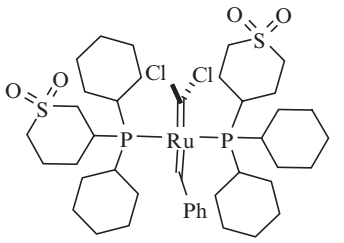
Since the outstanding achievements of Schrock and Grubb, the olefin metathesis is now a very useful tool for C=C bond formation in organic synthesis.[74]

The olefin metathesis (ROM, RCM, etc.) in aqueous media has been applied to the synthesis of a wide range of compounds. One example of RCM is shown in Eq. (40) by means of Grubb's catalyst and this reaction has been extensively used in aqueous conditions, for the preparation of many bioactive substrates.



(40)

For example, RCM of dienes proceeds efficiently in aqueous media using a Ru-carbene containing amino hydrochloride moiety.[75] More recently an active ruthenium alkylidene complex with a sterically bulky and electron-rich phosphine ligand **12** has been applied to RCM in aqueous media. In addition to combination of water–methanol, this ligand is also soluble in almost any solvent (methylene chloride, benzene) Figure. 3.

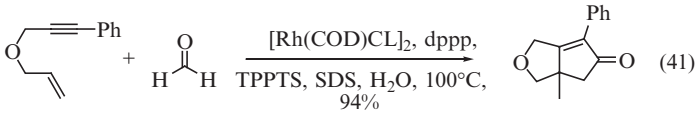


12

Figure 3. Ruthenium–alkylidene complex sterically hindered.

5.3. PAUSON–KHAND REACTION (PK)

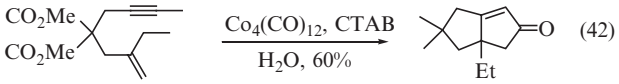
The Pauson–Khand reaction has proved to be one of the most effective methods of forming cyclopentanone derivatives. An aqueous $(RhClCOD)_2$-catalyzed PK of enynes in the presence of formaldehyde as the water source of carbon monoxide was developed by Kakiuchi et al. Eq. (41).[76]



(41)

The decarboxylation takes place in aqueous phase and carbonylation processes are believed to proceed independently in different phases of the reaction system to result in a more efficient catalytic carbonylation reaction.

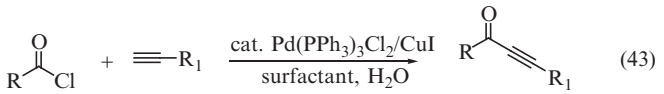
The use of cationic surfact using $Co_4(CO)_{12}$ and CTAB is also an effective catalytic system, Eq. (42).[77]



(42)

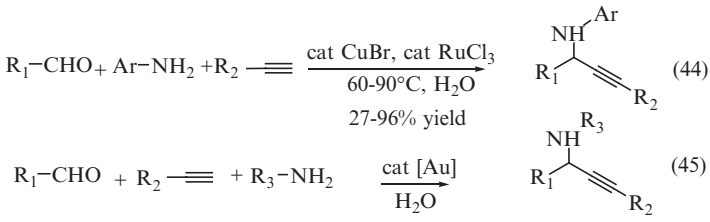
5.4. REACTION OF TERMINAL ALKYNES

A highly effective direct coupling of acid chlorides with terminal alkynes catalyzed by Pd (II) salts and Cu (I) additive with catalytic amount of sodium lauryl sulfate as the surfactant provided in water high yields of corresponding ynones, Eq. (43).[78]



(43)

The direct 1,2- addition of terminal alkynes to the C=N double bond in imines is a convenient route to synthesize propargylamines. Li et al. have reported highly efficient coupling in water using ruthenium, copper or gold as catalyst, Eqs. (44) and (45).[79]



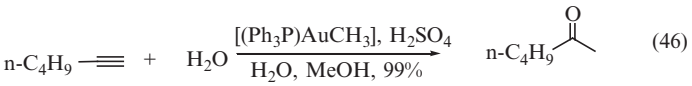
(44)

(45)

5.5. REACTION OF C≡C BONDS

Gold catalysts have been found to be particularly effective in catalyzing the nucleophilic addition of oxygen nucleophiles to alkynes. Au (I)-catalyzed addition of water in aqueous methanol provided an efficient synthesis

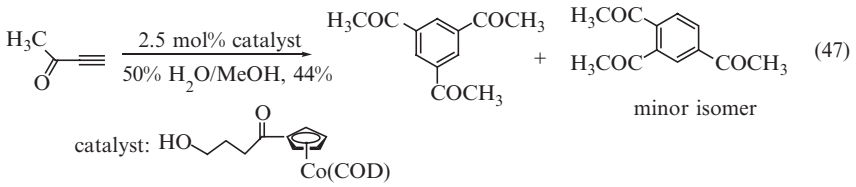
of carbonyl compounds, Eq. (46). This procedure is an alternative to the Wacker oxidation reaction.[80]



(46)

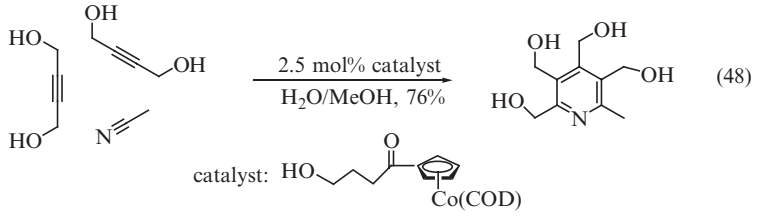
5.6. CYCLOTRIMERIZATION OF ALKYNES

A new water-soluble cobalt(I) catalyst, catalyzes the (2 + 2 + 2) cyclotrimerization of alkyne in aqueous media under mild conditions, Eq. (47).[81a]



(47)

This catalyst has also been used in the synthesis of highly functionalized pyridines via cyclization of two alkynes and one nitrile, Eq. (48).[81b]



(48)

6. Conclusions

A large number of water-soluble catalysts (Pd, Rh, Pt, Ru, Ni, and Au) are tolerant of a broad range of functional groups. Water medium can promote various old and new reactions. Theses catalysts are available for making C–C, C–X bond formation, viable in aqueous medium. This was not expected some years ago even by experts in the catalysis. The transition metal-catalyzed reactions with water-soluble phosphines provides the advantages of a two-phase aqueous system: easy separation and recycling of the expensive metal and ligand. Some reactions are unprecedented in water. The presence of water is crucial in some reactions since some substrates do not react under anhydrous conditions in organic solvent.

However in some cases the use of water is not beneficial. Thus, there is still a need to find more active water-soluble catalysts and the design of new ligands by fine-tuning the steric and electronic properties.

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HOMOGENEOUS AND HETEROGENEOUS CATALYSIS USING BASE METALS FROM GROUPS 10 AND 11

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Abstract: Recent developments on the use of nickel-in-charcoal (Ni/C) as a catalyst for several cross-couplings assisted by microwave irradiation are presented. The new reagent for synthesis, nickel-on-graphite (Ni/C_g) is presented as a means of catalyzing the reductions of aryl tosylates and mesylates. Another reagent under development, copper-in-charcoal (Cu/C) is described and its potential to effect heterogeneous asymmetric hydrosilylations in the presence of an inexpensive silane is disclosed.

Keywords: asymmetric reductions, organocopper and organonickel chemistry, heterogeneous catalysis

1. Introduction

OK; so here's the deal: give two 1-h lectures in return for 10 days at the Certosa di Pontignano on the outskirts of Siena. How could anyone, at least anyone not from Florence, refuse? I had been to Siena before, but under far more trying times: waylaid while waiting for a flight home just after 9/11. This trip to Italy would be very different.

The stories chosen for this NATO school would focus on two metals: first, organonickel chemistry, to be discussed within the context of heterogeneous catalysis. Then, catalysis with copper (I). Each lecture would be an opportunity to highlight the virtues of these two "base" metals; i.e. not only using both Ni and Cu as the sources of transition metal catalysts, but also to acknowledge that both metals are of limited cost to the practitioner. Other points to accentuate

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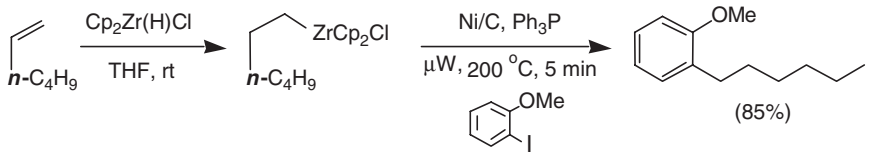
would include the benefits of such catalysis under heterogeneous conditions, as well as the potential for microwave irradiation to enhance reaction rates associated with cross-coupling reactions mediated by these ligated metals. The Boolean overlap of base metals + heterogeneous catalysts + microwave chemistry is still minimal,[1] and therefore, we intended to do something about that existing "gap" in methodology. Asymmetric processes using an inexpensive coinage metal (i.e. copper) would also be accentuated.

2. Lecture 1: Organonickel Chemistry

2.1. NICKEL-IN-CHARCOAL (NI/C)

It may seem odd that while palladium-on-charcoal (Pd/C) has been in textbooks for decades, the analogous "nickel-on-charcoal" (Ni/C) was unknown as a reagent in modern synthetic organic chemistry.[2] We presumed that it would effect cross-couplings with aryl chlorides, but it was not obvious that sensitive organometallics, e.g. involved in Negishi couplings,[3] would tolerate the typical high temperature conditions of microwave chemistry.[4] The potential deleterious effect of even small amounts of air and/or moisture might be accentuated as well with heating; we would just have to do the experiments. Along the way we realized that since the catalysis is taking place within the pores of the charcoal matrix,[2] the reagent is more accurately thought of as "nickel-*in*-charcoal", rather than nickel-on-charcoal.

Starting with vinyl zirconium intermediates, prepared in the usual way via hydrozirconation of terminal alkynes, it was quite encouraging to find that Ni/C smoothly catalyzed these couplings with various aryl halides in good isolated yields in minutes under microwave irradiation.[5] Thus, the 14–24-h time frames originally reported by Negishi[6] for related examples on bromides or iodides could be significantly reduced, not to mention the successful utilization of inexpensive and more thermally stable aromatic chlorides. Noteworthy is the case of an sp^3-based alkyl zirconocene, where an initial hydrozirconation of a terminal alkene followed by Ni/C-catalyzed coupling leads to the regiospecifically alkylated aromatic (Scheme 1).



Scheme 1. Hydrozirconation – Ni/C + μW-catalyzed cross-coupling.

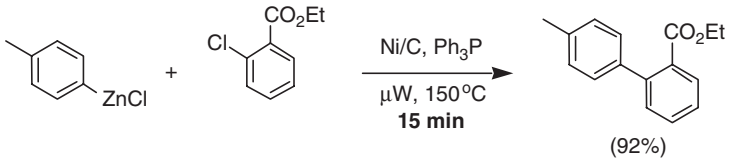
Several related "name" reactions normally reserved for palladium(0) catalysis were subsequently selected for study using Ni/C + μW (microwaves). While such obvious candidates as Stille, Heck, and Sonogashira couplings would be valued contributions, we have yet to examine these under conventional heating conditions. Thus, since time and temperature conditions were in hand for Negishi couplings,[7] Buchwald–Hartwig aminations,[8] and Suzuki couplings using Ni/C,[9] these three were chosen for comparison purposes.

Traditional preparations of organozinc halides,[10] both aryl and alkyl in nature, allowed for facile testing in standard 2–5-mL microwave vials. Since the zinc halides were all formed in dry THF, and the catalyst was prepared in dioxane, both constituted the solvent system in which all substrates were reacted. Reactions at 180°C over 30 min led to complete conversion using 15% Ni/C, along with 30% Ph_3P. It was soon realized that less catalyst (8%) and phosphine (16%), lower temperatures (150°C) were quite satisfactory, and in fact, under these milder conditions the cross-couplings were done in 15 min (Scheme 2). These conditions were in stark contrast to those used previously involving conventional means (i.e. refluxing THF for up to 14 h).[7] Moreover, it is worthy of mention that while 15%, or even 8% catalyst, sounds like a considerable amount of metal being invested, the fact that a base metal is involved as part of a catalyst (Ni/C) that can be recycled removes the usual incentives to maximize turnover numbers.

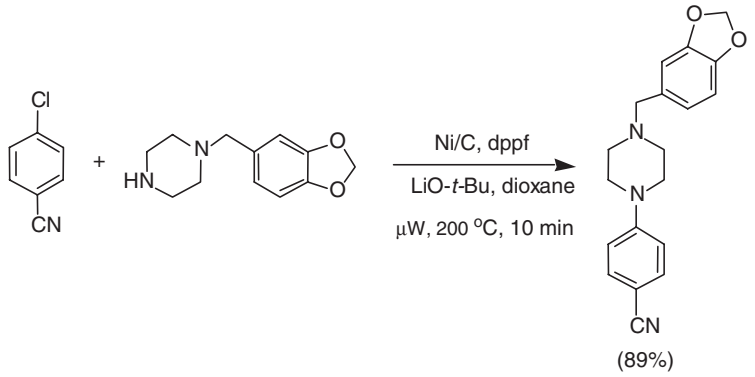
Introduction of amines onto aromatic rings via group 10 metal-catalyzed cross-couplings has greatly expanded access to these important resulting functional group arrays. While Ni/C had been shown to catalyze these desired C–N bond constructions,[8] they occur slowly, oftentimes requiring up to 2 days to reach full conversion. Application of microwave technology, however, was found to shorten these times to 10–40 min. Most aryl chlorides were reactive at 200°C and afforded good isolated yields in only 10–15 min (Scheme 3).

Not surprisingly, the more electron-rich cases demanded longer times, but nonetheless, gave the expected anilines cleanly. While Ph_3P was the ligand of choice for most Ni/C-catalyzed processes, aminations were found, both for conventional and microwave heated reactions, to give best results using dppf.

Suzuki-like couplings to form biaryls via Ni/C-catalysis usually take place in refluxing dioxane.[9] At concentrations of ~0.25 M, a reaction time on the



Scheme 2. Representative Negishi coupling by Ni/C + μW.



Scheme 3. Representative amination by Ni/C + μW.

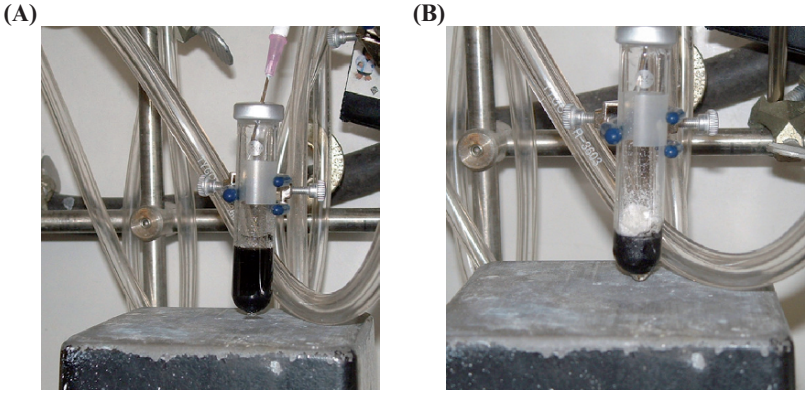
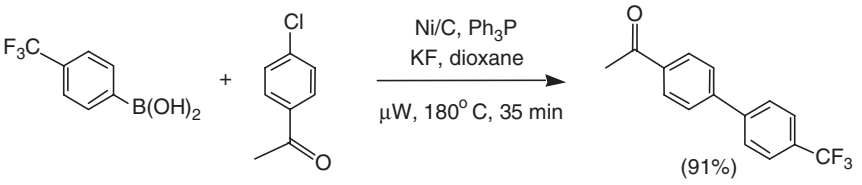


Figure 1. **(A)** Solids in μW-assisted reaction fully covered by solvent; **(B)** improper, unsafe reaction mixture, with solids exposed.

order of 18–24-h is typical. Moreover, the presence of a base, e.g. K_3PO_4, is necessary. In a microwave vial, however, the amount of solids added becomes important, since if not covered by solvent, e.g. as in Figure 1, localized heating occurs leading to potentially explosive mixtures. Low-molecular weight bases, therefore, are preferred given that, by definition, solid material in the form of the catalyst (Ni/C) is already present.

Fortunately, the far lower molecular weight LiF, oftentimes together with LiOH, is a combination that works well affording good yields of biaryls (Scheme 4). The boronic acid was used in excess (1.5 equivalents), and at 180°C, reaction times dropped to 35 min.



Scheme 4. Representative Ni/C-catalyzed Suzuki-like coupling.

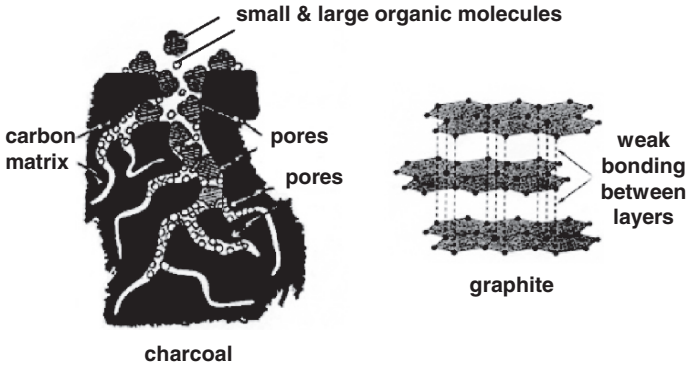


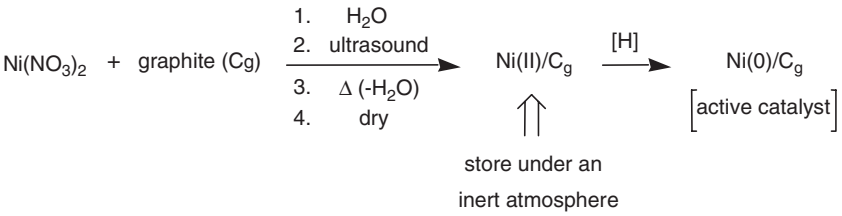
Figure 2. Comparison of charcoal with graphite.

2.2. NICKEL-ON-GRAPHITE (NI/C_G)

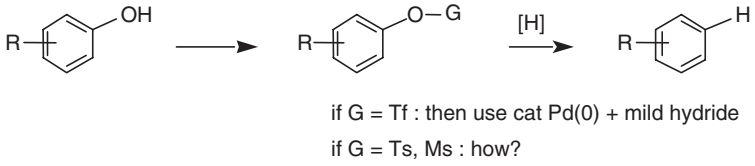
Among the four allotropic forms of carbon, charcoal is the only one that we had previously considered as a support for impregnated nickel. While diamond and buckminsterfullerene are impractical alternatives, graphite remained as another attractive possibility, being structurally quite different (Figure 2).

Nickel atoms embedded within the graphite sheets (with ~3.3 Å between the sheets) can presumably only react with coupling partners in solution upon exposure at the graphite termini. Thus, while bond formations occur within a charcoal matrix, related cross-couplings can only take place when nickel is available as the sheets slide.

Aside from the apparent less costly nature of this species relative to activated charcoal (at least insofar as the Aldrich catalog is concerned; #28,286-3), graphite is free-flowing making its handling somewhat easier than charcoal at the 1–2-μ mesh size level. Graphite is also relatively "clean", although this remains an assumption until a more careful ICP-AES analysis is done on material "out of the bottle".



Scheme 5. Preparation of nickel-on-graphite (Ni/C_g).



Scheme 6. First application of Ni/C_g: reduction of aromatic OH groups.

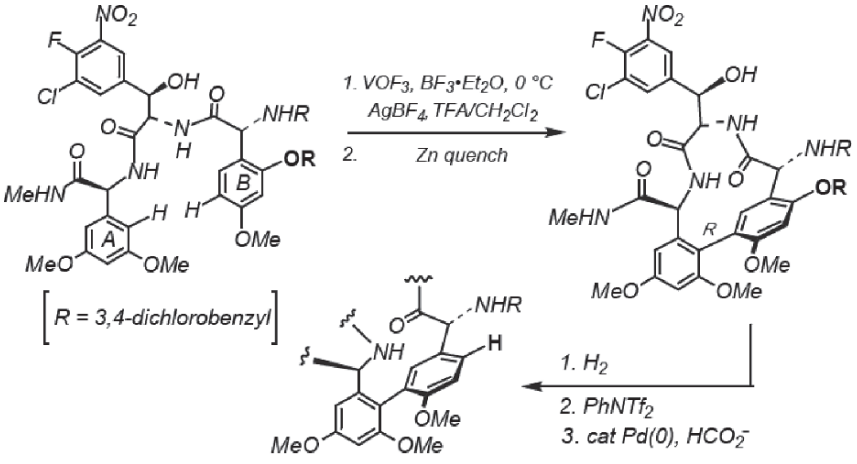
Formation of nickel-on-graphite was approached in precisely the same manner used to prepare Ni/C[11]; that is, with $Ni(NO_3)_2$. And, as with Ni/C, it was anticipated that after mixing with graphite in water, ultrasonication would distribute the nickel throughout the graphite sheets avoiding large clusters that might decrease accessibility and hence, reactivity. Also, upon distillation of the water, oxides of nitrogen would presumably be driven off, leaving nickel(II) as NiO/C_g. Subsequent reduction by *n*-BuLi would give rise to active Ni/C_g. Fortunately, all of this speculation could be reduced to practice, as generation of this catalyst could be achieved in a reproducible fashion (Scheme 5).[12]

With this species in hand, we endeavored to tackle a cross-coupling reaction other than the "name" reactions common to Pd (0) chemistry, or those already shown to occur under the influence of Ni/C. We settled on the reduction of aromatic OH groups to the corresponding hydrocarbon, since we were unaware of any *general* methods to effect this type of transformation that are heterogeneous, that use nickel, and can be applied to the far less expensive tosylate or mesylate derivatives (Scheme 6).

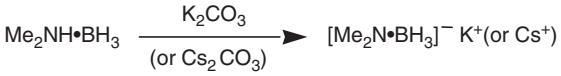
Cabri's work in 1991 was the closest in the literature,[13] albeit done under homogeneous conditions. That the catalyst functions such that most electrophilic centers (e.g. ketone, ester, amide, nitrile, etc.) are tolerated and that there is no loss in stereochemistry at acidic sites (e.g. in a polypeptide) were

of paramount concern. The importance of this reduction was brought to light in the landmark paper by Evans and co-workers describing the synthesis of the vancomycin aglycon.[14] In order to form the key A–B biaryl section via a vanadium(V)-based biomimetic-like oxidation (Scheme 7), a second oxygen residue was essential to adjust the innate oxidation potential of the B ring. Following biaryl coupling, the superfluous oxygen had to be excised by initial generation of a triflate derivative, followed by a Pd (0)-catalyzed reduction with Bu_3SnH.

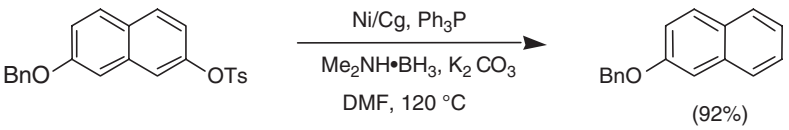
At first, use of Ni/C_g to reduce phenolic tosylates was not successful. The choice of $Me_2NH{\bullet}BH_3/K_2CO_3$, which supplies the stoichiometric reducing agent, had been used previously in this context[15] and was not the likely culprit. The amine–borane complex is a commercially available solid, but does lose activity over time and relatively fresh material well-stored under argon is needed for success. This combination of $Me_2NH{\bullet}BH_3$ and K_2CO_3 (or Cs_2CO_3) leads, upon pre-mixing, to the salt $Me_2N\text{-}BH_3K$, which contains no Lewis acidic character and hence, does not reduce most electrophilic centers (Scheme 8).



Scheme 7. Literature example of an aryl-OH reduction.

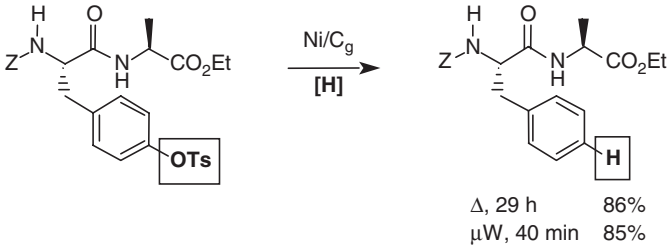


Scheme 8. Preparation of the stoichiometric reductant.



Scheme 9. Representative reductive detosylation catalyzed by Ni/C_g.

Since the observed product in each of three early attempts amounted to the starting phenol from which the tosylates derived, it was likely that water in the DMF was hydrolyzing the educts. Fortunately, use of dry DMF led to smooth detosylation at 120°C. Reactions take, on average, 6–24 h, where the substrate is 0.33 M and 5% Ni/C_g is sufficient (Scheme 9).



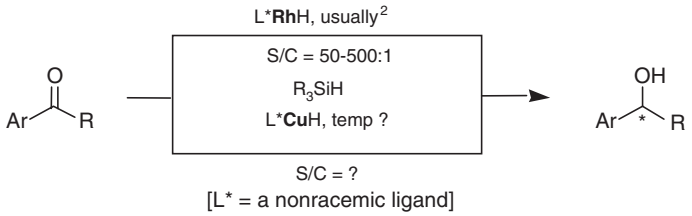
Scheme 10. Application of Ni/C_g: reduction of an aromatic tosylate.

Identical conditions can be employed for the corresponding mesylates with equal success. Since the K_2CO_3 is pre-mixed with $Me_2NH•BH_3$ to form the kaliated salt prior to introduction of the sulfonate, it was not surprising that reduction of a nonracemic tyrosine-containing dipeptide under either conventional or microwave conditions led to the corresponding phenylalanine derivative without erosion in stereo-chemical integrity. Carrying out the detosylation at 215°C in DMF using microwaves decreased the reaction time from 29 h to 40 min (Scheme 10).

3. Lecture 2: copper-catalyzed hydrosilylation reactions

3.1. HOMOGENEOUS REACTIONS OF CATALYTIC CuH/R_3SiH

As the reviews would lead one to believe,[16] the field of asymmetric hydrosilylation (of aryl ketones, in particular), is primarily dominated by rhodium catalysis. The origins of this area date back to the early 1970s, when complexes based on ligands such as DIOP[17] and Glucophinite,[18] along with a



Scheme 11. Asymmetric hydrosilylation: Rh vs Cu catalysis.

silane such as Ph_2SiH_2, were found to afford product alcohols on workup, albeit in modest ee's. The switch to copper had its early origins some 12–13 years later (1984),[19] but it was not until the late 1990s that development of asymmetric copper hydride (CuH) chemistry began in earnest.[20] The economic benefits of copper-catalyzed hydrosilylations relative to rhodium are obvious, and given the relatively low reactivity of ligated Rh–H bonds compared to those in Cu–H, as well as the modest substrate-to-catalyst ratios (~50–500:1) commonly used with such rhodium catalysts,[21] it seemed quite reasonable that competitive processes based on copper(I) might be uncovered (e.g. in the case of aryl ketones; Scheme 11). Of course, success would be intimately tied to the search for nonracemic ligands that imported not only kinetic reactivity but high efficiency in chirality transfer to the substrate via the metal hydride. If the ee's realized with CuH are comparable to those using Rh catalysis, another factor determining acceptance would likely be turnover numbers (TONs).

Fortunately, we have found over time that three ligands, in particular, show remarkable selectivity in hydrosilylation reactions of their complexed CuH derivatives. All share the bis-phosphine motif, but clearly, the biaryl nucleus is not a requirement.

Thus, Takasago's SEGPHOS[22] and Roche's BIPHEP[23] series of ligands (Figure 3) are outstanding in their ability to deliver CuH to an aryl ketone enantioselectively, with ee's usually in the mid 90% range when run at low temperatures.[24] For unsaturated ketones, Solvias' JOSIPHOS derivative PPF-P(*t*-Bu)$_2$ is exceptionally selective as the CuH complex.[25] In most cases, PMHS[26] (polymethyl-hydrosiloxane, Figure 4) is the stoichiometric silane of choice (except for the case of aryl imines, where TMDS, tetramethyldisiloxane leads to better results).[27] DTBM-SEGPHOS was selected for further development, and in studying its chemistry when complexed with CuH, found to exhibit exceptional facial discrimination in delivering hydride in a 1,4-sense to cyclic enones,[28] α,β-unsaturated esters and lactones,[29] as well as in a 1,2-sense to aryl imines.[27]

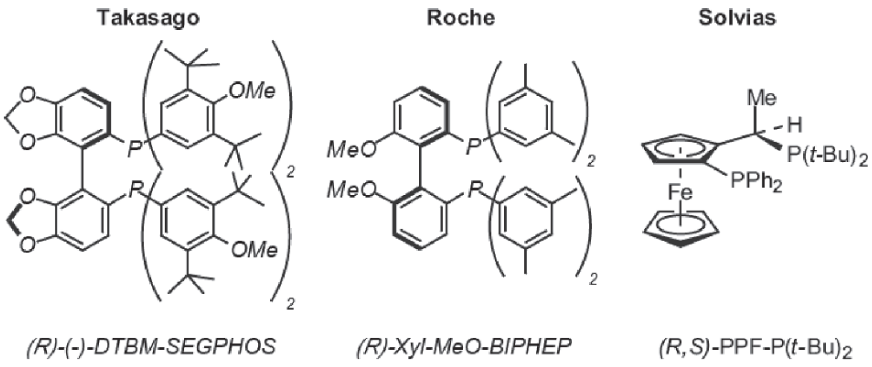


Figure 3. Extremely effective ligands for asymmetric CuH chemistry.

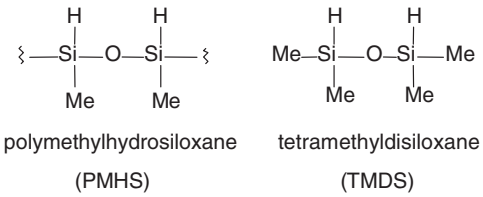
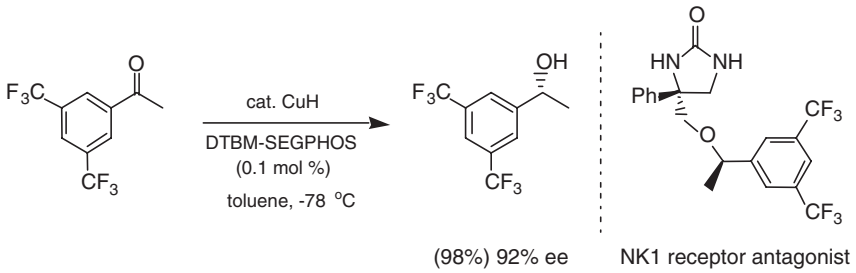


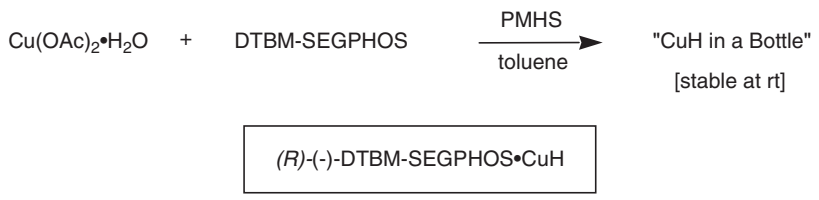
Figure 4. Silanes used in CuH-catalyzed asymmetric hydrosilylation.



Scheme 12. Hydrosilylation of an aryl ketone of medicinal interest.

Recently, this catalytic system has been applied to several aryl ketones that serve as useful precursors to intermediates in the pharma industry.[30] One such target is an NK1 receptor antagonist, where an aryl ketone can be effectively reduced to a nonracemic benzylic alcohol in good yield and in high ee (Scheme 12).

Due to the broad scope of (R)-(-)-DTBM-SEGPHOS-CuH, we endeavored to provide stability data on this complex, speculating that if thermodynamically stable at room temperatures for days it might serve the community as



Scheme 13. Formation of "CuH in a Bottle".

a readily available "CuH in a Bottle". By pre-complexing Cu(OAc)2•H_2O with DTBM-SEGPHOS in toluene followed by introduction of PMHS (2 equivalents), a 0.001 M solution was easily prepared (Scheme 13).

This was chosen so that a 1 mmol reaction would require 1 mL of this solution and would correspond to a substrate-to-catalyst ratio of 1,000:1. The choice of Cu(II) acetate was predicated on the notion that Cu–O bonds other than that in CuO-t-Bu (generated using the Stryker protocol from CuCl + NaO-t-Bu)[31] should lead to CuH in the presence of a silane. Both the Yun (Ajou University in Korea)[32] and Buchwald (MIT)[33] schools had already described this precursor to CuH, although our study was far broader, including the salts: CuOAc, $Cu(OTf)_2$, $Cu(acac)_2$, $Cu(bzac)_2$, Cu_2O, CuO, $Cu(O_2CCF_3)$, CuOPh, and CuOBHT (i.e. the Cu(I) salt of butylated hydroxytoluene).[34] Although the "winner" in this study in terms of extent of conversion and rate was $Cu(OAc)_2•H_2O$, CuOPh was a close second where in situ generated, homogeneous reactions of CuH were involved. The precursor salt, NaOPh, would later prove to be the additive of choice in the case of heterogeneous CuH impregnated into charcoal (*vide infra*).

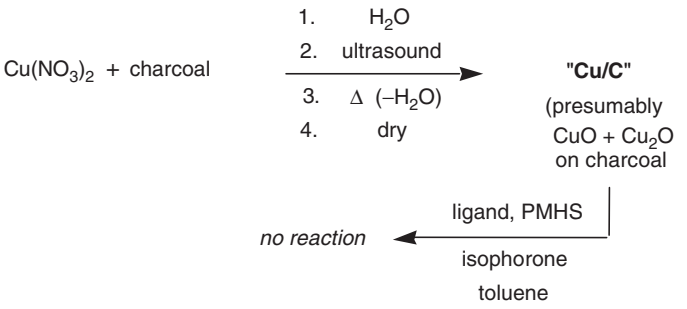
The newly formed "CuH in a Bottle" did, in fact, exhibit excellent shelf life at room temperature over at least 2 weeks of uninterrupted storage, using isophorone as the test case.[34] A modest loss of ee over 2 months (99– 94% ee) was noted, although the cause was traced to the quality of the seal on the bottle and thus, introduction of adventitious air. Use of an Oxford cap, as opposed to an Aldrich SureSeal, appeared to provide a solution to this practical problem.

3.2. HETEROGENEOUS REACTIONS OF ASYMMETRICALLY LIGATED CuH: Cu/C

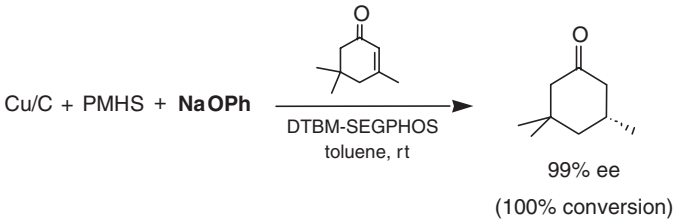
Considering the enormous success of organocopper chemistry as a tool in organic synthesis, it might seem odd that no readily available, heterogeneous source of catalytic copper of any generality yet exists. It was towards

this goal that the notion of impregnating copper into charcoal was born. Unfortunately, it did not take long to find that the concept was far from novel; that "copper-on-charcoal" is a well-known species.[35] But upon further inspection it also became obvious that no synthetic applications, in particular cross-couplings, had been considered. Moreover, it was surely not a given that our method of impregnation, using ultrasound and mild heating (~110°C), would lead to the same reagent "Cu/C" normally prepared by others using a much higher temperature regime (oftentimes at ~400°C). Our experience in "nickel-in-charcoal" was our guide,[11] and thus, $Cu(NO_3)_2$ was the appropriate choice as metal precursor. Using the same source of charcoal (Darco KB activated carbon, Aldrich #24,407-4, 100 mesh) copper was loaded into the solid support by simply applying ultrasound to the $Cu(NO_3)$/charcoal mix in water, followed by filtration, distillation of freshly added water, and azeotropic drying with toluene (Scheme 14). While the protocol seemed to follow smoothly the Ni/C prepared in this manner, our initial attempts to use Cu/C in the presence of PMHS and DTBM-SEGPHOS failed to consume any of the isophorone selected as a test case.

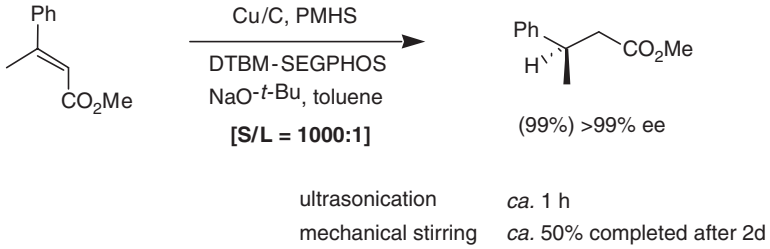
The explanation for these early tribulations was soon to surface upon realization that the impregnated copper was in the form of CuO (and possibly mixed with lesser amounts of Cu_2O). Neither of these salts was an acceptable precursor to CuH, judging from prior studies in solution (*vide supra*),[34] and hence, ligand exchange from oxide to another ligand on copper was needed to arrive at a copper (I) species that readily reduces with silane to CuH. The obvious first choice was *t*-butoxide (a la Stryker).[31] By adding NaO-*t*-Bu to the Cu/C-silane mix (2 equivalents relative to Cu), a smooth asymmetric hydrosilylation of isophorone took place to afford fully consumed educt in high ee.[34] Replacing *t*-butoxide with phenoxide (i.e. NaOPh; Scheme 15) led to an even faster rate of reduction without compromising the level of stereoinduction.



Scheme 14. Preparation of copper-in-charcoal (Cu/C).



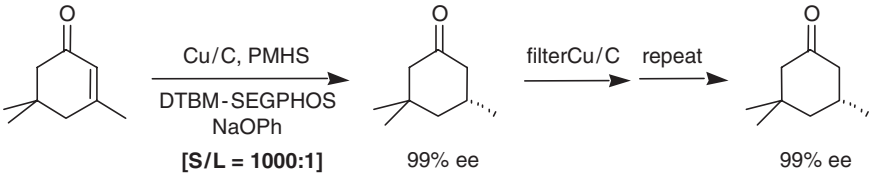
Scheme 15. Activation of Cu/C toward asymmetric 1,4-reductions.



Scheme 16. Use of ultrasound in asymmetric hydrosilylations: an enoate.

To examine the scope of this heterogeneous process, various substrate types were screened and comparisons made with the corresponding reactions of DTBM-SEGPHOS-CuH in solution. Notably, hydrosilylation of an enoate took far longer than does the corresponding reaction in solution, not only indicative of a heterogeneous event but necessitating an alternative strategy (Scheme 16). Speculating that the problem was one of mixing (using a magnetic stir bar in our small-scale trials, usually 0.5–1.0 mmol), the reduction was carried out in an ultrasonic bath. Applying this technique resulted in both a rapid reduction (<1 h at identical concentrations) along with a high level of facial discrimination.

While the "trick" of employing ultrasonic mixing could be extended to other substrates (e.g. aryl imines), the issue of reagent recycling had yet to be addressed. Could a CuH/C reaction mixture be filtered, and the Cu/C reclaimed and re-used? This idea was readily tested using, again, isophorone. Upon completion of the 1,4-asymmetric reduction, filtration, and then catalyst isolation and drying afforded material that could be re-used directly in a second asymmetric hydrosilylation of isophorone. No change in rate, yield, or ee was observed, suggesting no loss in catalyst activity (Scheme 17). To push the recyclicability question even further, a new series of experiments



Scheme 17. Preparation and re-use of copper-in-charcoal (Cu/C).

was executed where the spent Cu/C was filtered as before, but no further processing was carried out; i.e. it was simply added without isolation into the next reaction. Based on the well-known, strong dative association of a phosphine with copper, it was surmised that DTBM-SEGPHOS might remain on the metal throughout the reduction, in which case no additional ligand would be required for subsequent reactions. This exciting possibility was indeed borne out, as the "wet" Cu/C, without additional bis-phosphine, was equally as effective as the initially run reaction. The extent of ligand retention on copper has yet to be quantified, but to the extent that TLC analyses reveals no DTBM-SEGPHOS in the filtered reaction mixture suggests that the minimal ligand present in the mixture, which it sees as pseudo first order in copper, remains fully bound.[34]

4. Summary and outlook

So how is it possible that with catalytic organocopper chemistry dating back to Kharasch's work in 1941,[36] that no heterogeneous equivalent of common usage exists today? It's meant as a rhetorical question, of course, but such a reagent thus seems long "overdue". And while asymmetric CuH chemistry itself is a newcomer to the field of homogeneous, ligand-accelerated catalysis, whether copper (II) mounted within the pores of a charcoal matrix is generally applicable to the plethora of reactions under the umbrella of organocopper chemistry remains an open question. The "pay-off" to such studies can be substantial, since catalyst recycling minimizes waste disposal of transition metal-involving processes. Early returns look encouraging; venturing back to our roots in modern organocopper chemistry using catalytic Cu/C and Grignard reagents to effect heterogeneous conjugate additions to cyclic enones appears to give higher ratios of 1, 4- : 1, 2-adducts than does the original Kharasch method, which employed 1% CuCl and excess RMgX. Nonetheless, additional successful cross-couplings will be needed before Cu/C is likely to achieve common reagent status.

Acknowledgements

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AN INTRODUCTION TO SUPERCRITICAL FLUIDS: FROM BENCH SCALE TO COMMERCIAL PLANT

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Abstract: This chapter aims to give the Reader an introduction to the application of supercritical fluids (SCFs) especially supercritical carbon dioxide ($scCO_2$) as an environmentally benign alternative solvent and, in Section 3, describes the scaling up of hydrogenation reactions in $scCO_2$.

Keywords: Green Chemistry, supercritical fluids, heterogeneous catalysis, industrial application

1. Introduction: Green Chemistry

With an increase in environmental awareness, much of the global chemical industry is searching for new "cleaner" alternatives to its current processes. Green Chemistry, as an independent discipline, was conceived some 15 years ago by Paul Anastas and John Warner who were moved to produce a set of guidelines that have since been adopted as a mantra for the design of environmentally benign processes. "The Twelve Principles of Green Chemistry"[1] try to instill a philosophy in the mind of the experimental chemist that is similar in many ways to the Hippocratic oath of the medical practitioner, i.e. first of all, do no harm, to the environment. More recently, the key concepts embedded within these Principles have been presented in the form of an easy to remember acronym, "*PRODUCTIVELY*",[2] (Figure 1) constructed from the initial letters of a condensed form of Anastas and Warner's original Principles.

Research in the field of Green Chemistry is very active but it may be conveniently divided into three main themes, catalysis, renewable feedstocks/energy and solvent replacement. This chapter aims to give the Reader an introduction to the application of supercritical fluids (SCFs) especially

A. Mordini and F. Faigl (eds.), New Methodologies and Techniques for a Sustainable Organic Chemistry, 171–191.

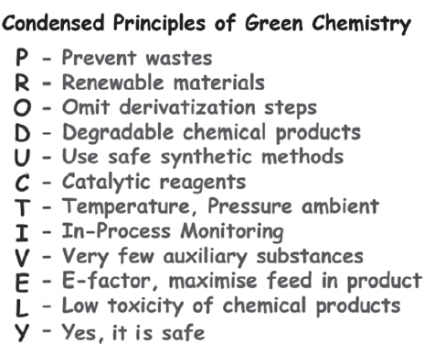


Figure 1. The twelve principles of Green Chemistry written in the form of a mnemonic: productively.

supercritical carbon dioxide ($scCO_2$) as an environmentally benign alternative solvent and, in Section 3, describes the scaling up of hydrogenation reactions in $scCO_2$.

2. Supercritical Fluids (Scfs); A Brief Introduction

A supercritical fluid (SCF) is a gas that has been compressed until its density is close to that of a liquid. More formally, it may be defined as any substance that is held above its critical temperature (T_c) and critical pressure (p_c), and having a density close to, or higher than its critical density.[3] This definition can be understood with a phase diagram[4] such as that shown in Figure 2. The unique physical properties associated of SCFs, most notably their "tunable solvation abilities" render them excellent replacements for many environmentally damaging volatile organic solvents and poly-halogenated hydrocarbons including CFCs. Indeed SCFs are used in a variety of day-to-day processes including the decaffeination of coffee,[5] the production of fine chemicals,[6] and even the dry-cleaning of clothes.

The critical parameters, T_c, p_c and indeed the critical point are characteristic of the material of interest and the values of these figures vary greatly, for instance the critical point of H_2 is defined by $T_c = -240°C$, p_c 12.98 bar, consequently H_2 is supercritical when stored in high pressure cylinders as received from gas suppliers. The critical parameters of commonly employed reaction solvents are detailed in Table 1.

Carbon dioxide is chemically inert under most conditions; it is non-protic and neither strongly Lewis acidic or basic. In addition, it is inert to both radical and oxidizing conditions. One major drawback to $scCO_2$ as a solvent for synthetic transformations is its incompatibility with primary or secondary amines, due to carbamate formation and precipitation of solid residues: $scCO_2$

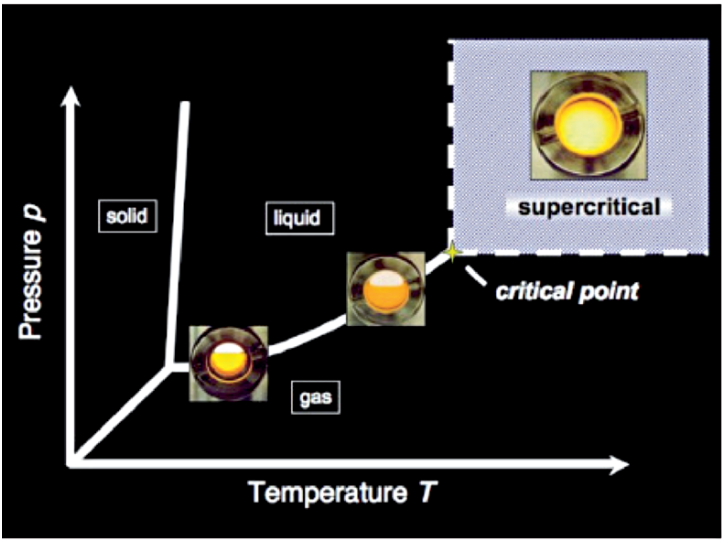


Figure 2. Phase diagram for a pure substance showing the critical point defined by the critical temperature (T_c) and pressure (p_c).

TABLE 1. Critical parameters of commonly employed SCFs.

Fluid	T_c/°C	p_c/bar
Water (H_2O)	374.1	220.6
Carbon dioxide (CO_2)	31.1	73.8
Propane (C_3H_8)	96.7	42.5
Sulfur hexafluoride (SF_6)	45.6	37.6

is a non-polar molecule with poor solubilizing power (e.g. its solvent power comparable to *n*-hexane), and this has considerably restricted the choice of catalysts, reagents, and substrates to a narrow range of non-polar, non-ionic, and low molecular weight compounds. However several methods have been developed to overcome this limitation. The strategies employed have included increasing the bulk density of the $scCO_2$ by increasing the applied pressure, the addition of co-solvents (modifiers such as MeOH or toluene that enable strong specific interactions such as hydrogen bonding with the solute), modification of the solute to make it more CO_2-philic (by introducing hydrocarbon, fluorocarbons, or silane side chains), careful choice of counter-ion including for example $[(3,5\text{-}(CF_3)_2C_6H_3)_4B]^-$ "BArF", or $CF_3SO_3^-$) for the solvation of charged complexes.

2.1. HOMOGENEOUS CATALYTIC HYDROGENATION

Present studies on hydrogenation in supercritical media mainly capitalize on the enhanced mass transfer as a result of the increased solubility of hydrogen into SCFs. This often has a marked influence on the reaction rate and selectivity. Homogeneously catalyzed reactions have been extensively reviewed[4, 7, 8] and compared to analogous heterogeneously catalyzed reactions.[9, 10] $scCO_2$ has already been successfully employed as both reaction medium and reactant in the synthesis of formic acid and its derivatives[11–13] with reaction rates comparing favorably with those achieved in conventional solvents. The homogeneous catalytic synthesis of *N,N*-dimethylformamide (DMF) and methyl formate (MF) from carbon dioxide are also reported.[9, 11, 12, 14–16] Heterogeneous variants of the above solvent-free homogeneous processes have also been designed.[13, 17] Indeed, the hydrogenation of cyclopropene by $MnH(CO)_5$ via a radical mechanism was the first example of $scCO_2$ being employed as a solvent in such reaction systems.[18] Custom-designed Rh complexes have been described as active catalysts for hydrogenation reactions.[19, 20] Homogeneous enantioselective asymmetric hydrogenation of prochiral α-enamides,[21] and hydrogenation of α,β-unsaturated carboxylic acids such as tiglic acid have been reported.[22] Leitner also reported the use of $scCO_2$ as a reaction medium for the homogeneous iridium catalyzed enantioselective hydrogenation of prochiral imines.[23]

2.2. HYDROFORMYLATION REACTIONS IN $SCCO_2$

Hydroformylation is the catalytic addition of CO and H_2 (*syn-gas*) to olefinic precursors. In 1991, Rathke described the first example of the homogeneous hydroformylation in $scCO_2$.[24] Subsequently, Leitner reported that a CO_2-soluble Rh complex with a polyfluoroalkyl-substituted triarylphosphine ligand facilitated the hydroformylation of 1-octene to linear aldehyde in a good yield with 82% selectivity,[25] with very little evidence of side reactions such as hydrogenation or isomerization of the olefin. In 1998, the same group reported the asymmetric hydroformylation of styrene.[26] A continuous process for the selective hydroformylation of higher olefins in $scCO_2$ can also be found.[27, 28] Recently, Xiao and co-workers synthesized a fluorous polymeric phosphine which when combined with $scCO_2$ and rhodium, effects unprecedented, fast and highly chemoselective hydroformylation of acrylates, one of the least reactive olefins in hydroformylation reactions (Figure 3).[29,30]

2.3. DIELS–ALDER CYCLOADDITION REACTIONS IN $SCCO_2$

Using a series of different dienes and dienophiles, with varying steric and electronic properties, the Diels–Alder reaction was investigated in $scCO_2$. In

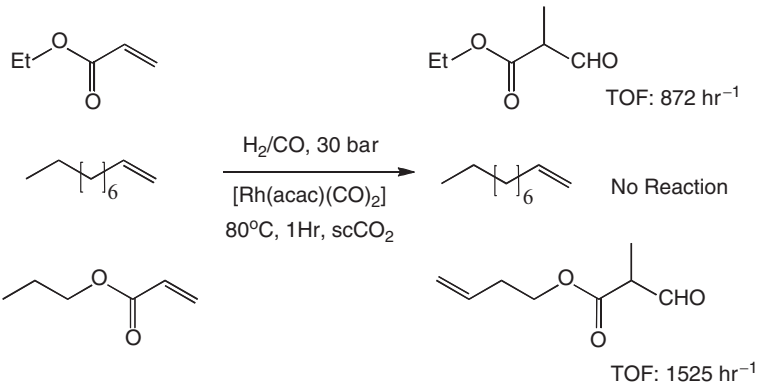


Figure 3. Chemoselective hydroformylation of C=C bonds in $scCO_2$.

1987, Paulaitis and Alexander reported the Diels–Alder reaction of maleic anhydride with isoprene; it was one of the earliest reported synthetic reactions in a SCF media.[31] In all of the investigated cases, regioselectivities similar to those observed in conventional solvents were achieved. In 1998, Chapuis et al. reported the first SCF Diels–Alder reaction controlled by a chiral auxiliary.[32] Danheiser reported a silica catalyzed Diels–Alder reaction in $scCO_2$.[33] Kobayashi reported the application of scandium perfluoroalkanesulfonates as Lewis acid catalysts in Diels–Alder reactions.[34] Roberts investigated the effect of pressure on the bimolecular rate constant of the Diels–Alder reaction between maleic anhydride and isoprene,[35] a further discussion of the kinetics of this reaction has been described.[36]

2.4. OXIDATION REACTIONS IN $scCO_2$

A wide range of studies of heterogeneously catalyzed oxidations in SCFs can be found, in contrast to homogeneously catalyzed oxidations. A recent paper[37] reviewed the catalytic oxidations in dense CO_2. The functionalization of alkanes by oxidation has been of interest both in liquid solvents and in SCFs. The aerobic oxidation of cyclohexane in the presence of an iron-porphyrin catalyst FeCl(tpfpp) (tpfpp = 5,10,15,20-tetrakis(pentafluoroph enyl)porphyrin) and acetaldehyde in $scCO_2$ was reported by Koda.[38] Jiang reported a palladium(II) catalyzed oxidation of acrylic esters to acetals.[39] Recently, Wei and co-workers have shown that CO_2-expanded solvents provide optimal properties for maximising oxidation rates.[40] Epoxidation of alkenes by hydroperoxides in $scCO_2$ in the presence of $Mo(CO)_6$,[41–44] or other transition metal catalysts have also been examined.[43, 45, 46] A continuous epoxidation of propylene with oxygen and hydrogen over a Pd-Pt/TS-1

catalyst has been developed.[47] Leitner has also reported the steel-promoted oxidation of olefins using oxygen in the presence of aldehydes.[48]

2.5. PALLADIUM-MEDIATED COUPLING REACTIONS IN $scCO_2$

Palladium-catalyzed coupling reactions in $scCO_2$ have received much recent attention. Tumas reported work on the development of the Heck and Stille coupling reactions in $scCO_2$.[49] Stille cross-coupling reactions catalyzed by perfluoro-tagged and un-tagged Pd complexes have been developed.[50] Intramolecular Heck cyclization reactions in $scCO_2$ have also been reported, suppressing the double bond isomerization reaction often present in conventional solvents.[51] Arai detailed a Heck reaction employing water-soluble catalysts in a $scCO_2$–water biphasic system.[52] The reaction of aryl iodides with a variety of olefins in $scCO_2$ in the presence of triethylamine and an immobilized palladium catalyst has been reported.[53, 54] Carroll and Holmes[55] prepared unusual polyfluoroalkylphosphine ligands to enhance the solubility of Pd(II) catalysts for coupling reactions of phenyl iodide. Dendrimer-encapsulated nanoparticles have also been shown to be versatile catalysts for both the hydrogenation of styrene and Heck heterocoupling of iodobenzene and methacrylate.[56] However, the few studies done so far suggest that most cyclization and coupling reactions (Suzuki and Sonogashira couplings) are neither faster nor offer greater yields in $scCO_2$ than in liquid solvents, Heck reactions being the possible exception. Jessop suggested that the potential advantage to using SCFs for these reactions may lie in the tunable dielectric constant[57] or local solute/solute clustering effects that have been beneficial in noncatalyzed reactions.[58]

2.6. MISCELLANEOUS CATALYTIC REACTIONS IN scFS

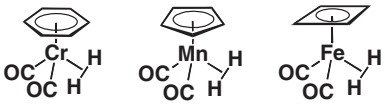
$scCO_2$ has been shown to be a unique solvent in which to perform polymer synthesis, reflected in the commercialization of some supercritical polymerization processes. DeSimone and co-workers have carried out a large proportion of the research in this area.[59, 60] Recently, the ionic ring-opening polymerization of several heterocycles in $scCO_2$ has been described for the first time.[61] Hydrosilation of poly(methylhydrosiloxane) with a fluorinated olefin in $scCO_2$ using a Pt catalyst has been successfully demonstrated.[62] Catalytic intermolecular Pauson–Khand reactions in $scCO_2$ have also been described.[63, 64] Transition metal catalyzed olefin metathesis, and ring-opening metathesis polymerization (ROMP) of a number of cyclic olefins in both liquid CO_2 and $scCO_2$ are reported.[65–67] The chemical yield and molecular weight of the polymers are comparable to those in conventional solvents.

Leitner found that some carbene complexes effected ring-closing metathesis (RCM) of even functionalized dienes to cyclic olefins.[20, 66] Yoshida reported the use of $scCO_2$ both as the reaction media and carbonyl source for the production of urethanes from amines.[68] This is an attractive catalytic one-pot alternative to the use of phosgene in urethane synthesis. Poliakoff, Ross and co-workers have used a fixed bed heterogeneous supported acid catalyst to perform continuous Friedel–Crafts alkylation of aromatics in SCF media.[69, 70] Using the same continuous flow reactor apparatus, the acid catalyzed dehydration of alcohols in $scCO_2$ was also investigated.[71–73] Tumas reported a Rh-catalyzed alkene hydroboration reaction in $scCO_2$.[74] Li Fan investigated the effect of SCFs on alkylation reactions on Y-type zeolites.[75] Finally, the prospect of using enzymes as heterogeneous catalysts in SCF media has created a significant interest since the mid-1980s. A large amount of literature exists, reporting enzymatic catalysis in $scCO_2$, performing hydrolyses, oxidations, esterifications and transesterification reactions.[76] The broader application of SCFs in materials processing is the subject of an excellent and recent review by Beckman.[77]

3. The Commercial Scale-Up of the Hydrogenation of Isophorone

The remainder of this chapter is based, with permission, on an article published by the authors in the Royal Society of Chemistry Journal, Green Chemistry,[6, 78] The story is important because one of the major aims of Green Chemistry is the implementation of new technologies on a large scale. However, to date, there are very few concrete examples of this aim being realised in practice.[79, 80] The project is important for a second reason, namely that the plant itself is a large-scale Green Chemistry experiment and a rare example of a new technology being put to the test in public. Like all such projects, the full history is quite convoluted. Here we highlight only the most significant events.

Originally, the motivation at Nottingham for carrying out chemical reactions under supercritical conditions was to provide a better route for the photochemical generation of unstable organometallic dihydrogen[81] and dinitrogen[3, 82] complexes such as those shown in Scheme 1. One of the keys to the success of this early work was the relatively high concentrations of H_2 and



Scheme 1. Examples of unstable organometallic species prepared in supercritical fluids.[3]

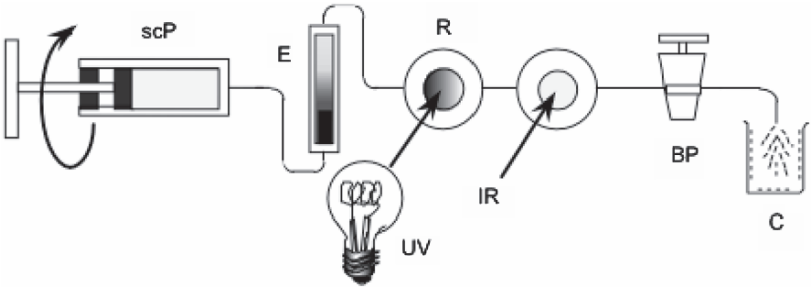


Figure 4. Schematic view of a flow reactor[88] used for the isolation of $Cr(CO)_5(C_2H_4)$ from supercritical C_2H_4, scC_2H_4. Parts are labeled as follows: scP, the scC_2H_4 pump; E, reservoir for solid $Cr(CO)_6$; R, the photolysis chamber for converting reactant to product; UV, photolysis lamp; IR, IR cell for optimizing the reaction, BP, back-pressure regulator to release the pressure and to precipitate the product into the container C.

N_2 that could be readily achieved because, as explained above, such gases are totally miscible with most SCFs. This concentration effect was later exploited for catalytic hydrogenation in SCFs by Noyori[83] and others.[84]

All of these reactions[3] were initially carried out in small spectroscopic cells (volume < 2 mL) which afforded little chance of isolating the "unstable" products, even though many of them appeared to be surprisingly long-lived. This meant that miniature continuous reactors had to be devised for carrying out such reactions on a preparative scale (see Figure 4),[85–87] which subsequently enabled a number of novel ethene and dihydrogen complexes to be isolated, one of the few occasions when *new* compounds have been successfully isolated with the aid of SCFs.[3]

A key aspect to scale-up is a strong and effective collaboration between academia and industry. In this case, collaboration began in a most unusual way. The organometallic work at Nottingham was included by David Bradley in his New Scientist feature article[89] on SCFs entitled *Solvents get the Big Squeeze*. The article covered a number of applications of SCFs, ranging from the decaffeination of coffee[5] to the development of new reactions and polymerization techniques.[90] Crucially to this project, it also included M. Poliakoff's semi-humorous vision of SCF chemistry in the future as being *as simple as operating a drinks vending machine. The chemist will simply press a button and the machine will add the appropriate reagents to the supercritical CO_2 and pump the mixture into the reactor*. This frivolous statement caught the eye of Professor Tom Swan OBE, owner of the fine chemicals manufacturer, Thomas Swan and Co. Ltd., who recognized the potential that such "dial a chemical" technology could bring to his business. He was also attracted by $scCO_2$ as a cleaner solvent because, at that time, it was feared that all chlorinated solvents might be banned. He contacted Nottingham, nine months of discussions began, and a collaboration was set up.

3.1. THE STRATEGY

It was decided to target continuous hydrogenation in $scCO_2$ using heterogeneous catalysts. This built on existing Nottingham expertise[86, 88] in constructing flow reactors involving H_2. Thomas Swan and Co. Ltd. did not have any hydrogenation equipment and therefore, if successful, the project would lead to a new capability for the company. This again was an important point; it is always easier to introduce a new technology if there is no need to justify the replacement of pre-existing equipment. Heterogeneous rather than homogeneous catalysis was chosen because it was experimentally simpler and there were more obvious routes to scale up under high-pressure conditions. The objectives were ambitious: to develop a technology for hydrogenating a wide range of organic functionalities, with high selectivity, and on *a scale equivalent to tons p.a. in the laboratory*.

It became clear that a multidisciplinary team would be required including organic chemists, high-pressure engineers and catalyst developers (Figure 5). Thus, links were formed, at an early stage, with the German catalyst manufacturers, Degussa AG, who had experience of catalysis in SCFs,[91] and with, NWA GmbH, a small German company that specializes in the manufacture of high pressure SCF apparatus.[92, 93] Finally, a German post-doctoral researcher, Dr. M. Hitzler, was recruited to co-ordinate the research efforts.

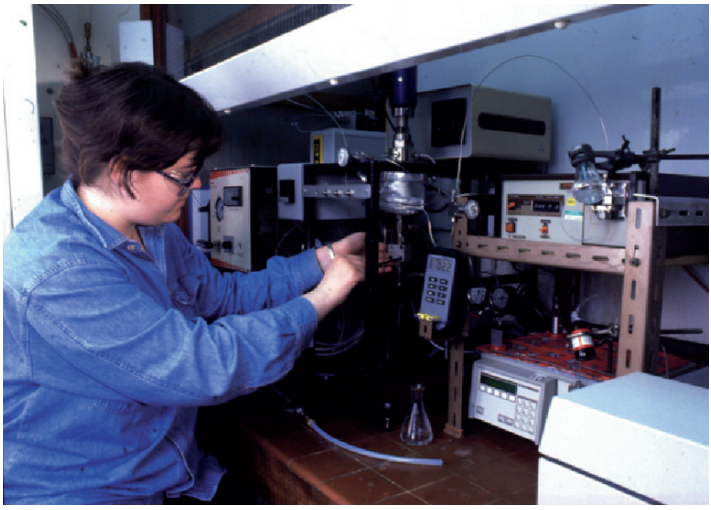


Figure 5. Picture of Dr. F. R. Smail operating the first SCF reactor in Nottingham (for a schematic view see the Figure 6).

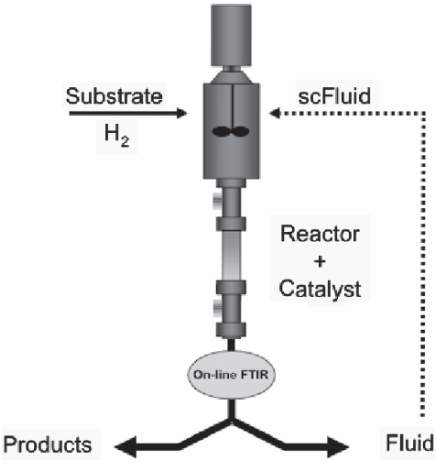
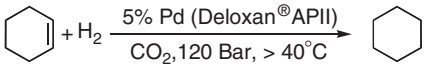


Figure 6. Block diagram of the key components of the continuous reactor for hydrogenation of organic compounds at Nottingham.[94] $scCO_2$, H_2 and the organic substrate were mixed in a heated mixer. The mixture was then passed through a reactor containing a fixed bed catalyst (usually a supported noble metal). There was optional on-line FTIR monitoring before the product and CO_2 were separated by expansion. More recent reactors have used static rather mechanical premixers.

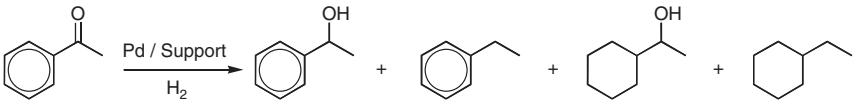


Scheme 2. The hydrogenation of cyclohexene under supercritical conditions, the reaction proceeded quantitatively with a very high LHSV (e.g. 300 h^{-1} from a 5 mL reactor).

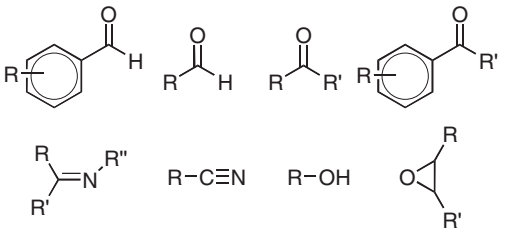
3.2. PROOF OF CONCEPT

The project started in November 1995. The first reaction involved the hydrogenation of cyclohexene in supercritical CO_2, (Scheme 2). The results were striking, with a quantitative conversion being observed. The reaction proceeded with a very high linear hourly space velocity (LHSV) (e.g. 300 h^{-1} from a 5 mL reactor),[94, 95] equivalent to a rate of 1,200 mL/h or 7.5 t p.a.

These results complemented those of Härröd and co-workers who were working on the hydrogenation of oleochemicals in supercritical propane.[84, 96] A detailed investigation at Nottingham into the hydrogenation of acetophenone (Scheme 3), showed that $scCO_2$ allowed reaction conditions to be optimised very effectively to maximise the yield of particular hydrogenation products.[94] An interesting aspect was that the reactor delivered product free from any solvent. Thus, early in this project, all analysis was performed merely by diluting the product



Scheme 3. The range of products obtained in the hydrogenation of acetophenone. Conditions could be chosen to maximize the yield of any one of these products.[94, 95]



Scheme 4. Some of the functionalities that have been successfully hydrogenated under supercritical conditions as part of our project.

with deuterated solvent and running the ^{1}H NMR spectrum.[94, 95] Later, the analysis was switched to more conventional methods, e.g. GC-FID, and GC-MS.

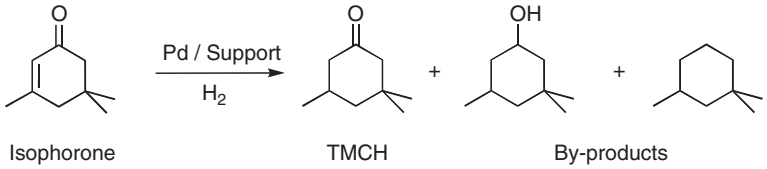
The range of functionalities which could be hydrogenated in this way was quickly extended[94] and soon included those shown in Scheme 4. Most of these could be hydrogenated with high selectivity. There were some limitations, inherent to $scCO_2$, particularly the fact that aliphatic amines react with CO_2 to form insoluble carbamates,[97, 98] which effectively terminate the reactions by precipitating in the pipework and blocking the reactor.

3.2.1. Extending the chemistry

It was quickly realized that the SCF reactor was not restricted to hydrogenation reactions and could, in principle, be adapted to any type of solid or supported catalyst. Successful reactions included Friedel–Crafts alkylation,[70] etherification,[71] hydroformylation[28] and base-catalyzed transesterification.[99] The success of such reactions prompted Thomas Swan and Co. Ltd. to set up their own SCF equipment in their research laboratories at Consett, UK. At the end of the first year, a Ph.D. student, Fiona Smail was recruited to the project.

3.3. THE DEVELOPMENT OF THE PROCESS

It was now important to identify a model compound, which could be used by the two laboratories, Nottingham and Thomas Swan and Co. Ltd. as the



Scheme 5. Reaction scheme illustrating the range of products obtained in the hydrogenation of isophorone.

basis for developing a viable SCF process. It was also important to choose a reaction of potential commercial interest where the ease of optimization in $scCO_2$ could be exploited. The chosen reaction was the hydrogenation of isophorone to trimethylcyclohexanone (TMCH) (Scheme 5).[94] This reaction is a good model because the industrial end-users require high purity product. The problem with conventional hydrogenation technologies is that they can easily lead to a mixture of TMCH and the over-hydrogenated by-products, trimethylcyclohexanol and trimethylcyclohexane.[100] All of these compounds, and isophorone itself, have similar boiling points, and the need to separate and purify TMCH from these mixtures adds greatly to both the cost and the environmental impact of the overall process.

This reaction was initially carried out on a laboratory-scale at Nottingham where it was found that conditions in $scCO_2$ could be adjusted to give quantitative conversion of isophorone to TMCH at a rate of up to 7 mL/min[94] Clearly, if this process could be scaled up, one would eliminate the need for any purification steps following the hydrogenation. The work was then transferred to the laboratories at Thomas Swan and Co. Ltd. where the industrial environment was better suited to investigating the feasibility of scale-up to a production scale. These investigations focussed particularly upon the choice of catalyst and catalyst lifetime.

Catalyst: The initial studies at Nottingham were carried out using catalysts supported on Deloxan, a polysiloxane material from Degussa.[91] Deloxan was found to be very durable and gave a good catalyst lifetime with up to 3 kg of product produced per gram of catalyst without significant loss of selectivity.[94] At this point, the decision was taken to commission a full-scale plant from the Swedish engineering company Chematur Engineering AG.

Then, there was a major setback. The Deloxan range of catalysts was suddenly withdrawn from commercial production; an alternative source of catalysts was urgently required. Having screened a variety of catalysts, it was evident that a wide range of conversions and catalyst lifetimes could be obtained for a given noble metal, depending on the nature of the support. It was quickly recognized that the key criterion was the yield of TMCH *per*

g of Pd rather than the yield *per g of catalyst*. These results supported previous work carried out by Hutchenson et al. in that Deloxan outperformed most other catalysts with respect to conversion.[101] Eventually, alternative catalysts were identified that gave excellent catalyst life whilst retaining a level of conversion and product selectivity comparable to Deloxan, see Table 2. Here again, there is an important lesson for scale-up of biphasic catalysis. An apparently small change in catalyst supplier caused a major change in the process economics.

3.4. REACTION OPTIMIZATION

Table 3 summarizes the optimized conditions for the hydrogenation of isophorone in the laboratory. Particularly striking is the range of concentrations of isophorone which can be successfully reacted, 2–48 w%. Supercritical reactions generally involve high pressures and considerable compression costs, in contravention of the 6th principle of Green Chemistry.[1, 79] Clearly, maximizing the concentration of isophorone will minimize the energy requirements of the process. At the same time, working with such high concentrations raises the whole issue of phase behavior in the reaction mixture.

TABLE 2. Catalyst screening results for the selective hydrogenation of isophorone to trimethylcyclohexanone (TMCH).

Catalyst	Metal loading	kg TMCH/ g cat.	kg TMCH/ g Pd	Selectivity/%
Deloxan	Pd 5%	3.0	60	100
A	Pd 5%	0.4	8	91
B	Pd 2%	1.2	60	100
C	Pd 2%	1.1	55	>99
D	Pd 5%	3.0	60	98
E	Pd 2%	0.05	1	94

TABLE 3. Optimized laboratory conditions for hydrogenation of isophorone to TMCH.

Reactor size	0.85 cm id, 25 cm long
Catalyst	2% Pd
Temperature	Inlet 56°C
	Outlet 100°C
Hydrogen	1.7–2.75 equivalents
Substrate feed	2–48 w%

Phase behaviour: Considerable scientific argument has revolved around the question of whether supercritical hydrogenation reactions proceed faster and more efficiently in either a single or multiple phases; indeed conflicting reports have been published.[14, 102–104] Much of this debate has revolved around the LHSV of a reaction, but this parameter only addresses part of the issue from an industrial perspective. Other important factors which have to be taken into account include catalyst lifetime, overall conversion and product selectivity as well as solvent compression costs need. The situation has been at least partly resolved by a key paper by Nunes da Ponte and co-workers.[105] They have shown that biphasic reactions can sometimes be faster than monophasic ones, because the concentration of substrate (as opposed to H_2) is lower under monophasic conditions.

A study was undertaken of the phase behaviour of four mixtures of varying composition, isophorone/CO_2/H_2 across six experimentally determined isotherms at 40, 60, 80, 100, 120 and 140°C. This established the boundary between the one- and two-phase regions of the phase diagram for this system; see **Figure** 7.

The measurement of these phase equilibria clearly reveals that, for mixtures with a composition in excess of around 5% isophorone, quite substantial pressures and temperatures are required to render the system

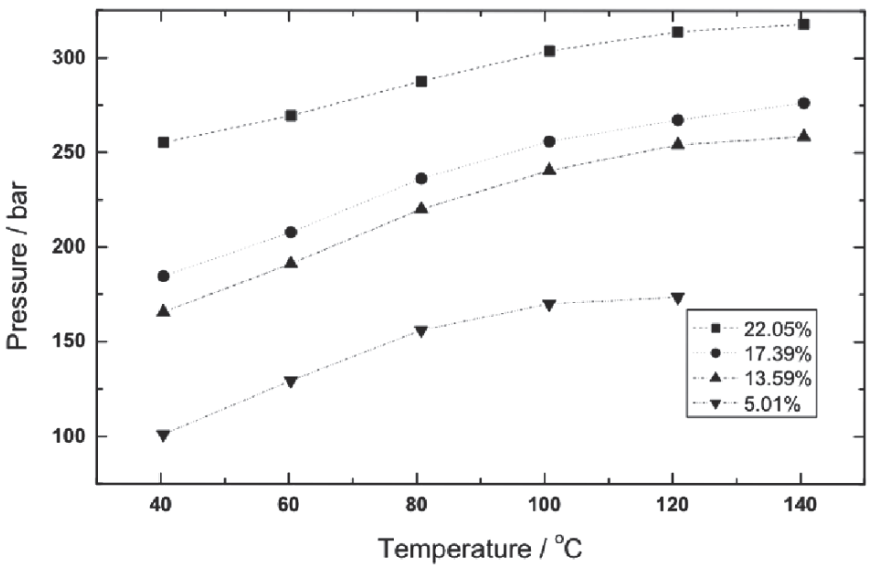


Figure 7. Plot illustrating the experimentally determined phase boundaries of four mixtures of isophorone/CO_2/H_2 of varying composition. (Isophorone w/w 5–22% w/w, molar ratio of isophorone: hydrogen was fixed at 1:1.7), N.B. 100 bar = 10 MPa.

monophasic, a condition that has been reported to be essential for efficient and rapid hydrogenation.[103] By contrast, it has been shown that this reaction can be carried out with excellent selectivity and conversion with as much as 50% isophorone in the reaction stream, conditions that are clearly not single phase. Furthermore, when conditions that facilitate single phase reactions are employed, a loss of desired product selectivity is observed as the high temperatures that are required often lead to the formation of unwanted side products. Similar considerations are likely to apply to many of the biphasic reactions described in this chapter.

3.5. THE PLANT

Figure 8 shows the schematic design of the Thomas Swan and Co. Ltd. plant. It has a production capacity of ~100 kg/h (1,000 t p.a.). It therefore represents a ×400 scale-up of the laboratory reactor in terms of production.

The plant is multi-purpose. The catalysts within the reactor can be changed to change the chemistry. A photograph of the actual reactors may be seen in Figure 9. It is designed to work only with CO_2 as the SCF. (A rather smaller plant for reactions in supercritical propane has recently been built in Göteborg).[103] The Thomas Swan and Co. Ltd. plant went on stream in June 2002.

The hydrogenation of isophorone was the first reaction to be run on the plant. The optimized conditions are shown in Table 4, and it is immediately clear that these conditions are very close to the optimized conditions in the

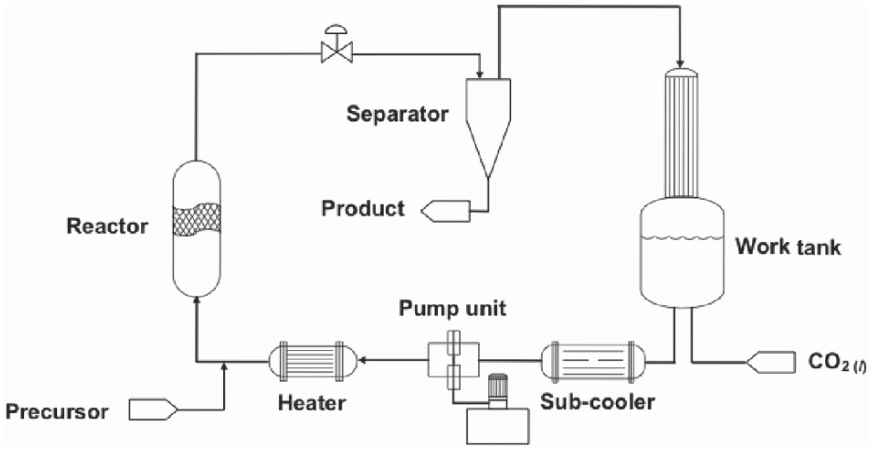


Figure 8. Schematic flow diagram of the SCF plant at Thomas Swan and Co. Ltd., constructed by Chematur Engineering AG.

Figure 9. Photograph of the reactor array in the Thomas Swan and Co. SCF reactions plant.

TABLE 4. Optimized plant conditions for hydrogenation of isophorone to TMCH.

Catalyst	2% Pd
Temperature	Isothermal 104–116°C
Hydrogen	1.7 equivalents
Substrate feed	9–17 w%

laboratory, Table 3. If this transferability applies to other reactions, it will have considerable significance; reactions can be optimized in the laboratory and transferred almost directly to the plant.

TABLE 5. Customer specification and product analysis for TMCH produced under supercritical conditions.

Specification	Customer	SwanSCF
Colour (Hazen scale)	10 max	<10
Assay (%)	99 min	99.4
Trimethylcyclohexanols (%)	1 max	0.3
Isophorone (%)	0.4 max	0.08
Acid Value, mg KOH/g	0.1 max	0.08[a]

[a]Value measured after discharge of dissolved CO_2, corresponding value before discharge was 8

It is not always apparent to academic researchers that the specification of a commercial chemical product can be much wider than the purity criteria used in typical journal publications. Thus, Table 5 summarizes the customer specifications for TMCH and an actual analysis of the raw product, direct from the plant. It can be seen that the product exceeded the specification in all five categories, although the acid value is only reached after residual CO_2 is removed by a brief application of vacuum. Thus, in the case of TMCH, SCF technology has eliminated the need for any downstream purification of the product.

4. Conclusions

SCFs, and $scCO_2$ in particular, are rapidly emerging as versatile media for carrying out a diverse range of synthetic organic reactions, and we are only just beginning to see the real potential and benefits they offer in addition to environmental aspects. Either used as solvents or reactants, SCFs provide several opportunities to enhance and control homogeneous and heterogeneous catalytic reactions. Most SCF processes, including those described in this chapter, will have to face more conventional economic tests. Despite the high costs of supercritical process technology, the reactivity of SCFs will continue to be explored as an opportunity in the fixation of gases, the recovery of catalysts and many others aspects. Furthermore, several classical spectroscopic techniques are becoming amenable to high-pressure investigations. SCFs have already established themselves as useful solvents in material applications,[106] in pharmacy,[107] and in industry, with several classical industrial processes (ethylene polymerization,[108] ammonia synthesis,[109] and methanol synthesis[110]) and for the extraction of hops, spices, flavours, perfumes and for the decaffeination of coffee.[5] Dupont have build a $40M development plant for

producing fluoropolymers in $scCO_2$.[111] The technology works; now the key is to demonstrate whether it is commercially competitive.

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SOLVENTLESS REACTIONS UNDER MICROWAVE ACTIVATION: SAFETY AND EFFICIENCY AT THE SERVICE OF CUSTOMER-FRIENDLY CHEMISTRY

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Abstract: A range of solvent-free organic reactions performed under microwave irradiation is reported and the advantages with respect to the corresponding thermal protocols outlined. Good assets like the dramatic shortening of the reaction times, the higher efficiency, and the absence in a number of cases of toxic or polluting reagents are highlighted.

Keywords: microwaves, solventless reactions, organic synthesis, green protocols

1. Introduction

Traditional chemical synthesis focuses on optimising yields, with little regards to a chemical's impact on the environment and its long-term viability. Optimising yields is important but other issues need to be addressed, including minimising the number of steps, simplicity, waste, atom efficiency, energy usage, safety, and whether the chemistry is environmentally acceptable. Reducing the use of organic solvents can minimise the generation of waste, which is one of the requirements of sustainable chemistry. Alternative media to classical organic solvents include ionic liquids, liquid or supercritical CO_2, water. There is also the possibility of avoiding the use of any reaction medium as solventless reactions which is the main theme of this chapter (Figure 1).

The advantage of solventless reactions include: (i) the possibility of direct formation of high purity compounds; (ii) the possibility of sequential

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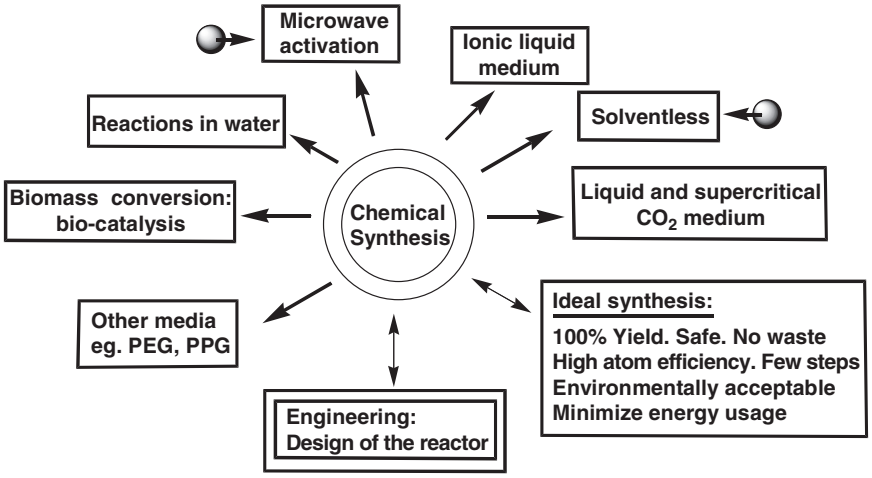


Figure 1. Alternative methods for benign chemical synthesis.

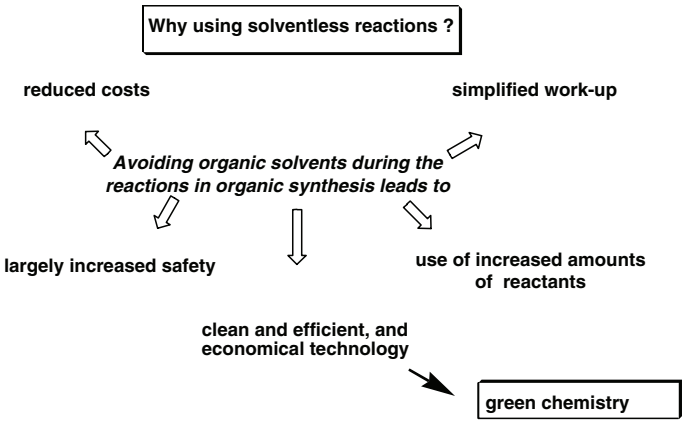


Chart 1. Advantages of solventless organic reactions.

reactions; (iii) fast kinetics; (iv) lower energy usage; (v) simplicity and low equipment cost; and (vi) the possibility of avoiding functional group protection–deprotection (Chart 1).

In solventless (neat) organic reactions, reagents (solid–solid or solid–liquid) react together in the absence of any solvent and have been well reviewed as a fast developing technology.[1] There are also several disadvantages in solventless reactions like hot spots formation and the possibility of runaway reactions but these drawbacks can be easily avoided, mainly for small-scale reactions, by simple technical and operational devices. However, when considering reaction between solids, it is important to distinguish between solid phase synthesis, solvent-free synthesis and solid state synthesis (Figure 2).

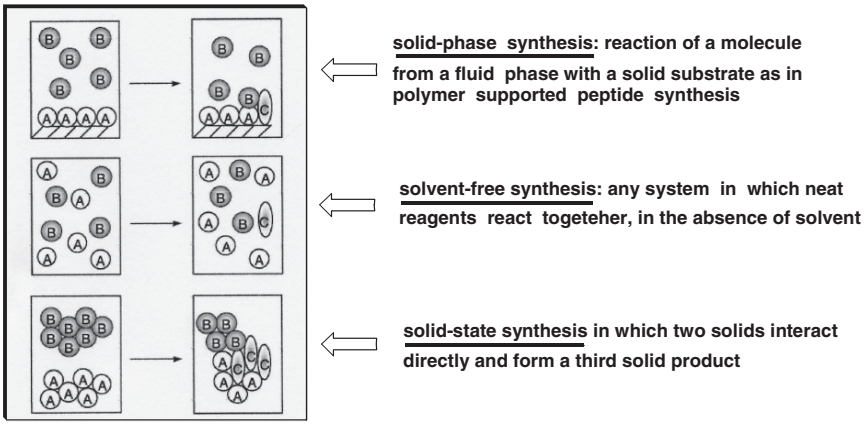


Figure 2. Differences among the solid-phase, solvent-free and solid-statereactions.

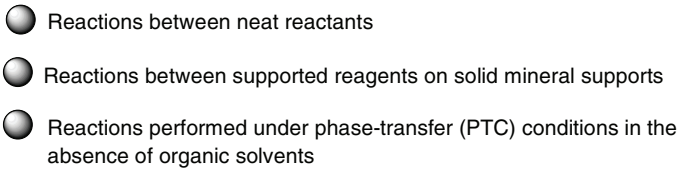


Chart 2. Types of solventless reactions initiated by microwave irradiation.

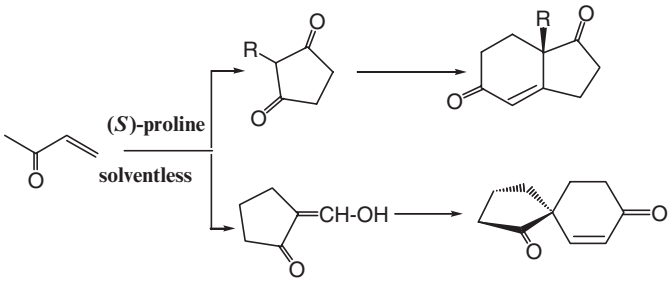
Solvent-free conditions are especially adapted to microwave activation and lead to increased safety and environmental respect. The exposure of net reactants to microwave (MW) irradiation also in conjunction with catalytic species and/or solid supports can result in fast and high-yielding reactions because of the selective absorption of microwave energy by polar molecules.

Solventless reactions under microwave (MW) irradiation are generally of the three types shown in Chart 2 and will be separately treated in this chapter.

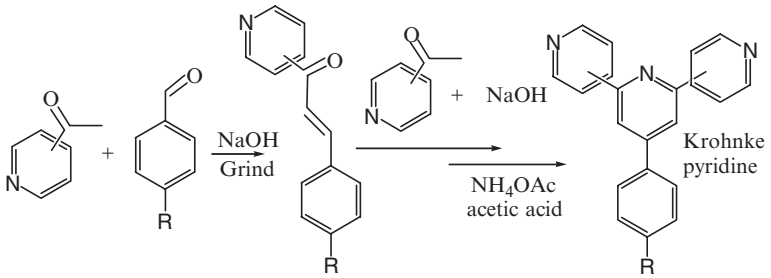
2. Neat Reactions with Microwave Methodology

Several elegant solvent-free routes to target molecules are known in the literature to occur even in the absence of MW irradiation.

The enantioselective synthesis of optically active enedione compounds in high yields is shown in Scheme 1, and also the synthesis of sydnone-containing 3'-arylcyclohexenone derivatives by simply grinding chalcones and ethyl acetoacetate in the presence of potassium carbonate, has been reported.[2]



Scheme 1. Enantioselective synthesis of enedions in solventless reactions.



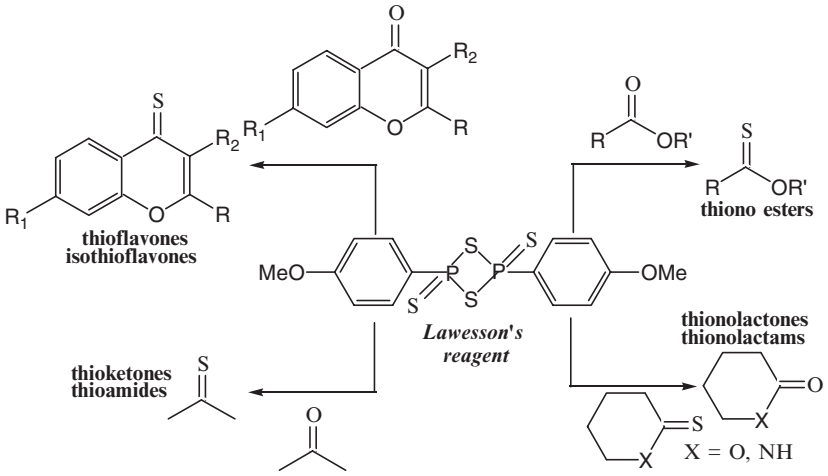
Scheme 2. Synthesis of the krohnke type pyridines.

Following the "Green Chemistry" principles a new and indeed more versatile protocol has been envisaged for the synthesis of the Krönke type pyridines with applications in liquid crystals and pharmacologically important compounds. The solventless reactions occur[3] for combinations of liquids, liquids and solids, and solids. The greener route is estimated to be 600% more cost-effective not taking into account the cost of energy. Moreover, the traditional route generates as much as 29 times more solid waste than the "greener" route (Scheme 2).

Even though a solventless green route to synthetic organic chemistry exists, additional benefits can be introduced by running the reactions in neat under microwave irradiation.

2.1. MICROWAVE-ACCELERATED FUNCTIONAL GROUP TRANSFORMATION

Among numerous expeditious chemical transformations that can be accomplished under MW and under solventless conditions, the functional group transformation is especially useful. The conventional synthesis of thioketones

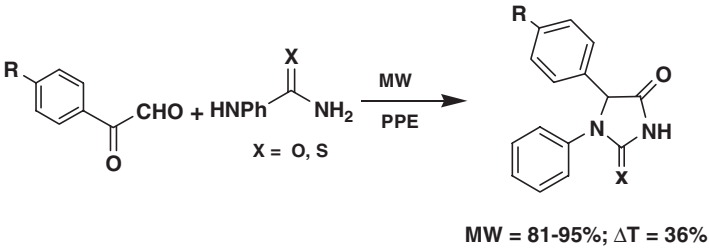


Scheme 3. Synthesis of thioketones.

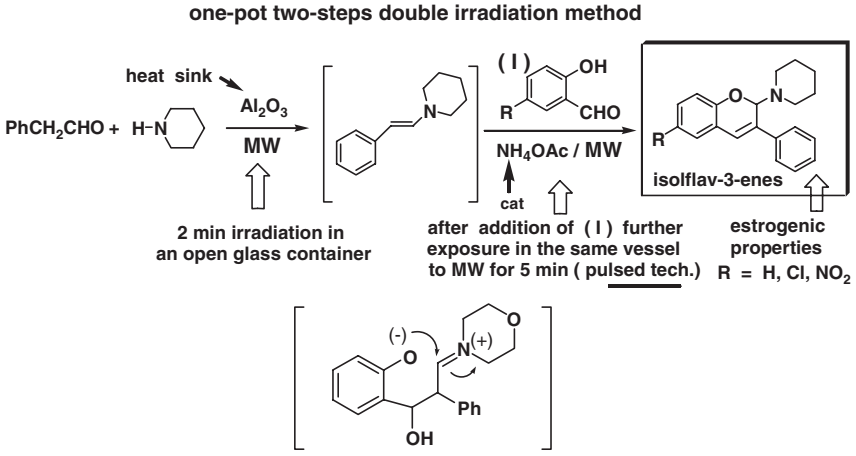
(Scheme 3) is highly representative. Using the MW approach no acid or basic medium is used and the carbonyl derivatives are simply admixed with neat Lawesson's reagent and irradiated under solvent-free conditions.[4] This eco-friendly protocol uses comparatively smaller amounts of Lawesson's reagent and avoids the use of dry hydrocarbon solvents such as benzene and toluene. Moreover, almost quantitative yields (92–98%) are achieved after very short reaction times (3 min).

2.2. MICROWAVE-ASSISTED SOLVENTLESS SYNTHESIS OF HETEROCYCLES

Heterocyclic chemistry has been a major beneficiary of MW-expedited solvent-free chemistry using solventless conditions. The multigram formation of 3-aryl-4-hydroxyquinolin-2(1H)-ones from aniline and malonic esters derivatives that normally requires many hours at room temperature in highly boiling solvents under MW irradiation takes place in 15 min. No supported reagents are needed for this reaction. In the synthesis of hydantoins (Scheme 4), compounds that have a reactive urea core and well known for diverse biological activities, the MW-assisted protocol allows the elimination of solvents and strong mineral acids.[5] Further attraction of this method is the possibility of running these reactions on synthetically useful preparative scale. The occurrence of a not purely thermal effect can be noticed by comparing the chemical yields of the thermal and MW-induced reactions.



Scheme 4. MW assisted synthesis of hydantoins.

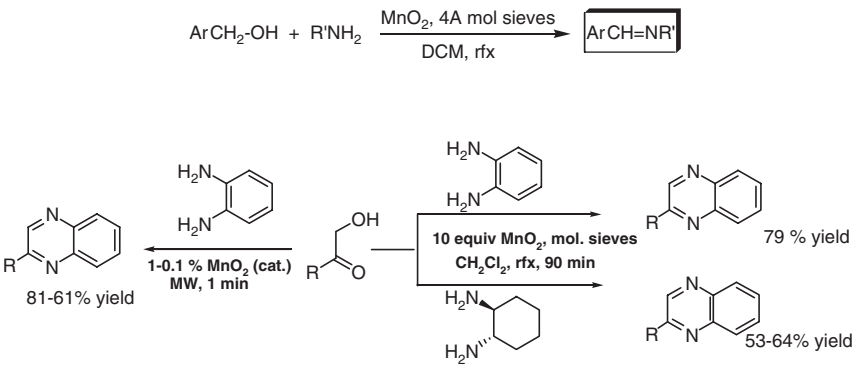


Scheme 5. One-pot two-steps irradiation method for the synthesis of isoflav-3-enes.

A pulsed microwave technique that entails irradiating the reaction mixture at a lower power for successive intervals avoids overheating thus allowing the in situ generation of thermally unstable intermediate reaction products.

This one-pot procedure based on a two-steps irradiation method, has been successfully applied (Scheme 5) to the expeditious synthesis of 2-amino-substituted isolflav-3-enes, important class of intermediates useful in the synthesis of natural products and medicinal agents, via the in situ generation of enamines and their subsequent reaction with salicylaldehydes.[6] A beneficial effect of this environmentally friendly procedure lies also in the fact that the MW-assisted elimination of water avoids the use of a Dean Stark setup.

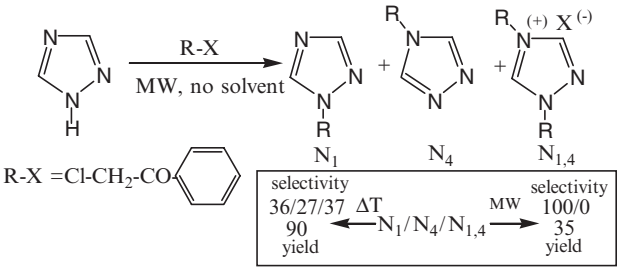
The use of MnO_2 as in situ oxidant for the one-pot conversion of alcohols into imines[7] recently evolved into a tandem oxidation process for the preparation of quinoxalines, dihydropyrazines, pyrazines, and piperazines, important bases of many insecticides, fungicides, as well as receptor antagonists



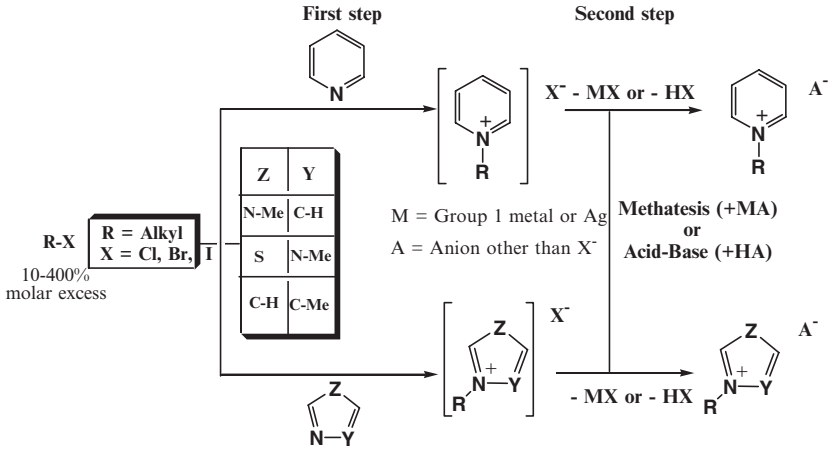
Scheme 6. Classical vs. MW assisted synthesis of heterocyclic compounds.

and chemotherapeutic agents.[8] The use of chlorinated solvents, of molecular sieves and of excess (10 equivalents) of oxidant outlines several drawbacks of this procedure. An important methodological evolution concretized when this reaction was run under MW irradiation and solventless conditions.[9] The obtainment (Scheme 6) of the expected products in 80% yield ca within 1 min and in the presence of catalytic amounts (1%) of MnO_2, highlighted the big advantages of using the MW-based technique. Remarkably even at a lower catalysts loading (0.1%) the reaction resulted highly effective leading to the heterocyclic compounds in 60% yield.

Scaling up beneficially solvent-free reactions under MW activation from gram quantities to several hundred grams with yields equivalent to those obtained under similar conditions in laboratory-scale experiments is viable.[10] This scaling up is necessary for drug development, as this is a discouraging bottleneck for present-day process chemists. Many milligram- and gram-scale syntheses cannot be replicated, or even attempted for safety reasons on larger scale. Development chemists must start from the beginning. MW technology provides the possibility that the same chemistries used in the initial route can be safely scaled up, enabling to spend their valuable time creating novel synthetic methods, not recreating them. Main limitations of microwave scale-up being the restricted penetration depth of MW irradiation into absorbing materials that causes heating by convection of reagents in the center of the reaction vessel, several technological improvement have been devised based on the development of continuous flow reactors or of parallel batch processing techniques. The phenacylation of 1,2,4-triazole performed on 140 g scale,[11] outlines (Scheme 7) the feasibility of the MW-scaled-up mediated organic synthesis under solventless conditions and envisages the advantages in terms of reactivity and regioselectivity with respect to the same reaction under conventional heating.



Scheme 7. Phenacylation of 1,2,4-triazole using MW activation.



Scheme 8. Synthesis of ionic liquids using MW irradiation.

2.3. PREPARATION OF IONIC LIQUIDS USING MICROWAVE IRRADIATION

Ionic liquids based on nitrogen-containing heterocycles continue to receive much attention as green solvents.[12] However, several drawbacks of the conventional heating methods in the synthesis of ionic liquids, lie in the long reaction times and in the usually large molar excess (100–400%) of haloalkane to achieve good yields in the first step. Therefore their own purification is a flawed process, often requiring large volumes of organic solvents to extract impurities. Moreover, the second step of the ionic liquid synthesis produces stoichiometric amounts of halide waste (MX or HX). The use of microwaves under solventless conditions is focused towards the minimisation of waste generation and to accelerate the first step (Scheme 8).

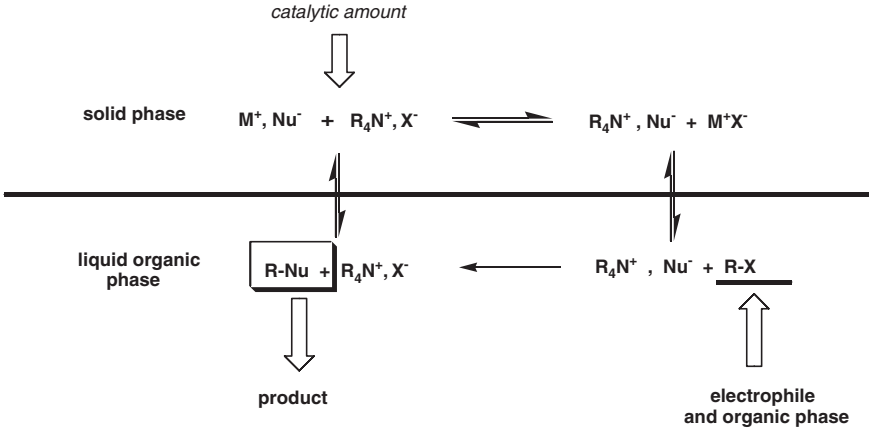
Serious limits arise from the use in this reaction of domestic MW apparatus: (i) realistic power control cannot be achieved; (ii) container limitations allow only reactions on small scale; (iii) difficulty in reproducing reactions; (iv) high excess of haloalkanes required; and (v) overheating and the possibility of runaway reactions due to the no effective dissipation of heat in solvent-free reactions and to the strong microwave absorption of the halides salts more polar than the starting materials. To set up the optimized conditions for any ionic liquid, several technological and methodological improvements are required.[13] Among them running the reactions in a sealed quartz reaction vessel fitted with T and P probes, ensures the T control by adjusting the MW power whereas the latter monitors the autogenous pressure. The sealed vessel preparation, avoiding evaporative loss, allows to work with only 10% excess of the haloalkanes. Conversions of 99.95% were obtained with this improved methodology. The medium scale up was attempted successfully by running the reactions in an open vessel equipped with a reflux condenser. All reactions gave conversions of 99.95% and isolated yields of 85% with an excess of 10% haloalkane and the reaction times were 20–400 times shorter as compared to conventional heating.

3. Microwave Activation Under Phase Transfer Catalysis

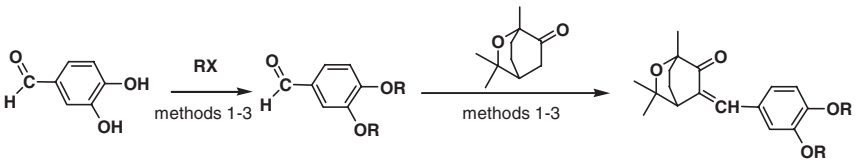
By coupling microwave technology and solvent-free solid–liquid PTC conditions, heating can result from the previous ion-pair exchange which is favoured by the presence of a liquid phase.[14] The presence of a solvent is prejudicial as it induces a dilution of reactants and, consequently, a decrease in reactivity. The electrophile RX in these reactions is therefore both the reactant and the organic phase for the reaction. Taking into the account that the nucleophilic ion pair $R_4Nu^+ Nu^-$ (Scheme 9) is a highly polar species it will be especially prone to undergo specific microwave activation.

The solid–liquid solvent-free transfer catalysis (PCT) is specific for anionic reactions as it involves “anionic activation”. Therefore this methodology appears especially useful for poorly reactive systems involving for instance hindered electrophiles or long chain halides.

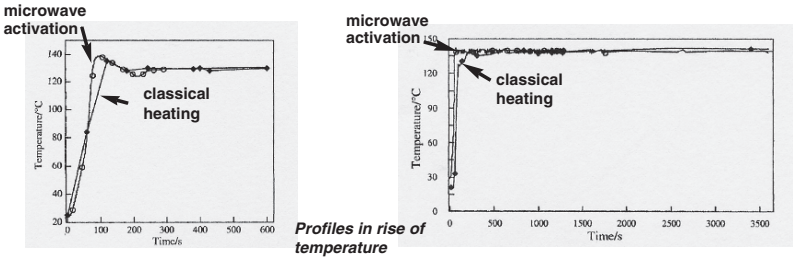
A typical example of PCT under microwave irradiation,[15] reveals an important specific non-thermal microwave effect which can be attributed to the evolution of the polarity of the system during the progress of the reaction (Scheme 10). The use of microwaves under solventless conditions is focused towards the minimisation of waste generation and to accelerate the first step. This is evidenced by the strict comparison of MW and ΔT activation leading to substantially different products yields, the profiles in rise of temperature being almost identical (Figure 3).



Scheme 9. Phase transfer catalysis in solid-liquid reaction system.



Scheme 10. Synthesis of enones using different PCT conditions.

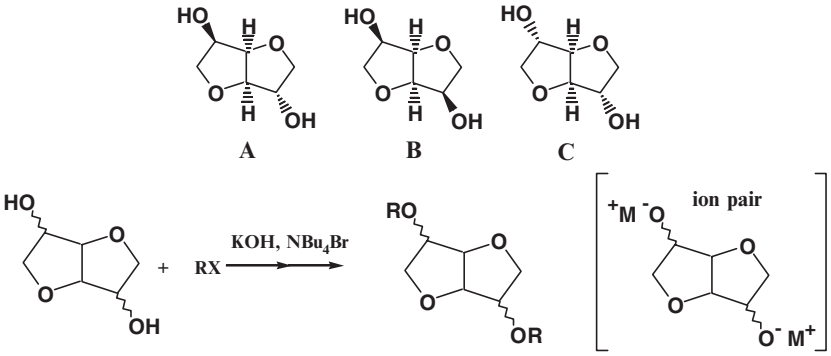


Specific non-thermal microwave effects

method 1: MW, PTC conditions (**KOH + K_2CO_3/TBAB**)
10 min,130°C, **80-86% yield**
method 2: thermostatted oil bath, PTC conditions
10 min, 130°C, **109%**
method 3: classical heating, MeONa/THF
1440 min, rfx, 66%

method 1: MW, PTC conditions (**KOH + K_2CO_3/TBAB**)
60 min, 140° C, **78-87% yield**
method 2: thermostatted oil bath, PTC conditions
60 min, 140°C, **19%***
method 3: classical heating, MeONa/THF
1440 min, rfx, 51-68%

Figure 3. Temperature profiles of the different enone forming PTC reactions.



RX	t(min, T (°C)	Yield %					
		A		B		C	
		MW	Δ	MW	Δ	MW	Δ
$PhCH_2Cl$	5, 125	98	13	98	15	97	20
$nC_8H_{17}Br$	5,140	96	10	74	10	95	10

Scheme 11. Dialkylation of dianhydroheditols under PTC conditions.

A very important specific microwave effect can be envisaged (Scheme 11) in the dialkylation under PTC conditions of dianhydroheditols, important by-products of biomass.[16] The observation of the specific MW effect is consistent with the reactive species being constituted from tight ion pairs between cations and the alkoxyde anions resulting from abstraction of hydrogen atoms in A,B, and C.

4. Microwave-Accelerated Solvent-Free Organic Transformations Using Clay-Supported Reagents

In contrast to conventional homogeneous reaction procedures, the use of surface active catalysts and inorganic reagents has received much attention in recent years because of the enhanced selectivity and milder conditions. The combination of the use of reactants and reagents immobilized on mineral oxide

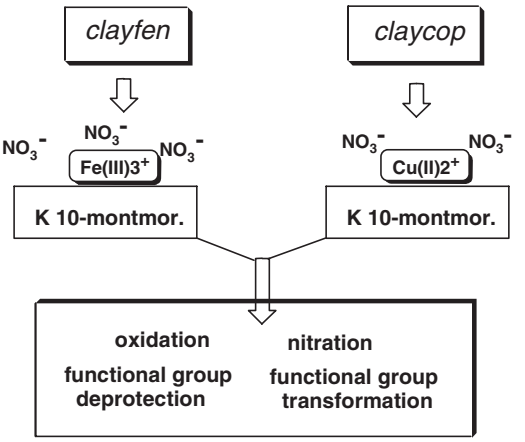
surfaces has blossomed into a powerful technique with numerous attractive applications under relatively benign, solvent-free conditions.[17] The deliberate introduction of a reagent into or onto an inert generally porous, inorganic support gives rise to supported reagents. Engaging a supported reagent in organic synthesis gives rise to the following advantages: (i) remarkable ease of handling and using; (ii) reduced product contamination; (iii) safe handling having the reagent fully bound to the solid support; (iv) reduced environmental problems upon work-up; (v) good thermal and mechanical stabilities, allowing higher stirring rates; (vi)-good dispersion of active (reagent) sites; and (vii) improvement in reaction selectivity due to the constraints of the pores. Clays minerals, the mostly common used inorganic supports, are made by layered silicates. Two basic building blocks, namely tetrahedral and octahedral layers, are common to clay minerals. Tetrahedral sites in clay minerals are mainly occupied by $Si^{4(+)}$ but isomorphous substitution by $Al^{3(+)}$ is also common. On the other hand, octahedral sites are occupied by $Mg^{2(+)}$ but isomorphous substitution by other divalent cations such as $Fe^{2(+)}$ or $Ni^{2(+)}$ or by $Li^{(+)}$ can also take place. Three important features of clays, mainly in connection with their use in catalytic applications, are the followings:

Ion exchange = isomorphous substitution of cations in lattice by lower-valent ions

Swelling = many clay minerals absorb water between their layers, which move apart and the clay swells

Intercalation and cation-exchange = in swelling clay minerals, the interlayer cations can undergo exchange with cations from external solutions

Considering clay-supported reagents, impregnation of Fe(III) and Cu(II) nitrates onto K-10 montmorillonite, produces a novel class of multipurpose reagents termed *clayfen* and *claycop* (Scheme 12).

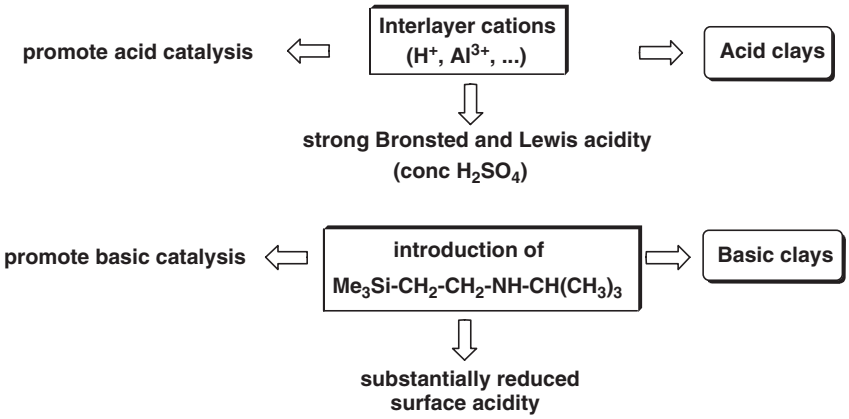


Scheme 12. Preparation and application of clayfen and claycop.

The interlayer cations contribute to the acidity of clay minerals. The higher the electronegativity of M(+), the stronger are the acid sites generated. The acid strength of clay minerals can be comparable to that of concentrated sulfuric acid. Surface acidity of clays can be reduced substantially by introducing silylpropylethylenediamine. These modified clays are weakly basic and can be employed for base-catalyzed reactions (Scheme 13).

Featuring aspects of the microwave irradiation with the use of mineral-supported reagents are shown in the following Chart 3. However, several drawbacks cannot be ignored such as the fact that higher localized temperatures (*hot spots*) may be reached, the difficult accurate recording of the temperature, and a relative poor understanding of the dramatic rate acceleration.

A good asset of the reaction on clay under MW irradiation, lies on the fact that on changing the nature of the solid support from acid to basic a general synthetic scheme can be envisaged in which molecular diversity emerges. This is the case of the reaction involving α-tosyloxyketones and thioureas from



Scheme 13. Modified clays for catalytic reactions.

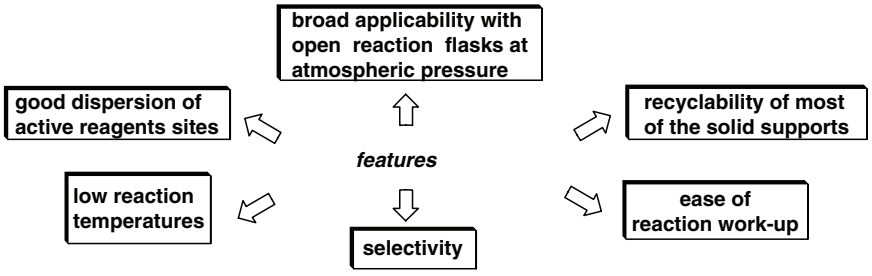
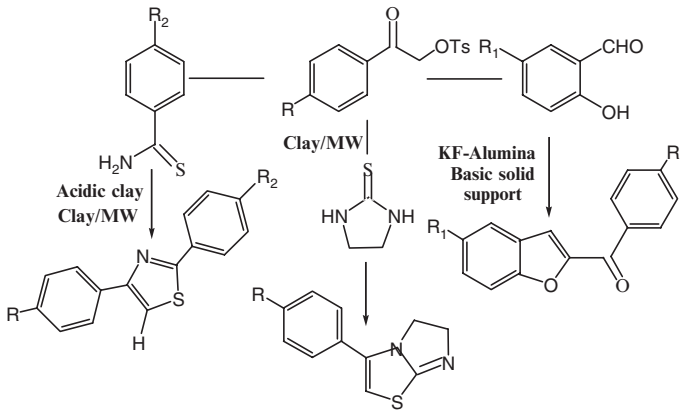


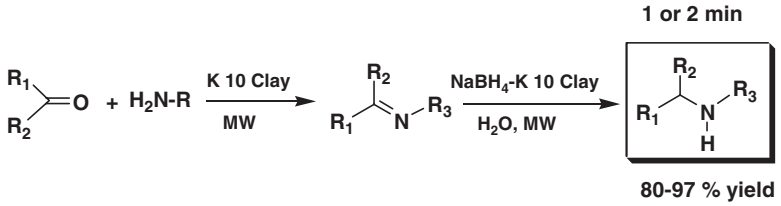
Chart 3. Featuring aspects of MW irradiation in the presence of mineral supported reagents.

which in the presence of acidic montmorillonite K-10 clay and brief exposure of the reaction mixture to 2–5 min of MW irradiation, the assembly of several thiazole derivatives occurs in very high yields (Scheme 14). However, on changing the chemical nature of the solid support as in the case of KF-doped alumina, due to the presence of the basic solid support reactions proceeding via enolate can be envisaged as substantiated by the preparation of benzofuran derivatives from α-tosyloxyketones and salicylaldehydes.[18]

The conventional preparation of thiazoles requiring the use of lacrimatory α-haloketones could be avoided by using the MW-based procedure. In the formation of all these heterocycles from the reaction intermediates, the elimination of water molecules occurs which couples very efficiently with microwaves leading to a much faster formation of these heterocycles when compared to classical heating conditions. The beneficial effect of water in the microwave-accelerated solvent-free organic transformations using clay-supported reagents can be generalized, considering that in the solvent-free reductive amination of carbonyl compounds leading[19] within a few minutes in high yields to secondary amines (Scheme 15), clay not only behaves as an acid catalyst, but also provides



Scheme 14. Synthesis of tyhiayole derivatives using clay catalyst and MW irradiation.



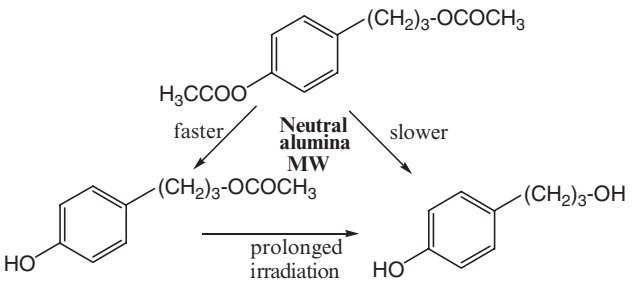
Scheme 15. Solvent-free reductive amination.

water from its interlayers that is responsible for the acceleration of the reducing ability of $NaBH_4$. That the effect may not be purely thermal is evident from the fact that for similar product yields a much longer time (5 h) is required for completion of the reaction at the same T using an alternate heating mode.

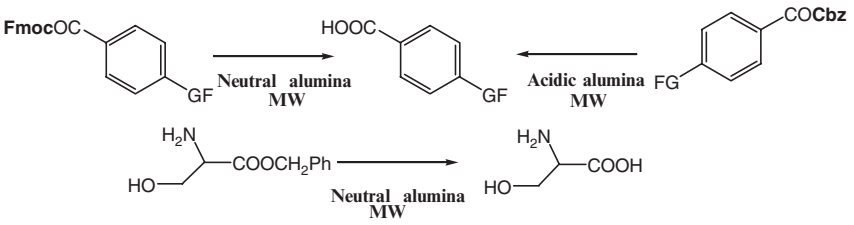
4.1. PROTECTION–DEPROTECTION ON SOLID SUPPORTS

The protection–deprotection reaction sequences form an integral part of organic manipulations and often involve the use of acidic, basic, or hazardous reagents, and toxic metal salts. The solventless MW-accelerated cleavage of a variety of functional groups on solid support provides and attractive and safer alternative to conventional deprotection reactions. The utility of recyclable neutral alumina as a viable support surface for the orthogonal deprotection of alcohols under solvent-free conditions is shown in Scheme 16 and most interestingly selectivity between alcoholic and phenolic groups in the same molecule can be achieved simply by varying the reaction time.[20]

An efficient process of debenzylation (Scheme 17) can be performed for the cleavage of carboxylic esters[21] on neutral alumina surface and by changing the surface characteristic of the solid support from neutral to acidic the cleavage of 9-fluorenylmethoxycarbonyl (Fmoc) group can be achieved in a similar manner.



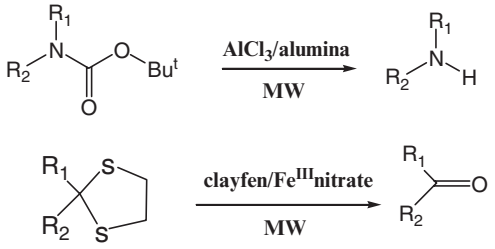
Scheme 16. Orthogonal deprotection of alcohols.



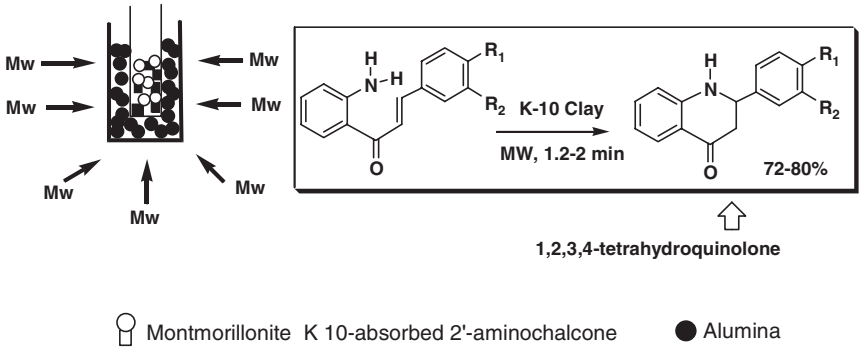
Scheme 17. MW-assisted deprotection of functional groups on alumina.

Moreover, also the deprotection of the *N*-tert-butoxycarbonyl (Boc) group with neutral alumina doped with aluminum trichloride[22a] envisages (Scheme 18) a practical application, among the others, to typical peptide-bond-forming reactions, thus eliminating the use of irritating and corrosive chemicals such as trofluoroacetic acid and piperidine. Finally, the search for a solvent-free deprotection procedure has led[22b] to a solid-state dethioacetylation reaction (Scheme 18) that proceeds in high yields using montmorillonite K-10 clay-supported iron(III)nitrate (clayfen). Even in this case the use of toxic heavy metals such as Hg^{2+}, Ag^{1+}, Ti^{4+}, Cd^{2+}, Tl^{2+} is avoided.

A careful optimization of the solid support is necessary when using MW irradiation. So far in the MW-assisted isomerization of 2'-aminochalcones different reaction outcomes are obtained[23] by varying the solid support (Scheme 19). This procedure under solvent-free "dry" conditions on montmorillonite K-10, provides a manipulative easy, environmental benign protocol suitable to be scaled up. A screening of the surface to be used is needed in that with silica gel no reaction takes place and neutral and basic alumina result destructive. On the other hand reasonable yields can be achieved with silica gel doped with *p*-TSA and excellent excellent results (72–80% yields) are obtained with K-10 montmorillonite.



Scheme 18. Deprotection of amines and carbonyl compounds.



Scheme 19. MW-assisted isomerization of 2'-aminochalcones.

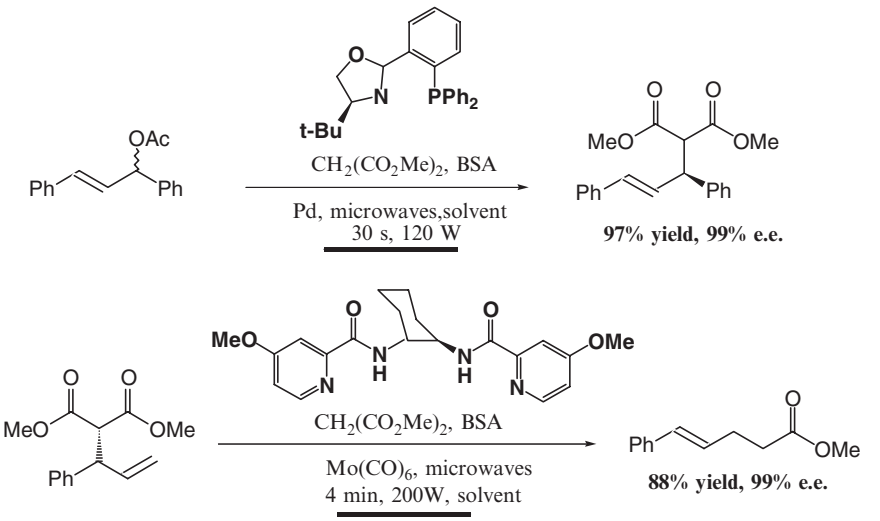
Usual procedures for the formation of tetrahydro-quinolines involve the use of corrosive reagents, such as orthophosphoric acid, acetic acid, and strong alkalis. Worth noting is the use of alumina bath as a heat sink.

5. Microwave Activation in Catalysed Reactions

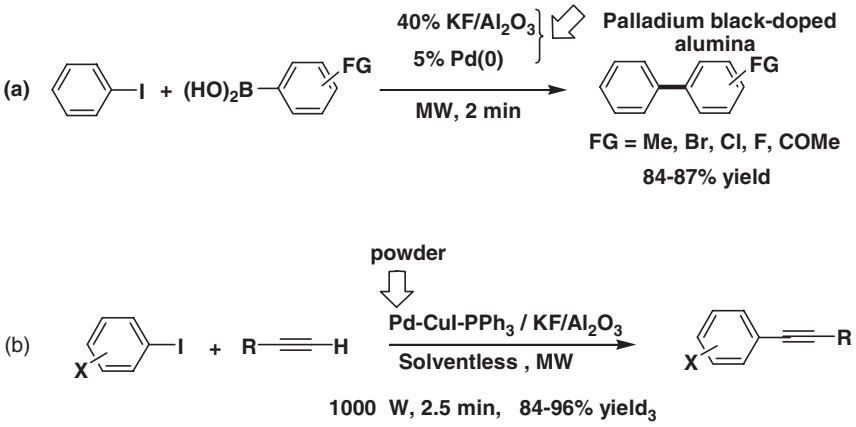
Metal-catalysed reactions enjoy a beneficial effect from MW irradiation. Although high yields and selectivities may equally well result from conventional heating, MW irradiation offers several advantages. It is energy efficient, only the sample is heated, and high temperatures are reached in a short time.[24] Furthermore, often lower amounts of catalysts are required than under the conventional conditions. Two examples of these benefits regarding reactions run in solvents are shown in Scheme 20.

5.1. MW-ACTIVATED METAL-MEDIATED CATALYSED REACTIONS UNDER SOLVENTLESS CONDITIONS

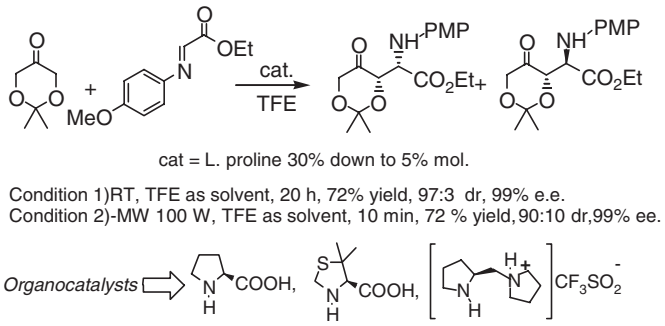
Under solventless conditions microwave-assisted reactions on doped supports with catalytic metals, provide a modified and highly efficient version of the classical catalytic C–C couplings. Two examples regarding the Suzuki and Sonogashira coupling reactions, are reported in Schemes 21a and b, respectively.



Scheme 20. Metal-catalysed reactions with MW irradiation.



Scheme 21. Microwave assisted Suyuki (a) and Sonogashira (b) reactions.

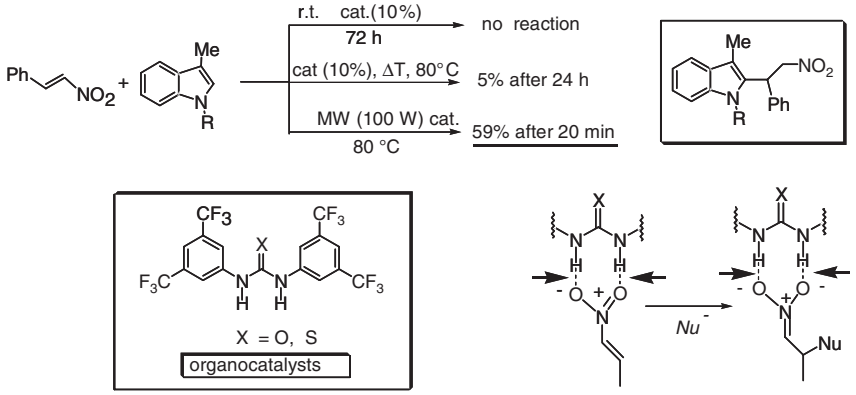


Scheme 22. Comparison of the efficiencies of the classical and MW-assisted organicatalytic reactions.

In the first example[25] noteworthy is the use of ligandless Pd catalysis and an additional advantage lies in recycling of the catalytic system (Pd-doped alumina) by simple filtration. In the Sonogashira coupling[26] on the other hand, the reaction in the absence of Al_2O_3 leads to very low yields (20%) and the solid support also acts as a temperature moderator avoiding runaway reactions occurring between the liquid reagents in the presence of Pd.

5.2. MW-ACTIVATED ORGANOCATALYSED REACTIONS UNDER SOLVENTLESS CONDITIONS

Also the emerging field of organocatalysis can be beneficially affected by MW irradiation. To date very few MW-mediated organocatalyzed reactions



Scheme 23. Effect of MW irradiation on organocatalytic alkylation reactions.

are known. From the few available reports (Scheme 22) the outcome of the asymmetric organocatalysis seems do not experience erosion of yields or of e.e. moving from the thermal to the MW-mediated conditions[27] whereas highly reduced reaction times and in many instances lower catalytic loadings are observed.

The impact of MW activation in aldol reaction, conjugate addition, and Diels–Alder reaction with different organocatalytic species, also shows dramatic shortening of the reaction times without loss of selectivity. Most importantly also in some of these cases the catalyst loading could be decreased.[28] However, solventless organocatalysis under MW irradiation is still an almost unexplored area. One of the first reports regarding the feasibility of this kind of approach deals with the Friedel–Crafts-type alkylation with nitroolefins of electron rich heterocycles such as indole, a privileged structure in medicinal chemistry.[29]

In Scheme 23 the strikingly different outcome of the reactions run at room temperature, under conventional thermal heating and under MW activation are outlined, by using in all cases a thiourea-based organocatalyst containing a double hydrogen bonding motif. Worth noting the efficacy of the organocatalysis under MW irradiation and the absence of any background (uncatalysed) reaction under the same conditions is strongly suggestive of a tolerance of the hydrogen bonding to the MW irradiation and outlines many potentialities of the microwave activation in the catalysed reactions driven by weak interactions as is the case of organocatalysis.

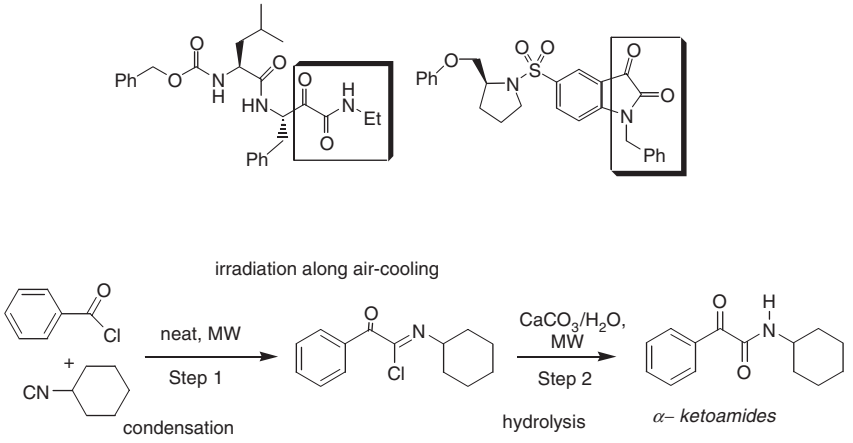
6. Optimization of reactions under microwave activation

Several methods can be envisaged for the optimization of the organic reactions under MW activation. In the conventional microwave synthesis (CMS)

the bulk T (Tb) is rapidly increased to the desired set point by the initial microwave power. Upon reaching this temperature, the MW power decreases or shuts of completely in order to maintain the desired bulk temperature without exceeding it. When MW irradiation if off, *classical thermal chemistry takes over losing the full advantage of MW-accelerated synthesis*. Recently, an alternative method for performing MW-assisted organic reactions, termed "Enhanced Microwave Synthesis" (EMS), has been examined. By external cooling the reaction vessel with compressed air, while simultaneously administering microwave irradiation, more energy can be directly applied to the reaction mixture while keeping the temperature low. MW enhancement of chemical reactions will only take place during application of microwave energy and EMS ensures that a high, constant level of microwave energy is applied. Greater chemical yields and cleaner chemistries are achieved by using EMS technique which can be applied to the reaction with solvent or under solventless conditions.[30]

One of the first applications of the irradiation-simultaneous cooling method was to rapidly prepare a series of structurally diverse α-ketoamides (Scheme 24) core key units incorporated in the P_1 site of many transition-state protease inhibitors.[31]

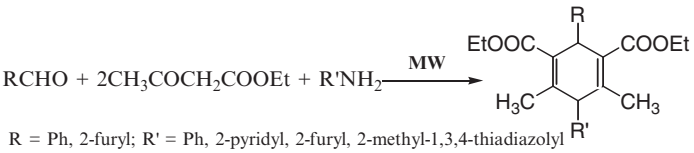
The optimization of the reaction conditions reported in Table 1 moved along the following lines: (i) the classical Hugi's method was converted into MW-based technology and the solvent was eliminated from the original protocol to reduce environmental impact and reagent cost. Irradiation of benzoyl chloride and isonitrile at 60 W for 2 min, led to a product whose purity was comparable to the original method. (ii) On rising the MW power



Scheme 24. Synthesis of a-ketoamides using MW irradiation-simultaneous cooling method.

TABLE 1. The optimization of reaction conditions.

Optimization of microwave conditions				
Step 1	T_1 (min)	2	1	1
	W	60	100	100
	Cooling	Off	Off	On
	T_{max}	149°C	150°C	100°C
Step 2	T_2 (min)	2	2	1
	W	60	60	60
	Cooling	Off	Off	On
	T_{max}	195°C	195°C	125°C
Yield (%)		45	Decomp.	74



Scheme 25. MW assisted synthesis of 1,4-dihydropyridine derivatives.

to 100 W only a black tar product was produced. (iii) By applying 100-W irradiation along with air cooling to both condensation and hydrolysis steps to eliminate overheating, the yield was improved and the total reaction time was further reduced to 2 min.

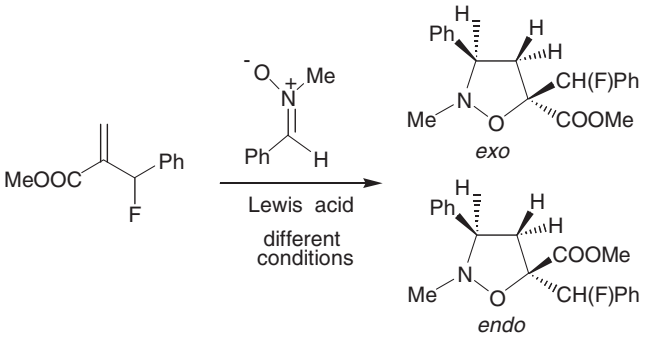
A further example of optimization of an organic reaction directed towards the synthesis of a target compound can be envisaged (Scheme 25) in the preparation via a multicomponent approach of the 1,4-dihydropyridine moiety of current interest because of its recognition as a core structure in calcium antagonists.[32]

Classical synthetic methodologies for the above compounds even after modifications suffer from the use of expensive reagents and require longer reaction time. For a drive to a cleaner and more rapid approach to these products, the MW technology was taken into consideration. The advantages in terms of reaction time and yields of the microwave irradiation over the classical heating of the reagents in organic solvents emerge by comparing the results reported in Table 2.

Moreover an advantage of the neat protocol with respect to the "solid supported" one, lies in the fact that the latter requires appreciable amounts of solvent at the pre- and post-reaction stages and this gives an answer to the crucial question: "In the solventless reactions, is the presence of solvents completely avoided ?".

TABLE 2. The advantages of the microwave irradiation over the classical heating of the reagents in organic solvents in terms of reaction time and yields.

		Solution phase (conventional)		Solid support (microwave)		Neat (microwave)	
		Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)
Phenyl	Phenyl	40	12	83	4.0	87	3.5
Phenyl	2-Pyridyl	38	16	81	4.5	83	4.0
Phenyl	2-Furyl	32	24	79	5.5	80	5.5



Lewis acid = $In(OTf)_3$, $Yb(OTf)_3$, $Sc(OTf)_3$

Toluene, 110°C, 24 h = 46%; Toluene, 120 W (110°C), 10 min = 48%; H_2O, rt, 72 h= 50%; H_2O, 90 W (100°C), 7 min,= 49%; Bimim BF_4, 80°C, 16 h = 19%; Neat, 60 W (100°C), 10 min = 85 %

Scheme 26. Yields of cycloaddition reactions accomplished under different conditions.

In many cases optimization of the MW-assisted reactions can be achieved under solventless conditions not only with respect to the classical organic solvents, but also to more unconventional and environmentally compatible reaction media such as water and ionic liquids. The following example (Scheme 26) illustrates[33] the reaction outcome of a [3 + 2] cycloaddition run under a range of different conditions outlining the relevant advantage offered by MW in the absence of any solvent. Operational simplicity coupled with high efficiency outline in many cases good assets of this methodology.

The advantage of the MW-based optimization of organic reactions far from being limited to increasing yields and to shortening reaction times, plays an important role in affecting selectivities. So far steric course and chemo- and regioselectivity of reactions can be altered under microwave activation when compared to conventional heating.[34]

When competitive pathways are involved in a reaction, the ground state is common for both processes. However the more polar transition state (TS_1) is more stabilized by the dipole–dipole interactions with the electric field and therefore more prone to microwave effects (Figure 4).

Typically the multistep reaction reported in Scheme 27 leading to the formation of an 2-oxazoline moiety taking place through two polar transition states interacting with the MW field, will be highly favoured with respect to the same reaction performed under conventional thermal conditions.[35]

This concept is even better highlighted in the cycloaddition reaction leading to pyrrolidine derivatives shown in Scheme 28. Comparison under solventless conditions between the thermal and the MW-assisted reactions clearly shows how the latter is able to drive the stereoselectivity of this reaction towards the sole formation of the endo-2 isomer.[36]

The high stereoselectivity favouring the formation of this isomer is due to the higher polarity, higher hardness and lower polarizability and therefore

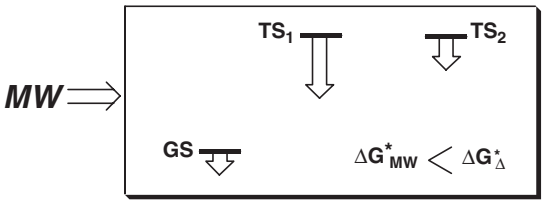
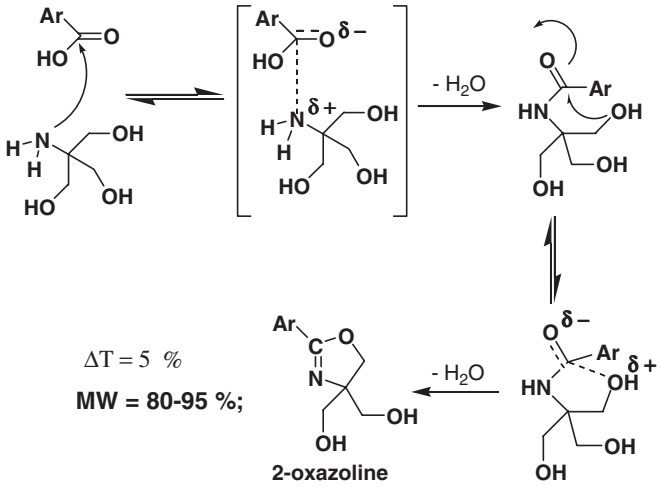
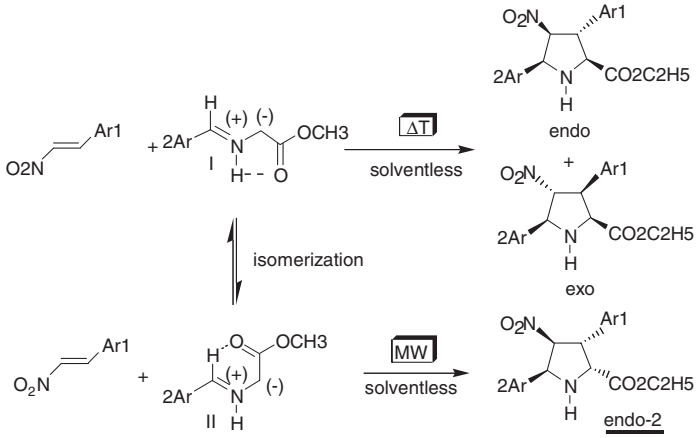


Figure 4. Effect of MW irradiation on the transition state energies.



Scheme 27. Formation of a 2-oxazoline derivative under heating vs. MW irradiation.



Scheme 28. Synthesis of pyrrolidine derivatives.

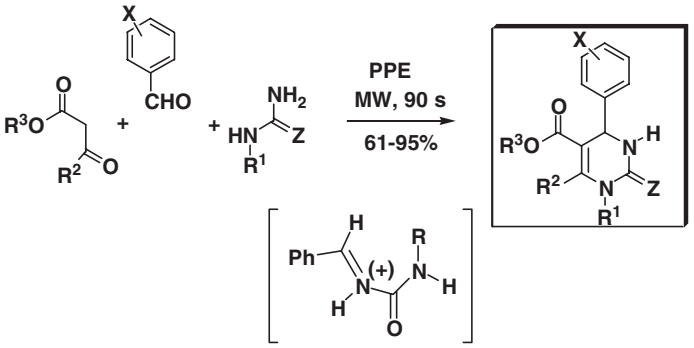
more suitability to be affected by MW effects of dipole II with respect to dipole I.

7. Microwave Activation in Multicomponent Reactions

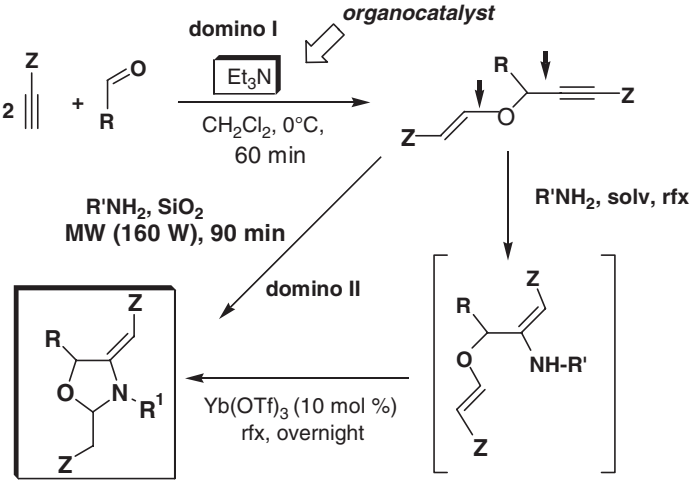
The ideal synthesis should lead to the desired product in as few steps as possible, in good overall yields and by using environmentally compatible reagents and conditions. Multicomponent reactions (MCRs) are convergent reactions in which three or more starting materials react to form a product, where basically all or most of atoms contribute to the newly formed molecule.[37] The use of MW irradiation combined with the solvent-free conditions outlines a highly helpful operational methodology for performing these reactions.

One of the classical MRCs, the Biginelli condensation, leading to the formation of 4-aryl-3, 4-dihydro-2(1H)-pyrimidone (DHPM) esters, heterocyclic systems of remarkable pharmacological efficiency, takes sizeable advantage of MW irradiation in the absence of any solvent (Scheme 29).

Apart from its simplicity and speed and the possibility of operating with open vessels thus avoiding the risk of high-pressure development, an important feature of this protocol is the ability to tolerate variations in all the three building blocks. In this reaction[38] the polyphosphate ester (PPE) operates as an excellent mediator and interacts with the intermediate acyl iminium ion which is particularly prone to undergo specific activation by MW. Under the solventless conditions scale up to 50 mmol, affords 88% yield of the desired product and the synthesis results suitable to high-speed parallel synthesis of DHPM libraries.



Scheme 29. Multicomponent synthesis of dihydropyrimidone derivatives.



Scheme 30. Multicomponent synthesis of polysubstituted 1,3-oxayolines using thermal and MW activation.

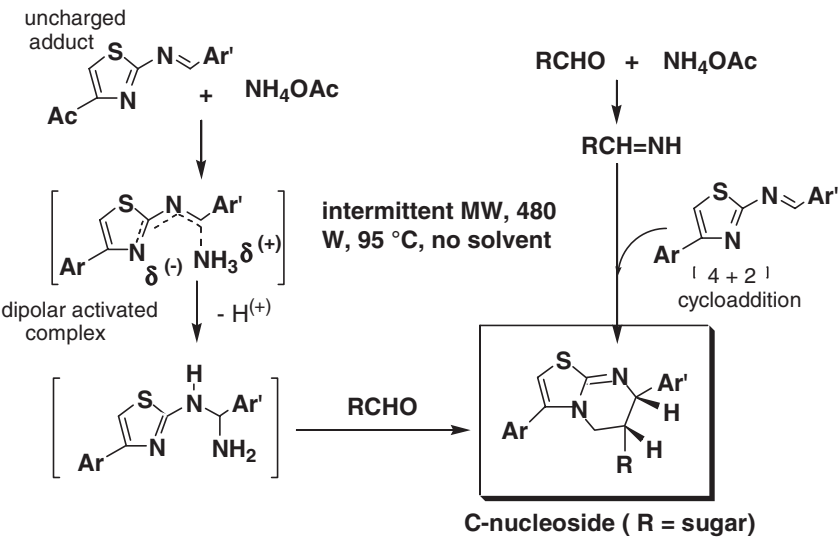
In a more elaborated MRC reaction based on the four-component synthesis of polysubstituted 1,3-oxazolidines a thermal and transition-metal catalyzed one-pot, three-step four component process has been reported.[39] Although the traditional thermal approach based on a one-pot, three-step, four-component process with an $Yb(OTf_3)$-catalyzed cyclization in the final step proved quite satisfactory in terms of chemical efficiency the concern with the imperative use of metals led to a fully organocatalyzed metal-free, one pot, two-step 4-MRC that builds up two C–C bond, one C–O bond, two C–N bonds, and a ring, the second step (domino II) being performed under MW irradiation. Both methods outlined in Scheme 30, complement each other, offering a wide scope of diversity-oriented molecular collections of polyfunctionalized valuable products.

A further support to the added high value provided by MW irradiation to MCR methodology, is highlighted in the three-component one-pot reaction of thiazole Schiff's bases, ammonium acetate and an aldose under solvent-free MW irradiation (Scheme 31).

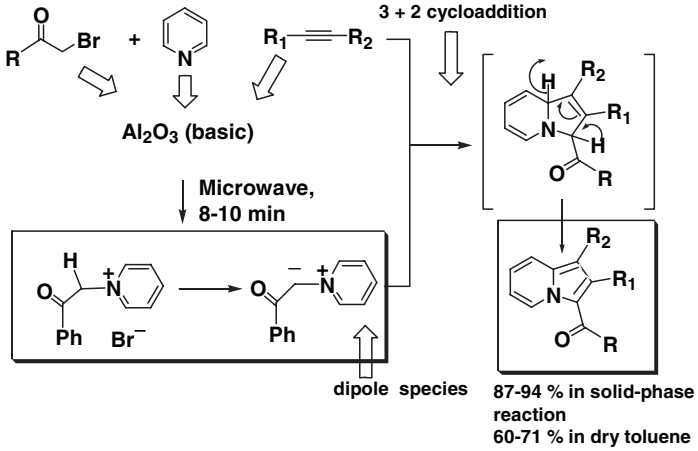
Higher yields (76–88%) under MW irradiation were obtained as compared to those (19–31%) achieved under thermal conditions at the same T, thus supporting the existence of a specific MW effect.[40] The formation of a dipolar activation complex from an uncharged educt and its greater stabilisation by dipole–dipole interaction with the electric field of MW as compared to the less dipolar educt may reduce the activation energy (G*) resulting in a rate enhancement. Moreover the much higher diastereoselectivity leading to a 99/1 *cis*/*trans* ratio under MW (as compared to the 59:41 ratio under ΔT), may be explained if the formation of the *cis* isomer under MW irradiation occurs via a more polar activated complex which will be strongly favoured by microwaves.

Taking into consideration that solid mineral supports can display catalytic activity, the viability of MCR reactions under MW energy in the presence of basic alumina for in situ dipole generation was attempted aimed at the synthesis of indolizines (Scheme 32).[41]

The usefulness of this methodology lies in the fact that the three-component reactions are carried out rapidly under MW-promoted environmentally benign, solventless conditions to give the expected products in excellent



Scheme 31. Multicomponent, MW-assisted synthesis of C-nucleosides.



Scheme 32. MCR + MW synthesis of indolizines.

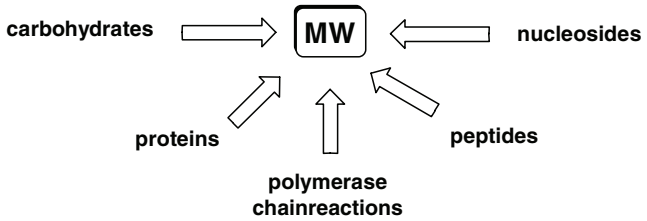


Chart 4. Bio-organic compounds for which preparations MW irradiation is potentially serviceable.

yields. The intermediate dipole species are positioned to benefit from exposure to MW irradiation. The catalytic effect of basic alumina was found more prominent in solid-phase 3-CRs than liquid-phase 3-CRs.

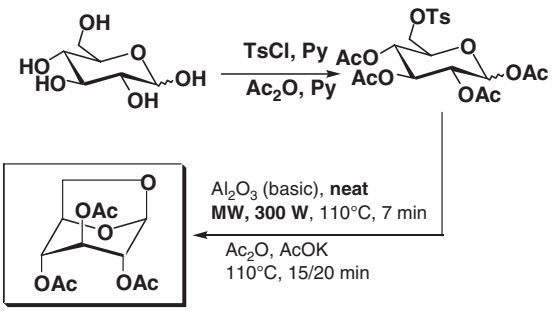
8. Microwave Activation in Bio-organic and Biochemical Applications

The hesitancy, compared to organic synthesis, in using MW irradiation as a source of energy for bio-organic and biochemical applications, is most likely due to the high temperature usually associated with MW-assisted transformations. In fact many of the biochemical molecules are temperature-sensitive. Now with the current technology, temperatures as low as 35–40°C can be maintained by precise power input. The bio-organic molecules for which microwave irradiation is potentially serviceable are reported in Chart 4.

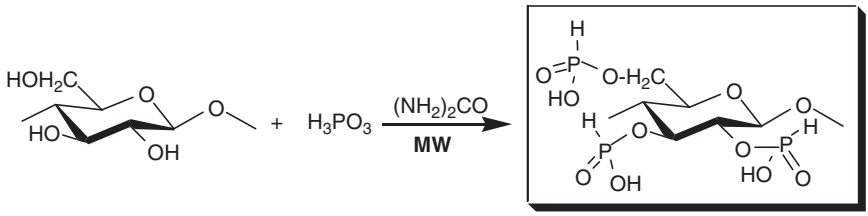
Among the limited number of examples available to date under solvent-less conditions, carbohydrates appear the candidates of choice. A mild rapid and solvent-free procedure for the preparation of 1,6-anhydro-β-D-hexopyranoses, valuable intermediates in the synthesis of a large variety of biologically important natural products has been reported (Scheme 33) by classical thermal reaction or irradiation under microwave.[42]

Cellulose is the most abundant compound among naturally occurring polysaccarides. It is renewable, recyclable and biodegradable and by introduction of various functional groups onto the main polysaccaride chain, additional properties can be defined. Phosphorilated microcrystalline cellulose displays promising properties for its anticoalgulant capacity, high absorption of serum protein, flame retardant properties and high absorption of heavy metals. An efficient solvent-free phosphorilation of microcrystalline cellulose has been devised (Scheme 34) under microwave irradiation[43] which leads without nay previous swelling in appropriate solvent, to higher degree of substitution (DS = number of P atoms per cellulose repeating unit) with respect to the conventional methods.

Increase of the diffusion rate and sorption in cellulose could be enhanced if MW induces orientation of the OH groups by resonance absorption of



Scheme 33. Synthesis of 1,6-anhydro-β-D-hexopyranose.



Scheme 34. Solvent-free phosphorylation of microcrystalline cellulose.

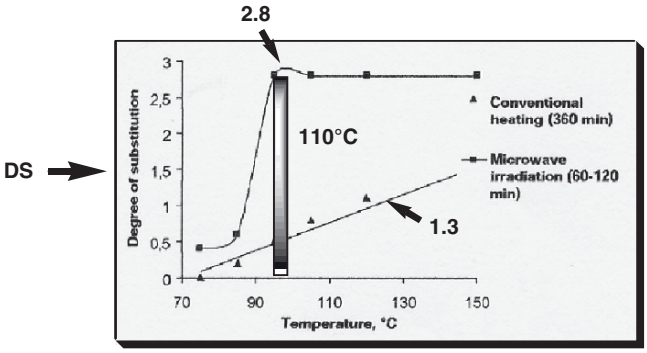


Figure 5. Comparison of the effect of classical heating and MW irradiation on the substitution degree of cellulose.

microwave energy. The orientation will reach the maximum when the frequency of the electromagnetic wave is coincident with the frequency of the macromolecular motion. The appropriate T range corresponding to the maximum group orientation can be calculated and lies for mycrocrystalline cellulose in the range 112–150°C (Figure 5).

This is a promising example of the usefulness of microwaves in the field of cellulose modification.

9. Conclusions

An overview has been provided regarding the advantages of performing a variety of organic reactions under MW activation and in the absence of any solvent. Besides the remarkable shortening of the reaction times this methodology allows a sizeable improvement of yields and in several instances a better stereoselectivity control. The possibility of employing phase transfer catalysis or supported reagents, adds additional benefits and widens the scope of these solventless reactions in solving synthetic organic problems.

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ADVENTURES IN MICROWAVE-ASSISTED ORGANIC SYNTHESIS: CONTRIBUTIONS FROM THE KAPPE LABORATORY 2000–2005

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Abstract: This review highlights work in the field of microwave-assisted organic synthesis (MAOS) originating from the Kappe research laboratories in Graz, Austria. The focus of the article is on synthetic applications in the area of heterocyclic chemistry, multicomponent reactions, transition metal-catalyzed processes, solid-phase synthesis and combinatorial chemistry.

Keywords: multicomponent reactions, microwave heating, homogeneous catalysis, solid-phase synthesis

1. Introduction

High-speed microwave synthesis has attracted a considerable amount of attention in recent years.[1,2] Since the first reports on the use of microwave heating to accelerate organic chemical transformations were published 20 years ago almost simultaneously by the groups of Gedye[3] and Giguere/Majetich,[4] more than 3,000 articles have been published in the area of microwave-assisted organic synthesis (MAOS). The initial slow uptake of

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the technology in the late 1980s and early 1990s has been attributed to its lack of controllability and reproducibility, coupled with a general lack of understanding of the basics of microwave dielectric heating. The risks associated with the flammability of organic solvents in a microwave field and the lack of available systems for adequate temperature and pressure controls were major concerns. Although most of the early pioneering experiments in MAOS were performed in domestic, sometimes modified, kitchen microwave ovens, the current trend clearly is to use dedicated instruments for chemical synthesis which have become available only in the last few years. Since the late 1990s the number of publications related to MAOS has therefore increased dramatically to a point where it might be assumed that, in a few years, most chemists will probably use microwave energy to heat chemical reactions on a laboratory scale. Not only is direct microwave heating able to reduce chemical reaction times from hours to minutes, but it is also known to reduce side reactions, increase yields and improve reproducibility. Therefore, many academic and industrial research groups are already using MAOS as a forefront technology for rapid reaction optimization, for the efficient synthesis of new chemical entities, or for discovering and probing new chemical reactivity. A large number of review articles[5,6] and several books[7–9] provide extensive coverage of the subject.

Our own interest in the area of microwave chemistry began in the late 1990s and apart from ~50 original research contributions till date we have published several review articles and book chapters in this field, highlighting the use of microwave technology in organic synthesis,[5] combinatorial chemistry,[10–12] medicinal chemistry,[13] drug discovery,[14] solid-phase synthesis,[15] and in conjunction with immobilized reagents.[16] In 2005 a book authored by C. Oliver Kappe and Alexander Stadler entitled "Microwaves in Organic and Medicinal Chemistry" containing ~1,000 references was published by Wiley-VCH.[8]

In the present book chapter, selected contributions from the Kappe research laboratories focusing on preparative aspects of MAOS technology from the period 2000–2005 are summarized. Detailed accounts on the theory of microwave dielectric heating, microwave effects, available equipment and processing techniques will not be discussed herein as those aspects have been summarized extensively in other publications.[5–8,17]

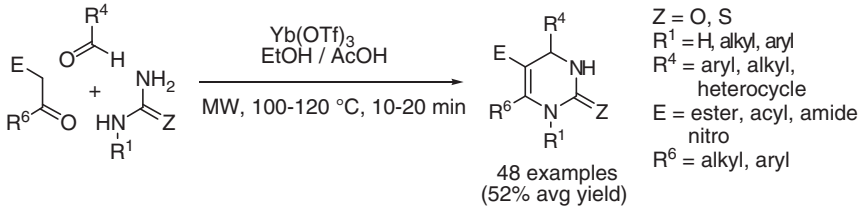
2. Multicomponent Reactions

2.1. THE BIGINELLI DIHYDROPYRIMIDINE SYNTHESIS

An important multicomponent reaction (MCR) for the synthesis of biologically active dihydropyrimidines (DHPMs)[18] is the Biginelli dihydropyrimidine synthesis, involving the acid-catalyzed condensation of aldehydes,

CH-acidic carbonyl components and urea-type building blocks (Scheme 1).[19–21] Our research group has a long-standing interest in this powerful synthetic principle and therefore our endeavors in microwave chemistry began by investigating the Biginelli MCR utilizing microwave conditions. Our initial approach involved a solvent-free condensation of the three building blocks under open-vessel microwave conditions employing polyphosphate ester as catalyst.[22] The DHPMs were obtained in good yields in a domestic microwave oven within less than 2 min, allowing for the parallel synthesis in individual reaction vessels. Subsequently, the reaction conditions in solution – in particular the influence of the HCl catalyst at higher temperatures and the involvement of microwave effects – were studied in more detail.[23] In 2001 we have described the generation of a library of 48 dihydropyrimidines, introducing the concept of automated sequential microwave synthesis using a dedicated single mode microwave reactor with incorporated robotics.[24] While under conventional thermal conditions this MCR typically requires several hours of heating at reflux temperature (~.80°C) in a solvent/catalyst system such as ethanol/HCl,[19,20] microwave-assisted protocols using Lewis acids as catalysts employing sealed vessels can be completed within 10–20 min providing improved product yields.[24] Having optimized conditions for the Biginelli reaction at hand, a diverse set of 17 CH-acidic carbonyl compounds, 25 aldehydes, and 8 urea/thioureas was used in the preparation of a dihydropyrimidine library. Out of the full set of 3,400 possible dihydropyrimidine derivatives a representative subset of 48 analogs was prepared within a 12 h timeframe using automated addition of building blocks and subsequent sequential microwave irradiation of each reaction vessel in a single-mode microwave reactor equipped with suitable robotics (Scheme 1).[25]

While the above-mentioned transformations were carried out on a relatively small scale (<1 g) in a single-mode microwave reactor,[24,25] it was demonstrated that these reactions were directly scalable in a multimode microwave instrument using an identical temperature/time profile, allowing the generation of ~.100 g of product quantity in a single run.[26] More recently, we have reported the same transformation in continuous flow mode, employing a flow cell immersed in a single-mode microwave instrument.[27] This



Scheme 1. Biginelli three-component library synthesis of dihydropyrimidines

technology has the potential to generate much larger product quantities than a microwave-heated batch reaction.

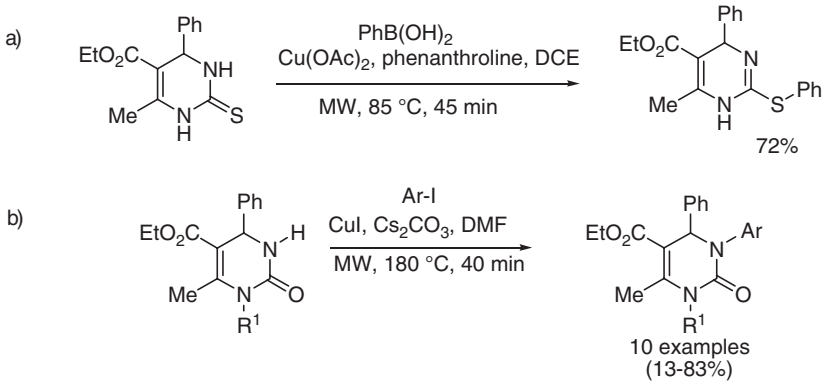
2.2. SCAFFOLD DECORATION OF THE BIGINELLI DIHYDROPYRIMIDINES

Having access to large numbers of DHPMs synthesized via one-pot Biginelli condensation[24,25] we next focused on decorating the scaffold of this privileged core using high-speed automated microwave-enhanced processes, that in many instances relied on transition metal-catalyzed transformations.

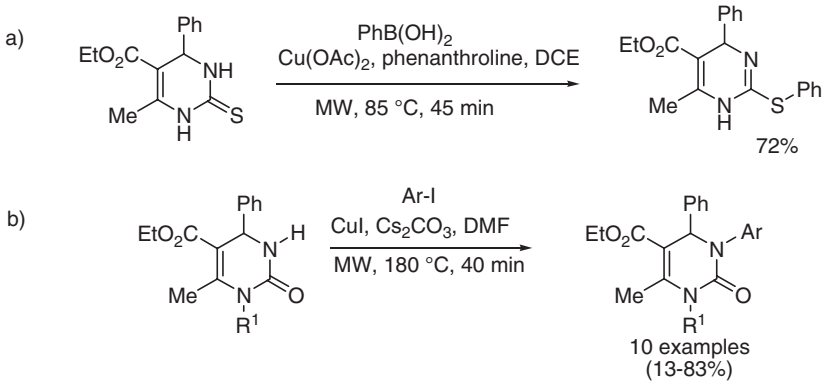
Addressing the C2 position of the pyrimidine nucleus, we have reported a microwave-assisted version of the Liebeskind–Srogl cross-coupling reaction in 2004 (Scheme 2).[28] Here, rapid carbon–carbon bond forming was achieved, employing a 2-methylthio-1,4-dihydropyrimidine derivative as starting material (Scheme 2a). Coupling with phenylboronic acid was performed at 130°C under microwave conditions, providing a 84% isolated yield of the desired product within 25 min. Optimum yields were achieved using 3 mol% of $Pd(PPh_3)_4$ as catalyst and 2.5 equivalents of copper(I) thiophene-2-carboxylate (CuTC) as an additive. Interestingly, it was also possible to perform carbon-carbon coupling directly with the corresponding cyclic thiourea structures (DHPM-2-thiones) using similar Pd(0)-catalyzed, Cu(I)-mediated coupling conditions (Scheme 2b). The methodology was used to synthesize a small focused library of 2-aryl-1,4-dihydropyrimidines which are highly potent non-nucleosidic inhibitors of hepatitis B virus replication having in vitro and in vivo antiviral activity.[28]

One example of carbon–sulfur bond formation in DHPM-2-thiones is displayed in Scheme 3a. In contrast to the Pd(0)/Cu(I) mediated process described in Scheme 2b leading to *carbon–carbon* bond formation, reaction of the same starting materials in the presence of one equivalent of Cu(II) acetate and two equivalents of phenanthroline ligand furnished the corresponding *carbon–sulfur* cross-coupled product.[28] Whereas the reaction at room temperature needed 4 days to reach completion, 45 min of microwave irradiation at 85°C in 1,2-dichloroethane provided 72% isolated yield of the product.[28]

In order to introduce novel diversity in the *N*3-position of the DHPM scaffold we decided to investigate the Goldberg procedure, i.e. the Cu(I)-catalyzed *N*-arylation. The most general Goldberg protocol identified used a concentrated mixture of 20 mol% of CuI as catalyst, 1.5 equivalents of Cs_2CO_3 as base and 5 mol equivalent of DMF as solvent (Scheme 3b). The reactions were conducted at 180°C for 40 min with a set of eight differently substituted aryl iodides, providing the desired *N*3-aryl-DHPMs in low to excellent isolated yields (13–83%).[29]



Scheme 2. Pd(0)-catalyzed, Cu(I)-mediated Liebeskind–Srogl-type couplings.



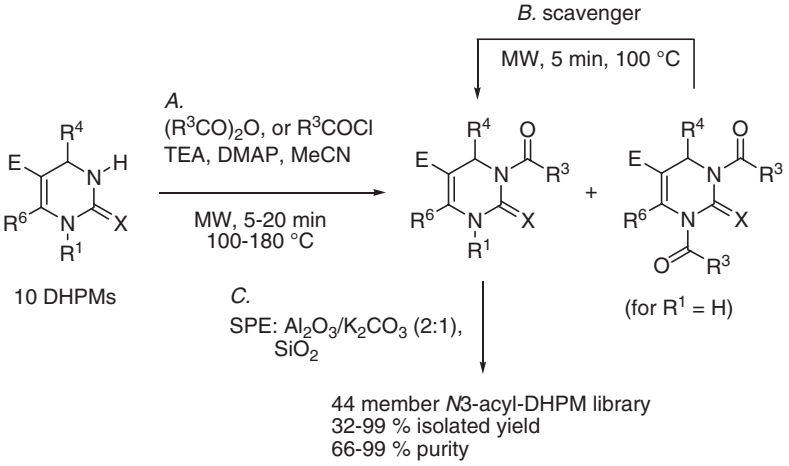
Scheme 3. (a) Cu(II)-mediated carbon–sulfur and (b) Cu(I)-mediated carbon–nitrogen cross-coupling (Goldberg reaction).

Another alternative for the selective high-speed functionalization of the N3 position in DHPMs is the microwave-induced *N*3-acylation of the dihydropyrimidine scaffold using different anhydrides or acid chlorides (Scheme 4).[30,31] Since most of the pharmacologically attractive DHPM derivatives are *N*3-acylated analogs,[18] we became interested in developing a rapid method for accessing libraries containing this structural motif in high-throughput format. In general, these acylations are known to occur regioselectively at the more nucleophilic *N*3 position, requiring many hours of heating at high temperatures even for reactive anhydrides such as acetic anhydride. After experimentation with a variety of solvents, tertiary bases, and catalysts we quickly arrived at conditions where complete and clean conversion of a model substrate with acetic anhydride could be achieved within 10 min using microwave flash heating to 130°C in sealed vessels.[30]

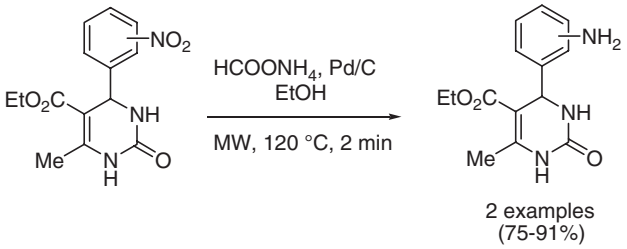
The process also involved purification of the crude reaction mixture by a microwave-assisted scavenging technique.[30,31] Volatile acylating agents such as acetic anhydride could be simply removed by evaporation while other non-volatile anhydrides such as benzoic anhydride required a more elaborate work-up suitable for a high throughput format. Several scavenging reagents possessing amino functionalities with different loadings have been applied to sequester the excess of benzoic anhydride (Bz_2O) from the reaction mixture.[31] Ultimately, the *N*3-benzoylated DHPMs could be isolated selectively from the reaction mixture by passing the solution through a short SPE column filled with layers of basic alumina impregnated with K_2CO_3 and silica gel. Elution experiments have shown that the basic Al_2O_3/K_2CO_3 (2:1) layer retains the excess acid, whereas the acidic silica gel will retain the DMAP catalyst (Scheme 4).

One microwave functionalization principle that allows for considerable diversity to be introduced on the DHPM C4-aryl substituent is the rapid reduction of a nitroarene to the corresponding aniline (Scheme 5). The reduction method of choice to be carried out under microwave conditions here is catalytic transfer hydrogenation using hydrogen donors such as ammonium formate and a Pd catalyst like Pd-on-charcoal. Scheme 5 shows how this technique can be used to rapidly generate DHPMs that possess an aniline function at C4 that can be utilized for further derivatization.[32]

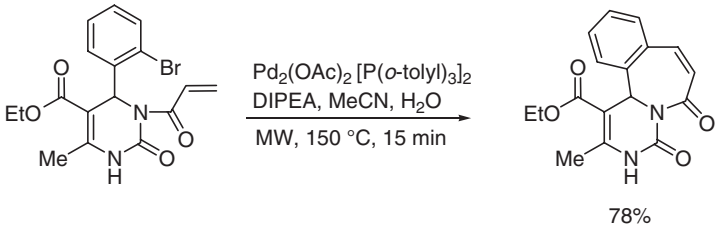
In an attempt to build more complex structures derived from monocyclic DHPMs, we decided – in collaboration with the group of Mats Larhed – to attempt to connect the 4-aryl group and the dihydropyrimidone ring using an envisioned *endo*-cyclic Heck reaction from a suitable precursor, delivering a fused benzoazepine-DHPM system after a formal *trans* palladium(II)



Scheme 4. *N3*-Acylations of dihydropyrimidines.



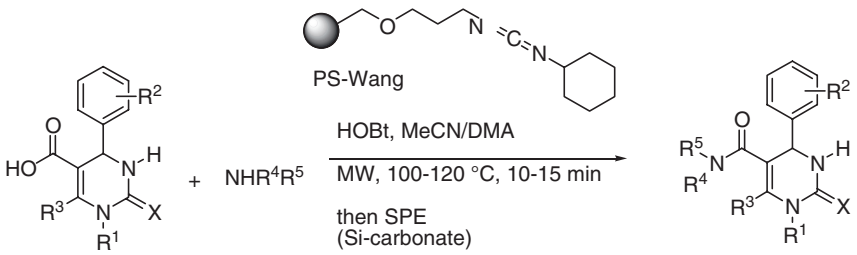
Scheme 5. Catalytic transfer hydrogenations.



Scheme 6. Intramolecular seven-membered Heck *endo*-cyclization.

β-hydride elimination (Scheme 6). Using classical Heck-coupling conditions, it was quickly realized that complete ring-closure could be obtained by heating an appropriate olefin precursor, 5 mol% of Herrmann's palladacycle and 3 equivalents of DIEA in MeCN/H_2O at 150°C for 15 min, providing a 78% product yield.[29] Examples of other palladium-catalyzed cross-couplings involving 4-(bromophenyl)-DHPMs, engage Suzuki reactions, amino- and alkoxycarbonylations, and direct *N*-amidations.[29]

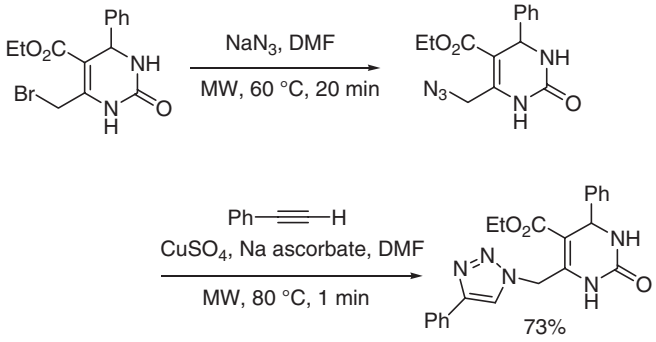
In order to readily introduce diversity into the C5 position, appropriate DHPM C5-acids were prepared by microwave-assisted debenzylation or deallylation methods from the corresponding benzyl and allyl esters, respectively (not shown).[33,34] Subsequent amidation of the DHPM acids using a polystyrene-bound carbodiimide and suitable amines allowed for convenient and rapid synthesis of a diverse set of amides (Scheme 7).[33,34] An equimolar mixture of DHPM acid, corresponding amine and 1-hydroxybenzotriazole (HOBt) in a MeCN/DMA solvent mixture was admixed with 2 equivalents of the polymer-bound carbodiimide and irradiated for 10–15 min at 100–120°C. After cooling, the mixture was diluted with methanol and subjected to solid-phase extraction utilizing silica carbonate. Evaporation of the filtrate furnished the desired compounds in excellent purity.[34] Alternatively, the DHPM C5 acids could also be derivatized with primary and secondary alcohols using fluorous or conventional Mitsunobu reagents.



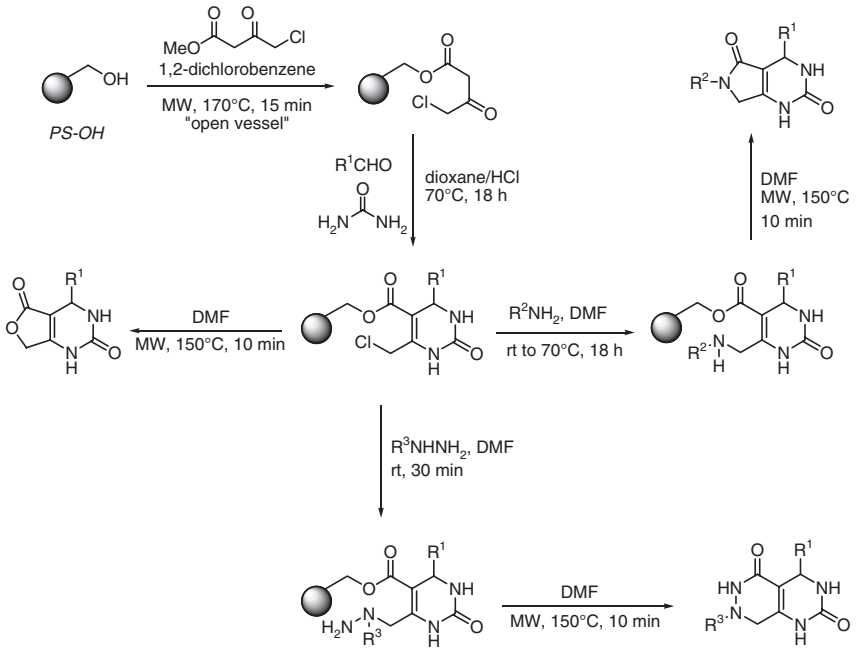
Scheme 7. DHPM C5 amide synthesis utilizing polymer-bound carbodiimide.

Finally, the C6 position on the DHPM ring was addressed using cycloaddition chemistry. Specifically, we have exploited a microwave-assisted version of the Cu(I)-catalyzed azide–acetylene ligation process ("click chemistry") for the preparation of 6-(1,2,3-triazol-1-yl)-dihydropyrimidones (Scheme 8).[35] Here, a suitable heterocyclic DHPM C6 azidomethyl intermediate (obtained by microwave-assisted azidation) was treated with phenyl acetylene in *N,N*-dimethylformamide employing 2 mol% of $CuSO_4$/sodium ascorbate as catalyst precursor. After completion of the cycloaddition process, the triazole product was precipitated in high yield (73%) and purity by addition to ice/water. For the model reaction displayed in Scheme 8, full conversion at room temperature required 1 h. By carrying out the same reaction utilizing controlled microwave heating at 80°C, complete conversion was achieved within 1 min A library of 27 triazolyl-dihydropyrimidones was prepared with four points of diversity.[35]

Applying the microwave-enhanced scaffold decoration protocols outlined above, a large number of diversely substituted DHPM derivatives can now be rapidly prepared and screened for biological function. In addition to classical solution phase protocols we have also developed several microwave-assisted



Scheme 8. Copper(I)-catalyzed azide–acetylene ligation.



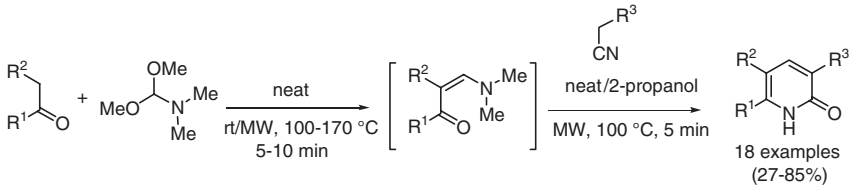
Scheme 9. Preparation of various bicyclic dihydropyrimidinones employing cyclative cleavage.

solid-phase protocols. One such approach (Scheme 9) utilized the synthesis of a 4-chloroacetoacetate resin as the key starting material, which was prepared by microwave-assisted acetoacetylation of hydroxymethyl polystyrene resin.[36] In analogy to earlier work[37] this transesterification was best carried out under open vessel conditions in 1,2-dichlorobenzene (170°C) in order to allow the formed methanol to be removed from the equilibrium. This resin precursor was subsequently treated with urea and various aldehydes in an acid-catalyzed Biginelli multi-component reaction (dioxane, 70°C), leading to the corresponding resin-bound dihydropyrimidinones. The desired furo[3,4-d]pyrimidine-2,5-diones were obtained by cyclative release in DMF at 150°C. Alternatively, pyrrolo[3,4-d]pyrimidine-2,5-diones were synthesized using the same pyrimidine resin precursor, which was first treated with a representative set of primary amines to substitute the chlorine. Subsequent cyclative cleavage was carried out at temperatures between 150°C and 250°C, leading to the corresponding pyrrolopyrimidine-2,5-dione products in high purity. The synthesis of pyrimido[4,5-d]pyridazine-2,5-diones was carried out in a similar manner, employing hydrazines for the nucleophilic substitution, prior to cyclative cleavage.[36]

2.3. OTHER MULTICOMPONENT REACTIONS

In 2004 we have described a multicomponent, one-pot, two-step pathway to 3,5,6-substituted 2-pyridones (Scheme 10).[38] In the first step equimolar mixtures of a CH-acidic carbonyl compound and *N,N*-dimethylformamide dimethyl acetal (DMFDMA) were reacted to form the corresponding enamines, either at room temperature or under microwave conditions. After addition of a methylene active nitrile (1 equivalent), 2-propanol as solvent and catalytic amounts of piperidine base, the reaction mixture was heated to 100°C for 5 min under microwave conditions. In most cases, the desired heterocyclic product precipitated directly after cooling of the reaction mixture and could be collected by filtration.[38]

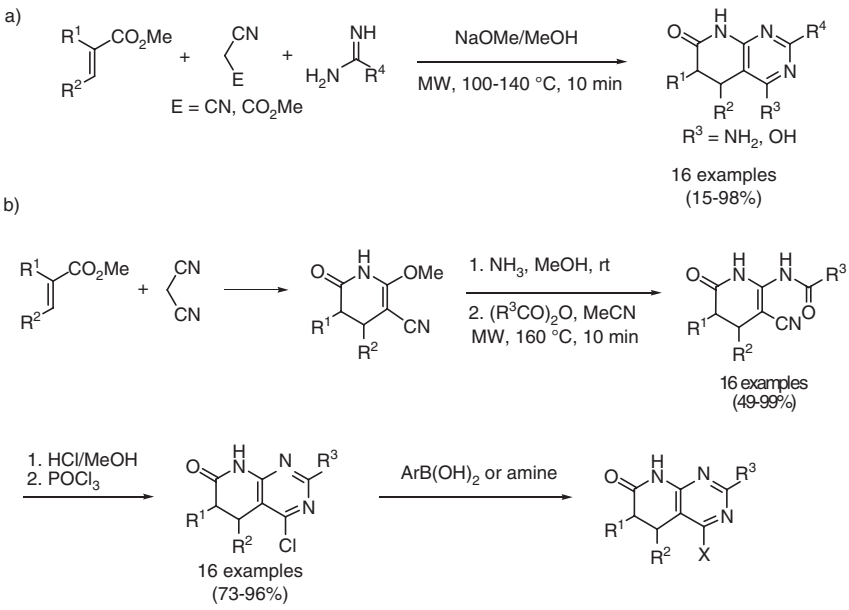
In collaboration with the group of Jose Borrell we have investigated a number of different microwave-assisted approaches to biologically active pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones.[39–41] In the multicomponent method described in Scheme 11a, the target structures were obtained in a one-pot fashion by cyclocondensation of α,β-unsaturated esters, amidines or guanidines, and CH-acidic nitriles (malononitrile or ethyl cyanoacetate).[39,40] Employing sodium methoxide as base in methanol as solvent, low to excellent yields were obtained by microwave heating to 100–140°C for 10 min. Typically, the resulting pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones possessing 4 diversity centers crystallized directly from the reaction mixture in high purity. In a modification of this strategy (Scheme 11b),[41] we subsequently disclosed a step-wise protocol, that allowed the isolation of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridin-3-carbonitrile intermediates under conventional reaction conditions, which were subsequently transformed to 2-aminopyridones by treatment with ammonia at room temperature. Microwave-assisted acylation of the amino group with carboxylic acid anhydrides (R^3) in acetonitrile at 160°C for 10 min furnished 2-acylaminopyridones which were subsequently cyclized with hydrochloric acid in methanol to the corresponding 4-oxopyrido [2,3-*d*]pyrimidines in almost quantitative yield.[41] Further incorporation of a chloro substituent by treatment with phosphorous oxychloride provided an ideal substrate for further decoration of the pyrido[2,3-*d*]pyrimidine scaffold using Suzuki chemistry, or nucleophilic displacement reactions with amines.



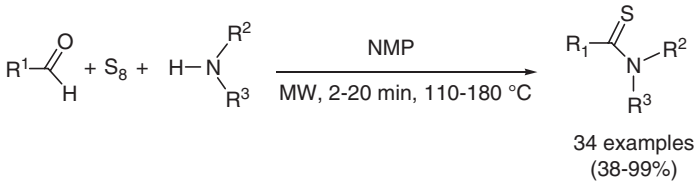
Scheme 10. Three-component synthesis of fused pyridones.

For both types of transformations, rapid microwave-assisted protocols were utilized, allowing access to a diverse set of pyrido[2,3-*d*]pyrimidines with four diversity centers.[41]

Another frequently used multicomponent reaction is the Kindler thioamide synthesis (the condensation of an aldehyde, amine and sulfur). In 2003 we have described a microwave-assisted protocol that utilized a diverse selection of 13 aldehyde and 12 amine precursors in the construction of a representative 34-member library of substituted thioamides (Scheme 12).[42] The three-component condensations of aldehydes, amines, and elemental sulfur were carried out using 1-methyl-2-pyrrolidone (NMP) as solvent, employing microwave flash heating at 110–180°C for 2–20 min. A simple workup protocol allowed the isolation of synthetically valuable primary, secondary, and tertiary thioamide building blocks in 83% average yield and >90% purity.[42]



Scheme 11. Formation of pyrido[2,3-*d*]pyrimidines.

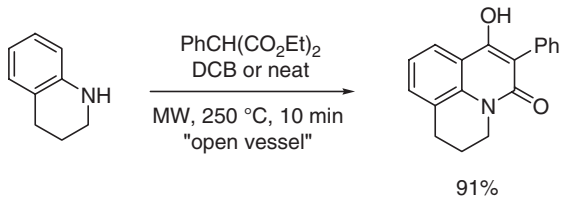


Scheme 12. Kindler thioamide synthesis.

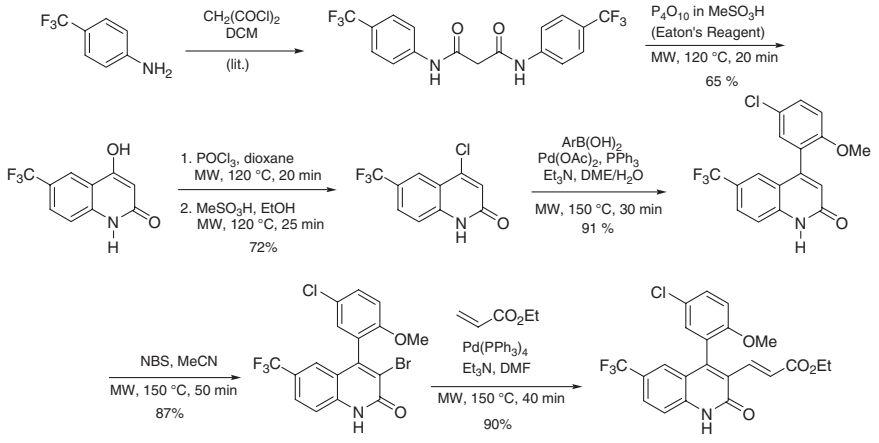
3. General Heterocycle Synthesis

Many of the traditional condensation reactions leading to heterocycles require high temperatures and conventional reaction conditions very often involve heating of the reactants in an oil, metal, or sand bath for many hours or even days. One example published by our research group recently is illustrated in Scheme 13, namely the formation of 4-hydroxyquinolin-2-(1*H*)-ones from anilines and malonic esters.[43] The corresponding conventional, thermal protocol involves heating of the two components in equimolar amounts in an oil bath at 220–300°C for several hours (without solvent), whereas similar high yields can be obtained by microwave heating at 250°C for 10 min.[43] Here it was essential to use open-vessel technology, since two equivalents of a volatile byproduct (ethanol) are formed that under normal (atmospheric pressure) conditions are simply distilled off and therefore removed from the equilibrium.

A related synthesis of a 4-hydroxyquinolin-2-(1*H*)-one derivative which was subsequently manipulated into a highly functionalized and biologically active analog is shown in Scheme 14. Note that all the six linear steps



Scheme 13. Formation of 4-hydroxyquinolin-2-(1*H*)-ones from anilines and malonic esters.



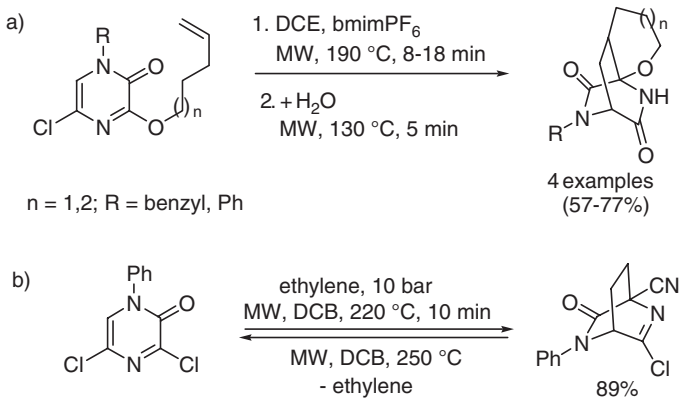
Scheme 14. Six step "all microwave" synthesis of a 4-aryl-2-quinolinone maxi K^+ channel opener.

involving cyclization, chlorination, hydrolysis, Suzuki reaction, bromination and Heck coupling in the synthesis of the 4-aryl-3-alkenyl-2-quinolinone maxi K^+ channel opener are performed under microwave conditions.[44] A rapid synthesis of pyrimido[1,2-*a*]pyrimidines via a solvent-free microwave method was disclosed in 2001.[45]

4. Cycloaddition Reactions

Inter- and intramolecular hetero-Diels–Alder cycloaddition reactions in a series of functionalized 2(1*H*)-pyrazinones have been studied in detail by our group in collaboration with Erik Van der Eycken.[46–48] In the intramolecular series, cycloaddition of alkenyl-tethered 2(1*H*)-pyrazinones requires 1–2 days under conventional thermal conditions involving chlorobenzene as solvent under reflux conditions (132°C). Switching to 1,2-dichloroethane doped with the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ($bmimPF_6$) and sealed vessel microwave technology, the same transformations were completed within 8–18 min at 190°C reaction temperature (Scheme 15a).[46] Without isolating the primary imidoyl chloride cycloadducts, rapid hydrolysis was achieved by addition of small amounts of water and resubjection of the reaction mixture to microwave irradiation (130°C, 5 min). The isolated overall yields of the desired cycloadducts were in the same range as reported for the conventional thermal protocols.

In the intermolecular series, Diels–Alder cycloaddition reaction of the pyrazinone heterodiene with ethylene using pre-pressurized microwave vessels led to the expected bicyclic cycloadduct (Scheme 15b).[46,47] Similar cycloaddition reactions have also been studied on solid-phase.[48] Further scaffold decoration



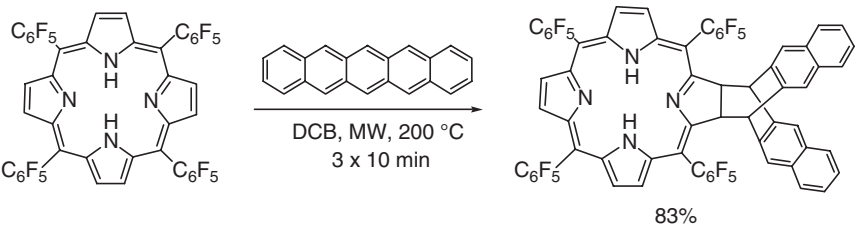
Scheme 15. Hetero-Diels–Alder cycloaddition reactions of 2(1*H*)pyrazinones.

transformations of the pyrazinone core involving transition metal-catalyzed reactions[49] and "click chemistry"[50] have also been reported.

A collaborative project with José A. S. Cavaleiro led us to study the cycloadditions of porphyrines with various cyclic dienes (Scheme 16).[51] In order to evaluate the benefits of microwave irradiation in the synthesis of barrelene-fused chlorins, we decided to explore the Diels–Alder reaction of tetrakis (pentafluorophenyl)porphyrin with pentacene since under classical heating conditions this reaction gives the chlorin cycloadduct in very low yield (22% after 8 h at 200°C). We were able to favor the formation of the chlorin cycloadduct by using a very concentrated reaction mixture. A high yield of the cycloadduct was obtained when the reaction was performed by adding the pentacene in small portions (3 × 1 equivalents) leading to the isolation of the cycloadduct in 83% yield after purification by column chromatography (Scheme 16).[51]

5. Transition Metal-Catalyzed Reactions

Homogeneous transition metal-catalyzed reactions represent one of the most important and best studied reaction types in MAOS. Using traditional heating under reflux conditions, transition metal-catalyzed carbon–carbon and carbon–heteroatom bond forming reactions typically need hours or days to reach completion and often require an inert atmosphere. Several research groups have demonstrated over the past few years that many of those transformations can be enhanced significantly employing microwave heating under sealed vessel conditions ("microwave flash heating"), in most cases without an inert atmosphere.[5–8] The use of metal catalysts in conjunction with microwaves may have significant advantages in comparison with traditional heating methods, since the inverted temperature gradients under microwave conditions may lead to an increased lifetime of the catalyst by elimination of wall effects.[5] Scheme 17 shows a recent example of a standard Heck reaction reported by our group involving aryl bromides and acrylic acid to furnish the corresponding cinnamic acid derivatives.[26] Optimization of the reaction conditions under small scale

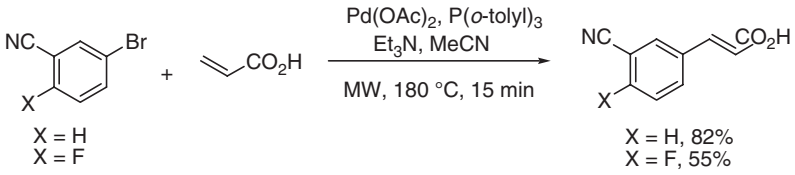


Scheme 16. Diels–Alder reaction of tetrakis(pentafluorophenyl)porphyrin with pentacene.

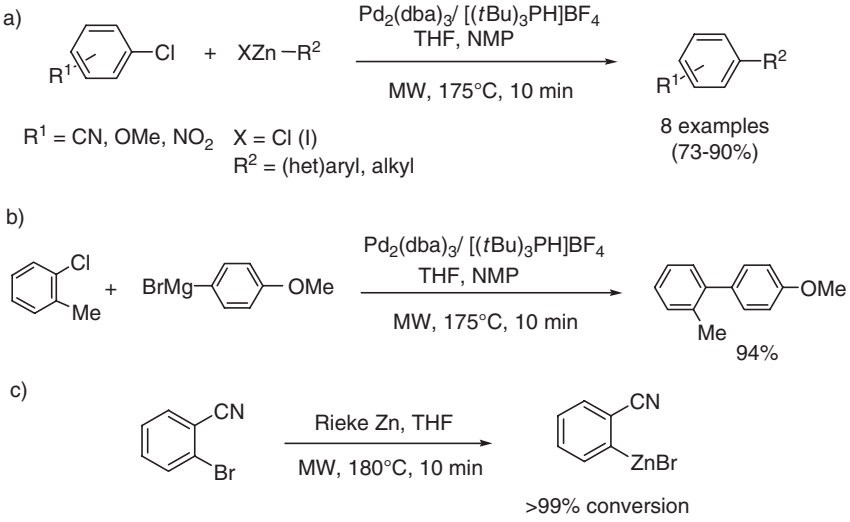
(2 mmol) single-mode microwave conditions led to a protocol that employed acetonitrile as solvent, 1 mol% of palladium acetate/tri(*ortho*-tolyl)phosphine as catalyst/ligand system, triethylamine as base and 180°C reaction temperature for 15 min. The rather expensive homogeneous catalyst system can be replaced by 5% palladium-on-charcoal (<0.1 mol% concentration of palladium)[16] without the need to change any of the other reaction parameters.[26] Yields for the Heck reaction providing cinnamic acids (X = H) were very similar using either homogeneous or heterogeneous Pd catalysis.

A general procedure for high-speed microwave-assisted Negishi and Kumada couplings of unactivated aryl chlorides was recently reported by our group (Scheme 18). This procedure uses 0.015–2.5 mol% of $Pd_2(dba)_3$ as a Pd source and the air stable tri-*tert*-butylphosphonium tetrafluoroborate as ligand precursor. Successful couplings were observed for both arylorganozinc chlorides and iodides (Scheme 18a).[52] Using this methodology it was also possible to successfully couple aryl chlorides with *alkyl*zinc reagents such as *n*-butylzinc chloride in a very rapid manner without the need for an inert atmosphere. Optimized conditions utilized sealed vessel microwave irradiation in a THF/1-methyl-2-pyrrolidone mixture at 175°C for 10 min. Applying the same reaction conditions Kumada cross-couplings with organomagnesium (Grignard) reagents were also carried out successfully (Scheme 18b).[52] Furthermore it was also possible to prepare the corresponding organozinc and magnesium compounds by insertion of Riecke zinc or magnesium metal, respectively, into aryl halides using microwave heating (Scheme 18c).[52]

An application of this high-speed Negishi coupling methodology for the preparation of enantiopure 2,2′-diarylated 1,1′-binaphthyls was carried out in collaboration with the group of Martin Putala (Scheme 19).[53] Reaction times as short as 40 s in some cases were sufficient to achieve complete conversions in the stereoconservative Negishi coupling of commercially available 2,2′-diiodo-1,1′-binaphthyl (DIBN) with arylzinc chlorides. The catalyst loading for typical runs was 5 mol% $Pd(PPh_3)_4$ but could be lowered to 0.5 mol% in some instances without appreciable reduction of coupling efficiency. The formed enantiopure 2,2′-diarylated 1,1′-binaphthyls are of interest in material sciences application. In the same article, the corresponding Negishi alkynations using zinc phenylacetylide and zinc trimethylsilylacetylide were also described.[53]



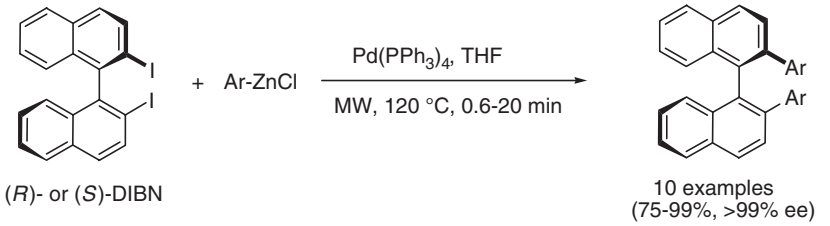
Scheme 17. Heck reactions with acrylic acids



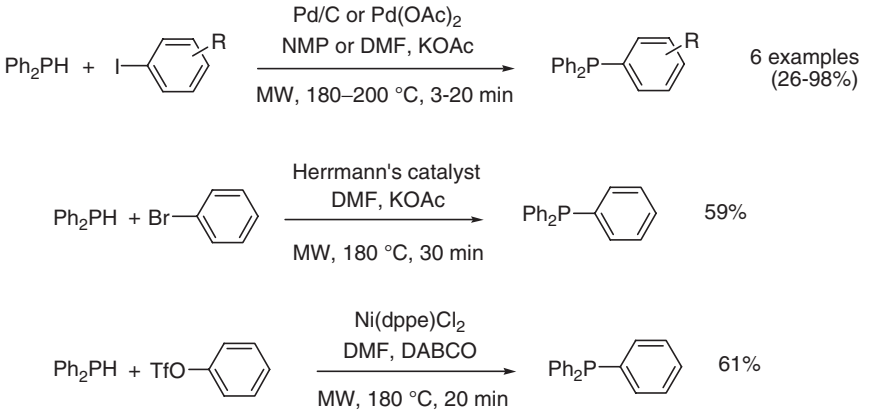
Scheme 18. Negishi and Kumada cross-coupling reactions.

Tertiary phosphines are very important types of ligands in transition metal-catalyzed reactions. We have demonstrated that aryl iodides, bromides, and triflates can be successfully directly coupled with diphenylposphine under microwave conditions (Scheme 20).[54] Optimized reaction conditions for aryl iodides utilized combinations of 1-methyl-2-pyrrolidone, KOAc, and 2.5 mol% of $Pd(OAc)_2$ as catalyst. A 50% excess of iodobenzene was found to give the best yields and within 20 min a conversion of >90% was typically achieved at 180–200°C. At higher temperatures decomposition of the Pd(II) catalyst was observed, resulting in lower isolated product yields and in the deposition of a very thin film of Pd black on the microwave process vial. The reaction was also successful using Pd-on-charcoal (<0.1 mol% palladium) as a catalyst. For the less reactive aryl bromide and triflate precursors more active catalytic systems had to be employed (Scheme 20).[54]

The ruthenium-catalyzed ring-closing metathesis (RCM) has emerged as very powerful method for the construction of small, medium and macrocyclic ring systems. In general, metathesis reactions are carried out at room temperature or at slightly elevated temperatures (e.g. at 40°C in refluxing dichloromethane), sometimes requiring several hours of reaction time to achieve full conversion. Employing microwave heating, otherwise sluggish RCM protocols have been reported to be completed within minutes or even seconds, instead of hours at room temperature. Examples of microwave-assisted RCM chemistry studied in our laboratories in collaboration with Olivier Lavastre are presented in Scheme 21.[55]



Scheme 19. Synthesis of enantiopure 2,2′-diarylated 1,1′-binaphthyls utilizing stereoconservative Negishi cross-coupling reactions.

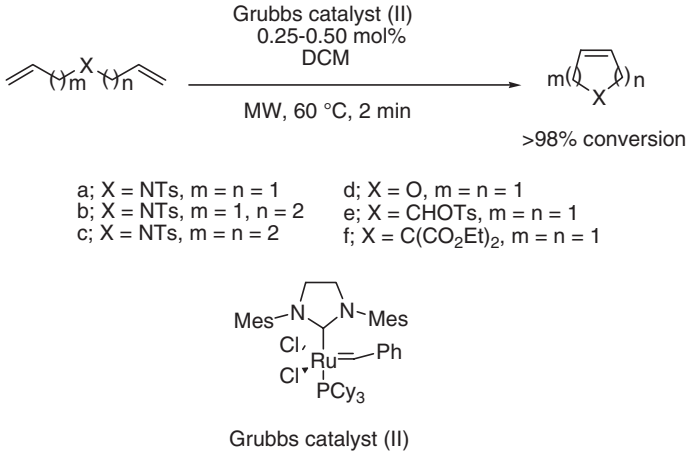


Scheme 20. Palladium-catalyzed carbon–phosphorous cross-coupling.

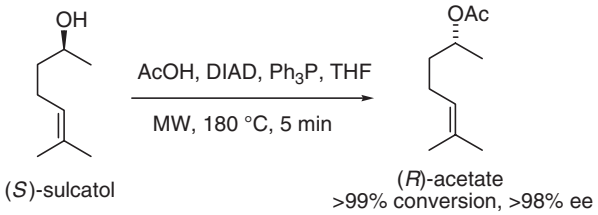
6. Miscellaneous Solution-Phase Organic Transformations

In 2001, we established that Mitsunobu chemistry can be carried out using high-temperatures in the context of an enantioconvergent approach to the aggregation pheromones (*R*)- and (*S*)-sulcatol (Scheme 22).[56] While the conventional Mitsunobu protocol carried out at room temperature here proved to be extremely sluggish, complete conversion of (*S*)-sulcatol to the (*R*)-acetate (S_N2-inversion) using essentially the standard Mitsunobu conditions (1.9 equivalents diisopropylazodicarboxylate, 2.3 equivalents triphenylphosphine) was achieved within 5 min at 180°C under sealed vessel microwave conditions. Despite the high reaction temperatures, no by-products could be identified in these Mitsunobu experiments, with enantiomeric purities of sulcatol (*R*)-acetate being >98% ee (80% isolated yield).[56]

An acid-catalyzed double Michael addition of water to the bridged bisdioxine moiety in a larger macrocyclic framework was facilitated by microwave irradiation (Scheme 23).[57] While conventional reaction conditions



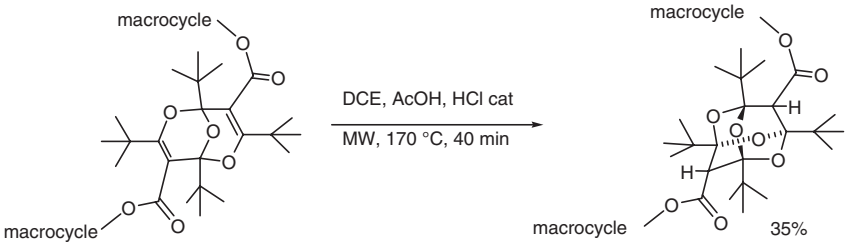
Scheme 21. Ring-closing metathesis using Grubbs II catalyst.



Scheme 22. Mitsunobu reactions.

failed to provide any of the desired functionalized 2,4,6,8-tetraoxaadamantane product, microwave heating of the hydrophobic macrocyclic bisdioxine in a 1:1 mixture of 1,2-dichloroethane and acetic acid containing excess of concentrated hydrochloric acid at 170°C for 40 min provided a 35% isolated yield of the desired oxaadamantane compound.

Another area of interest to us in microwave chemistry in super-heated water.[58] Water around its critical point (374°C, 221 bar) possesses properties very different from those of ambient liquid water and is attracting increased attention as a medium for organic chemistry. The so-called near-critical (also termed subcritical) region of water at temperatures between 200°C and 300°C (NCW) is of greater importance to organic synthesis. High-temperature near-critical water (NCW) under autogenic pressure provides a more favorable reaction medium for organic synthesis than under supercritical conditions (>374°C). At 250°C, water exhibits a density and polarity similar to those of acetonitrile at room temperature. The dielectric constant of water (ε′) drops rapidly with temperature and the ionic product (dissociation constant) of water is increased by three orders of magnitude on going from



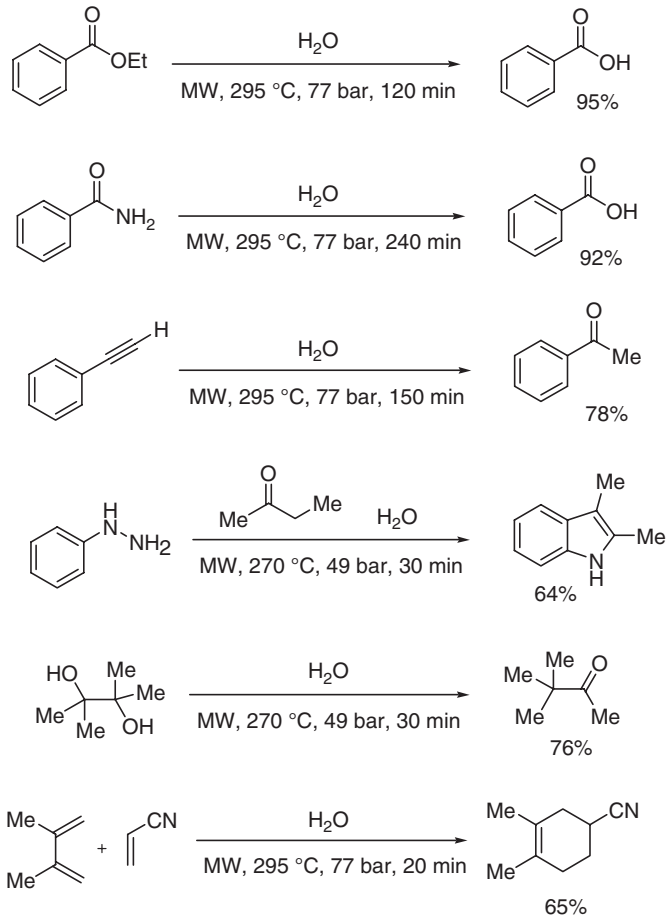
Scheme 23. Formation of 2,4,6,8-tetraoxaadamantanes via double Michael addition.

room temperature to 250°C. NCW can therefore act as an acid, base, or acid-base bicatalyst without the need for costly and cumbersome neutralization and catalyst regeneration. In this context we have investigated microwave-assisted organic synthesis in near-critical water (NCW) in the 270–300°C temperature range in a dedicated multimode microwave reactor utilizing heavy-walled quartz reaction vessels.[58] Several different known transformations like the hydrolysis of esters or amides, the hydration of alkynes, Diels–Alder cycloadditions, pinacol rearrangements and the Fischer indole synthesis (Scheme 24) were successfully performed in microwave-generated NCW without the addition of an acid or basic catalyst.[58]

7. Solid-Phase Organic Synthesis

Solid-phase organic synthesis (SPOS) exhibits several advantages compared with classical protocols in solution. In order to accelerate reactions and to drive them to completion a large excess of reagents can be used, as these can easily be removed by filtration and subsequent washing of the solid support. In addition, SPOS can easily be automated using appropriate robotics, and applied to "split-and-mix" strategies useful for the synthesis of large combinatorial libraries. However, SPOS also exhibits several shortcomings, due to the inherent nature of the heterogeneous reaction conditions. Nonlinear kinetic behavior, slow reactions, solvation problems, and degradation of the polymer support, due to the long reaction times are some of the problems typically experienced in SPOS. A technique such as microwave-assisted synthesis which is able to address some of those issues is therefore of considerable interest, particularly for research laboratories involved in high-throughput synthesis.[11,12,15] As far as the polymer supports for microwave-assisted SPOS are concerned, the use of cross-linked macroporous or microporous polystyrene resins has been most prevalent. In contrast to the common belief that the use of polystyrene resins limits the reaction conditions to temperatures below 130°C, it has recently been amply demonstrated that these resins can withstand microwave irradiation for short periods of time even at temperatures above 200°C.

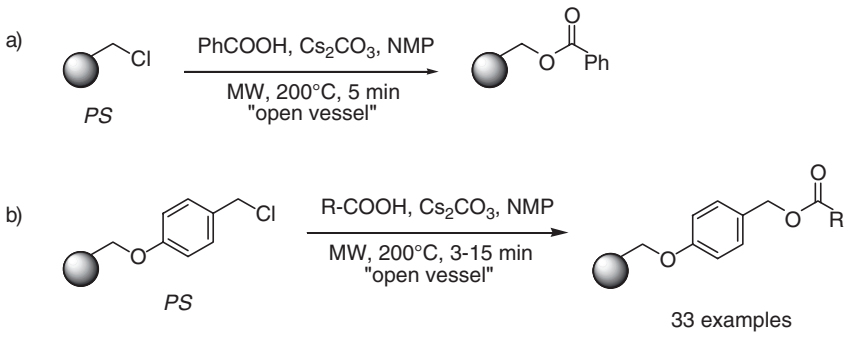
As a suitable early model reaction, we have investigated the coupling of various substituted carboxylic acids to polymer resins in 2001 (Scheme 25).[59] The resulting polymer bound esters served as useful building blocks in a variety of further solid-phase transformations. In a preliminary experiment, benzoic acid was attached to Merrifield resin under microwave conditions within 5 min (Scheme 25a). This functionalization was additionally used to determine the effect of microwave irradiation on the cleavage of substrates from polymer supports. The benzoic acid was quantitatively coupled within 5 min via its cesium salt utilizing standard glassware under atmospheric reflux conditions at 200°C. In a more extended study 34 substituted carboxylic acids were coupled to chlorinated Wang resin, employing an identical reaction protocol (Scheme 25b).[59] In a majority of cases the microwave-mediated



Scheme 24. Microwave synthesis in near-critical water.

conversion reached at least 85% after 3–15 min at 200°C. These microwave conditions represented a significant rate enhancement, in contrast to the conventional protocol, which took 24–48 h. The microwave protocol has additional benefits in comparison to the conventional method, as the amounts of acid and base equivalents can be reduced and potassium iodide as an additive can be eliminated from the reaction protocol. While no attempt was made to optimize all 34 examples, a number of substituted benzoic acids were selected to compare their coupling behavior under microwave conditions with the thermally heated protocol. High loadings of the resin-bound esters could be obtained very rapidly; even sterically demanding acids were coupled successfully. Importantly, in all the examples given, the loadings accomplished after 15 min of microwave irradiation were actually higher than that achieved using the thermally heated protocols.[59] In a related study we have examined the effect of microwave irradiation on carbodiimide-mediated esterifications on solid support, employing benzoic acid.[60]

In a dedicated combinatorial approach, we have reported the rapid parallel synthesis of polymer-bound enones.[37] This approach involved a two-step protocol utilizing initial high-speed acetoacetylation of Wang resin with a selection of common β-ketoesters and subsequent microwave-mediated Knoevenagel condensations with a set of 13 different aldehydes. These transesterifications are believed to proceed by the initial formation of a highly reactive α-oxoketene intermediate, with the elimination of the alcohol component of the acetoacetic ester being the limiting factor. Subsequent trapping of the ketene intermediate affords the transacetoacetylated products. For better handling of the polymer support, the reactions can be carried out under atmospheric pressure in open PFA vessels, using 1,2-dichlorobenzene as the solvent. Acetoacetylations were performed successfully within 1–10 min under these microwave conditions at 170°C. Furthermore, the



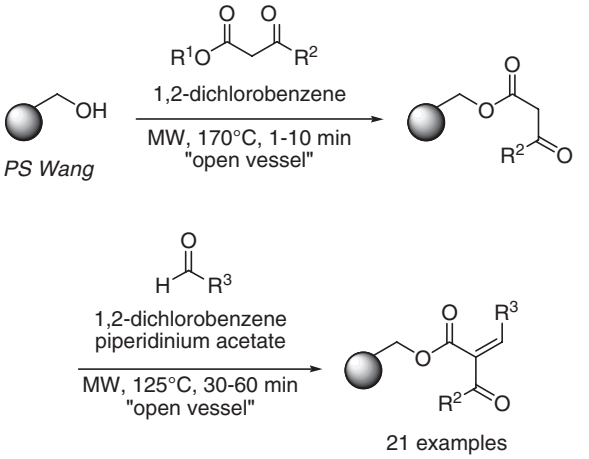
Scheme 25. Resin functionalization with carboxylic acids using Merrifield resin (a) and chlorinated Wang resin (b) as the polymer support.

acetoacetylated products can be obtained in a parallel fashion in a single 10 min run employing a multi-vessel rotor system. It is worth mentioning that these transesterifications need to be carried out under open vessel conditions, so that the alcohol by-product can be removed from the reaction mixture.[37]

To ensure complete conversion in the subsequent Knoevenagel step for all examples of a 21-member library, irradiation times of 30–60 min were used, employing a multi-vessel rotor system for parallel microwave-assisted synthesis. These examples of Knoevenagel condensations illustrated that reaction times could be reduced from 1–2 days to 30–60 min employing parallel microwave-promoted synthesis in open vessels, without effecting the purity of the resin-bound products.[37]

Subsequent reaction of the resin bound enones with thioureas under conventional conditions resulted in the formation of combinatorial libraries of 2-amino-1,3-thiazines.[61,62]

Surprisingly, although solid phase synthesis was originally introduced in the peptide field (solid-phase peptide synthesis, SPPS), there are only a few reports on the use of microwave irradiation for the preparation of peptides and related species on solid phase. While many of these studies have discussed the beneficial effects of microwave irradiation for solid-phase peptide synthesis in a qualitative way, not all of the reported experiments were conducted in dedicated microwave reactors that allow an adequate temperature control of the reaction mixture. We have recently conducted the preparation of nonapeptide WDTVRISFK by microwave-assisted solid-phase synthesis using an Fmoc/Boc orthogonal protection strategy. The protocol was based on the use of cycles of pulsed microwave irradiation with intermittent cooling of the reaction mixture to sub-ambient temperature for both the coupling



Scheme 26. Parallel synthesis of polymer-bound enones.

and Fmoc deprotection step. The desired nonapeptide was obtained in high yields and purities employing MicroKan technology in conjunction with a standard single-mode microwave reactor, monitoring the reaction temperature with a fiber-optic probe.[63]

Apart from the more synthetically oriented projects described in this contribution, our research group also has an interest in studying more fundamental aspects of microwave chemistry such as "microwave effects",[5,23,37,55,59] or issues relating to scale-up under batch[26,43] and continuous flow[27,64] conditions which are not discussed here.

8. Conclusion

The diverse examples of microwave chemistries provided in this contribution – although representing only a small fraction of the published literature – should make it obvious that many types of chemical transformations can be carried out successfully under microwave conditions. The simple convenience of using microwave technology will make this non-classical heating method a standard tool in the laboratory within a few years. In the past, microwaves were often used only when all other options to perform a particular reaction have failed, or when exceedingly long reaction times or high temperatures were required to complete a reaction. This practice is now slowly changing and due to the growing availability of microwave reactors in many laboratories, also routine synthetic transformations are now being carried out by microwave heating. Microwave chemistry has opened up several new avenues in organic synthesis. Many reactions that previously were not possible, or resulted in a low yield, can now often be performed quickly, safely and efficiently in a few minutes. In summary, MAOS has changed the world of organic chemistry and it would be wise to embrace this new technology or be left lagging behind with conventional heating methodologies.

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DEVELOPMENT OF NEW SUPPORTED REAGENTS FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE MOLECULES

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Abstract: As a consequence of the changes associated with the need for preparing arrays of compound for hit discovery in pharmaceutical and fine chemical research laboratories, the research of new technologies that allow for the automation of synthetic processes has been developed. Since the pioneering work by Merrifield, polymeric supports have played a key role in this field. Polymer assisted solution-phase synthesis, which utilizes immobilized reagents and catalysts has more recently entered in the organic chemistry laboratories. It has various advantages over conventional solution-phase chemistry, such as the ease of separation of the supported species from a reaction mixture by filtration and washing and the opportunity to use an excess of the reagent to force the reaction to completion. On the other hand, as the reactions are performed in solution, the analytical techniques are the same of conventional synthesis. Various strategies for employing functionalized polymers stoichiometrically have been developed and this chapter reports some selected examples of use of reagents covalently attached to the polymeric backbone. This selection is intended to attract synthetic chemists to use this technique highlighting the use of the methodology to solve synthetic problems and pointing out which reagents and scavengers may have potential applications in sustainable and more secure chemical processes.

Keywords: combinatorial chemistry, polymer-supported reagents, scavengers, catch and release, library, organic synthesis

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1. Introduction

Through society, we observe a rapid increase in recycling initiatives that affects many aspects of day-to-day living. From office to house and school, people are forced by law and social habits to separate used objects for a potential recycling. We often think to carry out our task of "good citizens" just separating the glass from the paper in the dustbin. Demanding to others the effective recycling is not the optimal process for a true contribution to "sustainability". On the other hand, carrying out material recycling by ourselves is impossible in everyday life. This is not true for scientists, and in particular organic chemists, regarding their research activities.

Although solvents and bulk chemicals are generally separated and (if possible) recycled at the end of a process, less attention is paid to the fate of reagents, by-products and catalyst. Organic chemistry is traditionally a science in solution as reagents, catalysts and products are used and produced in a solvent that is responsible of the homogenous phase of the reaction. To separate a product and to recycle a chemical entity, it must be spitted from the phase where the other reaction components are. This goal is reached fractioning by crystallization, distillation, or by chromatography. From 1963 and the article *Solid Phase Peptide Synthesis I. The Synthesis of a Tetrapeptide* by Merrifield on solid phase peptide methodology,[1] it is possible to follow an alternative strategy. One of the players of the reaction can be linked to an insoluble support (called also resin), the reaction occurs on the resin surface and the product can be easily separated from the rest of the reaction and the resin, if required, recycled. As the most common supports employed are organic macromolecules, this technique is called "Polymer Assisted Organic Synthesis" and consists of three different approaches:

- Solid phase synthesis: the product is linked to an insoluble support and the reagents are added in solution. At the end of the process the product is cleaved from the resin. This is the Merrifield approach, useful for synthesis of arrays of peptides or organic molecules but unsuitable for recycling.
- Scavengers: an excess of one of the reagents, employed to drive the reaction to completion. At the end of the reaction, the excess can be scavenged by an insoluble reactive that may allow the recovery.
- Supported reagents and catalysts: the reagent (or the catalyst) is liked to an insoluble support in order to simplify the separation from the products and, eventually, to recycle it.

All these approaches have advantages and disadvantages and can be selected depending on the synthetic task. Whereas solid phase synthesis has been employed at the beginning for peptide synthesis and combinatorial synthesis

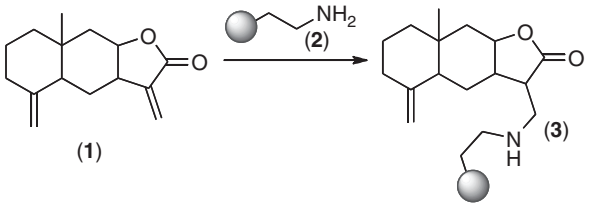
of large libraries of organic molecules, nowadays the use of supported reagents, catalysts and scavengers is particularly useful for the preparation of focused libraries of biologically active compounds. Medicinal chemists mainly employ the process at the stage of "hit discovery" and in structure activity relationship studies. However the principle may found application in development of sustainable processes, as the elimination of complex work-up and purification procedures implies a reduction in waste solvents and the reagent in excess can be recovered. Moreover, the supported regents (and the associated by-products) are less volatile and then less toxic than not-supported ones.

This chapter is an overview on the use of supported reagents and scavengers in organic synthesis with the aim of attracting synthetic chemists to use this technique. It is not as a comprehensive review, but highlights the use of the methodology to solve synthetic problems and points out which reagents and scavengers may have a potential application in sustainable and more secure chemical processes. The author hopes that this method of presentation will prove a valuable addition to the exhaustive review articles that preceded it.[2]

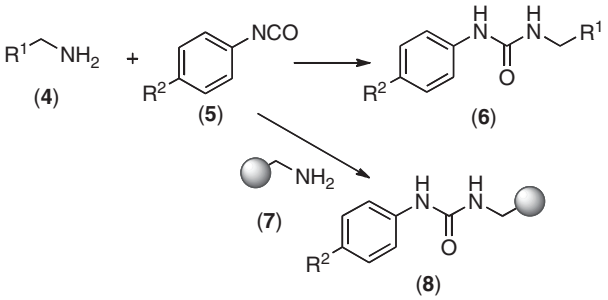
2. Scavengers

2.1. HISTORICAL BACKGROUND

The use of a polystyrene base primary ammine for the selective binding and removal of α-methylene-γ-butyrolactone allergens from a complex mixture of organics derived from a natural matrix is considered the first example of the use of polymer-supported scavenger.[3] The allergenic activity was hypothesized to be related to the presence of Michael acceptor molecules (**1** in Scheme 1). Thus the mixture was submitted to chromatographic analysis and allergenic test and afterwards it was treated with resin **2**. The further allergenic test was negative and the comparison of the chromatograms before and after the treatment with the resin **2** allows the identification of the compound responsible for the activity.



Scheme 1. The first example of the use of polymer supported scavenger.



Scheme 2. Acylation of amines followed by removing of the unreacted acylating agent with solid phase scavenger.

Sixteen years later a preparative application of this methodology appeared in the literature. At the dawning of the combinatorial chemistry age, Kaldor reported the alkylation and acylation of amines employing solid phase scavenging agents.[4] In this approach, the acylated amines **6** are formed in solution phase reaction and unreacted excess of the acylating agent is selectively removed from solution in a subsequent "quenching" step involving covalent bond formation to a solid supported electrophile **7** (Scheme 2).

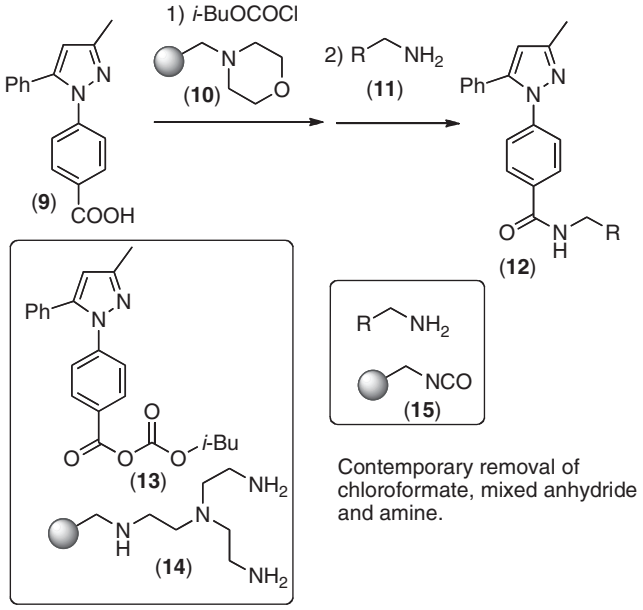
Filtration and evaporation provided products of high purity in an operationally simple manner, which could be applied to parallel processing and automation.

2.2. SEQUESTRATION OF REACTANTS AND BY-PRODUCTS

In relation to the formation of amides, the product is present together with the amine and the acylating reagent in the final solution of crude reaction mixture. One of the advantages of the use of solid supported scavengers is the possibility of contemporary use resins with functional groups that reacts together. In the synthesis of a library of differently substituted pyrazoles **12** (Scheme 3),[5] the carboxylic acid **9** was converted to a mixed anhydride **13** by treatment with isobutyl chloroformate in the presence of the supported tertiary amine **10**.

In a further step, the solution containing the mixed anhydride **13** was treated with a primary amine to give the corresponding amide **12**, which was obtained in mixture with unreacted **11** and **13**. Treatment with polystyrene-divinylbenzene-supported derivatives of tris(2-aminoethyl)amine **14** and methylisocyanate **15** removed this reactant and traces of the carboxylic acid **9** to give **12** also of excellent purity by ^{1}H-NMR and HPLC (Scheme 3).

A very useful synthetic transformation is the conversion of alcohol into the corresponding bromides using bromine and triphenylphosphine.[6]

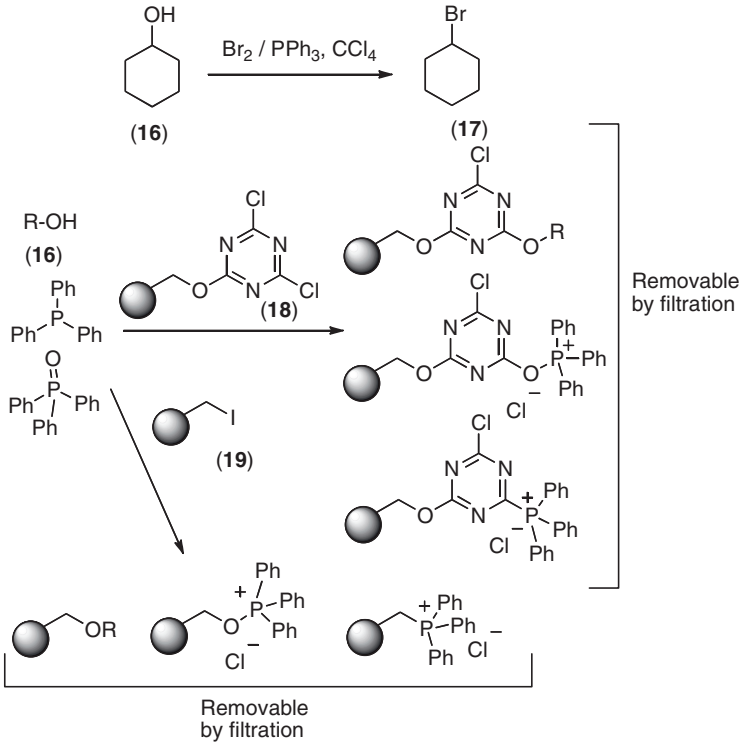


Scheme 3. Synthesis of a library of pyrazoles using polimer supported scavengers **14** and **15**.

Common by products in this reaction are unreacted alcohol and triphenylphosphine together with triphenylphosphine oxide. A strong nucleophilic scavenger can be used in this case to remove all the contaminants of the reaction. Two examples have been described using either a supported version of cyanuric chloride[7] (**18**) and the simple benzyl iodide (**19**) derived from the Merrifield resin,[8] as reported in Scheme 4.

This example shows clearly how the imagination of chemists can try to solve the problem of simplify the purification of a reaction using a strong electrophile linked to the resin. This can apply to any kind of reaction. If the by products, impurities or unwanted reaction products are present in the reaction mixture (and they have a reactivity different from the desired product) it is possible to remove them by scavenging with a reactive resin. The resin may be commercially available or eventually prepared for the goal. An extremely simple example is the use of ion exchange resin to remove polar by-products (or products) at the end of a reaction.

One of the first examples of this approach was the use of acid ion exchange resins to remove the urea derivatives obtained in coupling reactions carried out with EDC (**20**). Coupling of a carboxylic acid with an amine can be carried out with EDC, DMAP in DMF. Working with an excess of all these reagents respect to the acid, all the by products **21** and **22** at the end of the process are basic. Treatment with a benzensulfonic acid resin (**23**)

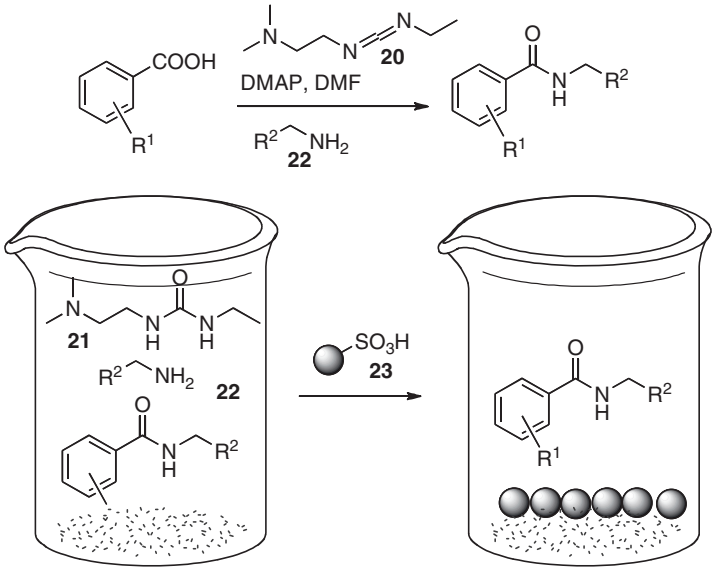


Scheme 4. Conversion of cyclohexanol into cyclohexyl bromide in the presence of solid phase scavengers.

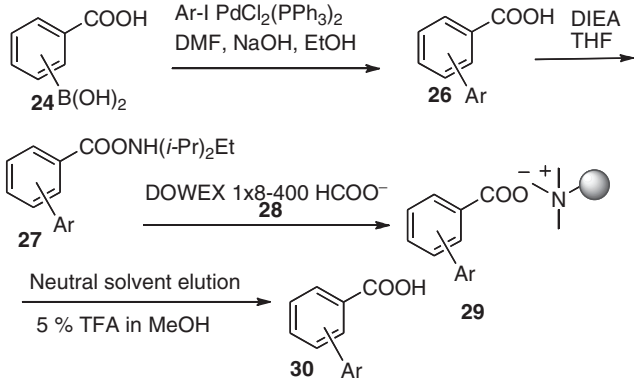
removes all the basic components of the mixtures and gives the amides in good yields and a good level of purity (Scheme 5).[9]

An analogous approach can be carried out to selectively remove a basic or acid product of a reaction. One of the first example of this strategy was applied to the preparation of a large array of bi-phenylic carboxylic acids (as **30** in Scheme 6) obtained by Suzuki–Miuara coupling of the boronic acid derived from benzoic acid and different aryl (and heteroaryl) iodides **26**. The products are carboxylic acids (as **24** in Scheme 6) that were blocked on a Dowex basic resin. The by-products and the catalysts were removed by simple filtration. After washing, the products **30** were removed by elution with a dichloromethane solution containing TFA.

An analogous approach can be done in the preparation of basic compounds, for example by reductive amination of aldehydes **31** with an array of secondary amines **32**. Independently form the reductive agent (generally supported cyanoborohydride) when the reaction is forced to complete disappearance of the aldehyde, the required tertiary amine **33** is obtained together with the excess of the secondary (**32**) employed in the reduction. In this case

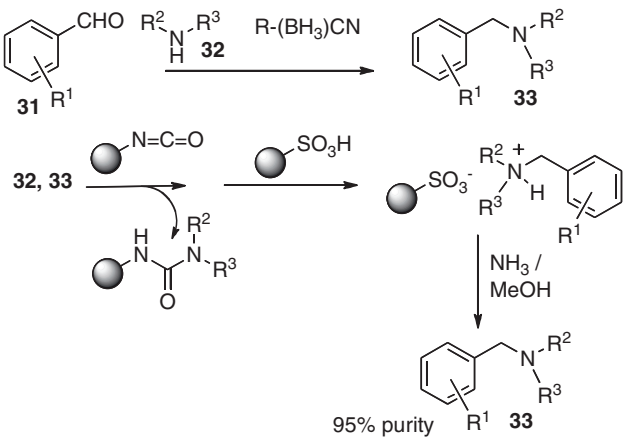


Scheme 5. Withdrawal of the basic byproducts of acylation reaction by benyenesulfonic acid resin.



Scheme 6. Isolation of the acidic products of a Suzuki coupling reaction using a Dowex basic resin.

it is necessary first to scavenge the secondary amine with an electrophilic resin (e.g. RSO_2Cl, RNCO or RCOCl) and eventually afterwards purify the product by selective extraction with an acid resin followed by filtration, washing and elution with a solution of ammonia in MeOH (Scheme 7).[10] This process provides the amine in good yields and with a high level of purity (generally higher then 95% by ^1H NMR and HPLC).

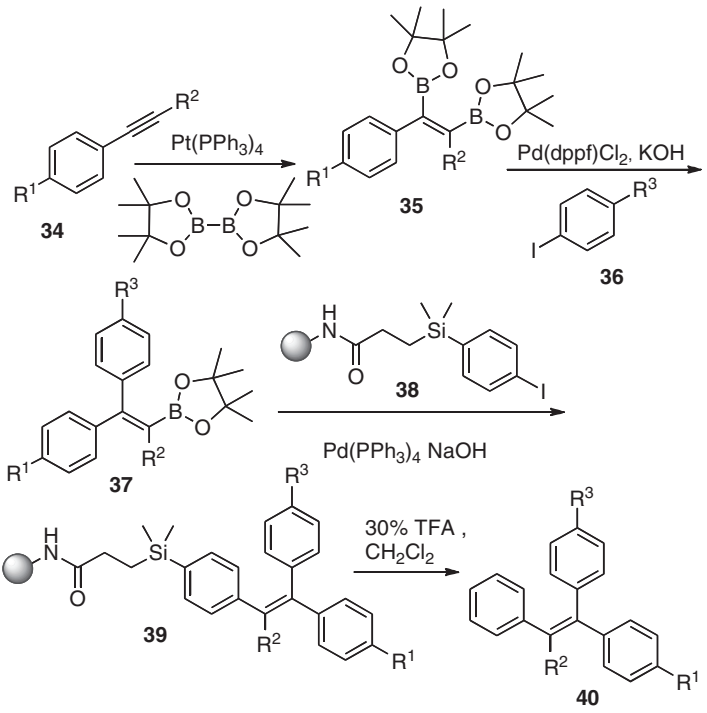


Scheme 7. Separation of the products of reductive amination using electrophilic and acidic resins.

2.3. CATCH AND RELEASE

The "catch and release" approach is the further extension of the last method. In this case the reaction product is captured by the reaction mixture onto a polymer via a covalent or an ionic bond. The polymer is filtered (or in any case separated from the reaction mixture) and washed several times to remove the by-products or excess of reagent. Further chemical transformations on the linked products are possible at this stage. However, this possibility must be limited as much as possible in order to avoid determining the amount of products on the resin.[11] Finally the product is removed from the resin. The first example of this approach has been applied to the preparation of a series of arrays containing 24 analogues of Tamoxifen. The 25-member library (**40** in Scheme 8) was synthesized using 5 alkynes, 5 aryl halides, and a polymer bound aryl iodide as reagents. The alkynes **34** were converted into bis(boryl)alkenes **35** in solution in the presence of a platinum-based catalyst. The crude intermediates **35** were submitted to Suzuki reactions with an excess of aryl halide to generate **37** as a mixture of two possible regioisomers. When all **35** were consumed, the resin **38** was introduced in the reaction mixture. Exclusively **37** participated in the second Suzuki reaction on solid support. Side products (such as deboration or products derived from Suzuki reactions on **35** with the aryl halides) remained in solution and were washed away during workup.[12] Finally the products were obtained by removal from the silylated resin by treatment with TFA in DCM.

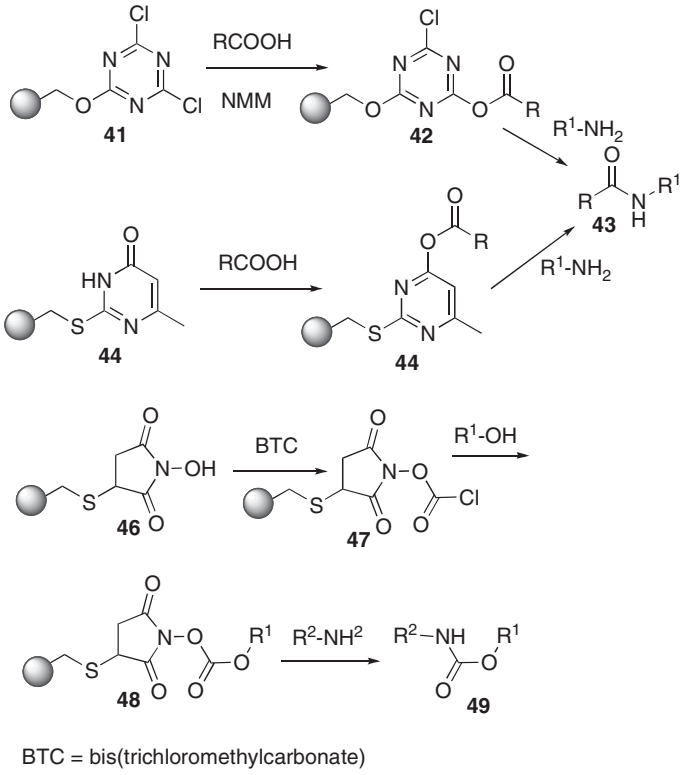
Catch and release can be used in simple formation of amides by activation of the carboxylic acid on resin. The following two examples report analogues



Scheme 8. Synthesis of a library of Tamoxifen analogs.

approach. The acid is linked to the resins (**41** or **44**) with the formation of an activated ester (**42** or **45**) that is sufficiently stable for being separated from the acid but that can be removed from the support by reaction with a strong nucleophile (the amine) giving the amide **43** in solution.[13] In all these cases the intermediate "catch" on the resin must be used in excess, alternatively the amine must be scavenged with an acid or other nucleophilic resins. In the two cases reported the resin could be recycled at the end of the process and reused in the process. Analogously it is possible to prepare urethanes through a supported intermediate chloroformate **47** that can undergo selective double nucleophilic substitution with two different reactive nucleophiles such as an alcohol and a primary amine to give urethane **49**. Even in this case the resin can be recycled at the end of the process.[14]

The catch and release approach can be successfully applied to the synthesis of heterocycles. An intermediate is elaborated in solution, then catch on a resin in a somehow activated form and finally cyclized and contemporary removed from the resin. As the cyclization is the last step, the reagent that induces this reaction is present in solution together with the products



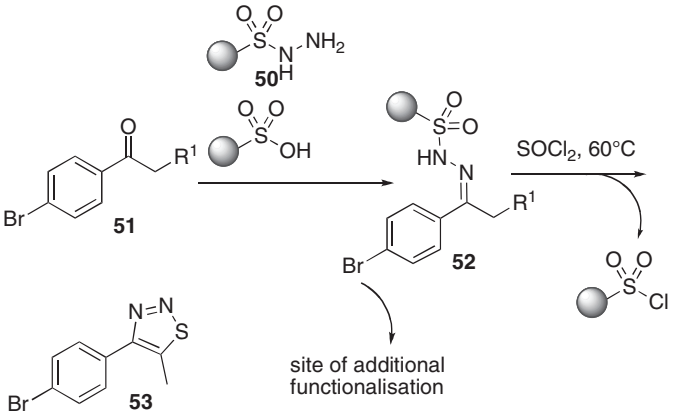
Scheme 9. Activation of carboxylic acids for acylation using supported reagents.

and must be removed. The solution of choice is to use a volatile reagent as described in the following selected examples.

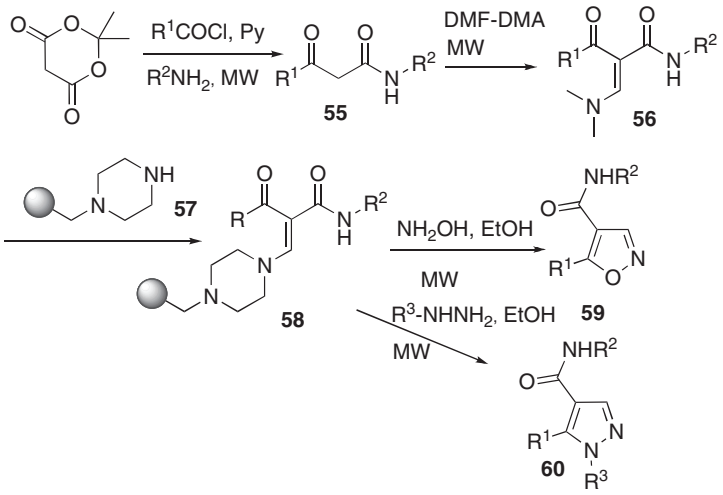
A sulfonyl hydrazine linked to the resin **50** is reacted with different p-bromophenyl ketones **51**. The reaction, catalyzed by a resin-supported sulfonic acid, gives the hydrazone **52** that is separated from the reaction mixture by filtration. The resin is then mixed with $SOCl_2$ neat and heated at 60°C (Scheme 10).[15]

Cyclisation occurs to give the thiadiazole **53** after evaporation of the excess of $SOCl_2$. It is worth to note that the aryl group in supported **52** contains bromine that can be used for an additional functionalisation on the resin.

A similar approach was applied for the synthesis of isoxazoles and pyrazoles. Following different procedures in solution a series of β-ketoesters (or amides) have been prepared in a parallel fashion. In the first strategy a β-ketoamide is obtained by parallel ring opening of the Meldrum acid under microwave activation. Amide **55** is reacted with DMF-DMA under microwave activation to give the enamino derivatives **56**.[16]



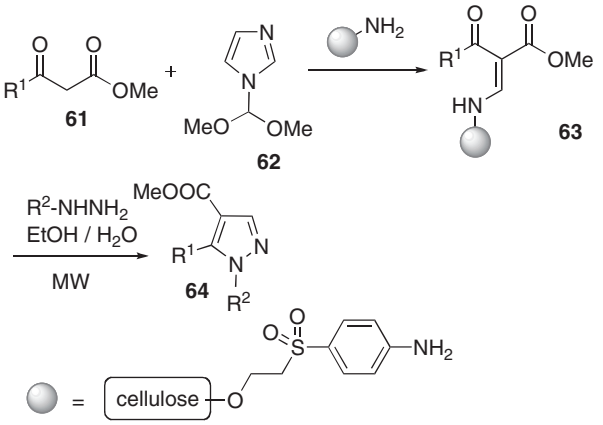
Scheme 10. Synthesis of thiadiayole 53 using supported sulfonyl hidrazine.



Scheme 11. Synthesis of isoxazoles and pyrazoles using supported piperazine.

At this stage the product is obtained as a mixture with unreacted β-ketoamide **55** and other minor by-products coming from the previous reactions. The product is than catch by a secondary amine linked to a resin **57** froming the enamine **58**. This product is then separated, cleaned and finally cyclized with hydroxylamine in EtOH to produce the isoxazole **59** or with substituted hydrazine to give pyrazolamides **60** that resulted pure after filtration of the resin and evaporation of the solvent (Scheme 11).

A more simplified approach was used to produce a library of pyrazoles. In this case the β-ketoester is directly reacted with a supported version of



Scheme 12. Synthesis of pyrazoles using the Brederick reagent.

the Brederick reagent prepared from imidazole **62** and a primary amine supported on cellulose beads (Scheme 12).[17]

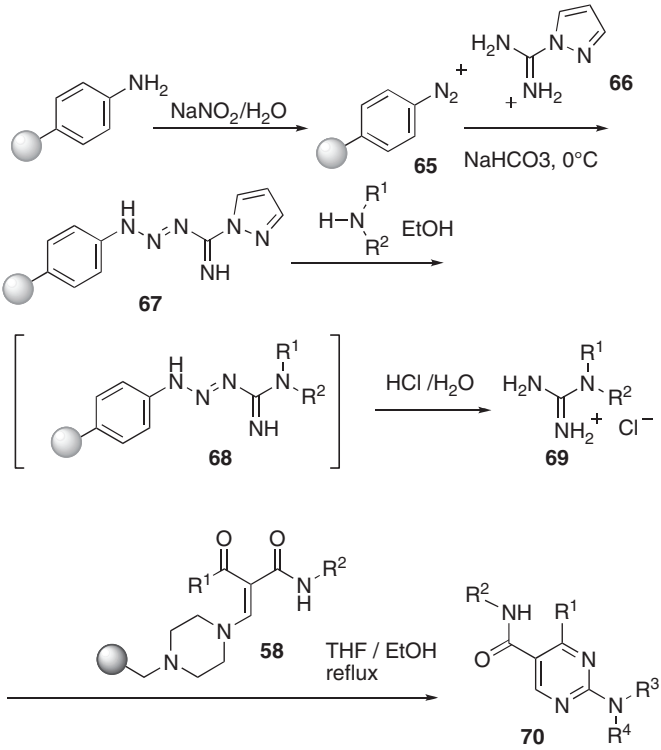
The unsaturated enamine **63** was isolated on the resin and finally cyclized using a series of monosubstitutued hydrazines in a mixture EtOH and water under microwave irradiation. In this case the use of cellulose as the support is justified by the cyclisation that occurred exclusively in a solvent that is not well compatible with PS-type resins.

The same approach has been also successfully applied to the synthesis of amino pyrimidines **70**,[18] one of the more important heterocycles in medicinal chemistry. A very interesting application of this strategy is that the guanidines **69** used as intermediates for this cyclisation can be obtained by a catch and release approach. Supported aniline is transformed in two steps into a triazene-guanylating agent using the imidazolyl derivative **66** (Scheme 13). This compound is reacted with an array of primary amines and the supported intermediate **68**, after separation from the crude reaction mixture, is released as a monosubstituted guanidine hydrochlorides by treatment with aqueous HCl.[19] This compound is then ready for cyclisation with the other array of supported enamines **58** for the construction of a library of 2-aminopyrimidines **70**.

3. Supported Reagents

3.1. HISTORICAL BACKGROUND

A detailed story of supported reagents has been described by Sherrington in 2001.[9] From this review I would like just to point out that the first examples of application of ionic exchange resin as acid or basic catalyst or additive



Scheme 13. Synthesis of amino pyrimidines starting from supported aniline.

(reagents) in organic chemistry are dated to late 1940s and early 1950s. At that time several industrial chemists starts to use this approach to simplify the procedure of isolation and purification of industrially relevant compounds. Hundreds of patents claimed the use of supported (heterogeneous) reagent for alkylation, dehydration, epoxidation, esterification, and etherification, hydrolysis, cyclization and other applications. Remarkably, the first review of ion-exchange resin catalysis was published in 1957,[20] 6 years before Merrifield discovery of solid phase synthesis. However, the born of this new branch of synthetic chemistry is dated 1971 when Castelles,[21] and Heitz[22] independently developed polymer-supported triphenylphosphine, for the simple transformation of an alcohol into the corresponding alkyl chloride. Triphenylphosphine is a standard reagent in organic synthesis, although the by-product triphenylphosphine oxide often complicates purification of the reaction mixture. The use of polymer-supported triphenylphosphine (PS-PPh_2) leads much simpler workups and product isolations. (PS-PPh_2)-CCl4 or (PS-PPh_2)-CBr_4 reagent systems have many applications in organic

synthesis. This reagent can be used, for example, to convert alcohols into chlorides,[23] primary carboxamides and oximes into nitriles, amides into imidoyl halides[24] and acids into acid chlorides.[25] An attractive feature of this conversion is that no HCl is evolved, so the conditions are essentially neutral. This technique can be used to generate esters by treating the carboxylic acid with poly-TPP/CCl_4 in the presence of an alcohol.[26]

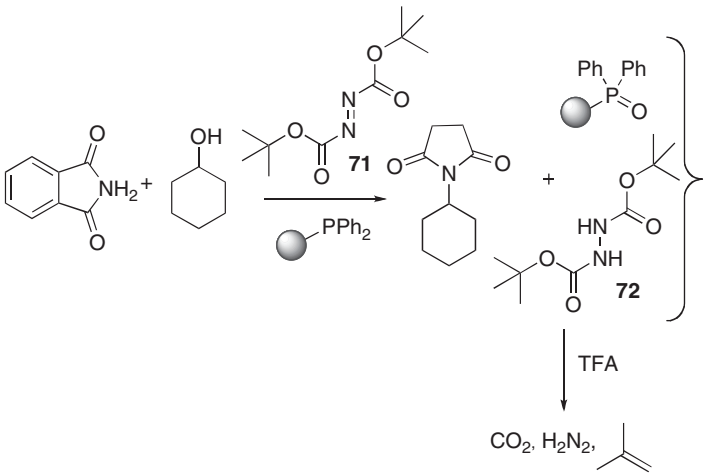
One of the most common and useful transformations employing triphenylphosphine is the Wittig reaction. A number of groups have explored this reaction using (PS-PPh_2). A somehow problem related to this transformation is that different conditions are required to make the phosphonium salts from different alkylating agents, and different bases equally required for different resins. One report describes the use of a phase transfer catalyst in the presence of the polymer-supported phosphonium salt and carbonyl compound. However, irrespective of the method of preparation, the polymer-supported Wittig reagents react with a variety of aldehdyes to give good yields of olefins.[27] It should be noted that (PS-PPh_2) is not the only supported species that can be used to prepare olefins. Phosphonates with electron-withdrawing groups can be supported on ion-exchange resin and the supported reagent reacts with aldehydes and ketones in excellent yields.[28]

Another very popular application of supported triphenylphosphine is the Mitsunobu reaction. As seen before, a possible alternative to scavengers, is the use of (PS-PPh_2). However the use of diazacarboxylate in the reaction still remains as a problem. A possible alternative is the use of *tert*-butyldiazacarboxylate **71** together with (PS-PPh_2). The supported phosphinoxide is removed at the end of the reaction and the unreacted diazacarboxylate and the urea derived **72** were treated with acid to generate the free carboxylic acids that decomposed in components simple to remove (Scheme 14).[29]

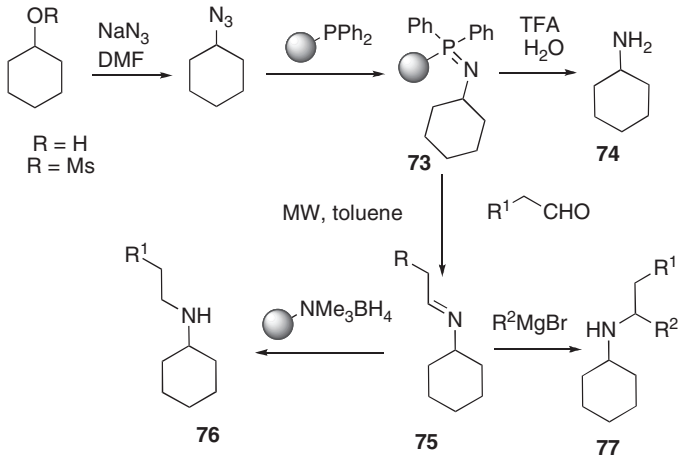
A part from the use as ligand to immobilize different transition metal catalyst, another popular application of PS-PPh_2 has been the development of the Staudinger reduction of azides and the generation of the intermediate aza-Wittig reagent. A simple alcohol can be transformed into an azide and this one can be reacted with PS-PPh_2. The intermediate phosphinimine **73** can be separated from the reaction mixture and further transformed in different conditions (Scheme 15).[30]

A simple aqueous acid hydrolysis liberates the free primary amine **74** derived from the alcohol. Alternatively the supported **73** can be reacted with an aldehyde (under microwave activation) to liberate the corresponding immine **75** in solution that can be reduced with a supported reducing agent to the secondary amine **76**, reacted with a Grignard reagent to give **77** or eventually employed in the synthesis of different heterocycles by cycloaddition.

Oxidation and reduction are reactions where supported reagents have been largely employed starting form the early 1970s. This is understandable as



Scheme 14. Application of supported phosphine ireagent in the synthesis of a phtalimide deivative.



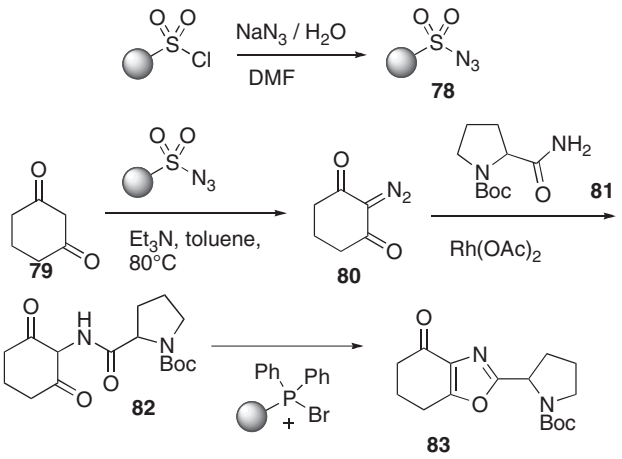
Scheme 15. Synthesis of amines using supported diphenylphosphine.

red-ox reagents are generally ionic and can be easily linked to ionic (organic or inorganic) supports to simplify the removal at the end of the process. There are exhaustive reviews on the argument where it is possible to find the best choice of supported reagent for this kind of transformation.[2e,f,g]

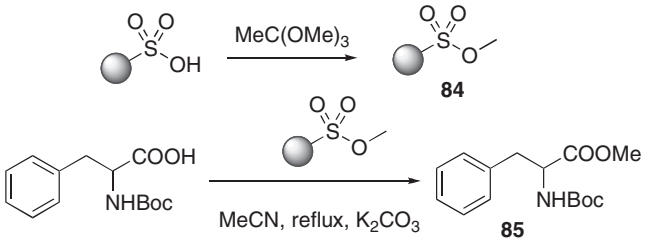
Supported reagents can be used also in reaction where dangerous reactives are required. The reaction between an arylsulfonyl azide and a substrate containing an active methylene group is a useful method for the preparation of diazo carbonyl compounds. Unfortunately, sulfonyl azides are potentially

hazardous due to their propensity for explosive decomposition under various reaction conditions. Polymer-supported benzenesulfonyl azide provides a diazo transfer reagent with improved process safety characteristics and thus offers an excellent reactant for laboratory use. The polymer-supported benzenesulfonyl azide resin **78** is prepared in one step from commercially available polymer-supported benzenesulfonyl chloride by treatment with sodium azide at room temperature.[31] This product has been employed for the preparation of the diazo compound **80** (Scheme 16), that reacted with a protected amino acid amide **81** to give the amido ketone **82**. This compound was then cyclized in the presence of a PS-PPh_2-bromide to give a bicyclic isoxazole **83**, a cyclic non-planar original platform ideal for combinatorial chemistry.[32]

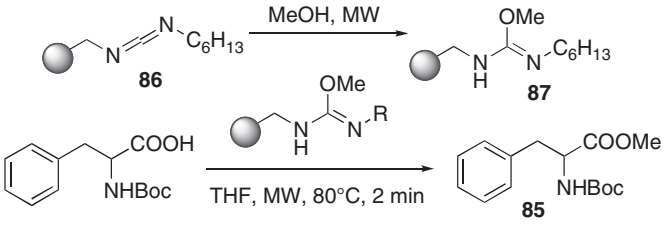
Another potentially dangerous procedure is the methylation of carboxylic acids, phenols, alcohols and other nucleophilic compounds. This approach generally employs volatile reagents that are very toxic due their ability to methylate DNA. The low boiling point of these reagents let them to be easily inhalate during the reaction work up with potential danger for the workers. Different supported alternatives are available for methylation of acid organic compounds. Polymer-supported methyl sulfonate **84** was prepared by the reaction of polymer-supported sulfonic acid, with trimethyl orthoacetate without a solvent at room temperature. Then, various aromatic and aliphatic carboxylic acids were treated with this reagent in the presence of K_2CO_3 to provide the corresponding methyl esters (**85** in Scheme 17) in high yields.[33] Simple filtration of the reaction mixture and removal of the solvent gave methyl esters with high purity (>98%) (Scheme 16). *O*-Methylisourea has been known as a selective alkylating agent for 50 years.



Scheme 16. Application of supported benzenesulfonyl azide in the synthesis of isoxazole 83.



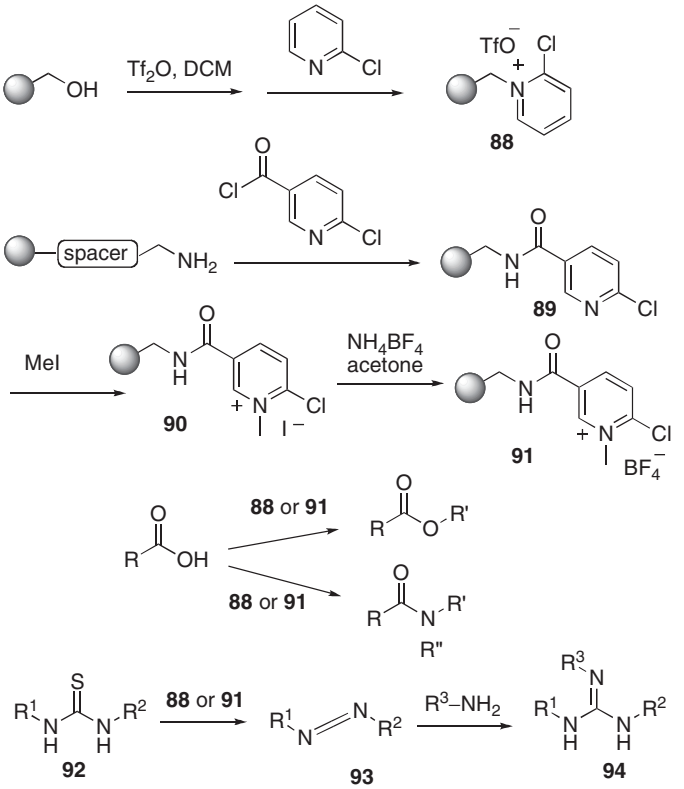
Scheme 17. Methylation with supported methylsulfonate reagent.



Scheme 18. Applicaton of supported O_methylisourea for methylation of protected phenylalanine.

The mild reactivity of *O*-methylisourea allows for selective ester formation of heavily functionalized substrates and has been used in the final stages of complex natural products synthesis. A supported version of *O*-methylisourea **87** was prepared through the reaction of commercially available carbodiimide resin **86** in dry methanol in a focused microwave (Scheme 18). Carboxylic acids can be selectively methylated using this reagent at 60°C in DCM in the presence of alcohol, phenol, and amide functional groups. Apart from resin filtration and solvent evaporation, no further purification was required.[34]

An analogous approach for methylation (and esterification) of carboxylic acid has been described with a supported version of the Mukaiyama reagent. Two different versions have been described (**88** or **91**, Scheme 19), but all of them are able to carry out almost all range of reaction generally done by the classical reagent in solution. In the most direct approach a Wang resin was activated in situ with trifluoroacetic anhydride, forming a triflate ester, which was immediately substituted by 2-chloropyridine.[35] The so obtained product was in the form of a 2-chloropyridinium triflate (**88**), avoiding the presence of iodine in the final product. It is well documented that the iodide anion can substitute the chlorine in the pyridinium salts and that the resulting 2-iodopyridinium salts do not activate carboxylic acids. A more complex approach starts form a resin carrying a NH_2 on the surface (linked through a spacer). This group was reacted with 6-chloro nicotinoyl chloride and the

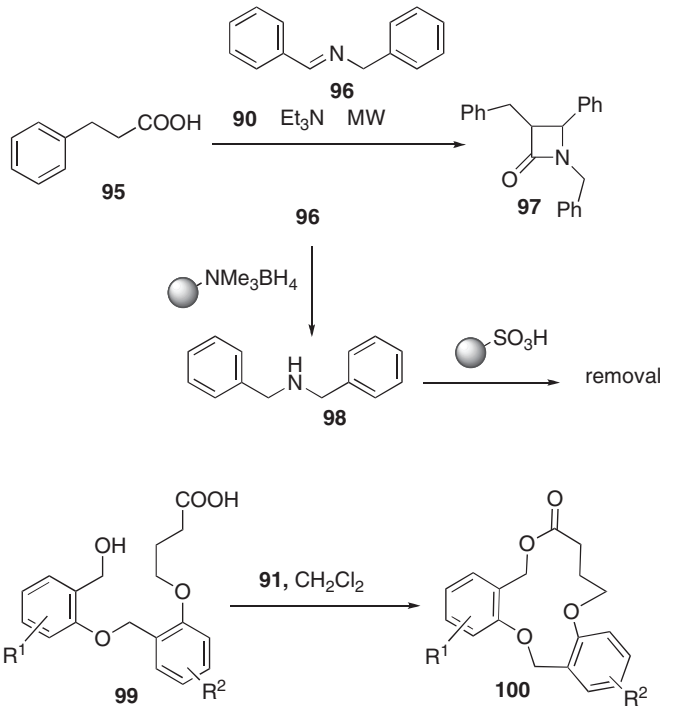


Scheme 19. Application of the supported Mukaiyama reagent (**89** and **91**) for methylation.

so formed amide **89** was methylated at the nitrogen with MeI. The resulting product **90** was used in this form (as iodide) or after iodine – BF_4 exchange **91** to avoid the already cited problems due to the presence of iodine.[36]

Both of the reagents have been successfully employed for the transformation of carboxylic acids into esters or amides or in the transformation of thioureas **92** into guanidines **94** through the formation of intermediate carbodiimides **93**.[37]

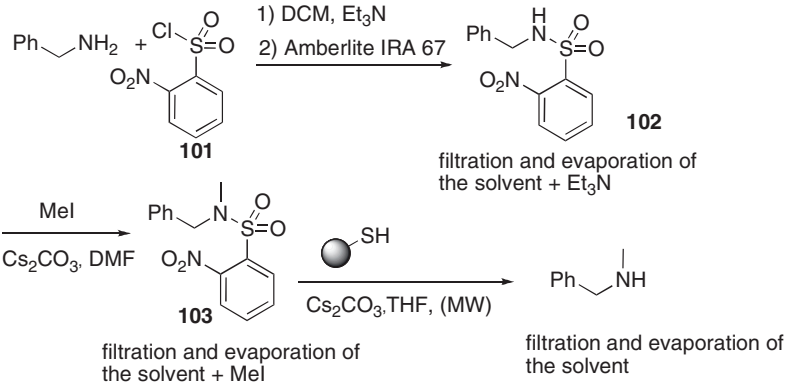
On the other hand, reagent **90** was also employed for a parallel version of the Staudinger cycloaddition of ketenes and imines and for macrolactonisation. Different carboxylic acids (as **95** in Scheme 20) have been activated with **90** and reacted at 60° with imines under microwave irradiation to give the corresponding β-lactams (**97**). This reaction required the use of at least 2 equivalents of the imine **96** to go to completion. The excess of imine was then removed by reduction to amine **98** in the crude reaction mixture using supported borohydride and further scavenging with an acid ion exchange resin.[38] On the other hand, a series of hydroxyacids as **99** in Scheme 20 were



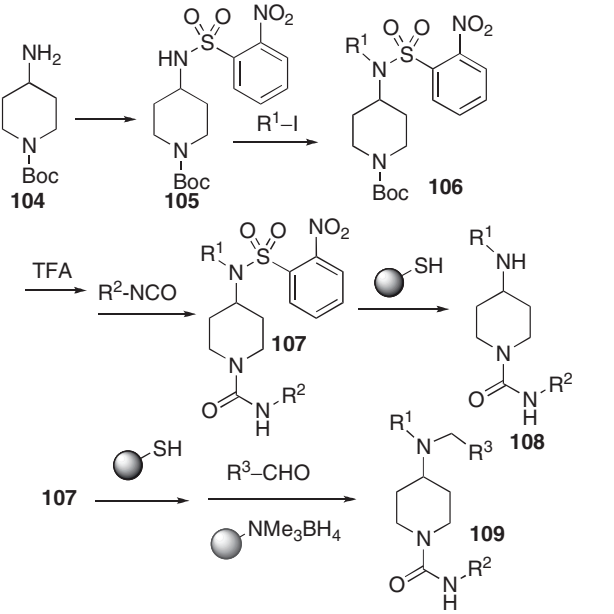
Scheme 20. Synthesis of biologically active compounds using supported reagents.

submitted to macrocyclisation using reagent **91** for the preparation of an array of antitumor compound radicicol analogues.[39]

The versatility of the use of different supported regents and scavenger can be proved by the following series of reaction that describes different approaches to the synthesis of polysusbtituted amines based on the use of an *o*-nitrobenzensulfonyl group. A primary amine can be transformed into the corresponding o-nitrobezensulfonamide **102** with the simple reaction in solution of the sulfonylchloride and the amine in the presence of Et_3N (Scheme 21). Unfortunately, the crude product resulted contaminated with triethylammonium hydrochloride that was removed by alkaline exchange adding a resin (Amberlite IRA-67 free base) to the reaction mixture. The triethyammonium hydrochloride was neutralized, the free Et_3N reintegrated in solution and removed, after filtration, by evaporation under vacuum. The so formed sulfonamide can be easyl alkylated with an excess of an alkyl iodide in solution. The products so obtained **102** can be deprotected to the secondary amine in the presence of a supported aryl thiol. This reagent carries out the nucleophilic substitution on the *o*-nitrobenzensulfonyl moiety generating the free secondary amine in solution.[40]



Scheme 21. Synthesis of benzyl_methylamine using supported scavenger.

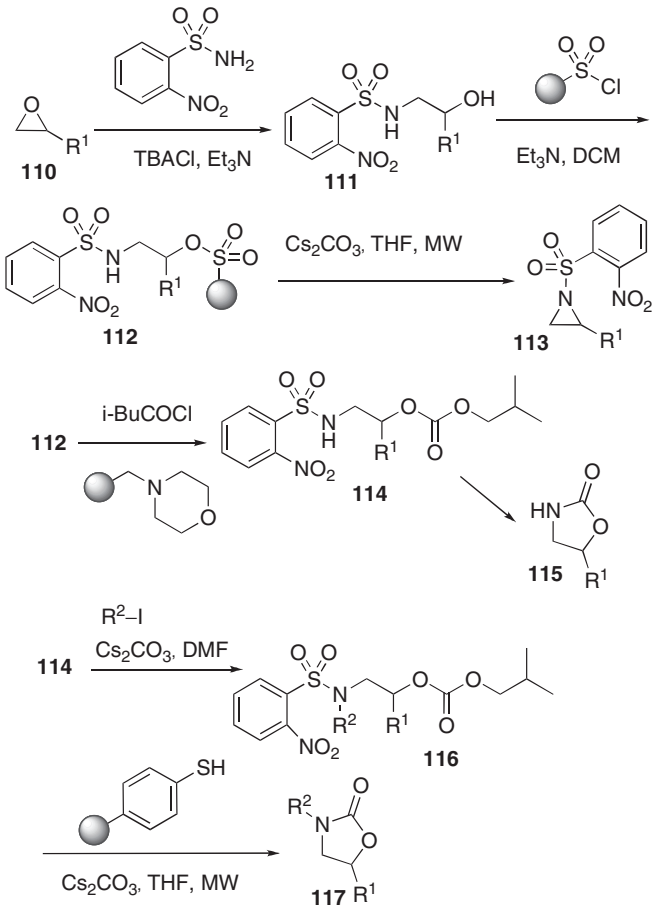


R_1(*1-6*): *1* = CH_3-; *2* = CH_3CH_2-; *3* = CH_2=$CHCH_2$;
4 = CH_2=$CH(CH_2)_3$-; *5* = $PhCH_2$-; *6* = *p*-$MeOC_6H_4CH_2$-.
R_2(*1-2*); *1* = Ph- *2* = CH_3-CH_2-.
R_3 (*1-3*); 1= Ph- 2 = p-$OMeC_6H_4$; 3 = $PhCH_2$-

Scheme 22. Synthesis of piperidine derivatives using supported reagents.

Following this procedure an arrays of substituted secondary 4-amino-piperidine derivatives (**108** in Scheme 22) was prepared.[41] Product **104** was nosylated under standard conditions and was divided in 12 vials that were submitted to the full procedure of alkylation, deprotection of the Boc and

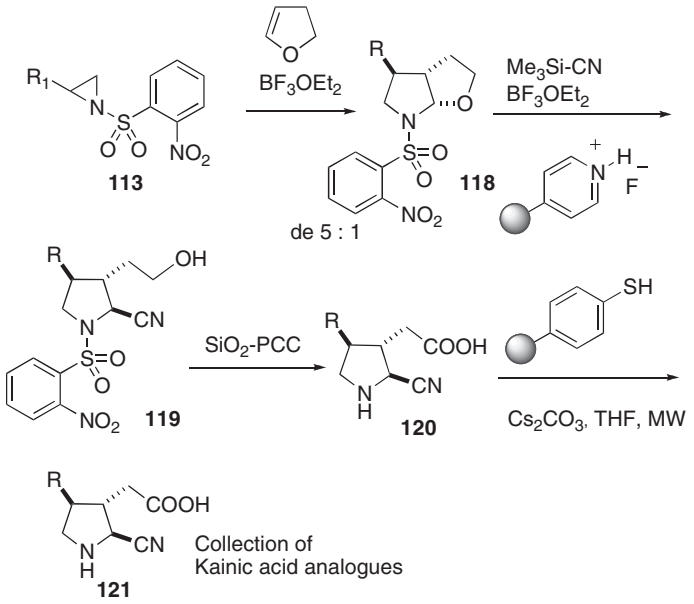
acylation, followed by deprotection of the nosyl group with the supported thiols. After 24 h at room temperature (and a second addition of PS-Thiophenol after the first 12 h) the contents of the vials was filtered and the solvent evaporated to give the chemset **108**. Passage through an SCX column followed by elution with a solution of ammonia in methanol gave the products that were fully characterized. In same cases, an excess of the alkylating agent was required to have complete alkylation of the intermediate nosylamide. The excess of the halide employed was then removed with the same arylthiol resin employed for deprotection of the sulfonamide. Taking advantage from the possibility to use two different supported reagents together, the deprotection was carried out in the presence of an aldehyde and supported cyanoborohydride. The reductive amination occurred and a set of tertiary amines **109** was obtained.



Scheme 23. Applications of supported reagents in the synthesis of oxazolidinones.

The same system of deprotection has been applied to a parallel transformation of a series of epoxides **110** into the corresponding aziridines **113**. The monosubstituted epoxides were submitted to ring opening with *o*-nitrobenzensulphonamide. The reaction has been carried out in the presence of TBACl as a phase transfer catalyst. To avoid purification, the alcohol was catch on an arylsufonic chloride resin giving supported product **112**. This transformation was done in order purify the products and to activate the substrate towards intramolecular substitution. This reaction occurred treating the isolated resin with Cs_2CO_3 under microwave irradiation that generated the sulfonylaziridines **113** in solution. A quite similar approach can be carried on the same interermediate **112** that was treated with an excess of isobutylchloroformate to generate the intermediate carbonate **114**. This product was purified by the excess of reagents by treatment with a supported primary amine that scavenged the chloroformate.

This product was cyclized using the supported thiols to form a series of oxazolidinones **115**. An additional increase of the molecular diversity could be realized by alkylation of the sulfonamide with standard conditions (Cs_2CO_3 and excess of alkyliodide under microwave irradiation). The final arrays of potentially oxazolidinones based antibiotics **11** was obtained by ring closing that occurred after deprotection with the supported aryl thiol.[42]



Scheme 24. Synthesis of Kainic acid analogues.

On the aryl aziridine **113** obtained following this procedure, an acid mediated cycloaddition was carried out with dihydrofurane. This reaction afforded a mixture of diastereoisomers of bicyclic compounds **118** that were treated with Me_3SiCN and selectively opened in position 2. The silylated intermediated **119** could be deprotected with a supported source of fluoride ion and further oxidized with supported PPC. This compound was then deprotected with supported thiol to give an array of kainic acid analogues **127**.[43]

In this chapter several aspects of the use of supported reagents have been reviewed, highlighting the aspect of safety, recycling and efficacy in organic synthesis. In any case reported, however, the amounts of products obtained is low as this approach has not found a multigram preparative application. Due to the high efficacy of the process it is advisable that more efforts will be done in this direction to let this technique can really enter in the arsenal of sustainable synthetic methods.

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PHOTOCHEMISTRY AS A GREEN SYNTHETIC METHOD

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Abstract: The photon is the green reagent par excellence. It is absorbed leaving no residue and induces deep-seated chemical transformations under mild conditions. Reactions via electronic excited states often reach the target via a shorter path than thermal alternatives, with excellent atom economy. Photochemistry also offers a way for the mild generation of highly reactive intermediates such as radicals or ions. This is illustrated by the example of arylation reactions via photo S_N1 process, a method that under some aspects rivals Pd-catalyzed reactions.

Keywords: photochemistry, arylation

1. The Contribution of Photochemistry to Green Chemistry

1.1. ROLE OF PHOTOCHEMISTRY

The increasing awareness of the damage that chemical plants can cause to the environment and the need of minimizing the use of any kind of resources has made the industry much more attentive to every aspect of the chemical process that may contribute to the overall environmental balance. Green chemistry takes cares of this aspect and is now a discipline of its own, being active toward two main aspects, i.e. (i) ameliorating presently used chemical processes, which is obviously most important in the short time and mainly involves chemical engineering aspects, and (ii) devising new environmentally friendly chemical processes that are conceived as such from the start and may in the long range substitute the present ones.

The development of new methods and techniques that allow the introduction of such new processes has now an important place in the agenda of many laboratories around the world and is an essential part of green

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chemistry. Photochemistry is one of the most neglected, yet potentially most powerful of these methods.[1]

1.2. A PRECURSOR: GIACOMO CIAMICIAN

It may be interesting to note that much before that the present idea of green chemistry was introduced, indeed at the very beginning of the development of chemical industry and thus before that chemical pollution became manifest, the principles of this discipline were clearly expressed as the result of an intellectual need for the development of science rather than as a remedy to the negative side of industrial growth. In fact, this was due to Giacomo Ciamician, a brilliant professor of chemistry at Bologna, the world oldest university. In the fist part of his career, he had become well known for having revealed and rationalized important aspects of the chemistry of pyrrole. He was induced to take a new direction when he contrasted natural vs artificial synthesis.

He reflected that the very brightness of the advancement of chemistry at that time (around 1900) made it apparent the difference between man-made chemicals and natural substances. One could now obtain in the lab the same products that were present in nature, but these were obtained under severe conditions (high temperature, pressure, treating with strong acids, oxidants or other chemicals), while the natural ones were apparently synthesized by vegetables under really mild conditions. What may be the difference? Ciamician thought that absorption of light was the secret that made green plants so efficient and set out to explore whether light might reach such accomplishments in the lab as well, when on a solution in a test tube. This extraordinary perception (in the years when Einstein in a different context rationalized the interaction between light and matter) guided his work for about 15 years.[1, 2]

As we now know, the key idea was in part wrong, since vegetables do acquire chemical" energy from solar radiation, but then carry out the actual chemical synthesis through thermal (enzymatic) reactions. He did realize this fact, and indeed the last few years of his work (after *c*.1914) were devoted to the study of how plants manipulate chemicals (via glycosidation) as a first step towards understanding chemistry in the cell. However, in the period 1900–1914 he laid the foundation of photochemistry, indeed discovered many of the presently known classes of photochemical reactions.

1.3. EXCITED STATE REACTIONS AND THEIR USE IN SYNTHESIS

Excited states may be not in use in nature for synthesis, but certainly are ideal "green" reactions, since light is adsorbed (thus leaving no residue differently from chemical reagents or catalysts) and generate electronically excited states

of molecules, species often more reactive that those formed by interaction with the aggressive chemicals otherwise used for promoting chemical processes. As a result, a clean reaction often ensues, which satisfies the postulate of atom economy, since a deep-seated transformation takes place (excited states lie at a high energy, comparable with that of covalent bonds) and occurs under unparalleled mild conditions.

Despite these early findings, organic photochemistry is far from having developed the synthetic potential it undoubtedly has, in particular as far as industrial applications are concerned. However, a large variety of synthetically meaningful photochemical methods are now available, examples are introduced in every modern text book, and specific presentation are easily available.[3–5] A recent book on photochemical reactions of *preparative significance* included 15 chapters on different classes of useful transformations.[3]

A wealth of photochemical reactions is thus available and it is expected that these will become more and more used in synthesis as long as the increasing drive towards clean methods further develops and photochemical steps will be routinely included in synthetic plans, in the industry too.

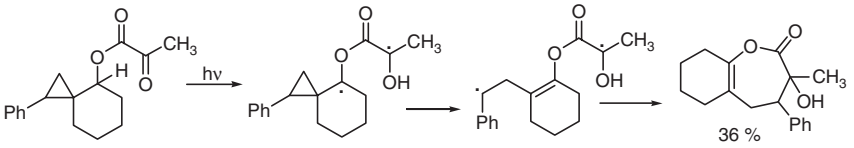
The most important contribution of photochemistry to synthetic methods is the introduction of novel reactions, which have no thermal counterpart, as it is to be expected, since excited states can be considered (highly reactive) electronic isomers of the corresponding excited states and usually little resemble the corresponding ground states in their reactions.

Just to mention a few cases, important and well known examples are in the field of alkenes and polyenes, where selective isomerizations, sigmatropic rearrangements, including the characteristic rearrangement of 1,4-dienes to vinylcyclopropanes, and electrocyclic reactions have found several applications, of aromatics, where the "meta" cycloaddition between benzene derivatives and alkenes leads to such versatile intermediates as tricyclo[3.2.1.$0^{2,8}$]octenes; of ketones, in the ground state behaving as weak C-electrophiles, while they are aggressive O-centered radicals in the nπ^*excited states.

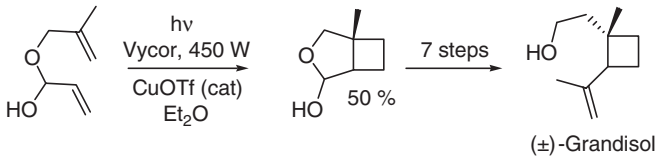
1.4. PHOTOCHEMICAL GENERATION OF ACTIVE INTERMEDIATES

For the present discussion it has been chosen to renounce the systematic introduction of the varied field of such classes of reactions, for which the reader is referred to one of the above-mentioned treatises.[3–5] It has rather been decided to discuss another field of application of the photochemical method that is perhaps more easily compared to thermal reactions. This is the generation of highly reactive intermediates. In this case, the photochemical method is used for the production under mild conditions of a key intermediate that might, at least in principle, be reached also by a reaction non involving photochemistry (Schemes 1–5).

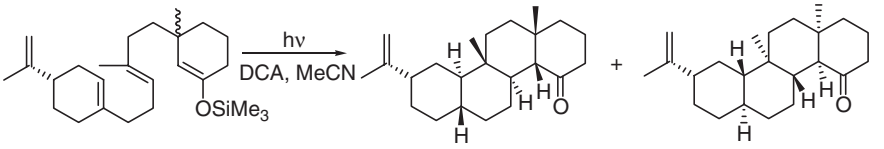
A typical such case would be the fragmentation of a bond for the generation of radicals or of ions, where the photochemical method is used to "activate" that bond, as one would otherwise do by using a catalyst or a strong acid/base as the case would demand. A largely developed implementation of such idea is the fragmentation of diazo compounds to give carbenes.[6] Differently from thermal, electron transfer induced or catalyzed cleavage reactions, the photochemical method has here the added versatility of allowing to generate selectively the desired carbene in the singlet or in the triplet state.



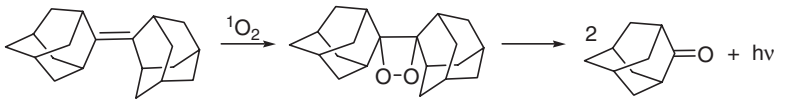
Scheme 1. A photochemical reaction initiated by (intramolecular) hydrogen abstraction.[7]



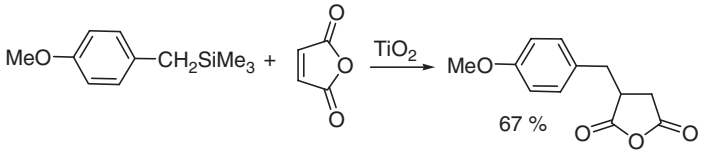
Scheme 2. A synthetic scheme based on a photochemical cycloaddition reaction.[8]



Scheme 3. An example of electron transfer photosensitized reaction.[9]



Scheme 4. An example of photosensitized oxygenation.[10]



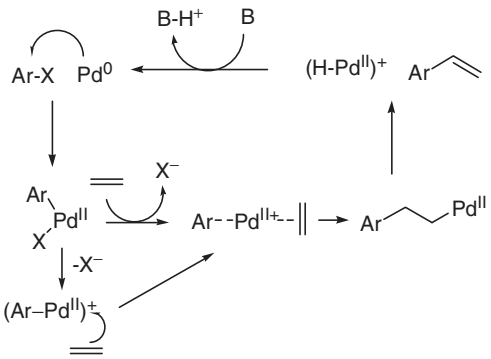
Scheme 5. Generation of radical by photosensitized fragmentation.[11]

2. Arylation Reactions via Photoinduced S_N1 Path

2.1. AROMATIC NUCLEOPHILIC SUBSTITUTION: TERMAL VS PHOTOCHEMICAL REACTIONS

In the following the generation and synthetic application of a less common, but equally useful intermediate will be discussed. This is the phenyl cation. As is well known, nucleophilic aromatic reactions, whether aiming to the formation of aryl-heteroatom or aryl-carbon atom, are not as generally applicable as aliphatic S_N processes. The S_N2Ar reaction is viable only when a strongly electron-withdrawing substituent is present on the ring, and then often only under harsh conditions. On the other hand, monomolecular reactions have a relatively small role. The appealing $S_{RN}1$ reaction has shown to encounter several limitations that make it not as general as had been hoped. A S_N1 mechanism rarely applies. Most of the arylation reactions via diazonium salts involve a reductive activation and thus take place via the aryl radical, not the cation.

The aryl cation has indeed be characterized, but under conditions ill suited for synthetic applications, such as photolysis of diazonium salts in matrix[12] or of phenyl iodide in matrix,[13] or by exploiting the decay of tritiated benzene.[14] This has led to intensive research for metal-catalyzed reactions that has indeed revolutionized the field with methods such as the Heck reaction, the Suzuki coupling, the Sonogashira reactions and many other ones.[15] In such processes the metal, most often palladium, activates the aromatic derivative, e.g. a halide, via oxidative addition. Halide elimination and coordination of the (π) nucleophile then induce the condition for the generation of the new bond (Scheme 6).



Scheme 6. Metal-catalyzed couplings.

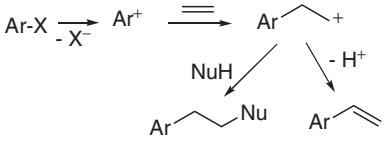
2.2. PHENYL CATION: PHOTOGENERATION AND CHEMISTRY

Thus, although the entire process occurs on the metal, its mechanism resembles a S_N1 reaction with the aryl cation as the intermediate.[16] One may thus wonder whether the photochemical method may serve to generate the "free" aryl cation and use it directly as the intermediate in the same syntheses (Scheme 7).

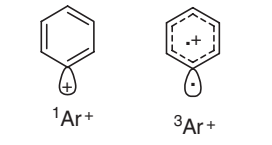
A spontaneous objections that comes to mind is that previous experience for the solvolytic generation of phenyl cation has been quite disappointing, since it has been successful only in a couple of cases and then it has been shown to be non susceptible of control, resulting in the unselective addition to the solvent. The latter anticipated limitation is perhaps not insurmountable, when remembering that phenyl cations, as other divalent species such as the above considered carbenes, come in two states, the singlet and the triplet.[16–19] While the former state is a C_1 localized cation of $\pi^6\sigma^0$ structure, the second one is a delocalized state of $\pi^5\sigma^1$ structure, where the reactive C_1 center resembles more a carbene (with the second electron delocalized over the ring) than a cation (Scheme 8).

Light absorption first leads to the excited singlet, but it allows reaching the triplet either by direct irradiation when intersystem crossing (ISC) to the triplet precedes fragmentation, or by triplet sensitization when this is not the case (Scheme 9).

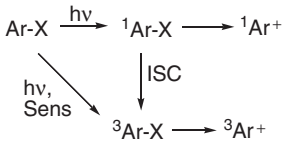
Explorative studies showed that a variety of electron-donating substituted benzenes (anilines, anisoles and phenols, thiophenols and other ones) bearing a nucleofugal group such as chloride, fluoride, mesylate, triflate or phosphate



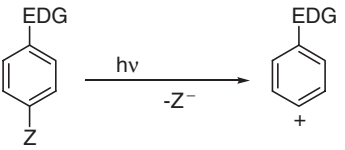
Scheme 7. Photogeneration of aryl cations.



Scheme 8. Aryl cations.



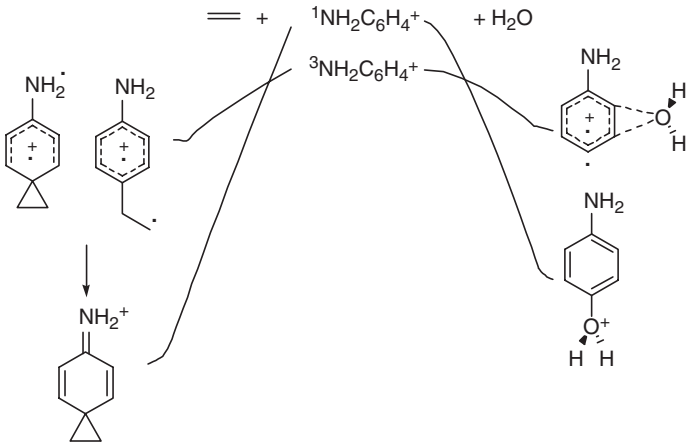
Scheme 9. Light absorption process.



EDG = $NH_2(R_2)$, OH(R), SR

Z = Cl, F, OSO_2CH_3, OSO_2CF_3, $OP(O)(OEt)_2$

Scheme 10. Heterolytic photocleavage.



Scheme 11. Reaction of 4-aminophenyl cation with nucleophiles.

do undergo heterolytic photocleavage with efficiency from medium to high in polar solvents. In most cases, it is the triplet that is formed (Scheme 10).[20]

Calculations for the case of 4-aminophenyl cation confirmed that the singlet state reacts indiscriminately with both n (H_2O) and π (CH_2=CH_2) nucleophiles, while the triplet does not bond to water (it only forms a complex), while it does to ethylene (Scheme 11).[19–21]

Experiments supported this view and it was found that, e.g. trapping of phenyl cations by alkenes led conveniently to stilbenes, allylbenzenes and (β-substituted) alkylbenzenes, via an intermediate adduct cation (presumably with phenonium structure, see Scheme 11).

2.3. EXAMPLES OF PHOTOINDUCED ARYLATION REACTIONS

Thus, processes that are analogues to metal-catalyzed reactions can be carried out by photochemical excitation and have indeed some mechanistic kinship with them. A few examples are presented below and compared to a corresponding Pd-catalyzed reaction.

Thus, irradiation of 4-chloroanilines in the presence of 1, 1-diphenylethylene gave a stilbene (Scheme 12).[21]

In the presence of a substituted aliphatic alkene as well as of an allylsilane allylbenzenes were obtained, via deprotonation or desilylation of the initial cationic adduct.

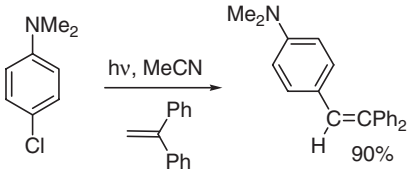
In the absence of such good electrofugal groups, the reaction ended by nucleophile addition to form a β-substituted alkylbenzene (or a plain alkylbenzene when the nucleophile was sodium borohydride, see Scheme 13).[22]

A variety of modifications are possible. As an example, with unconjugated cyclic dienes, secondary trapping of the cation occurred, leading to bicyclic derivatives (Scheme 14).[23]

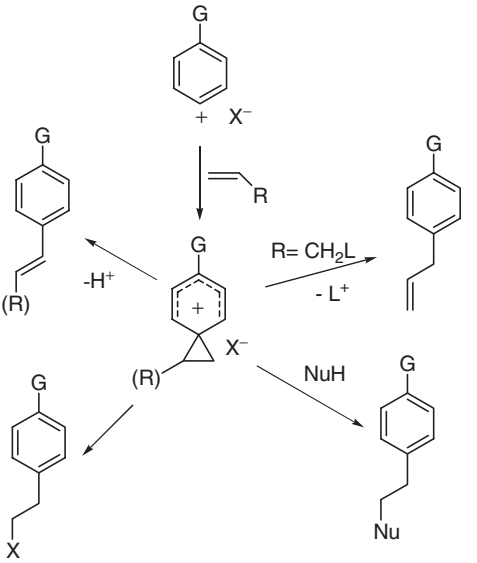
On the other hand, at least in ion stabilizing media such as methanol or trifluoroethanol, the adduct cation underwent the typical rearrangements of aliphatic cations (Wagner–Meerwein type) with 1,2-shift either of a hydrogen or of the carbon chain (Scheme 15).[24]

Such arylation have been carried out with several other π nucleophiles, e.g. with (silyl) enol ethers yield esters of (α-substituted)phenylacetic acids were obtained. Arylalkynes were formed in the presence of terminal alkynes and their silyl derivatives (see Scheme 16). Intramolecular variations of this synthesis were also developed (Scheme 17).[25]

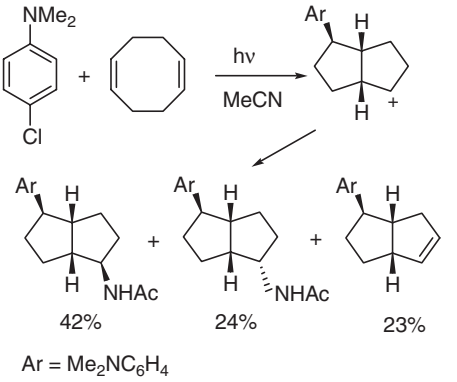
Likewise, aromatics and electron-rich (five-membered) heterocycles were conveniently arylated under these conditions (Schemes 18 and 19).[26]



Scheme 12. Irradiation of 4-chloroanilines.



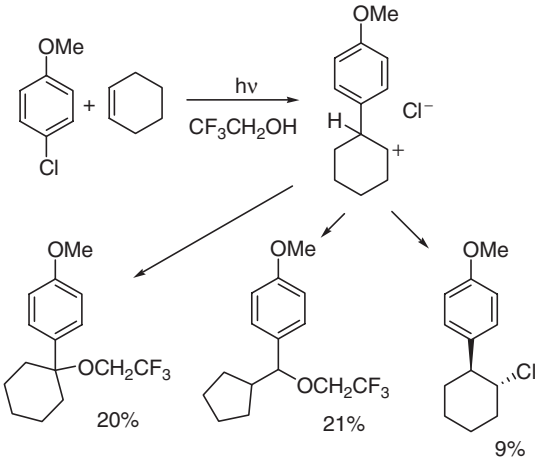
Scheme 13. Nucleophile addition to β-substituted alkylbenzenes.



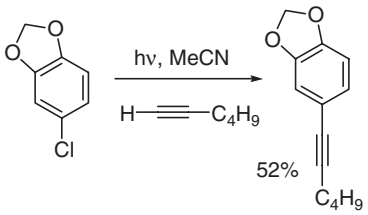
Scheme 14. Secondary trapping to bicyclic derivatives.

As mentioned, the arylations presented above are typical of electron-donating substituted benzenes, since in that case photoheterolysis is most effective. This does not detract from the interest of the method, since it makes the photochemical reaction complementary to metal catalysis, the implementation of which is generally much easier with electron-withdrawing substituted derivatives.

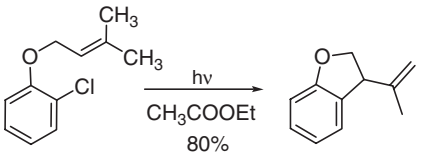
At any rate, this limitation could be removed by using diazonium salts that undergo efficient photofragmentation independently from the substituent.



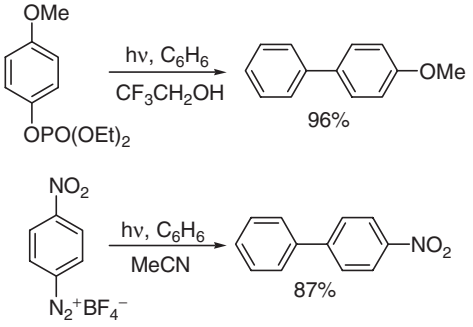
Scheme 15. Typical Wagner–Meerwein-type rearrangements of aliphatic cations.



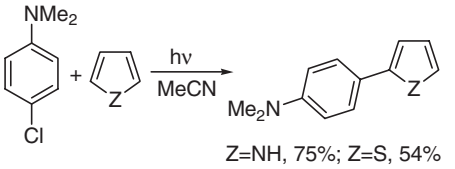
Scheme 16. Synthesis of arylalkynes.



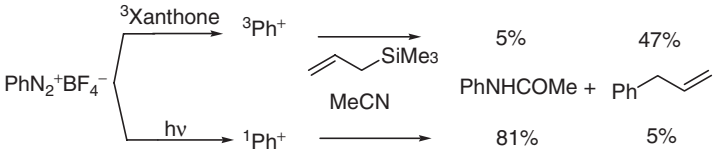
Scheme 17. Intramolecular cyclization of chloroarenes with alkenes.



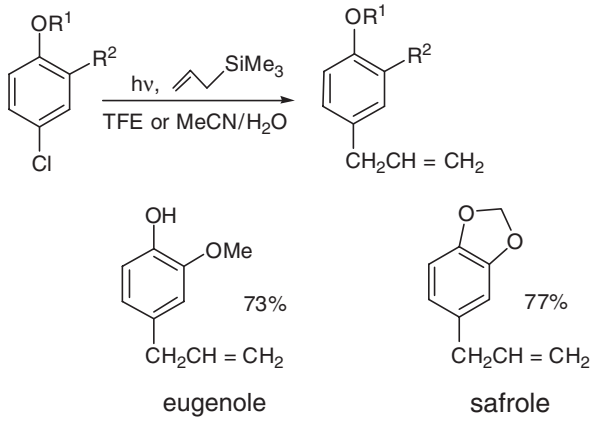
Scheme 18. Arylation of electron-rich arenes.



Scheme 19. Arylation of electron-rich heteroarenes.



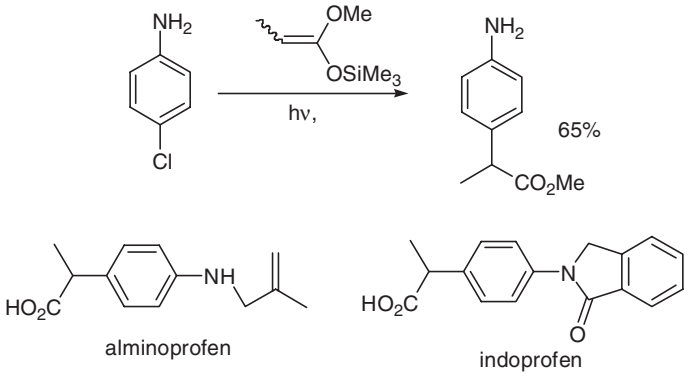
Scheme 20. Decomposition of benzenediazonium fluoborate and reaction with alkenes.



Scheme 21. Synthesis of eugenole and safrole.

The substituting group, however, determined from which state will the cleavage occur. Thus, nitrophenyldiazonium salts cleaved from the triplet and gave the corresponding triplet phenyl cation, in turn selectively reacting with π nucleophiles as those previously considered. On the other hand, parent benzenediazonium fluoborate cleaved from the singlet, resulting in the phenylation of the solvent. However, when the decomposition was photosensitized by xanthone, the phenyl cation was formed in the triplet state and reacted selectively with alkenes (Scheme 20).[27]

This method has been applied to the straightforward synthesis of compounds of commercial interest, such as medicinally active phenols and phenyl ethers, e.g. eugenole and safrole[28] (see Scheme 21) as well as of intermediates



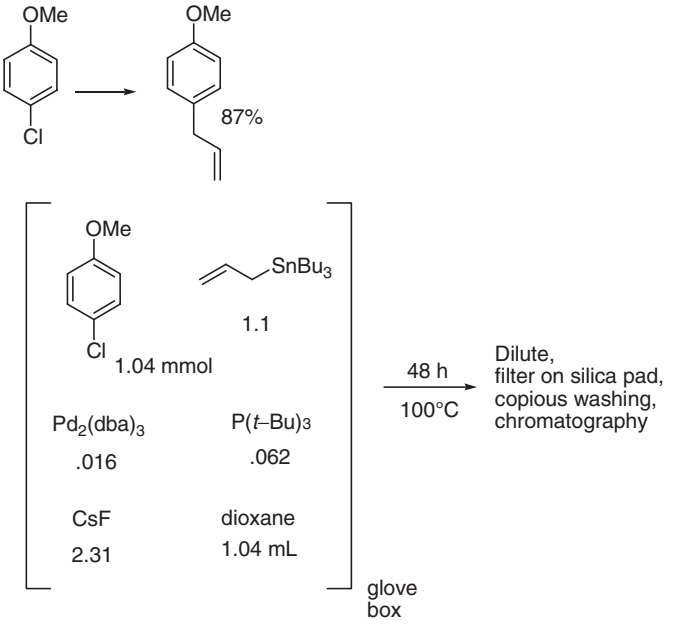
Scheme 22. Synthesis 4-aminophenylproprionic acid.

for largely used drugs, such as 4-aminophenylpropionic acid,[29] an industrial intermediate for the anti-inflammatory drugs alminoprofen and indoprofen (Scheme 22).

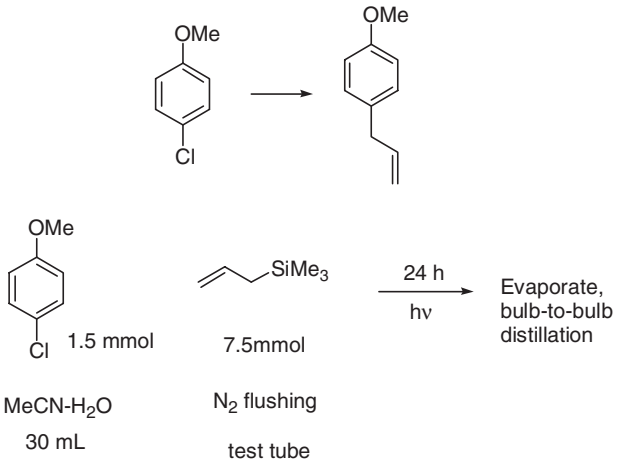
2.4. EXPERIMENTAL ASPECTS

From the green chemical perspective, it is important to highlight the experimental difference in carrying out a photochemical reaction vs a Pd-catalyzed reaction. As an example, 4-allylanisole has been prepared from 4-chloroanisole by both methods (in hundreds of milligram scale). In the thermal reaction,[30] this is treated with allyl-*tris*-butylstannane in dioxane in the presence of 0.016 equivalents of $Pd_2(dme)_2$ and *tris*-(*n*-butyl)phosphine as catalyst and cocatalyst and of 2.3 equivalents of CsF. The mixture is heated at 100°C for 48 h, then diluted, filtered on silica gel, copiously washed and chromatographed to yield the product in 87% yield. All of the operations must be carried out in a glove box, some of the reagents are quite expensive and labile, and it must be taken care of the careful elimination of trace metals if the product is designed for medicinal or alimentary use (Scheme 23).

On the other hand, the photochemical reaction was carried out by simply irradiating for 24 h the chloroanisole in acetonitrile/water in the presence of allyltrimethylsilane in a text tube by using an inexpensive low pressure lamp.[28] No air-exclusion or extensive purification of reagents and solvent was required, the work-up was quite simple and consisted in bulb-to-bulb distillation to yield the desired product in 75% yield. Limitations were (i) the use of excess allylating agent (5 rather than 1 equivalents, in part compensated by the fact that the silane rather than the stannane was used,



Scheme 23. Palladium-catalyzed coupling.



Scheme 24. Photochemical-induced process.

and that recover was possible) and (ii) the use of a more diluted solution (100 mg of reagent in 10–30 mL rather than in 1 mL, but again the solvent could be recovered and, as mentioned above, no accurate purification was required, see Scheme 24).

In this case the advantage is apparent. Obviously, this does not held in every case, or not to this degree. Certainly, the photochemical arylation cannot compete with the much more extensively investigated catalytic method in terms of versatility or general scope. However, when it can be applied, it does show a remarkable advantage in terms of directness, simple operation, atom economy, i.e. of the green chemistry identifying characteristics.

Future years will clarify whether the, in part due to the lack of a habit, barrier to use more largely photochemical reactions in organic synthesis will be overcome due to the incentive to use a "greener" chemistry.

Acknowledgements

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NOVEL METHODS FOR THE SEPARATION OF OPTICAL ISOMERS

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Abstract: Recent developments in the field of racemate resolution has been reviewed and illustrated with examples. The excellent results achieved by the novel pH-controlled crystallization of diastereoisomeric salts, application of derivative resolving agents, complex forming resolution of chiral alcohols with O,O'-dibenzoyltartaric acid, enzymatic resolutions and dynamic kinetic resolutions demonstrate that the synthesis of racemic mixtures followed by optical resolution of the racemate represent nowadays an environmentally benign and economic alternative for preparation single enantiomers.

Keywords: pH-controlled optical resolution, kinetic resolution, enzymatic methods, second-order asymmetric transformation, dynamic kinetic resolution

1. Introduction

Biosphere contains different optically active molecules (α-amino acids, sugars, catecholamine type messengers, hormones, steroids, etc.) therefore big part of the cell receptors and enzymes in humans, animals, and plants have chiral recognition abilities. Numerous examples are known from the literature for different smell, taste, biological activity and toxicity of mirror image molecules.[1] Since the big Contergan scandal[2] strict rules have been introduced in many countries for pharmacological investigations of all stereoisomers of new drug candidates before administration and introduction into the market. Nowadays similar rules should be used in the other fields of applications like pesticides, food additives and cosmetic or plastic ingredients.

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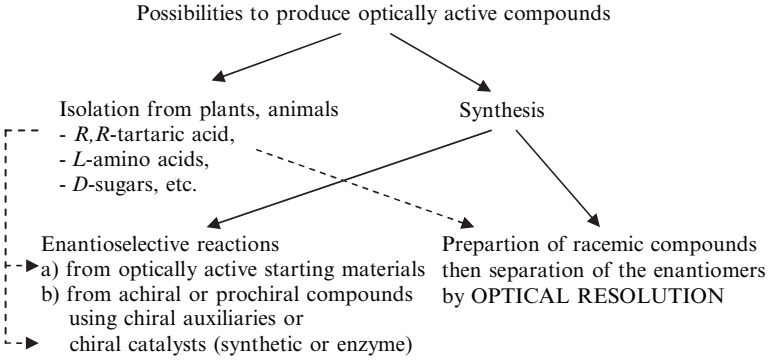
Even it has serious economic consequences, we should keep in mind that in the most cases one enantiomer of a chiral biologically active compound is responsible for the positive biological effects, the other isomer(s) pollutes the environment. That is why a really green, environmentally benign solution would be the exclusive production and application of the good or at least neutral stereoisomers, only.

In the last decades tremendous efforts have been focused on the development of highly enantiomer selective synthetic methods.[3–5] Nowadays, we have such tools in hands as asymmetric catalysis using metals, chiral organic catalysts without any metals and series of enantioselective reactions in the presence of whole living cells or isolated enzymes.[6,7] However, these methods are used mainly in laboratory scale because of the high price of the efficient chiral ligands and catalysts and also because of the lack of efficient, scalable processes for industrial purposes. Therefore synthesis and optical resolution of racemic mixtures remained an economical and frequently used procedure at the fine chemical and pharmaceutical industries.[8,9] A brief overview of the methods for producing optically active compounds is given in Scheme 1.

Theoretically the whole amount of the (prochiral or achiral) starting material could be converted into the desired optically active product by asymmetric synthesis (e.g. we could create a new stereogenic center of a molecule via diastereomeric intermediates or transition states using chiral tools). On the other hand, classical optical resolution of a racemic mixture (via diastereoisomeric intermediates or transition states) provides only the half of the starting material as single enantiomer while the other optical isomer remains unchanged. However, efficient methods are known for racemisation of the unnecessary enantiomer, too.[10]



Scheme 1. Methods for producing optically active compounds (dotted lines indicate the application of natural products as resolving agents or chiral auxiliaries).

There are several other problems which can be solved by optical resolution: preparation of chiral ligands for enantioselective catalysts, preparation of both mirror image isomers of drug candidates for pharmacological investigations. As a consequence, optical resolution methods are still under intensive and continuous development and numerous theoretical and technical improvements have been achieved in the last decade.

This chapter contains a comprehensive review on the methodologies applied recently in the field of optical resolution via diastereoisomeric salt and complex formations. Special examples of enzyme-catalysed kinetic resolution are also discussed.

2. Methods of Resolution

In historical order we have to mention Pasteur's very first enantiomer separation experiment. In 1848 he sorted manually (using a microscope and pincers) the mirror image crystals of the conglomerate forming sodium ammonium tartarate. Later on he has also developed resolution methods by induced crystallization and by diastereoisomeric salt formation.[11] Most part of the racemic biologically active compounds (having basic or acidic functions, or transformed into such derivatives) can be resolved into single enantiomers using the different variations of the diastereoisomeric salt formation method. An economic and efficient variation is, for example, the use of half an equivalent amount of the resolving agent, that was introduced by Pope and Peachy in 1899.[11] A practically useful modification of this "half equivalent method" has been developed by us, about 20 years ago.[12,13]

Differences between the solubilities of diastereoisomers containing covalent bound between the enantiomer and the resolving agent can also be applied for the separation of racemates. That time however we should also find selective methods for cleaving the covalent bound, existing between the enantiomer and the resolving agent, without any racemisation of the target compound.[10]

Much easier is the recovery of an enantiomer from diastereoisomeric complexes if one can find complex forming resolving agents for a given racemate. Therefore, diastereoisomeric salt and complex formations are among the most popular resolution methods in this field of chemistry. Of course, diastereoisomeric complexes are formed during chromathographic separations, too. However, in these cases the interactions among the chiral stationary phase and the enantiomers do not result crystalline materials but such an equilibrium system which, finally, results in retention time difference between the enantiomers. Details on the theory and practice of GC, HPLC and LC methods for enantiomer separation have been reviewed recently in different articles and books,[14,15] therefore these methods are not discussed in this chapter.

Kinetic resolution of racemic mixtures using optically active reagents or catalyst are also well-known methods for separation of enantiomers. While the enzymatic resolutions usually result in efficient separations due to the high energy difference between the diastereoisomeric transition states (built up by the enzyme, the achiral reagent and the enantiomers, separately), classical kinetic resolutions using chiral reagents rarely provide good ee values of the products.[16,17] An overview on the above-mentioned resolution methods and the applied chiral tools is given in Table 1.

Combination of optical resolution and racemisation (epimerisation) of the unnecessary isomer can be carried out under thermodynamic control (second-order asymmetric transformation: SOAT) or kinetic control (dynamic kinetic resolution: DKR), too (Scheme 2).

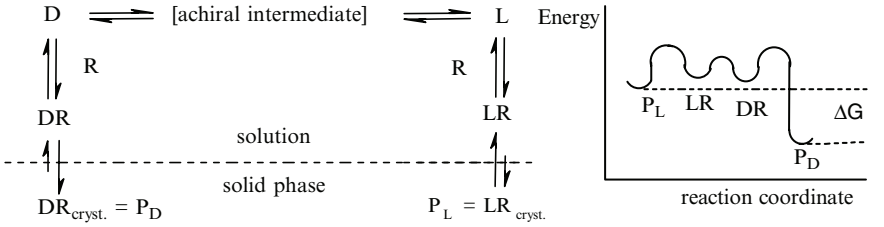
Both methods result in full conversion of a racemic mixture into one, the desired enantiomer. Even these methods are known since many years, successful combination of enzymes and other catalysts for parallel kinetic resolution and racemisation together with several technical improvements have resulted the renaissance of DKR and numerous publications have appeared in the last 5 years dealing with such resolution processes.[18] Comparison of the different methods let us to conclude that, in many cases, preparation and optical resolution of a racemic mixture is cheaper than the alternative asymmetric synthesis. In other words, efficient SOAT or DKR processes may be the best solutions for producing single enantiomers on a green and economic way by the fine chemical industry.

TABLE 1. Optical resolution methods and the applied chiral tools for producing diastereoisomeric transition states or intermediates.

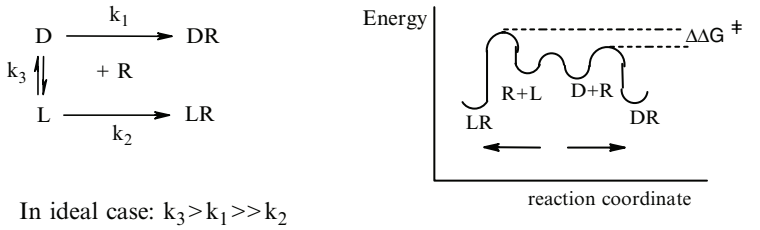
Method	Chiral tool
(A) Induced crystallization of conglomerates $D,L \rightarrow D\downarrow + L_{\text{in solution}}$	Surface of the seeding crystal
(B) Preparation of diastereoisomeric pairs as Salt, Complexes, Covalent compounds then separation by crystallization $D,L + 2R^* \rightarrow DR^*\downarrow + LR^*_{\text{in solution}}$	Optically active resolving agent
(C) Separation of enantiomers by GC, HPLC or LC $D,L \rightarrow D_{\text{fast elution}} + L_{\text{slow elution}}$	Optically active stationary phase
(D) Kinetic resolution	
With an optically active reagent	Optically active resolving agent
With an enzyme $k_1 \neq k_2$ $DR^* \leftarrow D,L + R^* \rightarrow LR^*$	Active site of the enzyme

R*: resolving agent or achiral reagent in enzymatic process

a) Thermodynamic control: Second Order Asymmetric Transformation



b) Kinetic control: Dynamic Kinetic Resolution



In ideal case: $k_3 > k_1 >> k_2$

Scheme 2. General reaction schemes and energy profiles of second-order asymmetric transformation (SEOAT) and dynamic kinetic resolution (DKR).

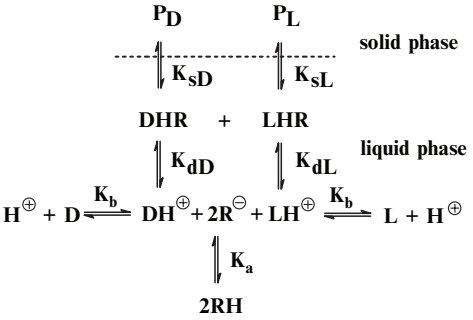
3. Optical Resolutions via Diastereoisomeric Salt Formation

3.1. THE "PH-CONTROLLED" RESOLUTION

Investigation of the equilibrium system of a diastereoisomeric salt pair formation reaction was attempted first by Jacques and his co-workers.[11] Our group has developed a more detailed equilibrium model for that system[19] (Scheme 3.) and postulated the result of an optical resolution (S = selectivity) as the production of the yield and optical purity of the crystallized diastereoisomeric salt (S = yield × optical purity).[20]

On the basis of our equilibrium model the result of a resolution (S) can be calculated using the equilibrium constants of solubilities (K_{sD} and K_{sL}) and dissociations (K_{dD}, K_{dL}) of the salts, the acid (K_a) and the base (K_b) at a given pH value and initial concentration of the racemate (c_0) and the resolving agent $[RH]_0$. The equilibrium constants have been determined for several diastereoisomeric salt pairs and model calculations were carried out using these data. The computed and the experimental results were in good accordance in every cases.[21,22]

On the other hand, the equilibrium model let us to shed light the physicochemical background of several known practical rules, as follows.[19,23]

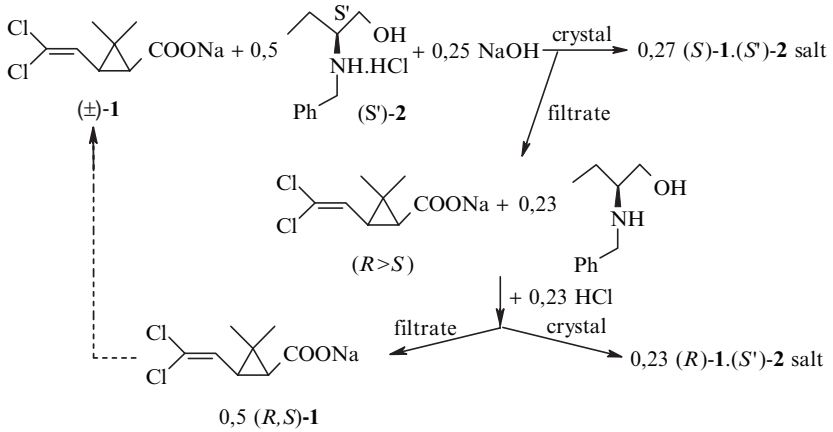


$$0.5c_o\,S = K_{sD} - K_{sL} + \left(1 + \frac{K_b}{[H^{\oplus}]} + \frac{[H^{\oplus}]}{K_a} + \frac{K_b}{K_a}\right)\frac{K_{sD}K_{dD} - K_{sL}K_{dL}}{|RH_o| - 0.5c_o y - (K_{sD} + K_{sL})}$$

Scheme 3. Equilibrium model of optical resolution via diastereoisomeric salt formation (D,L: racemic base, RH: resolving agent).

(a) In some cases (e.g. nonprotic media) the second part of the equation in Scheme 3 is negligible and the efficiency of resolution (S) depends on the solubility difference, only. In every other cases however, the hydrogen ion concentration has strong influence on the result of the resolution.
(b) The extreme values of S as a function of the hydrogen ion concentration can easily be calculated. Minimum efficiency of a resolution can be achieved using an equivalent amount of resolving agent (at $[H^+] = (K_{a,}\,K_b)^{0.5}$ in the case of a monoacid and a monoamine).
(c) The best separation can be approached by the use of half an equivalent amount of resolving agent ($[RH]_0 \approx 0.5c_0 + K_{sD} + K_{sL}$). That is the theoretical explanation of the practical success of the half-equivalent method, too.

Optical resolution of *cis*-permethrinic acid (**1**) with (*S′*)-2-benzylaminobutanol ((*S′*)-**2**) was the very first example of such a pH-controlled optical resolution process in which the configuration of the precipitated diastereoisomeric salt could be determined by the appropriate amount of an achiral base additive (Scheme 4).[21] Thus, the (*S*)-**1**.(*S′*)-**2** diastereoisomeric salt crystallized in practically pure form, when the sodium salt of (*R,S*)-**1** was reacted with half an equivalent amount of (*S′*)-**2**.HCl in the presence of 0.25 equivalent excess of sodium hydroxide (Scheme 4). The other pure diastereoisomeric salt ((*R*)-**1**.(*S′*)-**2**) was crystallized from the filtrate by simple neutralisation of the sodium hydroxide excess. Advantage of our "pH-controlled" method compared to the classical (equivalent, Pasteur) and the half equivalent (Pope-Peachey) resolution methods is demonstrated by two set of data.



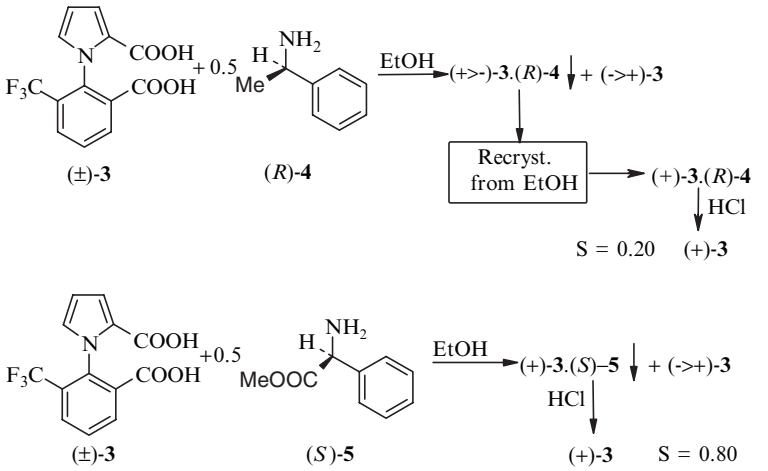
Scheme 4. The pH-controlled resolution of *cis*-permethrinic acid (**1**).

TABLE 2. Efficiencies of the different salt forming resolution methods for compound **1**

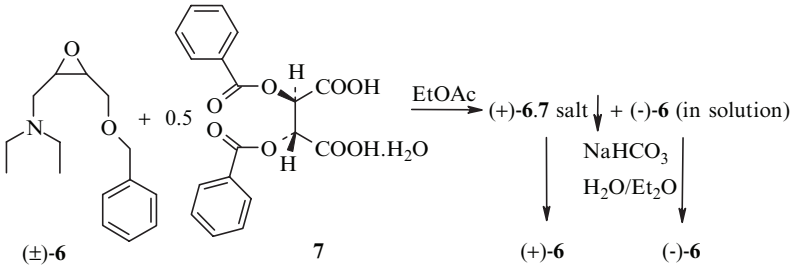
Method	(*S'*)-**2**/NaOH (mol/mol)	S (efficiency)	Volume of the solvent for 1 g of optically pure salt (mL)
Equivalent	1/1	0.27	750
Half equivalent	0.5/1	0.45	115
pH controlled	0.5/1.25	0.54	16

First the S values provided by the different methods can be compared (Table 2). Second: much less solvent is necessary for the preparation of 1 g of optically pure diastereoisomeric salt (*S*)-**1**.(*S'*)-**2** by our method (Table 2).

Hydrogen ion concentration can be influenced by the molar ratio of the racemate and the resolving agent, too. In addition, the pH value of a reaction mixture of a dicarboxylic acid monoamine salt is also shifted by the second, "free" carboxylic group. It is the situation during optical resolution of compound **3** with half an equivalent amount of optically active **4** (Scheme 5).[24] The efficiency of this resolution is about 20% (S = 0.20) but much better results could be achieved (S = 0.8) with another resolving agent ((S)-**5**) in which the methoxycarbonyl group represent a much better function for second-order interactions than the corresponding methyl group in resolving agent (*R*)-**4** (Scheme 5).[25] The impressive improvement of the resolution efficiency can be rationalised if we take into account that the energy difference between two diastereoisomeric salts is determined by the difference in their second-order bond system.



Scheme 5. Optical resolution of dicarboxylic acid **3** with different resolving agents.

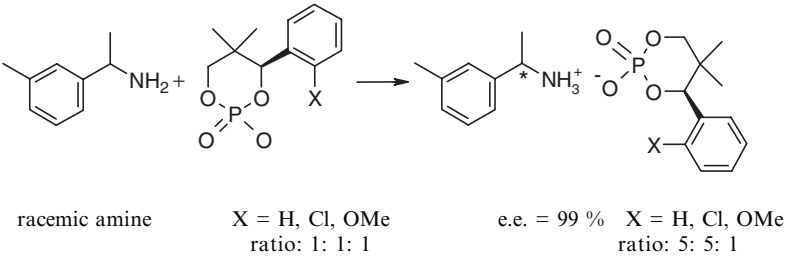


Scheme 6. Optical resolution of aminooxirane 6 with half an equivalent resolving agent **7**.

While the induced crystallization of conglomerates is a kinetically controlled process, the above-mentioned diastereoisomeric pair forming methods are usually treated as resolutions under thermodynamic control. It has to be mentioned however, that in several cases kinetics of crystallization and solid–liquid exchange reactions may determinate the configuration and optical purity of the crystallized salt. When the thermodynamically favoured salt crystallizes faster, the two effects amplify each other but in some cases the thermodynamically less stable diastereoisomer crystallizes faster. In these resolutions the configuration and the optical purity of the enantiomer in the solid phase strongly depend on the crystallization time. During optical resolution of aminooxirane **6** with acid **7**, the yield of the crystallized salt did not changed too much in time, but the optical purity of the salt increased significantly, showing an exchange of the aminooxirane enantiomers between the solid phase and the solution (Scheme 6 and Table 3).[26]

TABLE 3. Effect of the crystallization time on the efficiency of resolution of compound **6**.

Crystallization time (h)	Yield of the diast. salt (%)	Optical purity (%)	Efficiency of resolution (S)
1	57	87	0.50
2	46	86	0.40
16	64	84	0.53
72	55	<98	0.54
144	47	<98	0.46



racemic amine X = H, Cl, OMe ratio: 1: 1: 1 e.e. = 99 % X = H, Cl, OMe ratio: 5: 5: 1

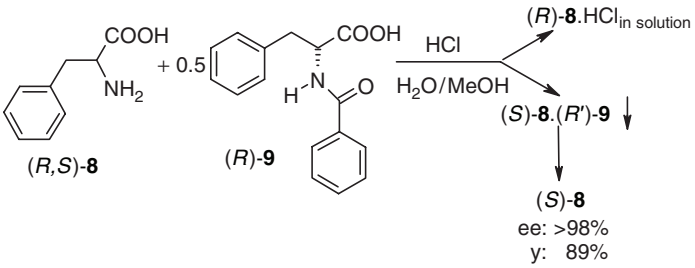
Scheme 7. "Dutch resolution" of racemic 1-(3-methylphenyl)ethylamine.

3.2. NOVEL METHODS FOR SELECTION OF A GOOD RESOLVING AGENT

In spite of theoretical considerations and practical analogy, selection of a good resolving agent for a new resolution has remained a trial and error game until now. In order to decrease the experimental work for such a selection, two different strategies have been developed recently.

In "Dutch resolution" trials[27] the authors used small libraries of structurally similar resolving agents (such as the chiral phosphoric acids in Scheme 7) with the hope that at least one of these resolving agents will form crystalline diastereoisomeric salt with the given racemic amine. Surprisingly enough the crystallized salt contained always more than one resolving agent but the molar ratio of these reagents in the solid phase was completely different from the composition of the starting reagent mixture. Detailed investigation of several resolving agent mixtures confirmed that the probability of successful resolutions increases in these cases compared to the trials with individual resolving agents and the components of the mixture showed synergistic effects in numerous cases.[27]

Another approach to the selection of a good resolving agent was developed in our laboratory[9,28] starting from the experimental fact that the chiral



Scheme 8. Optical resolution of compound **8** via diastereoisomeric salt formation with its "derivative resolving agent" ((*R′*)-**9**).

acids and bases tend to form more stable heterochiral associates (racemates) than homochiral ones. Statistical data on the strong racemate forming tendency (85%) of chiral acids and bases against conglomerate formation (10%) confirmed our working theory. In other words, the best resolving agent of a given racemic mixture should be its own single enantiomer. In practice, we have to use an optically active derivative of the racemic compound with opposite chemical character for salt formation. The "derivative resolving agent" can be prepared by simple reactions such as, for example, the acylation of the amino group of an amino acid.[23]

An example for this resolving agent selection method is the resolution of β-phenylalanine ((*R,S*)-**8**) with its optically active *N*-benzoyl derivative ((*R′*)-**9**, Scheme 8). Using the pH-controlled version of the half equivalent method resulted in excellent separation. A practically pure "quasi-racemate" type diastereoisomeric salt crystallized in good yield (S = 0.87).[28] Other examples of the successful application of the "derivative resolving agent approach" can be find in the literature.[23]

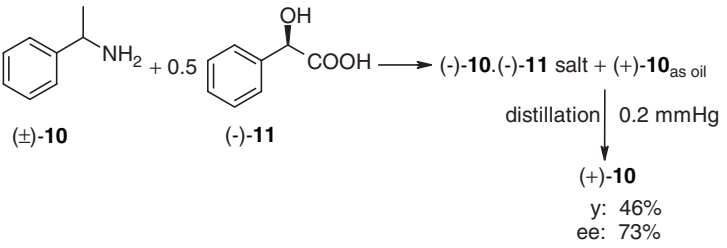
3.3. ALTERNATIVE METHODS FOR SEPARATION OF A DIASTEREOISOMERIC SALT FROM THE FREE ENANTIOMER

The crucial step of the before mentioned resolutions is selective crystallization of one diastereoisomeric salt while the other salt should remind in solution. In many cases however, hard to find any resolving agent –solvent pairs for producing crystalline salt. In order to get rid of crystallization problems, two alternative methods have been developed in our laboratory.[25,29] The basis of these separation methods is the application of half an equivalent resolving agent. That time one part of the starting racemate forms a salt with the resolving agent and the other half of the racemic compound remains free. Thus, one can separate a diastereoisomeric salt from the free enantiomer (amine or acid) by distillation (if the free enantiomer is volatile) or by extraction.[23]

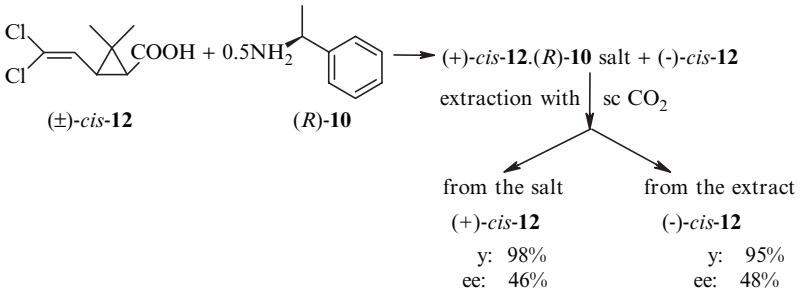
For example, racemic α-methyl-benzylamine (an oil, **10**) was mixed with half an equivalent amount of (*R*)-mandelic acid (**11**) and the excess of the amine **10** was removed from the mixture by low pressure distillation in optically active form (ee: 73%, Scheme 9).[25]

Another example is the optical resolution of *cis*-permethrinic acid (**12**) using half an equivalent amount of (*R*)-**10** as resolving agent.[29] The diastereoisomeric salt forming reaction was carried out in alcohol, then celite was added and the solvent was stripped of by distillation. The solid residue was treated with supercritical carbon dioxide. The free acid ((−)-**12**) was recovered from the extract in optically active form (ee: 48%) while the solid residue contained the diastereoisomeric salt enriched in (+)-**12** (Scheme 10).

Both examples demonstrate that these alternative methods usually provide partially resolved enantiomers in one step. Enantiomeric enrichment can be achieved by repeated resolutions using the same methods and this way one can prepare the very first optically active samples starting from a new racemic compound. Further improvement of the resolution method is much easier if one can determine the properties of clean diastereoisomeric salts by thermoanalytical methods.



Scheme 9. Optical resolution of (±)-**10** by distillation of the free enantiomer from the diastereoisomeric salt.



Scheme 10. Optical resolution via separation of the free enantiomer of **12** from the diastereoisomeric salt by supercritical fluid extraction.

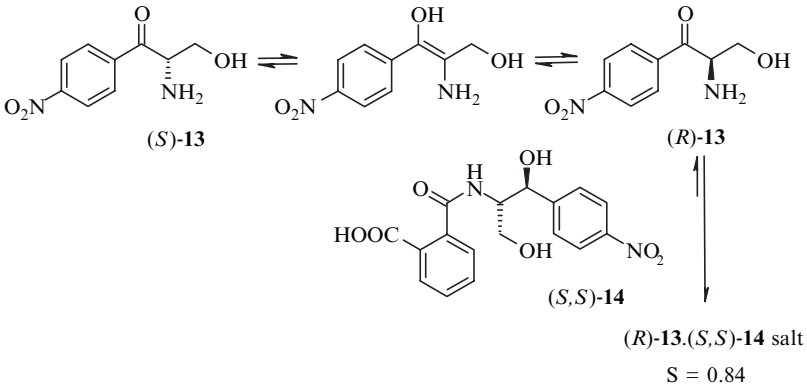
3.4. CONVERSION OF THE RACEMATE INTO ONE ENANTIOMER BY SECOND-ORDER ASYMMETRIC TRANSFORMATION

Combination of crystallization of a diastereoisomer with simultaneous racemisation (epimerisation) of the unwanted optical isomer is known from the literature as second-order asymmetric transformation.[10] In spite of the obvious advantages of this optical activation method, only few examples have been published in this field until now. Transformation of 2-amino-1-(4-nitrophenyl)-3-hydroxy-propanon (**13**), a key intermediate of chloramphenicol (antibiotic), into its optically active form demonstrate the versatility and efficiency of the combination of our "derivative resolving agent" concept with the simultaneous racemisation–diastereoisomeric salt crystallization system (Scheme 11).[9,30]

Because of the strong electron-withdrawing effect of the 4-nitrophenyl group in compound **13**, the aminoketone is configurationally stable in acidic medium but fast keto-enol equilibrium was observed under slightly basic conditions (pH = 7.5). On the other hand, the derivative resolving agent (*S,S*)-**14** form an acidic salt with (*R*)-**13** which is practically insoluble in aqueous methanolic solution. According to these facts, practically the whole amount of racemic **13** could be transformed into (*R*)-**13**.(*S,S*)-**14** salt within several minutes (efficiency S = 0.84, Scheme 11) by dropwise addition of the resolving agent to the solution of the racemate.

4. Resolutions by Diastereoisomeric Complex Formation

In the last decade numerous chiral complex forming agents have been published as resolving agents of wide range of racemic compounds. However, practical



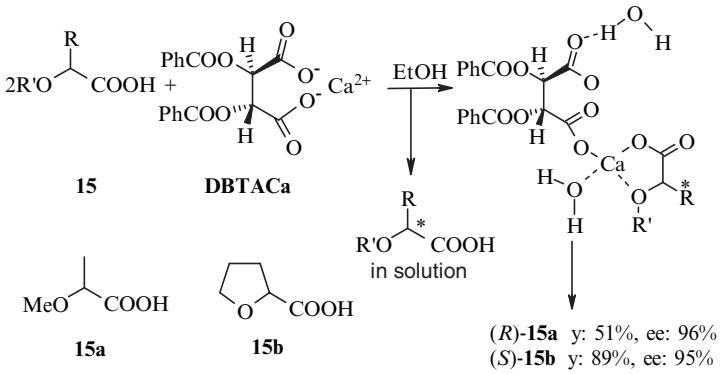
Scheme 11. Second-order asymmetric transformation of compound **13** using a "derivative resolving agent" (*S,S*)-**14**.

application of these enantiomer separation methods strongly depend on the availability and price of these resolving agents. O,O′-dibenzoyl-(*R,R*)-tartaric acid (DBTA) has been used frequently in industrial scales for separation chiral amine enantiomers via diastereoisomeric salt formation. Recently, the excellent complex forming ability of this resolving agent has been recognised in our laboratory.[31] Thus, for example, racemic α-alkoxycarboxylic acids **15a** and **b** could be resolved using the calcium salt of DBTA in alcoholic solution (Scheme 12).[32]

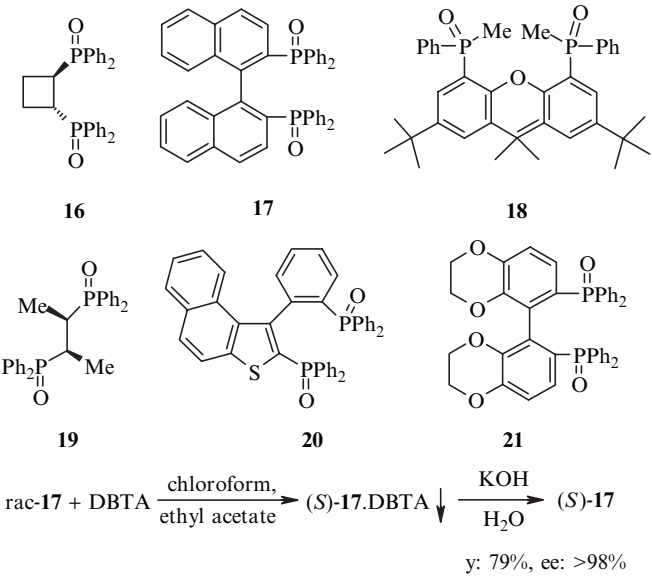
It has to mention that this diastereoisomeric complex forming reaction does not requires special conditions. The monohydrate form of DBTA was used and the calcium salt was prepared in situ by direct addition of the calculated amount of calcium oxide to the alcoholic solution of the resolving agent. Decomposition of the crystalline complex and recovery of DBTA is simple, **15a** and **b** enantiomers were isolated in 95–96% ee. Copper and zinc salts have been also used for similar diastereoisomeric coordination complex formation with great success.[32]

DBTA itself is an excellent resolving agent of chiral phosphine oxides, too. The very first resolution of BINAP (**17**, Scheme 13) was accomplished by Noyori and his co-workers[33] 20 years ago and the method has been widely used nowadays for the separation of enantiomers of racemic phosphine oxides.[31] Several examples are collected in Scheme 13.

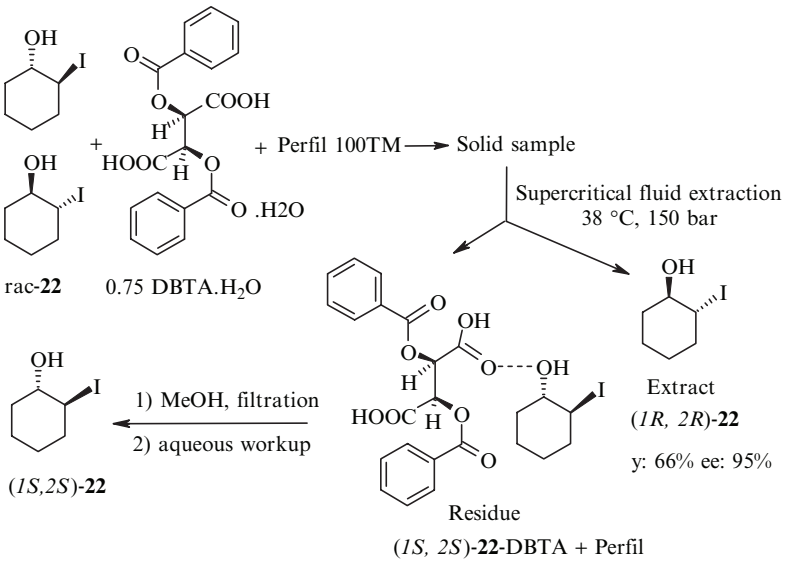
Recently, optical isomers of chiral secondary alcohols were resolved by diastereoisomeric complex formation with DBTA.[31] An example[34] of these type of resolutions is presented in Scheme 14. The method is quite simple and efficient: half an equivalent amount of solid DBTA powder was added to the hexane solution of the racemic alcohol (**22**) and the mixture was stirred together with Perfil as solid support. Then the solvent was evaporated in vacuo and the solid residue was extracted with supercritical carbon dioxide.



Scheme 12. Optical resolution of racemic alkoxycarboxcylic acids (**15a** and **b**) with DBTA. Ca salt.



Scheme 13. Chiral phosphines (**18–21**) resolved via their diastereoisomeric complex with DBTA.



Scheme 14. Optical resolution of 2-iodocyclohexanol (**22**) with DBTA under supercritical extraction conditions.

The free **22** enantiomer could be recovered from the extract in 95% ee, while the other isomer was isolated from the solid residue after decomposition of the diastereoisomeric complex by addition of methanol. Neither

halogenated solvents nor strong acid or bases were necessary, DBTA and carbon dioxide could also be recovered. Thus, this method represents a really benign technology for separation optical isomers.[34]

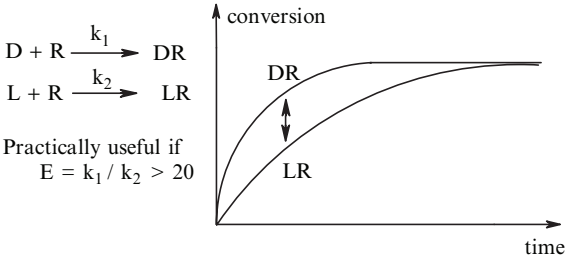
5. Recent Methods for Kinetic Resolution

The basis of kinetic resolution is the fact that the mirror image isomers react with an optically active compound (resolving agent) in different rates and the same phenomenon can be observed when the racemate react with an achiral reagent in the presence of an optically active catalyst (Scheme 15).[10] Efficiency of the enantiomeric enrichment in the product or in the unreacted residue strongly depends on the rate constants ratio ($E = k_1/k_2$).

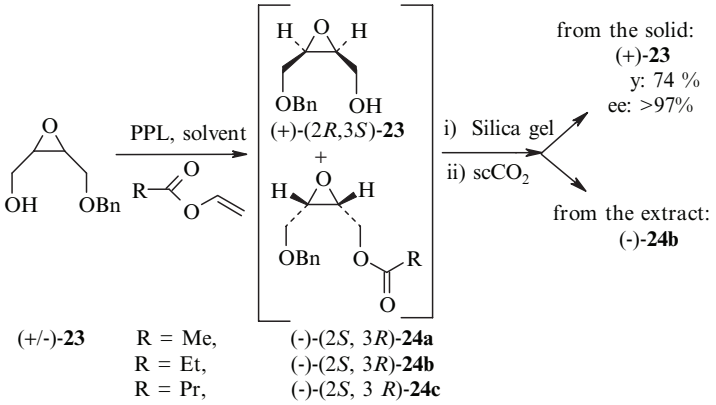
Practically useful kinetic resolution can be accomplished if E >20 and the covalent bond forming reaction is interrupted at about 50% conversion. Classical chiral reagents rarely give highly selective reactions with optical isomers therefore alternative methods have been developed to override this problem.

5.1. ENZYME-CATALYSED ACYLATION FOR KINETIC RESOLUTION

Application of enzymes instead of chiral reagents may improve the efficiency of a kinetic resolution. Nowadays dozens of enzymes are available form catalogs and can be tested as chiral catalysts in acylation, hydrolysis, oxidation and other reactions. In the most cases excellent enantioselectivities of the applied enzymes are reported (E >30–300) and the experimental conditions are usually simple.[35] A combination of enzymatic kinetic resolution of **23** with separation of the acylated alcohol enantiomer from the unreacted alcohol by supercritical fluid extraction represent a novel, efficient and environmentally soft resolution technology (Scheme 16).[36]



Scheme 15. Reaction schemes and conversion curves of DR and LR formation during kinetic resolution of D,L racemate with a resolving agent R.



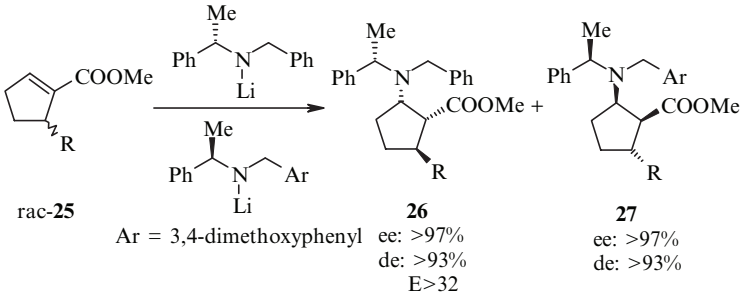
Scheme 16. Lipase (PPL)-catalysed kinetic resolution of **23** coupled with supercritical fluid extraction of the unreacted enantiomer from the supported reaction mixture.

The alkyl chain of the acylating agent did not influence the enantioselectivity. In the same time separation of the formed ester from the alcohol residue by supercritical fluid extraction was much more efficient with a propionate or butyrate ester than in the case of an acetate. Of course, the same enzyme can be used for hydrolysis of the optically active esters **24a, b** in ethanol or in buffered aqueous solution, too (Scheme 16). Some examples are known from the literature for enzyme-catalysed reactions under supercritical conditions but the above-mentioned protocol was the very first example when the enzymatic resolution was combined with the separation of the products by supercritical fluid extraction.

5.2. PARALLEL KINETIC RESOLUTION

In classical cases the rate difference between the reactions of two optical isomers with the same chiral reagent continuously decreases because the relative concentration of the slower reacting enantiomer gradually increases. In order to get rid of this problem the concentration of the slower reacting enantiomer should be decreased by another, parallel reaction (parallel kinetic resolution). A tricky and very efficient version of this method has been published by Davies and his co-workers (Scheme 17).[37] In this resolution a *pseudo*-enantiomeric mixture of two chiral lithium amides was reacted with the racemic compound **25**.

The two diastereoisomeric products (**26** and **27**) formed in 93% diastereoisomeric excess and 97% ee, respectively. It has to mention that the reaction is a combination of a parallel kinetic resolution and an asymmetric synthesis



Scheme 17. Parallel kinetic resolution of compound **25** (R = iPr, Ph, tBu, etc.) with a pseudo-enantiomeric mixture of chiral lithium amides.

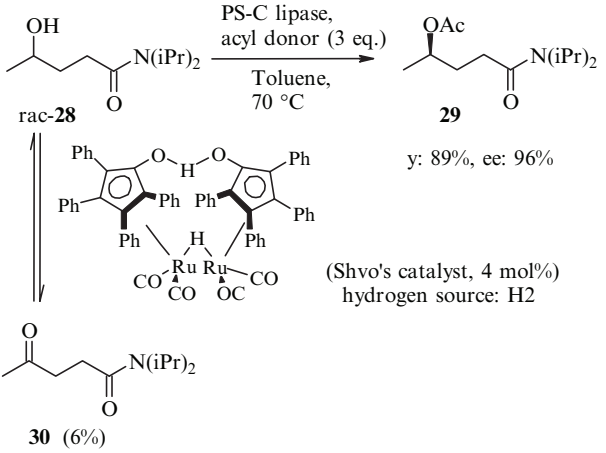
because two new stereogenic centers were also formed during the enantiomer separation process.

5.3. DYNAMIC KINETIC RESOLUTION

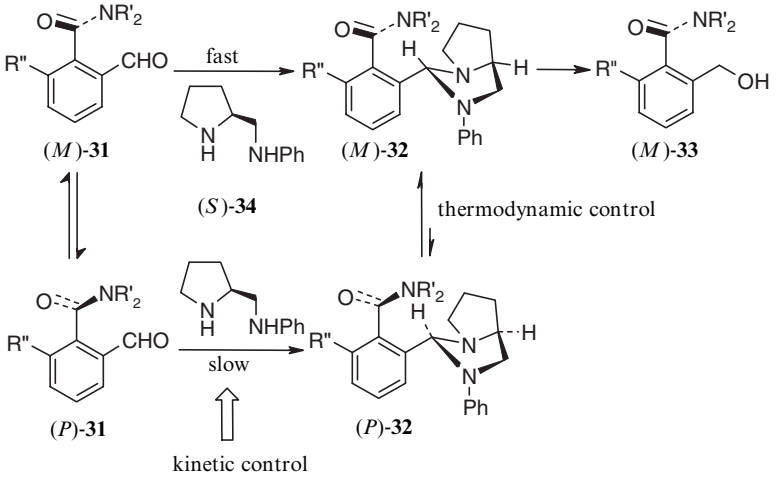
In special cases the slower reacting enantiomer can be converted into the mirror image isomer under the conditions of kinetic resolution and in this way the whole amount of the starting racemate is transformed into one, the desired enantiomer (dynamic kinetic resolution: DKR). The method has been known since many years but intensive development has started in the last few years only.[38] The research work in this field involves the development of coupled catalytic systems, too. Dynamic kinetic resolution of compound **28** represents a specially interesting example of such coupled systems (Scheme 18).[39]

Enantioselective acylation (kinetic resolution) of **28** is catalysed by a PS-C lipase enzyme, while racemization of the slower reacting **28** enantiomer (via its oxidized form **30**) is catalysed by 4% of a ruthenium complex (Svoh's catalyst[40]) in the presence of hydrogen. Racemisation has to be the fastest reaction in this system, and it is really the fact at 70°C. Fortunately, the enantioselectivity of the enzyme does not decreased at this temperature and the whole amount of racemic **28** was converted into optically active acetate **29** in 89% yield and 96% ee.

In some cases the result of a dynamic kinetic resolution can be influenced by thermodynamically controlled asymmetric transformation. It was the case when an atropisomeric mixture of compound **31** was resolved with (*S*)-**34** diamine (Scheme 19).[41] Product (*M*)-**32** formed faster in the kinetically controlled reaction but it was equilibrated with the slower forming (*P*)-**32** isomer. Fortunately (*M*)-**32** was the most stable compound, thus the endproduct (*M*)-**33** could be isolated in excellent enantiomeric purity.



Scheme 18. Dynamic kinetic resolution of **28** using a coupled catalyst system: PS-C lipase enzyme and Shvo's ruthenium complex.



Scheme 19. Dynamic kinetic resolution of compound **31** combined with thermodynamic equilibration of the diastereoisomeric intermediates ((M)-**32** and (P)-**32**).

6. Conclusions

Developments in the fields of biotechnological-, pharmaceutical- and fine chemical industries require continuous improvement of chemical methods to manipulate and create substances of increasing complexity and diversity with enhanced efficiency. An extremely important branch among the

highly sophisticated materials is the family of optically active compounds. In this field, optical resolution has remained a key challenge for chemists and engineers during the synthesis and manufacture of single enantiomers. If the enantiomers can be separated and the unwanted isomer racemised and recycled, or the resolution and racemisation can be accomplished in one reaction mixture, the resolution can be an efficient and environmentally friendly process. Recent techniques for separation of optical isomers include classical resolution, kinetic resolution (including enzymatic methods), second-order asymmetric transformation and dynamic kinetic resolution. Significant improvement of these methods have been accomplished by introduction of the pH-controlled version of the diastereoisomeric salt forming resolution, application of an optically active derivative of the original racemate as resolving agent, and successful combination of different separation techniques (e.g. distillation, supercritical fluid extraction) with the "half equivalent resolution method" or with an enzymatic kinetic resolution. The selected examples demonstrate that racemate synthesis and enantiomer separation or transformation of the whole amount of the racemic material into a single enantiomer by SOAT or DKR represent environmentally friendly and economic alternatives of asymmetric synthesis.

Acknowledgements

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HIGHLY SELECTIVE METALATION REACTIONS

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Abstract: The chapter will focus on the tools available for performing a selective replacement of a hydrogen by a metal in organic substrates. In addition some applications to the synthesis of valuable building blocks or target compounds using simple and selective strategies with alkali metals will be also presented.

Keywords: metalation, superbases, selectivity

1. Introduction

The present book is intended to cover the field of new methodologies and techniques available to the organic chemists to solve synthetic problems with regard to environmental issues. Several topics have been covered in the book particularly concerning the use of new and efficient catalysts, of new alternative energy sources like microwaves, of new reaction media and environmentally benign reagents. This chapter will focus on the search for new selective and efficient organic transformations particularly in the field of organometallic chemistry and metalation reactions.

A short survey on the tools available for performing a selective replacement of a hydrogen by a metal in organic substrates will be first presented followed by some applications to the synthesis of valuable building blocks or target compounds using simple and selective strategies with alkali metals.

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2. Selective Replacement of Hydrogen by Metal

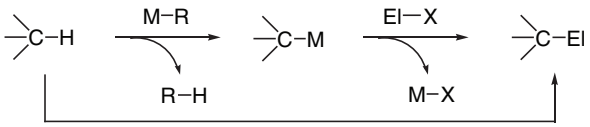
Metalation reactions (Scheme 1) are powerful tools for organic chemists because they easily allow the direct replacement of a hydrogen by a metal atom followed then by the introduction of virtually any kind of electrophilic reagent.[1–6]

Such a statement is true of course if some requirements are meet: first of all the substrate needs to be acidic enough to be deprotonated by an organometallic base, then the deprotonation and the following nucleophilic substitution have to be selective in order to be synthetically useful. The first issue can be often solved by an appropriate choice of activating substituents on the substrate to be deprotonated[7–9] or by the use of strong organometallic base or so-called superbasic mixtures.[3–6] Several powerful tools are available nowadays for facing the issue of selectivity, both concerning the stereoselectivity and the regioselectivity of metalation/substitution processes.[1,2,7,8,10,11]

2.1. ENANTIOSELECTIVE METALATION REACTIONS

The necessity of selectively removing one of two enantiotopic hydrogen atoms in a prochiral molecule can be overcome nowadays in most cases by the use of an organolithium reagent in the presence of a chiral ligand, mainly (-)-sparteine.[12]

The reaction sequence which leads from the prochiral substrate to the chiral functionalized molecule is not easy even apparently very direct and simple. A chiral ligand may influence the stereochemical course of either the formation of the organolithium intermediate (Asymmetric Deprotonation) or its following reaction with the electrophilic species (Asymmetric Substitution) or both. In addition the configurational stability of the organolithiums and the possible equilibration of the two epimeric species are also important issues to account when trying to explain mechanistically the outcome of enantioselective deprotonations with added chiral ligands (Scheme 2). All



Scheme 1. Metalation reactions.

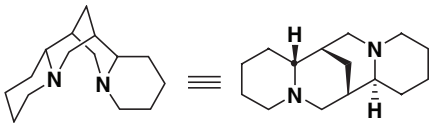
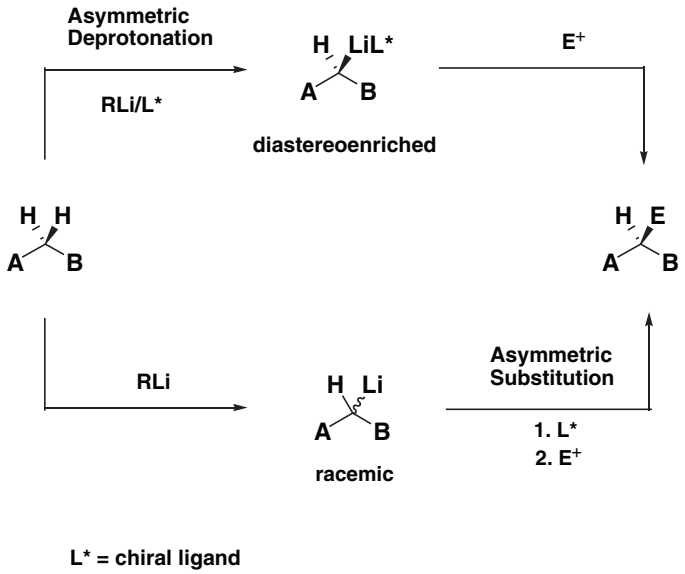


Figure 1. (−)-Sparteine.



Scheme 2. Enantioselective metalation/substitution reactions.

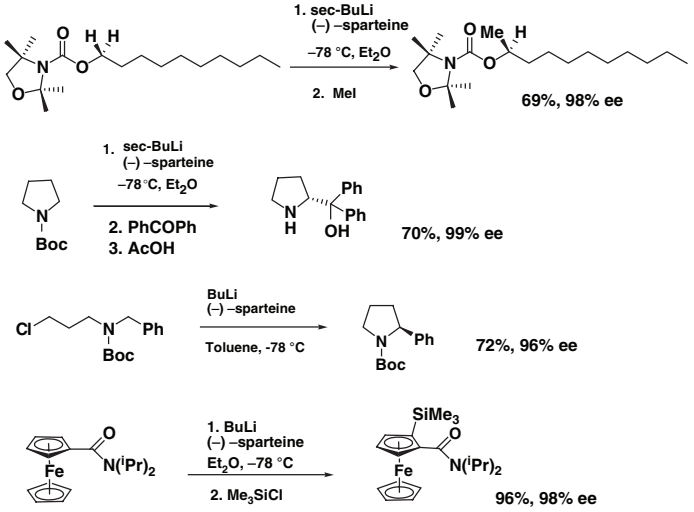
these aspects are far beyond the scope of this chapter and are well described in other books and reviews on the topic.[1,2,10,13]

Even if the mechanistic aspects are not always fully understood (−)-sparteine mediated lithiations have been widely employed giving access to a large variety of enentioenriched functionalized sutstrates.

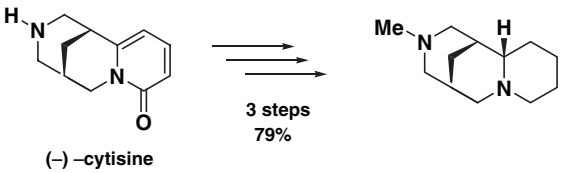
Enantioselective lithiation reactions were first discovered in the early 1970s by Nozaki and coworkers who reported that (−)-sparteine could induce modest enantioselectivities when used as added ligand in the asymmetric lithiation of ethylbenzene.[14] A big impulse in the study of enantioselective lithiation was given by the work on the functionalization of carbamates carried out by Hoppe in the early 1990s[15] who then fully developed this chemistry in the following years.[10,16] Extensive studies on the potential of sparteine in the synthesis and use of lithio carbanions α to nitrogen[13,17] have been conducted by Beak who has also carried out exhaustive works on the mechanism[13,18] of enantioselective lithiation with sparteine and on the comparison of the efficiency of several different chiral diamines ligands.[17]

Some typical examples of enantioselective lithiation are reported in Scheme 3.

(−)-Sparteine has the big advantage of being readily available from natural sources (it is extracted from the seeds of a variety of legumes such as Scotch broom) and commercially available. Unfortunately its (+) enantiomer is not equally available and its synthesis is quite lengthy. Quite recently however a (+)-sparteine surrogate has been synthesized[19] from (−)-cytisine (Scheme 4)



Scheme 3. Examples of enantioselective metalation/substitution reactions.

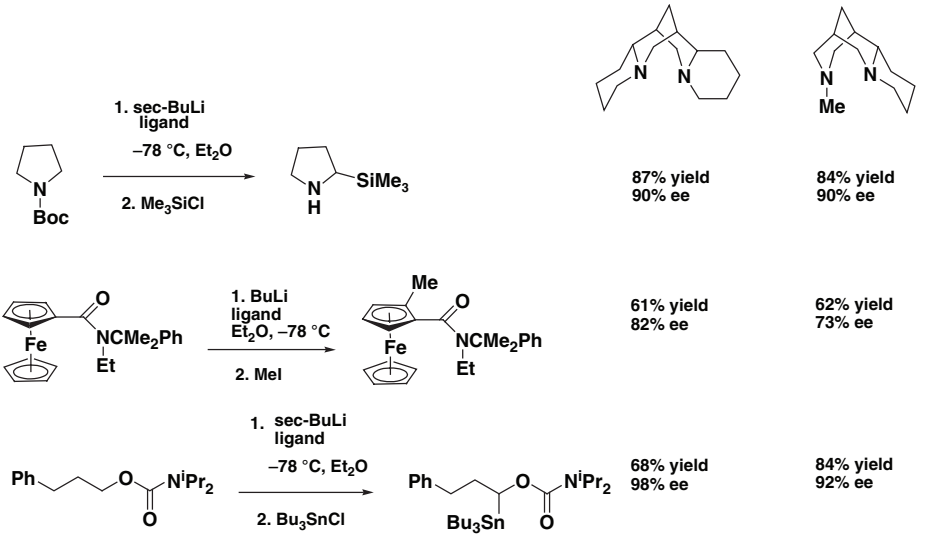


Scheme 4. A (+)-sparteine surrogate derived from (−)-cytisine.

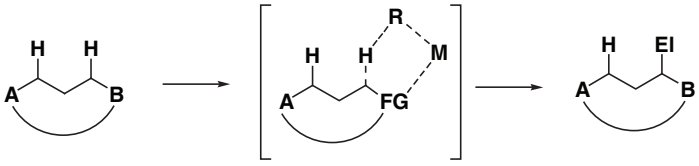
and early results suggest that it can perform as well as (−)-sparteine in asymmetric deprotonation reactions[20] even in substoichiometric amounts.[21,22] A few example are reported in Scheme 5 where both results with (−)-sparteine and its surrogate are indicated.

2.2. REGIOSELECTIVE METALATION REACTIONS

The problem of directing a deprotonation reaction on one of the available positions in an organic substrate can be faced in several different ways but those which deserve particular attention due to their wide use in the modern synthetic chemistry are essentially based on the concept of *complex induced proximity effect* (CIPE)[9,11] and in particular the *directed ortho-metalations* (DoM) (Scheme 6).[8,23,24]

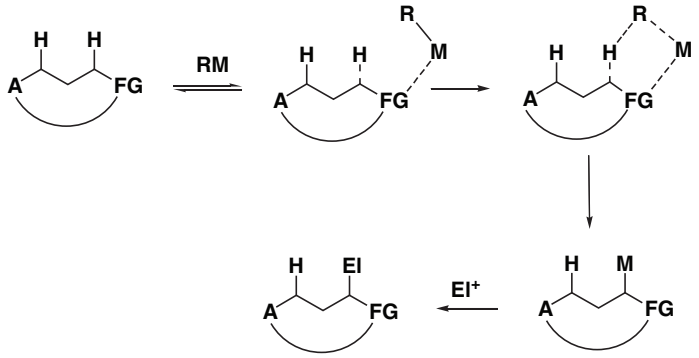


Scheme 5. Examples of enantioselective metalation/substitution reactions. Comparison between (−)-sparteine and its (+)-surrogate.



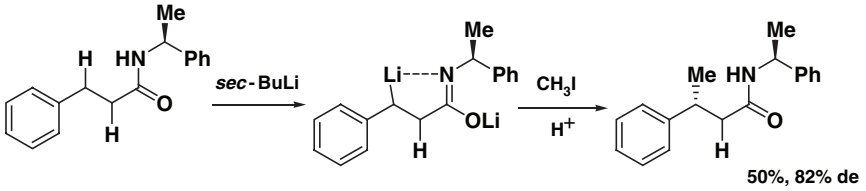
Scheme 6. Regioselective deprotonations.

According to this concept a hydrogen atom is more easily removed by a base if it is adjacent to a temporarily activating group. The typical CIPE is illustrated in Scheme 7.



Scheme 7. Complex induced proximity effect.

Most of the examples of CIPE are found in the metalation of nitrogen containing substrates. Scheme 8 shows how the presence of an amidic group directs the metalation of the phenyl ethyl amide into the benzylic position exclusively. After reaction with methyl iodide the final desired methylated product is obtained with high diastereoselectivity. Ethylbenzene (the unsubstituted reference substrate) under similar reaction conditions gives mainly lithiation on the aromatic ring. [11]



Scheme 8. CIPE in the metalation of phenylethyl amides.

CIPE has been largely used in the lithiation of amides,[25] carbamates,[9] formamidines,[26] in the nitrogen-containing substrates series and carbamates[10] when lithiation of oxygenated compounds is required. Milestones in this research area are outlined in Figure 2.

A particularly useful and widely explored class of metalation reactions guided by CIPE is the directed *ortho*-metalation (DoM). Altough the first examples of DoM had been discovered already in 1938,[23,27] its systematical use and exploitation has begun much later[8] but has lead to an extensive coverage of almost all kind of aromatic metalation directed by activating groups in the *ortho*-position. Many different *ortho*-directing groups are available to the purpose of doing DoM and a careful choice permits to perform selective reactions even on polysubstituted aromatic compounds in a sequential process. A partial list of activated aromatic substrates is shown in Scheme 9, while Scheme 10 illustrates typical examples of the application of DoM principles in the synthesis of industrially relevant products.

DoM principles have been largely explored in the metalation of heteroaromatic substrates also.[7,28–30] A complete coverage of the chemistry of lithiated heterocycles is far beyond the scope of the present chapter and it has already reported in several reviews and books.[3,28,29] An instructive

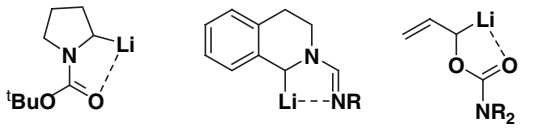
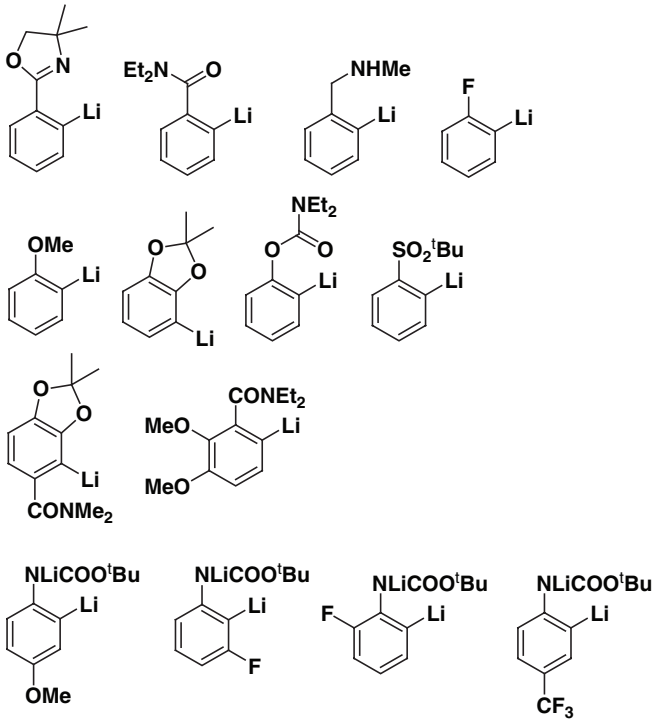


Figure 2. Typical lithiations of activated N and O-containing substrates.



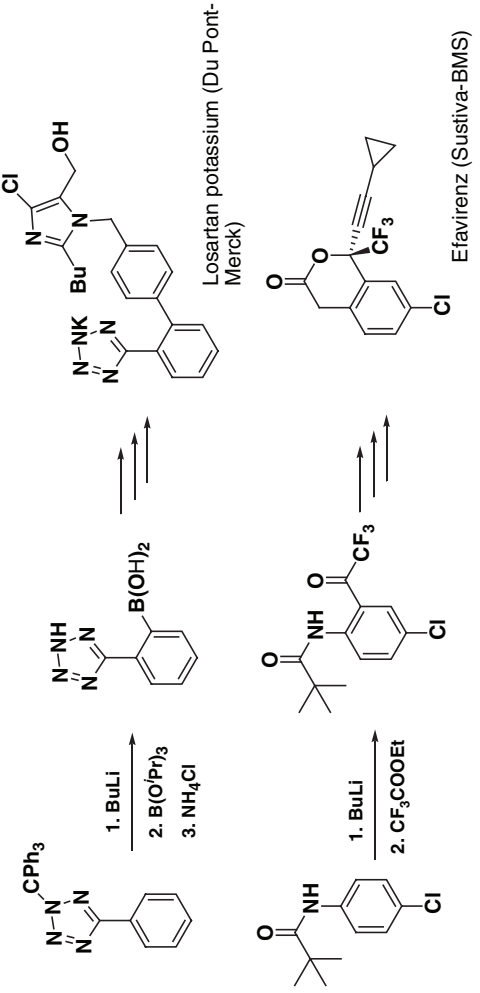
Scheme 9. Activated substrates for directed *ortho*-metalations.

example in which three consecutive *ortho*-directed lithiations followed by an additional lithiation, a bromine–lithium exchange and a final *ortho*-directed lithiation are used for the synthesis of the antibiotic atpenin B, is shown in Scheme 11.

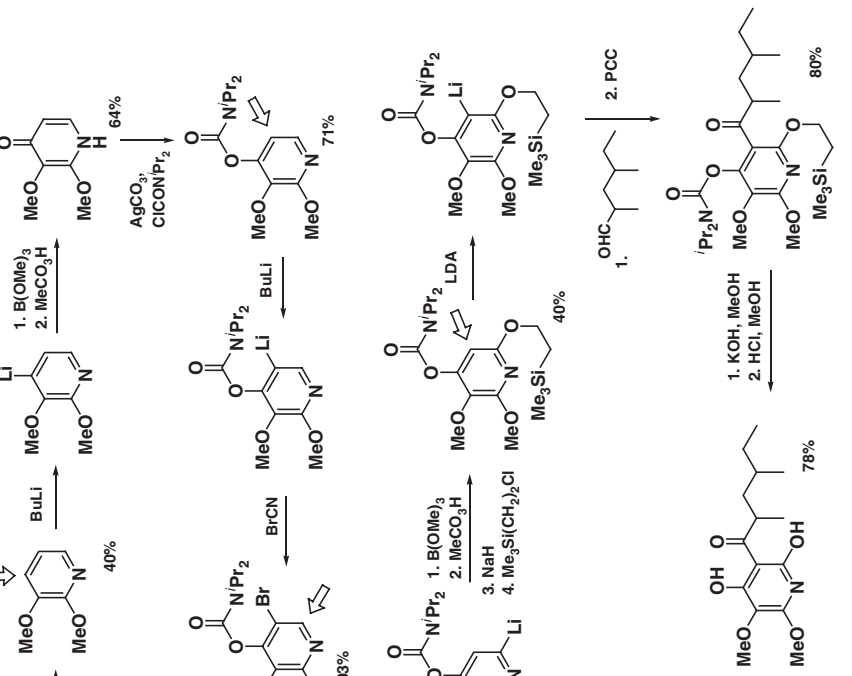
2.3. METALATIONS WITH SUPERBASES

As outlined above superbases can often be highly useful when substrates possessing low acidity need to be deprotonated. In addition they can often solve regio- as well as stereoselectivity problems in metalation reactions. Superbases are highly reactive organometallic species formed by mixing organolithium compounds and sodium or potassium alcoholates.[31] They have found many applications in the metalation of low acidic hydrocarbons as witnessed by many reviews on this subject by Schlosser[5,6,32–34] and by Mordini.[3,4,35,36]

Despite a long and still open debate concerning their nature in solution, the real constitution of superbases still remains obscure. The few safe conclusions which can presently be drawn concerning the nature of superbasic



Scheme 10. Example of DoM applied to the synthesis of industrially relevant compounds.



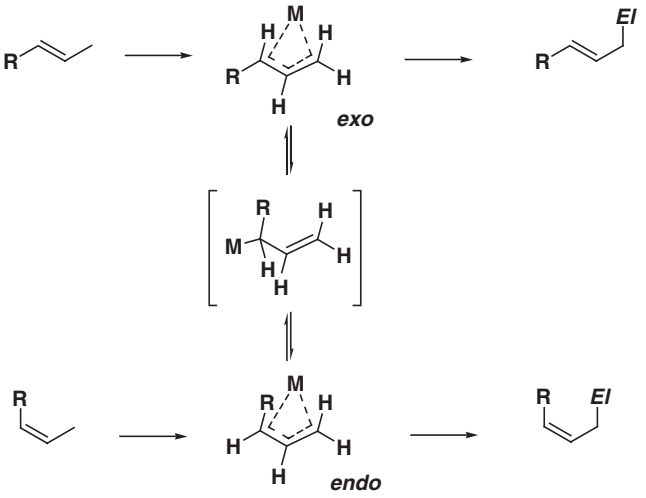
Scheme 11. Synthesis of atpenin B.

reagents are that when an alcoholate and an organolithium reagent are combined, a mixed aggregate is probably formed which contains strongly polarised organometallic bonds endowed with high reactivity; the metalation product after reaction with a superbasic reagent contains mainly, though not exclusively, the heavier alkali metal; the butyllithium/alkali metal alkoxide mixtures show different chemical behaviour compared to simple butylsodium or butylpotassium and offer major practical advantages over the latter reagents.

These features have allowed them to be widely and successfully employed in organic synthesis.

The main areas in which superbases have found interesting applications are the stereoselective metalation of alkenes,[34] the metalation of arenes and heteroarenes[7] and the selective rearrangements of oxiranes and aziridines.[37,38] While the latter will be discussed in more details in the following paragraph, some examples of lithiation of alkenes and arenes are illustrated below. Milestones in this field are the stereoselective metalation of 2-alkenes[34,39–47] which allows the preparation of stereochemically pure substituted alkenes and the metalation of aromatic and heteroaromatic compounds. The stereochemical control in alkene metalation is due to the fact that once the allylic derivative of potassium is formed, after metalation with a superbase, it generally shows a high preference for adopting mainly one of the two possible conformations if the reaction mixture is submitted to torsional isomerization under thermal[39,48,49] or catalytic conditions.[50] Once the equilibrium is reached, the *endo*: *exo* distribution is strongly in favour of the former.[34] As a consequence, if a 2-alkene is treated with butyllithium/potassium *tert*-butoxide (LIC-KOR) in THF at low temperature for a sufficiently long reaction time (usually 15–20 h) and then quenched with an electrophile, the functionalized *cis*-alkene is obtained almost exclusively. In addition, if the starting alkene is chosen either as a pure *cis*- or *trans*-stereoisomer and is then sequentially treated with LIC-KOR and an electrophile without equilibration of the allylpotassium intermediate, the pure *cis*- or *trans*-olefin is obtained respectively. Such behaviour of the allylpotassium reagents has been widely employed in the synthesis of stereochemically pure alkenes and is illustrated in Scheme 12.

Even if simple organolithium reagents can be often basic enough to deprotonate heterosubstituted arenes, the use of a superbasic reagent may result in a different regiochemical behaviour.[7] We have already discussed above about the directed *ortho*-metalation concept. The *ortho*-directing effect has been attributed either to the electronegativity of the heterosubstituent[51] or to the coordinating property of the electron-donor ligand particularly towards lithium atoms.[52] These two effects (inductive and coordinative) often operate simultaneously[6] and the higher contribution of one with respect to the other depends not only on the heterosusbstituent but also



Scheme 12. Stereochemical behaviour of allylpotassium compounds.

on the deprotonation reagent used. As a rule of thumb, weakly solvated organolithium compounds optimally exploit the coordinative capacities of a substituent, whereas the superbasic mixture butyllithium/potassium *tert*-butoxide preferentially deprotonate such positions where charge excess is most efficiently stabilized.[53] This mechanism-based matching of neighboring groups and reagents has allowed the metalation of a large number of arenes carrying two different heterosubstituents, with the so-called *optional site selectivity*.[6,7,53,54]

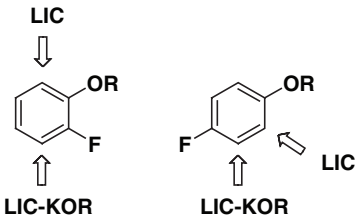
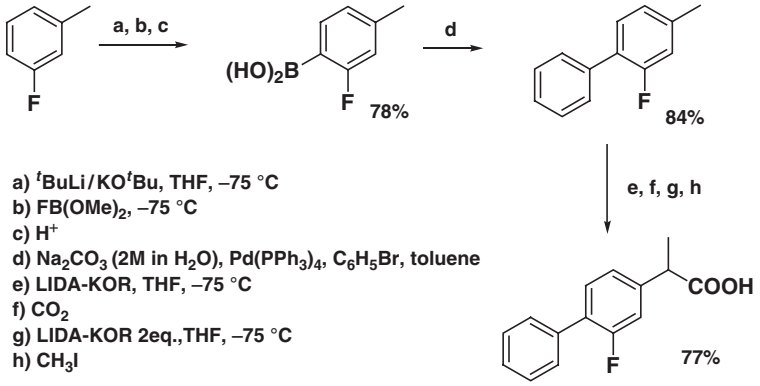


Figure 3. Optional site selectivity.

The concept of optional site selectivity is better illustrated by a few examples (Figure 3). Both 2- and 4-fluoroanisole undergo clean deprotonation of an oxygen-adjacent position[55] by butyllithium alone which takes advantage of the coordination by the methoxy group. Contrarily when LICKOR is used, the metalation occurs at the fluorine adjacent position.[55] The reagent being optimally coordinated this time from the beginning, the relative basicities of the organometallic intermediate becomes now the crucial factor.

The optional site selective metalation of fluorotoluenes[56] with the superbasic mixture of butyllithium and potassium *tert*-butoxide has been applied



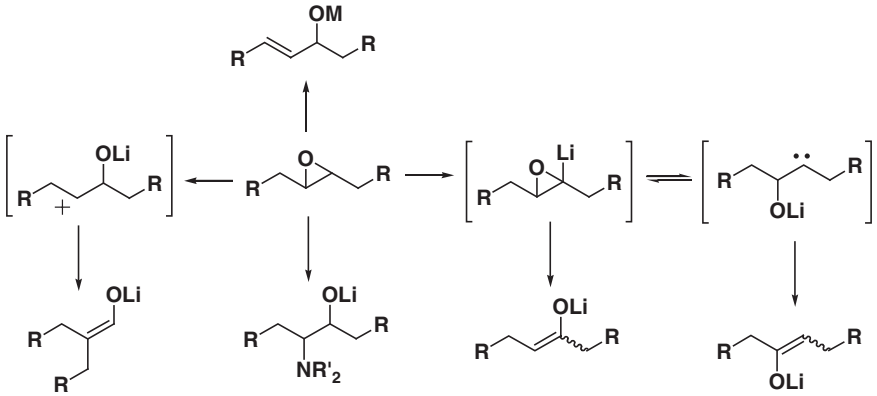
Scheme 13. Synthesis of flurbiprofen.

to the synthesis of the antiinflammatory and analgesic drug Flurbiprofen as illustrated in Scheme 13.[57] 3-Fluorotoluene is selectively metalated in the 4-position with LIC-KOR in THF at −75°C to afford, after reaction with fluorodimethoxyborane and hydrolisis, the corresponding boronic acid in 78% yield. A palladium catalyzed coupling with bromobenzene gives the 2-fluoro-4-methylbiphenyl in 84% yield. A double metalation with the superbasic mixture lithium diisopropylamide/potassium *tert*-butoxide (LIDA-KOR)[37,58] is then required to produce flurbiprofen.

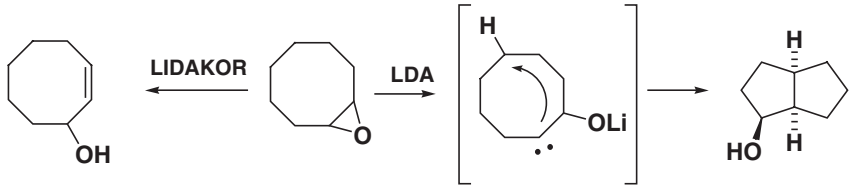
3. Superbases Promoted Rearrangements of Small Ring Heterocycles

It is well known that small ring heterocycles can undergo a number of synthetically useful transformations such as nucleophilic ring opening,[59–62] α-lithiation[63,64] and β-elimination[37,65–69] reactions. The latter isomerisation which leads to either allylic alcohols or allylic amines when oxiranes or aziridines are used as starting substrates respectively, is often characterized by low regioselectivity due to a series of concomitant reaction pathways such as α-deprotonation, carbene formation followed by rearrangement and nucleophilic ring-opening (Scheme 14). It has been shown that the use of the superbasic mixture lithium diisopropylamide/potassium *tert*-butoxide (LIDAKOR) has a strong influence on this process both with oxiranes[37] and aziridines[38] always leading to the expected β-elimination product exclusively.

The superbase-promoted isomerization (Scheme 15) shows good selectivity on simple alkyl substituted oxiranes as well as epoxycycloalkanes, the latter being usually more difficult substrates to be rearranged to allylic alcohols. As an example, epoxycyclooctane is transformed into 2-cyclooctenol by LIDAKOR[37] while treatment with LDA leads to the bicyclic alcohol as



Scheme 14. Reaction pathways in the treatment of oxiranes with bases.



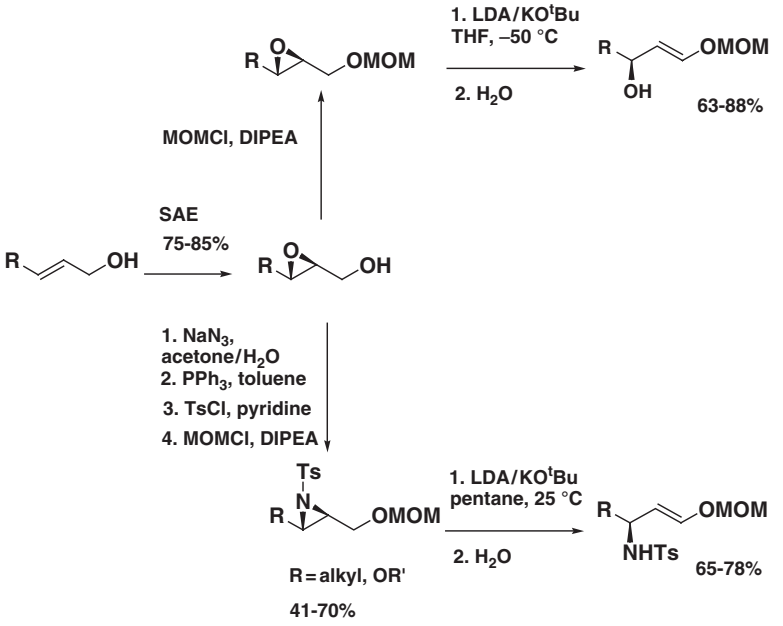
Scheme 15. Isomerization of epoxycyclooctane.

the main product which derives by α-lithiation followed by formation of a carbene species and a transanular C–H insertion reaction.

It has soon clearly appeared that the superbase promoted isomerization of small ring heterocycles offers its best potentialities when applied to heterosubstituted substrates in sight of further synthetic application of the rearranged products. Most of the efforts have been devoted[70–72] to alkoxy substituted compounds which can be obtained from allylic alcohols through Sharpless asymmetric epoxidation.[73–75] The oxiranyl ether is simply alkylated to give the corresponding alkoxy oxirane or submitted to ring opening by azide, ring closure with triphenyl phosphine, tosylation of nitrogen and alkylation to give the aziridinyl ether.

The alkoxy substituted heterocycles when treated with the superbasic mixture LIDAKOR are selectively transformed into the corresponding hydroxy- or amino vinylethers. Such reaction is quite general and occurs with high selectivity and yields. Due to a *syn*-periplanar β-elimination pathway, the vinylic ether is usually obtained with a high *E*-selectivity (Scheme 16).

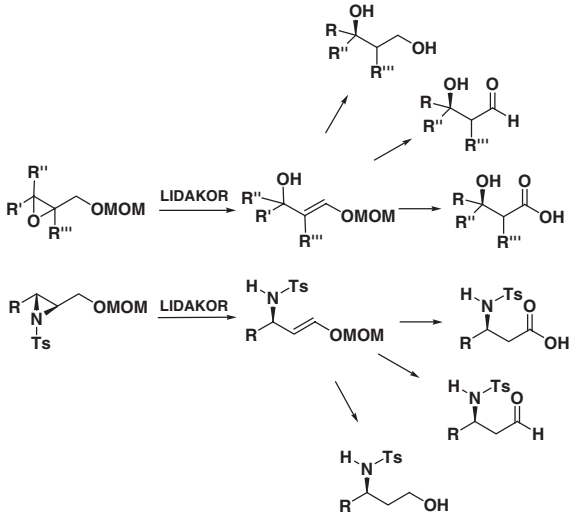
The rearranged products can be conveniently transformed first into either 3-hydroxy or 3-amino aldehydes by simple deprotection, and these intermediates can then undergo a number of synthetically useful transformations



Scheme 16. β-Elimination of oxiranyl- and aziridinyl ethers.

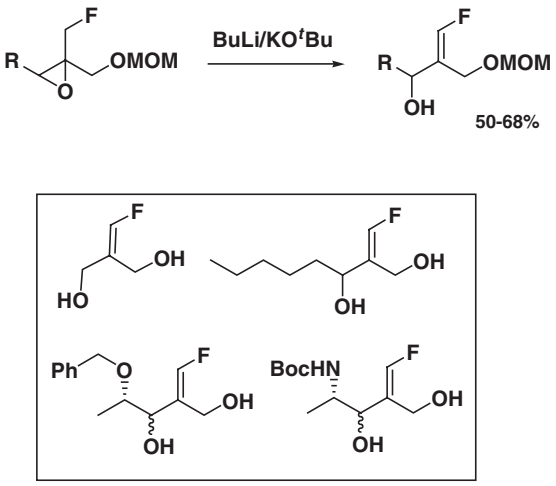
leading for example to β-hydroxy or β-amino acids or to β-hydroxy- or β-amino alcohols (Scheme 17).[71,76]

Interestingly oxiranyl ethers can also contain additional functional groups then allowing the rearrangement to highly functionalized compounds without



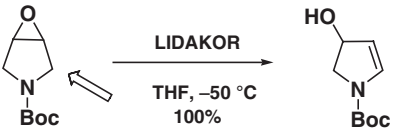
Scheme 17. Syntethic elaborations of hydroxyl- and amino vinylethers.

loosing the high selectivity mentioned above. As an example fluoro oxiranyl ethers, obtained in a multistep synthetic sequence starting with a Baylis–Hilmann condensation of the desired aldehyde and ethyl acrylate, are rearranged to dihydroxy vinyl fluorides with a surprisingly high regio- and stereoselectivity, the *E*-vinyl fluoride being the only detected product in most cases (Scheme 18).[77]



Scheme 18. Base-promoted isomerisation of epoxy fluorides.

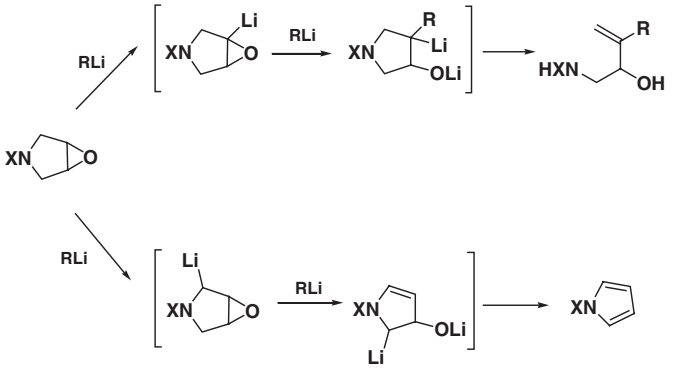
Amino oxiranes also undergo a clean rearrangement to hydroxy enamines as illustrated by the example of the N-Boc-3,4-epoxy pirrolydine which clearly isomerizes to N-Boc-4-hydroxy-2,3-dihydro pyrrolidine in quantitative yield (Scheme 19).



Scheme 19. Superbase-promoted isomerisation of epoxy pyrrolidine.

Interestingly when the same rearrangement is attempted by using usual organolithium reagents, completely different pathway are followed[78,79] leading either to N-Boc pyrrole or to ring-opened product (Scheme 20).

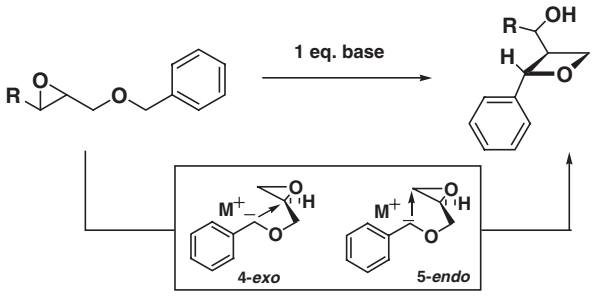
Superbases have also shown their high synthetic utility when applied to the intramolecular nucleophilic ring opening of oxiranes. Benzyl oxiranyl ethers, when treated with LIDAKOR, undergo a clean 4-*exo* ring closure eventually leading to disubstituted oxetanes[72,80] with a good stereocontrol the 2,3-*trans*



Scheme 20. Organolithiums-promoted isomerisation of epoxy pyrrolidine.

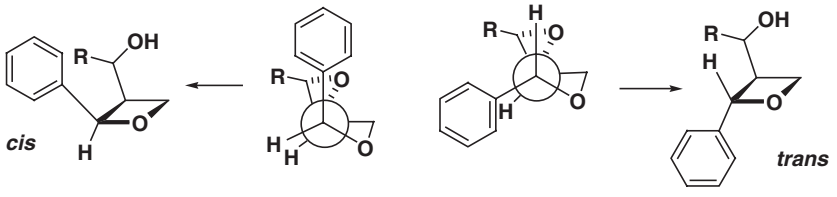
disubstituted heterocycle being formed preferentially (Scheme 21). No trace of the product deriving form a 5-*endo* rearrangement is found.

The reaction is quite general and several 2,3-*trans* oxetanes have been prepared following this procedure from the isomeric epoxyethers.



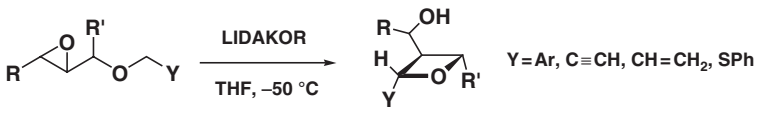
Scheme 21. Benzyl oxiranyl ethers rearrangement to oxetanes.

The main drawback of such process is that only benzyl ethers of epoxy alcohols undergo such rearrangement (Scheme 22); any other ether such as allylic, propargylic, phenylthiomethylic undergo mainly the β-elimination process to the corresponding hydroxy vinylether according to the process described above.



Scheme 22. Stereoselectivity in the benzyl oxiranyl ethers rearrangement.

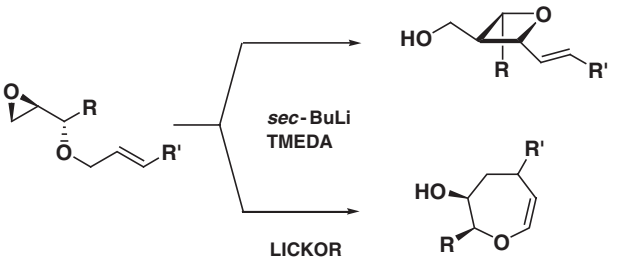
On the other hand, the formation of trisubstituted oxetanes from secondary allylic alcohols derived oxiranyl ethers is general (Scheme 23). The presence of a substituent on the carbon between the epoxy ring and the alkoxy group, renders the β-elimination process more difficult thus favouring the 4-*exo* ring closure.



Scheme 23. Oxiranyl ethers rearrangement to trisubstituted oxetanes.

The stereochemical control is pretty good even in the trisubstituted oxetanes formation. Again the 2, 3-*trans* isomer is generally the major one while the relative stereochemistry at position 3, 4 depends on the configuration of the starting epoxyether.

The use of allylic ethers represents an instructive example of the selectivity control due to superbases. It is known[81,82] that the allylic ethers of monosubstituted oxiranes when treated with organolithium reagents give a mixture of the isomeric oxetane and tetrahydrooxepine deriving from a 4-*exo* and a 7-*endo* ring closure respectively (Scheme 24). It is not possible to con-



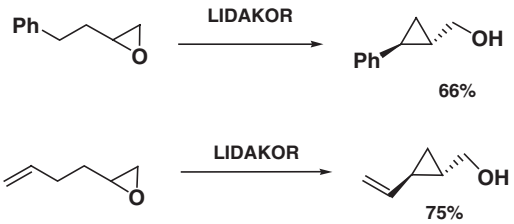
Scheme 24. Oxiranyl allyl ethers rearrangement to tetrahydrooxepines.

trol the outcome of this reaction by using simple organolithium reagents as base. But when the superbasic mixture butyllithium/potassium *tert*-butoxide (LICKOR) is used, the reaction becomes highly selective leading exclusively to the tetrahydrooxepines.[83] Also this rearrangement is general, several functional groups being tolerated both on the allylic double bond and on the carbon α to the oxirane.

In addition to the 4-*exo* and 7-*endo* ring closures described above, superbase can also efficiently promote 3-*exo* rearrangements. It is known that cyclopropanes can be obtained from oxiranes through cyclizations

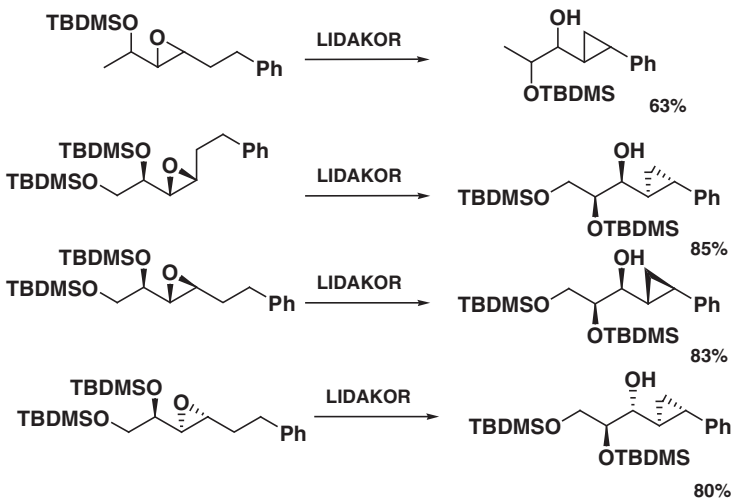
induced by carbanions. Usually the formation of the carbanionic species is performed on substrates possessing good activating groups (nitriles,[84–86] esters,[87,88] amides,[89] ketones,[90] sulfones,[91–93] sulfides[94]) while very little is known on similar processes performed on oxiranes without a heterosubstituent able to stabilize the carbanionic intermediates. The only known results in this field date back to the 1970s when it was first reported[95,96] that lithium amides in the presence of HMPT as a cosolvent were able to convert a few 1-aryl- and 1-alkenyl-3,4-epoxyalkanes into the corresponding cyclopropanes. Drawbacks of this reaction were the use of the highly toxic HMPT, the low stereoselectivity and the quite limited number of examples.

Once more the use of superbases reveals its high efficacy in promoting selective carbanionic processes. Both phenyl- and allyl-substituted oxiranes undergo a clean and selective conversion to the corresponding cyclopropanes with high yields and selectivities (Scheme 25).



Scheme 25. Oxirane to cyclopropanes rearrangements.

The reaction is quite general. It can be done with di- and trisubstituted oxiranes and more importantly, with highly functionalized substrates as those reported in Scheme 26 below.



Scheme 26. Rearrangements of functionalized oxiranes to cyclopropanes.

4. Conclusions

The utility of metalation reactions for organic chemists is greatly enhanced by the possibility of controlling both its regio- and stereochemical outcome. Nowadays such controls have been made accessible by the use of methodologies which allows to selectively replace hydrogen atoms virtually from any position in a sufficiently activated molecule. Most of such processes are selective and efficient enough to meet the criteria required for a sustainable chemistry.

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