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Angela Patti

Green Approaches To Asymmetric Catalytic Synthesis

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Preface

The importance of chirality in molecular recognition processes and the biological activity of many chiral pharmaceutical drugs and agrochemicals is nowadays well accepted and there is a continuous need for synthetic methods leading to single or enriched enantiomers. Chiral compounds also find application in the development of specific sensors for biological molecules and new materials with peculiar properties related with ordered spatial arrangements.

Hystorically, nature has been the main source of chirality and many synthetic processes relied on compounds from "chiral pool" as starting materials, resolving agents for the separation of enantiomers from their racemate, or chiral auxiliaries in diastereoselective synthesis. In the last 20 years asymmetric catalytic reactions, based on the ability of non natural chiral compounds in sub-stoichiometric loading to promote the synthesis of a single enantiomer in large amount through selective chiral multiplication effect, have became largely predominant exerting a tremendous impact on the production of chiral compounds from achiral molecules. The relevance of this approach has been acknowledged by the Nobel prize awarded to Sharpless, Noyori and Knowles for their fundamental research in this field. Most catalysts are complexes of chiral ligands with transition metals and fine tuning of sterical and electronic properties of the ligands has provided in many cases high levels of stereoselectivity, even at very low catalyst loading, suitable for industrial scale-up.

At the beginning of the 90s, the increased attention to the protection of human and environmental health led to the development of "green chemistry", which gives central emphasis to the design of new chemicals and processes aimed to reduce or eliminate the use and generation of hazardous substances. This goal could be achieved with a substantial modification of all the aspects of a chemical process from the more obvious use of renewable sources or waste minimisation to conceptual changes in synthetic reactions in order to maximize atom economy and limit derivatization steps whenever possible. Fundamental approaches of research in this field are well summarised in the "twelve principles of Green chemistry" and, in this context, catalysis is a milestone in that it is often compatible with the

use of less toxic reagents, reduction in energy requirements, high productivity and simplification of separation procedures.

Since the effects of chiral drugs or agrochemicals in most cases reside on a single enantiomer while the other is inactive or displays antagonist and/or adverse effects, there is an increasing demand of formulations containing stereochemically pure active ingredients that beneficially allow reduced total administered dose, enhanced therapeutic window or activity and suppression of the risks associated to the "inactive" enantiomer. In this context, asymmetric catalysis has gathered a key role in organic synthesis and much research has been focused on its advance in a more sustainable direction.

Considerable efforts have been carried out for structural optimization of the catalysts, since asymmetric induction is directly related with their chemical, stereochemical, electronic and steric properties. In transition-metal catalysis, besides the most investigated C_2-symmetrical ligands, unsymmetrically disubstituted or monodentate ligands and bifunctional catalysts have been also explored in conjunction with the use of less toxic and/or less expensive metals, leading to an expanded portfolio of effective asymmetric reactions today available. Simultaneously, the first report ten years ago of a proline-catalysed direct asymmetric aldol reaction opened the door to "organocatalysis" that has emerged as a powerful methodology, complementary to biocatalytic and metal-transition catalysis, with attractive features in high operational simplicity, low cost and toxicity of catalysts and the possibility to perform several reactions through different activation modes.

In the search for more benign alternatives to organic solvents, many of which are volatile, flammable and harmful for human and environmental health, water, ionic liquids and fluorinated solvents have been largely investigated and biphasic liquid-liquid systems based on these non conventional reaction media have allowed the selective recover and recycle of chiral catalysts, providing that they were suitably labeled with ionic or fluorous substituents in order to increase their phase-affinity. In a complementary recycle strategy, a variety of active catalysts have been immobilized on macromolecular supports and recovered by solid–liquid separations. The productivity of some asymmetric reactions has been markedly improved through the application of microwave irradiation as non-conventional heating source or the development of continuous-flow reactors, which have provided more prolonged catalyst life, reduction of solvent waste and simplification of workup procedures. As concerns the design of new synthetic strategies, enantioselective cascade reactions represent an emerging and exciting research field for their potential in the construction of complex molecules from simple precursors in a single process, thus avoiding the costly protection/ deprotection steps and purification of intermediates.

Herein is presented a general overview of the approaches currently applied for "green" optimization of the different factors contributing to the overall efficiency of an asymmetric catalytic process together with selected examples taken from seminal references in the field and the past five-year literature. Rather than a comprehensive discussion of each argument this text offers a concise manual of the

fundamental concepts with the aim to stimulate the interest of readers in new opportunities offered to chemists for synthetic buildup of stereochemical and molecular complexity, preserving at the same time human and environmental resources.

Acknowledgements

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Contents

Abbreviations

AcOH	acetic acid
ATH	asymmetric transfer hydrogenation
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaftile
BINOL	1,1′-Bi-2-naphthol
BIPHEMP	2,2′-bis(diphenylphosphino)-6,6′-dimethyl-1,1′-biphenyl
BIPHEP	2,2′-Bis(diphenylphosphino)-1,1′-biphenyl
Bn	benzyl
BOX	bis-oxazoline
bpy	2,2′-bipyridine
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
CAN	cerium(IV) ammonium nitrate
CBS	Corey-Bakshi-Shibata
CBz	Benzylcarboxycarbamate
CHIRAPHOS	2,3-bis-(Diphenylphosphino)butane
CHMP	cumylhydroperoxide
COD	cycloocta-1,5-diene
cPME	cyclopentyl methyl ether
CSP	chiral stationary phase
DAD	diode array detection
DAIPEN	1,1-Bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine
DANB	2,2′-diamino-1,1′-binaphtalene
DET	diethyl tartrate
DHQ	hydroquinine
DHQD	hydroquinidine
DIPT	di-*iso*-propyl tartrate
DKR	dynamic kinetic resolution
DMF	dimethylformamide
DMSO	dimethylsulphoxide

DOPA	3,4-dihydroxy-phenylalanine
DPEN	1,2-diphenylethylendiamine
DS	dodecyl sulphate
DuPHOS	1,2-Bis[(2*S*,5*S*)-2,5-diphenylphospholano]ethane
EPA	Environmental Protection Agency
FSPE	fluorous solid-phase extraction
HMDS	hexamethyldisilazane
hPG	hyperbranched polyglycerol
IL	ionic liquid
LDA	lithium di-*iso*-propylamide
MBH	Morita-Baylis-Hillman
Mes	1,3,5-trimethylbenzene
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
MTMP	2,2,6,6-tetramethylpiperidine
MW	microwave
NADH	nicotinamide adenin dinucleotide hydride
NP	nanoparticle
OTf	triflate = trifluoromethanesulphonate
PEG	polyethylene glycol
PHAL	1,4-phthalazine
Salen	salyciden ethylendiamine
SMB	simulated moving bed
SOMO	singly occupied molecular orbital
TADDOL	trans-α,α'-(Dimethyl-1,3-dioxolane-4,5-diyl)-bis(diphenylmethanol)
TBDMS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Trisyl	2,4,6-tri-*iso*-propylbenzenesulfonyl
Ts	tosyl = (4-methyl)phenyl sulphonyl

Chapter 1
Methods for the Preparation of Optically Active Chiral Compounds

Abstract The biological activity of chiral compounds is markedly affected by their chirality and there is a growing demand for the synthesis of such molecules in enantiopure form in order to limit and/or suppress adverse effects deriving from the use of the racemic mixtures. This tendency is in agreement with the objectives of "green chemistry", that gives a central emphasis to the protection of human and environmental health through the design of new chemicals and processes. Among the different methods for the preparation of optically active compounds, racemic resolutions can be improved by addition of racemization step to recycle the unwanted enantiomer or by using automated chromatographic methodologies. In stoichiometric asymmetric synthesis the use of chiral substrates or auxiliary groups allows to control the stereochemical outcome of several reactions through intramolecular transfer of chirality. Although these methodologies continue to be widely employed, asymmetric catalysis has emerged as more sustainable option and some processes have been yet applied at industrial level.

Keywords Green chemistry · Enantioenriched compounds · Racemate resolution · Chiral pool · Chiral auxiliares · Asymmetric catalysis

1.1 Introduction

A large number of naturally occurring compounds with important biological activities exist as single enantiomers and also amino acids and sugars, the building blocks of proteins and nucleic acids ubiquitously present in living systems, are chiral. The fundamental biological activities of these biopolymers can be related with their assembling into highly ordered supramolecular architectures that might ultimately derive from the homochirality of their constituent units. The most part

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of living processes occurs stereoselectively as a consequence of the fact that the chirality of a biological receptor can fit well only with a molecule having a specific spatial atomic disposition, according the called "lock and key" recognition mechanism.

Therefore, chirality is an essential dimension in the earth's life and the origin of homochirality in biology is a continue subject of debate. According to a recent suggestion homochirality could be ultimately resulted from biased destruction of one enantiomer of the early amino acids, formed in comet dust, by means of the action of circularly polarised radiation that makes up 17% of stellar radiation [1, 2]. The phenomen of optical self-purification by fractional sublimation has been also considered for a prebiotic origin of chirality [3]. A complementary chemical theory has been proposed by Soai et al. on the basis of the finding that some chiral compounds, even with extremely low enantiomeric excess (*ee*) induced by a chiral initiator, are able to acts as chiral catalysts for their own production increasing significantly their optical purity during the reiteration of the process [4, 5]. Even the low *ee* (<2%) induced by the circularly polarised radiation in [6]-helicene was proved sufficient for the activity of this compound as chiral initiator in a reaction of asymmetric autocatalysis with amplification of chirality [6]. An evolution of chirality from the achiral nucleobase cytosine has been also suggested on the basis of its spontaneous crystallization into helically enantioenriched crystals shown to be active as chiral trigger for asymmetric autocatalysis [7].

The stereoselectivity of biological processes implies that the pharmacological and agrochemical efficacy of drugs and pests often resides on one enantiomer, the other one being inactive or showing antagonist or adverse effects [8]. In the early 1960s thalidomide, a chiral drug marketed as racemic mixture, began to be prescribed as sedative for pregnant women but the increase in the number of babies with malformations was soon related with the teratogenic activity of (*S*)-thalidomide. Although thalidomide was banned in many countries, the case dramatically evidenced the need of more stringent rules for the evaluation of pharmacological activity and side-effects of a chiral drug. The actual regulatory guidelines [9] impose biological tests and pharmacokinetic analyses on separated enantiomers and there is a continuously growing need for the production and marketing of chiral drugs in enantiopure form [10] in order to gain better performances and limitation of risks. Other applications of chiral compounds range from flavours, fragrances and food additives to chiral materials, as polymers and liquid crystals, in which peculiar properties can be imparted by the presence of structurally asymmetric monomers or dopants [11, 12].

The widespread demand for chiral compounds in optically active form is in accordance with the increased attention to the minimization of human and ecological risks that at the beginning of 1990s has led to the development of the "environmental sustainability" concept as a new philosophy aimed to make the progress compatible with environmental well-being and savings of natural resources. In this context, the regulation of pollution and waste disposal, the search for alternative energies, the development of more degradable or recyclable materials have been recognised as imperative actions for the protection of the

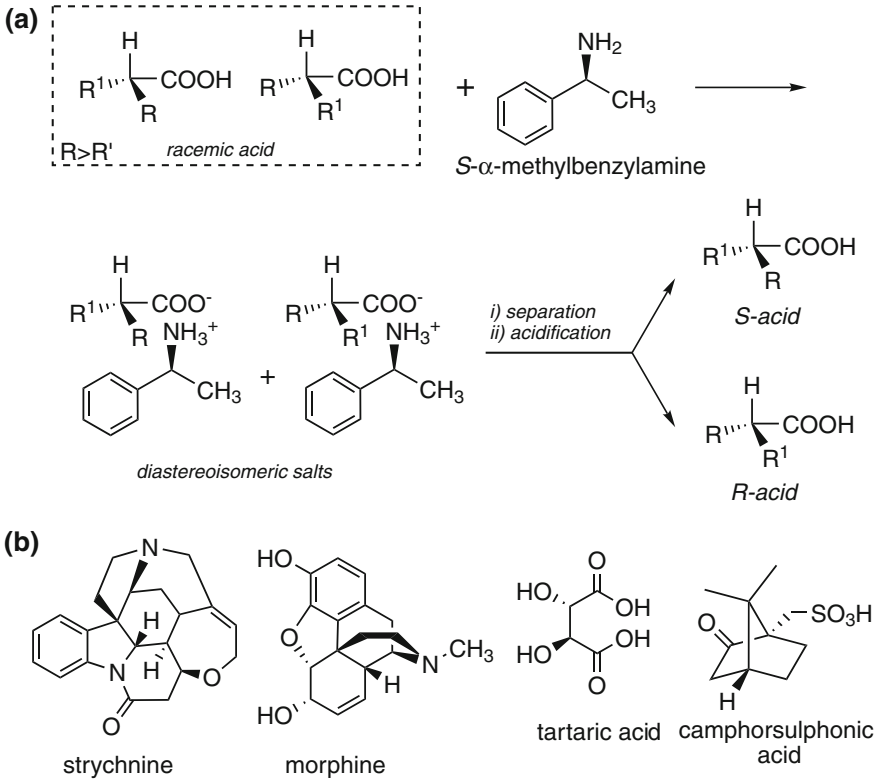
environmental and human health. These strategies have been also extended to chemical sciences and in 1991 the term "green chemistry" was coined to define the design of new chemicals and processes that reduce or eliminate the use and generation of hazardous substances. The different approaches to the development of more sustainable chemical production are well summarised in the "twelve principles of Green chemistry" [13, 14] according to which substantial modifications of all the aspects of a chemical process, from the more obvious use of renewable sources or waste minimisation to the more challenging design of novel reactions and simplification of the purification procedures, are greatly encouraged. The measure of the environmental acceptability of a given chemical process can be expressed by *E factor* (environmental factor) [15], defined as the mass ratio of waste to desired product, or by *atom efficiency* (or *atom economy*) [16] calculated from the ratio of molecular weight of the product to the sum of molecular weights of all the substances involved in the stoichiometric equation of the considered reaction. Whereas the atom efficiency is a theoretical number, for which a 100% chemical yield is assumed and all the substances that does not appear in the stoichiometric equation are ignored, the E factor gives a more realistic description of the chemical process since all the component of the reaction are taken into the account also including the solvent, the salts generated in the work-up and the excess of reagents. The comparative evaluation of environmental hazards and fate, cost and performances with respect to a currently used chemical process have been also considered in the U.S. EPA procedure for the assessment of cleaner technologies [17].

In light of green chemistry principles intensive research has been devoted to development of efficient methods for the preparation of enantiopure compounds by improving the currently used processes in an evolutionary (short-medium term) approach or by introducing innovative concepts and solutions in a breakthrough (long-term) approach.

The classical methods for the production of optically active compounds are usually grouped into three categories: (a) resolution of racemates, based on the differential interactions, either covalent or non-covalent, of each enantiomer in the racemic mixture with a chiral agent; (b) chemical modification of chiral pool; (c) asymmetric synthesis, in which the stereochemistry of new formed asymmetric carbons or other stereogenic elements can be controlled by the chirality of substrates, reagents or catalysts. In this section a short survey of all these methodologies is presented together with some selected examples of their applications.

1.2 Resolution of Racemates

The historical method for the production of optically active compounds is the resolution of racemates [18, 19] through a reaction with a stoichiometric chiral reagent that converts the two enantiomers into a couple of diastereoisomers, separable with the common separation techniques for their different physical

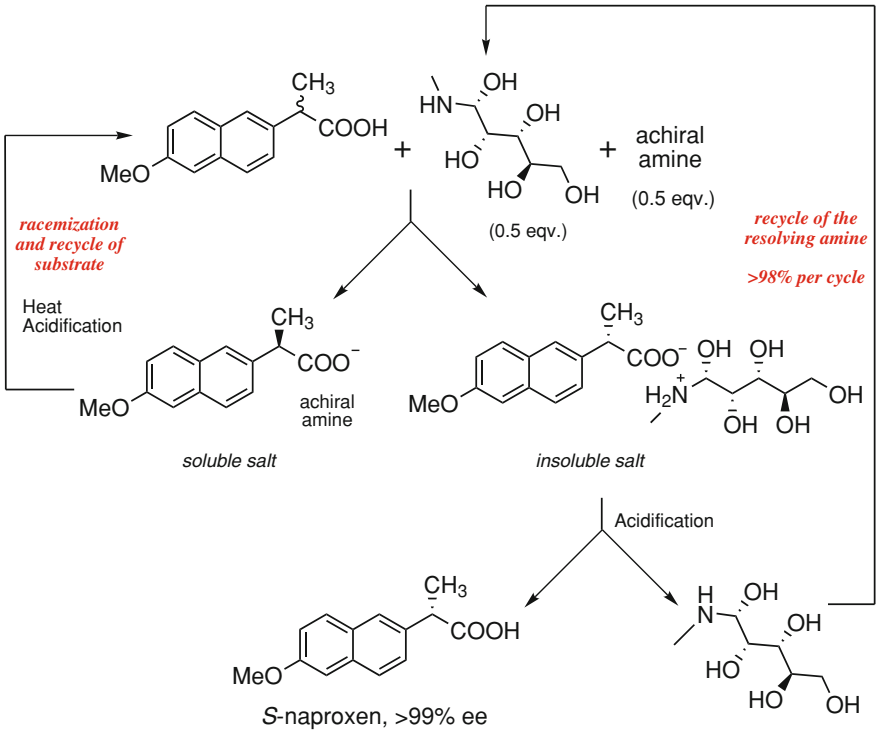


Scheme 1.1 Resolution of racemates by cristallization (**a**) and some common resolving agents (**b**)

and chemical properties, from which the chiral reagent and the enantiomers are then recovered.

The simplest racemic resolutions exploit the formation of diastereoisomeric salts with chiral acids or bases (Scheme 1.1) and the preferential crystallization of one of them. The search of the optimal chiral resolving agent, routinely carried out with a trial-and-error method, can be improved by a selection based on different criteria, as structurally analogy, thermodynamic data, use of additives [20], or by a combinatorial approach based on performing the resolution in the presence of a mixture of chiral compounds belonging to the same "family of resolving agents" [21].

The advantage of easy recover of both enantiomers and the resolving reagent from the separated diastereoisomeric salts by simple pH variation makes the method largely applied at industrial level [22]. When only one optical antipode is required, as in drug formulations, the sustainability of the process can be increased through an additional step for racemization of the unwanted enantiomer to be recycled in repetitive resolution procedures until a satisfactory overall yield of the



Scheme 1.2 Industrial Syntex process for the resolution of Naproxen

desired enantiomer is obtained. This approach has been applied in the Synthex resolution technology for the production of (*S*)-naproxen [23], one of the few anti-inflammatory drugs in the family of arylpropionic acids marketed exclusively in optically active form (Scheme 1.2).

In the extension of this method, especially useful for compounds with chemical functionalities other than acid and basic groups, the resolution can be achieved through the enantioselective complexation, driven by hydrogen bonds and other weak interactions, of a racemate with a suitable chiral host. Diastereoisomeric inclusion host–guest complexes are separated in many cases as crystals and synthetic hosts based on a variety of molecular scaffolds have been developed for the resolution of different classes of compounds. For example, some cholic acids have been reported as enantioselective receptors for sulphoxides, epoxides and lactams [24] whereas arylalkanols have been resolved by selective inclusion into supramolecular helical architectures constructed from pairs of organic achiral acid/chiral diamines [25].

Host-mediated enantioselective liquid–liquid extractions have been applied when the substrate-receptor interaction is sufficiently high to drive an active transport across liquid phases with different polarity, from a feeding solution

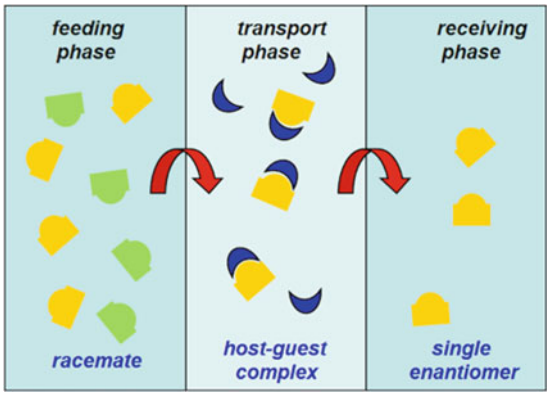


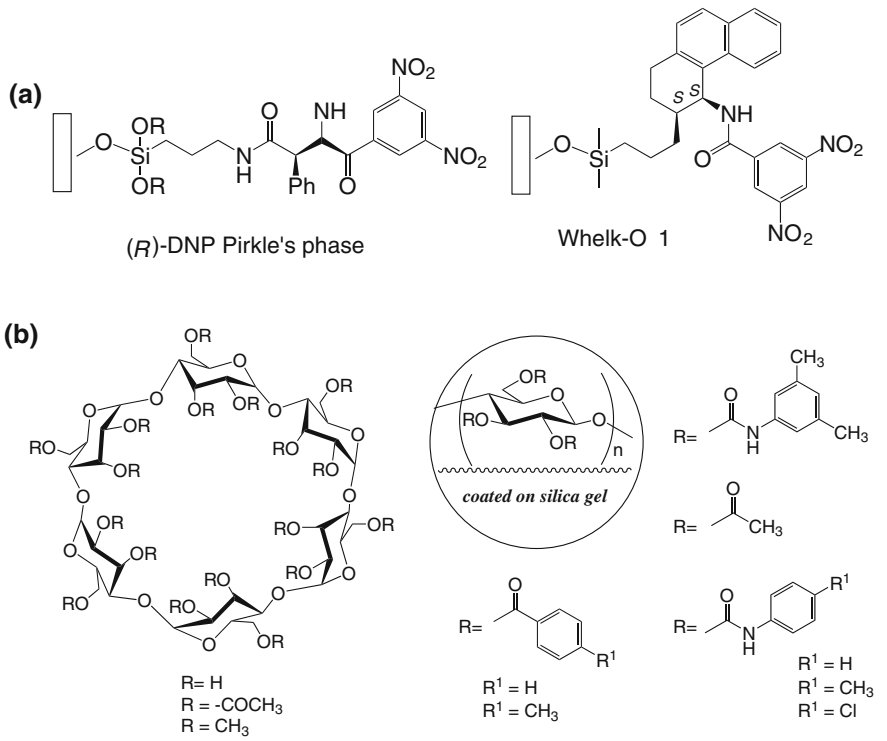
Fig. 1.1 Schematic representation of host-mediated liquid–liquid extraction

containing the racemate to a receiving phase through a transport phase containing a solution of the chiral host (Fig. 1.1). The selective extraction of *N*-acylated amino acids has been described using a solution in heptane of cinchona alkaloids kept in contact with two aqueous phases buffered at different pH values [26].

Methods based on diastereoisomeric salts or complexes are preferred for the reversibility of the involved interactions that allow simple recover of the chiral reagent, but the conversion of enantiomers into diastereoisomeric derivatives by covalent reaction with a chiral auxiliary has been also considered in the racemate resolution. Enantiopure camphorsulphonic acids, phenylacetic acids, menthol or benzyl amines are easily available and widely used in the synthesis of diastereoisomeric esters and amides, whereas chiral *vic*-diols as 2,3-butanediol are a popular choice for the resolution of ketones through ketalization. The diastereoisomeric derivatives are usually purified by chromatography and the optically active antipodes of substrate are then recovered by removal of auxiliary group.

Physical methods as ultrafiltration on chiral polymeric membranes are still limited to the resolution of few compounds, mainly amino acids, but this technique could be promising in the future for large-scale separations in conjunction with the development of novel and more selective membranes. More recent approaches deal with the immobilization of chiral ligands, as cyclodextrins and crown ether derivatives, or large biological macromolecules, as proteins or DNA, on natural and synthetic polymers for the preparation of membranes with different mechanism of selectivity (diffusion, sorption or affinity). In other cases, the polymerization of specific monomers in the presence of an inducer for chirality or one-handed helical conformation has been exploited for the preparation of achiral polymers that retain the "chiral memory" after the removal of the chiral template and are able to display some degree of enantioselectivity in the permeation process [27].

Reversible non-covalent interactions are also responsible for the dynamic separation of enantiomers by liquid chromatography on chiral stationary phases (CSPs) [28], a technique that is extensively used for the analytical determination of enantiomeric purity but can be easily scaled-up at preparative level without



Scheme 1.3 Brush-type (**a**) and polysaccharide-based (**b**) chiral stationary phases for liquid-chromatography

sacrificing selectivity. Many brush-type stationary phases with a chiral selector covalently bonded on silica are available and π–π interactions between π-donor and π-acceptor aromatic rings of analyte and CSP as well as hydrogen bonding and dipolar interactions are mainly involved in the differential retention behaviour of two enantiomers that are then eluted from the column at different times. Additional inclusion phenomena occur when chiral macrocycles, as native or derivatized cyclodextrins, or chiral polymers, as functionalised cellulose or amylose that provide a chiral helical environment, are coated or covalently immobilised on silica support (Scheme 1.3). Polysaccharide-based CSPs coupled with different elution modes [29–31] today account for over 90% of the reported enantioselective separations [32] and their high cost is partially balanced by the automation of the chromatographic process.

Simulated moving bed (SMB) chromatography is a continuous purification technique that have attracted a growing interest in the industrial production of chiroptical compounds and shows significant benefits with respect to batch chromatography in terms of solvent consumption and productivity, allowing to achieve high purities even when the resolution factor on a single column is <1.2 [33]. The technique makes use of several chromatographic columns arranged in a four

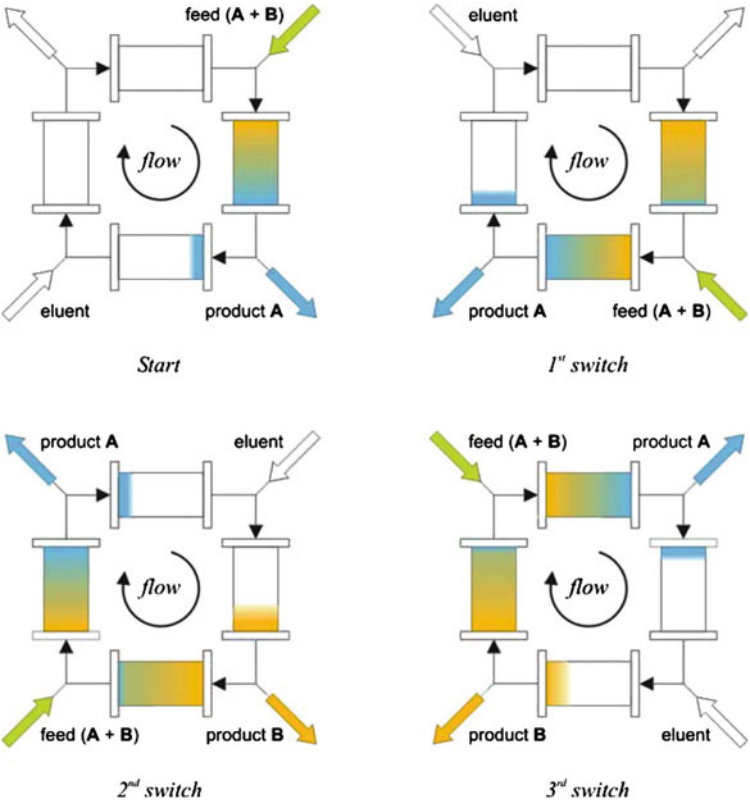


Fig. 1.2 Schematic representation of the separation of two compounds by simulated moving bed chromatography

section ring, containing one or more column for section, with two inlet streams (feed and eluent) and two outlets streams (extract and raffinate) directed in alternating order to and from the columns' loop. The countercurrent movement of the liquid mobile phase with respect to the stationary phase is then simulated shifting at regular time intervals the position of the ports by one column in the direction of the solvent flow (Fig. 1.2).

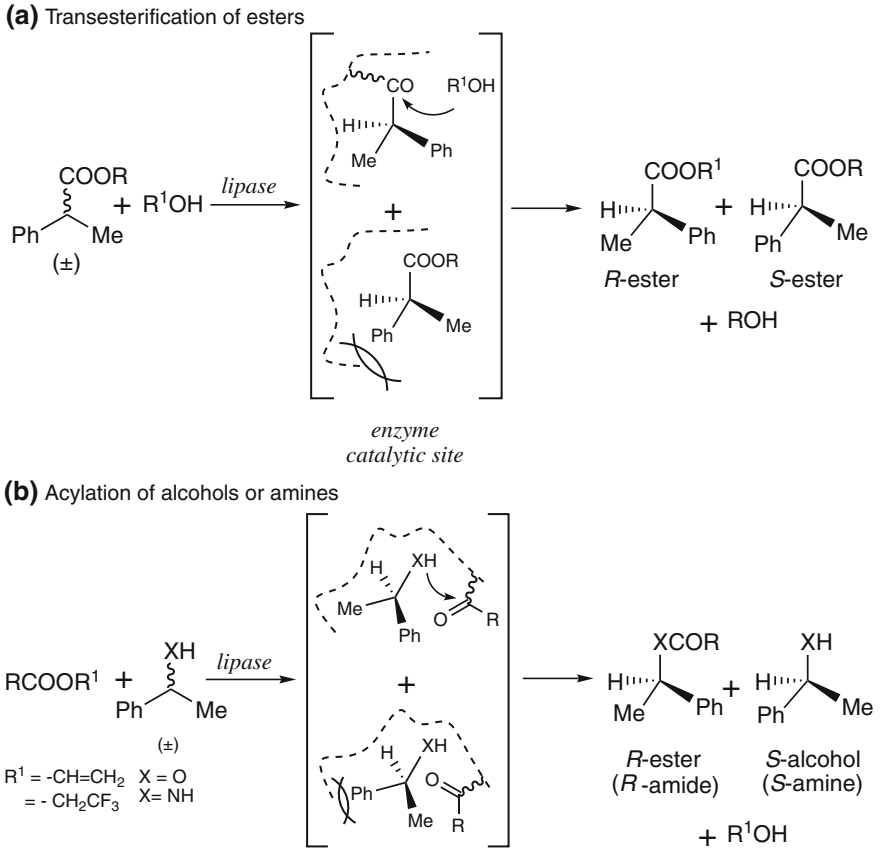
Biocatalysed resolutions in which a racemic substrate reacts under enzymatic control constitute another important method for the preparation of enantiopure compounds. Although in most cases an aqueous reaction medium is strictly required in order to preserve the native conformations essential for the activity of the biological catalysts, the Klibanov's group firstly demonstrated that some enzymes save their catalytically active conformations even if they are surrounded by a water monolayer in a bulk organic solvent and in this context polar solvents are less suitable than the hydrophobic ones because they tend to strip out the water from the enzyme surface [34]. Using nearly dry organic solvents some advantages come from better solubility of substrates, enhanced enzyme stability and the

possibility to recover the enzyme by simple filtration and carry out reactions that are impossible in water because of kinetic or thermodynamic restrictions.

Hydrolytic enzymes as lipases and esterases are widely employed in organic synthesis [35–37] due to their large substrate acceptance, stability in both aqueous and organic solvent, relatively low cost and the possibility to modulate their stereoselectivity and/or substrate specificity by changing the solvent [38] or by using suitable additives. In the cellular aqueous medium they catalyze the hydrolysis of esters through the formation of an acyl-enzyme intermediate that undergoes the nucleophilic attack of water to give the free acids and alcohols. Instead, in organic solvent the cleavage of the acyl-enzyme intermediate by other nucleophiles becomes feasible due to the low water content and results in the synthesis of new esters or amides. Because of the intrinsic chirality of enzymes, the enantiomers of a racemic substrate can be transformed with different reaction rate according their tendency to be accommodated into the catalytic site and the overall process is described as a kinetic resolution. The enzyme enantioselectivity ($E = k_R/k_S$) is expressed by the ratio of the reaction rates for the two enantiomers and a model for the rationalization of the *R*-stereopreference observed for the majority of lipases has been also developed [39, 40].

Varying the experimental conditions lipase-catalyzed stereoselective reactions have been designed for the resolution of several racemic esters, alcohols or amines and vinyl esters or activated trifluoroethylesters are usually chosen as acyl donors in order to suppress the reversibility of enzymatic processes. In an ideal case ($E > 200$) for a lipase showing *R*-stereopreference, the biocatalysed acetylation of a racemic alcohol (Scheme 1.4b) should afford the *R*-acetate and the unreacted *S*-alcohols, both compounds in >95% *ee* and theoretical 50% yield. At lower *E* value, the enantiomeric profile of the enzymatic reaction is strongly dependent by the conversion according Sih's equations [41] but the product and the substrate can be obtained in high optical purity below or beyond 50% of substrate conversion, respectively.

An interesting improvement in lipase-catalysed acylation of racemic alcohols relies on the dynamic kinetic resolution (DKR) methodology, based on the presence of both the enzyme and a racemization catalyst in the reaction mixture so that meanwhile an enantiomer is selectively acylated by lipase the other one is continuously racemized in situ and becomes prone to be resolved again. In this way all the racemic starting material can be virtually converted into a single enantiomer and in one of the early applications of this approach a serie of *S*-cianohydrin acetates was obtained in 70–96% yield and 70–91% *ee* by reaction of the racemic cianohydrins with isopropenyl acetate in the presence of *Pseudomonas fluorescence* lipase and an anion-exchange resin (OH^- form) as one-pot racemisation catalyst [42] (Scheme 1.5a). The Bäckvall's group has then developed some pentaphenylcyclopentadienyl ruthenium complexes active in 2–15% mol as catalysts for the racemisation of simple and functionalised alcohols in mild conditions compatible with lipases [43] (Scheme 1.5b). Since it was shown that racemisation proceeded via hydrogen transfer mechanism within the coordination sphere [44] of the ruthenium catalyst, in some instances the yield efficiency of DKR process was

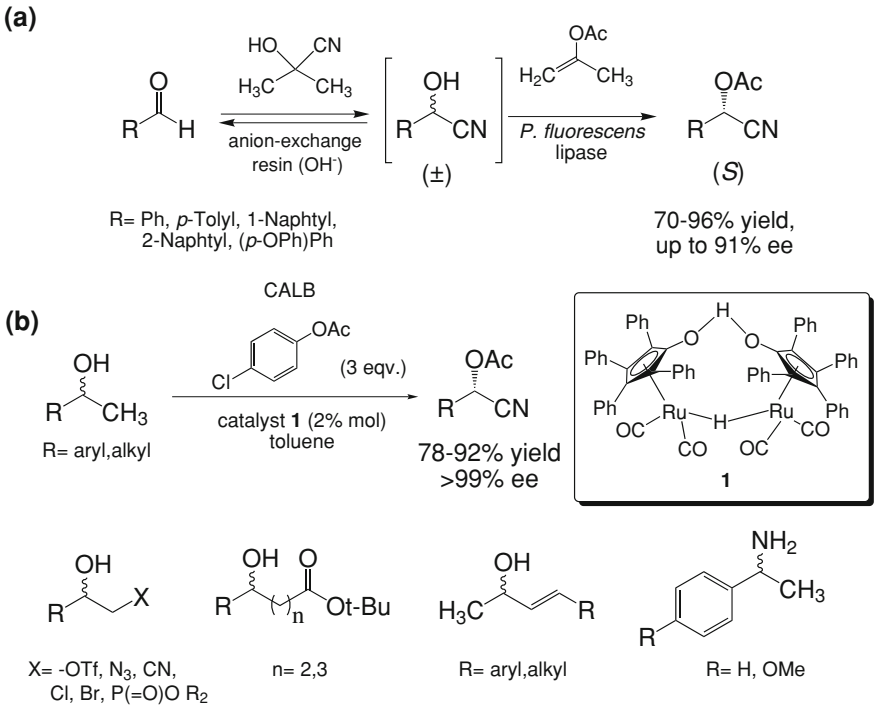


Scheme 1.4 Racemic resolutions through lipase-catalysed reaction in organic solvents

increased by adding a suitable hydrogen source and *p*-chlorophenylacetate was proven the best acyl donor.

1.3 Synthesis from Chiral Pool

In the chiral pool approach [45] naturally occurring enantiopure substances are used as relatively inexpensive and renewable source of starting materials and their chirality is retained in the target products through successive reactions with achiral reagents. Carbohydrates, aminoacids and terpenes are the most common building blocks exploited for the synthesis of compounds with large structural diversity [46–48]. The preparation of (–)-platensimcyn, a selective inhibitor of *β*-ketoacylsynthase, from (*R*)-carvone [49] and the enantiodivergent synthesis of both enantiomers of the gypsy moth pheromone disparlure from L-(+)-tartaric acid

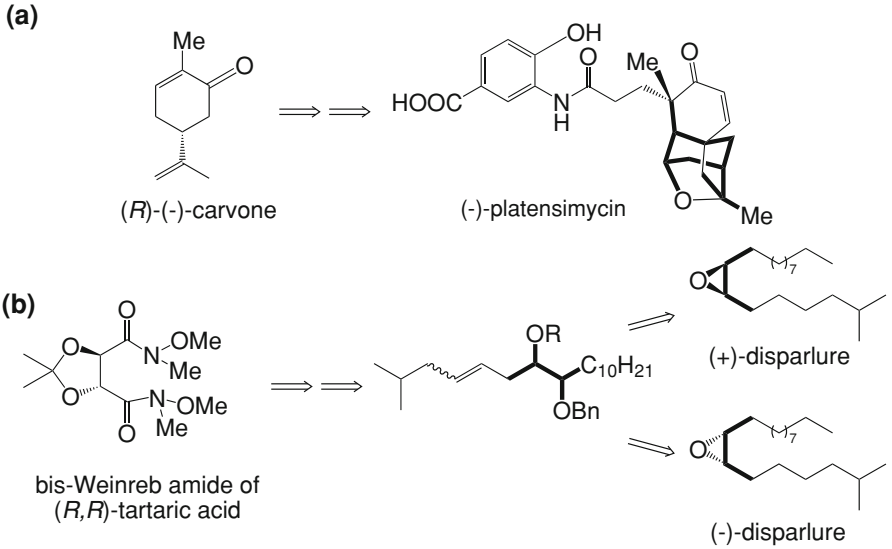


Scheme 1.5 Dynamic kinetic resolution of cianohydrins (**a**) and alcohols (**b**)

[50] are two selected examples of recent application of this strategy for the synthesis of biological molecules (Scheme 1.6). The major drawback of chiral pool synthesis is connected with the availability in most cases of a single enantiomer of the starting material, the other one being often prohibitively expensive or unavailable. Despite of this problem and the presence of other methods for the access to chiral compounds the chiral pool synthesis is still valuably considered whenever feasible.

1.4 Asymmetric Synthesis

The term asymmetric synthesis refers to the chirally biased generation of a new stereogenic element in the substrate by means of a reaction carried out in a chiral environment and it is the most powerful strategy for the production of enantiomerically enriched compounds. The majority of asymmetric syntheses involves the stereoselective conversion of a planar trigonal carbon into a tetrahedrical one during the introduction of the required functionalities, but processes resulting in a defined axial or planar chirality have been also developed. The starting source of

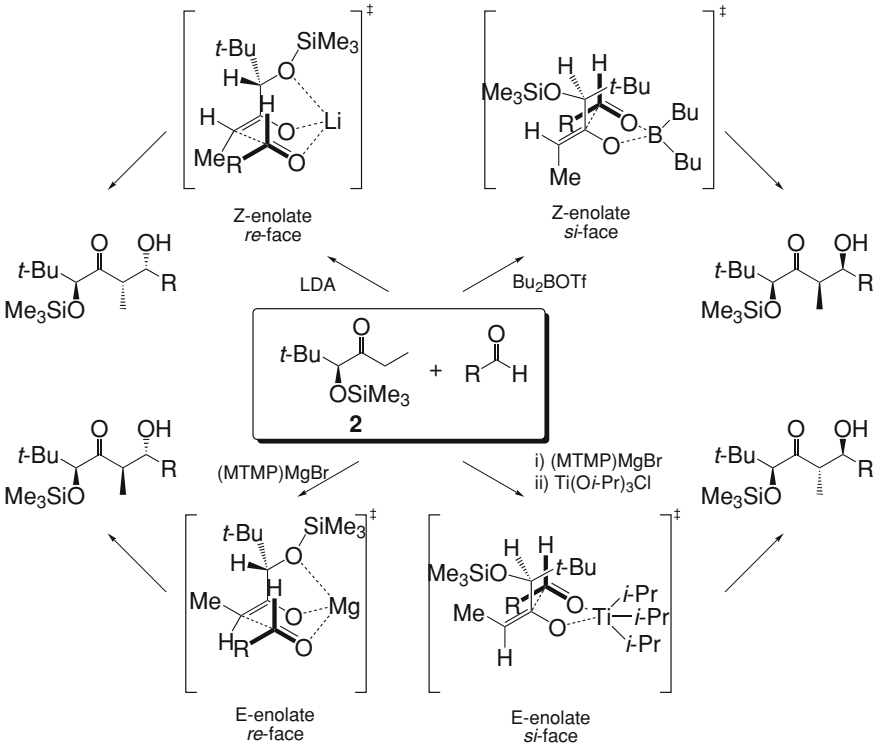


Scheme 1.6 Synthesis of (–)-platensimcyn (**a**) and (+)- and (–)-disparlure (**b**) from chiral pool

chirality can be furnished by the substrate itself or the reagent, stoichiometrically reacting with intramolecular or intermolecular chirality transfer, or by a catalyst that in addition furnishes chirality multiplication with obvious benefits deriving from the small amounts of a natural or man-made chiral catalyst required for the production of large quantities of enantioenriched compounds.

In *substrate-controlled asymmetric synthesis*, a pre-existing chiral group present in the substrate exerts some influence in directing the attack of an achiral reagent on nearby carbons in the molecule leading to an unbalanced mixture of diastereoisomers and the sense of *intramolecular induction* can be strongly influenced by the substituents in the substrate as well as the reagent properties.

Chelation-enforced transfer of chirality is an essential feature in controlling the stereochemical outcome of such asymmetric reactions as it has been demonstrated by the elegant procedure developed by Heathcock [51] for the preparation all the four possible diastereoisomers deriving from the aldol condensation of aldeydes with (*S*)-4-trimethylsilyloxy-5,5-dimethyl-3-hexanone, **2**. The choice of different bases resulted in the stabilization of *Z*- or *E*-geometry of the enolate by stereoselective chelation and the additional coordination of trimethylsilyloxy substituent with metal directed the alkyl attack on the *re*-face of enolate. When this three-point coordination was not possible for steric hindrance and/or dipolar reasons the opposite enantiomers are obtained (Scheme 1.7). In a more recent report on the alkylation of fluorinated α-alkoxyesters and glycinates with potassium bis(trimethylsilyl)amide (KHMDS) as base, the conformational fixing of the enolates through intramolecular potassium-fluorine interactions has been considered crucial for the attainment of good levels of diastereselectivity [52].

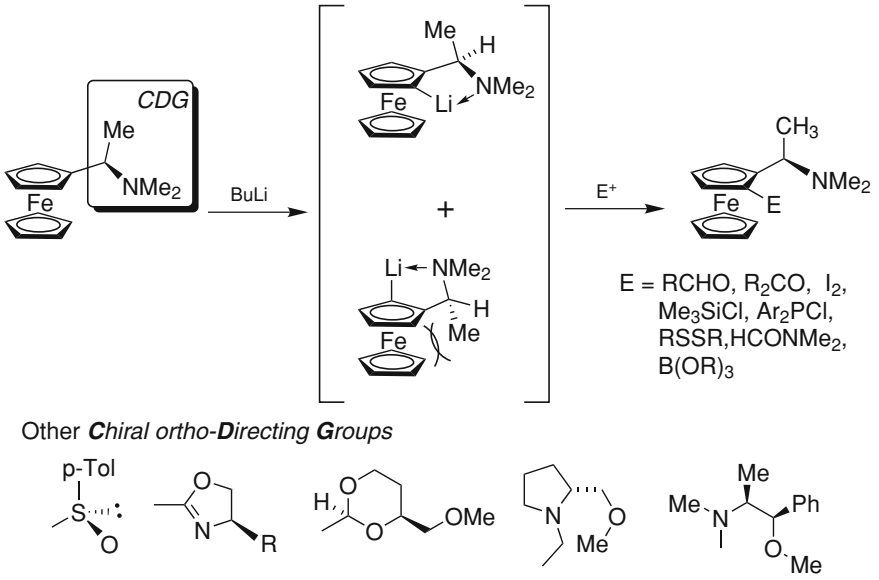


Scheme 1.7 Chelation-directed stereoselective aldol condensation

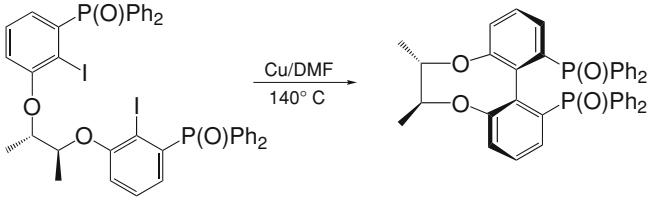
The peculiar planar chirality of 1,2-disubstituted ferrocenes can be efficiently generated by applying a diastereoselective metalation-electrophilic quenching sequence on suitable monosubstituted chiral ferrocenes. The presence in such substrates of a heteroatom able to coordinate with lithium and direct the preferential proton abstraction from one of the two possible *ortho*-positions results in an efficient intramolecular transfer of central chirality to planar one [53] (Scheme 1.8).

In the same way, the intramolecular coupling of two aryl systems joined through a chiral bridge has been exploited for the synthesis of some biaryls with efficient central-to-axial chirality transfer [54, 55] (Scheme 1.9).

In *chiral auxiliary mediated asymmetric synthesis* a chiral group is covalently bonded into the substrate deliberately for the transfer of the chiral information and then removed at the end of the synthetic sequence. Although two additional steps are required, it remains an important method of asymmetric synthesis since the majority of chiral auxiliaries are derived from rather inexpensive natural compounds [56, 57], can serve to protect reactive functional groups simultaneously to the transfer of chiral information and are able to provide high level of diastereoselection in many reactions [58, 59]. Among the phletora of chiral auxiliaries



Scheme 1.8 Correlation of central and planar chiralities in 1,2-disubstituted ferrocenes

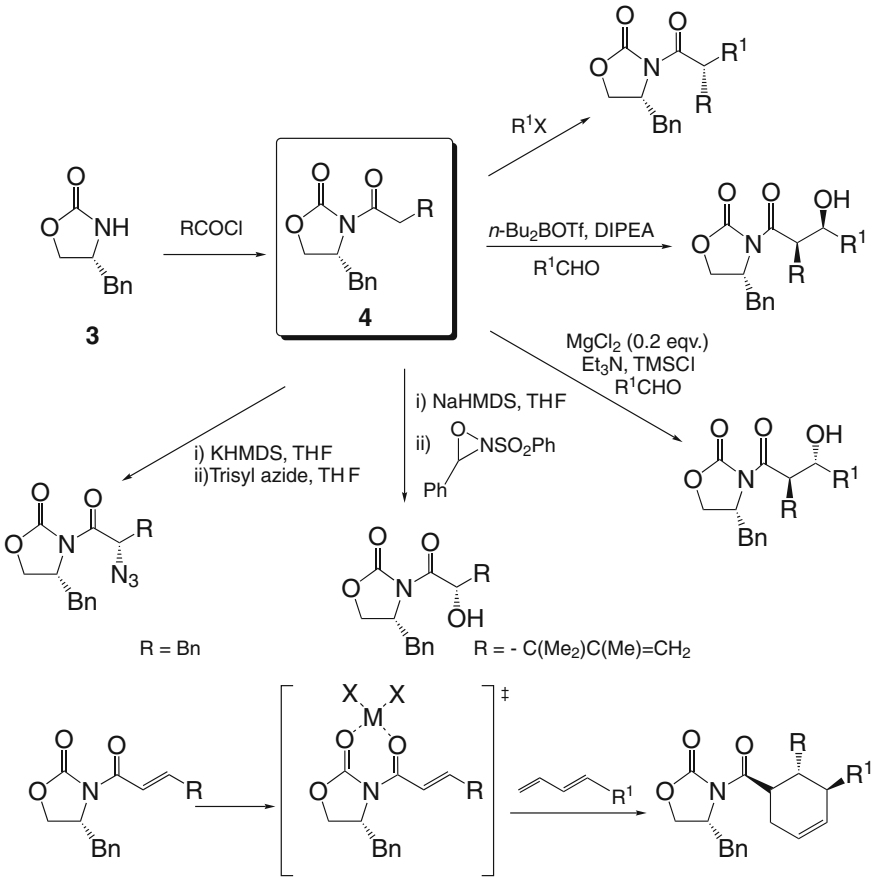


Scheme 1.9 Atroposelective synthesis of biaryls by intramolecular chirality transfer

today available [60], the Evans' oxazolidinone **3** developed in the first 80s is still very popular for its versatility with a broad range of substrates in different reactions, including enolate alkylation, aldol condensation, conjugate addition and Diel-Alder reaction [61, 62] (Scheme 1.10).

The corresponding *N*-acyloxazolidinones **4** provide selective stabilization of boron enolates in the *Z*-geometry (Z/E > 100:1) leading to *syn*- stereochemical outcome, are easily removed by reaction with alkaline hydrogen peroxide to obtain the corresponding acids and have been also applied for the synthesis of macrolides and other natural products [63, 64] with an efficient control of up to 10 stereogenic centers.

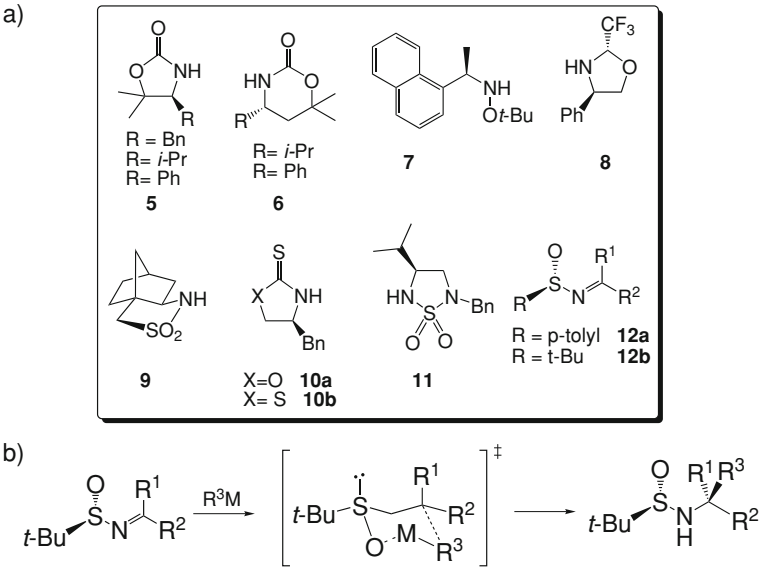
The search for mild cleavage conditions and direct access to aldehydes has led to the development of SuperQuat oxazolidinones **5** [65] and oxazinanones **6** [66] by Davies' group, chiral Weinreb amide equivalents **7** [67] and fluorinated oxazolines **8** [68] as effective auxiliaries with enhanced selectivity, increased



Scheme 1.10 Stereoselective reactions of *N*-acyloxazolidinones

stability to hydrolysis and expanded applicability. Sulphur-containing chiral auxiliaries as Oppolzer's sultam **9** [69], oxazolidinethiones and thiazolidinethiones **10** [70], cyclosulfamides **11** [71] and *N*-sulfinylimines **12** [72–74] have also found application in the stereoselective generation of chiral enolates (Scheme 1.11a). Ellman's sulfinylimines **12b**, prepared from readily available aldehydes or ketones and sulfinamides, have proven versatile auxiliaries in the preparation of enantiopure α-branched and tertiary amines, α- and β-aminoacids derivatives and aminoalcohols through the stereoselective addition of carbon nucleophiles, activated by the electron-withdrawing sulfinyl group, and subsequent cleavage with acids (Scheme 1.11b).

Boron esters and dialkylboranes (Scheme 1.12) are other important chiral auxiliaries with application in asymmetric allylboration and crotylboration for the preparation of non racemic homoallylic alcohols from aldehydes. After the initial reports of camphor-based derivative **13** [75] and tartrate-derived boronic ester **14**

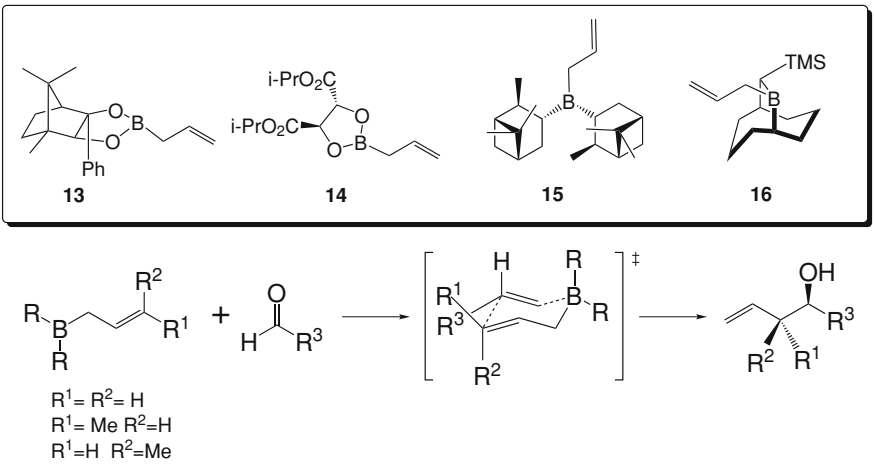


Scheme 1.11 Nitrogen-heterocyclic and sulphur-containing chiral auxiliaries (**a**) and synthesis of amines from chiral *N*-sulfinylimines (**b**)

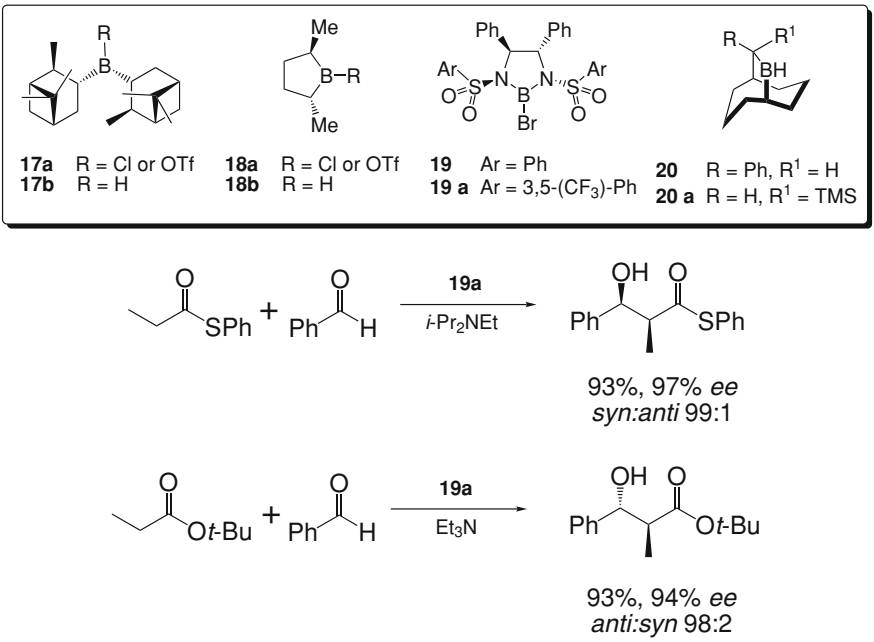
[76], the diallyl Brown's reagent from pinene **15** [77] and the more recent Soderquist's reagent **16** [78] have been preferentially used since they exert increased asymmetric induction due to the lack of heteroatom spacers around the boron center and can be removed under non-oxidative conditions so allowing the recycle of the chiral boron moiety. Chiral boron derivatives [79] have also played a key role in the development of *reagent-controlled asymmetric synthesis* in which a prochiral substrate is converted into a chiral product under the influence of a chiral reagent able to exert an *intermolecular control* of the stereochemical outcome of the reaction.

Pinene-derived **17a**, [80] C_2-symmetric borolane **18a** [81] and diazaborolidines **19** [82] have been proved effective chiral reagents in a variety of aldol condensations that proceeded with high stereocontrol through the formation of highly stabilized chiral enol borinates as reaction intermediates. Different aldol diastereoisomers have been prepared with up to 98% *ee* by suitable choice of the starting carbonyl substrate and boron ligand (Scheme 1.13). Chiral boron reagents have been also applied in the hydroboration-oxidation of both *E*- and *Z*-alkenes [83, 84] to afford the corresponding alcohols in nearly enantiopure form, but moderate levels of asymmetric induction have been reported up to now with 1,1′-disubstituted olefins.

The evolution of the concept of reagent-controlled asymmetric synthesis has led to the development of *asymmetric catalytic synthesis* in which the conversion of prochiral substrates into enantiomerically enriched products is promoted by a sub-stoichiometric chiral compound, the catalyst, able to regenerate itself so

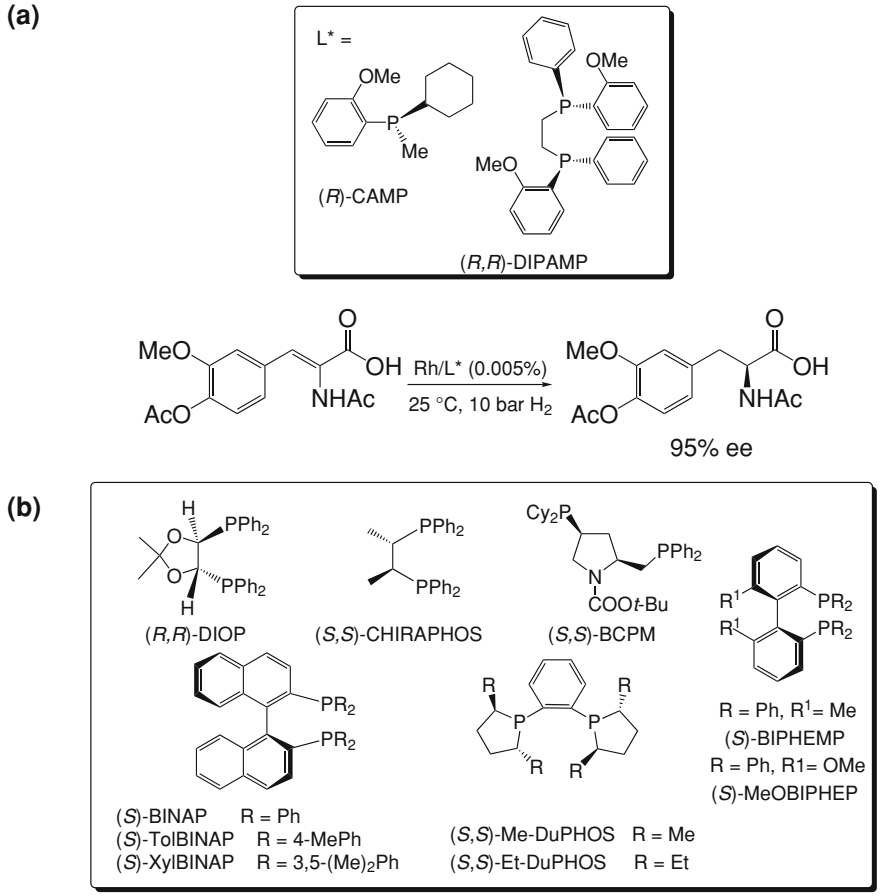


Scheme 1.12 Boron chiral auxiliaries for aldheyde allylations



Scheme 1.13 Chiral boron reagents

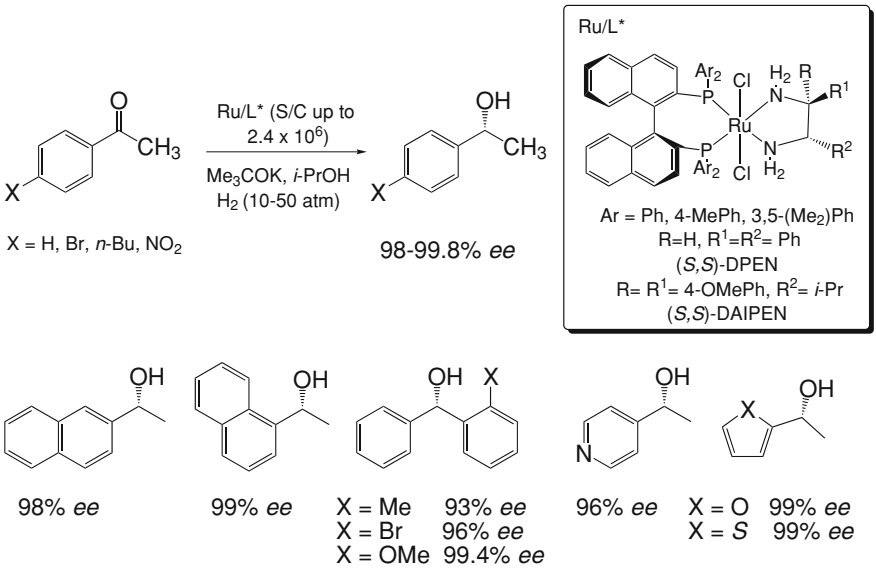
continuously inducing intermolecular chirality transfer. Chirality multiplication effect and high selectivity are key features of enzymatic catalysis in all living systems and biocatalysed reactions, not covered here, are currently used in the industrial preparation of aminoacids, alcohols, amines and epoxides [85, 86].



Scheme 1.14 Knowles' process for production of L-DOPA at Monsanto (**a**) and chiral phosphine ligands for asymmetric hydrogenation (**b**)

Although many purified enzymes or whole cells from a variety of microorganisms have been identified as useful catalysts for different classes of reactions, their high substrate specificity, the need in some instances of cofactors and/or auxiliary enzymatic systems and the difficulty or impossibility in reversing the natural stereopreference can sometimes represent troublesome tasks.

Since the first report of a man-made catalyst for asymmetric cyclopropanation [87] and the first application of a catalytic asymmetric process at industrial level (Monsanto) in the production of the anti-Parkison drug L-DOPA [88], the organic chemists have been faced with the challenge to discover a variety of efficient catalytic stereoselective reactions that complement the biological ones. A part the obvious advantage that a minimal amount of chiral compound is needed, the catalytic approach has opened a new era in the field of asymmetric synthesis for the possibility to modulate and enhance the selectivity by an appropriate catalyst



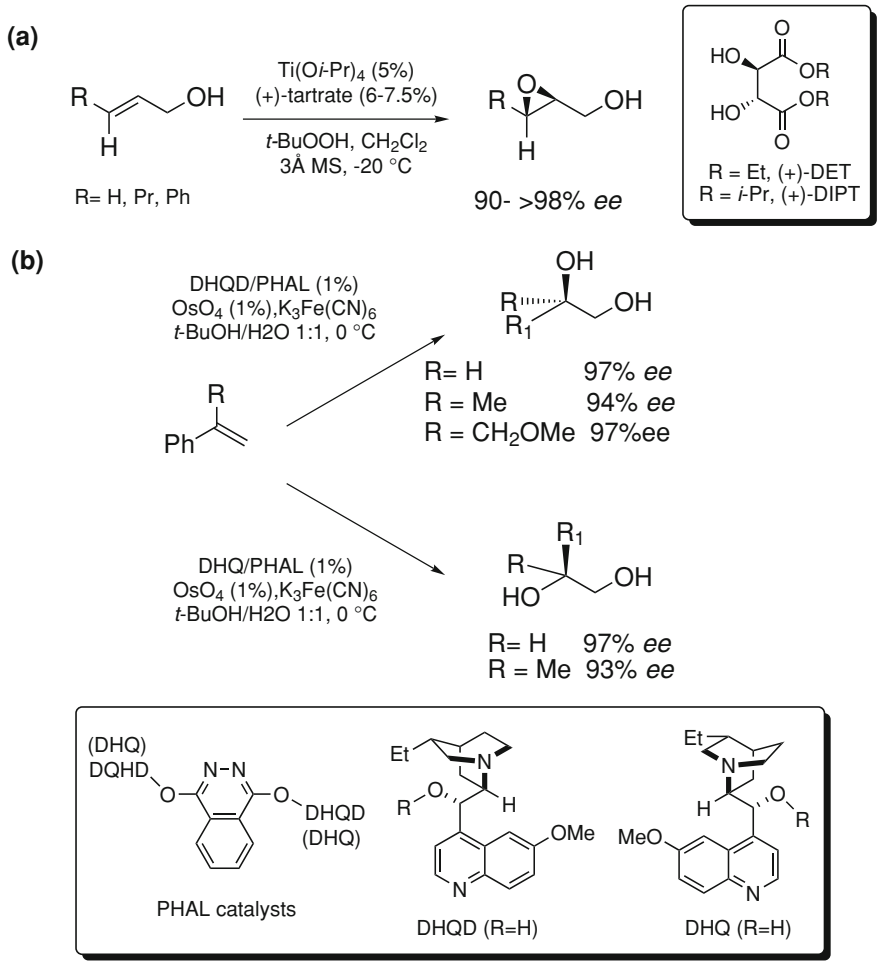
Scheme 1.15 Asymmetric hydrogenation of ketones with Noyori's [Ru/BINAP/diamine] catalysts

design, driven by the knowledge of its chemical properties and the elucidation of reaction mechanism.

Asymmetric catalysis has now became a predominant methodology for the production of chiral compounds from achiral molecules and its continuously growing importance has been acknowledged by the Nobel prize awarded in 2001 to Knowles, Noyori and Sharpless for their fundamental research in this field [89–91]. Hydrogenation of olefins, firstly reported using Rh-diphosphine catalysts bearing stereogenic phosphorous atoms [92], has been improved through the introduction of a variety of ligands with carbon backbone chirality [93] (Scheme 1.14) and then extended to ketone substrates thanks to the development of ruthenium complexes with axially chiral binaphtyl- and biaryldiphosphines, whose coupling with chiral 1,4-diamines as ancillary ligands has allowed to achieve extremely high selectivity even with sterically hindered substrates [94] (Scheme 1.15).

Asymmetric epoxidation of allylic alcohols, initially described as a stoichiometric process and then developed in its catalytic version [95, 96], and alkene *cis*-dihydroxylation promoted by *Cinchona* alkaloid derivatives [97] as highly specific catalysts proved to be powerful C–O bond forming reactions with large scope and predictability of the induction sense (Scheme 1.16).

A catalytic reaction evolves through a cyclic sequence of coordination of the reactants to the catalyst in a well-organized transition state followed by the formation of the reaction product, that is then released regenerating at the same time



Scheme 1.16 Sharpless' asymmetric epoxidation of allylic alcohols (**a**) and dihydroxylation of olefins (**b**)

the catalyst. In this context, transition metal complexes with chiral ligands act as effective enantioselective catalysts for their ability in coordinating the prochiral centre of a given substrate in the metal close proximity and for the intrinsic electronic properties of transition metals that change their oxidation state during the cycle giving rise to different oxidative or reductive reactions (addition, elimination, insertion) in their coordination sphere. The chiral ligands play a key role in the discrimination of the possible diastereoisomeric reaction states leading to the opposite enantiomers and the stabilization of one of them over the others, in many cases through additional secondary interactions between ligands and substrates, determines the enantioselectivity of the process.

As an example, in the hydrogenation of *N*-acyl-dehydroaminoacids catalysed by Rh(I)-chiral phosphines complexes the substrate is fastly coordinated to Rh(I), through the interaction of both the olefinic bond and amide carbonyl oxygen with the metal centre, to give the chelate complex **I**. In the rate-limiting step **I** undergoes the irreversible oxidative addition of H_2 to afford a five-membered Rh(III)-intermediate **II** and following a migratory insertion step, hydrogen is then transferred to the olefinic bond of enamide. A reductive elimination final step accounts for the simultaneous release of the aminoacid reaction product and regeneration of the initial Rh-ligand [98–100] (Scheme 1.17).

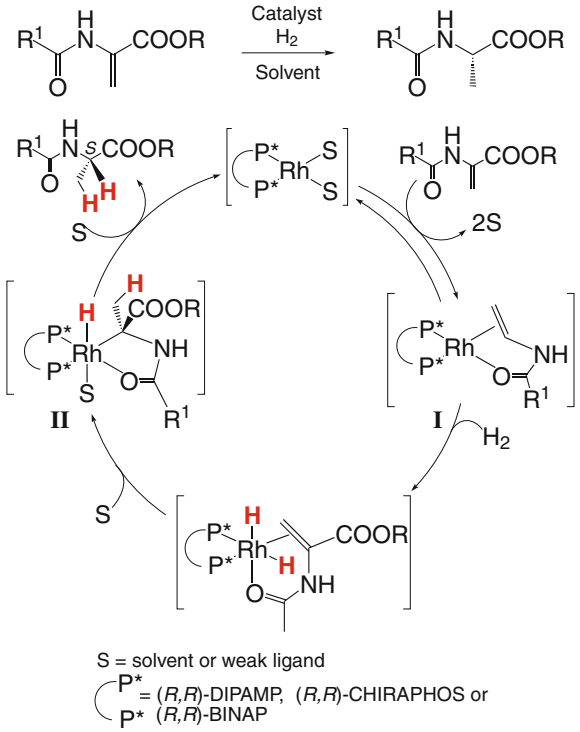
The origin of efficient transfer of chirality resides in the use of C_2-symmetrical ligands to reduce the possible diastereoisomeric transition states and in the asymmetric array of diphosphine substituents in the ligands bound to the metal in cyclic chelates, whose absolute λ or δ configuration determines the sense of asymmetric inductions in agreement with a quadrant diagram model [101] (Scheme 1.18).

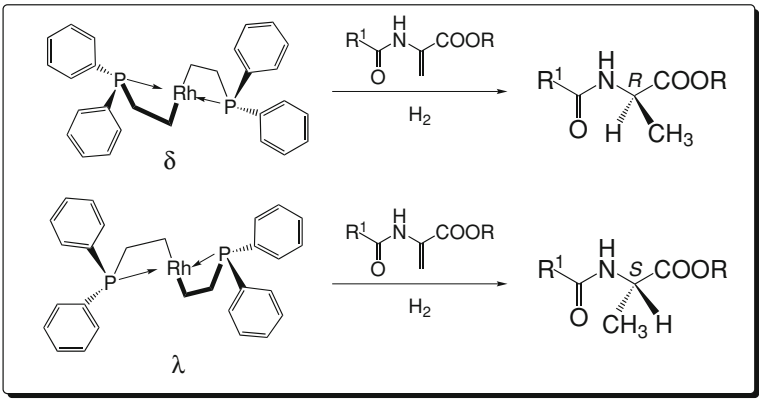
The elucidation of a reaction mechanism, usually supported by kinetic isotope effects studies [102], NMR structural characterization of intermediates [103] and computer-aided calculations [104, 105] is often complicated by the presence of different metal complexes as active catalysts, as in the Ti-binaphtol promoted glyoxylate-ene reaction [106], or by the occurrence of different catalytic pathways becoming operative in function of the reagents' features, as in Pd-catalysed allylic alkylations [107].

The performance of a catalyst is mainly expressed by its *enantioselectivity*, i.e. the enantiomeric excess of the obtained products, but other parameters need to be also taken into the account in determining the effectiveness and the scale-up feasibility of an asymmetric catalytic reaction. Functional group tolerance and chemoselectivity are especially important when a complex substrate must be transformed selectively whereas the catalyst productivity, given as turnover number (TON = mol product/mol catalyst) or substrate/catalyst ratio (*s*/*c*), and catalyst activity, given as turnover frequency (TOF = mol product/mol catalyst/reaction time, h^{-1}), have an obvious incidence on the overall costs of an enantioselective process. Hydrogenation of olefins and ketones are by far the predominant asymmetric chemical transformations that have been successfully developed at industrial level [108, 109] followed by epoxidation and hydroxylation reactions whereas addition to C=C or C=O and C=N bonds and carbon–carbon bond forming reactions are currently limited to bench-scale development, despite of their high synthetic potential and the large number of new catalysts reported in last years [110, 111].

Among the production processes shown in Scheme 1.19 the Solvias hydrogenation of imine **21** to give an intermediate for (*S*)-metolachlor herbicide makes use of Ir-complex **23** as catalyst, whose excellent performances (TON 2.000.000; TOF 400000 h^{-1}) were achieved through a careful structural tuning of the planar chiral ferrocenylphosphine ligand [112]. The Astra-Zeneca production of anti-ulcer drug esomeprazole relies on the Ti/diethyltartate catalysed stereoselective oxidation at the sulphur atom of **26** [113] while asymmetric allyl isomerisation,

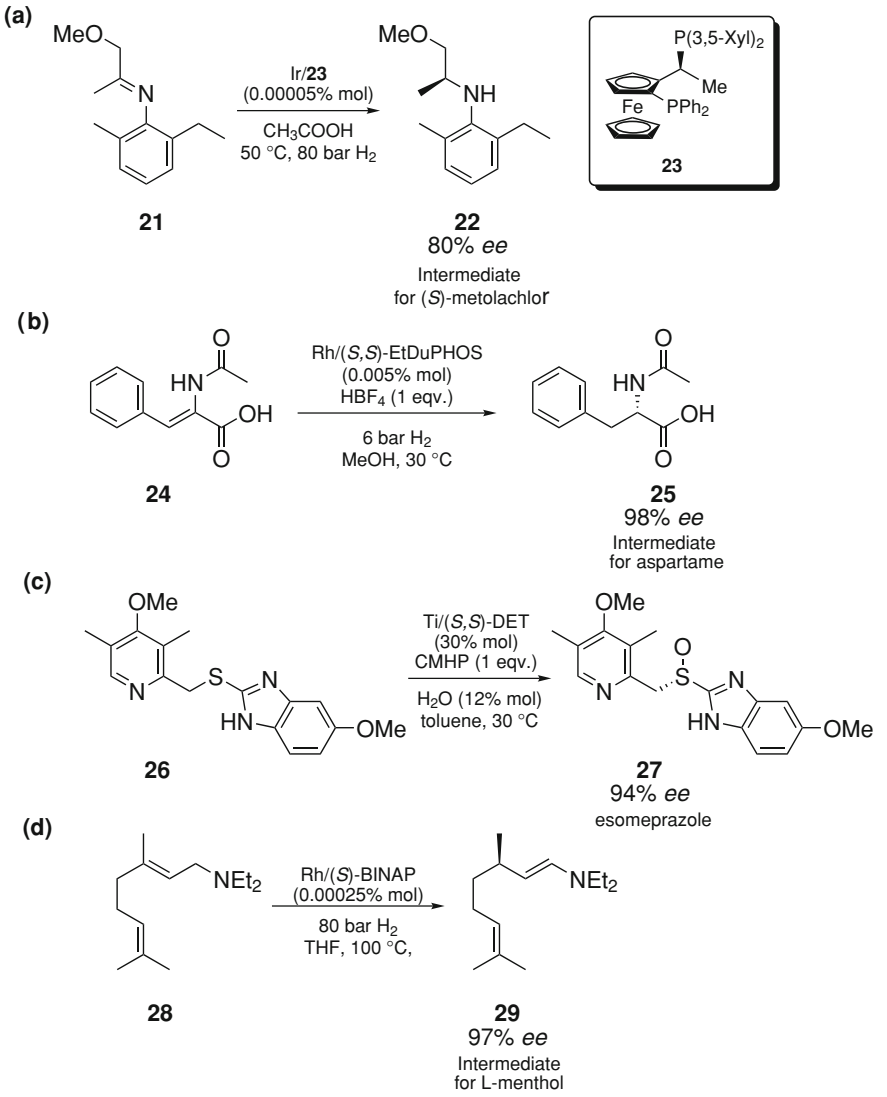
Scheme 1.17 Catalytic cycle in the Rh-promoted hydrogenation of enamides





Scheme 1.18 Phosphine-Rh complex conformations and sense of induction in the hydrogenation of enamides

allylic alcohols epoxidation and hydrogenation of ketone derivatives have been fruitfully applied for production of L-menthol [114], glycidol [115] and chiral aminoalcohols as pharmaceutical building blocks [116], respectively.



Scheme 1.19 Catalytic enantioselective reactions in industrial production

The intensive research aimed at even more enantioselective processes has led to a growing structural diversity of catalysts besides the traditional transition-metal complexes and to an astonishing variety of asymmetric reactions, whose systematic classification and discussion [117–120] goes beyond the scope of this text, stimulating at the same time the development of new appealing concepts and strategies for modern organic synthesis.

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Chapter 2
"Green" Asymmetric Synthesis: The Catalysts

Abstract The structural optimization of catalysts is a key topic in the development of more sustainable asymmetric catalysis. An astonishing variety of chiral ligands for transition-metal complexation is today available and the identification of novel active compounds has been aided by computational and mechanistic studies as well as combinatorial methodologies. Besides the most investigated C_2-symmetrical ligands, the potentiality of unsymmetrically disubstituted or monodentate ligands has been explored in conjunction with less toxic and/or less expensive metals whereas chiral amplification and enantiomer-selective effects resulted in the option to use non-enantiopure ligands saving satisfactory enantioselectivity. In the last years different classes of simple organic molecules have been shown highly effective in promoting a range of catalytic enantioselective transformations of carbonyl and iminic substrates through a number of general activation modes and organocatalysis has been recognised as a powerful methodology complementary to metal-based asymmetric synthesis. More recently, the concept of dual activation has led to the development of bifunctional catalysts with excellent performances.

Keywords Privileged ligands · Monodentate ligands · Environmentally benign metals · Non-linear chiral effects · Organocatalytic activation modes · Bifunctional catalysts

2.1 Introduction

In an eco-compatible context, catalysis can be considered a foundational pillar since catalytic reactions often permit a decrease in the energy requirements, a simplification of the separation procedures due to a better selectivity and the use of reagents less toxic or in minimized amount. Also for the production of optically

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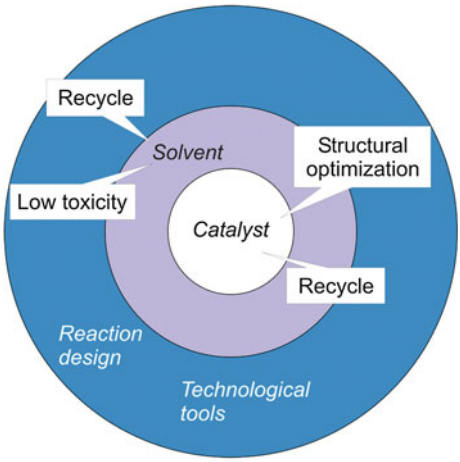


Fig. 2.1 General approaches to green asymmetric catalytic synthesis

active compounds asymmetric catalytic synthesis represents by itself a more powerful methodology with respect to the other stoichiometric counterparts (according to ninth principle of "green chemistry") but opportunities for substantial improvements in combining the high performances, of catalytic reactions with the increasing need of sustainability demanded by the modern industrial chemistry are enormous. Taking into the account all the factors influencing the overall efficiency of a catalytic process different strategies, used alone or in a synergistic combination, have been successfully developed (Fig. 2.1) and they will be discussed in this and the following chapters with main focusing on the concepts rather on a systematic classification of their applications by reaction type.

Since the effectiveness of an enantioselective catalytic reaction mainly resides in the nature of the catalyst, whose chemical, stereochemical, electronic and steric features all contribute to the control of asymmetric induction, the development of a green asymmetric process cannot be detached from the intensive search of new catalysts and innovative methodologies deriving from a better understanding of the reaction mechanisms. Both these approaches have been fruitfully explored leading to an expansion in the portfolio of enantioselective catalysts and asymmetric reactions today available. In this section different classes of catalysts and the related applications are surveyed together with some cost-effective strategies aimed to achieve good enantioselectivity even employing non enantiopure or racemic ligands.

2.2 Metal Based Catalysts

Most asymmetric catalysts developed so far are metal-complexes with chiral organic ligands that are able to influence the reactivity and selectivity of the metal center, so inducing the preferential formation of one of the possible

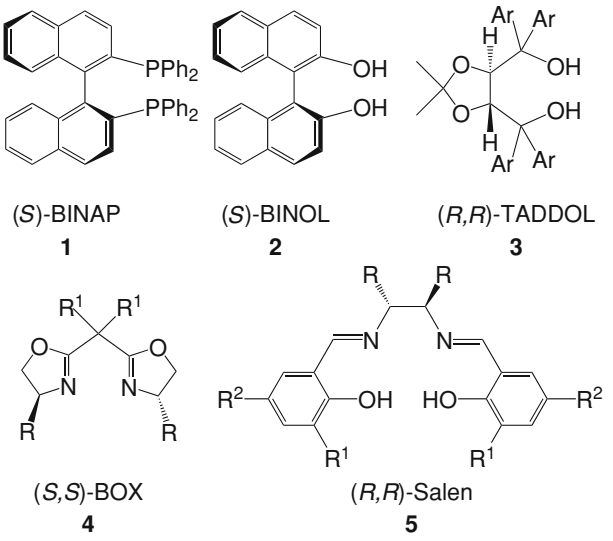
enantiomeric products. Many thousands of chiral ligands have been reported up to now and their number surely will grow since no constraints virtually exist in terms of molecular design. Single or combined modifications in the stereogenic elements and molecular symmetry of carbon skeletons, in the nature of coordinating atoms and metals as well as in the electronic and steric properties of substituents can give rise to a huge structural diversity of ligands, the only limit being imposed by their synthetic accessibility.

Despite of the large number of effective ligands available, a relatively small number of compounds, called "*privileged ligands*" [1], have displayed broad applicability in mechanistically unrelated asymmetric reactions with high levels of enantiocontrol.

These ligands (Scheme 2.1) share the common structural feature of C_2-symmetry, advantageously considered as a way to reduce the number of possible isomeric metal complexes, substrate-catalyst arrangements and reaction pathways with a beneficial effect on enantioselectivity and in mechanistic studies [2]. In symmetric bidentate diphosphines, as BINAP **1** [3, 4] and related atropisomeric derivatives [5, 6], the formation of a sterically constrained seven-membered metallacycle (Fig. 2.2a) with a skewed conformation in which the P-substituents are strongly oriented forward past (pseudo-equatorial) or away from (pseudo-axial) the metal is thought to be responsible for the efficient transmission of the backbone axial chirality. Although the best known applications of BINAP and its analogues concerned the enantioselective hydrogenation of olefins and ketones, complexes of these ligands with different metals have been reported as effective catalysts in many C–C bond forming reactions [5, 7]. Fine optimization of enantioselectivity has been obtained by tuning the size and the electronic properties of substituents introduced on suitable positions of the binaphtyl- or biaryl backbones, with direct consequences on the biaryl dihedral angles and basicity at phosphorous atoms [8–11]. The influence of bite angle [12] in metal-diphosphines complexes has been evidenced in Pd-allylic alkylation and, within a serie of diphoshines, the creation of a larger chiral pocket around the metal provided a more effective embracing of the allyl group, that became prone to be attacked by the nucleophile at one end preferentially [13, 14].

In the group of privileged ligands, C_2-symmetric *O,O*-bidentate BINOL **2** [15] and TADDOL **3** derivatives [16] bind well to many main-group and early transition metals and their Ti(IV)-complexes have found extensive application in Lewis acid mediated reactions as carbonyl-ene additions, nucleophilic additions of organometallic reagents to aldehydes, Diels–Alder reactions and other cycloadditions [17]. Noteworthy, good levels of asymmetric induction have been achieved with TADDOL ligands despite of the distance of dioxolane stereocentres from the metal, in consequence of the fact that upon complexation a *trans*-fused bicyclic system is formed in which the rigid geometry and the stereochemistry of the ketal ring strongly influence the positioning of aryl groups in the metallacycle in a pseudoequatorial/pseudoaxial arrangement, with the pseudoaxial substituents believed to act as stereocontrolling elements (Fig. 2.2b).

Bis-oxazolines, **4** (BOX) and the related semicorrins [18] are popular families of *N,N*-bidentate ligands with large structural diversity achieved through their modular



Scheme 2.1 Structures of "privileged ligands"

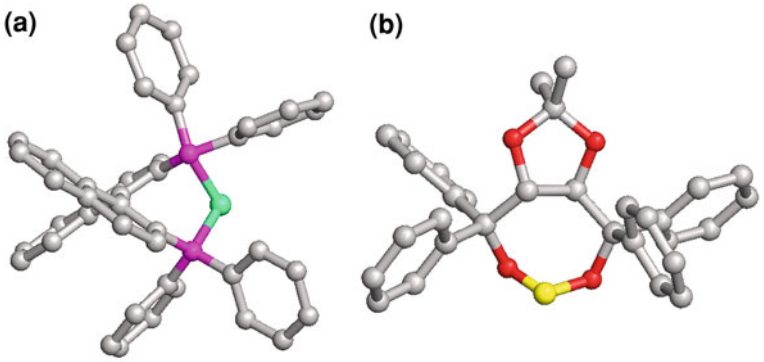


Fig. 2.2 Structures of BINAP-metal (**a**) and TADDOL-metal complexes (**b**)

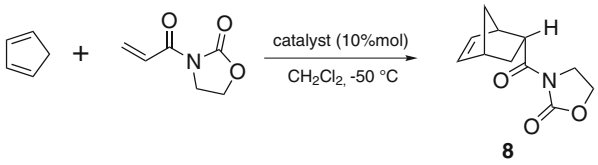
synthesis from simple amino alcohols as chiral precursors. The flexibility in the standard synthetic protocols and the ability in complexing several metals have allowed the introduction of different substituents on both the oxazoline rings or methylene bridge and the tailoring of BOX-catalysts in many C–C bond forming reactions [19]. Besides the first application of a BOX-ligand in Cu(I)-promoted cyclopropanation of olefins with diazoacetates, more recent examples include Friedel–Crafts acylations of indoles [20–22] and addition of aldehydes to α-lithiated sulfones [23] that proceed with excellent diastereo- and enantio- selectivity. The coordination of the two oxazoline nitrogen atoms with a metal gives rise to a

nearly planar structure with limited conformational flexibility and the stereogenic substituents in the close proximity of the metal shield it from two opposite directions. In addition to the two points coordination with BOX ligand, two to four metal sites are available for coordination with substrate, solvent molecules or metal counter-anion and different geometries for tetra-, penta- or hexacoordinates complexes have been demonstrated by X-ray analyses [24].

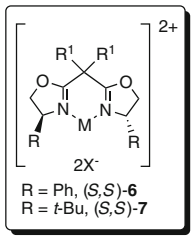
Interestingly, going from the tetrahedral to square-planar (or octahedral in plane) geometry a reversal in the selectivity could be expected since the corresponding movement of the coordinated substrate changes its accessible face and in this way both enantiomers of a given product could be prepared from a single ligand by promoting the switch between these two geometries with the choice of suitable metals or additives. The feasibility of this approach has been nicely demonstrated in Diels–Alder reaction of cyclopentadiene with 3-acryloyl-1,3-oxazolidin-2-one and in the presence of Mg(II)-**6** · ClO_4 catalyst a complete reversal of stereoselectivity was observed upon addition of 2 eqv. of water, in agreement with the expansion of the metal coordination number from 4 to 6 and the consequent switch from a tetrahedral to octahedral in plane geometry of the catalyst-substrate intermediate [25]. In the same way, parallel reactions with Cu(II)-**6** · OTf and Zn(II)-**6** · SbF_6 or Cu(II)-**7** · OTf and Zn(II)-**7** · SbF_6 catalysts gave complementary enantioselectivities that were related with the stabilization of planar or tetrahedral complexes by varying the oxazoline substituent from phenyl- to *tert*-butyl- group [26] (Scheme 2.2).

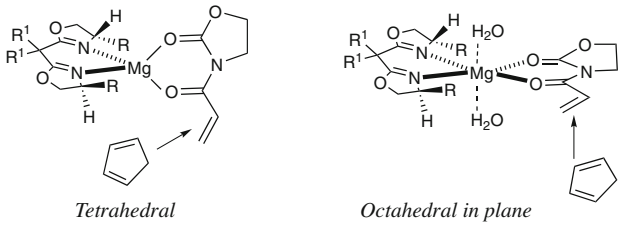
Since the first reports of Jacobsen [27] and Katsuki [28], tetradentate *salen-type ligands*, as **9,** complexed with Mn(III)- or Cr(III) have became the catalysts of choice for asymmetric epoxidation of unfunctionalised *cis*-alkenes, conjugate dienes and polyenes, Z-enynes and cyclic dienes [29], so expanding the scope of this useful reaction previously limited to allylic alcohols. Mechanistic studies and fine catalyst tuning by varying the diimine backbone and substituents on the aryl rings led to the second-generation catalysts, in which additional axial chirality was introduced at 3,3′-positions [30], and the influence of other reaction parameters (oxidant, donor coligands) was also intensively investigated. These Schiff base-type ligands [31], able to coordinate different metals stabilizing them in various oxidation states, have found interesting applications in cyanohydrin synthesis (VO-complexes) [32], addition of organometallic reagents (Zn-complex) [33], Ti-promoted pinacol coupling [34] and sulfoxidation [35], hydrolytic kinetic resolution of epoxides (Co-complex) [36] and Passerini multi-component reaction (Al-complex) [37] (Scheme 2.3).

Starting from privileged ligands, other C_2-symmetric families of catalysts have been developed for more specific applications, some examples including phosphoramidites of BINOL, mainly developed for the asymmetric copper-promoted 1,4-addition of dialkylzinc reagents to enones [38], and biaryl phosphites that have been shown effective in Pd-catalyzed allylic substitution reactions [39, 40]. The finding that phosporamidites **10**, a class of C_2-symmetric but monodentate ligands, catalyzed asymmetric hydrogenation of standard substrates with enantioselectivity comparable with that of classical bidentate phosphorous based catalysts [41, 42] has



catalyst	*endo:exo*	**8** *ee*%
Mg(II)-**6**•ClO_4	93:7	72 (*S*)
Mg(II)-**6**•ClO_4 + $2H_2O$	95:5	73 (*R*)
Cu(II)-**6**•OTf	95:5	30 (*S*)
Zn(II)-**6**•SbF_6	98:2	92 (*R*)
Cu(II)-**7**•OTf	97:3	98 (*S*)
Zn(II)-**7**•SbF_6	95:5	38 (*R*)

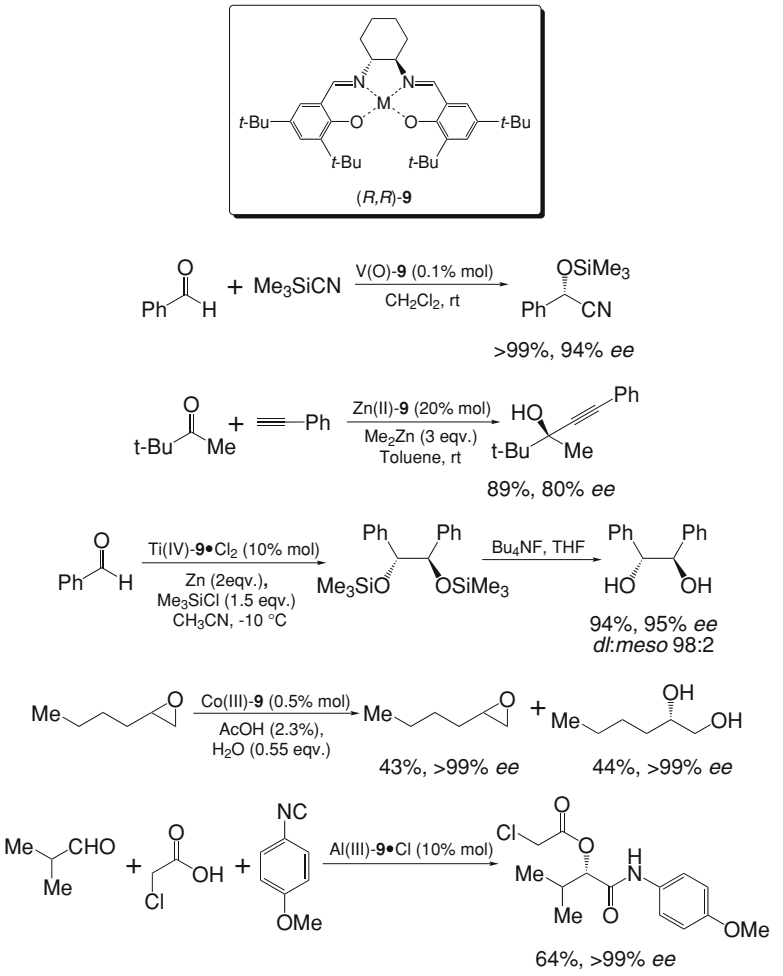




Scheme 2.2 Reversal of stereoselectivity in the oxazoline-promoted Diels–Alder reaction

opened the way to the development and catalytic application of different classes of monodentate phosphorous derivatives [43–46], previously ignored on the basis of the assumption that a bidentate coordination fashion was essential to ensure conformational rigidity of the catalyst as a key feature for effective chiral induction (Scheme 2.4). The great potential of monodentate ligands, whose synthesis is more straightforward and economical than that of their bidentate counterparts, is still far from being fully explored and progress in this field is highly expected.

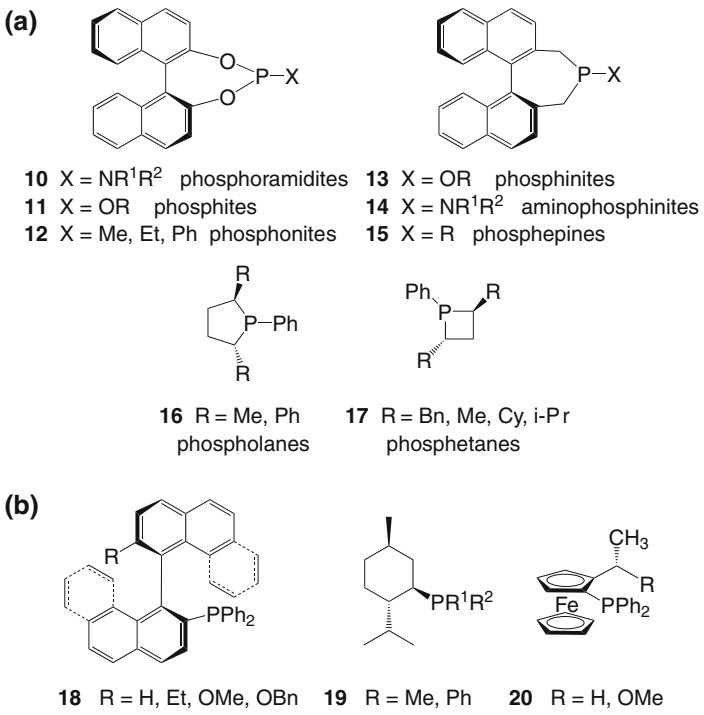
Mechanistic studies for many reactions have also highlighted that intermediates in catalytic cycles are in most cases nonsymmetrical and in such occurrences the use of sterically and electronically divergent coordinating groups should permit more effective enantiocontrol than C_2-symmetric ligands. In this context, phosphineoxazolines (PHOX) have been developed by Pfaltz [47] as mixed *P,N*-bidentate ligands and the distinct features of a π-acceptor *P*-group and a σ-donor *N*-group have been successfully exploited, among different reactions, in Pd-catalyzed allylic substitution. Indeed upon substrate complexation, the two allylic termini were differentiated by a combination of steric and electronic effects and the nucleophile preference in attacking the allylic carbon *trans* to the phosphino group resulted in excellent selectivity and up to 99% enantiomeric excesses (Scheme 2.5). A variety of mixed ligands containing an oxazoline ring in



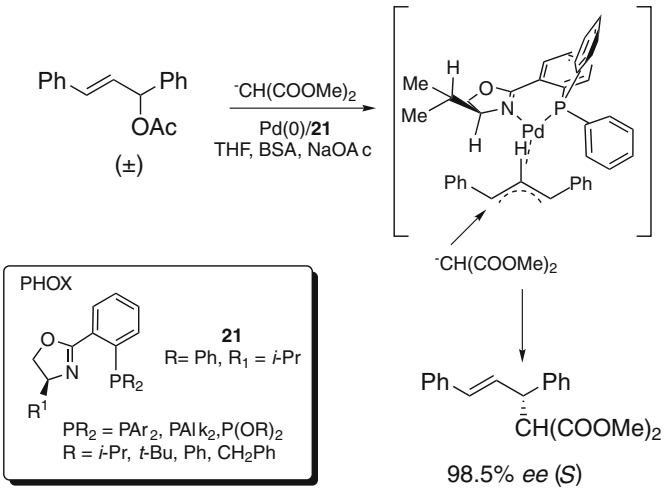
Scheme 2.3 Beyond alkene epoxidation: versatility of salen ligands

conjunction with additional P-, N-, O- or S- coordinating atoms and different chiral elements, as stereogenic carbon(s), axis or plane, are today available and widely employed in asymmetric synthesis [48].

In the same way, dialkylzinc addition to aldehydes has gained selectivity in many instances by using *N,O*- heterobidentate ligands and chiral aminoalcohols have became very popular catalysts for this reaction [49–51]. In a comparative study on the performances of C_2- versus C_1-symmetrical catalysts the latter were found more effective in several reactions [52] and the development of new ligands with less usual combinations of coordinating atoms, such as the P,S-, P,O- and N,S-variety, is a promising way to expand the molecular diversity of asymmetric catalysts. Mixed phosphine-phosphinites and phosphine-phosphites are other



Scheme 2.4 C_2-symmetric (**a**) and C_1-symmetric (**b**) monodentate phosphorous ligands



Scheme 2.5 Pd-promoted allylic alkylation with phosphinooxazoline ligands

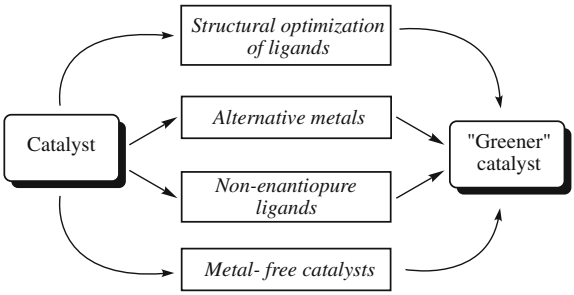


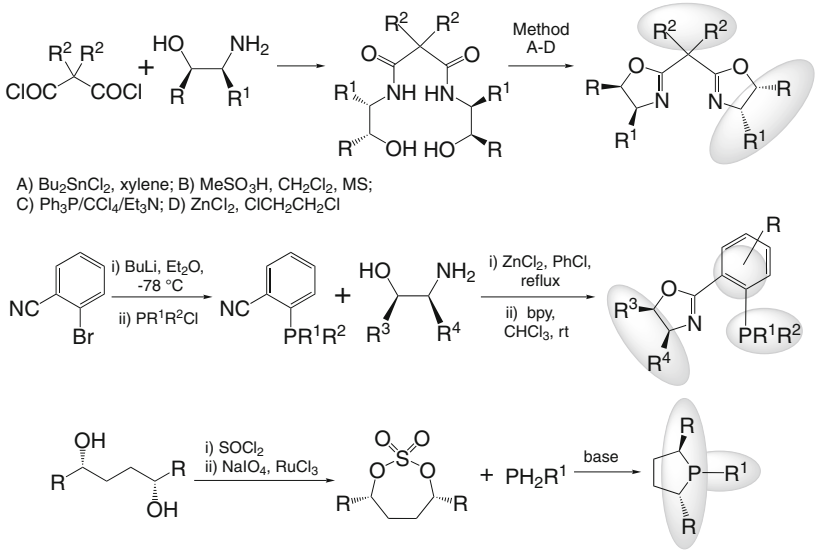
Fig. 2.3 Strategies toward more sustainable catalysts

interesting examples of bidentate non-symmetrical ligands, characterized by two phosphorous atoms with different π-acceptor properties, that have shown comparable and in some cases superior activity with respect to the milestone ligands in Rh-mediated hydrogenation and hydroformylation reactions [53].

Although several transition-metal based catalysts are nowadays routinely used in the preparation of chiral fine chemicals, further improvements in a "green" direction are possible in order to overcome the drawbacks related with the generation of metal residues and organic solvent wastes, the use of special equipments to ensure dry and inert reaction conditions, the costs connected with some precious metals and the synthesis of enantiopure ligands.

In this context, the availability of even more active and selective ligands can allow lower catalyst loading and simplification in the purification steps for the products with direct consequences on waste reduction. Other promising approaches concern the use of alternative metals or non enantiopure ligands whereas organocatalysis has emerged as a powerful strategy in metal-free asymmetric synthesis (Fig. 2.3).

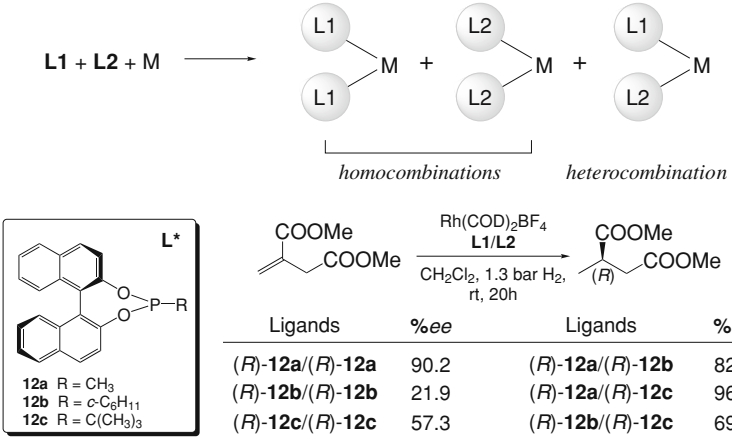
Since subtle variations in the ligand structure can sensibly affect the asymmetric induction by modifying the chiral environment around the metal, the identification of the suitable catalyst for a given transformation still poses one of the most challenging endeavour in the development of effective processes and it is often the result of knowledge based intuition or serendipity as well as of time-consuming trial and errors optimization of other concurrent factors (metal, solvent, additives etc.). In the traditional iterative approach, based on the synthesis of one catalyst at a time and evaluation of its performances, ligands accessible through *modular synthesis* are preferred since structural modifications can be easily tailored by joining small units together through high yielding reactions. As some examples, the diversity of ring substituents in bis-oxazolines and phosphinooxazolines comes from readily available chiral aminoalcohols whereas libraries of Schiff-bases can be obtained by systematic variation of both the aminic and aldehydic moieties. Structural modifications on carbon backbone or phosphorous atom of phospholanes can be easily introduced through a two step synthesis in which chiral 1,4-diols are converted into the corresponding cyclic sulphates and then treated with primary phosphines (Scheme 2.6).



Scheme 2.6 Examples of modular ligands

In an alternative strategy, *combinatorial methods* have been applied to enantioselective catalysis as a powerful tool for the generation and simultaneous test of a considerably larger number of candidates, leading to enhanced chances to find the catalyst with higher performances and the best reaction conditions [54]. It has been also underlined that large structure-selectivity databases from combinatorial approach can be particularly useful to optimize novel and unexplored reactions and to promote the related mechanistic studies.

Some libraries of modular catalyst have been prepared by automated solid-phase synthesis technology [55] and, despite of the enormous number of accessible compounds in a "split-and-pool" method, the parallel approach has been preferentially used since it does not require deconvolution and the composition of each vessel is easily defined by its position in a multi-well array. To the synthesized ligands, usually tested in their resin-bound form for preliminary screenings and in solution after cleavage for subsequent refinement, the reagents are added and the reaction course monitored by using a suitable high-throughput system capable of assaying activity and/or enantioselectivity in reasonable time. The search for reliable access to these data has stimulated the development of different detection systems[56–59] among which circular dichroism detection applied to HPLC on non-chiral stationary phases [60] and capillary electrophoresis on parallel columns containing a chiral selector as electrolyte coupled with laser-induced fluorescence or DAD detection [61, 62] have been reported as super-high-throughput analytical tools for simultaneous determination of yields and enantiomeric excesses of the products.

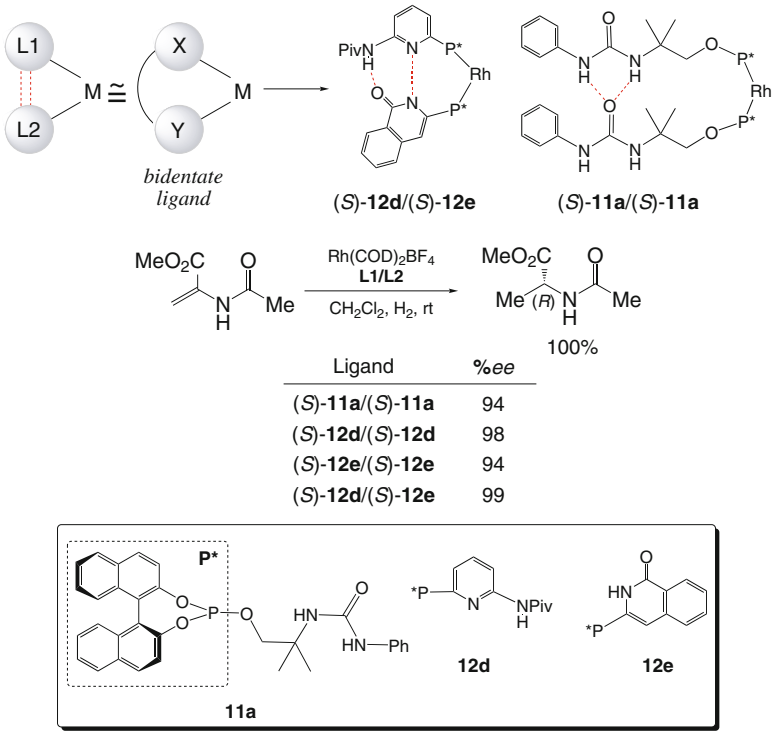


Ligands	%*ee*	Ligands	%*ee*
(*R*)-**12a**/(*R*)-**12a**	90.2	(*R*)-**12a**/(*R*)-**12b**	82.4
(*R*)-**12b**/(*R*)-**12b**	21.9	(*R*)-**12a**/(*R*)-**12c**	96.4
(*R*)-**12c**/(*R*)-**12c**	57.3	(*R*)-**12b**/(*R*)-**12c**	69.1

Scheme 2.7 Catalytic activity of mixtures of monodentate ligands

More recently, the application of supramolecular principles to catalysis [63] has promoted the development of *dynamic combinatorial libraries* as collections of transient compounds reversibly assemblied under thermodynamic control from a number of building blocks [64, 65]. For given experimental conditions, the library composition is biased toward those members that form the most stable assemblies or aggregates. One of the most appealing application of this strategy makes use of a mixture of monodentate ligands, in place of a bidentate one, and their self-assembly in all the possible combinations around the metal allow to expand the size of library and catalyst diversity without the need to really synthesize new ligands. Indeed, for n monodentate ligands not only n homocombinations [M-L_xL_x] or [M-L_yL_y] are possible but also $n(n-1)/2$ heterocombinations [M-L_xL_y] and even mixtures of chiral ligands with achiral ones can be effective in their heterocombinations [66]. Enhanced enantioselectivities for heterocombinations of two monodentate ligands with respect to the corresponding homo-complexes have been observed in Rh-catalyzed hydrogenation of different olefins with monophosphonites or monophosphites [67–69] (Scheme 2.7) as well as in conjugate addition of aryl boronic acids to enones or nitrostyrenes with Rh-phosphoramidite complexes [70].

In an alternative approach, the emulation of a catalytically active chelate complex between a metal and a bidentate ligand has been achieved by using monodentate ligands bearing substituents with complementary binding sites that mutually interact through a range of non covalent interactions (van der Waals, π-stacking and dipole–dipole interactions, hydrogen bonding) [71, 72]. Some monophosphites covalently bound to urea derivatives and mixtures of phosphonites containing aminopyridine or isoquinolone moieties have been reported as interesting examples of supramolecular catalysts in which two molecules of ligands, held together by means of multiple hydrogen bonds, behave as a bidentate

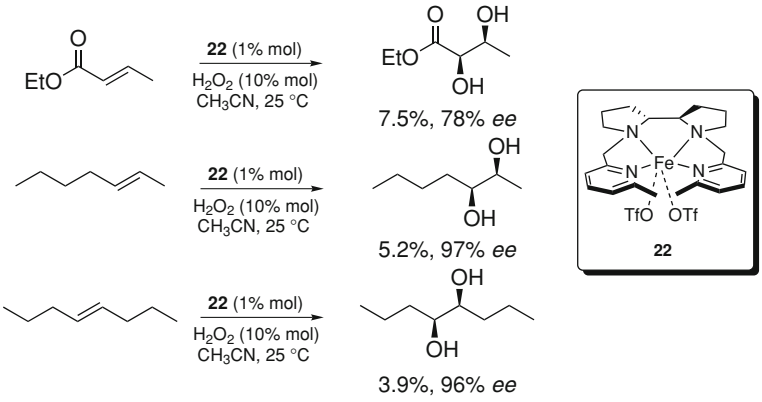


Scheme 2.8 Emulation of a bidentate ligand by supramolecular assembly of monodentate ligands

ligand in creating a chiral environment around rhodium in asymmetric olefin hydrogenation (Scheme 2.8) [73, 74].

In the optimization of catalysts for asymmetric synthesis, some studies has been focused toward the use of more environmentally benign metals [75], since it is well-known that the majority of "heavy metals" display bioaccumulation and toxic effects on many living systems [76], despite of some of them (iron, copper, manganese and zinc) are essential for human health at suitable doses. However, classification of "light" beryllium as a human carcinogen [77] gives clear evidence that biological toxicity of metals results from different factors other than the atomic mass and correlation scales with "softness" of metal ions, charge and K values for their binding to soft ligands have been proposed [78–80].

Among the metals more recently taken into consideration, iron is economical and relatively nontoxic and iron-complexes have displayed valuable potential as catalysts for reduction, oxidation and coupling reactions [81–83]. Some achiral iron catalysts mimicking the active site of non-heme iron enzymes as the Rieske dioxygenase have been shown able to catalyze *cis*-dihydroxylation of olefins with H_2O_2 [84, 85] and the development of the asymmetric version of such process could represent a promising benign alternative to the osmium-based Sharpless'



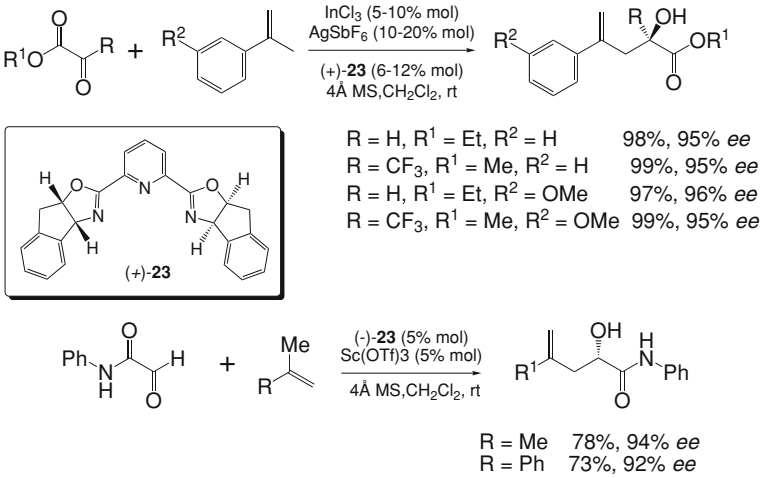
Scheme 2.9 Iron-promoted asymmetric *cis*-dixydroxylation of olefins

dihydroxylation. However, asymmetric iron-promoted reactions have been mainly restricted to transfer hydrogenation of ketones [86, 87] and a single example of *cis*-hydroxylation of olefin was reported with complex **22** (Scheme 2.9) to give the corresponding diols in high *ee* (up to 97%) but rather unsatisfactory yields [88].

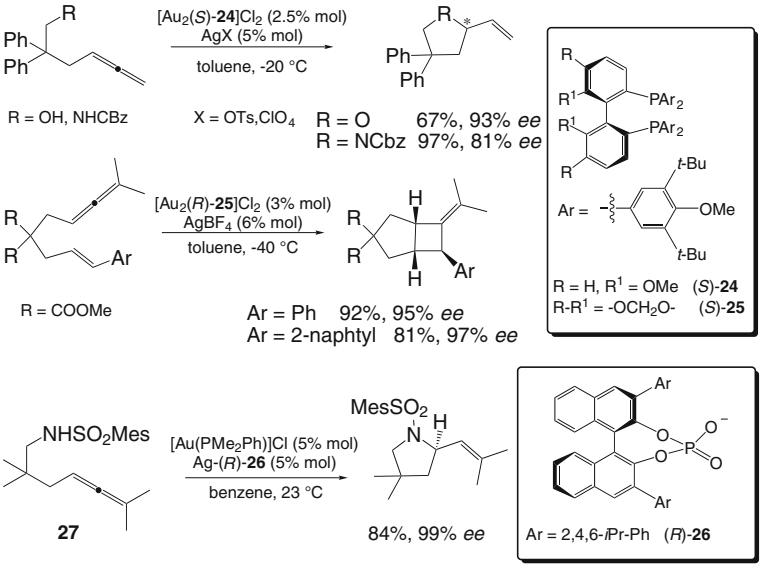
Indium and scandium have been also evaluated as useful metals for their low toxicity and high stability to air and moisture, the latter feature offering the possibility to recover and recycle the catalysts and perform reactions in water-based solvents. The moderate Lewis acidity and low heterophilicity of these metals make their complexes effective catalysts for C–C bond-formation reactions with good tolerance of different functional groups.

The asymmetric carbonyl-ene, an important reaction for the atom-economic synthesis of homoallylic alcohols, has been carried out with "pybox" complexes of scandium or indium [89, 90] and a significant counterion effect on the reaction rate and selectivity was evidenced [91] (Scheme 2.10). Other interesting applications in enantioselective allylation of ketones [92, 93], Mannich-type reaction of aldimines [94] and asymmetric ring opening of meso epoxides [95] have been reported using *N,N′*-dioxide chiral ligands.

Enantioselective catalysis with gold(I) is still in its infancy but future developments could be expected due to the peculiar features of this metal that behaves as a high electrophilic but relatively non-oxophilic Lewis acid and displays stability to air oxidation, good chemoselectivity and good functional group compatibility. Complexes of gold(I) with phosphines have been mainly used in the activation of alkynes and allenes toward nucleophilic addition [96, 97] and some asymmetric intramolecular hydroarylation [98], hydroalkoxylation [99] and hydroamination [100] reactions leading to carbocyclic and heterocyclic compounds have been developed by Widenhoefer's and Toste's groups (Scheme 2.11). A pronounced counterion effect was evidenced in some cases and the use of a 1:1 mixture of an achiral gold complex and phosphoric acid (*R*)-**26** as sole source of chirality was sufficient to achieve excellent



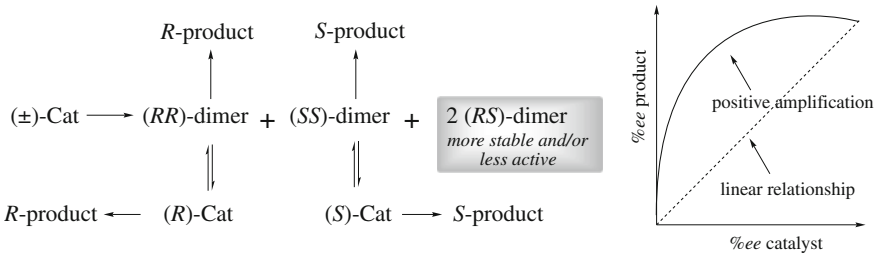
Scheme 2.10 Indium- and scandium-catalyzed carbonyl-ene reactions



Scheme 2.11 Gold(I) activation of allenes

asymmetric induction in the hydroamination of allene **27** to afford the cyclic product in 88% yield and 98% *ee* [101].

Although in catalytic asymmetric synthesis a 100% optical purity of the catalyst is assumed as a condition to gain the maximum enantioselectivity, the use of non-enantiopure chiral sources increases the sustainability of a catalytic process in



Scheme 2.12 Asymmetric amplification of chirality

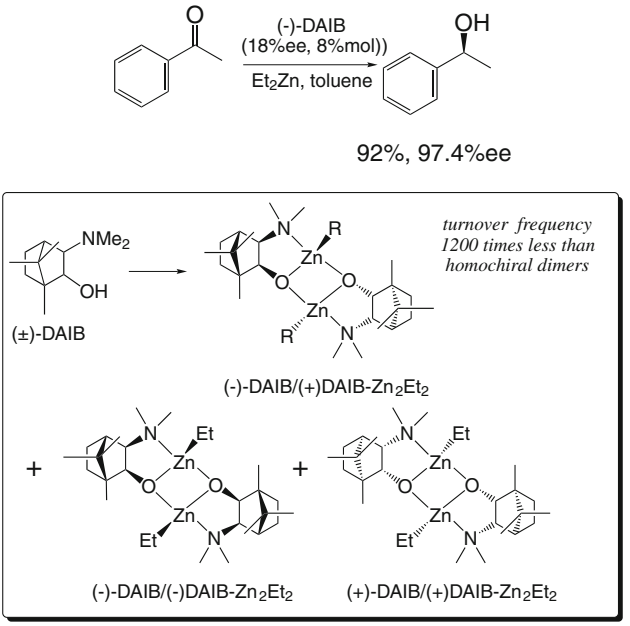
terms of "chirality economy", defined as the ratio (*ee*% × yield % of product)/(*ee* % × mol% of catalyst), other than the obvious advantages in the efforts required for the synthesis and/or resolution of chiral ligands. Different effects leading to a non linear relationship between the optical purities of the catalyst and the product have been mechanistically investigated and high levels of enantioselectivity have been reported for some catalytic systems based on non-enantiopure or racemic ligands.

Asymmetric amplification effects observed with some scalemic ligands have been rationalised with the formation of heterochiral (*RS*) or homochiral (*RR* or *SS*) dimeric species of the catalyst and two models, differing in the nature of the active catalyst, have been proposed by Kagan [102] and Noyori [103]. In both models the formation of a less active heterochiral (*RS*) dimer results in the subtraction of the minor enantiomer of the ligand from the catalytic system, so that the reaction can be stereocontrolled by the more active homochiral dimer (*RR* or *SS*), in this form or in equilibrium with its monomers (Scheme 2.12). Since the amount of available catalyst in the reaction system is siphoned off by the formation of less active aggregates, the asymmetric amplification comes at expense of reaction rate and kinetic studies have been proved useful diagnostic tools for mechanistic insight and identification of active catalytic species [104].

Strongly positive deviations from linearity, resulting in optical purity of the products higher than that of catalysts, have been observed in nucleophilic addition of dialkylzinc to carbonyls (Scheme 2.13), 1,4-addition of organozinc or organocuprates to enones and titanium-catalysed epoxidation, sulfoxidation, Diels–Alder and carbonyl-ene reactions [105].

In *chiral poisoning* approach [106], a rather inexpensive chiral additive deactivates one enantiomer of the catalyst by selective complexation, so leaving the other enantiomer in more enantioenriched form available for catalysis and in an ideal case the addition of one-half an equivalent of poison to a racemic catalyst would leave one-half of an equivalent of active homochiral catalyst, with a process assimilable to a in situ resolution. In any case, the level of asymmetric induction can not exceed the level obtained with the enantiopure catalyst.

The feasibility of this approach was impressively demonstrated in the hydrogenation of methyl-3-oxobutanoate with Ru-complex of racemic diphosphine (±)-**28** in the presence of diamine (*S*)-**29** that gave the (*R*)-product in 99.3% *ee*, a value perfectly comparable with 99.9% *ee* obtained with (*R*)-**28**/Ru-catalyst, in

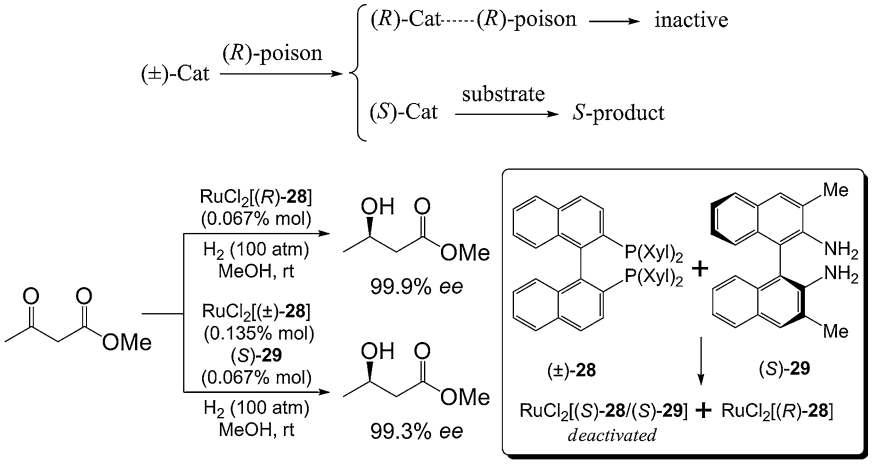


Scheme 2.13 Positive asymmetric amplification in dialkylzinc addition to aldehydes

consequence of quantitative formation of deactivated $RuCl_2$[(*S*)-**28**/(*S*)-**29**] [107] (Scheme 2.14). The addition of catalytically inactive (–)-DIPT-Ti(O-*i*-Pr)$_4$ to (±)-BINOL-Ti(O-*i*-Pr)$_4$ led to a moderately efficient poisoning system for chloralene reaction [108] whereas better enantioselectivities were achieved in the addition of allyltributyltin to aldehydes [109], in both cases as result of the deactivation of (*R*)-BINOL enantiomer.

In the conceptually opposite strategy of *asymmetric activation* the addition of a chiral modifier to a racemic catalyst generates two diastereoisomeric complexes with matched and mismatched chiralities, one of which is more active and enantioselective than the original catalyst, so that the product *ee* is dependent on their relative concentrations, turnover frequencies and enantioselectivities [110]. This approach, effectively applied by Noyori in asymmetric hydrogenation of ketones with racemic Ru-BINAP catalyst in the presence of enantiopure (*S,S*)-DPEN [111], has found advanced application in the activation of atropisomerically flexible (*tropos*) ligands whose axial chirality can be fixed upon dynamically controlled complexation with a metal under the influence of a chiral additive [112]. In such way, achiral pro-atropisomeric ligands can be used instead of chirally rigid racemic ones, that lead to the formation of competitive complexes from each enantiomer.

As an example, the treatment of BIPHEP-Pd$(SbF_6)_2$ **30** with 1 eqv of (*R*)-2,2′-diamino-1,1′-binaphtalene (DANB) gave an initial 1:1 diastereoisomeric mixture that by heating at 80 °C underwent complete tropoinversion to the more stable



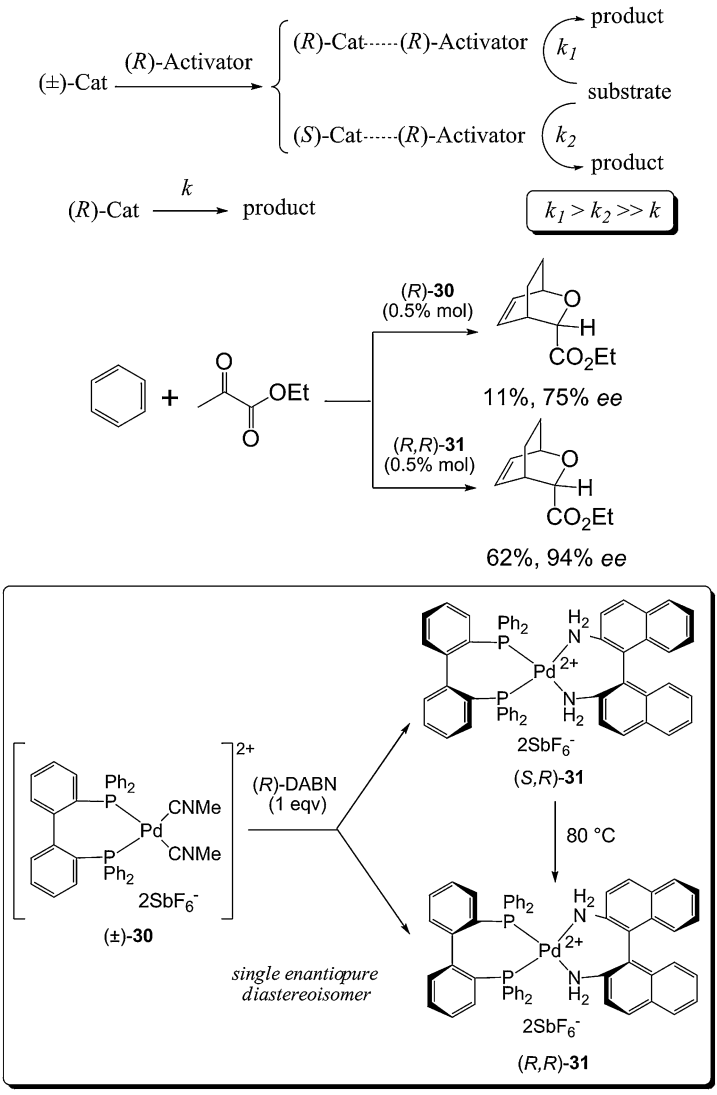
Scheme 2.14 Chiral poisoning approach

complex (*R*)-BIPHEP-(*R*)-DANB **31**, structurally characterised by X-ray analysis, able to act as an enantiopure catalyst in asymmetric hetero Diels–Alder reaction of ethylglyoxylate and 1,3-cyclohexadiene [113] (Scheme 2.15). Following the same approach, BIPHEP-Rh and 2,2′-biphenol-Ti complexes were activated with (*S*)-2′-amino-1,1′-binapht-2-ol [114] and cinchonine [115], respectively, to give highly entioselective catalysts for ene-type cyclization of 1,6-enynes and Strecker reaction of *N*-tosylimines.

2.3 Metal-Free Catalysts

The first examples of enantioselective intramolecular aldol cyclizations catalyzed by (*S*)-proline **32** without the participation of any metal were independently reported by Hajosh and Parrich [116] and Eder et al. [117] (Scheme 2.16a) in early 70s but the potential of this catalytic reaction was not fully realised by the scientific community until 2000 when List described the first direct intermolecular aldol condensation between different aldehydes and acetone promoted by 30% mol of the same aminoacid (Scheme 2.16b) [118]. High excess of acetone was required to suppress the reaction of aldehydes with the catalyst and aldols were obtained with optical purities ranging from 60% up to 96% *ee* with isobutyraldehyde. Since aldol condensation under classical Lewis acid catalysis required manipulation of substrates, converted into more reactive derivatives as silyl enol ethers, this report provided an atom economically breakthrough in this C–C bond forming reaction.

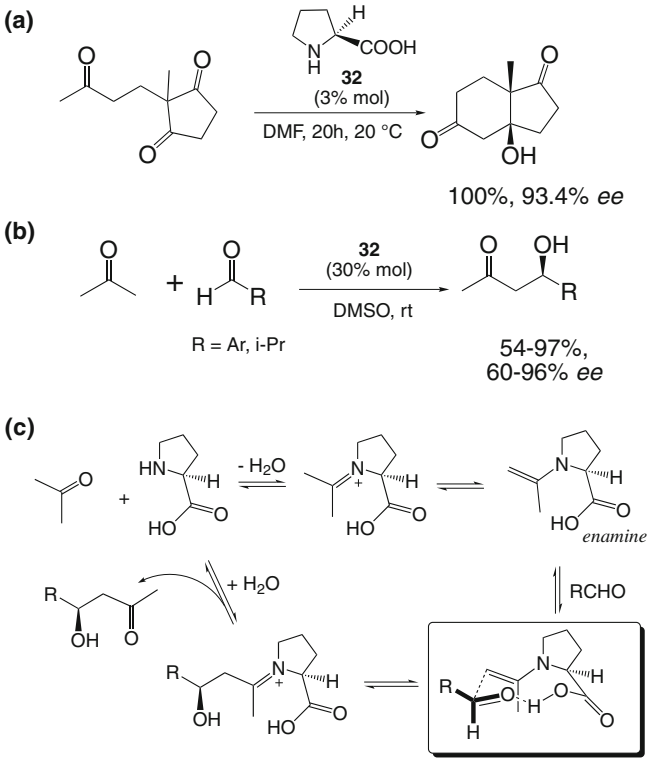
The proposed mechanism, clearly resembling the action mode of class I aldolase and successively supported by experimental [119] and computational



Scheme 2.15 Catalyst activation of a *tropos* ligand

[120] data, involves the activation of ketone through an enamine intermediate followed by its reaction with an electrophile component assisted by the adjacent carboxylic group in an ordered transition state (Scheme 2.16c).

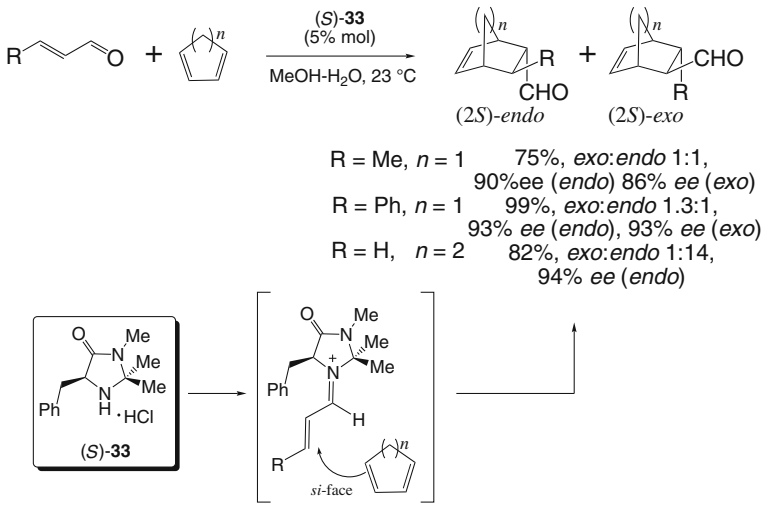
In the same year MacMillan reported the enantioselective Diels–Alder condensation of enals with different dienes in the presence of chiral imidazolinone **33** as catalyst and the activation of substrates through a catalyst-substrate iminium intermediate was envisioned as a useful alternative to classical Lewis acid



Scheme 2.16 Organocatalytic intra- and inter-molecular aldol reactions (**a**–**b**) and proposed mechanism (**c**)

catalysis [121]. The origin of stereocontrol resides in the selective formation of (*E*)-iminium isomer, driven by sterical hindrance of the geminal methyl substituents, and in the shielding of the *re*-face of olefinic bond by benzyl group of **33** that leaves the *si*-face of substrate exposed to cycloaddition (Scheme 2.17).

After these two pioneering researches an explosion of papers appeared in the literature witnessing the interest of organic chemists toward "organocatalysis", a term coined to indicate catalysis promoted by low molecular weight organic molecules, that has then emerged as a powerful strategy complementary to metal-based asymmetric catalysis. Organocatalysts meet several criteria established in green chemistry since they are non-toxic, stable to air and moisture with consequent operational simplicity and, in many cases, are available from natural sources or easy to prepare at relatively low cost. Beside proline other classes of effective organocatalysts have been discovered and most of them can be classified on the basis of their Lewis acid/base and Brönsted acid/base character [122] or in function of the activation modes [123], strictly related to the nature of intermediates generated from catalyst interaction with the substrate fuctional groups (carbonyl, alkene or imine) in a highly organized and predictable manner.

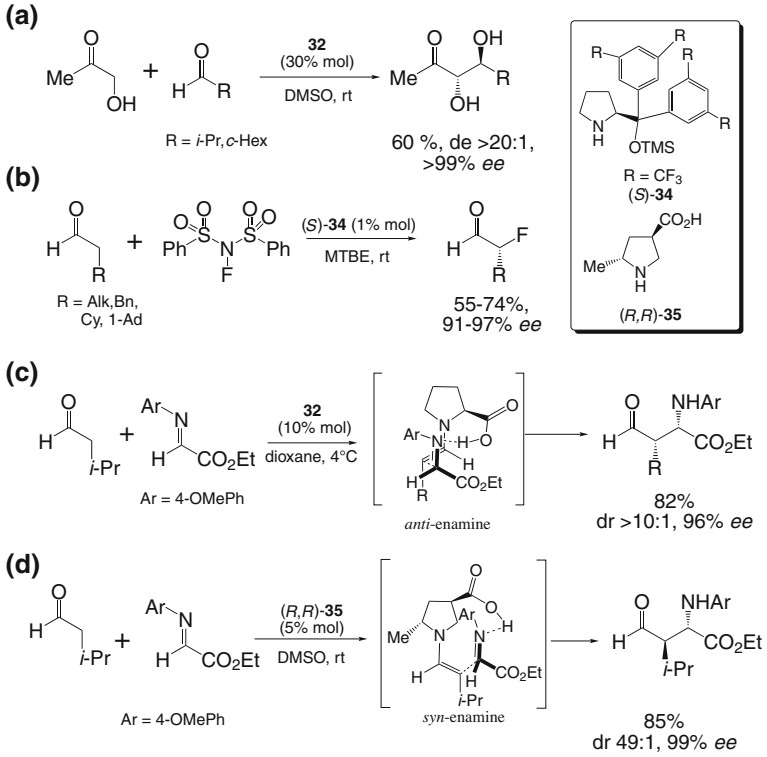


Scheme 2.17 Organocatalytic Diels–Alder through iminium intermediate

Enamine-based oganocatalysis with proline and diamines has been extended to different aldol, Michael or Mannich reactions [124] whereas α,α-diarylprolinol silyl ether **34** showed to be an excellent catalyst with general applicability in asymmetric direct α-functionalisation of carbonyl compounds [125]. Among the most notable examples, proline-catalyzed aldol reaction of hydroxyketones to afford *anti*-diols [126] revealed to be an effective protocol complementary to Sharpless dihydroxylation while α-fluorination of aldehydes in the presence of **34** offered a general procedure for the introduction of C–F bonds (Scheme 2.18a–b). Interestingly, the reversal of the *syn*-diastereoselectivity observed in proline-catalyzed Mannich reaction of aldehydes and protected α-iminoglyoxylate was achieved through a computer-aided rational design of catalyst **35** [127]. It allowed better stabilization of the *syn*-enamine intermediate evolving toward the *anti*-Mannich products thanks to the sterical contribution of C-5 methyl substituent and the larger distance between amino and C-3 carboxylic groups (Scheme 2.18c–d).

In *iminium catalysis*, the higher reactivity of iminium ion compared to carbonyl species activates α,β-unsaturated aldehydes and ketones to 1,4-addition of several nucleophiles and cycloadditions [128]. The enantioselective addition of malonates to enones and enals has been screened with different organocatalysts and valuable application in the formal syntheses of (−)-paroxetine and (+)-femetoxine was reported by Jørgenson's group [129]. Imidazolinone **36** gave high asymmetric induction in the addition of electron-rich benzenes and heteroaromatic nucleophiles to enals [130] (Scheme 2.19) and useful intermediates for the synthesis of biologically active compounds, as homotryptamines, (+)-curcuphenol and rhazinilam-related alkaloids, have been prepared by this route.

More recently the iminium-activation platform has been extended to heteroatom-containinig nucleophiles and prolinol **34** displayed versatility in promoting



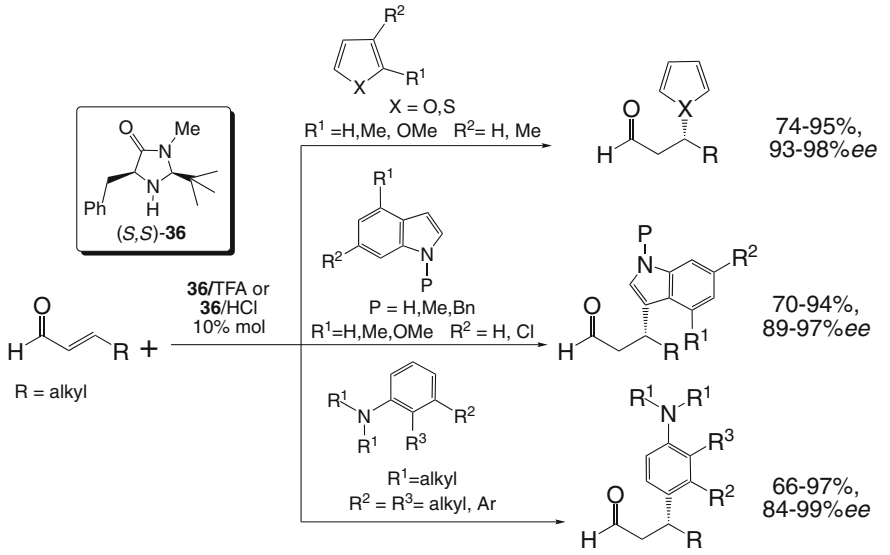
Scheme 2.18 Examples of reactions with enamine activation mode

effective conjugate addition of oximes, *N*-and *S*-nucleophiles to α,β-unsaturated aldehydes [131, 132] (Scheme 2.20a). Good selectivity and substrate scope have been also reported in the hydride reduction of a variety of β,β-disubstituted enals with catalyst **37** and dihydropyridine NADH analogues as hydrogen source.

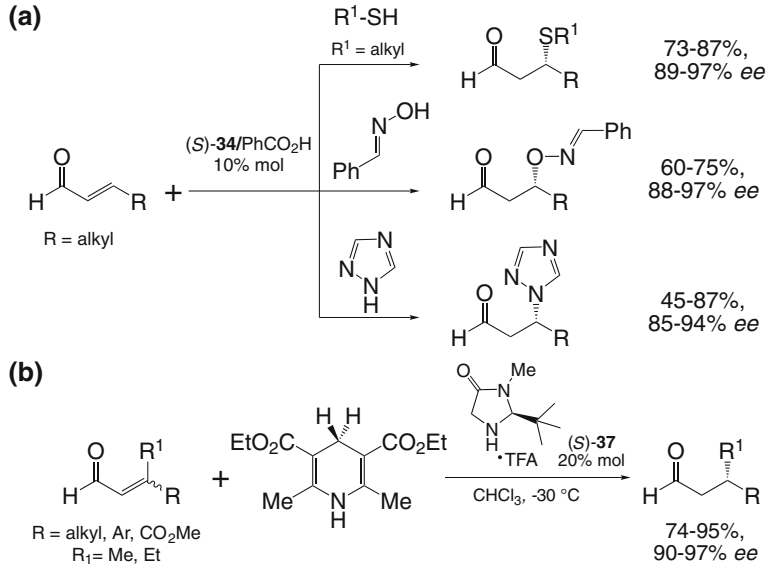
Remarkably features in such reaction were found in tolerance of other groups susceptible to reduction, such aldehyde and aromatic halogens, and enantioconvergence toward the (*S*)-enantiomer so that geometrically pure substrates were not required [133] (Scheme 2.20b).

The reaction of chiral tertiary amines with ketene, α-halogenocarbonyl compounds or enones has been exploited in the generation of *chiral ammonium enolates* with nucleophilic character that can be intercepted by reactive electrophiles [134]. In this context, *Cinchona* alkaloids are the most used bases providing a well-defined chiral environment and they have found interesting application in the enantioselective synthesis of β-lactones from ketenes, or acyl chlorides as ketene precursors, with a range of aldehydes and in Staudinger reaction of imines with the same reactants to afford β-lactams.

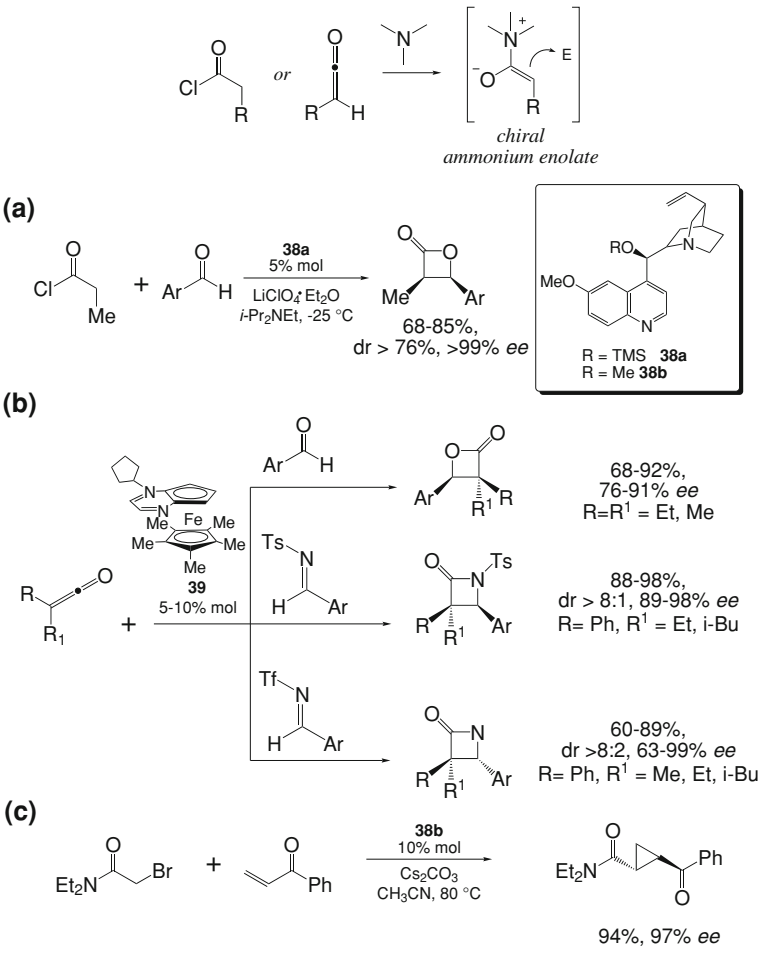
The efficiency of both these processes was sensibly improved by addition of Lewis acid cocatalysts [135] or by using planar chiral ferrocene catalyst **39** that, in



Scheme 2.19 Addition of aromatic nucleophiles to enals through iminium activation mode



Scheme 2.20 Examples of other reactions with iminium activation mode

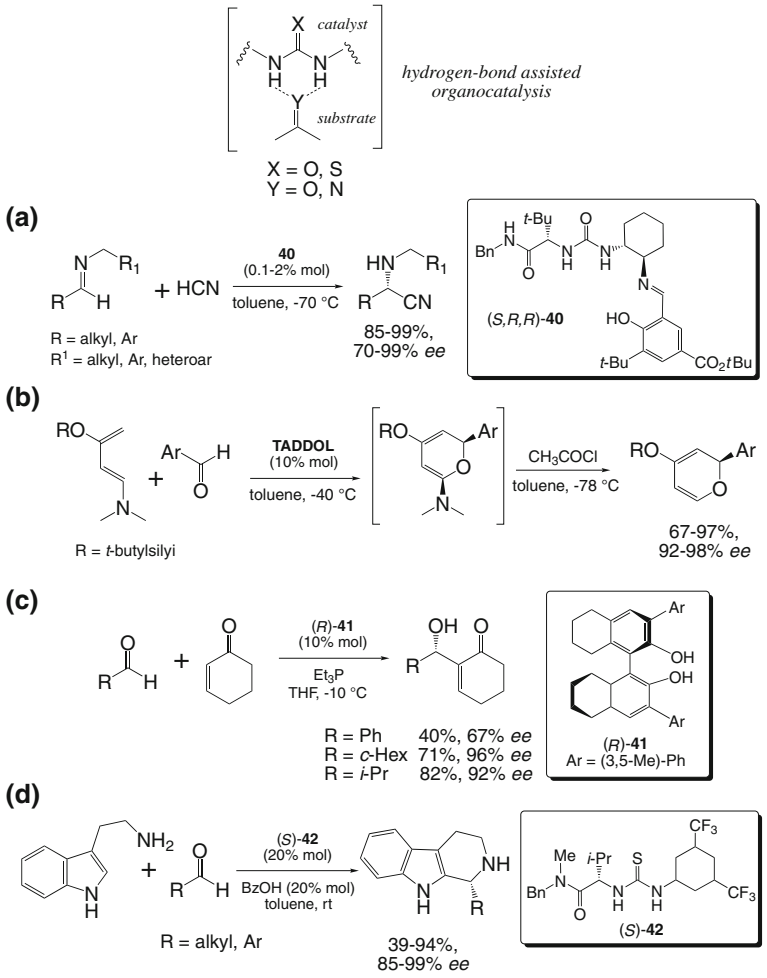


Scheme 2.21 Synthesis through ammonium enolates

addition, induced reversal of diastereoselectivity going from tosyl- to triflate imine substrates [136] (Scheme 2.21a–b). A mechanism involving ammonium ylides was also proposed by Gaunt for inter- and intramolecular cyclopropanation of α-haloketones with activated enones promoted by *Cinchona* alkaloids in the presence of a base [137] (Scheme 2.21c).

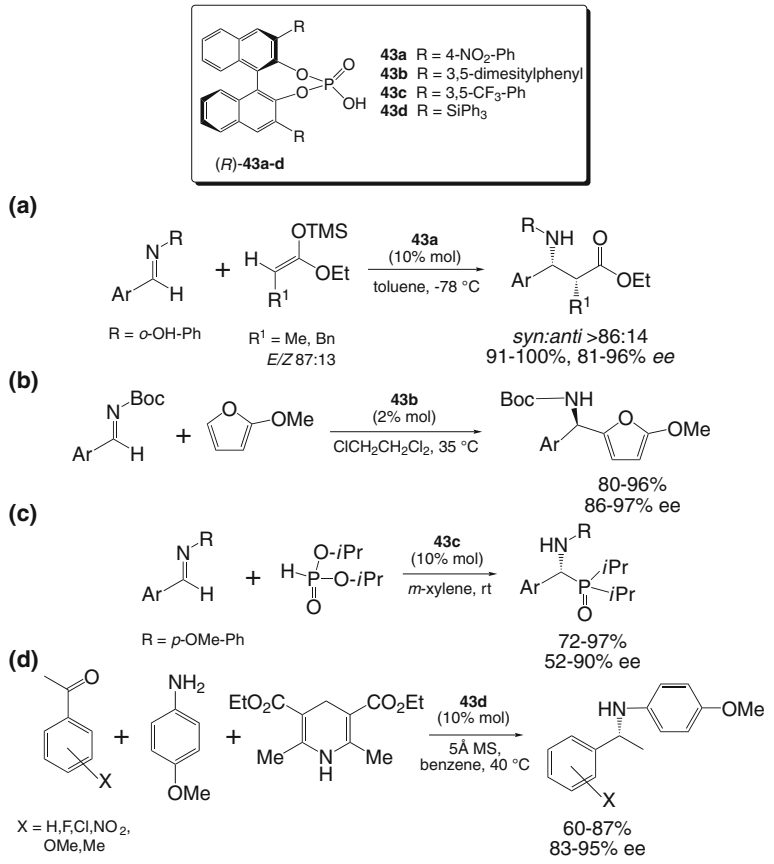
Another interesting class of organocatalysts is constituted by chiral urea and thioureas derivatives that are able to held carbonyl or imines in their close proximity by means of a well-defined array of hydrogen bonds, so exerting a control in the transition-state organization and activating the substrates to nucleophilic attack with a mechanism that may be described as a general acid catalysis.

Fundamental work of Jacobsen gave experimental demonstration of the key role of a dual H-bond interaction between the urea catalyst and imine substrate in the



Scheme 2.22 Hydrogen-bond assisted organocatalysis

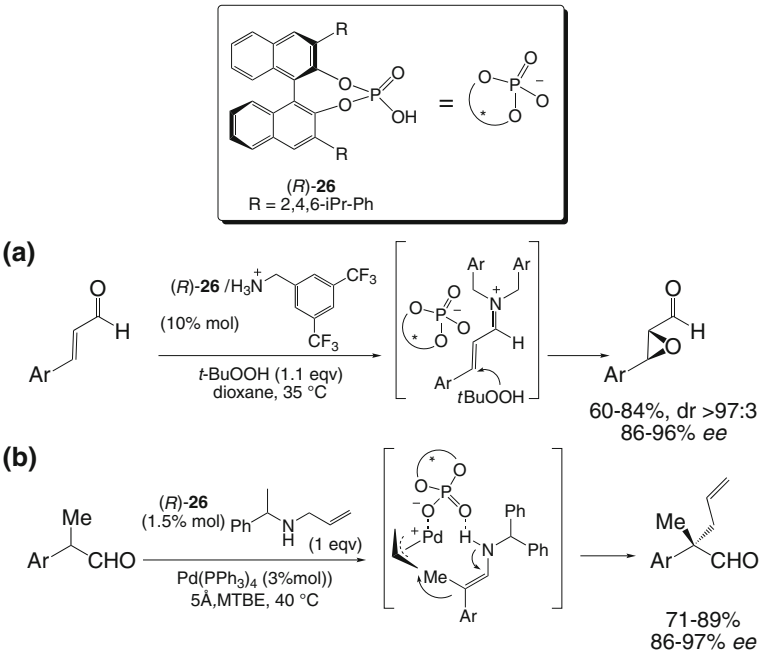
enantioselective hydrocyanation of imines [138] (Scheme 2.22a) and opened the way to the development of other H-bond donors as versatile organocatalysts for mechanistically distinct reactions. In this context TADDOL and BINOL derivatives have been considered as chiral Brönsted acids acting as single H-bond donors and have found useful application in hetero Diels–Alder cycloadditions [139] as well as in Morita-Baylis–Hillman reaction to afford functionalised allyl alcohols [140] (Scheme 2.22b–c). A range of conjugate additions to nitroalkenes and Mannich reactions were successfully promoted by *Cinchona*-alkaloid or thiourea-based organocatalysts [141], the latter being active also in Pictet-Spengler reaction to give functionalised indoles as intermediates in the synthesis of alkaloids [142] (Scheme 2.22d).



Scheme 2.23 Organocatalysis with strong Brönsted acids

BINOL-derived phosphoric acids **43** have been designed as strong Brönsted acid catalysts capable to activate substrates by way of protonation and induce efficient chirality transfer through their tight ion-pairing with the cationic intermediates so generated. Density functional calculations have supported this mechanism [143] and different addition reactions to imines [144] (Scheme 2.23a–c) as well as reductive amination of methyl ketones with amines [145] (Scheme 2.23d) have been optimized by tuning the 3,3′-substituents in binaphtyl scaffold of **43**.

Dia- and enantio-selective epoxidation of a variety of di- and tri-substituted enals [146] (Scheme 2.24a) and transfer hydrogenation of *β*,*β*-unsaturated aldehydes [147] were efficiently performed in the presence of (*R*)-**26** phosphate salts with an achiral ammonium cation. Such *counteranion-directed* strategy has been also applied to transition metal catalysis, that in this way can be effectively carried out without the need of chiral ligands in the metal complexes, and excellent results have been obtained in Pd-promoted α-allylation of aldehydes (Scheme 2.24b) for

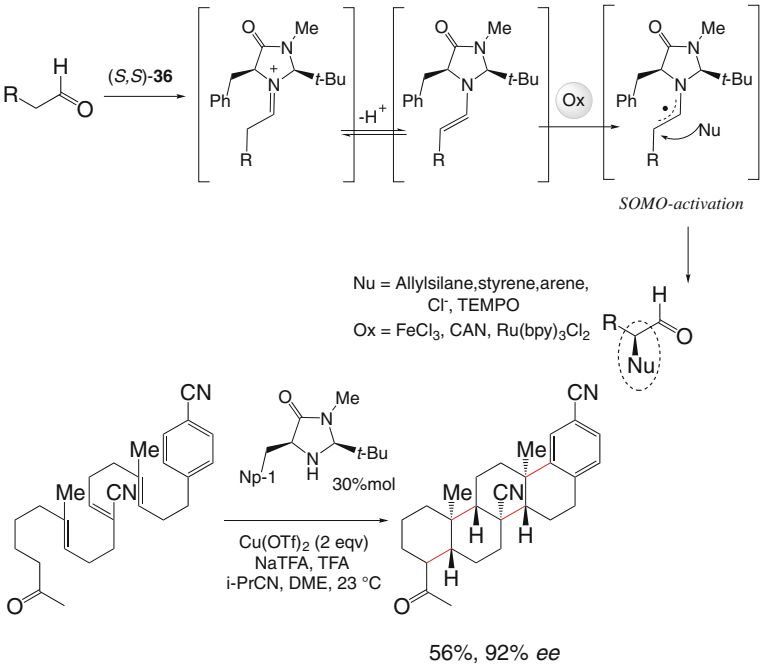


Scheme 2.24 Counterion-directed catalysis

the construction of carbon-quaternary stereogenic centers [148, 149] other than the above cited gold(I)-catalyzed intramolecular hydroamination of allenes.

Last advance in organocatalysis concerns the development of a novel activation mode, independently described by MacMillan's [150] and Sibi's [151] groups in 2007, based on the shift of the 2π–4π electron equilibrium between iminium and enamine species toward the formation of a transient 3π radical cation with a singly occupied molecular orbital (the SOMO intermediate), that can be trapped by non conventional coupling partners giving products otherwise difficult to achieve. The *SOMO-activation* of carbonyl-catalyst intermediates, operationally accomplished by including a one-electron oxidant in the catalytic system, has been mainly exploited for direct α-functionalization of aldehydes and ketones with π-rich olefins [152] and in a sophisticated application to intermolecular polyene cyclization up to 6 new C–C bonds and 11 contiguous stereocenters were generated in a cascade process [153] (Scheme 2.25). In order to overcome the required excess of chemical oxidant, phodoredox systems in catalytic amount have been recently proposed as alternative oxidant source under light excitation and a substantial improvement in SOMO-strategy is expected from coupling of these two classes of catalysts [154].

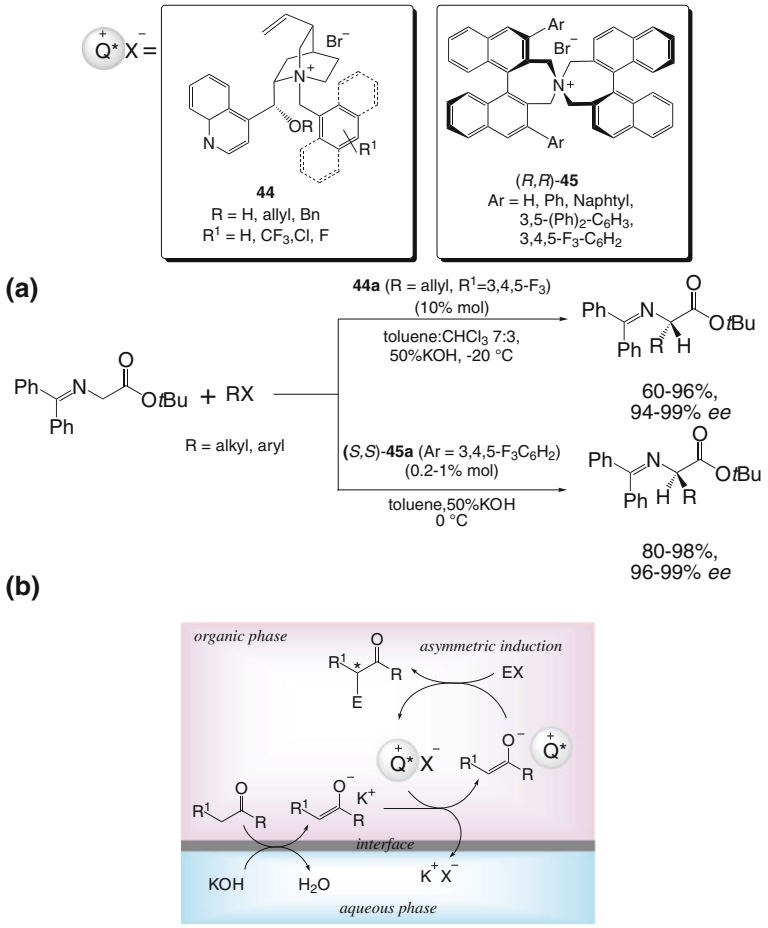
A quite specific group of organocatalysts has been developed for *phase transfer catalysis*, a methodology in which compounds with different solubility can react in biphasic aqueous-organic solvent mixtures in the presence of a catalyst able to provide great rate acceleration facilitating the transport of reagents or



Scheme 2.25 α-Functionalization of aldehydes via SOMO-activation

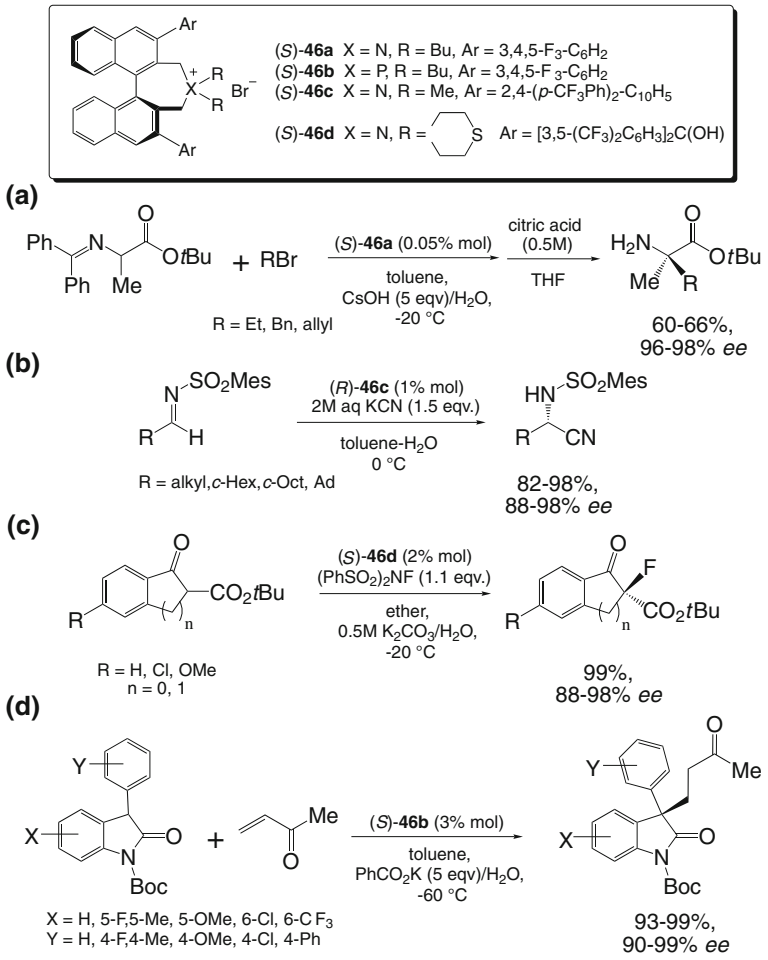
intermediates from the interfacial surface to the organic phase wherein the reaction really occurs. Phosphonium or quaternary ammonium salts with hydrophobic organic cations have been traditionally used as phase transfer catalysts since they promote the fast ion-exchange of metal enolates, generated from substrates with acidic protons at the interface with a basic aqueous solution, to form liphophilic onium enolates that are moved deep into the organic phase in which the reaction with an electrophilic partner takes place under the stereochemical control of chiral cation with concomitant regeneration of the catalyst (interfacial mechanism, Scheme 2.26b) [155]. Despite of the methodology has been dated since the end of 1960s, its application in asymmetric synthesis emerged later with the development and design optimization of *Cinchona*-alkaloid derived (**44**) [156] or *N*-spiro binaphtyl (**45**) quaternary ammonium salts as the most versatile families of phase transfer chiral catalysts [157]. Due to their well-defined chiral environments these catalysts, often active in remarkably low amount, provide effective shielding of one of the two enantiotopic faces of enolate anion so stereochemically controlling the enolate-electrophile reaction. The advantages of mild experimental conditions, increased selectivity, simplification in work-up procedures and applicability in large-scale preparations, make asymmetric phase-transfer reactions an attractive "green" alternative to homogeneous processes.

Alkylation of glycinate Schiff bases with alkyl halides under basic (usually KOH or NaOH) conditions has been widely exploited for the preparation of



Scheme 2.26 Representative examples of phase transfer catalysts (**a**) and action mechanism (**b**)

several α-aminoacids [158] and natural products in high optical purity and a beneficial effect on the selectivity was evidenced when electron-withdrawing substituents were present in the molecular structure of the catalysts (Scheme 2.26a). The extension of such reaction to the preparation of α,α-dialkyl-α-aminoacids (Scheme 2.27a)[159] and modified peptides [160] afforded unnatural derivatives potentially useful as enzyme inhibitors or in mechanism elucidation of enzymatic reactions and sensible rate acceleration was sometimes achieved by addition of achiral crown ethers as cocatalysts, for their known ability to extract metal cations [161]. In order to avoid the need of two different chiral binaphtyl moieties in catalysts of type **45**, a new generation of onium salts has been developed through the introduction of selected substituent on the 3,3′-positions of binaphthyl scaffold and modification of the amine functionality [162]. Novel derivatives **46** have been reported as effective chiral phase transfer catalysts for

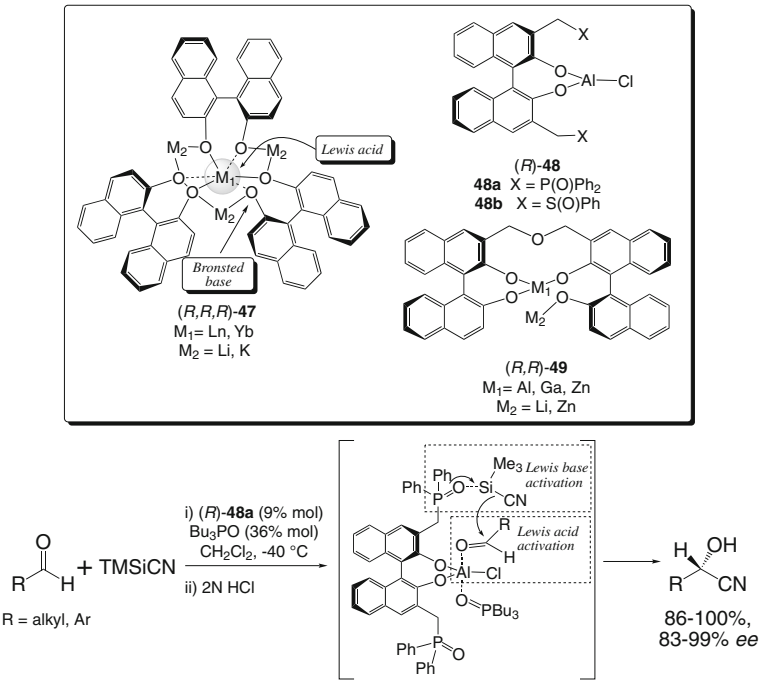


Scheme 2.27 Examples of reactions with chiral onium salts

Strecker reaction [163], fluorination of β-ketoesters [164], and a variety of conjugate additions [165–168] (Scheme 2.27b–d).

2.4 Bifunctional Catalysts

In the search for more active and enantioselective catalysts and taking inspiration from enzymes, whose efficiency is often due to the presence of multiple catalytic sites working in synergistic fashion, some interest has been shifted toward the development of bifunctional systems for the simultaneous activation of both partners of a given reaction. Contrary to conventional asymmetric catalysts, that

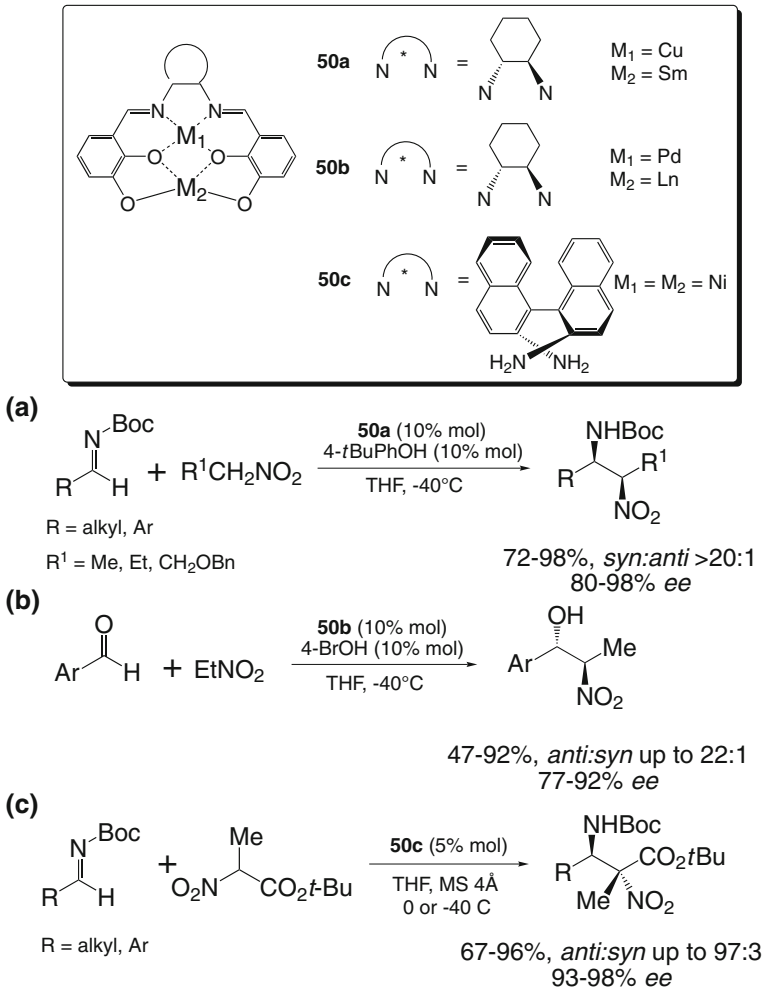


Scheme 2.28 Transition-metal bifunctional catalysts with BINOL-derived ligands

activate one reactant by a Lewis acid or base group present in their molecular structure, bifunctional systems are designed to have two different functionalities with complementary features in order to promote in concert electrophilicity and nucleophilicity in reactive partners and concentrate them in the proximity of catalyst chiral environment, so that enhanced activity and level of stereodifferentiation in milder conditions can be expected.

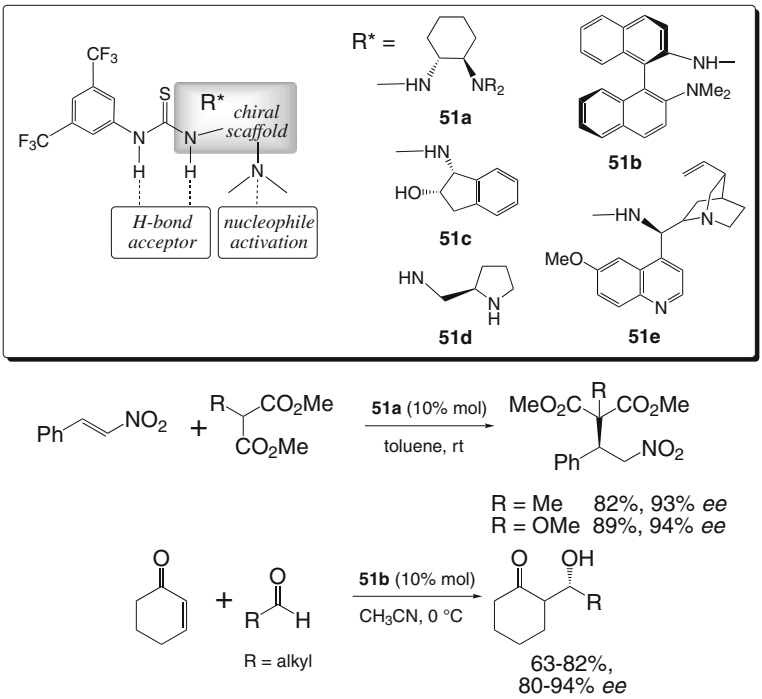
Among selected examples of transition-metal based *bifunctional catalysts*, heterobimetallic complexes **47**, containing three BINOL units, three alkali metals and a lanthanide metal, were reported by Shibasaki's group as versatile platform for a variety of asymmetric reactions. Good to excellent performances were achieved through cooperative action of BINOLate moieties as Brönsted base sites and rare earth metal as Lewis acid center [169]. The evolution of such scaffold has led to the development of BINOL ligands **48**, functionalised with Lewis basic phosphine oxide or sulphoxide groups, that have been applied for Al(III)-promoted cyanide addition to aldehydes, imines (Strecker reaction) and quinolines (Reissert reaction) [170]. Other useful ligands have been prepared by joining two BINOL units or BINOL-achiral biphenyls units through a heteroatom and the application of their Ga(III)- or Zn(II)- complexes in Michael and Mannich additions has been recently reviewed [171] (Scheme 2.28).

Salen-type Schiff bases **50** bearing additional phenolic substituents have been designed as effective ligands in controlling the position of two different metals



Scheme 2.29 Bimetallic salen-complexes in bifunctional catalysis

through selective complexation of a transition metal into the inner N_2O_2-cavity, meanwhile an oxophilic rare earth metal with larger ionic radius can be accommodated in the outer O_2O_2-cavity. In a screening of metal combinations for *syn*-selective nitro-Mannich reaction, $Cu(OAc)_2$ and $Sm(O\text{-}i\text{Pr})_3$ gave optimal results and substrate scope and enantioselectivity were further improved by addition of 4-*t*Bu-phenol that promoted dissociation of less selective oligomeric species. In the proposed mechanism the Sm-OAr moiety of the catalyst would act as Brönsted base favouring the Sm-nitronate formation while Cu would function as Lewis acid for imine activation [172]. Interestingly, the Pd/La combination enabled to reverse the diastereoselectivity in the related nitroaldol reaction [173] (Scheme 2.29a–b). Changing the substituent on diimine bridge with the more rigid

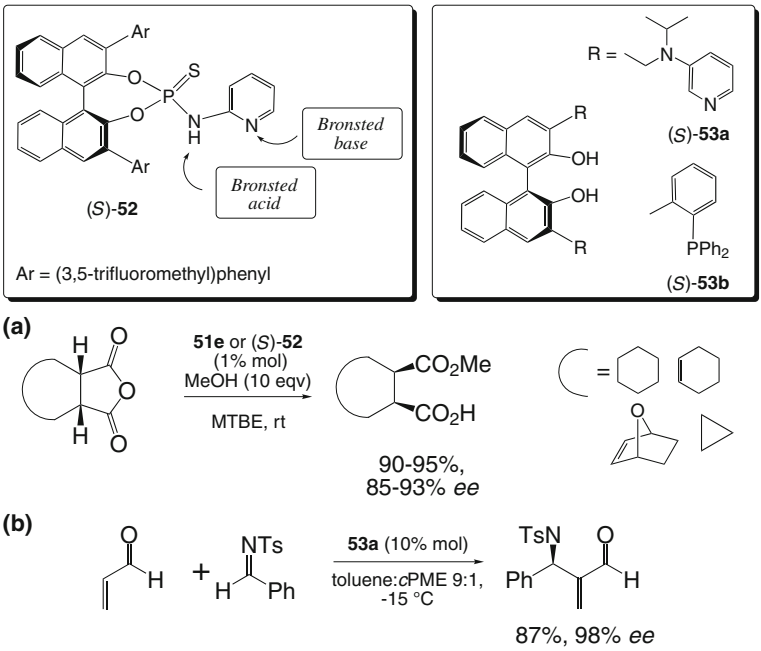


Scheme 2.30 Thiourea-based bifunctional organocatalysts

binaphtyl unit also metals with smaller ionic radius can be held into the O_2O_2-cavity and the bench-stable complex **50c** with two Ni atoms showed higher performances in Mannich addition of different nucleophiles to imines with respect to the corresponding mononuclear complex, so confirming the importance of cooperative activation [174] (Scheme 2.29c).

The concept of dual activation is also applicable to organocatalysis and the simplest examples of bifunctional organocatalysts are represented by proline and related prolinol derivatives, that are able to activate one reactive partner through the formation of a covalent enamine intermediate and the other one by non-covalent interactions with the carboxylate or hydroxyl substituent on the catalyst [175]. Thiourea derivatives bearing an additional nitrogen substituent form the main group of effective bifunctional organocatalysts and exert dual activation and stereocontrol by means of a network of hydrogen bonds with the reagents in a strong oriented transition state resulting from the proximity of acid and basic functionalities on the same chiral framework.

In most cases one of the substituents on thiourea moiety is the electron-withdrawing 3,5-trifluorophenyl group, that increases NH acidity and conformational rigidity of the molecule through additional H-bonding interaction with the sulphur



Scheme 2.31 BINOL-derived bifunctional organocatalysts

atom, while basic amine functionality derives from a variety of chiral scaffolds as *trans*-cyclohexanediamine, pyrrolidine, binaphtyldiamine, indanol and *Cinchona*-alkaloids. The resulting catalysts gave excellent results in Michael addition of different nucleophiles to chalcones or nitroolefins, in Morita-Baylis–Hillman reaction of cyclohexenone with a range of aldehydes [176] (Scheme 2.30) as well as in the methanolytic desymmetrization of cyclic anhydrides [177], a process recently broadened in scope by using BINOL-related catalyst **52** with a bifunctional thiophosphoramide group (Scheme 2.31a) [178]. Other BINOL derivatives with aminic or phosphine substituents acting as Lewis basic centres have been designed as valuable alternatives to bifunctional thiourea catalysts for aza-MBH reaction [179] (Scheme 2.31b).

In summary, the conceptual evolution of catalyst design has led to effective systems for a large variety of asymmetric reactions. Organization of substrates in the chiral environments of catalysts is an essential requisite for asymmetric induction and it has been achieved by coordination with transition metals, formation of covalently bonded intermediates or through a network of H-bonding or electrostatic interactions. Simultaneous activation of both the reaction partners by using bifunctional catalysts has often resulted in higher chemical and optical yield of the products. Some asymmetric transformations have been yet applied to the synthesis of chiral biologically active compounds and their extension to large-scale preparation can be reasonably envisaged.

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Chapter 3
Alternative Solvents and Recycle of the Catalyst

Abstract In the search for more environmentally benign alternatives to common organic solvents water, ionic liquids and perfluorinated solvents display valuable features, being able in some cases to influence the outcome of asymmetric reactions and offering additional gain for the catalyst recycle by liquid–liquid extraction. Although some classical catalysts have been used in their native form in these non-conventional reaction media, in most cases a suitable structural modification of the ligands or organocatalysts is required in order to increase their phase affinity and recyclability. In a complementary approach, catalysts have been immobilized on a variety of unsoluble materials to be recovered from organic solutions by simple liquid/solid-phase separation. Since some limits in the catalytic performances could stem from the heterogeneous reaction conditions, there is an increased interest in the development of catalysts covalently bonded to soluble macromolecular supports and easily recyclable after selective precipitation or ultrafiltration.

Keywords Non-conventional solvents · Water-compatible catalysts · Catalyst recycle · Self-supported catalysts · Soluble macromolecular supports · Magnetic nanoparticles

3.1 Introduction

Solvent plays an important role in asymmetric catalytic synthesis taking part in the formation of several transition-metal complexes, stabilizing the reaction intermediates by non-covalent interactions, dissipating heat in exothermic reactions and ensuring the optimal dissolution of all the system components in a homogeneous phase. As a consequence, the solvent can markedly affect both

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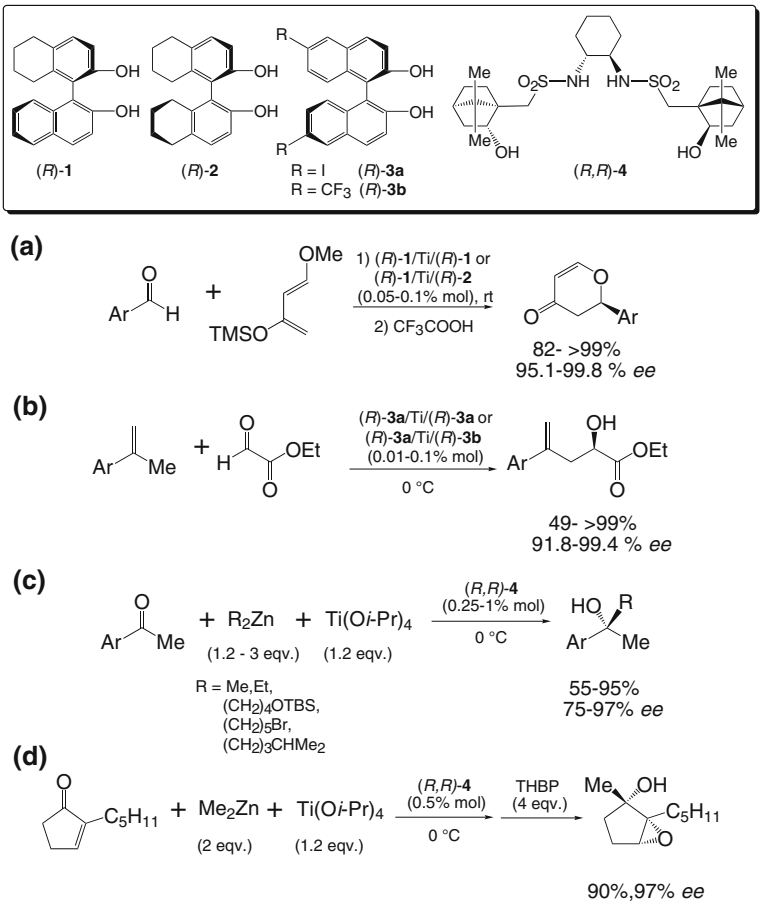
chemical yield and selectivity for a given reaction and evidences of "solvent effects" have been also useful in the mechanism elucidation. Solubility and stability of the majority of organic compounds are compatible with organic solvents, that have been extensively used also in the purification of products and represent about 85% of the total mass of chemicals in manufacture of pharmaceuticals leading to the largest contribution to the E-factor magnitude. Toxicity, volatility and flammability of many organic solvents constitute a source of hazards for workers and atmospheric pollution and even polar high boiling solvents such as dimethylformamide or dimethylsulphoxide present environmental concerns since they can not be easily removed by distillation and their separation by washing otherwise affords contaminated aqueous effluent.

Under the more stringent request of "green reactions" many industrial processes have been reconsidered using less volatile solvents or in minimized amounts [1] as well as more biodegradable or natural-derived solvents as ethanol, limonene and ethyl lactate but there is a growing academic and industrial research toward non-conventional and more benign alternatives. Options based on the use of non-toxic water or recyclable ionic liquids and fluorinated solvents as well as the development of solvent-free reactions have been explored in chemical and asymmetric synthesis [2]. The search for sustainable solvents has been intimately connected with the development of effective protocols, based on liquid–liquid separations, for selective recovery and reuse of catalysts [3], in many cases specifically designed in order to be compatible with non-conventional reaction media saving activity. Catalysts heterogenized on insoluble materials have been classically employed to be recovered from organic solutions by solid–liquid separations, but selective precipitation or ultrafiltration of catalysts immobilized on soluble macromolecular supports has been considered a useful alternative.

This chapter is focused on a general overview of "green" solvents and different techniques of catalyst recycle specifically applied to enantioselective transformations.

3.2 Solvent-Free Reactions

The most obvious way to minimize the solvent waste is to not use solvent at all or to perform highly concentrated reactions and additional cost-saving benefits can derive from reduced reaction time, energy consumption and reactor size. Although this approach has been applied to different polymerization, radical, ionic and photochemical reactions and in less extent to asymmetric catalysis, thermal safety considerations can not be neglected due to the possible occurrence of a rapid overheating in absence of solvent. In asymmetric catalysis under *solvent-free* conditions the important parameters of catalyst concentration and nature of the solvent are not operative and the composition of reaction medium changes as reactants are converted into products with unpredictable influence on the



Scheme 3.1 Examples of asymmetric reactions performed in solvent-free conditions

enantioselectivity so that is not unusual that lower performances are observed in comparison with the standard conditions with solvents.

However, some transition-metal and organocatalyst promoted reactions work well in solvent-free conditions [4] and excellent examples were found in hetero-Diels–Alder [5] and carbonyl-ene reactions [6] catalyzed by Ti-complexes of homo- or hetero-combinations of BINOL-type ligands in extremely low concentration (Scheme 3.1a, b). Bis-sulfonamide **4**-Ti complex was a very active catalyst for the addition of alkyl- and functionalized organozinc reagents to a range of aromatic and cycloalkylketones giving similar or better enantioselectivities compared to the reactions in solution with up to 40-fold decreased catalyst loading. The reaction afforded chiral tertiary alcohols with 80–99% *ee* and its combination with diastereoselective epoxidation in a one-pot procedure

allowed to prepare *syn*-epoxyalcohols with three contiguous stereocentres in high yield also on a 5 g scale-up [7] (Scheme 3.1c, d).

A solvent-free aldol reaction with 10% mol of proline gave the *anti*-aldol adducts in high optical purities and moderate to good diastereoselectivity and sensible decrease in the reaction time was achieved mixing the reactants with ball milling technology using 5-mm diameter balls of chemically inert and non abrasive zirconium oxide [8]. Under the same experimental conditions better reaction rate and selectivity were obtained with (*S*)-proline-(*S*)-phenylalanine methylester as organocatalyst [9].

3.3 Water as Solvent

If a solvent is needed for a reaction the most preferable alternative to organic solvent from a green chemistry perspective is water as the cheapest and most abundant solvent available, non-toxic and not inflammable. Although water provides a unique hydrogen-bond network that can beneficially influence the rate and selectivity in many organic reaction, its use has been strongly limited by the fact that the majority of organic compounds is poor soluble or unstable in this reaction medium.

An increase in solubility of non-polar reactants has been often achieved by pH variation, addition of additives as salts or surfactants and use of water-polar organic cosolvent mixtures and many stereoselective C–C bond forming reactions as well as oxidations and hydrogenations have been performed in these modified aqueous media [10]. However, the use of water as sole solvent remains still very challenging for asymmetric catalysis and, despite of the fact that some aspects of the greenness of water in organocatalysis have been recently questioned [11], it represents a very attractive research field.

In a debate on the most suitable terminology to describe reactions in water Sharpless proposed the term "on water" for reactions that take place in an emulsion of insoluble reagents stirred in neat water and display rate acceleration compared to the same reaction performed in organic solvent [12]. The positive effects observed in these conditions for many reactions [13] dismantled the concept of solubility as prerequisite for reactivity and has indicated a new way to organic synthesis. Hayashi suggested to term "in water" those reactions in which the reactants are homogeneously dissolved in opposition to "in presence of water" for reactions proceeding in a concentrated organic phase influenced by water as second phase, the latter definition also including the situation described as "on water" [14].

Since the gain in the use of water as more sustainable solvent needs to be conjugated with synthetic and chiral efficiencies, whose decrease could lead otherwise to an increase in cost and chemical waste, much efforts are continuously devoted to the development of new chiral catalytic systems compatible with water, in some cases driven by the knowledge of enzymatic processes that "naturally"

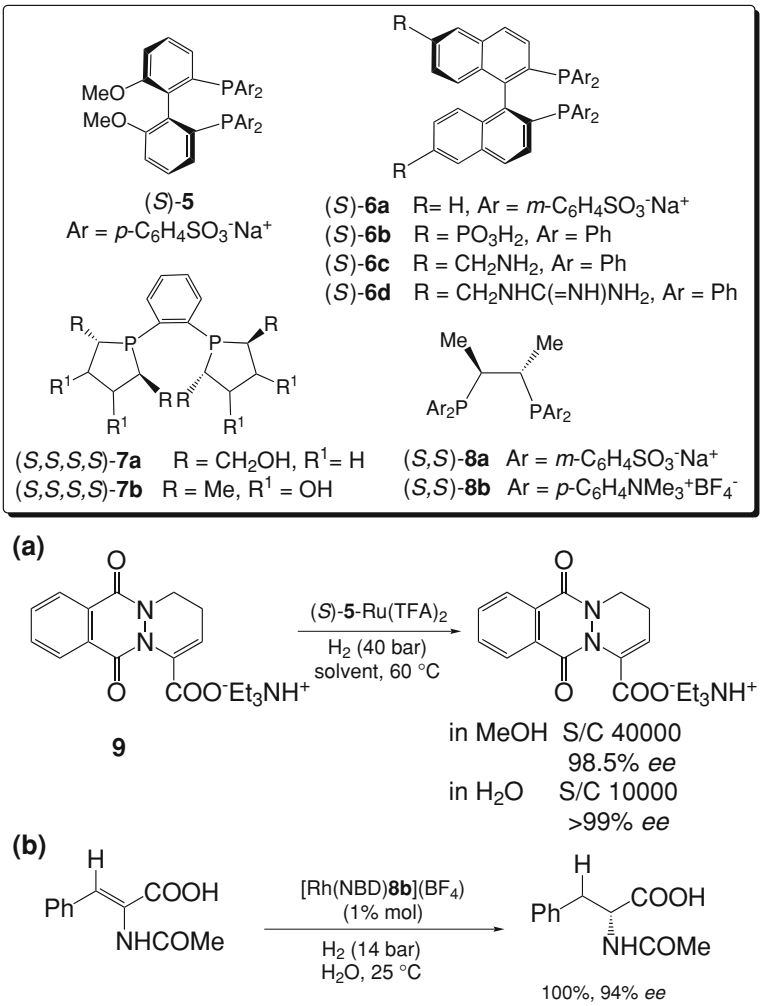
occur in water and the study of the relationships between the effects generated by water (hydrogen-bonding, hydrophobicity, acidity) and reactivity and stereoselection. The de novo design of chiral catalysts specifically targeted to their use in water has been rather unexplored while approaches relying on chemical modifications of yet known active catalysts in order to increase their hydrophilicity or, on the contrary, their hydrophobicity have been mainly investigated.

Water-soluble catalysts allow to fully exploit the properties of water to promote the dissociation of ionic species also providing their effective solvation, to modify the reactivity of Lewis acid species due to its nature of Lewis base, and to serve as acid, base or nucleophilic reagent. Furthermore, selectivity can be finely tuned by pH variation or addition of salts and the catalyst can be easily recovered for its recycle by simple phase extraction, this aspect being very attractive for large scale preparations. Since the use of a water-soluble catalyst can result in decreased activity in consequence of poor interactions with hydrophobic substrates, there is considerable interest also in the design of surfactant-like ligands bearing substituents with polar or ionic groups at the end of long aliphatic chains or ligands with adjustable solubility properties, as amine- or polyethylene glycol (PEG)-substituted catalysts whose hydrophilicity can be modulated by pH or temperature changes. On the other side, many organocatalysts have been functionalised with large apolar groups in order to cluster together the catalyst and reagents in the aqueous environment by means of hydrophobic interactions and it has been proposed that in such systems reactions occur in a concentrated organic phase constituted by reagents, catalyst and the formed products [15].

The hydrophilic character of chiral phosphines, the largest group of chiral ligands in transition-metal based catalysis, has been usually increased by the introduction, either on the carbon backbone or at phosphorous atom, of anionic sulphonate, phosphonate or carboxylate substituents that exist in ionic form over a broad range of pH, are stable under a variety of reaction conditions and do not interfere with the catalytic cycle due to their low tendency to bind late transition-metals. Functionalization with protonable basic groups or non-ionic polyhydroxyl or polyether substituents has also been explored for the preparation of water-soluble phosphines.

Despite of the obvious modifications in steric and electronic properties of such ligands with respect to the parent molecules for the presence of water-solubilizing groups, good results have been obtained in different reactions with a large predominance of enantioselective olefin hydrogenation [16]. In most cases the reactions have been performed in homogeneous water-organic cosolvent mixtures or in biphasic systems but a limited number of catalysts was also active in pure water.

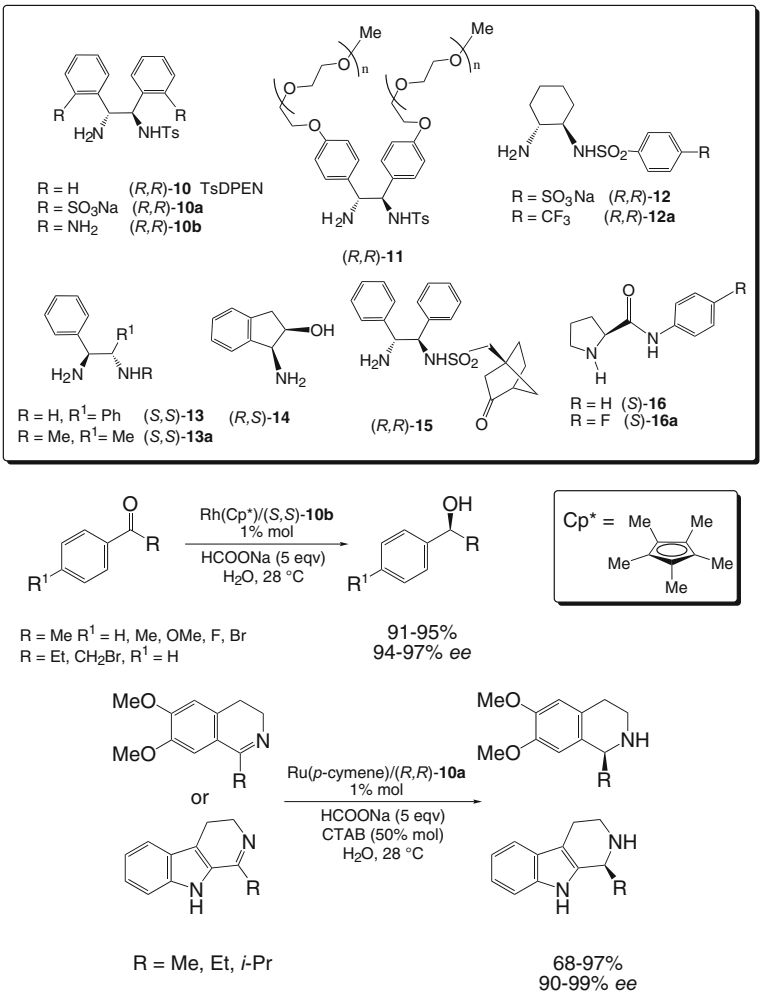
Hydrogenation of pharmaceutical intermediate **9** with sulphonated BIPHEMP **5/**Ru-catalyst proceeded in water with the same enantioselectivity reported in MeOH [17] (Scheme 3.2a) and also Ru-promoted carbonyl hydrogenation of ethylacetoacetate was effectively carried out in the presence of water-soluble ligand **6c**. In water as sole solvent, Rh(I)-complexes with hydroxylated DuPHOS **7a** [18] or CHIRAPHOS-analogue **8b** promoted hydrogenation of dehydroaminoacids in high



Scheme 3.2 Hydrogenations with water-soluble phosphines

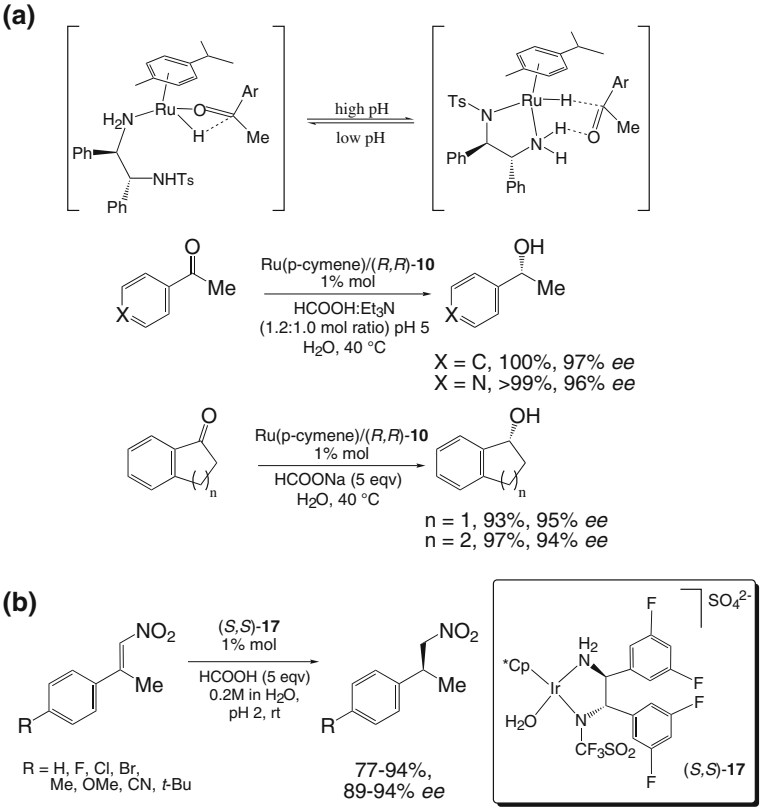
optical purities. Enhanced reaction rate in comparison with biphasic H_2O/AcOEt system was observed with **8b** and the presence of trimethylammonium groups in the ligand also facilitated the separation of Rh-catalyst, reused three times without loss of enantioselectivity [19] (Scheme 3.2b).

Asymmetric transfer hydrogenation (ATH) of ketones and imines promoted by Ir(III)- Rh(III)- or Ru(II)-complexes to give the corresponding chiral secondary alcohols and amines is an attractive green process since it avoids the use of hazardous molecular hydrogen using 2-PrOH or formic acid as hydrogen sources. Besides the most popular ligand TsDPEN **10**, originally developed by Noyori [20], a variety of diamines and aminoalcohols have been tested for ATH of several



Scheme 3.3 Asymmetric transfer hydrogenations in water

aromatic and heteroaromatic substrates in 2-PrOH or HCOOH/triethylamine with excellent performances in many cases [21]. Functionalization of TsDPEN with sulphonic [22, 23] or aminic [24] groups has led to water-soluble ligands whose complexes retained high enantioselectivity in ATH of ketones and cyclic imines with HCOONa as hydrogen source in neat water sometimes containing low amount of a surfactant to facilitate substrate solubilisation (Scheme 3.3). Derivatization of TsDPEN with hydrophilic polyethylene glycol (PEG) gave soluble polymer-supported ligands [25, 26] and ruthenium complex of **11** displayed excellent performances and recyclability in ATH of several ketones under aqueous conditions, being active without loss of enantioselectivity for up to



Scheme 3.4 Asymmetric transfer hydrogenation of ketones (**a**) and nitroalkenes (**b**) with unmodified DPEN ligands in neat water

14 cycles (tested in acetophenone reduction) with only 0.4% mol of metal leaching into the organic phase during the extraction of the product.

Quite unexpectedly, Xiao and coworkers found sensible rate acceleration of ATH of ketones using unmodified TsDPEN-Ru(*p*-cymene) complex in neat water [27], this behaviour being also observed with several of the ligands active in organic solvents [28] and TsDPEN-Ir(III)- or Rh(III)-complexes [29]. Using the "on water" protocol (substrate and catalyst are insoluble) or micellar catalysis [30] up to 10,000 S/C ratios became feasible and reactions could be performed without inert gas protection to give a variety of simple and functionalized secondary alcohols in high chemical and optical yields. Mechanistic investigation of Ru-(*R*,*R*)-TsDPEN promoted ATH of acetophenone in water with HCOOH/triethylamine azeotrope revealed a marked dependence of reaction rate and catalyst enantioselectivity with solution pH, so that the adjustment of initial pH to 5 was required in order to achieve results comparable with those obtained using HCOONa as hydrogen source. It has been suggested that the concerted mechanism proposed by Noyori

through a cyclic hydride intermediate could be operative at high pH, with formic acid mainly existing in its dissociated form, whereas at acidic pH the protonation of the coordinated ligand could lead to uncyclic and less-organized transition states giving rise to decreased selectivity [31] (Scheme 3.4a).

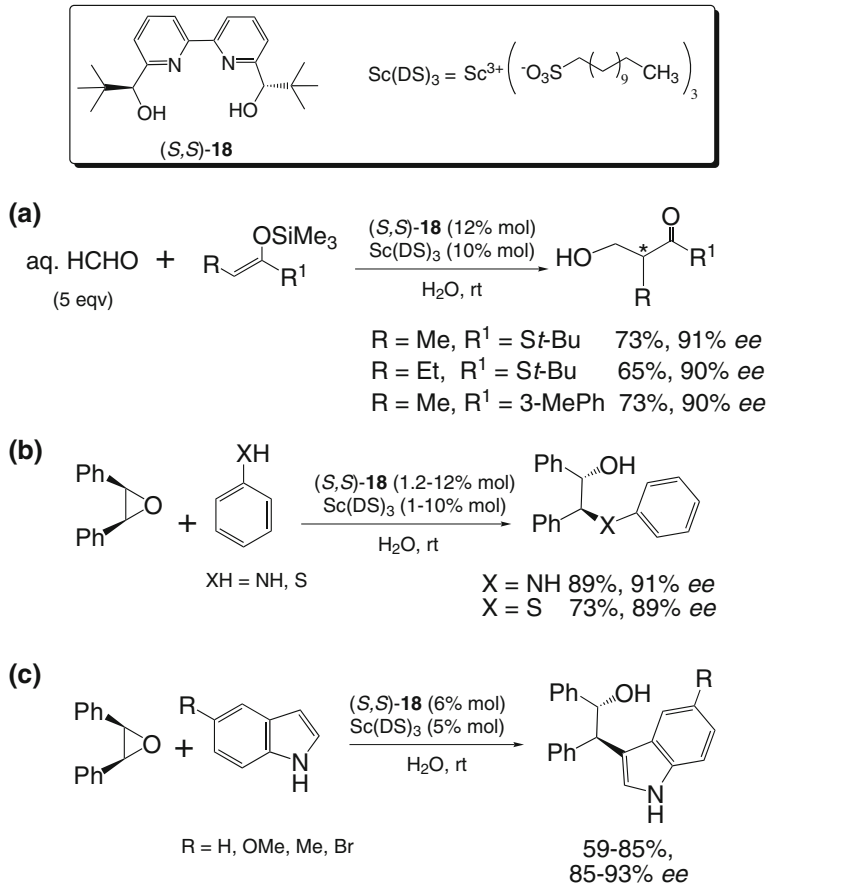
More recently ATH has been extended to C–C unsaturated bond and in the reduction of a series of β, β-disubstituted nitroalkenes using different aqueous conditions [32, 33] the highest enantioselectivities were obtained with Ir(III)-aquacomplex **17** (Scheme 3.4b), a catalyst shown to be effective also in the reduction of α-cyano and α-nitroacetophenones [34].

Enantioselective carbon–carbon bond forming reactions are usually carried under Lewis acid catalysis and the use of aqueous solvents has been long precluded since many metals react with water, that act as Lewis base, rather than with substrates. Strictly anhydrous conditions and suitable protection of reactive functional groups are often required for such reactions, but a substantial breakthrough in this field was achieved by Kobayashi and coworkers that developed Sc(III)-, Yb(III)- and Ln(III)-triflates as *water-compatible Lewis acids* and demonstrated an activation role of water in the Mukayama aldol reaction between benzaldehyde and trimethylsilyil enol ether of cyclohexanone, for which only 10% substrate conversion had been observed in THF with $Yb(OTf)_3$ [35].

The catalytic activity of several metal perchlorates, triflates and chlorides in a model aldol reaction was correlated with hydrolysis constants (K_h) and water exchange rate constants (WERC) for substitution of inner sphere water ligands. The screening revealed that other than rare earth metals also Fe(II), Cu(II), Zn (II), Ag (I), Mn(II) and In(III) worked as Lewis acid in aqueous medium, the optimal pK_h ranging from 4 to 10 with WERC values greater than $3.2 \times 106\ M^{-1}s^{-1}$ [36]. Within these intervals, cations are stable to hydrolysis maintaining sufficient Lewis acidity to activate the aldehyde, that can be coordinated to the metal only if a fast exchange with hydrating water molecules occurs.

Many triflates of the above metals have then been used in aldol reactions with moderate to good enantioselectivity in water-organic cosolvent mixtures [37–40] and sensible acceleration rate was observed in the presence of surfactants [41]. Taking this evidence, *Lewis acid-surfactant combined* (LASC) *catalysts* were developed by using dodecylsulphate (DS) as counterion for the active metal cations, the most common of which was scandium. The resultant $M(DS)_3$ salts formed stable emulsions and micellar aggregates (1 μm diameter) able to promote the concentration of organic substrates by hydrophobic interactions, so that effective reactions could be performed in water without the need of any organic solvent [42].

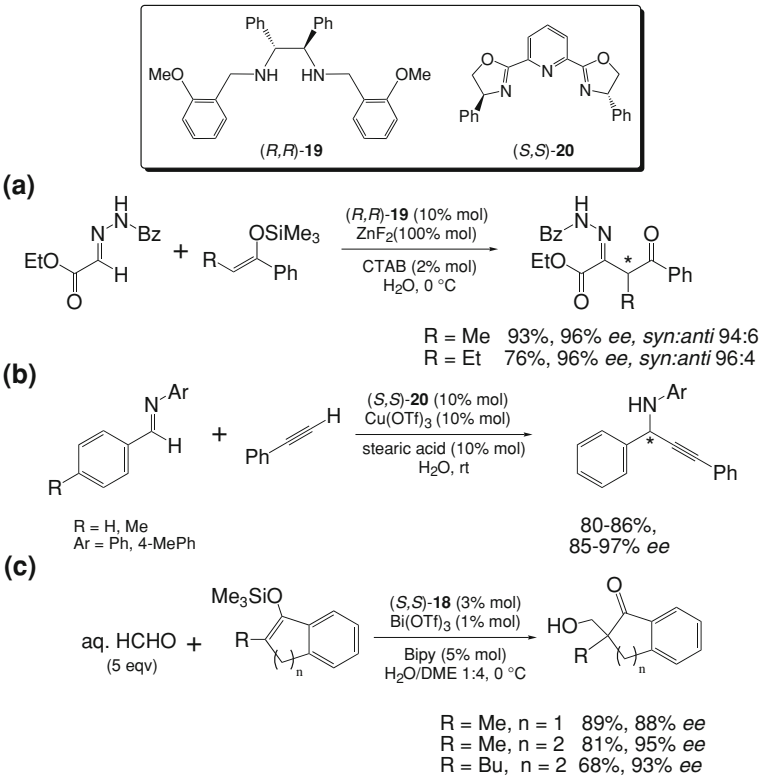
It has been recently found that also the reaction of silyl enol ethers with a hydrophilic reagent as formaldehyde can be positively carried out using LASC catalysts as $Sc(DS)_3$/bipyridine **18** (Scheme 3.5a) and it has been suggested that the salt could play a key role on the reactivity through Lewis acid–Lewis base interactions with HCHO leading to increased amount of the aldehyde in the hydrophobic environment [43]. The use of water-tolerant Lewis acids, compatible with commercial aqueous solution of HCHO, allows to avoid the tedious



Scheme 3.5 Examples of $Sc(DS)_3$-promoted asymmetric reactions

and harmful procedures required to generate the anhydrous aldheyde offering a notable simplification in hydroxymethylation reaction, an efficient method to introduce a C1-functional group at the α-position of carbonyls. The same system $Sc(DS)_3$/**18** catalyzed the ring opening of *meso*-epoxides with aromatic amines to afford optically active *β*-aminoalcohols without diol formation [44] and also *C*-, *O*- and *S*-nucleophiles reacted with comparable high yield and enantioselectivity [45] (Scheme 3.5b, c).

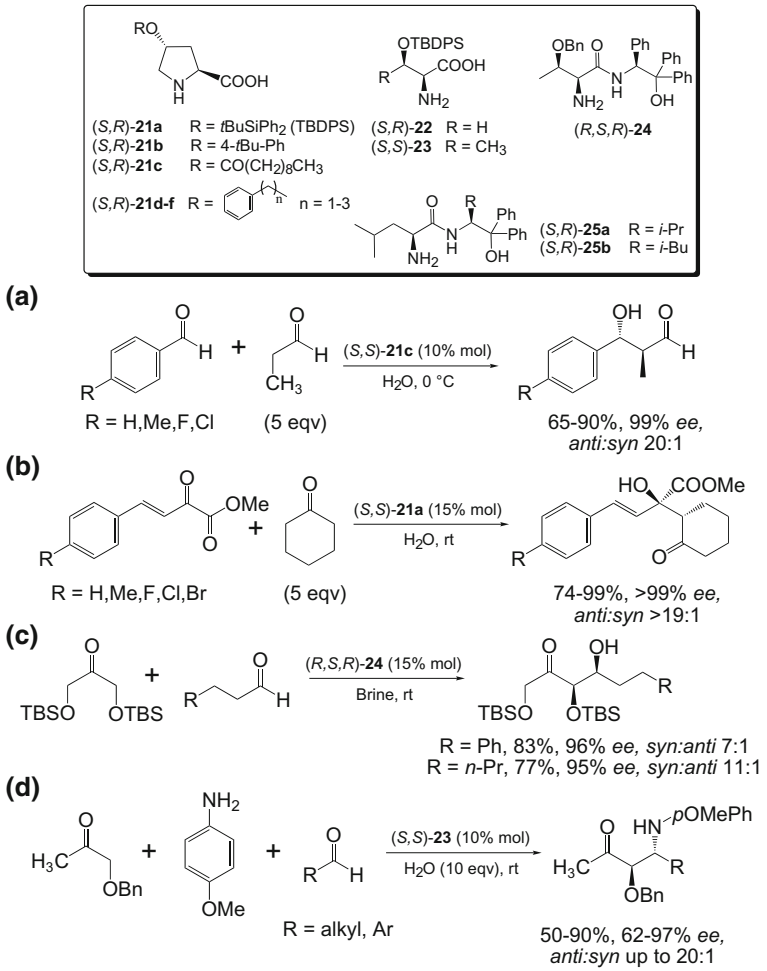
Among other examples involving Lewis acids in water, the Mannich-type reaction of enolsilanes and *N*-acylhydrazones, chosen as water stable surrogates of imines, in the presence of ZnF_2/ligand **19** and CTAB as surfactant gave nearly enantiopure *β*-aminoketones and the stereospecificity toward *syn*- or *anti*-adducts was found dependent on the enolate geometry [46] (Scheme 3.6a). In the addition of alkynes to imines promoted by $Cu(OTf)_2$/pybox-ligand **20** the use of stearic acid as additive was found essential for obtaining remarkable rate acceleration and high



Scheme 3.6 Reactions with water-tolerant or ligand stabilized Lewis acids

enantioselectivity [47] (Scheme 3.6b). The discovery that some water-sensitive Lewis acids can be beneficially stabilized upon coordination with chiral basic ligands made feasible Mukayama aldol reactions in the presence of $Bi(OTf)_3$ or $Ga(OTf)_3$ (Scheme 3.6c) and further application of this concept could expand the portfolio of asymmetric reactions in aqueous media [48].

In the organocatalysis field, besides chiral phase transfer catalysts yet discussed in Sect. 2.3 and used in biphasic water-organic solvent systems, the study of reactivity in aqueous media has been mainly focused on enamine based reactions and, in this context, proline could appear an ideal candidate for its availability and water solubility. However, proline-catalyzed aldol reactions in water or water/surfactant systems proceeded with low stereoselectivity and the addition of an organic solvent, an acid co-catalyst or large excess of the ketone subtrate was often necessary to improve catalyst performances. On the contrary, the introduction of large apolar substituents on proline skeleton in order to better promote hydrophobically directed assembling of catalyst with reagents proved to be a successful strategy to enhance catalytic activity. A number of 4-acyloxyprolines [49, 50] and *O*-protected 4-hydroxyprolines [51, 52] have been synthesized



Scheme 3.7 Organocatalysts for enamine based reactions in water

and used "on water" in the direct aldol reaction of ketones with aromatic aldehydes or β, γ-unsaturated α-ketoesters [53] providing higher yields and stereoselectivities than those obtained in organic solvents (Scheme 3.7a, b). It has been suggested that stereoselectivity in such reactions is controlled by the apolar substituents since the aldehyde, in its approach toward the enamine, preferentially lies in the hydrophobic region of the catalyst rather than in the hydrophilic one [50].

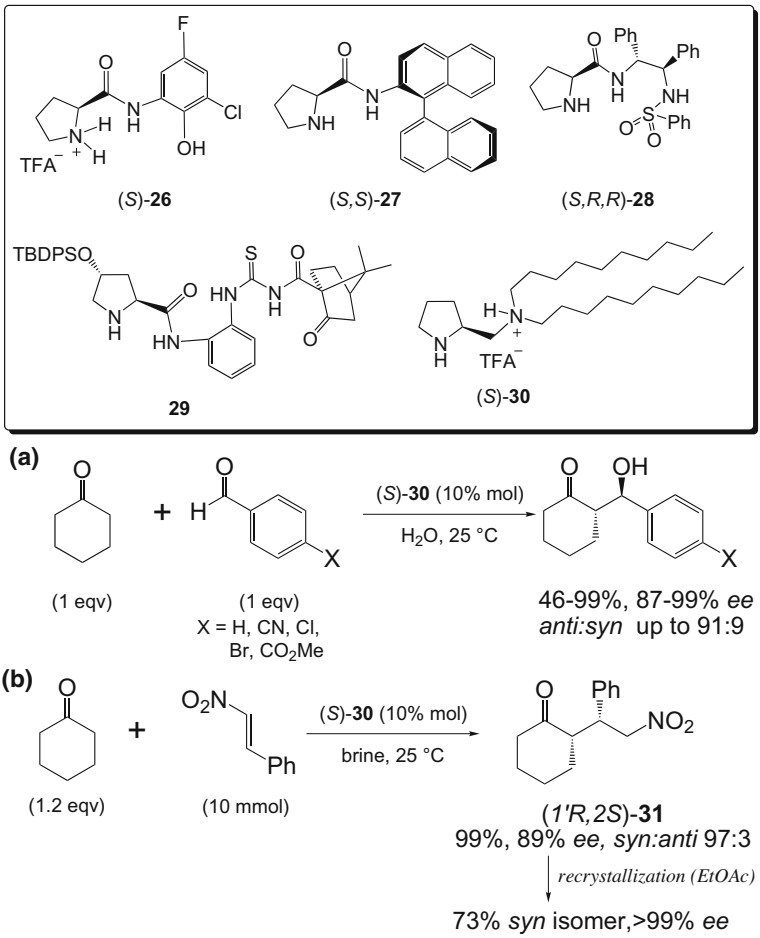
With the same approach, *O*-hydrophobically substituted threonine [54] or serine [55] as well as some peptide-type derivatives [56–58] have been prepared as useful catalysts for aldol condensation of ketones or silyl-protected hydroxyacetone and their performances were improved by addition of an acid co-catalyst to stabilize enamine formation or using brine as reaction medium to promote concentration of

catalyst and reagents by salting-out effect (Scheme 3.7c). More recently the catalytic activity of natural aminoacids in aldol reactions has been screened and those bearing more apolar residues, as trypthophan, leucine or isoleucine, displayed satisfactory selectivity further increased in some cases with 2,4-dinitrophenol additive [59, 60]. Three-component Mannich reactions of hydroxyacetone with aldehydes and *p*-anisidine were also performed with excellent yield and selectivity in the presence of threonine derivative **23** using water as sole reaction medium [61] (Scheme 3.7d).

Some proline-containing amides, sulphonamides and thioureas as **26–29** have been designed in order to have a secondary amino group for enamine formation, an amide group on a chiral center for hydrogen-bond directed stereocontrol and a hydrophobic group to promote aggregation of catalyst with reactants in water environment. All these elements contributed to fruitful catalysis in aldol and Michael reactions in aqueous systems [62] and even if the role of water was not fully rationalised [63] its positive effects could be ascribed to the increased acidity of amidic NH bond due to the hydrogen-bonding between the carbonyl of amide and water free hydroxyl groups at the hydrophobic interface of the catalyst. In some specific cases it has been proposed that the formation of an organized transition state could beneficially occur through a water molecule engaged in two hydrogen bonds bridging the catalyst on one side and the aldehyde approaching to the enamine on the other one [64, 65].

In the group of 2-substituted pyrrolidines, diamine salt **30** bearing long alkyl chains can be considered a hybrid surfactant-organocatalyst and it promoted aldol reactions in bulk water with excellent selectivity and high yields, remarkably obtained with reagents in stoichiometric ratio (Scheme 3.8a) [66]. More recently it has been reported that the aldol condensations valuably proceeded with only 1% mol of **30** in the presence of stearic acid; the reactions occurred in an emulsion rather than a biphasic system [67] and the products could be easily isolated by centrifugal separation leaving the catalyst to be recycled in water. Compound **30** was also active as catalyst in Michael addition of nitrostyrene to ketones in brine and in a multigram scale synthesis of adduct **31** the enantiopure product was isolated in good chemical yield by simple precipitation from reaction mixture and subsequent recrystallization [68] (Scheme 3.8b).

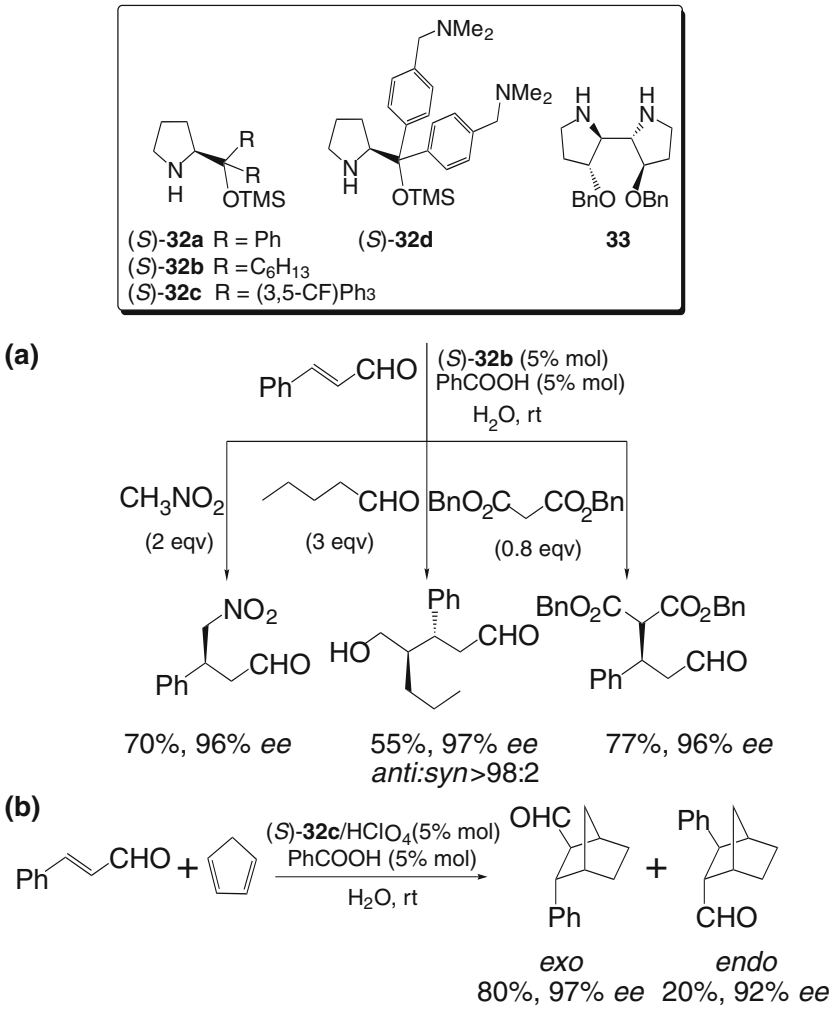
Although iminium activation seems to be less compatible with aqueous reaction media, the enantioselective addition of different nucleophiles to enals in water in the presence of benzoic acid as additive has been successfully achieved with prolinol catalysts **32a–c** [69, 70] or the water-soluble derivative **32d**, whose excellent stereoselectivity was maintained for at least six cycles adding fresh reactants to the aqueous phase after extraction of the reaction product with Et_2O:hexane 1:8 mixture (Scheme 3.9a) [71]. Perchlorate salt of **32c** also catalyzed Diels–Alder reaction of cyclopentadiene with aldehydes and the amount of water was crucial for high yield and selectivity (Scheme 3.9b). Since the stirring was not found essential, it was proposed that the reaction presumably occurred in the organic phase generated by reactants and catalyst rather than at the interfacial surface with water [72]. Water-soluble C_2-symmetrical bipyrrolidine catalyst **33**,



Scheme 3.8 Hydrophobic organocatalysts and related reactions in water

specifically designed for its easy recovery and recycle, also displayed good selectivity in the same asymmetric transformation and diiminium intermediate **33**/cynnamaldehyde was structurally characterised by X-ray analysis [73].

The activity of hydrogen-bonding and Brönsted acid organocatalysts, that exert stereocontrol through non-covalent interactions, could appear quite limited in aqueous medium since the strong hydrogen donor/acceptor character of water makes it competitive in the coordination with the chiral catalyst with respect to the reagents. However, following the approach to maximize the hydrophobic effect in order to overcome the competitive influence of water [74], BINOL phosphoric acid **34** was designed and successfully used in transfer hydrogenation of quinolines as the first example of asymmetric Brönsted acid catalysis in water (Scheme 3.10). Carrying out the reaction in deuterated water it was demonstrated that protons from solvent were specifically involved in 1,2-hydride addition step and the

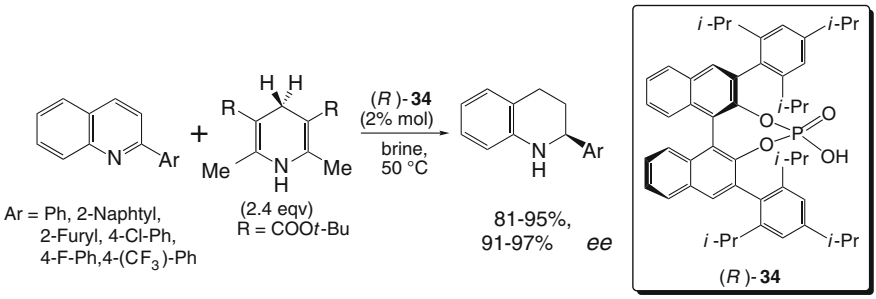


Scheme 3.9 Prolinol derivatives for iminium catalysis in water

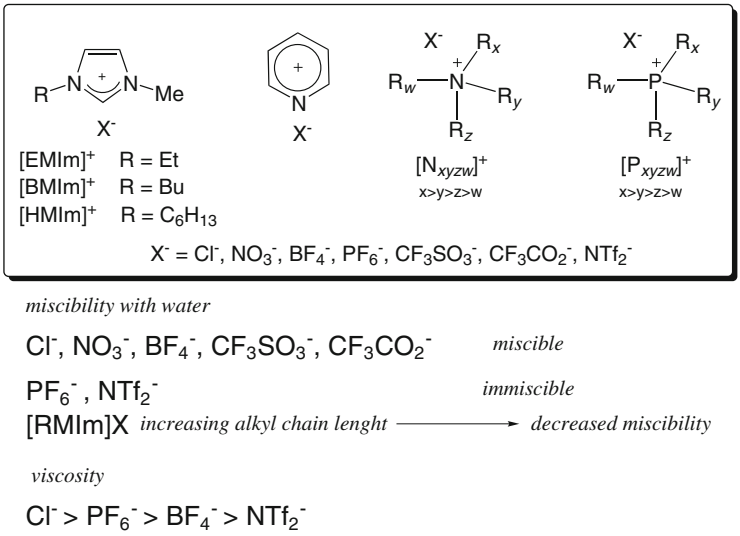
observed high enantioselectivity could reasonably result from the formation of a stable contact ion pair between catalyst and substrate inside the chiral hydrophobic pocket generated by large isopropyl substituents [75].

3.4 Ionic Liquids

Molten salts with melting point below 100 °C are defined as ionic liquids (ILs) and they are in most cases formed by 1,3-*N*,*N*-dialkylimidazolium, *N*-alkylpyridinium



Scheme 3.10 Chiral Brönsted acid catalysis in water



Scheme 3.11 Structures of the more common ionic liquids

or tetraalkyl- ammonium and phosphonium cations combined with either organic or inorganic anions. Their negligible vapour pressure accounting for the lack of release in the atmosphere in contrast to common organic solvents makes them very attractive as sustainable alternative in organic synthesis. Moreover, ILs are non-inflammable, thermally and chemically stable, display high density and viscosity, high conductivity and low dielectric constant as well as unique solvating properties through hydrogen-bonding, π–π, electrostatic and hydrophobic interactions [76]. Remarkably, physicochemical properties of ILs can be tailored through proper choice of cations and anions offering the possibility to design task specific compounds with broader versatility with respect to organic solvents. For example, non-symmetrical *N*,*N*-dialkylimidazolium cations give ILs with lower melting point whereas the nature of anion has a marked impact on viscosity and water

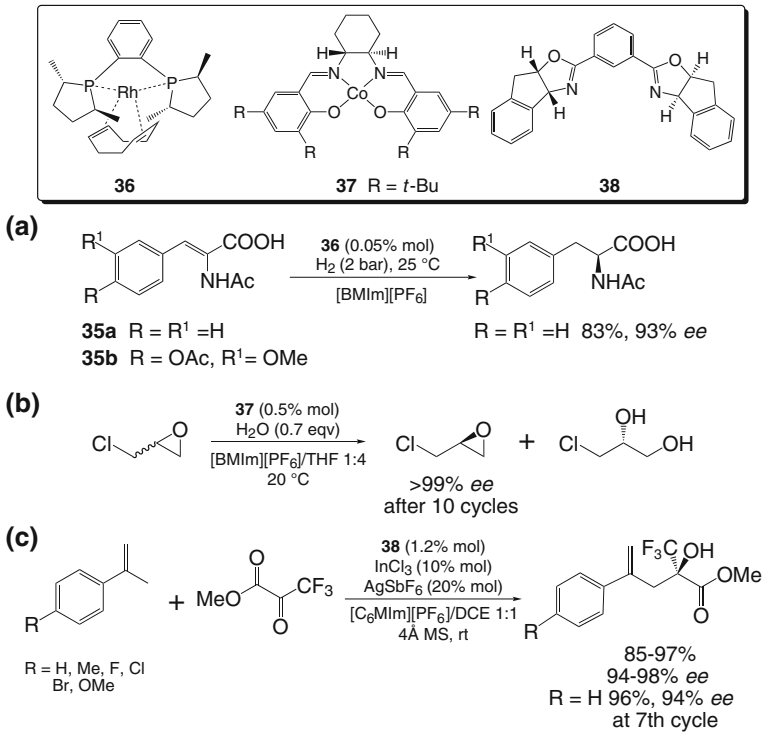
solubility. Salts with halide anions, BF_4^-, $CF_3SO_3^-$, CF_3COO^-, but not PF_6^- or NTf_2^-, are fully miscible with water whereas solubility in organic solvents can be finely tuned by modification of the length of alkyl chains on the imidazolium cation (Scheme 3.11).

Besides their use as solvents in a wide variety of organic reactions either in homogeneous or heterogeneous systems [77], ILs have found interesting applications as heat-transfer fluids, in chromatographic and electrophoretic separations [78], selective extractions [79], electrochemistry [80] and polymer science [81]. Although a significant collection of data has been set up in last decade regarding the synthesis of ILs and purification methods [82], the relationships between structure and solubility parameters [83], the influence of impurities and additives on physical properties [84], questions on their modes of toxicity and bioaccumulation remain still to be better investigated. From a number of ecotoxicity tests carried out on different bacterial strains or aquatic organisms and recently reviewed by Seddon et al. [85] it appeared evident that toxicity of ILs cannot be systematically estimated by the sum of effects of the cation and anion and, considering the immense diversity of possible formulations, a generalisation of ILs as entirely "green" or "toxic" solvents could be misleading.

Due to their cost, the synthetic efforts required for their preparation and their persistance in the environment, the use of ILs in green chemistry finds justification in conjunction with their efficient recycle and in the majority of synthetic applications the choice or "design" of a suitable IL has also allowed the selective separation of products and residual reactants by extraction with organic solvent or supercritical CO_2 ($scCO_2$). In this context, biphasic systems with $scCO_2$ appear very promising since ILs do not dissolve in this fluid so that cross-contamination is avoided and pure products can be recovered [86] while ILs can be reused after addition of fresh reactants.

The development of catalysts "pseudo-immobilised" in the IL phase offers a general strategy for simultaneous recycle of catalysts and solvent with direct cost reduction but also many unmodified transition-metal precursors and their chiral complexes as well as proline and prolinamides display good solubility in ILs. In such instances, satisfactory recovery of catalysts can be achieved by extraction from biphasic organic solvents/ILs mixtures and a variety of asymmetric reactions has been performed without the need of specially designed ligands [87–89].

In the first report of asymmetric alkene hydrogenation with BINAP-Ru(II) complex in *i*-PrOH/[BMIm][BF_4] 10:1 mixture, the enantioselectivity was found comparable with that obtained in pure alcohol and constant catalyst performances were maintained in four recycle runs [90]. In the hydrogenation of tiglic acid with the same catalyst, the enantioselectivity was found H_2-pressure dependent (low H_2 pressure and mass transfer rates for optimum selectivity) and, among different ILs, neat [BMIm][PF_6] was the best reaction medium for its higher viscosity, that provided lower concentration of dissolved H_2 [91]. When the carbonyl hydrogenation of methylacetoacetate was carried out in [N_{R222}][NTf_2]/MeOH 1:1 mixtures, both enantioselectivity and activity of BINAP-Ru(II) complex were

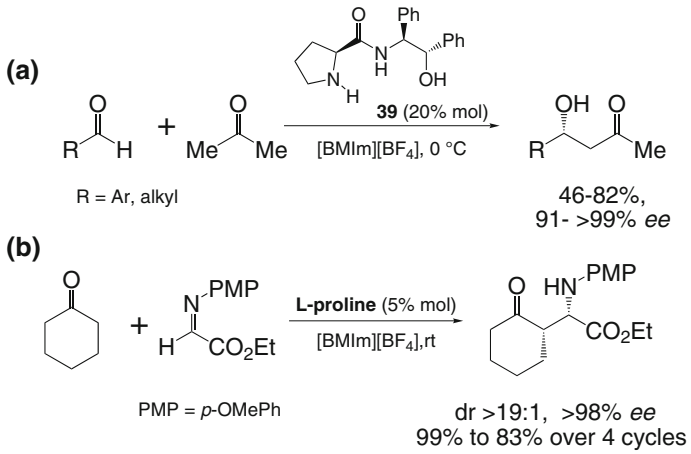


Scheme 3.12 Transition-metal catalyzed reactions in ionic liquids

influenced by the length of the R alkyl chain in the ammonium cation and excellent results were obtained with dodecyl substituent [92].

Catalyst Rh[Me-DuPHOS] **36** in [BMIm][PF_6] or in [BMIm][BF_4]/*s*CO_2 homogeneous phase was effective in the hydrogenation of methyl-α-acetamido cinnamate [93, 94] and the reaction was also exploited in the design of a novel process for industrial preparation of Levodopa starting from related substrate **35b** (Scheme 3.12a). The hydrogenation was optimized using 1-butyl-3-methylpyrrolidinium octylsulphate, as more stable and biodegradable reaction medium, whereas the product separation and recycle of catalyst in the IL phase were ensured by *s*CO_2 extraction. Moreover, the IL provided sensible stabilization of the air-sensitive rhodium catalyst thus extending its recyclability. Combining these two alternative solvents, notable reductions in the amounts of deactivated catalyst and solvent (120-fold and 90-fold, respectively) were estimated in comparison with the conventional process in MeOH [95].

Coupling of ILs with *s*CO_2 extraction has been also advantageously exploited in asymmetric dihydroxylation of *trans*-cinnamoyl methyl ester with the classical *Cinchona* alkaloid/Os-catalysts and [C_8MIm][PF_6] was found optimal in



Scheme 3.13 Organocatalyzed reactions in ionic liquids

minimizing the leaching of toxic osmium (<0.03%) in the diol product, isolated in good yield and optical purity over six reaction cycles [96].

When hydrolytic kinetic resolution of racemic epoxides is carried out in organic solvents the catalytically active Co(III)-salen complex is usually reduced to the inactive Co(II)-form, that needs to be reoxidized before reuse. In THF/[BMIm][PF_6] 4:1 mixture, instead, the Co(III) active form was stabilized against reduction and it could be recycled up to ten times without deterioration of its performances. In the same reaction medium also a Co(II)-precursor could be used since its aerobic oxidation was greatly facilitated by the IL [97] (Scheme 3.12b).

Carbonyl-ene reaction of methyl trifluoropyruvate and olefins in the presence of In(III)-**38** complex displayed marked rate acceleration, while enantioselectivity was not affected, in [C_6MIm][PF_6]/1,2-dichloroethane 1:1 mixture with respect to the same reaction performed in neat organic solvent and, after separation of products by extraction, the IL phase was reused for seven times without any loss of the catalyst activity [98] (Scheme 3.12c).

Organocatalytic aldol reactions, carried out in [BMIm][PF_6] using L-proline, gave moderate to good yields and enantioselectivities but the catalyst performances slightly declined in successive runs after extraction of products with diethyl ether [99]. Less common guanidinium-based ILs were also tested for these reactions and products with higher optical purities were obtained at −25 °C [100]. By using L-prolinamide **39** in [BMIm][BF_4] aldol adducts of acetone with aliphatic and aromatic aldehydes could be isolated in satisfactory yields and 91–99% *ee* (higher than in acetone) (Scheme 3.13a) [101].

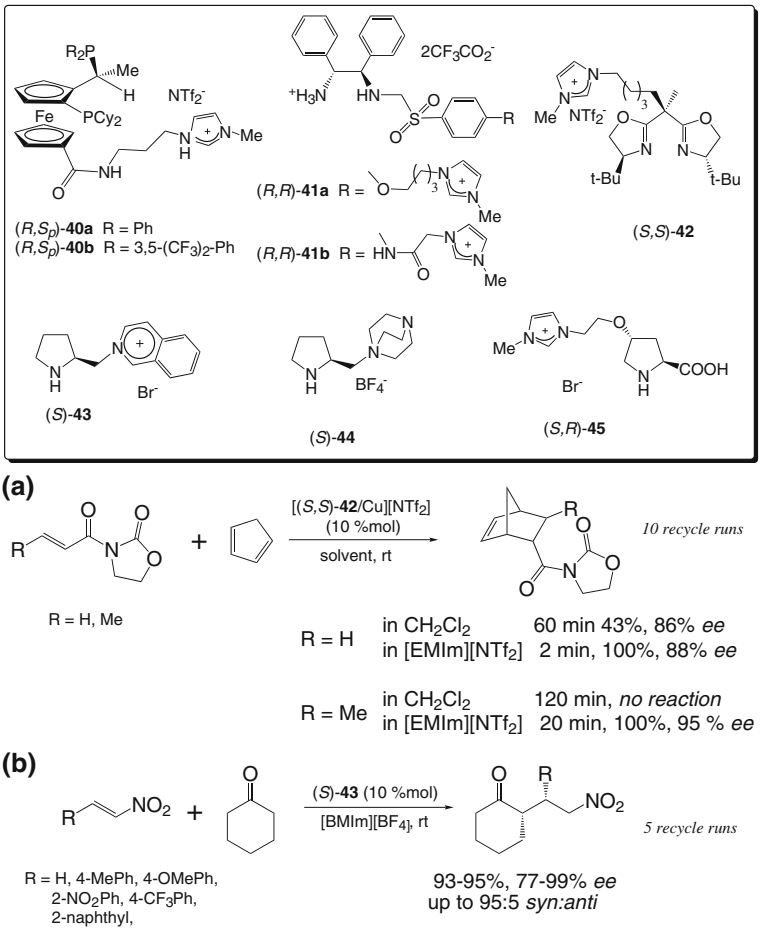
Remarkable acceleration rate was evidenced in the addition of cyclohexanone to *N*-protected α-imino ethylglyoxylate (Scheme 3.13b) [102] and α-aminoxylation of aldehydes with nitrosobenzene [103] catalyzed by proline in [BMIm][BF_4].

High conversions of substrates were achieved within 15–30 min with excellent steroselectivity, maintained for up to six cycles with only minor decreases in the products yields.

In order to improve the solubility of catalysts in ILs and thus enhance their immobilization in the ionic phase, decreasing their possible leaching in the extraction solvents, different classes of chiral ligands and organocatalysts have been tagged with a suitable onium cation to give IL-supported derivatives with increased recyclability [104].

Among selected examples of the application of *onium-tagged catalysts* in ILs media, ferrocenyl phosphines **40a–b** bearing an imidazolium moiety showed excellent performances (100% conv, 99% *ee*) as the native ligands in the hydrogenation of methyl acetamidoacrylate or itaconic acid in biphasic [BMIm][BF_4]/*t*-butyl methyl ether system. The affinity of rhodium complex for IL phase was significantly improved and only 0.1% of metal leaching in the organic phase was detected, this value found to be 23-fold lower than that determined in the reactions with unmodified catalysts [105]. In the same way, ruthenium(*p*-cymene) complexes with ionic ligands **41a** or **41b** homogeneously dissolved in [BMIm][PF_6] displayed nearly constant selectivity along 6 recycle runs in ATH of ketones with azeotropic formic acid/TEA mixture and slight higher conversions were achieved with respect to the original Noyori's catalyst in the same reaction conditions [106, 107]. Some Diels–Alder reactions of oxazolidinones and cyclopentadiene were comparatively carried out in [EMIm][NTf_2] or dichloromethane in the presence of Cu(II)-bis-oxazoline catalysts and a marked improvement of reaction rate (2 vs. 60 min for *N*-acryloyloxazolidinone) was evidenced the IL medium, also for less reactive substrates. The IL-supported ligand **42** displayed high enantioselectivity and more effective immobilization in the ionic phase with respect to the uncharged analogue, so that it could be recycled ten times without any erosion of its performances [108] (Scheme 3.14a).

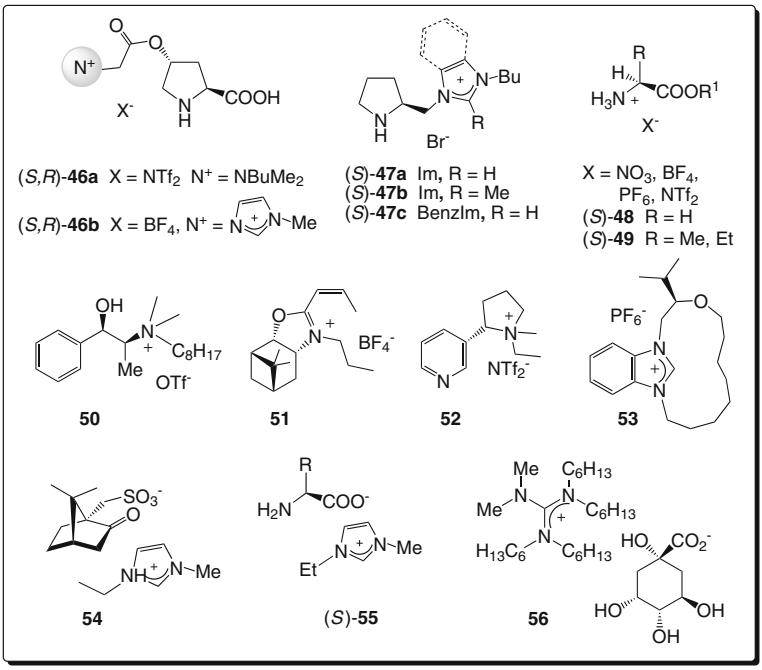
Michael addition of cyclohexanone to a number of nitroalkenes with pyrrolidine-pyridinium organocatalyst **43** well proceeded in [BMIm][BF_4] without any acid additive usually required for this reaction. In comparison with organic solvents, halved reaction times were sufficient in the IL to achieve full substrate conversion and good recyclability of **43** was also demonstrated (Scheme 3.14b). Furthermore, on the basis of the diminished selectivity observed in a parallel experiment using **43** in solvent-free conditions, the authors suggested that the IL might play an important role in stabilizing the iminium-ion transition state (evolving into the enamine intermediate) and synergistically operate with the organocatalyst in the improvement of asymmetric induction [109]. Satisfactory results in [BMIm][BF_4] were also obtained in the same reaction promoted by **44** [110] and aldol condensation of acetone with aromatic aldehydes catalyzed by proline salt **45**, that afforded aldol adducts in yields (53–94%) and optical purities (64–93%) higher than those achieved with DMSO as solvent [111]. Both **44** and **45** could be reused up to six times without significant decrease in their activity and selectivity.



Scheme 3.14 Imidazolium- and onium-tagged ligands and organocatalysts

Noteworthy, through a judicious choice of the counteranion many imidazolium-tagged organocatalysts displayed ILs characteristics (i.e. melting point below 100 °C, thermal stability, viscosity and phase behaviour) so that they can be viewed as *chiral ionic liquids* (cILs) able to provide expanded utility in asymmetric synthesis. Indeed, in addition to their use as catalysts in a variety of reaction media with enhanced recyclability due to the typical solubility features of ILs, they could also act as reusable solvents with unique chiral environments.

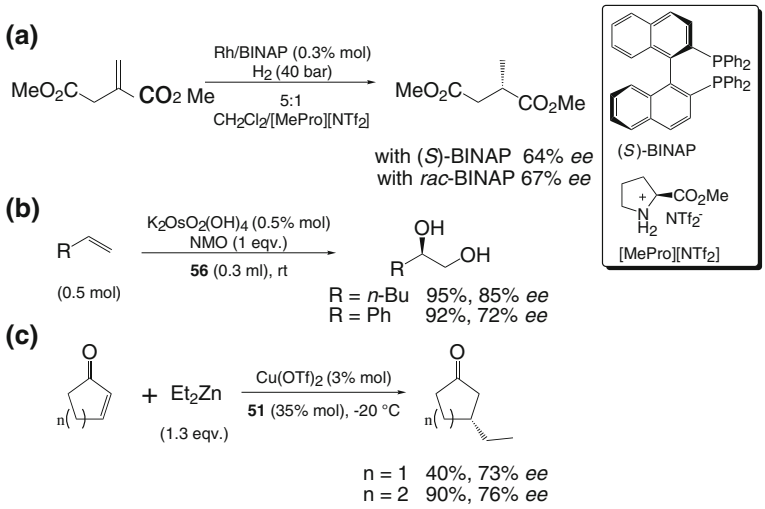
A variety of cILsbased on combinations of chiral cations or anions deriving from cheap and bio-renewable natural compounds as aminoacids, sugars and terpenes with an achiral counterion have been synthesized and their physical properties determined (Scheme 3.15). In the group of cILs with a chiral cation, besides those deriving from covalent introduction of imidazolium, pyridinium,



Scheme 3.15 Chiral cations and anions for chiral ionic liquids

azolinium or alkylammonium groups in suitable chiral precursors [112], others have been obtained from aminoacids or the corresponding alkyl esters by simple protonation of the nitrogen centre with acids, followed by anion methatesis when different anions are required to lower the melting point of the obtained salts [113]. More recently, cations based on protonated axially chiral spiro *bis*(heterocycles) or macrocycles with cyclophane-type planar chirality bearing an imidazolium ring have been designed and their promising chiral discrimination ability tested with enantiopure (*S*)-Mosher acid, but their optical resolution is still a challenging task [114, 115]. On the other side, easy access to cIL with chiral anions has been provided by neutralization of acidic groups of aminoacids, mandelic, lactic, quinic or camphorsulphonic acids [116, 117].

The application of these novel cILs as catalysts in asymmetric synthesis has been mainly focused on organocatalytic enamine based reactions [118] and, as an example, the addition of *β*-nitrostyrene to cyclohexanones in the presence of **47a** or **47c** and 5% of co-catalyst (TFA and salicylic acid, respectively) without any solvent afforded the nitro-adduct in 99% *ee* and nearly quantitative yield. As concerns the use of cILs as solvents, Leitner and coworkers have recently reported that hydrogenation of benchmark substrates in the presence of rhodium complexes with either (*S*)-enantiopure or racemic BINAP proceeded with the same level of enantioselectivity when the reactions were carried out in 5:1 CH_2Cl_2/[MePro][NTf_2] mixture [119] (Scheme 3.16a). Using *rac*-BINAP the formation



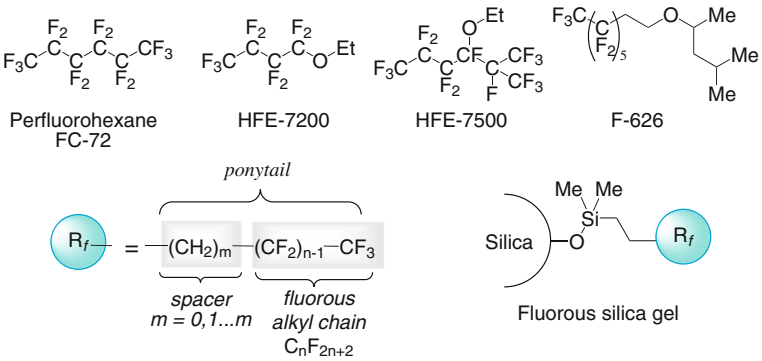
Scheme 3.16 Chiral ionic liquids as solvents in asymmetric reactions

of two diastereomeric species [(*R*)-BINAP-Rh-MePro][NTf_2] and [(*S*)-BINAP-Rh-MePro][NTf_2] in 2.5:1 ratio was assessed by ^{31}P-NMR spectra and the greater stability, with consequent less reactivity, of the former complex was also supported by kinetic measurements on separate BINAP enantiomers. From these data it was deduced that [MePro][NTf_2] can be used as the sole source of chirality through an unprecedented and effective chiral poisoning, so that the hydrogenation is controlled by (*S*)-BINAP even in the presence of the racemic catalyst.

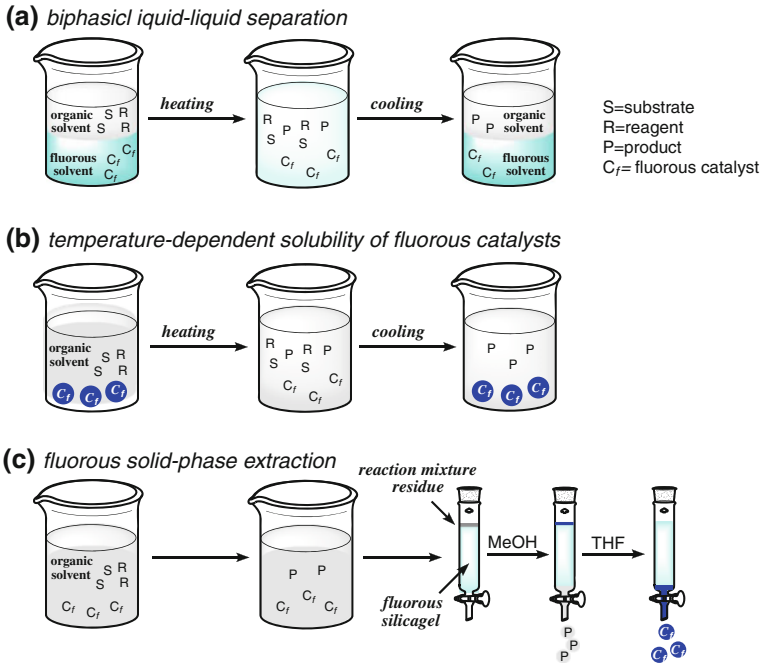
Other evidences of the still unexplored potentiality of cILs in inducing chirality came from Sharpless dihydroxylation of alkenes with $K_2OsO_2(OH)_4$ and **56** as solvent, that gave the corresponding diols in yields and *ee*s comparable with the ones obtained using classical conditions ([DHQD]$_2$PHAL catalyst in 1:1 *t*-BuOH/H_2O) [116]. In the same way, cIL **51** was able to induce moderate enantioselectivities (61–76% *ee*) in copper-catalyzed addition of diethylzinc to enones [120] (Scheme 3.16b, c).

3.5 "Fluorous" Solvents and Catalysts

In their seminal publication Horvath and Rabai [121] introduced the term "fluorous" in analogy with "aqueous" to emphasize the peculiar properties of perfluorohydrocarbons (and related perfluoroalkylethers and amines) as reaction media and quickly the word was extended to perfluoroalkyl-labeled organic compounds, that have today broad application in synthesis and separation techniques [122]. Fluorous solvents, some of which are shown in Scheme 3.17, display



Scheme 3.17 Fluorous solvents, ponytails and silica gel



Scheme 3.18 Fluorous protocols for catalyst recycle. **a** Biphasic liquid–liquid separation. **b** Temperature-dependent solubility of fluorous catalysts. **c** Fluorous solid-phase extraction

low isoelectric constants, high thermal stability, exceptional chemical inertness under almost all reaction conditions and considerable hydrophobicity; they are also rather lipophobic but miscibility with organic solvents is highly temperature-dependent [123].

The original idea was the development of an efficient methodology for large scale preparations, based on the use of biphasic fluorous/organic solvents systems, whose mutual miscibility could be switched on/off by changing the temperature within a given range. In practical terms, a reaction can be performed in the homogeneous phase resulting from the warming of fluorous/organic solvent mixture and after its completion the biphasic system is restored by cooling to allow the selective separation of fluorinated compounds from non-fluorinated ones. In this way, properly designed perfluorinated catalysts can be selectively recovered in the fluorous phase and reused after addition of fresh reactants (Scheme 3.18a).

The success of such “*fluorous biphasic catalysis*” obviously requires high partition coefficients of catalysts into the fluorous phase and the catalyst “fluorophilicity” is usually engineered by attaching a number of fluorinated alkyl chains (called “pony tails”) to known catalysts. The most common pony tails have a general formula -$(CH_2)_m(C_nF_{2n+2})$ but second-generation fluorous tags containing perfuoro-*tert*-butyloxy groups have been recently reported [124]. In modified “heavy fluorous” catalysts high fluorous solvent affinities are generally achieved with the introduction of a large number of fluorine atoms (usually 63 or more) while the spacer methylenic chain allows to modulate the electronic influence of the electron-withdrawing perfluoroalkyl substituents by insulating them from the reactive centre.

Although this approach could be considered “green” in that regards recycle of chemicals and decreased solvent waste, perfluohydrocarbons are quite expensive and other drawbacks are associated to their environmental persistence due to exceptionally long half-lives, significant global warming potential and toxicity of some products deriving from their atmospheric oxidation, as perfluorooctanoic and perfluorooctanesulfonic acids that bioaccumulate in higher organisms [125, 126]. Taking into account these concerns, the research in this field has been recently focused on the search for more benign fluorous solvents as hydrofluoroethers, that can be used in biphasic systems by “tuning” their partition coefficients with addition of small amounts of water or fluorocarbons [127]. Alternative protocols for the recovery of fluorous catalysts based on their thermomorphic (temperature-dependent solubility) properties in non-fluorous organic solvents have been also investigated (Scheme 3.18b) [128].

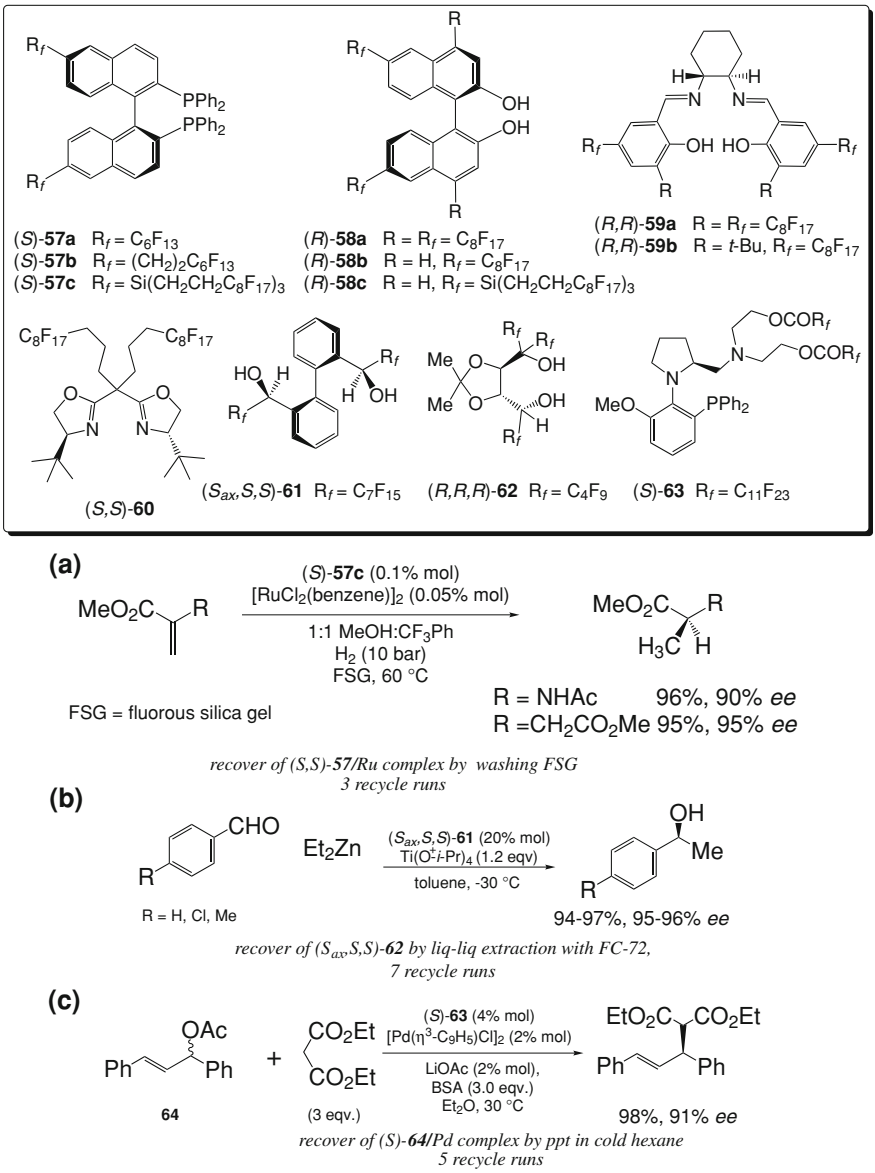
Moreover, the advent of fluorous solid-phase extraction (FSPE) has led to the development of “light fluorous chemistry” with growing application in small-scale medicinal chemistry, natural product synthesis and asymmetric catalysis [129]. Since “light fluorous” compounds are labeled with single perfluorohexyl or perfluorooctyl groups, they are usually more soluble in most organic solvents than in fluorous ones and their recovery from organic solutions is usually performed exploiting their selective affinity for fluorocarbon-bonded silica gel stationary phases in chromatographic-like separations. The fluorous solvent is no more required and at the end of a given reaction the organic solution is loaded on a fluorous silica gel cartridge, that is then eluted with fluorophobic solvents (pure or aqueous MeOH or CH_3CN) to give the organic components in the eluate while the fluorous compounds are adsorbed on the stationary phase. Subsequent elution

with more fluorophilic solvents (ether or THF) extracts the fluorous compounds off the column (Scheme 3.18c) [130]. The technique is fast, efficient, general and widely applied in manual or automated parallel purification of fluorous reaction mixtures.

Heavy flourous derivatives of privileged ligands for transition-metal based catalysis have been applied for different asymmetric transformations in biphasic fluorous/organic solvent systems and their efficiency has been tuned by changing the number, the position and the length of ponytails. In most cases the fluorous substituents acted as chemically inert phase-tagging moieties without affecting the stereoselectivity observed with the original catalysts [131, 132]. Liquid–liquid separations has often provided acceptable levels of catalyst recovery and metal leaching(<1%) into the organic phase, but increased tendency to oxidation was evidenced for some perfluoroalkyl-modified BINAP ligands [133].

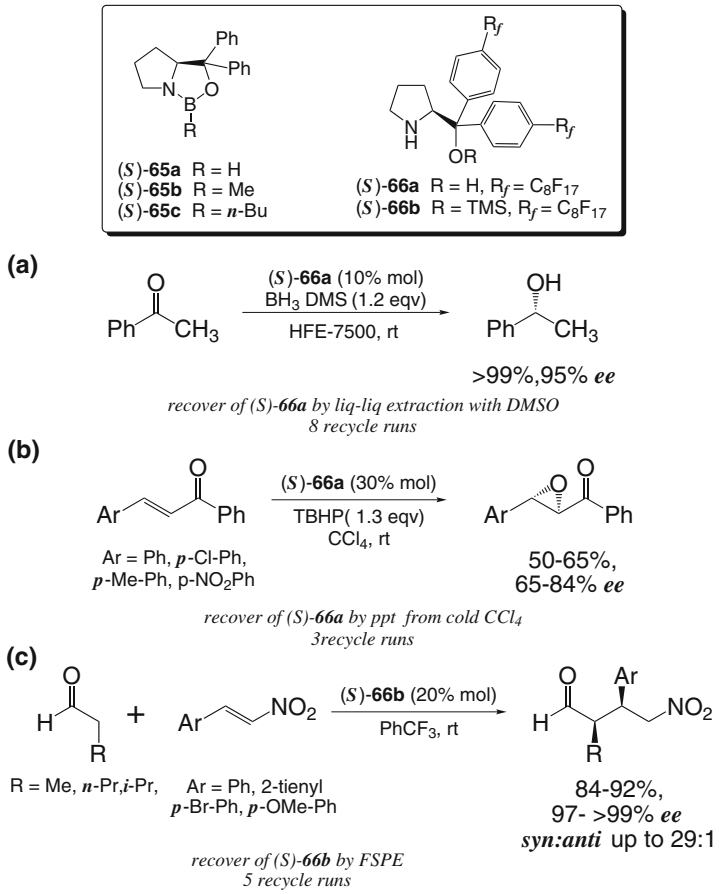
The non-covalent immobilization of Ru-**57c** complex on fluorous silica gel has been recently described as an efficient method to attain sufficient catalyst stabilization, so allowing its recover and reuse up to four cycles with only about 1.5% ruthenium leaching in the products [134] (Scheme 3.19a). In ligands **61** and **62** the perfluoroheptyl substituents worked not only as fluorous tags but, due to their electron-withdrawing character and the closeness to carbinol centres, also remarkably enhanced (by about a 10,000-factor) the acidity of the hydroxyl groups, that became prone to form more stable metal complexes. Indeed, complexes Ti/**61** [135] or Ti/**62** [136] gave excellent yields and *ee* values in the addition of Et_2Zn or less reactive Me_2Zn to aldehydes in toluene or hexane and were selectively extracted by partitioning the reaction mixtures between CH_2Cl_2 and perfluorohexane (FC-72). After removal of fluorous solvent by evaporation, the pure ligands were reused in successive runs with constant performances in seven consecutive runs (Scheme 3.19b). Aminophosphine **63** displayed good asymmetric induction in Pd-promoted allylic alkylation of **64** with malonate esters and the active catalyst was recovered by precipitation with cold hexane and reused five times without further addition of metal source [137] (Scheme 3.19c).

The Corey-Bakshi-Shibata (CBS) reduction of ketones [138] is a powerful methodology for the access to chiral secondary alcohols based on the use of chiral oxazaborolidines as catalysts and borane as hydrogen source. Oxazaborolidine **65a–c** derived from diphenylprolinol provided high levels of asymmetric induction in the reduction of a large variety of substrates [139] and their preparation by treatment of an aminoalcohol precursor with a boron source (borate esters or $BH_3 \cdot THF$) can sometimes require extended heating and excess of borane. In the fluorous version of CBS-reduction, *B*-methyl oxazaborolidine of prolinol **66a** displayed the same high enantioselectivity of the non-fluorous counterpart, but under the recycling conditions hydrolysis of the boron catalyst occurred and only the ligand was almost quantitatively recovered by FSPE. However, it was demonstrated that the in situ formation of the active catalyst from **66a** and $BH_3 \cdot THF$ was smoothly facilitated, may be due to the electron-withdrawing nature of perfluoroalkyl tags, so that successive runs could be easily performed by addition of borane reagent to the recovered aminoalcohol [140].



Scheme 3.19 Fluorous ligands for transition-metal catalysis

In an alternative protocol, the reduction of acetophenone with **66a**/$BH_3 \cdot$ DMS was carried out in hydrofluoroether solvent HFE-7500 to give 2-phenylethanol, selectively separated by extraction with DMSO, in >99% yield and 95% *ee*. Since the aminoalcohol **66a** was tightly immobilized in HFE-7500 the fluorous phase

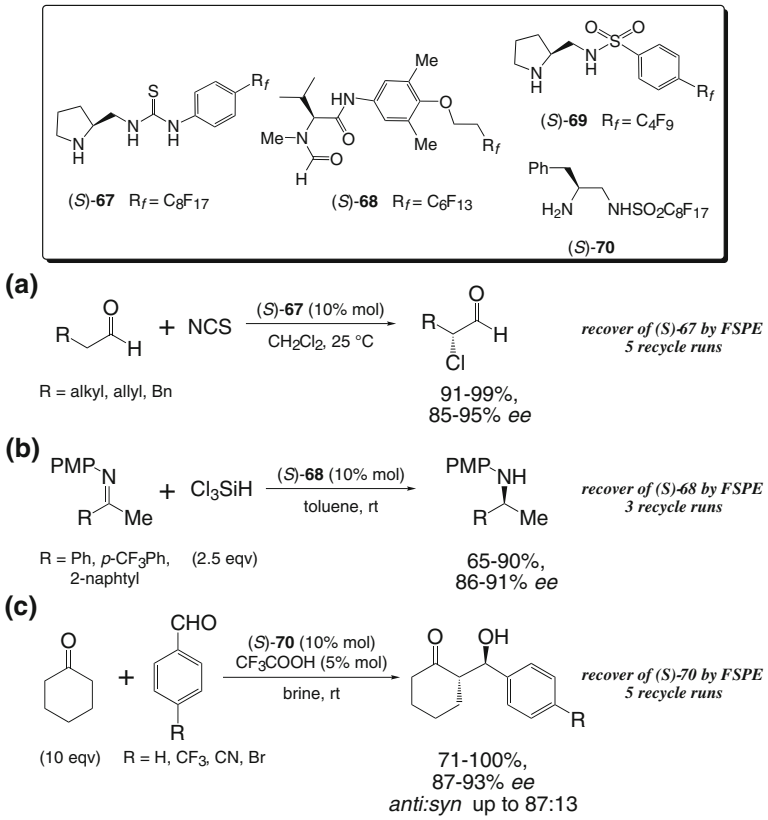


Scheme 3.20 Asymmetric reactions with fluorous prolinols

could be reused after addition of fresh $BH_3 \cdot$ DMS and consistent catalytic activity was maintained over five cycles [141] (Scheme 3.20a).

Fluorous prolinol **66a** also promoted the organocatalytic epoxidation of α,β-enones in CCl_4 with moderate to good enantioselectivities and it could be directly recovered by precipitation from the cooled reaction mixture [142]. The related silyl derivative **66b** was employed in Michael addition of aldehydes to nitroolefins and sensible enhancements of diastereoselectivity and reaction rate were observed in trifluoromethylbenzene compared with hexane as in the original procedure; the organocatalyst was recovered by FSPE and reused in successive six cycles maintaining excellent performances [143] (Scheme 3.20b, c).

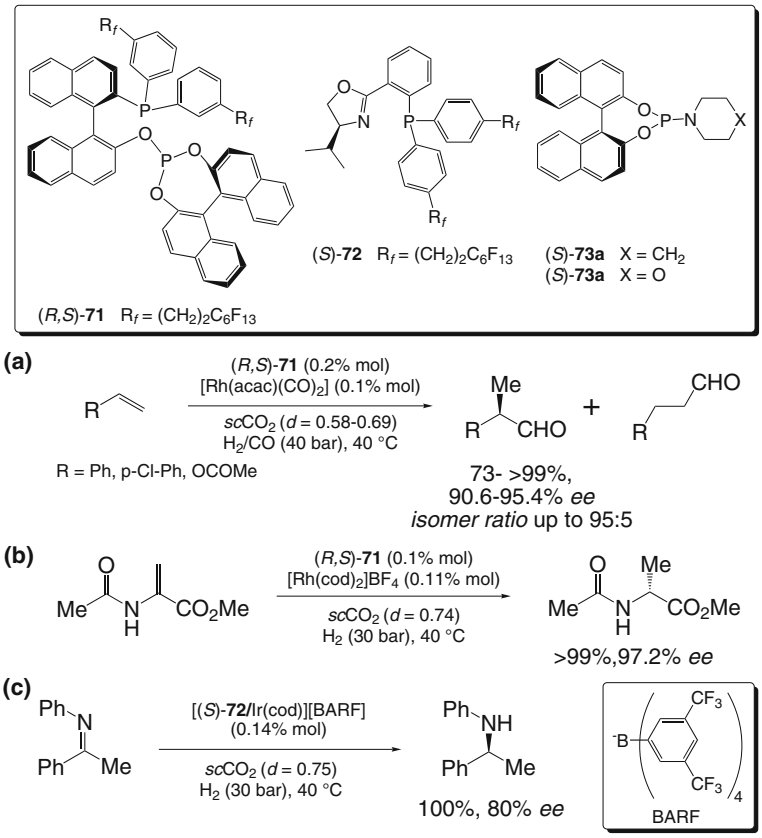
As other examples of fluorous organocatalysts, bifunctional pyrrolidine-thiourea **67** catalyzed the direct enantioselective α-chlorination of a variety of



Scheme 3.21 Reactions promoted by other fluorous organocatalysts

aldehydes in CCl_4 while valine-derived formamide **68** promoted the asymmetric reduction of imines with trichlorosilane (Scheme 3.21a, b). The catalysts were recycled after their FSPE extraction [144, 145] and quite low loading (1–5%) of **68** was sufficient to achieve the reaction products with high optical purities. Due to their high hydrophobicity, related with ponytails substituents, fluorous organocatalysts appear very suitable for reactions performed in water and additional gain can stem from fluorous-based recovery protocols. So, the addition of aldehydes and ketones to nitrostyrene [146] and some aldol reactions [147, 148] have been beneficially performed in neat water or brine in the presence of sulphonamides **69** and **70**, respectively, and the catalysts easily recovered by FSPE to be reused without significant loss of activity and stereoselectivity (Scheme 3.21c).

At the end of this section it should be mentioned that transition-metal complexes with fluorous ligands have also found application in some hydrogenation and hydroformylation reactions performed in *sc*CO_2 under controlled temperatures and pressures as nonconventional solvent and, due to the high diffusivity of the gaseous reagents in such supercritical fluid, better reaction rates and



Scheme 3.22 Asymmetric reactions in supercritical CO_2

selectivities in comparison with liquid organic solvents have been often observed. Although the selective recovery of catalyst from *sc*CO_2 is not straightforward [149], this reaction medium offers the advantage that it can be easily removed by simple depressurization and, therefore, no hazardous solvent effluent is produced. Furthermore, *sc*CO_2 has rather mild critical properties ($T_c = 31$ °C and $P_c = 74$ bar), is non-toxic, non-inflammable, chemically inert, readily available and inexpensive. The use of fluorous ligands, many of which derived from BINAP, or highly lipophilic tetrakis[3,5-bis(trifluoromethyl)phenyl] borate (BARF) as counteranion of cationic complexes has often led to satisfactory solubilisation of transition-metal catalysts in rather apolar *sc*CO_2 allowing to perform asymmetric transformations in homogeneous phase [150].

As a representative example, Rh(acac)-complex of fluorous BINAPHOS ligand **71** successfully promoted the hydroformylation of styrenes and indene in *sc*CO_2, displaying enantioselectivities and regioselectivities in favour of branched chiral aldehydes significantly higher than those achieved in the original procedure with

unsubstituted BINAPHOS **71** in benzene (Scheme 3.22a). However, it was demonstrated that regioselectivity was mainly affected by perfluoroalkyl-substitution of the ligand rather than the reaction medium features. Combination of **71** with $[Rh(cod)_2]BF_4$ was also active in *sc*CO_2 as hydrogenation catalyst and promoted the quantitative conversion of 2-acetamido methylacrylate into (*R*)-alanine with excellent enantiocontrol [151] (Scheme 3.22b).

Using fluorinated oxazoline **72**, a crucial role of BARF counteranion on the enantioselectivity was found in iridium-catalyzed hydrogenation of imines (Scheme 3.22c) and higher TON and TOF values were obtained performing the reaction in *sc*CO_2 in comparison with CH_2Cl_2 [152]. More recently, non-fluorinated monodentate phosphoramidites **73a–b** as sufficiently *sc*CO_2-philic ligands have been applied for Rh-promoted olefin hydrogenation in this supercritical fluid to afford some aminoacids in good to excellent optical purities (up to 97% *ee*) [153].

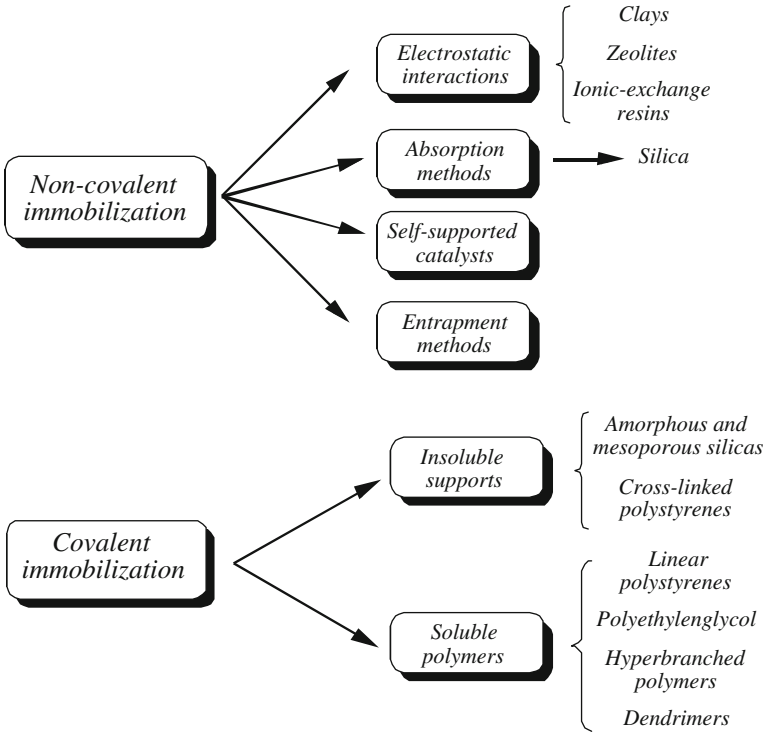
3.6 Immobilization of the Catalysts

Despite of the growing interest in non-conventional reaction media, in which suitable designed catalysts can be effectively immobilized and then recycled after liquid–liquid separations, most organic and asymmetric syntheses are still performed in organic solvents, wherefrom catalysts are usually recovered by solid–liquid phase separations (e.g. filtration) providing that they are heterogenized on insoluble inorganic materials or organic polymers. Immobilization methods can be roughly grouped into two main categories according to the non-covalent or covalent interactions between catalysts and insoluble supports, while further subclassification takes into account the different types of involved non-covalent interactions (electrostatic, van der Waals, H-bonding and coordinative) and the chemical nature of the used polymeric materials (Scheme 3.23).

In consequence of such variety in the immobilization methods and materials available, a huge number of supported catalysts have been prepared and their performances and recyclabilities have been the subject of many books and reviews [154–157].

Decreased activity and selectivity have been often reported for enantioselective supported catalysts in comparison with their soluble counterparts, due to the diffusion-limited mass transfer of reactants in the heterogeneous reaction conditions and some influence of the polymer structure in the closeness of catalytic sites. For this reason, research in the field has been mainly focused on the immobilization of catalysts deriving from privileged ligands [158–160], that are the most active ones in homogeneous phase, or proline and some related derivatives [161] as effective organocatalysts.

Although some ligands can be advantageously immobilized without any structural modification through non-covalent methods, in most cases the preparation of a heterogenized-catalyst demands synthetic extra steps. Other than the

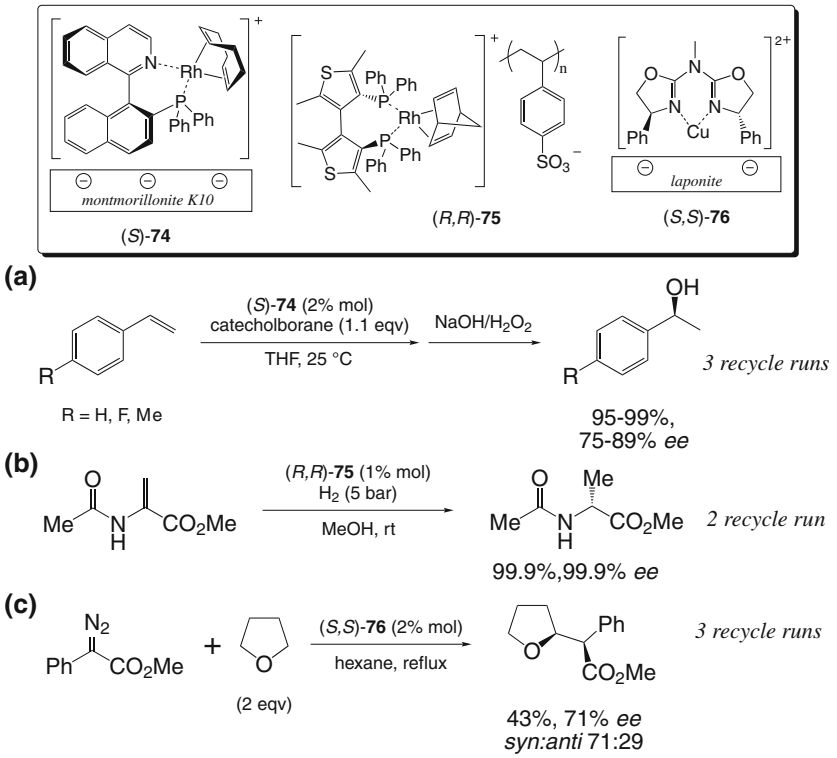


Scheme 3.23 Methods for catalyst immobilization

choice of the most convenient support, the anchoring point in the ligand and the design of a suitable linker able to ensure good accessibility of reactants to the catalytic site on the solid surface need to be carefully evaluated for covalently bonded catalysts. Therefore, the development of the supported version of a catalyst active in homogeneous solution could be a challenging task, becoming really convenient only when the final catalyst gains performances, substrate tolerance and stability [163], but it is anyway considered an important approach for industrial scale preparations [162] in batch as well as in flow reactors.

Inorganic materials as silicas, mesoporous solids, zeolites and clays have been used for the operationally simple immobilization of several chiral homogeneous catalysts by adsorption or electrostatic interactions. Although the resulting heterogenized catalysts are moderately stable and unacceptable levels of catalyst leaching can sometimes occur owing to competing interactions of solvents and/or substrates with supports, they are in many cases compatible with a broad range of reagents and harsh reaction conditions thanks to the superior chemical, thermal and mechanical resistances of inorganic solids with respect to organic polymers.

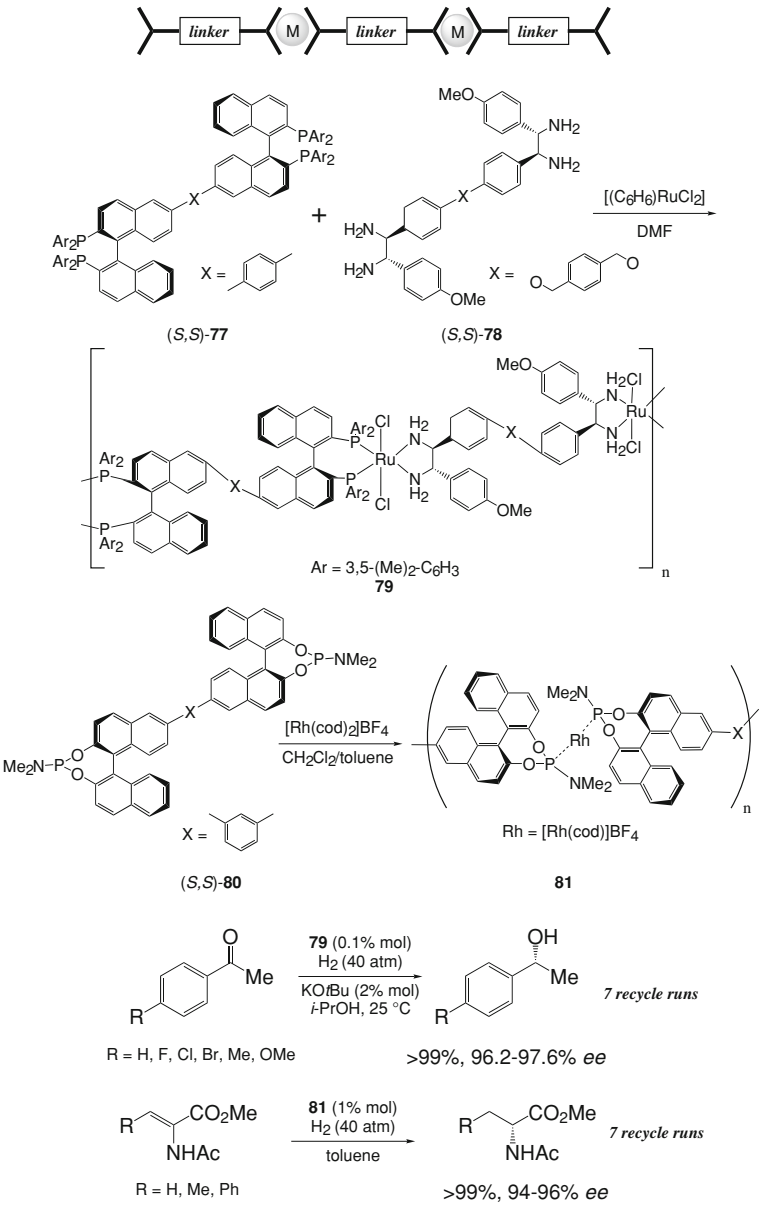
Among electrostatically immobilized catalysts, recently reviewed by Fraile and coworkers [164], some rhodium or iridium complexes of phosphines on montmorillonite, bentonite clays or DOWEX-50 WX2 (SO_3^{2-}) ionic-exchange resin



Scheme 3.24 Electrostatically immobilized catalysts

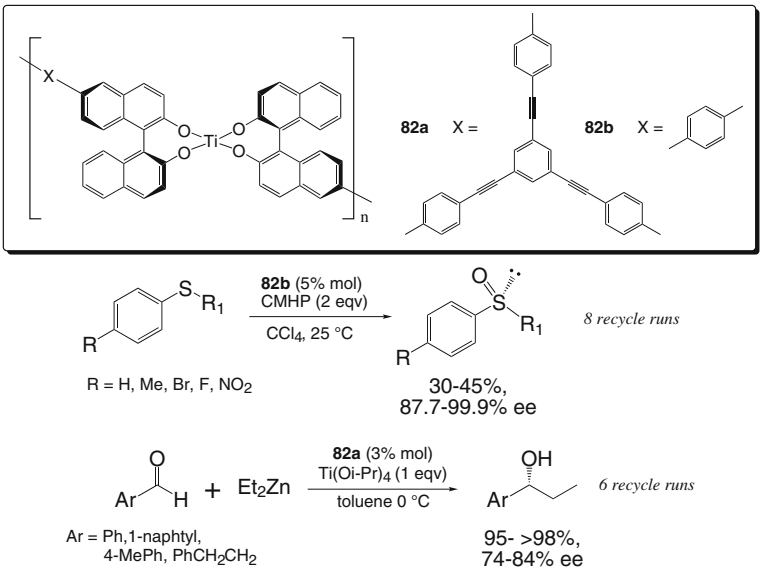
have been applied for styrene hydroboration [165] and olefin hydrogenation [166] (Scheme 3.24a, b). In comparison with the results obtained in solution, Cu(II)-bis-oxazoline complex **76** on laponite clay gave higher selectivity in C–H carbene insertion and it was recycled three times with about unchanged performances [167] (Scheme 3.24c).

The construction of metal–organic frameworks has recently attracted much attention as non-covalent immobilization method since a polymeric insoluble material can be obtained by means of coordination bonds between metals and specifically designed ditopic or polytopic ligands without any external support. Many of such *self-supported catalysts* [168] have been prepared by direct assembly of a ditopic ligand, in which two ligating units are joined by a suitable spacer, with a metal that plays the dual role of structural binder and catalytically active site. Application of this strategy to bis-BINAP/bis-DPEN system and Ru(II)-metal or bis-monophosporamidite ligands and Rh(I) gave polymeric catalysts **79** [169] and **81** [170] that displayed high enantioselectivity in ketone and olefin hydrogenation reactions, respectively, and maintained consistent activity after filtration from the reaction mixtures and reuse in successive seven cycles. (Scheme 3.25).



Scheme 3.25 Reactions with self-supported phosphorous-based catalysts

Self-supported bis-BINOL-Ti catalysts **82a–b** [171] with linear or trigonal linker-geometry enantioselectively catalyzed oxidation of sulphides with cumyl hydroperoxide (CMHP) as oxidant, glyoxylate-ene reaction and aldehyde alkylation with Et_2Zn, showing at the same time good recyclability (Scheme 3.26).

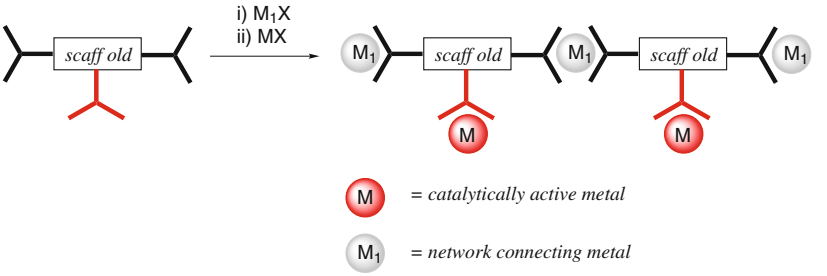


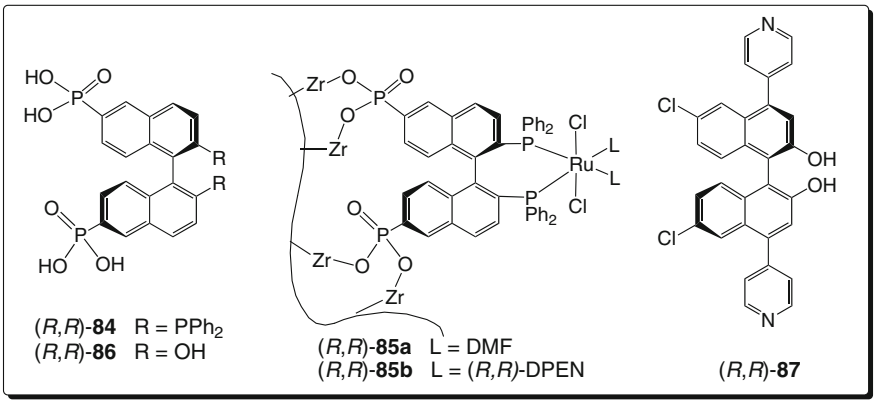
Scheme 3.26 Reaction with self-supported BINOL catalysts

In an alternative approach to the construction of metal–organic frameworks, the active ligands have been orthogonally modified with other groups (as pyridine rings or phosponate groups) possessing coordinating ability toward a metal different from that one involved in the catalytic reaction. In this way the chiral groups are used only for the generation of the asymmetric catalytic sites whereas the secondary functional groups are responsible for connecting the network-forming metals (Scheme 3.27). For example, refluxing BINAP-analogue **84**/Ru(II) complexes with Zr(O*t*-Bu)$_4$ in MeOH chiral zirconium phosphonates **85a–b** were obtained as amorphous solids active in the hydrogenation of ketones or β-ketoesters with excellent reproducibility over eight recycles [172] and enantioselective catalysts for alkylation of aldehydes with $ZnEt_2$ were achieved from Zr/**86** or Cd/**87** metal frameworks in combination with Ti(O*i*-Pr)$_4$ [173].

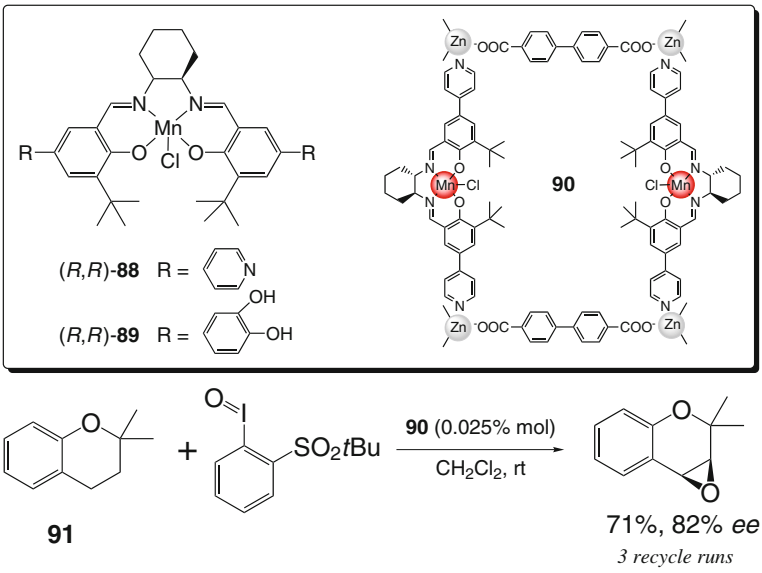
Crystalline solid **90**, obtained by treatment of pyridine-substituted salen/Mn complex **88** with $Zn(NO_3)_2$ and biphenylbicarboxylic acid, was tested as catalyst for the asymmetric epoxidation of **91** with iodosylbenzene as oxidant [174] and, in comparison with the homogeneous salen complex, enantioselectivity slightly decreased. However, the enhanced stability of the supported catalyst allowed its reuse for three cycles and even better recyclability was evidenced with polymer deriving from Cu(II)-chelation of catechol moieties in salen complex **89**.

Polystyrene cross-linked with various amounts of divinylbenzene is the most popular support for *covalent immobilization* of chiral catalysts, that can be incorporated in the polymer backbone by copolymerization of styrene and divinylbenzene with a styryl derivative of the chiral ligand or by reaction

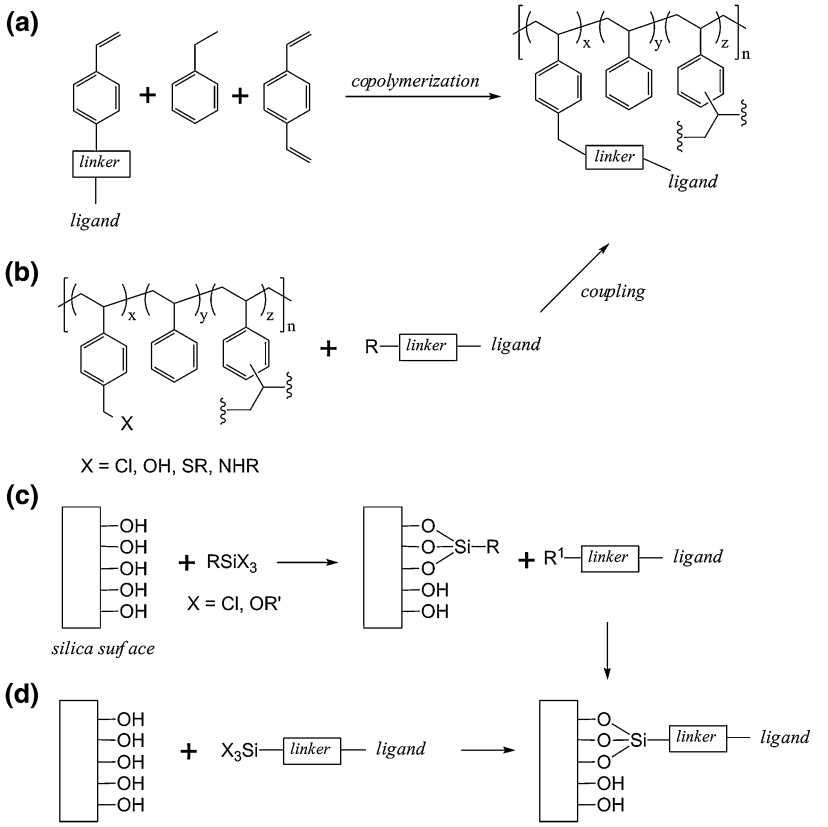




Scheme 3.27 Examples of orthogonally-substituted ligands for self-supported catalysts



Scheme 3.28 Self-supported salen catalysts for alkene epoxidation

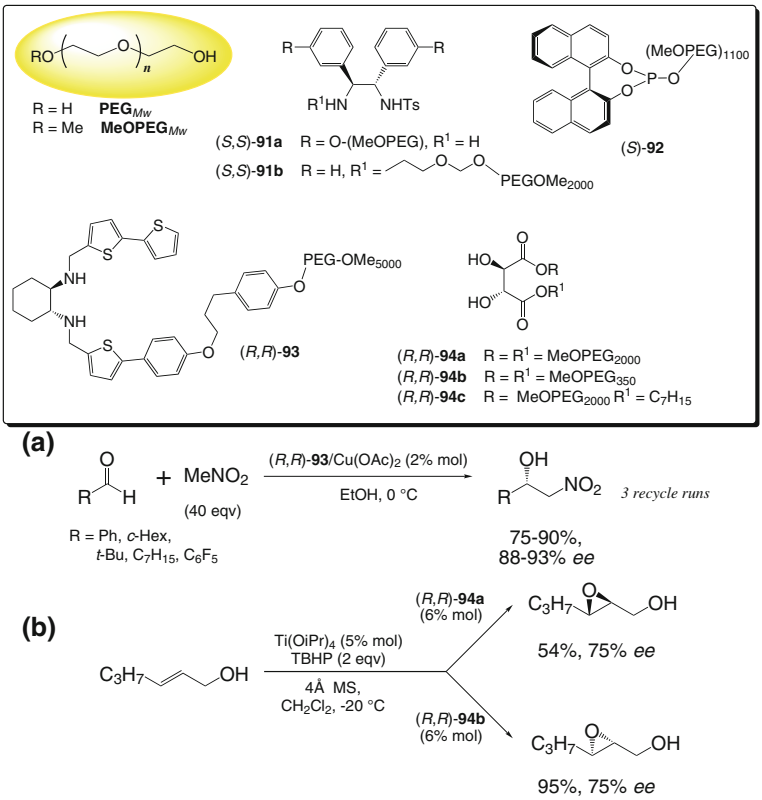


Scheme 3.29 Synthesis of catalysts covalently bound to cross-linked polystyrenes (**a**, **b**) or silica (**c**, **d**)

of a preformed polymer bearing suitable thiol, chloromethyl, amino or hydroxyl groups with a somewhat specifically designed ligand (Scheme 3.29a, b). Polymer functionalization, cross-linking degree and pore size all influence the swelling properties of the different polystyrenes as well as their loading capacity, flexibility and solvent compatibility Scheme 3.28.

Amorphous or mesoporous silicas have been also considered as versatile inorganic supports for the preparation of a large group of heterogenized catalysts and the covalent anchoring of chiral ligands or organocatalysts has been usually achieved through silanoxy bridges, formed by reaction of free silanol groups of the supports with silylating agents as trichlorosilanes, trialkoxysilanes or disilazanes. The direct reaction of suitable silyl functionalized ligands with the siliceous material is also feasible (Scheme 3.29c, d).

Such covalently immobilized catalysts have been widely applied in asymmetric synthesis [175–177], providing increased stability and recyclability with respect to the non-covalent analogues, but difficulties connected with the inherent



Scheme 3.30 Polyethylene glycol-supported soluble catalysts

heterogeneity of solid–liquid phase systems, that often precludes full catalyst characterization and predictability of matrix effects, have led to the growing development of *soluble polymers* as alternative supports. Indeed, macromolecular soluble catalysts could gain advantage in their performances from the lack of diffusion phenomena in the solution conditions and the possibility to apply conventional spectroscopic techniques for structural and reaction mechanism elucidation, making feasible at the same time their separation from reaction mixtures by selective precipitation, ultrafiltration [178] or Soxhlet-dialysis [179].

In this emerging research area, polyethylene glycol (PEG) polymers have found the most extensive use due to their solubility in some organic solvents (as DMF, dichloromethane, toluene) or in water and their commercial availability in various molecular weights. Several organocatalysts and ligands for transition-metal catalysis have been covalently bound to -CH_2OH end groups of PEG-polymers to afford catalysts well-suited for reactions in homogeneous conditions and recoverable in most cases by precipitation with hexane, diethyl ether or alcohols [180].

Among some representative examples of such soluble catalysts, PEG-supported Ts-DPEN derivatives **91a–b**, prepared by varying the anchoring point in the

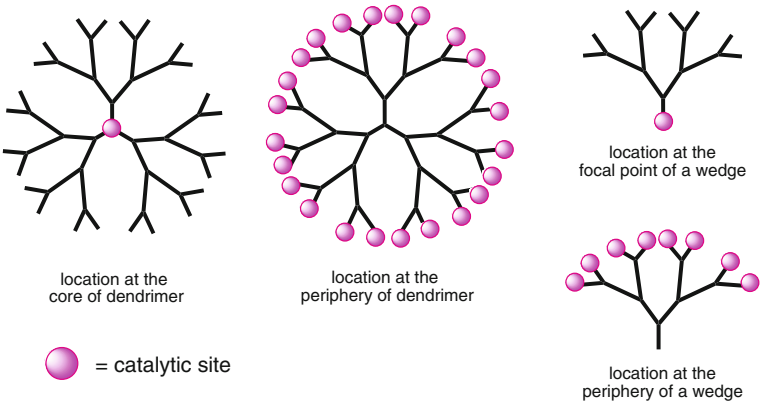
ligand, and BINOL-monophosphite **92** displayed broad substrate tolerance, excellent performances and good recyclability in ATH of ketones in water and Rh-promoted hydrogenation of enamides, respectively [181, 182]. The PEG-immobilized diamino-thiophene ligand **93** was employed in Cu-promoted addition of nitromethane to aldehydes with satisfactory activity and the catalyst was also used in successive reactions with different substrates without cross-contamination [183] (Scheme 3.30a).

A striking effect of support on the enantioselectivity was evidenced in the Sharpless epoxidation of *trans*-hex-2-en-1-ol with tartrate-PEG ligands **94a**–**b**, in which the sense of stereoinduction completely reversed going from PEG_{350} to PEG_{2000} derivative (Scheme 3.30b). Janda and coworkers [184] related the observed reaction outcomes with the occurrence of catalytic processes through complexes with different molecularity leading to opposite enantiomers and it was found that monomeric complex $Ti_2L(O\textit{i}\text{-Pr})_6$ (L = ligand), resulting in the (2*R*,3*R*)-epoxide, was more stabilized over $Ti_2L_2(O\textit{i}\text{-Pr})_4$ species as the length of PEG chains increased. Indeed, with longer PEG chains a greater number of oxygen atoms in the polymer could interact with metal preventing dimer formation.

The related complex **94c/**Ti, bearing an apolar aliphatic chain, was successfully employed in asymmetric oxidation of prochiral sulfides with CMHP oxidant showing constant activity and selectivity after its precipitation with Et_2O and reuse in four recycle runs [185].

Non cross-linked polystyrenes and thermomorphic polymers as poly(*N*-alkyl-acrylamides) [186], that can be easily recovered by changing the working temperature, have been also considered as alternative soluble polymers but until now they have found only limited application in asymmetric catalysis.

In contrast with linear polymers, whose conformational flexibility can sometimes result in a self-twisting that shields the immobilized catalytic sites lowering their activity, *dendrimers* are characterised by high structural rigidity deriving from sterical congestion of the polymeric chains around the core and well-defined structures with tailored shapes and dimensions related with the dendrimer-generation. Furthermore, the controlled synthesis of dendrimers, that proceeds through a series of iterative growth sequences of the branching units starting from a small "core", allows precise regulation of the number, location and environment of the immobilized catalytic sites as a very valuable tool for mechanistic studies. A variety of dendrimer-supported catalysts with finely tunable size and solubility properties can be constructed by locating the chiral catalytic centres at the periphery, at the core or at the focal point of either spherically-shaped (star) dendrimers or wedge-shaped dendrons, [187, 188] (Scheme 3.31). The different dendrimer topologies and catalyst location can exert marked influence on the activity, stability and hence recyclability of the catalytic system, through the so called "dendrimer effect" [189]. As an example, peripherally-functionalized dendrimers provide high local concentration of accessible catalytic sites with possible cooperative interactions so that performances comparable or even better to those achieved for mononuclear homogeneous catalysts could be expected. Otherwise, in dendritic catalysts functionalized at core or focal point the



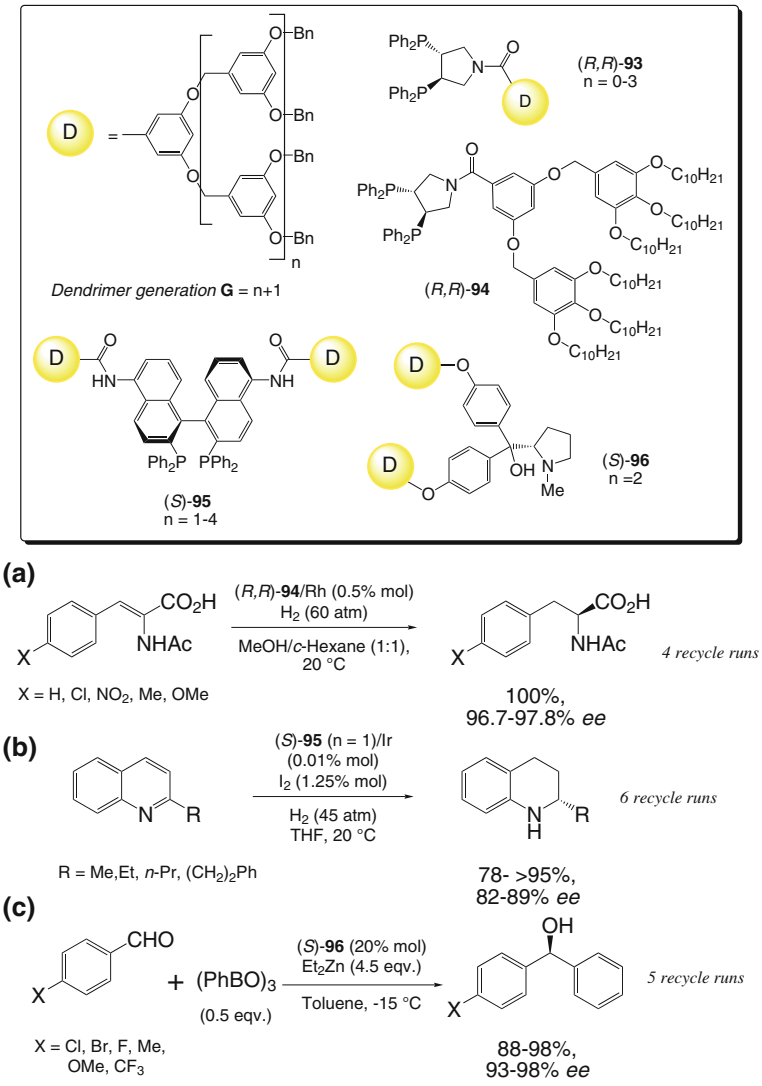
Scheme 3.31 Dendrimer-catalyst molecular architectures

"site-isolation" effect can offer a beneficial protection against degradation or aggregation processes.

Among dendrimer-supported catalysts shown in Scheme 3.32, Rh-complexes of **93**, bearing the phosphine ligand at the focal point of Fréchet-type dendrons, were employed in the hydrogenation of 2-acetamido cinnamic acid and marked decrease in the product yield was observed going from 3rd to 4th dendrimer-generation. The decreased catalytic activity was related with increased steric requirements of the dendritic branches that might cause a change from an extended dendrimer conformation to a more globular one in which the diffusion of substrates into the catalytically active core is more hampered [190]. Excellent performances in the same reaction have been recently reported for ligand **94** characterised by long alkyl chains on periphery of the dendritic support. Due to its enhanced solubility in non-polar solvents, **94**/Rh complex was extracted in more than 99% using MeOH/cyclohexane biphasic system and recycled four times without significant loss of activity and enantioselectivity [191] (Scheme 3.32a).

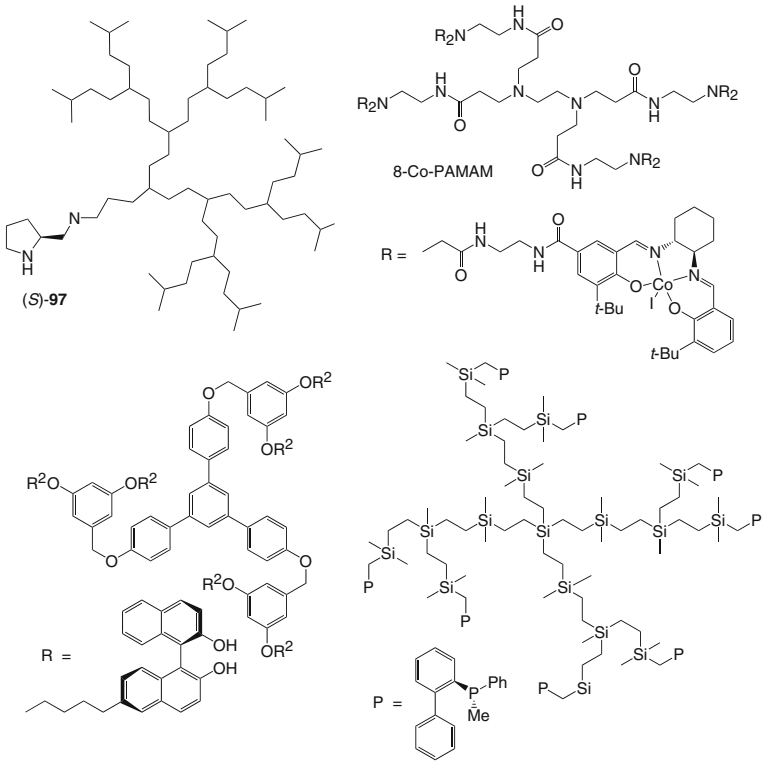
Compared to unsupported Ir(III)/(*S*)-BINAP complex, catalyst deriving from (*S*)-BINAP-cored dendrimer **95** displayed remarkable enhancement of activity in the hydrogenation of a variety of quinolines, that proceeded with satisfactory enantioselectivities and high conversions also under low catalyst loading giving a TON of 43,000, the highest value to date reported for this reaction (Scheme 3.32b). In contrast to the above discussed case, the reaction rate increased going to higher dendrimer-generations (from 1 to 4) indicating that the "isolation effect" of the dendrimer shell has a key role in preserving the activity of metal complex, retarding the possible irreversible formation of iridium dimers, a known pathway for catalyst deactivation [192].

In organocatalysis field, dendrimer-supported prolinol **96** ($n = 2$) was a versatile catalyst promoting asymmetric borane reduction of several ketones, epoxidation of enones and aryl transfer to aldehydes [193] (Scheme 3.32c) always with high to excellent enantioselectivities and typical yields in the 80–99% range. After



Scheme 3.32 Selected examples of catalysts immobilized on polyether dendrimers

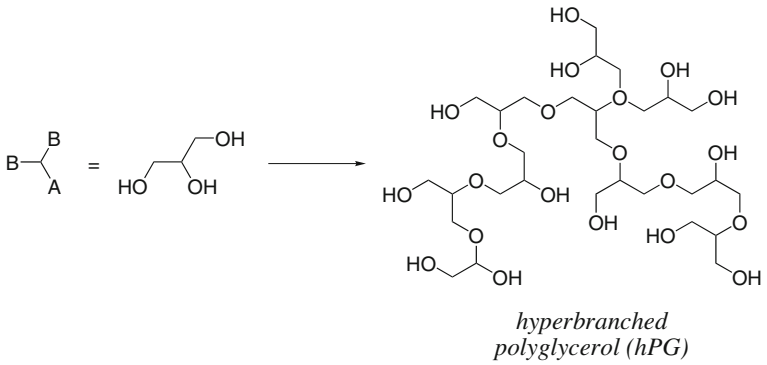
its selective precipitation with MeOH, compound **96** was reused throughout five cycles without performance erosion. More recently, all-hydrocarbon dendrons have been covalently bound to pyrrolidine and the resultant organocatalysts (as **97** in Scheme 3.33) tested in asymmetric Michael addition and aldol condensation of benchmark substrates in water. It was found that non-polar nature of the supports favoured the formation of emulsions, improving both the activity and enantioselectivity with respect to the non immobilized counterpart and facilitating the catalyst recovery by extraction with heptane [194].



Scheme 3.33 Dendrimers based on non-polyether scaffolds

Besides the popular polyether-based dendrons, star-shaped dendrimers with polyamidoamine (PAMAM) [195], chlorocarbosilane [196] or polyphenylene [197] backbones has been also developed and their peripheral functionalization with suitable chiral ligands has afforded a variety of recyclable catalysts applied for typical metal-based asymmetric reactions (Scheme 3.33).

Although the fine-tuning of steric and chemical features of dendritic environment offers great potentiality for performance optimization, the application of dendrimer-supported catalysts in large scale preparations is to date precluded by their expensive and multistep synthesis. A more economical alternative comes from *hyperbranched polymers* (hPs), that can be produced in large quantities by one-step polymerization of AB_x-type monomers ($x = 2$ or greater) and are characterised by intrinsic globular structure with a large number of randomly oriented terminal functional groups. Unlike dendrimers, hPs are polydisperse systems but in catalysis they have often displayed similar performances, showing that perfectly defined structures are not always required [198, 199]. Among commercially available hPs, hyperbranched polyglycerol (hPG) (Scheme 3.34) is chemically more stable than polyesters and polyamine counterparts and its high loading capacity, good solubility, excellent biocompatibility and non-coordinating

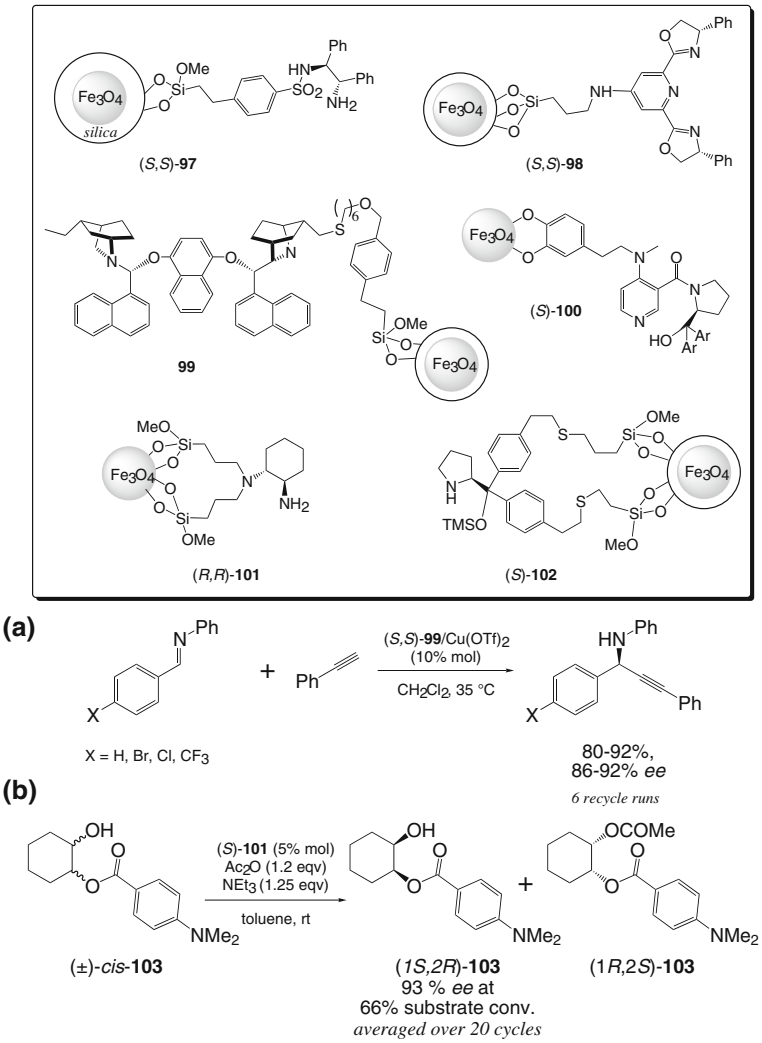


Scheme 3.34 Structure of hyperbranched polyglycerol

properties make it a very attractive support for catalyst immobilization and recycle [200, 201], so that increasing applications could be expected in the future.

At the interface between homogeneous and heterogeneous catalysis, *metal nanoparticles* (NPs), that are clusters containing from few tens to few hundreds of atoms with size in 1–100 nm range, have recently emerged as efficient alternatives for the immobilization of enantioselective catalysts and they could also be utilized as catalytically active parts of the chiral systems giving rise to unique reactivities [202] and modes of asymmetric induction. Due to their small size, metal NPs are characterised by large specific surface area, that provides high accessibility of active sites to reactants and high dispersion in liquid media. Consequently, reaction kinetics are not limited by diffusion and soluble, quasi-homogeneous or stable colloidal systems can be achieved in function of the particle dimensions, tunable according the NPs preparation methods. Since metal NPs are very prone to agglomeration, often leading to loss of catalytic activity, their stabilization with ligands, inorganic supports or macromolecules as polymers and dendrimers is the usual strategy for protecting the metal core [203]. A variety of stabilized metal NPs have been prepared and their potentiality in green catalysis has been object of recent reviews [204, 205].

Heterogenization of catalysts on magnetic NPs is particularly attractive in terms of recyclability since the recovery protocol could be reduced to a simple decantation after applying an external magnetic field to the reaction vessel. In the relatively young research field of magnetically separable nanocatalysts [206], the most used support is magnetite (Fe_3O_4) in form of monodisperse particles coated by a silica layer or entrapped in mesoporous silica (Fe_3O_4@SiO_2) to prevent particle aggregation and undesired interaction between the core metal and the anchored ligands. The grafting of some active chiral ligands on siliceous matrices containing magnetite NPs has afforded very selective catalysts with excellent recyclability [207], as TsDPEN **97** that was employed in Ru-promoted ATH of imines or ketones and reused up to nine times without loss of activity [208] (Scheme 3.35).



Scheme 3.35 Examples of catalysts supported on magnetic nanoparticles and their application in asymmetric synthesis

The direct addition of terminal alkynes to imines was carried out in the presence of Fe_3O_4@SiO_2-supported pybox-ligand **98**/Cu(I) complex [209] and the higher reactivity over other supported pybox catalysts was ascribed to the presence of the NPs, that also allowed an efficient recycle in successive five reaction runs (Scheme 3.34a). The grafting of magnetite NPs on the pore surface of mesocellular silica foam, followed by the covalent binding of *Cinchona* alkaloid ligand, gave catalyst **99** for Sharpless' asymmetric dihydroxylation that exhibited performances comparable with those of the homogeneous ligand. Moreover, constant

activity and enantioselectivity were maintained in eight recycle runs providing that fresh OsO_4 was added in every run [210].

In organocatalysis field, an unprecedented extent of recyclability was reported for prolinol-derived DMAP-analogue **100** in the acylative kinetic resolution (KR) of mono-protected *cis*-diols (Scheme 3.34b). The catalyst was active in only 5% mol loading and 93% *ee* of the recovered alcohol (1*S*,2*R*)-**103** at 66% substrate conversion, in agreement with a selectivity factor of 9.5, was averaged over 20 cycles. The same batch of catalyst was then applied to the KR of other *sec*-alcohols displaying wide substrate tolerance and good performances also after being exposed to overall 31 cycles [211]. Cyclohexanediamine heterogenized on Fe_3O_4@SiO_2 NPs (**101**) was effective in promoting up to 11 consecutive aldol condensations of cyclohexanone with *p*-nitrobenzaldehyde to give the corresponding adduct in consistent 98% yield and 98% *ee* [212]. Immobilization of Jørgensen catalyst (α, α-diphenylprolinol trimethylsilyl ether) on the same support has been recently reported and the resultant catalyst **102**, tested in asymmetric Michael addition of aldehydes to nitrostyrene in water, showed satisfactory selectivity but some loss of activity was evidenced in the third recycle [213].

The variety of supports, either insoluble or insoluble, and the combination of various immobilization techniques, as in the grafting of dendrimers on insoluble materials, have consistently enlarged the availability of robust and recyclable enantioselective catalysts with performances that in many cases are very close to those of homogeneous counterparts so that the development of an increasing number of asymmetric processes for large scale production could be reasonably expected.

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Chapter 4
Technological Tools and Design of New Chemical Processes

Abstract Although their impact on enantioselectivity is rather limited, technological tools can provide increased productivity with simultaneous energy and time savings. Under microwave irradiation as non-conventional heating source marked rate acceleration has been evidenced in many cases and continuous-flow reactors, among which microreactors display unique features in fast heat and mass exchange, have led to more prolonged catalyst life, reduction of solvent waste and simplification of workup procedures. In the context of the design of new chemical processes, multicomponent reactions or cascade sequences offer high potentiality in the construction of complex molecules from simple precursors in a single step, so avoiding the costly protection/deprotection procedures and purification of intermediates.

Keywords Microwave-assisted synthesis · Continuous-flow reactors · Microreactors · Cascade reactions · Multicatalyst systems

4.1 Introduction

The major costs of asymmetric catalytic processes are usually related with the preparation of chiral catalysts and much efforts have been devoted to their structural modifications in order to make them more efficient, more recyclable and compatible with environmentally benign solvents. However, the same strategies developed for the optimization of catalyst performances in terms of sustainability can be also applied to other reaction components with the aim to reduce the amount of toxic or hazardous reagents and introduce simplification in the purification procedures, that in many case are a non-negligible source of solvent waste. As an example, in the asymmetric hydroxylation of alkenes, promoted by

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Cinchona alkaloid-osmium complexes, toxicity and volatility of the metal oxide and its possible contamination in the products represent serious obstacles for industrial applications, more than the cost and availability of the chiral ligands. Since the use of supported ligands in some cases has not resulted in satisfactory suppression of osmium leaching, due to the reversibility of metal–ligand coordination, the direct immobilization of osmium tetroxide by microencapsulation into polystyrenes or by electrostatic interactions with amino-functionalized silica or resins has been explored as an alternative strategy [1]. Labelling of substrates or reagents with removable fluorous or ionic liquid tags offers great potentiality in multistep as well as in combinatorial synthesis, allowing selective separation of final products from reaction mixtures by liquid–liquid or fluorous solid phase extraction [2, 3].

Other contributes to the improvement of synthetic efficiency could come from the use of microwave irradiation and the development of continuous-flow reactors, as technological tools for the enhancement of reaction rate and productivity. Although these technologies have been mainly focused on organic synthesis, the interest in their application for asymmetric transformations is growing in parallel with the increased availability of more stable and selective catalysts.

Besides the modifications of the different factors influencing the outcome of known asymmetric processes in a "green direction", the discovery of novel reactivity and new reaction design could lead to a substantial and innovative advance in this field of organic chemistry. In this context, the development of multicomponent and "cascade" reactions could open new scenarios in the synthesis of chiral compounds bearing multiple stereogenic centers, with a direct advantage in decreasing the tedious and expensive steps of purification and protection/deprotection of the intermediates.

4.2 Microwave-Assisted Asymmetric Catalytic Synthesis

Since the first application in mid 1980s of microwaves (MW) as alternative and efficient heating source, the technique has been firmly established as a powerful way to achieve reaction rate acceleration compared to the conventional heating with oil baths, isomantles or hot plates. The possibility to consistently reduce both times and energy [4] required for full conversions of substrates through MW irradiation has been advantageously exploited in organic and combinatorial synthesis with a great impact in drug discovery [5–8] and these aspects are also relevant in the field of "green chemistry" [9]. The ability of solvents or reactants to absorb MW energy at 2.45 GHz, the frequency assigned for heating applications, results in the direct heating of the chemical species through the walls of vessels that are at lower temperature than the reaction mixture, due to the transparency of common borosilicate glass to microwave radiation. Wall effects, that in the conductive heat transfer can be responsible for decomposition of reactants/products over the time, are hence minimized under MW irradiation and usually

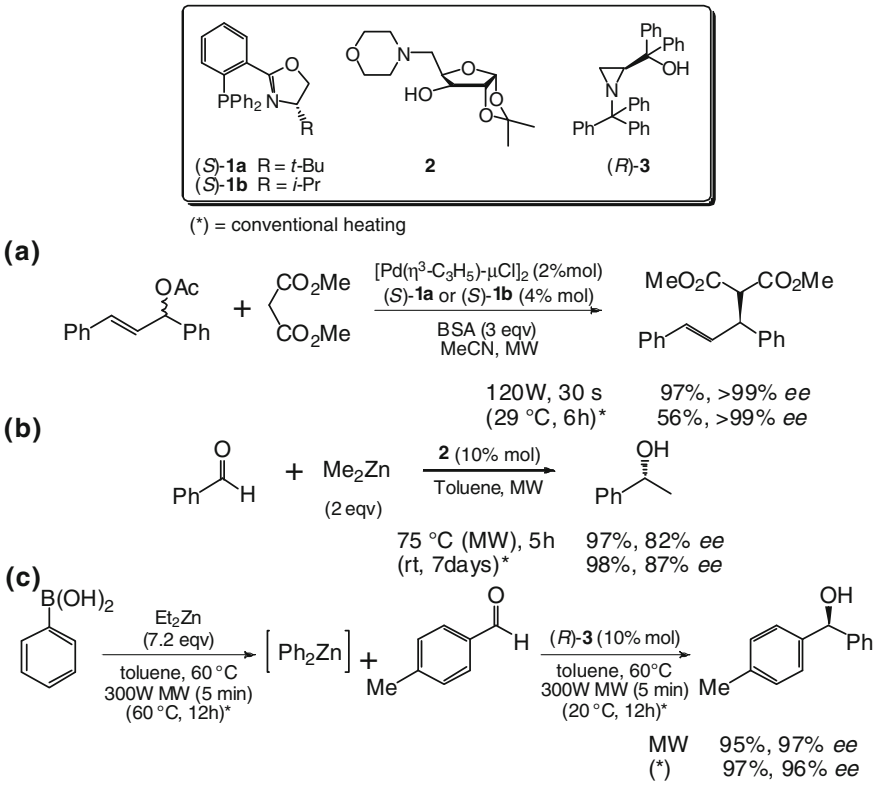
high yields and cleaner reactions are observed. The efficiency with which MW radiation is converted into heat is expressed by the dissipation factor tanδ that is proportional to the polarizability and electric conductivity of the absorbing chemical species. Polar and ionically conducting solvents (tanδ >0.1) are well-suited for microwave-assisted synthesis but also solvents lacking permanent dipole moments, as dioxane, carbon tetrachloride or benzene, or solvents with tanδ < 0.1 can be used if substrates, reagents or catalysts are strongly polar and therefore MW absorbing. In domestic ovens, used in the pioneering experiments in microwave assisted organic synthesis (MAOS), the MW radiation is reflected by the walls within the oven cavity generating non-coherent multiple 3D wave patterns, called "modes", responsible of areas with different field strength referred as "hot and cold spots". In consequence of this and in conjunction with the low-quality of magnetrons, the resultant fields were quite inhomogeneous and the lack of reproducibility was a serious drawback in MAOS. Technological advances have today made available new instrumentation with "single-mode" cavity, also equipped with devices for the control of pressure and temperature inside the sample, able to provide uniform heating pattern and higher reproducibility of the results.

It has been often claimed that interactions between the MW field and the material could also generate "not purely thermal" effects [10, 11] as a contributing factor for reaction rate enhancement. Such effects should lead to decreased activation energy or increased Arrhenius pre-exponential factor in consequence of the induced rapid molecular mobility, but their experimental evidence as well as their rationalization and role in predictive models are still a controversial matter.

In the field of asymmetric synthesis reduction of reaction times by heating is usually detrimental, since enantioselectivity is directly determined by the energy difference between the diastereoisomeric transition states leading to opposite enantiomers and this value decreases with raising temperature according to the relation

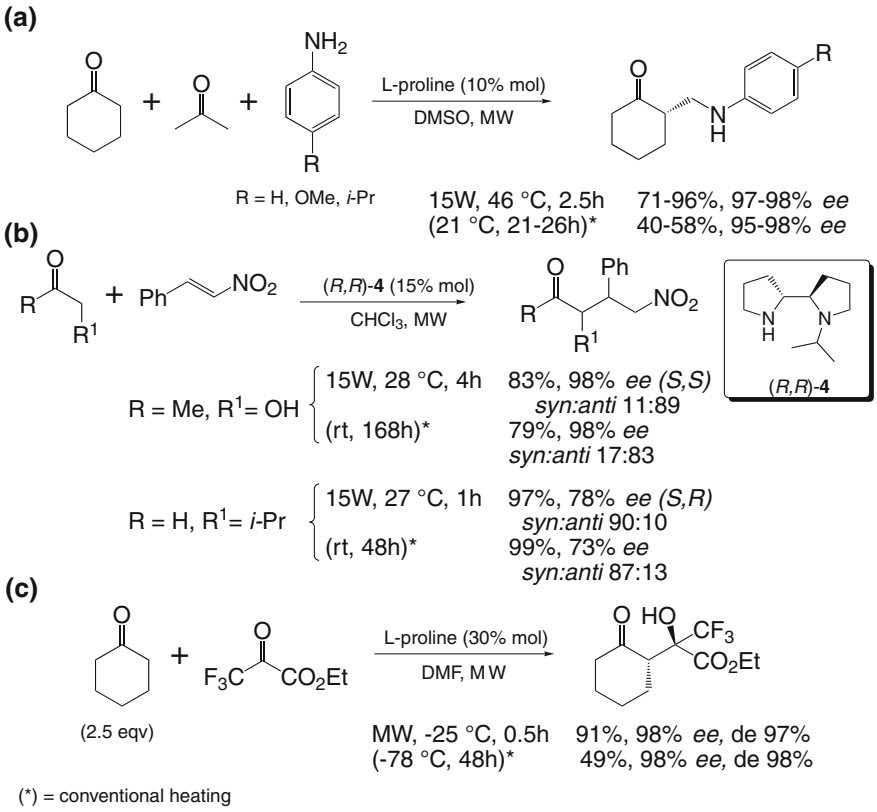
$$E = \frac{(R)}{(S)} = e^{-\Delta\Delta^{G\ddagger}/RT}.$$

However, highly selective reactions can be performed under MW irradiation and favourable reduction in catalyst loadings has been sometimes evidenced. Operationally, MW-assisted reactions have been performed following three protocols: (1) at constant MW power, that results in a rapid heating of the whole mixture at a temperature mainly dependent on the nature of solvent; (2) at constant temperature, so that the MW source is powered on–off during the reaction in order to maintain the fixed temperature and can act as a "flash-heating" source, really delivering low levels of MW power in the sample when solvents with high values of tanδ are employed; (3) at constant MW power or temperature with simultaneous external cooling, a technique that allows higher level of MW power administered to the reaction mixture but prevents overheating by continuously removing the heat [12].



Scheme 4.1 Microwave-assisted reactions with transition-metal catalysis

An impressive example of rate acceleration was reported for Pd-promoted allylic alkylation of (±)-1,3-diphenylallyl-1-acetate with dimethyl malonate in the presence of phosphinooxazoline catalysts **1a** or **1b**, in which >99% substrate conversion was reached in only 30 s under 120 W MW irradiation. In comparison with the reference conditions (56% conversion after 6 h at 29 °C conventional heating) TOF substantially increased from 3 to 3,500 while the same excellent enantioselectivity (*ee* > 99%) was maintained [13] (Scheme 4.1a). MW-assisted addition of low reactive Me_2Zn to aromatic aldehydes at 75 °C in the presence of catalyst **2** required only 1 h (*vs* several hours or days) to give high substrate conversion and the corresponding alcohols were obtained with slightly lower optical purities compared to standard conditions, but the same catalyst activity was also observed at reduced loading (5% mol) [14] (Scheme 4.1b). In the synthesis of diarylmethanols with aziridine catalyst **3**, 300 W MW irradiation at 60 °C markedly accelerated both the formation of zinc reagents from boronic acids and the addition to aldehydes (10 min *vs* 12 h for each step) without loss of enantioselectivity [15] (Scheme 4.1c). The addition of dialkylzinc to phosphinoylimines in the presence of prolinol ligands [16] and the synthesis of chiral binapthalenes



Scheme 4.2 Examples of rate acceleration in organocatalysis under microwave irradiation

via Suzuki–Miyaura or Negishi cross-coupling reactions with a ferrocenyl-Pd catalyst have been also performed with MW heating and improved yields and satisfactory enantioselectivities were reported [17].

Proline-promoted Mannich reactions have sometimes displayed temperature tolerance but usually require long reaction times and high catalyst loading (>10% mol); however, when the reaction was performed in DMSO with constant 15 W MW power and simultaneous air-cooling excellent stereoselectivities and good product yields were achieved within few hours with even 0.5% mol of catalyst [18] (Scheme 4.2a). The same reaction was also carried out in water at 130 °C under MW heating for the stereoselective preparation of a serie of β-aminoketones from different combinations of substrates [19]. In a specific study Kappe and coworkers [20] emphasized that a careful monitoring of the internal reaction temperatures with a fiber-optic probe is essential for the correct comparison of catalytic performances under conventional and MW heating and in Mannich condensation of α-iminoethylglyoxylate and acetone at 60 °C the authors evidenced the same reaction outcome regardless of the heating methodology.

The aldol reaction originally developed by List (4-nitrobenzaldehyde and acetone in DMSO and 30% mol of proline) showed sensible rate enhancement (from 4 h to 15 min) and unchanged selectivity under 10 W MW irradiation with simultaneous air-cooling. Under the same MW heating protocol, Michel addition of various donors to β-nitrostyrene with bipyrrolidine catalyst **4** in $CHCl_3$ gave slightly increased selectivity in remarkably shortened times and the occurrence of a non-thermal effect was suggested taking into account the transparency to MW of the used solvent [21] (Scheme 4.2b). In opposition to the above discussed examples, condensation of triethylpyruvate with ketones in the presence of proline required subzero temperatures in order to proceed with satisfactory selectivity and in a test reaction with cyclohexanone the adduct **5** was obtained with 98% *ee* and 49% yield after 48 h at −78 °C. Interestingly, by controlling the temperature with external cooling, the beneficial effects of MW irradiation were found operative also at −25 °C, so that **5** could be obtained in 91% yield and 98% *ee* after 30 min. Consistent results were also achieved with a variety of ketone substrates, but the origin of such MW activation was not further investigated [22] (Scheme 4.2c).

4.3 Continuous-Flow Reactors

Organic synthesis either in bench or industrial scale is traditionally carried out in batch reactors in which substrates, reagents and catalysts are mixed and left to react under controlled conditions (pressure, temperature, inert atmosphere, stirring) until the end point is reached. The catalyst, if supported on an insoluble polymer, is then separated from products by filtering off, washed and reused in another batch run by addition of fresh reactants. Automated procedures are useful alternatives in term of costs and time and, in this context, combinatorial and parallel synthetic methods have been effectively applied for pharmaceutical drug discovery and fast optimization of the reaction parameters. *Continuous-flow systems*, that have been long used in industrial processes in which gases passed over solid inorganic or organic catalysts, are experiencing a growing interest also for laboratory use, since they provide increased safety, reproducibility, facile automation and extension to larger scale continuous production [23, 24]. Development of microwave technology and engineering of flow-reactor devices in conjunction with the availability of a variety of supported catalysts and non-conventional fluids as sCO_2 or ionic liquids, have stimulated the design of novel continuous-flow processes [25] leading in most cases to a marked gain in space–time yields (amount of product per unit volume and per unit time).

According to macro- or micro- porous nature of the polymeric support, insoluble immobilized catalysts are mainly used in packed *fixed- or fluid-bed reactors,* that consist in thermostated glass or steel pipes filled with catalyst beads in which reagents and substrate are continuously pumped. By suitable adjustment of feed flow, the maximum conversion could be reached during the residence time of reactants inside the reactor and, in optimal conditions, the effluent should

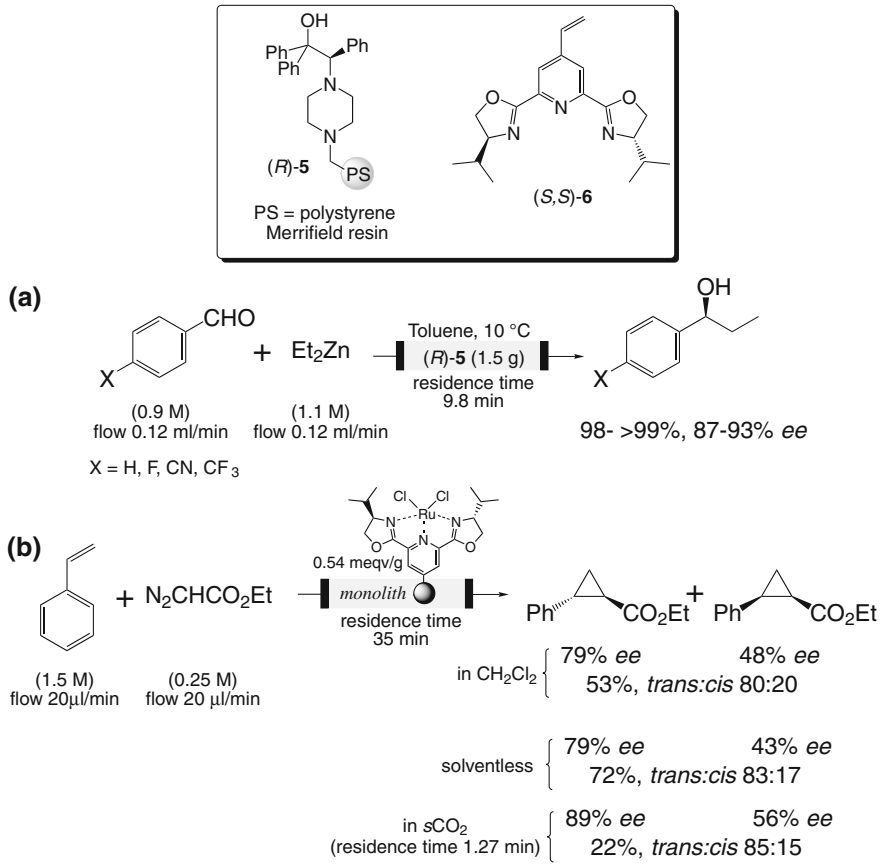
contain only the desired product, available in pure form after little or no workup. Compared to a batch process, the simultaneous occurrence of the reaction and catalyst recycle leads to reduced solvent waste while the lack of stirring preserves catalyst from its mechanical degradation.

Although inorganic supports are preferred to organic polymeric ones, that suffer some limitation deriving from their swelling properties, immobilized chiral catalysts on polystyrene resins [26] and self-supported catalysts [27] have found application in enantioselective hydrogenations [28] and some C–C bond forming reactions [29]. The addition of diethylzinc to aldehydes, performed in a packed bed reactor (10 × 70 mm) loaded with polystyrene-immobilized catalyst **5** under a flow rate of 0.24 ml/min, is a representative example from recent literature (Scheme 4.3a). In a single pass of 9.8 min benzaldehyde was completely converted with 93% *ee* and the residence time could be further decreased (at flow 0.72 ml/min) with highly reactive aldehydes. So, productivities up to 13.0 mmol/h per gram of **5** and up to 24-fold reduction of the reaction times in comparison with the results obtained in batch were calculated [30]. The same continuous-flow reactor gave excellent results also in consecutive reactions with different substrates as well as in the synthesis of diarylmethanols [31] with arylboronic acids/Et_2Zn.

Monolithic composite materials have been prepared by polymerization of suitable monomers inside the pore volume of a block of inert and highly porous organic or inorganic material (polystyrene, carbon, glass) to give small polymer bridged beads (1–5 μm) entrapped into the microchannels of the support. The small diameter of polymer particles results in large geometric surface area leading to enhanced accessibility of catalytic active sites, while the limited polymer swelling inside micropores strongly reduces the occurrence of uncontrolled fluid dynamics and pressure drops often observed with randomly packed beds of gel-type resins. Encapsulation of monoliths in glass, PTFE or stainless steel cases has allowed the construction of a variety of reactors for flow chemistry and their features have been tuned by adjustment of porosity, composition and shape [32, 33].

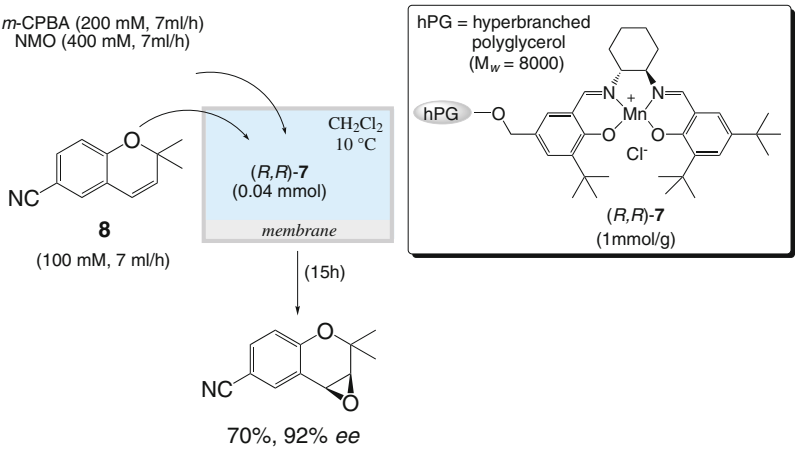
Copolymerization of chiral pybox ligand **6** with styrene and divinylbenzene in the presence of toluene/1-dodecanol as porogenic agent gave a monolith with low pore-size distribution and the corresponding Ru-complex was assayed as monolithic microreactor (700 μl volume) for cyclopropanation of styrene with ethyldiazoacetate. Under a continuous flow of reactants in CH_2Cl_2 (20 μl/min, 35 min residence time) catalyst performances were similar to those obtained in batch with homogeneous solution but increased product yields were feasible by direct pumping of pure reagents in solvent-free conditions. The monolithic reactor was also compatible with sCO_2 in higher flow rates, so that the residence time could be reduced to only 1.27 min while enantioselectivity and TOF were further enhanced in comparison with the previous conditions [34] (Scheme 4.3b)

Continuous-flow membrane reactors, introduced in enzymatic industrial processes in 1981 and constantly used since then, could represent an interesting option also in asymmetric homogeneous synthesis providing that a soluble catalyst is covalently linked to a polymer with sufficient high molecular weight to be

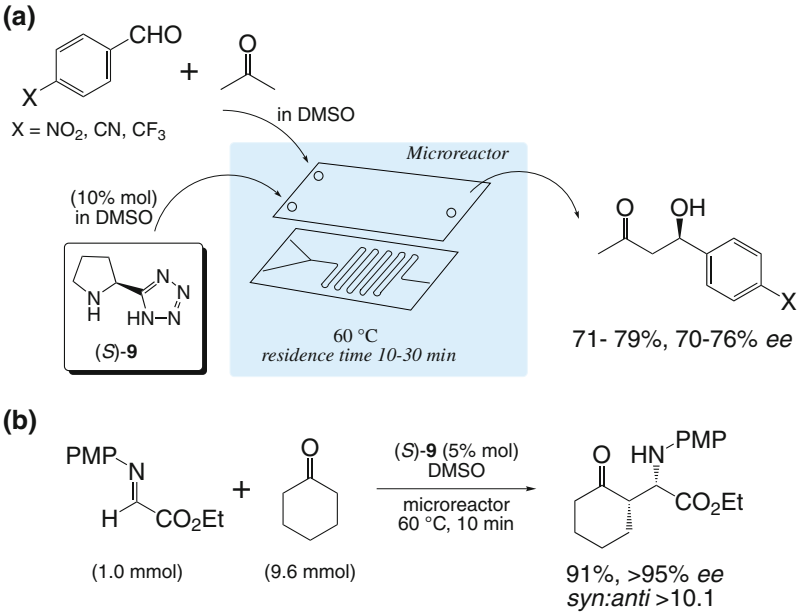


Scheme 4.3 Continuous-flow processes in packed bed reactors

retained behind an ultrafiltration membrane while the products are continuously removed in the permeate solution. Solvent-stable membranes with different permeability and molecular weight cut-off have became available and they have been mainly used for the selective separation of polyethylenglycol- or dendrimer-supported catalysts from reaction mixtures in batch reactors [35], but an increase in continuous-flow applications [36, 37] could be expected. A continuous-flow membrane reactor containing a CH_2Cl_2 solution of catalyst **7** supported on hyperbranched polyglycerol (mol weight = 8000) has been recently developed for salen-promoted epoxidation of chromene **8**. Maintaining simultaneous delivery of reagents and substrate into the reactor for 15 h the desired epoxide was collected at reactor outlet in 70% averaged yield and 92% *ee* with a calculated TON tenfold higher than that obtained for the same reaction in batch (Scheme 4.4). Furthermore, it was demonstrated that the continuous process ensured decreased catalyst leaching and deterioration, in comparison with four repetitive batches using catalyst recycled after its selective precipitation, [38].



Scheme 4.4 Continuous-flow asymmetric epoxidation in membrane reactor



Scheme 4.5 Organocatalyzed reactions in a microreactor

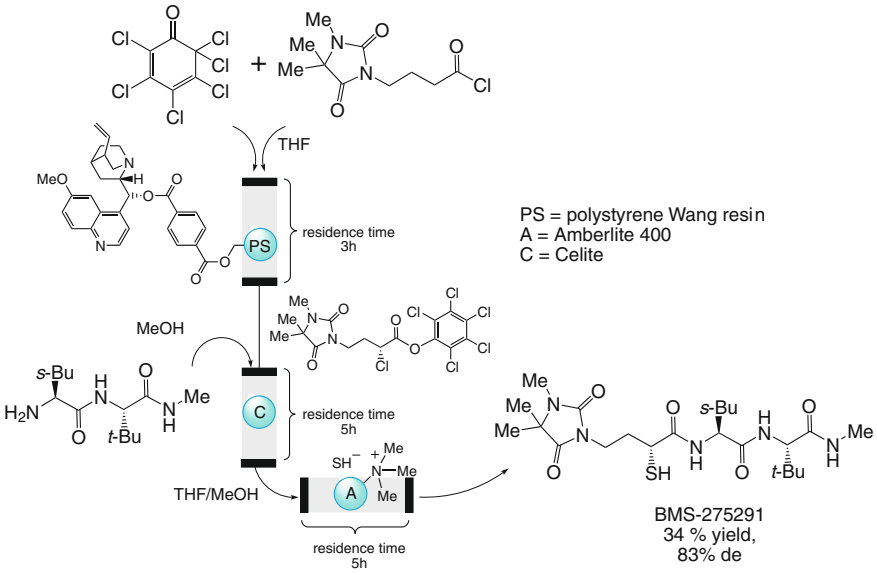
Along with advances in even more sophisticated techniques for device miniaturization, in most cases borrowed from the field of semiconductor microelectronics, microreactors have emerged as very attractive tool for "green" chemical reactions in both laboratory or preparative scale [39–41] and much research has been devoted to their engineering and manufacturing [42, 43]. In their simplest

form, a *microreactor* consists in a network of small size (10–500 μm) channels etched into different materials as silicon, glass, metals or polymers and connected to a series of reservoirs for reactants, products and waste to give a complete device ("chip") with overall dimensions of few cm. The narrow channel dimensions lead to unique advantages the most important of which are low solvent consumption and decreased waste, fast and homogeneous mixing of the reactants, efficient heat-exchange that allows better thermal control preventing hot spots and providing better safety in solventless or exothermic reactions [44], sometimes without need of external cooling. Furthermore, facile automation and short reaction times make microreactors well-suited for reactions involving labile intermediates [45], rapid catalyst screening and method optimization [46] or kinetic investigations [47]. Since the peculiar features of microreactors are strictly related to the small dimensions of the channels and copies of a given chip are accessible at low cost from replication of the master, once a chemical process is developed in such miniaturized systems, the productivity of the desired compound can be easily increased [48] by using multiple reactors in parallel (numbering up) so avoiding the classical costly and time-consuming scale-up.

Control of fluids in microreactors is mostly provided by hydrodynamic pumping with syringe pumps or peristaltic pumps, a method that is compatible with any liquid or material but is limited by capillary resistance that exponentially increases with decreasing the channel dimensions. As an alternative electrokinetic flow, driven by a potential difference applied between the inlet and the outlet of the reactor, can be used in the presence of polar solvents or when the device materials develop surface charges, as in glass or poly(dimethylsiloxane). Whereas in classical reactors mixing is induced by convection, that can give rise to inhomogeneity and concentration gradients often variable in function of vessel geometry or stirring conditions, in microreactors complete mixing is affected by diffusion alone and usually achieved in microseconds through T- or Y-shaped geometries joining the channels.

The number of catalytic organic reactions performed in microreactors is continuously growing [49–51] and increased reaction rates, yields and selectivities compared to those obtained in conventional reactors have been reported in most cases. However, the extension of such technology to enantioselective processes is still limited to few examples [52, 53].

Aldol condensation of aldehydes and acetone promoted by tetrazole **9** in a microreactor was reported in 2009 as the first application in organocatalysis field and, in comparison with the batch procedure, higher working temperature and lower catalyst loading were tolerated without enantioselectivity deterioration. Good results were achieved in 10–30 min at 60°C using a 1.0 ml or 250 μl glass chip reactor (Scheme 4.5a) and in the reaction of *p*-nitrobenzaldehyde with cyclohexanone the *ee* for *anti*-adduct was higher than that obtained using a batch process (81 *vs* 59% *ee*). The same conditions were also effective in the Mannich reaction of cyclohexanone with iminoglyoxylate [54] (Scheme 4.5b) and it was demonstrated that larger channel size (reactor volume 4.0 ml) resulted in slightly lower productivity.



Scheme 4.6 Synthesis of BMS-275691 in continuous-flow mode

It also need to be shortly mentioned that continuous-flow devices are ideally suited to perform multistep synthesis in which a given substrate can build up chemical complexity by flowing through serial assemblies of microreactors or columns. Indeed, after the substrate has been subjected to the first reaction of a synthetic sequence in a continuous-flow reactor, the outlet stream can be directed into a second reactor where another reaction step occurs and so on until the final product is collected at the end of the last reactor. The methodology, complementary to classical solid-phase synthesis, could gain benefits from avoidance of extensive workup protocols, fast optimization and control of the reaction conditions, and dramatic reduction of both time and manual handling.

As a representative example of this approach, the five step synthesis of metalloproteinase inhibitor BMS-275291 has been achieved in about 15 h, against several days required with conventional lab equipment, through a key step of asymmetric α-chlorination promoted by quinine loaded on Wang resin followed by amidation with a peptide and sulfidation reactions [55] (Scheme 4.6).

4.4 New Chemical Processes

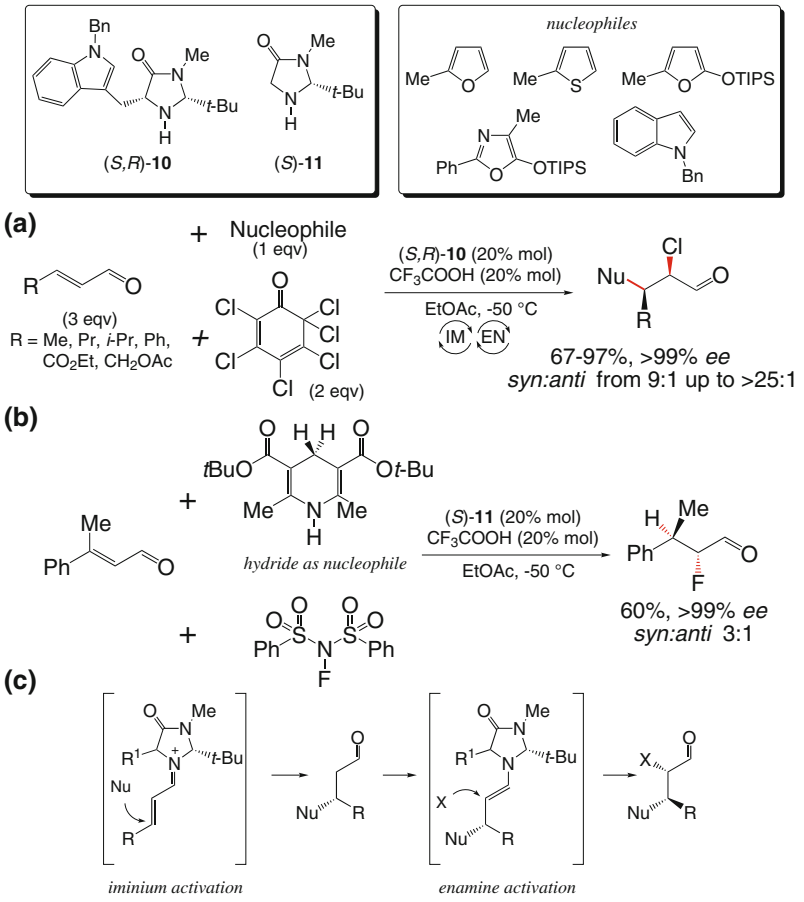
With the huge variety of reactions today available the real question for chemists is not what they can synthesize, but how they can do it fulfilling green chemistry guidelines. Great emphasis is given to the design of novel processes aimed at waste prevention (1st principle), little toxicity of reagents and products for human

health and environment (third, fourth and tenth principles), reduced energy requirements (sixth principle) and risks of chemical accidents as releases, explosions and fires (twelveth principle). Besides the intensive research of more environmentally benign and recyclable solvent and catalysts, the development of safer reagents is strongly demanded and in this context novel biomimetic oxidant systems based on molecular oxygen or hydrogen peroxide could provide high atom economy and negligible toxicity since water is the only by-product [56–58]. Advances in osmium-free hydroxylations [59] are also greatly expected whereas transfer hydrogenation has yet became a well-established alternative to the reaction with gaseous hydrogen for the conversion of ketones to alcohols at ambient pressure.

The design of new chemical processes addressed to achieve high atom economy, avoidance of derivatization steps and purification of intermediates as well as substantial decreases in time, labor and waste generation can be viewed as the ultimate goal of green chemistry. Therefore, great interest is reserved to *multicomponent reactions* (MCRs) [60, 61], defined as reactions in which more than two compounds react to form a product in such a way that the product retains the majority of atoms of starting material through the formation of many covalent bonds. In this context, the term *cascade* (or *domino*) *reactions* has been specifically introduced to underline that multiple formation of C–C bonds occurs under the same reaction conditions, without additional reagents or catalysts, through sequential and inseparable transformations of reactive intermediates whose chemical functionalities have been formed in the previous step [62]. Further classification according the mechanism involved in the formation of intermediates has been proposed [62] and one-pot combinations of reactions that could be executed independently (*tandem reactions*) have been also reported [63].

As very exciting and at the same time challenging research field, MCRs have attracted interest of organic chemists for long time and fundamental examples as Strecker, Mannich, Biginelli, Passerini and Ugi reactions were dated between the end of nineteenth and the half of twentieth century. Since then several cascade processes have been developed and applied for synthesis of complex molecules and natural products [64–66]. Final product stereochemistry has been in many cases diastereoselectively controlled using one of the substrates in enantiopure form, but multicomponent catalytic asymmetric transformations of achiral precursors have been successfully developed [67] and some examples of enantioselective Strecker, Mannich or Passerini reactions have been yet discussed in the previous sections.

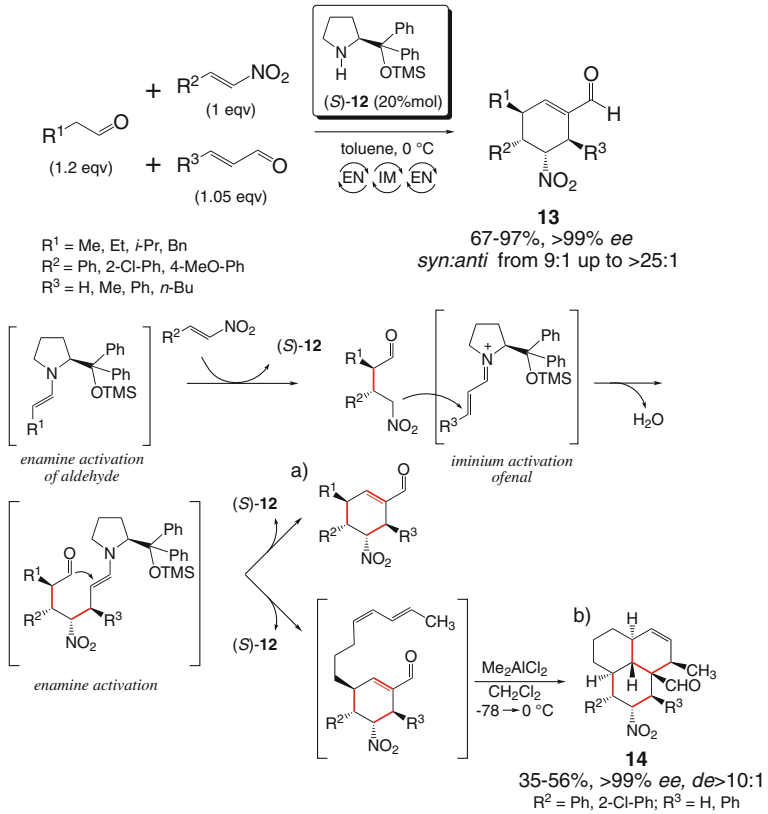
One-pot sequences of enantioselective reactions, directed at construction of multiple stereogenic centres, can be performed using a single catalyst able to promote different asymmetric transformation or a multicatalytic system, following an approach resembling biological cascades in which several enzymes in the cell convert simple precursors in complex molecules through a serie of coupled reactions. As concern the first strategy, secondary amine organocatalysts play a central role since they are able to promote either functionalization of aldehydes and ketone with electrophiles (through enamine intermediate) either addition



Scheme 4.7 Iminium-enamine cascade sequences (**a**–**b**) and proposed mechanism (**c**)

of nucleophiles to α, β-unsaturated compounds (through imininium intermediate) and different combinations of these activation modes have provided effective cascade processes [68].

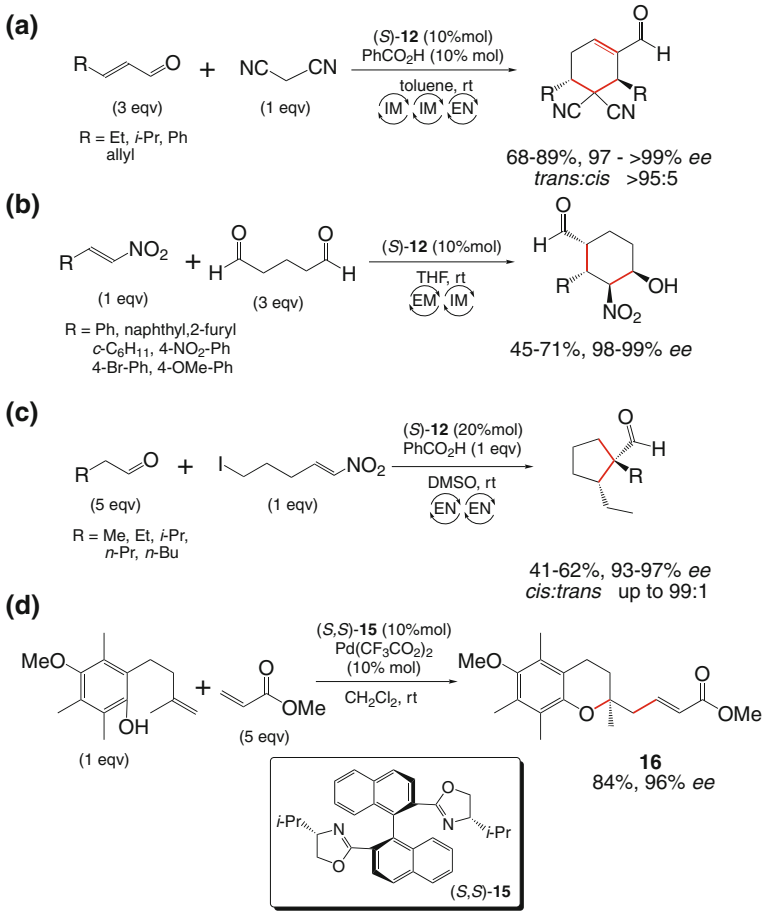
Using imidazolinone catalysts **10** or **11**, MacMillan's group developed a cascade sequence for consecutive addition of a variety of nucleophiles and chlorine (or fluorine) on double bond of enals with simultaneous and stereocontrolled generation of two chiral carbons [69] (Scheme 4.7a–b). According the proposed mechanism (Scheme 4.7c) for such *iminium-enamine sequence*, the substrate was firstly coordinated to catalyst giving an iminium specie that underwent nucleophilic attack leading to a saturated aldehyde whose enamine, formed in the second catalytic cycle, suffered α-halogenation. Final products were obtained in excellent yields and optical purities.



Scheme 4.8 Cascade sequences for synthesis of cyclohex-1-ene carbaldehydes (**a**) or tricyclic frameworks (**b**)

The Jørgenson catalyst **12** was active in triple Michael–Michael-aldol sequences leading to the synthesis of cyclohex-1-ene carbaldehydes **13** with up four new stereogenic centres from an aldheyde, an enal and nitrostyrenes through enamine-iminium-enamine catalytic cascade [70] (Scheme 4.8a). Remarkably, from 16 possible stereoisomers of **13** only two epimers differing for nitrogroup configuration were formed in a ratio ranging from 2:1 to 99:1 and an additional intramolecular Diels–Alder reaction occurred with aldehydes bearing suitable diene substituent, so allowing the synthesis of complex tricyclic derivatives **14** with new eight chiral carbons in a one-pot operation [71] (Scheme 4.8b).

The same prolinol catalyst **12** displayed high efficiency in the synthesis of other substituted cyclohexane derivatives and cyclopentane carbaldehydes bearing a stereogenic quaternary carbon through combination of Michael additions with aldol [72], nitroaldol [73] or *a*-alkylation [74] reactions in cascade fashion (Scheme 4.9a–c).

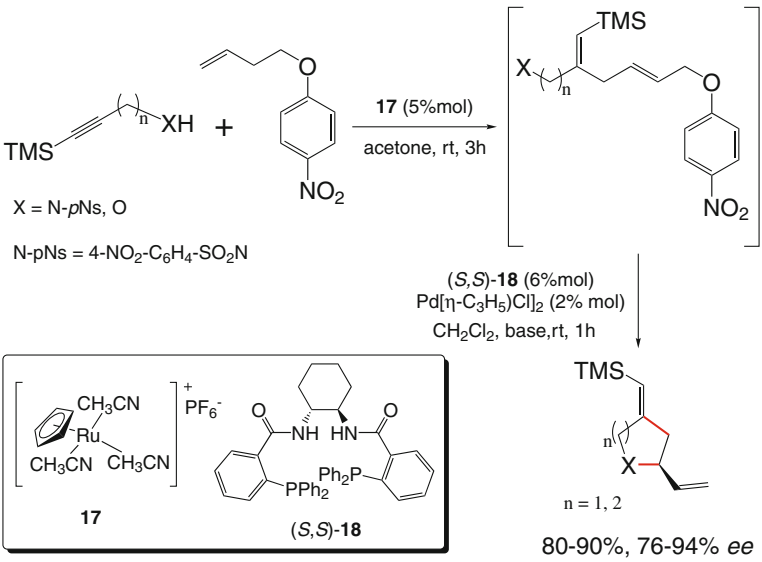


Scheme 4.9 Examples of prolinol (**a**–**c**) and transition-metal (**d**) promoted domino reactions

A more limited number of cascade processes have been promoted by Brönsted acid [75, 76] or transition-metal catalysts and synthesis of vitamin E intermediate **16** through enantioselective Wacker oxidation followed by Heck reaction, reported by Tietze and coworkers [77] is a representative example of efficient palladium-catalyzed domino reactions (Scheme 4.9d).

In a biomimetic approach, suitable combinations of transition-metal or organo-catalysts could provide not only a sensible expansion in the range of chemical reactions feasible in one-pot protocol, but also improved reactivity and selectivity due to cooperative effects. Furthermore, the use of two chiral catalysts could enable selective access to any product enantiomer or diastereoisomer from a given sequence through judicious combination of catalysts' stereochemistry.

However, the design of effective *multicatalyst reactions* [78] is a big challenge since each catalyst need to be compatible with the other one as well as with other

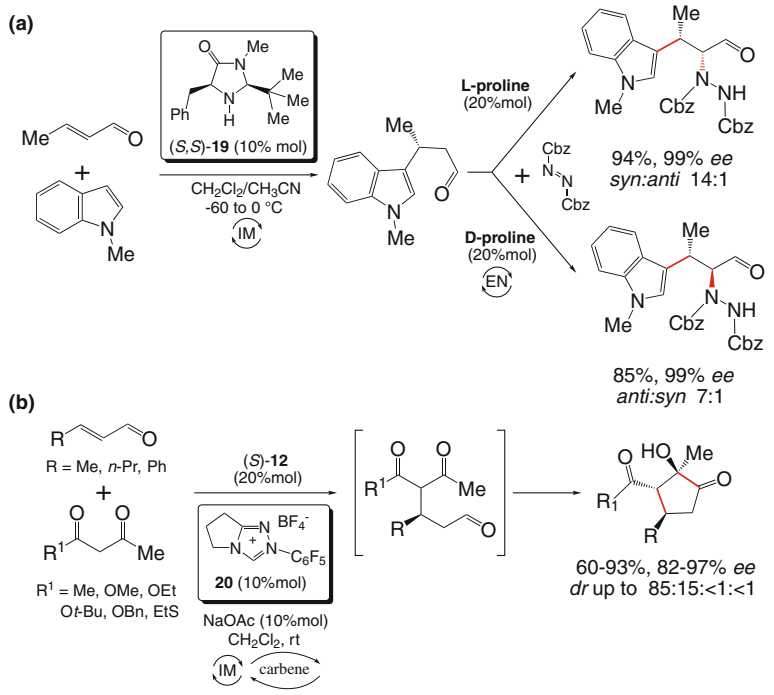


Scheme 4.10 Synthesis of *N*- and *O*-heterocycles through sequential Ru-Pd catalysis

reaction components (substrates, reagents, intermediates generated in situ) and every step in the sequence should proceed with high selectivity in order to avoid side reactions and formation of mixtures of isomers, difficult to purify.

Multiple metal complexes are often unsuitable due to scrambling of ligands in their coordination with metals leading to unpredictable structure of the active catalysts, but good results have been achieved in some instances by sequential addition of catalysts and substrates, in a process better described as a tandem rather than cascade reaction [79–81]. As a selected example, the synthesis of several functionalized *N*- and *O*-heterocycles was achieved through combined action of $[RuCp(CH_3CN)_3]PF_6$ **17** and Pd-complex with ligand **18**, providing that Pd-catalyst was added after completion of the Ru-promoted reaction. In such process the first step involved a Ru-promoted alkene/alkyne cross-coupling to give reactive allyl intermediates that were trapped by palladium and stereoselectively heterocyclised with simultaneous removal of *p*-nitrophenylether group initially present on olefin substrates. Large structural variety of alkynes was tolerated and further elaboration of the obtained enantio- and diastereo- pure heterocycles led to useful building blocks or natural compounds, as it was demonstrated with synthesis of 4-oxyproline derivatives, rose oil oxides or ring B of bryostatin [82] (Scheme 4.10).

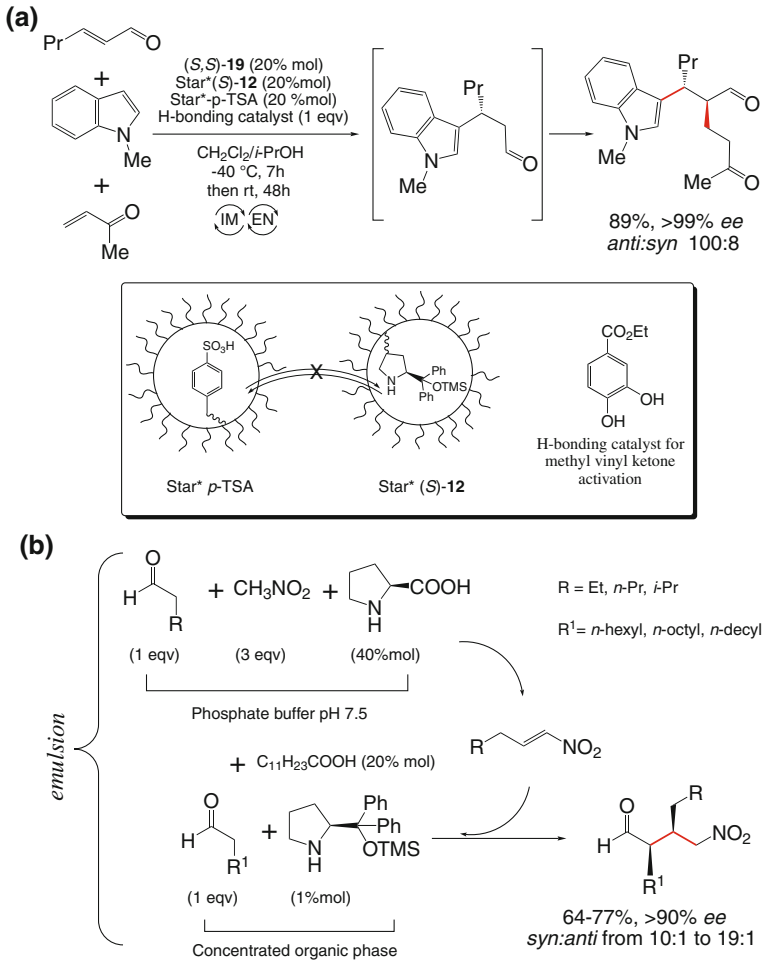
MacMillans' group has recently developed a general strategy for organocascade reactions based on the coupling of imidazolidinones as specific iminium catalysts and proline as selective bifunctional enamine catalyst in the same vessel or sequentially added to reaction mixture. Exploiting the orthogonal reactivity profiles of these organocatalysts a variety of olefin hydro-, alkyl- or aryl-aminations



Scheme 4.11 Examples of reactions with organocatalyst–organocatalyst combinations

have been carried out in excellent yield and selectivity and reversal of diastereoselectivity was easily achieved changing L-proline with D-proline [83] (Scheme 4.11a). Coupling of Jørgenson catalyst **12** with achiral carbene **20** gave access to highly functionalized cyclopentanones from enals and acetylacetone or *β*-ketoesters with 3 contiguous stereocentres and a quaternary carbon through Michael addition/benzoin condensation sequence [84] (Scheme 4.11b). Compared with the two step protocol, the multicatalytic cascade gave increased yields and stereoselectivities, attributed to the suppression of prolinol-mediated retro Michael reaction of intermediate aldehydes that were shuttled to products by the simultaneous presence of carbene.

In order to avoid possible catalyst–catalyst or catalyst-reagent interferences, site-isolation techniques proved useful and microencapsulation or physical separation in distinct liquid phases of one or more reaction components have been explored. So, nucleophilic addition of *N*-methyl indole to 2-hexenal promoted by imidazolidinone **19** in the presence of *p*-toluensulphonic (*p*TSA) acid became compatible with subsequent enamine-catalyzed step by encapsulating the acid and prolinol **12**, as the second catalyst, in star-branched polymers. In this way, small reagents and **19** freely diffused to the core of polymers whereas the activity of **12**, that was not able to penetrate into *p*TSA core, was preserved from the detrimental



Scheme 4.12 Site-isolation techniques in multicatalyst reactions

effect of sulphonic acid [85] (Scheme 4.12a). In a very interesting and recent report of Fréchet et al. [86] two aldehydes with the same chemical reactivity underwent distinct reactions by polarity-driven confinement into two different liquid phases, that enabled the selective formation of cross-cascade products instead of a statistically mixture of four possible products. Indeed, carrying out the process in aqueous phosphate buffer, L-proline, nitromethane and a hydrophilic aldehyde were preferentially dissolved in water phase whereas more hydrophobic prolinol **12** and long-chain aliphatic aldehydes formed a concentrated organic phase. After addition of nitromethane to the first aldehyde had occurred in water, the hydrophobic nitroalkene intermediate diffused into the organic phase wherein reacted with the second aldehyde to give the expected cross-product in excellent enantio- and diastereomeric purity (Scheme 4.12b).

The multicatalyst strategy in multicomponent tandem or cascade reactions is still in its infancy and enormous potentiality could be expected from coupling of organocatalysts and transition metal complexes, up to now mainly limited to counterion/gold (or palladium) catalysis yet discussed in the text, as an exciting research field in which these two complementary branches of asymmetric catalysis could merge opening the way to new concepts and synthetic tools.

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Chapter 5
Conclusive Remarks

In last decade asymmetric catalysis has firmly established its key role in the synthesis of optically active compounds and intensive research has been aimed to make it even more adherent to "green chemistry" as a new approach that involves all aspects of productive chemical processes.

In addition to classical criterions that define the goodness of chemical synthesis, asymmetric transformations have a fundamental parameter in enantioselectivity so that the structural optimization of catalyst directed to the enhancement of chiral induction is still an active research field. In transition-metal catalysis intensive mechanistic studies and sophisticated level of structural tuning have led to very efficient systems with performances resembling those of enzymes and suitable for industrial scale-up. Notwithstanding their growing popularity organocatalysts need to be more deeply investigated since they that are usually active in too high loading for large scale preparation, but impressive advances in the field could be expected.

For that concerns other factors contributing to overall synthetic efficiency, it is evident that the "ideal" solvent has not been yet found and non-conventional reaction media are not free of drawbacks, but it is no more time to overlook the heavy impact of organic solvents, most of which derive from oil industry, on human and environmental health. In a general view of resource saving, effective protocols for catalyst recycle and continuous flow processes can provide valuable waste minimization, simplification of manual handling and optimization of purification protocol. In this context, the discovery of novel reactivity based on less toxic reagents and cascade processes appears as a way to solve many problems simultaneously and is probably the most exciting challenge for chemists.

Since increased "greenness" in a given process results from a subtle balance of many concomitant factors, the optimal "sustainability" is probably still far to be reached. However, chemists have acquired consciousness of the importance of such parameter in developing new synthetic processes and they surely will contribute to success of green chemistry with the same creativity that has yet led to impressive advances in organic synthesis.

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The introduction of novel concepts is greatly expected and it is also advisable that chemistry, often associated to something toxic for human and environmental health, could become more appreciated for its valuable products and potentiality in improving social progress and life quality.