ANGEWANDTE CHEMIE

The picture shows the delicate white blooms of the giant Saguaro, a cactus found in the deserts of Arizona. The flowers first appear only when the plant is about 50 years old. An attractive parallel can be seen between this slowly maturing beauty and the development of asymmetric organocatalysis, the origin of which goes back to the emergence of the efficient homogeneous asymmetric catalysis.

Enantioselective Organocatalysis

Peter I. Dalko* and Lionel Moisan

Dedicated to Prof. Henry B. Kagan on the occasion of his 70th birthday

The last few years have witnessed a spectacular advancement in new catalytic methods based on metal-free organic molecules. In many cases, these small compounds give rise to extremely high enantioselectivities. Preparative advantages are notable: usually the reactions can be performed under an aerobic atmosphere with wet solvents. The catalysts are inexpensive and they are often more stable than enzymes or other bioorganic catalysts. Also, these small organic molecules can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry. Herein we focus on four different domains in which organocatalysis has made major advances: 1) The activation of the reaction based on the nucleophilic/electrophilic properties of the catalysts. This type of catalysis has much in common with conventional Lewis acid/base activation by metal complexes. 2) Transformations in which the organic catalyst forms a reactive intermediate: the chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle. 3) Phase-transfer reactions: The chiral catalyst forms a host–guest complex with the substrate and shuttles between the standard organic solvent and the second phase (i.e. a solid, aqueous, or fluorous phase in which the organic transformation takes place). 4) Molecular-cavity-accelerated asymmetric transformations: the catalyst can select between competing substrates, depending on size and structure criteria. The rate acceleration of a given reaction is similar to the Lewis acid/base activation and is the consequence of the simultaneous action of different polar functions. Herein it is shown that organocatalysis complements rather than competes with current methods. It offers something conceptually novel and opens new horizons in synthesis.

Keywords: asymmetric catalysis · chiral auxiliaries · synthetic methods

1. Introduction

Since the importance of the spatial arrangement within molecules to the fundamental properties of the substances was recognized, chemists have become increasingly interested in enantioselective synthesis. In the course of time, the field of enantioselective synthesis has outgrown the academic environment. The chiral drug industry has become a rapidly growing segment of the drug market and represents close to one third of all drug sales worldwide.[1] This has been driven by the increased regulatory control of enantiomeric composition of drug candidates, and the potential of isomerically pure drugs to provide improvements over the previously available racemates.

Undoubtedly, the more elegant and economically most attractive way to introduce chirality into a molecule is by using a catalytic amount of chiral controller to induce the chiral transformation. Enantiocatalytic reactions have had the most significant impact on the development of synthetic organic chemistry in the last 30 years. Among them, methods based exclusively on metal-free chiral organic catalysts have become more significant. Helped by intuition, persistence, and good fortune, these new reactions are becoming powerful tools in the construction of complex molecular skeletons.

Chiral organic molecules have been used from the early days of chemistry to promote reactions. The emergence of homogeneous enantioselective organometallic catalysis has had a decisive effect on the development of enantioselective organocatalytic reactions. With the advent of the first powerful ligands (4,5-bis[(diphenylphosphanyl)methyl]-2,2-dimethyl-1,3-dioxolane-4,5-diol, DIOP), rhodium complexes served as the basis for the development of enantioselective catalytic hydrogenation reactions (reduction of α-acylamino acrylic

---

[*] Dr. P. I. Dalko, L. Moisan
Laboratoire de Recherches Organiques associé au CNRS, ESCPI
10 rue Vauquelin, 75231 Paris Cedex 05 (France)
Fax: (+33) 1-40-79-46-60
E-mail: peter.dalko@espci.fr

1433-7851/01/4020-3727 $ 17.50+.50/0

acids, L-DOPA synthesis at Monsanto)[2b] and thus became the general precursors of enantioselective catalytic reactions. Thus the concept of asymmetric catalysis has become almost synonymous with the use of metals in a chiral environment.[3] But are metals really indispensable in these catalytic processes? Or can some of their functions be emulated by an organic system? In contrast to most synthetic methods, nature provides a subtle balance between metal-free and metal-mediated conditions. Metals certainly have considerable advantages over organic substances, for example, molecular and structural diversity and a large array of reactivity patterns that can easily be tuned by varying ligands. As well as the tremendous benefits that metal derivatives offer they are also the source of increasing problems such as high price, toxicity, pollution, waste treatment, and product contamination.[4] A large number of asymmetric transformations are based exclusively on organic reagents: there is an increasing tendency to devise reaction conditions that allow the regeneration of the chiral reagents. This concept will certainly help the development of a number of new organocatalytic reactions in the near future. On the other hand, roles that are typically associated with metals, for example, as Lewis acids/bases and as redox agents[5] can be emulated fairly well by organic compounds.

The last few years have witnessed a spectacular advancement in new catalytic methods based on organic molecules. In many cases, these small compounds result in extremely high enantioselectivities. Preparative advantages are notable: usually the reactions can be performed under an aerobic atmosphere with wet solvents. The catalysts are inexpensive and they are often more stable than enzymes or other bioorganic catalysts. Also, these small organic molecules can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues, and show promising adaptability to high-throughput screening and process chemistry.

There is a dichotomy between organic and organometallic/bioorganic catalysis, particularly with respect to their reactivity and applications. On one hand, organocatalytic reactions have evolved essentially from the ligand chemistry of organometallic reactions. A large array of ligands were developed for metal-mediated enantioselective catalytic reactions and are still among the most effective organocatalysts. It is thus not surprising that there are metal-catalyzed reactions in which the metal-free ligand is known to be active by itself, even in the same enantioselective transformations.[6] On the other hand, organocatalytic reactions can be more closely related to enzyme- or antibody-catalyzed reactions than to organometallic processes. Indeed, these small organic molecules, which are often also known as artificial enzymes[7] or enzyme mimetics, show some characteristic features of bioorganic reactions. They often follow saturation or Michaelis–Menten kinetics reminiscent of a mechanism that involves the reversible formation of an enzyme–substrate complex. However, this apparent similarity hides major differences, especially in the mode of action. Enzymes act essentially by stabilizing the transition state of the reaction by the subtle orchestration of a number of functions, whereas organic molecules promote the reactions as simple reagents. Enzymes are more than just highly evolved catalysts[8]—catalytic efficiency, selectivity, and high turnover are only part of the peculiar characteristics of the sophisticated system, which involves built-in feedback mechanisms and subtle intra- and intermolecular cooperation. Herein we show that organocatalysis complements rather than competes with current methods.[9] It offers something conceptually novel and opens new horizons in synthesis.

Organic molecules can catalyze chemical reactions through four different mechanisms:

- Activation of the reaction based on the nucleophilic/electrophilic properties of the catalysts. The chiral catalyst is not consumed in the reaction and does not require parallel regeneration. This type of activation is reminiscent of conventional Lewis acid/base activation.
- Organic molecules that form reactive intermediates. The chiral catalyst is consumed in the reaction and requires regeneration in a parallel catalytic cycle.
- Phase-transfer reactions. The chiral catalyst forms a host–guest complex with the substrate and shuttles between the standard organic solvent and a second phase (i.e. the solid,

Peter I. Dalko was born in 1960 in Budapest (Hungary). He studied chemistry at the Budapest Institute of Technology (Hungary) and he obtained his doctorate with Dr. S. D. Géro at Gif-sur-Yvette (France). After postdoctoral training with Sir Derek H. Barton at Texas A&M and then with Prof. Yoshito Kishi at Harvard, he joined the research group of Prof. Janine Cossy at the ESPCI in Paris. He is currently working on the development of new enantioselective reactions.

Lionel Moisan was born in Annemasse (France) in 1975. He studied chemistry at the Ecole Supérieure de Physique et de Chimie Industrielles, Paris and obtained his Diplôme d'Etudes Approfondies in organic and bioorganic chemistry at the Pierre et Marie Curie University, Paris. He his currently working at the Commissariat à l'Energie Atomique as a scientific fellow.

P. I. Dalko

L. Moisan

aqueous or fluorous phase in which the reaction takes place).
- Molecular-cavity-accelerated asymmetric transformations, in which the catalyst may select between the competing substrates, depending on size and structure criteria. The rate acceleration of the given reaction is similar to the Lewis acid/base activation and is a consequence of the simultaneous action of different polar functions.

2. Principal Factors That Govern the Stereoselectivity of the Organocatalytic Reactions

In metal-mediated enantioselective catalytic reactions, the metal plays an organizational role by translating chiral information and activating the reagents. In the absence of the metal, the well-organized transition state, which is required for the enantioselective transformation, can be formed either by passive or dynamic interactions, as is the case in biological systems. Passive binding refers to ordinary molecular recognition through hydrophobic, van der Waals, and electrostatic interactions. Dynamic binding refers to interactions between catalysts and substrates at the reaction centers. Hydrogen bonding plays a crucial role in the determination of the stereoselectivity of the reaction. Although this represents an energy contribution of only 1–6 $\text{kcal}\,\text{mol}^{-1}$ to the interactions, hydrogen bonding influences the conformational preferences by forming rigid three-dimensional structures and contributes to the affinity and selectivity of molecular recognition. Hydrogen bonding also plays an important role in stabilizing the reactive intermediates and in modulating the reactivity,[10] in a very similar way to enzyme catalysis. More and more evidence is being gathered on the complexity of the enantioselective transformation caused by the formation of aggregates (dimers) between substrates and catalysts in the most enantioselective path. These new findings challenge our traditional view, which is based essentially on the consideration of monomers.

3. Enantioselective Catalytic Transformations Based on the Nucleophilic/Electrophilic Properties of the Catalyst

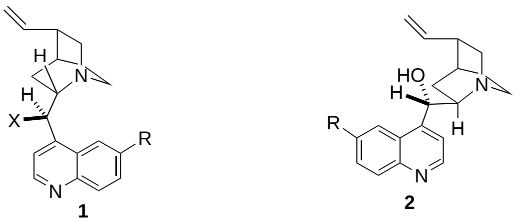
3.1. Principal Catalyst Classes

The Lewis acid/base function of organometallic reagents can be emulated by organic systems and applied to enantioselective catalytic processes. A particularity of organocatalysts is the facile equilibrium between the relatively electron-rich and electron-deficient states (i.e. the acidic and basic forms) of the same center. It is easy to conceive this equilibrium simply by considering protonation–deprotonation, which on one hand can activate the reagent and on other hand can contribute to the kinetic lability of the ligand. As a result of this equilibrium the same center can act as a Lewis acid or as a Lewis base, depending on the reaction conditions. Although in any given reaction one can have a clear idea of the role of the organic catalyst as an acid or a base, the classification based on the electron-donating or electron-accepting ability of the molecules can be ambiguous. This acid–base dichotomy is well known in biological systems. In ribonuclease A, one imidazole unit acts as a general base and the protonated form of the other imidazole unit acts as a general acid.[11] In the mechanism that is widely proposed for aspartic proteases such as pepsin, penicillopepsin, renin, and HIV protease, one carboxy group acts as a general acid and the ionized form of the other carboxy group acts as a general base or as a nucleophile.[12] Moreover, the acid/base classification of the catalysts is hampered by the fact that a number of organocatalysts, for example, amino acids, possess both acidic and basic functions and arguably mediate the reaction by a push–pull mechanism.

Most organic catalysts are well known to organic and organometallic chemists. These are either natural or synthetic chiral ligands that were developed for organometallic reactions.[13] Some natural products and catalysts derived from diversity-driven research by using, for example, combinatorial chemistry and biological screening, have been added to this pool of compounds. These techniques, which generate a large number of potential candidates and select those that perform best, is particularly useful for preparing peptide-based catalysts.

3.1.1. Catalysts Derived from Natural Products

Not many of the alkaloids that have been tested in organocatalytic reactions have been selected for further studies. Only a few possess a naturally occurring enantiomeric counterpart that would allow their convenient use in enantioselective synthesis. An exception is the readily available and inexpensive cinchona alkaloids, which have pseudoenantiomeric forms such as quinine **1a** and quinidine **2a** (Scheme 1). Both forms of this natural product and their derivatives produced impressive results in enantioselective catalytic reactions.



1

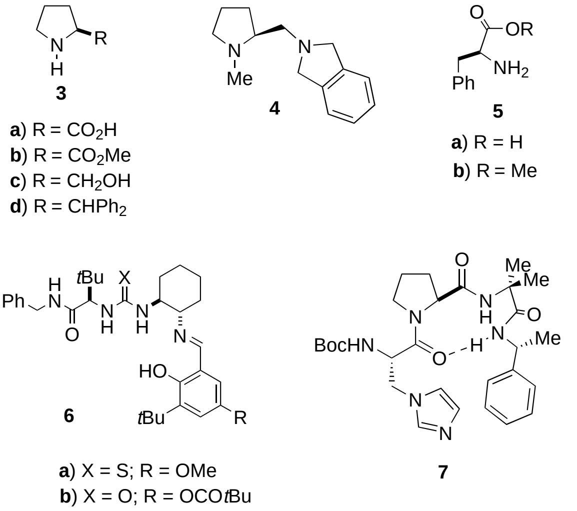
a) R = OMe, X = OH [(–)-quinine]
b) R = H, X = OH [(–)-cinchonidine]
c) R = OMe, X = OBz
d) R = OMe, X = NHBz

2

a) R = OMe [(+)-quinidine]
b) R = H [(+)-cinchonine]

Scheme 1. Cinchona alkaloids and some cinchona-derived chiral catalysts. Bz = benzoyl.

Although amino acids such as proline (**3a**) and phenylalanine (**5a**) and derivatives have been used for a long time in enantioselective catalytic reactions, the use of peptide-like enzyme mimics such as **6** or **7** is a recent development (Scheme 2). The “oligopeptide approach” has some advan-

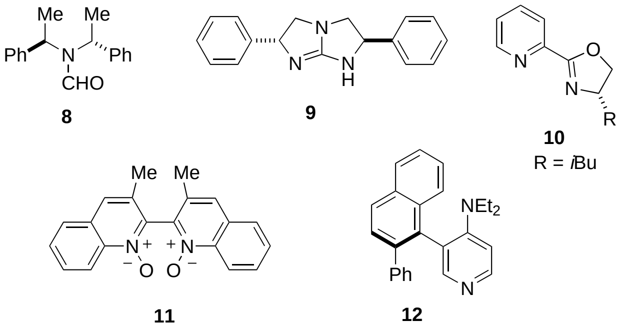


Scheme 2. Some catalysts derived from amino acids and peptides. Boc = *tert*-butoxycarbonyl.

tages. Firstly, the efficiency of the catalyst can be improved by varying the nature of the amino acids by using combinatorial synthetic methods. Secondly, the structural simplicity of the oligopeptides contrasts with the complexity of the enzymes and thus renders the mechanistic investigations easier. Thirdly, the flexibility of the method is of great use: it is easy to prepare the peptide sequence that can produce the opposite enantiomer or its epimer; this is not often possible with enzymes.

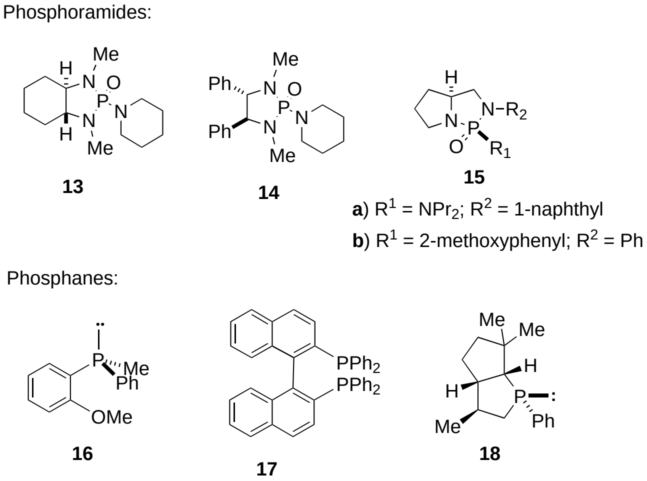
3.1.2. Synthetic Molecules

The main advantages of synthetic over natural molecules are that both enantiomers are readily available, and that the structure can be easily modified. Many synthetic molecules are known to be efficient organic catalysts: most originate from ligand chemistry. Among them, C_2-symmetrical molecules such as **8** and **9** (Scheme 3) attracted much interest.



Scheme 3. Some N-containing catalysts.

Symmetry, however, is not a structural requirement for a good catalyst (**10**). Also, atropisomerism (e.g. **11** and **12**) remains an efficient means of inducing chirality. Although there is no naturally occurring source of phosphorus-containing chiral compounds for enantioselective catalytic use, there is understandably intense synthetic activity to complete the gap.[14] Besides the potential complexation ability of the phosphorus atom, a particular advantage of this type of compound is its ability to act both as a nucleophilic site as well as a stereogenic center. Scheme 4 illustrates some of the principal phosphorus-containing organic molecules that are used as Lewis bases in enantioselective catalytic transformations.

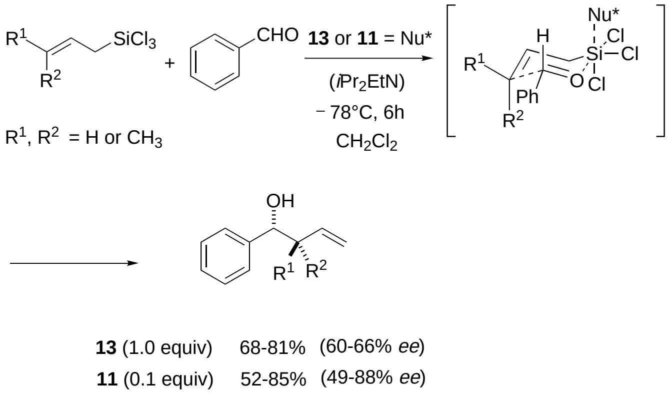


Scheme 4. Selected P-based catalysts used in enantioselective catalytic transformations.

3.2. Reactions and Applications

3.2.1. Allylation Reactions[15]

Chiral Lewis bases such as phosphoramides,[16, 17] formamide,[18] urea,[19] oxazolidine,[20] and amine *N*-oxide,[21] have been used in the enantioselective allylation of aldehydes. The work relies on the observation that hexamethyl phosphoramide (HMPA) considerably accelerates the addition of "activated" allylsilanes to aldehydes. The activation involves a decrease in the electron density at the silicon atom by using halogen substituents, which in turn increases the electrophilicity of this center. Trichlorosilanes were selected to facilitate the coordination of the Lewis base and to increase the coordination ability of the silicon center to the carbonyl group of the substrate. The asymmetric activation relies on the formation of a tightly bound chiral complex between the HMPA analogues and the silicon compounds. According to the postulated mechanism, the allyl transfer occurs via a well-defined six-membered transition state (TS). In the postulated TS, the octahedral hexacoordinated silicon center effects a rate acceleration and provides a chiral environment.[22] *Anti* and *syn* addition products can be prepared by using *E* or *Z* allyl silanes, respectively. This selectivity is undoubtedly an advantage over the metal-mediated Lewis acid activation in allylation, which provides the optically active *syn* homoallylic alcohols from either stereoisomer of crotyltrialkylsilanes and -stannanes.[23] The reaction gives good results with aromatic aldehydes, but most reactions with aliphatic analogues fail. When monodentate phosphoramide catalysts are used, the enantioselectivity of the allylation/crotylation reaction is sensitive to the amount of catalyst. For example, in the transformation depicted in Scheme 5, a large amount (1 equivalent) of catalyst **13** resulted in *ee* values of up to 66 %, but a decrease in the catalyst to 10 % afforded product with 53 % *ee*. This is the consequence of two parallel competing reaction paths: the less selective route involves the complex with a single bound base, and the more selective route involves the complex with two bound chiral bases.[24] The observed nonlinear effect and higher-order dependence on the concentration of phosphoramide accommodates the bis-ligated mechanistic picture well.[24] Tethered bis-phosphoramides result in better *ee* values and allow the concentration of the catalyst to be decreased to 5–10 % without a significant loss of selectivity. The reaction can be accelerated by the addition of diisopropylethylamine. The best enantioselectivity to date (*ee* up to 92 % with 10 % catalyst) was obtained in the simple alkylation reaction with bisquinoline *N*,*N'*-dioxide **11**.

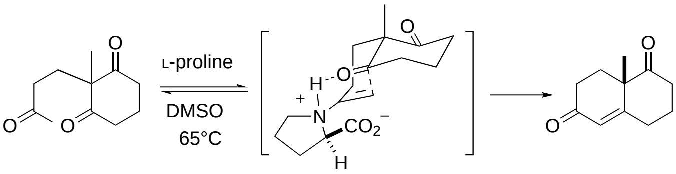


Scheme 5. Enantioselective catalytic allylation of benzaldehyde.

3.2.2. Aldol Condensations[25]

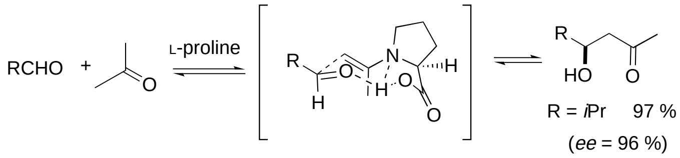
Aldol condensations under organocatalytic conditions have been the focus of extensive studies. Among them, chiral amine-catalyzed (Knoevenagel or Mannich) condensations and a novel, Lewis base mediated aldol reaction deserve particular interest. The enantioselective catalytic two-phase aldol reaction will be discussed in Section 5.2.3.

Since its discovery, the amino-acid catalyzed asymmetric Robinson annulation received a considerable amount of synthetic and mechanistic interest.[26] The reaction is mediated by a number of other natural and unnatural amino acids.[25a,b, 27] Amongst these, L-proline (**3a**) was shown to be the most general and L-phenylalanine (**5a**) the most efficient catalyst for the preparation of substituted enones.[28] In the original L-proline-catalyzed intramolecular version, the reaction is a desymmetrization reaction that discriminates between two enantiotopic carbonyl groups (Scheme 6). The reaction most probably proceeds via an enamine intermediate, at least in the proline-catalyzed version, in which a hydrogen bond between the protonated nitrogen atom of the proline moiety and a carbonyl group is a prerequisite for the asymmetric induction (Scheme 6). The length of the hydrogen bond is one of the criteria that allow selection between the diastereotopic carbonyl groups.



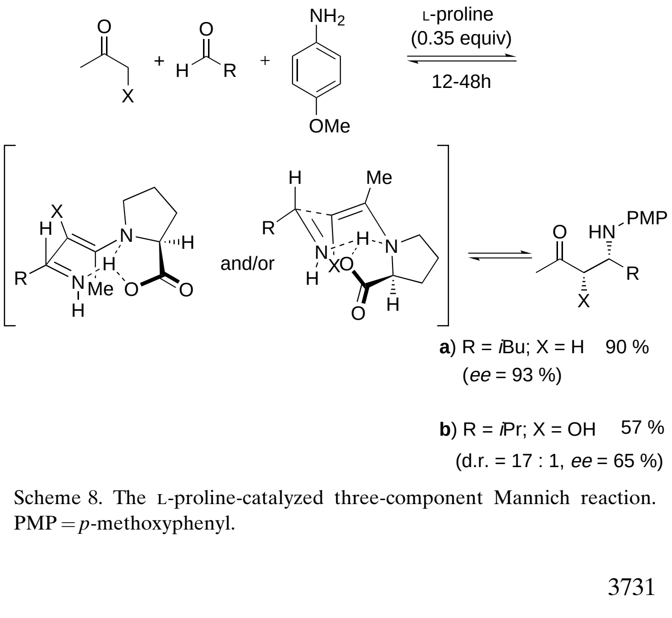
Scheme 6. The synthesis of the Wieland–Miescher ketone by using L-proline-mediated asymmetric Robinson annulation. DMSO = dimethyl sulfoxide.

Interestingly, it proved difficult to develop an intermolecular version of this aldol reaction. Only recently was the reaction of acetone and selected aldehydes reported, with *ee* values of up to 96 % (Scheme 7).[29] A limitation of the process arises, however, from the selfcondensation of the ketone and the aldehyde, which results in a low yield of the desired crosscondensation product. These side reactions can be minimized by using α-unsubstituted aldehydes.[30] It was pointed out that the catalyst functions as a micro-aldolase, reminiscent of natural class I aldolases. These enzymes work through an enamine-based mechanism and do not require a metal cofactor.



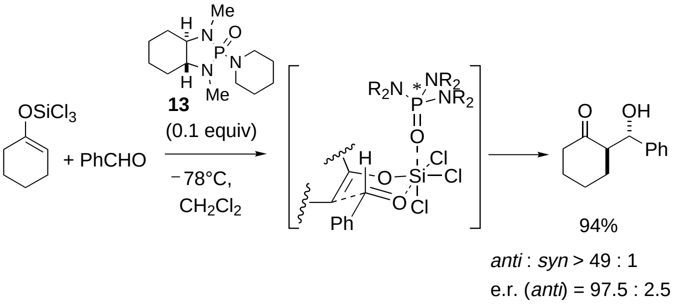
Scheme 7. The intermolecular asymmetric aldol reaction mediated by L-proline.

For a high selectivity in the enantioselective catalytic three-component (Mannich) coupling reaction, two conditions must be fulfilled: 1) the nucleophilic addition of the proline enamine (Scheme 8) must be faster to an imine than to an



Scheme 8. The L-proline-catalyzed three-component Mannich reaction. PMP = *p*-methoxyphenyl.

aldehyde; 2) the imine formation with a primary amine must be faster than the competitive aldol reaction.[31, 32] These conditions are not always true in practice and the side product of the reaction is the corresponding aldol product. Both α-substituted and α-unsubstituted aldehydes can be used and afford the corresponding β-amino ketones in good yields and enantiomeric excesses. However, the ketone component does not allow as much variation. Interestingly, despite the fact that both the previously discussed aldol reaction and the Mannich reaction proceed through an enamine mechanism, the opposite enantiofacial selectivity is observed in the reactions when L-proline or L-penicillamine derivatives[33] are used as catalysts.

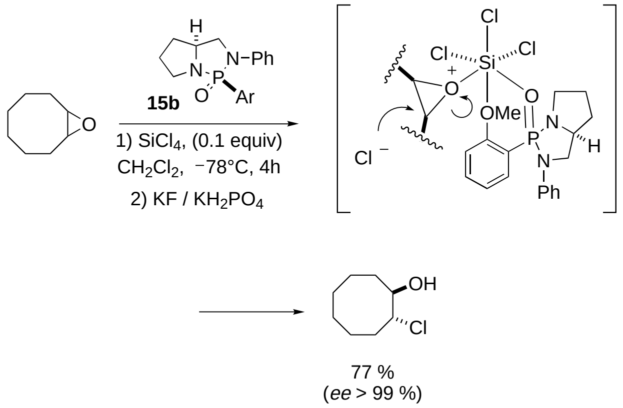


Scheme 9. Chiral-phosphoramide-mediated asymmetric aldol reaction.

The Lewis base activation of the reacting silyl enol ether is a conceptually novel approach in catalytic aldol reactions (Scheme 9).[34] The required trichlorosilyl enolates, which can be prepared in situ from the corresponding trimethylsilyl (TMS) ether by a mercury(II)-catalyzed transsilylation reaction, are reactive intermediates in the absence of any additives and react with aldehydes at ambient temperature or even below. This uncatalyzed reaction provides the aldol adducts in high yields, albeit with low diastereoselectivity. The aldol reactions are dramatically accelerated by the addition of a catalytic amount (10%) of HMPA or its asymmetric analogues, such as **13** or **14** (Scheme 4). The enantioselectivity of the process is sensitive to the enolate structure, with larger groups resulting in lower enantioselectivities. The structure of the aldehyde has a marked effect on the rate of the reaction: aliphatic and sterically hindered aldehydes are less reactive. Also, the reaction of the methyl ketone enolates that bear α substituents or the use of chiral aldehydes give rise preferentially to the *anti* product with predictable albeit lower enantioselectivity. As in the allylation reaction, the asymmetric activation relies on the formation of a tightly bound chiral complex between the HMPA analogues and the silicon compounds, which increases the rate of the reaction (Scheme 9). A careful analysis of the kinetic data supports a dual reaction path as was the case in the chiral phosphoramide mediated allylation reaction (Section 3.2.1). The complexity of the system makes it is difficult to draw transition structures that could explain the steric differentiation and thus the origin of the enantioselectivity is not currently well understood.

3.2.3. Nucleophilic Ring Opening of Epoxides[35]

Chiral organophosphorus Lewis bases such as **15a**, **b** are known to mediate the enantioselective ring opening of *meso*-epoxides.[36] Cyclic phosphonic amides such as **15b** with *ortho*-alkoxy substituents on the arylphosphane oxide moiety are superior catalysts in the desymmetrization of *meso*-epoxides than the compounds without alkoxy substituents (Scheme 10).[37] These compounds have been shown to mediate the asymmetric ring opening of *meso*-epoxides by $SiCl_4$ with 10% of catalyst loading with up to 99% *ee*. A decrease in the amount of catalyst from 10 to 5% considerably decreases the enantioselectivity. The catalyst and the substrate are organized around a hypervalent silicon intermediate in the putative mechanism, as is the case in the previously described aldol condensation. The required chloride anion is believed to be generated from the binding of the phosphoramide to the $SiCl_4$. The chlorohydrin is formed by the enantioselective ring opening of the activated oxirane ring by a chloride anion.

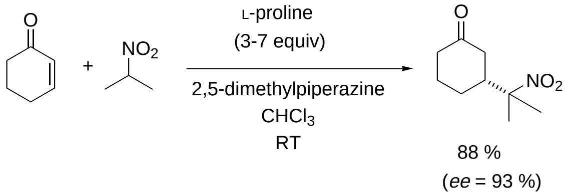


Scheme 10. Desymmetrization of *meso* epoxides by ring opening with a chiral phosphoramide catalyst.

3.2.4. Asymmetric Conjugate Additions to α,β-Unsaturated Carbonyl Compounds[38]

Cinchona alkaloids **1a**, **1b**, **2a**, and **2b** as well as L-proline (**3a**) were shown to mediate enantioselective alkylation reactions either under homogenous or biphasic (phase-transfer) conditions. The relatively low basicity of amines restricts the range of potential Michael donors and acceptors. Nitroalkanes were used, either with or without basic additives, in enantioselective catalytic reactions and under homogenous conditions.[39] Thiols,[40, 41] thioglycolic acids,[42] or azides[43] were used as heteroatom-containing nucleophiles.

Catalytic asymmetric additions of nitroalkanes to cyclic enones afford poor enantiomeric excesses when chiral metal complexes are used. These reactions can be mediated efficiently with L-proline in the presence of *trans*-2,5-dimethylpiperazine. Under these conditions, secondary nitroalkanes were added to cyclopentenone, cyclohexenone and cycloheptenone with 75–93% *ee* (Scheme 11).[44] Somewhat less selective results were observed when primary nitroalkanes were tested. The structure and the basicity of the



Scheme 11. Asymmetric L-proline-catalyzed conjugate addition of an α,β-unsaturated carbonyl compound.

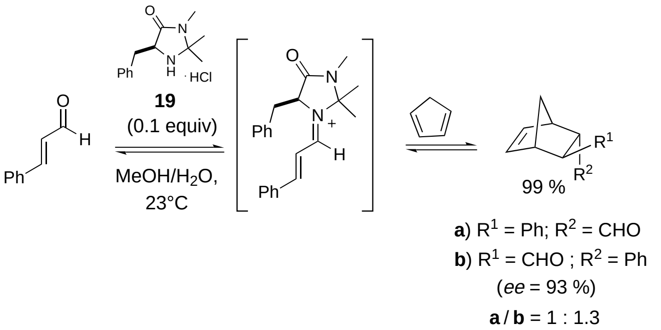
additive plays a major role in the stereodifferentiation step. An interesting nonlinear effect was observed when either the piperazine, quinine, or piperidine additives were used. Although no attempt was made to develop a mechanistic picture, the pronounced nonlinear effect indicates a complex multicomponent chiral catalytic system.

3.2.5. Cycloaddition Reactions

3.2.5.1 Diels–Alder Reactions[45]

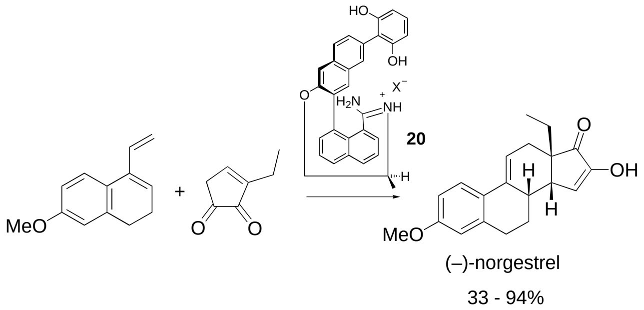
Organic systems, like metal-derived Lewis acids, can mediate Diels–Alder reactions by lowering the lowest-unoccupied molecular orbital (LUMO) of the dienophile. Chiral amines such as cinchona alkaloids, ephedrine, and prolinol derivatives have been known for more than a decade to catalyze [4+2] cycloadditions although with modest selectivities.[46, 47]

The reversible formation of iminium ions (Scheme 12), from α,β-unsaturated aldehydes and amines shows the characteristics of Lewis acid catalysis.[48] Naturally occurring amines (e.g. L-proline- and abrine (*N*-methyltryptophan) methyl ester) as well as synthetic linear and cyclic derivatives (e.g. **19**) were tested in this reaction and were shown to be efficient catalysts. Interestingly, the presence of water results in increased rates and enantioselectivities, which indicates that the iminium ion is hydrolyzed in the catalytic cycle.



Scheme 12. Asymmetric Diels–Alder reaction mediated by a cyclic L-phenylalanine derivative.

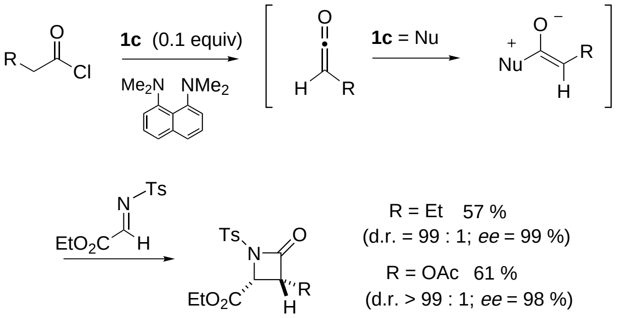
Chiral amidinium ions such as **20** may act as mild Lewis acids in the activation of α-diketones in Diels–Alder reactions.[49] Both the stoichiometric "host–guest" activation and the reaction with substoichiometric amounts of catalysts (as little as 0.1 equivalents) were tested in the construction of the (−)-norgestrel skeleton (Scheme 13). A considerable rate acceleration was observed in the presence of different substituted amidinium catalysts relative to the uncatalyzed reaction, although both the regio- and enantioselectivity remained low ($\leq 3.8{:}1$ and $\leq 2.5{:}1$, respectively).



Scheme 13. Enantioselective synthesis of (−)-norgestrel by means of an asymmetric Diels–Alder reaction mediated by a chiral immonium salt.

3.2.5.2. [2+2] Cycloaddition Reactions[50]

The cinchona alkaloid catalyzed asymmetric [2+2] cycloaddition reaction between ketenes and aldehydes has been known for almost two decades.[51] The product of this transformation is the corresponding β-lactone. Recently it was shown that the reaction can also be extended to the enantioselective preparation of β-lactams by using cinchona alkaloid derivatives (Scheme 14).[52] The reaction requires high dilution to obtain a high degree of asymmetric induction. The benzoylquinine catalyst **1c** plays two distinct catalytic roles and acts as a dehydrohalogenation agent and as a nucleophilic catalyst. The reaction is driven by a strong non-nucleophilic organic base "proton sponge" that regenerates the catalyst, thus forming a salt that precipitates from the toluene solution (Scheme 14).

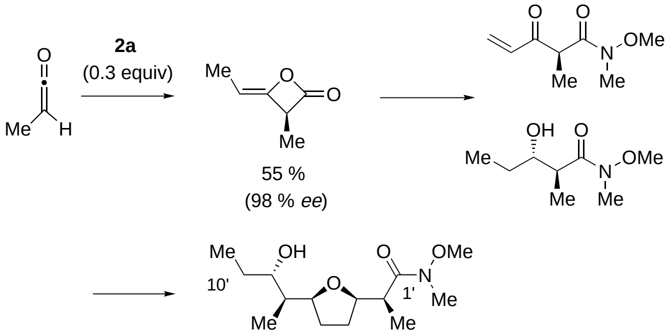


Scheme 14. Enantioselective catalytic cycloaddition of imines to ketenes catalyzed by cinchona derivatives. Ts = *p*-toluenesulfonyl.

Cinchona derivatives also mediate the enantioselective dimerization of ketenes (Scheme 15).[53] This reaction was used to prepare the $C_{1'}-C_{10'}$ segment of the macrocyclic antibiotic pamamycin 621A.[54]

3.2.5.3. [3+2] Cycloaddition Reactions

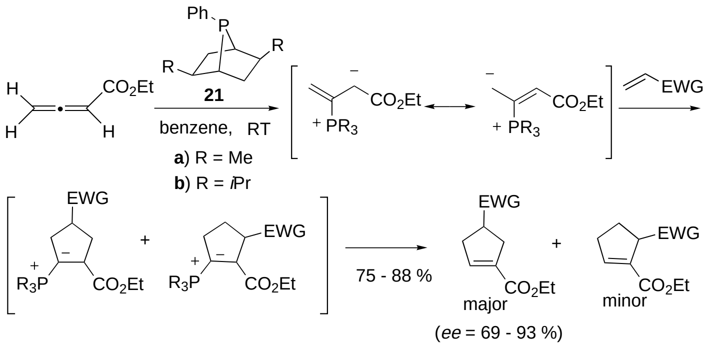
α,β-Unsaturated aldehydes are usually poor substrates for metal-catalyzed nitrone cycloadditions owing to the prefer-



Scheme 15. Synthesis of the $C_{1'}-C_{10'}$ fragment of the pamamycin 621A by using quinidine-mediated enantioselective catalytic dimerization of methyl ketenes.

ential coordination of Lewis acids to nitrone oxides. This reaction is amenable by using chiral amines such as **19**.[55]

Activated alkenes undergo a formal asymmetric [3+2] cycloaddition in the presence of allenic esters and a catalytic amount of chiral phosphane catalyst **21**.[56] The proposed mechanism of this transformation is depicted in Scheme 16.

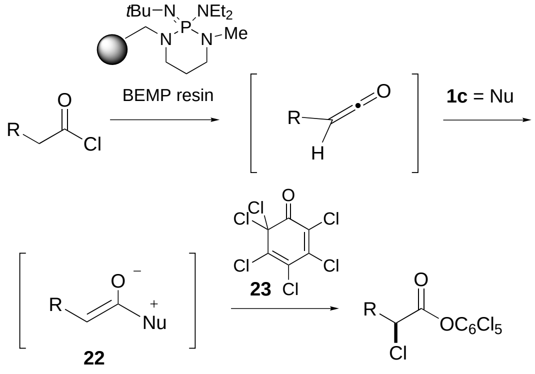


Scheme 16. The phosphane-catalyzed [3+2] cycloaddition reaction. EWG = electron-withdrawing group.

Although a mixture of both regioisomers were generally obtained, a pronounced selectivity in favor of the β-substituted cyclopentene derivative was observed.

3.2.6. α-Halogenation of Carbonyl Compounds

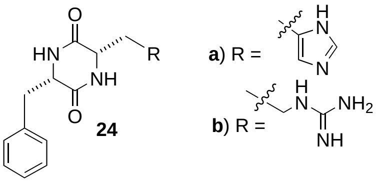
Ketenes derived from acyl halides may undergo asymmetric α-halogenation/esterification in the presence of halogenating agents such as **23** and cinchona alkaloids.[57] The reaction is based on the reversible addition of the chiral amine to the ketene to form the zwitterionic enolate **22**. An electrophilic halogenating reagent then reacts at the α-position of the enolate to afford an acylammonium salt, which is then transacylated to regenerate the chiral nucleophile and to give rise to an α-halo ester in yields of 50 to 81 % and with 80 to 99 % *ee* (Scheme 17). Interestingly, cinchona alkaloids such as **1c** are significantly more catalytically active than typical tertiary amines. The best yields were obtained when the ketene was preformed by using a solid-phase-supported base such as triaminophosphonamide imine on 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorin (BEMP) resin.



Scheme 17. Asymmetric α-halogenation of ketenes derived from carboxylic acids.

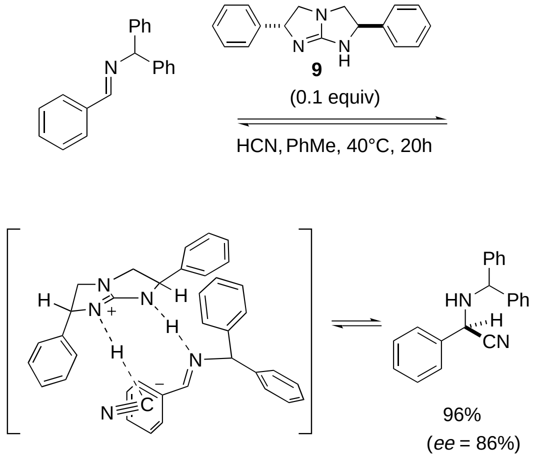
3.2.7. Hydrocyanation Reactions[58]

The hydrocyanation reaction of carbonyl compounds by using optically active alkaloids as catalysts was among the first organocatalytic reactions to be discovered.[59] The low enantioselectivity of the early systems were considerably improved. Synthetically useful asymmetric inductions have been obtained by using cyclic dipeptides such as **24a** (Scheme 18).[60, 64] It was postulated at this time that linear peptides are unsuitable for asymmetric catalysis because of their flexible structure and variable conformation. The mechanism of this reaction, however, remains confusing because of the complex experimental conditions required to obtain good asymmetric induction.[61]



Scheme 18. Cyclic dipeptides as catalysts for asymmetric hydrocyanation.

The organocatalytic variant of the asymmetric aminoalkylation reaction (the Strecker reaction) was the logical extension of the cyanohydrin synthesis.[62] The first catalyst employed was a cyclic dipeptide[63] **24b** which is structurally related to **24a**.[64] Interestingly, **24a** does not result in any asymmetric induction in the mechanistically similar aminoalkylation reaction. The replacement of the imidazole moiety with a more basic guanidine side chain provides a solution. Although efficient catalytic reactions give rise to α-aminonitriles from benzaldehyde derivatives with high enantioselectivities, a low selectivity was observed in the reactions of aldimines derived from aliphatic and heterocyclic aldehydes. The structurally related although more simple chiral guanidine **9** efficiently mediates the addition of HCN to achiral *N*-benzhydridylimines[65] (Scheme 19). The catalytic action of the bicyclic guanidine can be rationalized by the formation of a guanidium cyanide complex, which activates the Schiff base (aldimine) substrate by hydrogen bonding. The mechanism suggests an insight into the efficacy of the guanidine-bearing diketopiperazine catalyst **24b**.

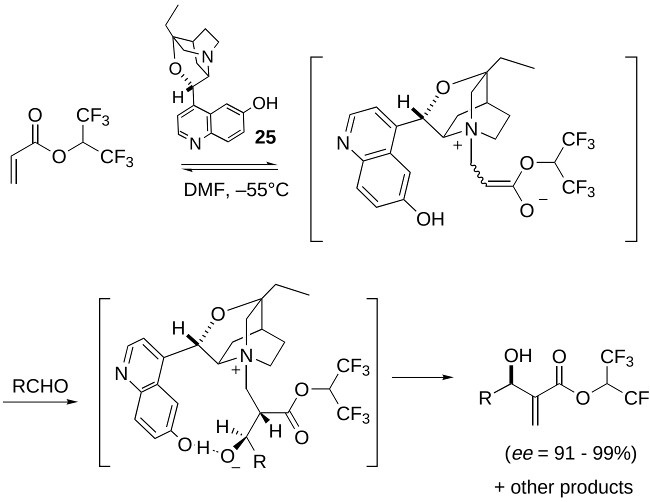


Scheme 19. The asymmetric hydrocyanation with the chiral guanidine catalyst **9**.

One of the most notable advantages of organic catalysts over organometallic reagents is that the former can be used in solid-phase reactions. High-throughput screening of resin-supported catalyst candidates was used to prepare oligopeptide-like catalysts and to select the most enantioselective library members for the Strecker reaction.[66] The selected compounds were validated by the preparation of soluble analogues such as **6a**, **b**. These small, acyclic, peptide-like molecules showed remarkable selectivity with aryl imine and selected cycloalkyl imine derivatives. Consistent with the notion that these catalysts emulate enzymes, the reaction follows a Michaelis–Menten kinetic profile, which indicates the reversible binding of the imine followed by the rate-limiting addition of HCN.

3.2.8. The Enantioselective Catalytic Baylis–Hillman Reaction[67]

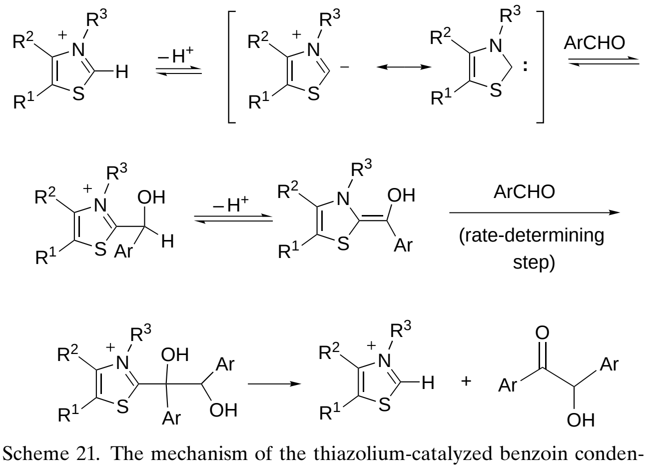
The reaction of aldehydes with activated alkenes such as acrylates (the Baylis–Hillman reaction) is typically catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) or tertiary phosphanes. Under asymmetric conditions both N- and P-based catalysts have been used. The asymmetric Baylis–Hillman reaction can be mediated efficiently by hydroxylated chiral amines derived from cinchona alkaloids such as **25** (Scheme 20).[68] The reaction is applicable either to aromatic or aliphatic aldehydes and results in high enantioselectivities. The selectivity can be rationalized by the formation of a betaine intermediate, which is stabilized by intramolecular hydrogen bonding between the oxy anion and the phenolic hydroxy group. This structure provides rigidity to the postulated activated complex and thus allows a higher selectivity.[69] In this arrangement the conformation is nearly ideal for the subsequent elimination process that is necessary for the regeneration of the catalyst. Phosphorus-based chiral molecules also mediate the asymmetric Baylis–Hillman transformation efficiently. Catalytic amounts of 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl (BINAP; **17**) were shown to catalyze the reaction with selected aldehydes with *ee* values of up to 44%.[70] The enantiomerically enriched chiral phosphane (−)-CAMP **16** has been shown to mediate the intramolecular reaction although in low enantiomeric excesses.[71] The low selectivity was attributed to the reversibility of the cyclization. The major drawbacks of the organocatalytic Baylis–Hillman reaction are its slow reaction rate and the limited scope of substrates. These shortcomings can be partly overcome by using metal-derived Lewis acids.[72]



Scheme 20. The asymmetric Baylis–Hillman reaction catalyzed with cinchona-derived **25**.

3.2.9. Asymmetric Synthesis with Chiral Heteroazolium Catalysts[73]

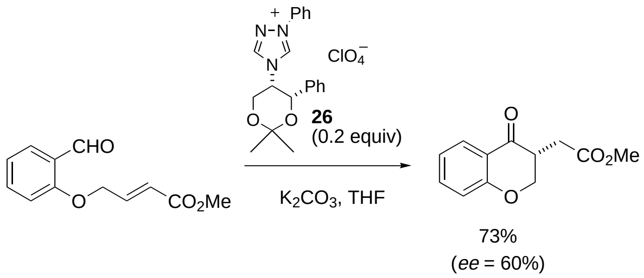
Thiazolium, 1*H*-imidazolium, and triazolium derivatives catalyze reactions such as the benzoin condensation and nucleophilic acylation reactions (the Stetter reaction) with a mode of action reminiscent of that of thiamine (vitamin B_1) under biochemical conditions. The mechanistic foundation of the condensation reaction was laid down more than four decades ago (Scheme 21).[74] Accordingly, the C(2) proton of the heteroazolinium derivative is ionized and the resulting anion (a resonance-stabilized carbene) adds to the electro-



Scheme 21. The mechanism of the thiazolium-catalyzed benzoin condensation.

phile, which is usually benzaldehyde or formaldehyde. Subsequent deprotonation leads to the formation of the corresponding enol which is stabilized by conjugation. This intermediate adds to the second electrophile, for example, an aldehyde, conjugated olefin, or enoate and finally affords the product and reforms the catalyst.

Although the achiral reaction proceeds well with a wide range of substrates and catalysts,[75] the asymmetric version is often limited by a low level of stereoinduction and low substrate compatibility. In most of the cases the stereocontrol is induced by a freely rotating chiral side chain. Some conformationally restricted analogues were also prepared and tested in benzoin condensation, with moderate success (20–30% *ee*).[76, 77] Significant synthetic results were obtained in the intramolecular Stetter reaction with triazolium catalyst **26** (Scheme 22).[78]

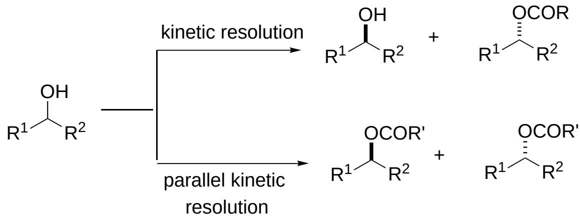


Scheme 22. The intramolecular Stetter reaction catalyzed by chiral triazolium salt **26**.

3.2.10. *Enantioselective Acylation*[79]

Probably the most thoroughly studied organocatalytic reaction is the kinetic resolution of secondary alcohols by means of enantioselective acylation. The origin of this transformation goes back to the late 1920's when Vavon and Peignier and then in the early 1930's Wegler showed that optically active alkaloids such as brucine and strychnine could induce enantiomeric enrichment either in the esterification of *meso* dicarboxylic acids or in the acylation of secondary alcohols.[80] Over the years the performances of the earlier systems were improved to become useful synthetic methods. The principle of the reaction remained the same: a nucleophilic chiral Lewis base and the acylating agent (usually anhydride) form a chiral activated complex which adds to the alcohol. However, much less is known about factors that play a role in the stereodiscriminating step, that is, the transition state preferences associated with different catalysts, which leads to questions about the 3D structure and the location of the carboxylate anion within the activated complex which may be involved as a general base in the proton-transfer step.

A considerable difficulty in overcoming the kinetic resolution is that during the progression of the reaction, the starting material becomes continuously enriched with the isomer that reacts more slowly. To obtain a synthetically useful *ee*, an exceptionally large difference in the rate is required between the enantiomers.[81a] Nevertheless, the enantioselectivity is sensitive to the progression of the reaction: one can optimize either the formation of the acylated product (low conversion) or the amount of recovered starting material (high conversion), and one is at the expense of the other. A solution to this problem is to run two reactions of approximately same rate, but of opposite sense and selectivity in the same pot; this affords two different products from each of enantiomers (parallel kinetic resolution, PKR) (Scheme 23).[81]



Scheme 23. Enantioselective acylation of prochiral secondary alcohols.

To improve the selectivity in the fully catalytic version of PKR, a three-phase system that uses an immobilized acylation catalyst and a polymer-supported reagent ("phase isolation") has been developed.[82] By using this system, a good enantiomeric purity (*ee* > 90%) was obtained for both products with a high conversion ($\geq$85%), even though the enantioselectivities of the two catalysts were not closely matched. Although most of the initial efforts were directed at the kinetic resolution of aryl alkyl carbinols, considerable progress has been made with substrates that contain more versatile functions such as allylic alcohols, cyclic 1,2-diols, aminoalcohols, and bromohydrins. Whereas the use of a chiral nitrogen catalyst is almost trivial in the acylation reaction, the first example of chiral phosphanes as catalysts is recent.[81b] A particular advantage of this atom is its dual function as a stereogenic center and as a nucleophilic site towards the transferable acyl function. Although lipase resolution is still more efficient, it was the first time that the selectivity factor *s*[83] reached 12 or 15 for a nonenzymatic system with an achiral acyl donor.

In the rational design of a chiral catalyst, the eternal dilemma arises from the relative positions of the active center and the chiral environment, that is, selectivity versus reactivity. If the reaction center cannot be rendered chiral, the most straightforward approach is to introduce the stereogenic center near to the active site. This steric hindrance of the chiral handle unfortunately often reduces the reactivity of the nucleophilic site of the catalyst. Another approach relies much more on enzyme-like structures. The strategy consists of building a simplified version of a complex chiral environment around the catalytic site, very much like in enzymes, in which the chiral handle is distant from the active site (as in **7**). Such artificial enzymes may consist of a short oligopeptide sequence with an active site (imidazole), and a basic secondary structure, for example, a β-turn or a β-hairpin. Hydrogen bonding plays a dominant role in the stabilization of the secondary structure of the catalyst and the substrate–reagent complex (see Section 2).

3.2..10.1. *Nitrogen-Based Catalysts*

The main body of work is related to the variation of the 4-dimethylaminopyridine (DMAP) structure in a chiral environment.[84–86] One of these approaches consists of placing the stereogenic center at the *meta* position of the pyridine ring, as in **12**, whereas such a center at the *ortho* position is known to be deleterious to catalytic activity.[86] Another approach consists of introducing the stereogenic center far from the active site of the DMAP analogue.[84] This modification allows the the catalytic activity of the achiral molecule to be preserved. The asymmetric induction occurs in a similar way to the induced-fit mechanism in enzymes.

The proline-derived chiral catalyst **4** was shown to be very efficient in the kinetic resolution of both cyclic and acyclic *meso*-1,2-diols with benzoyl halides as the acylating agent.[87, 88] Alcohols were recovered with up to 97% *ee*. High enantioselectivities ($s > 100$) were also found in the kinetic resolution of several bromohydrins.[89] This class of ligands has been utilized in other applications, such as in the asymmetric Mukaiyama-aldol reaction[90] and in the asymmetric rearrangement of allylic imidates to form allylic amides.[91] Recently, the catalyst was immobilized on a polymer support and used for the kinetic resolution of racemic mixtures of secondary alcohols.[92]

Small peptide catalysts that contain modified histidine residues are efficient catalysts in enantioselective acylation reactions.[93] In particular, tetrapeptide β-hairpins such as **7** exhibit result in selectivities.[93a] Some recently prepared octapeptide catalysts perform even better than the earlier tetrapeptide β-turns.[93b] Catalyst rigidity and structural complexity contribute to the enantioselectivity. Good enantiomeric excesses were obtained with substrates that allow hydrogen bonding to the peptide (i.e. *trans* aminocyclohexanols) under conditions that favor hydrogen bonding (nonpolar solvents, aprotic conditions). Substrates that are not subject to hydrogen bonding have lower selectivities. Kinetic studies indicate that the enantioselectivity is the consequence of a specific acceleration of reaction for one substrate enantiomer rather than the deceleration of the reaction for the other. The enantioselective acylation reaction can also be used for the desymmetrization of cyclic *meso*-anhydrides.[94] A variety of chiral amines such as ephedrine and cinchona alkaloids efficiently mediate the enantioselective ring-opening of different symmetrical anhydrides. The product of the reaction is the corresponding *hemi*-ester. The reaction can be rendered catalytic by using stoichiometric amounts of sterically hindered bases that liberate the alkaloid. The catalytic protocol affords products in high yields and up to 98% *ee*.

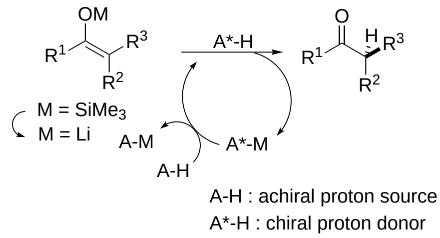
3.2.10.2. *Chiral Phosphorus-Based Acylation Catalysts*

Chiral phosphane catalysts may promote the enantioselective acyl transfer reaction of bulky and slowly reacting anhydrides such as *m*-chlorobenzoic or isobutyric anhydride. Among the tested catalysts, the 2-phosphabicyclo[3.3.0]octane derivatives such as **18** were particularly selective in the kinetic resolution of racemic aryl or alkyl carbinols.[95] Notably, **18** performs well over a broad range of temperatures and substrates. Either the esters were obtained (*ee* ≤ 98.7%, 44.4% conversion, $s = 369$) or the alcohols were recovered (*ee* ≤ 95.3%, 50.1% conversion, $s = 145$). The enantioselectivity of the reaction is very sensitive to the optical purity of the phosphane catalysts.

4. Organic Molecules Forming Reactive Intermediates

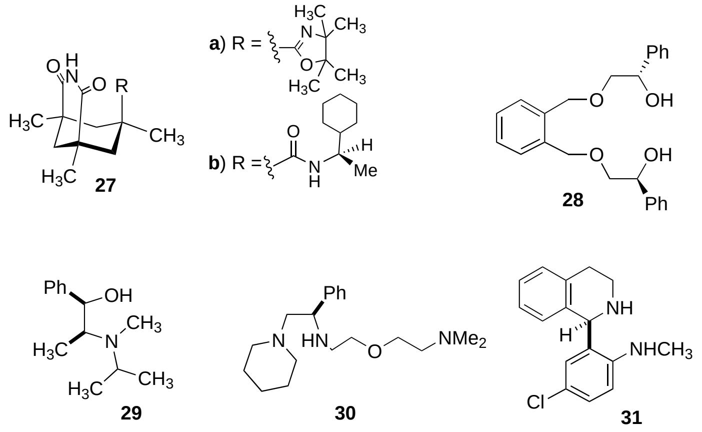
4.1. Catalytic Enantioselective Protonation[96]

The rational design of catalytic systems for enantioselective protonation remains largely empirical, although important advances have been made. The role of chiral additives in the reaction has not been fully elucidated. Besides their primary functions as chiral proton sources, they can also act as ligands for the metal. The asymmetric protonation of metal enolates fundamentally takes place catalytically if a coexisting achiral proton source (A–H) reacts with the deprotonated chiral proton source (A*–M) faster than with the metal enolate (Scheme 24).[97] The consumed chiral proton source is regenerated by subsequent protonation with the achiral proton source. Thus a higher reactivity of A*–M toward A–H than toward the metal enolate is the key to the success of the catalytic cycle. If proton transfer from the achiral proton source (A–H) to the enolate occurs quickly at low temperature, the selective deprotonation of one enantiomer of the resulting racemic ketone by A*–M is a possible alternative catalytic mechanism. To diminish the competing reaction between the achiral and the chiral proton source with the enolate, the chiral catalyst was added before the achiral proton source.



Scheme 24. Enantioselective catalytic protonation of prochiral lithium enolates.

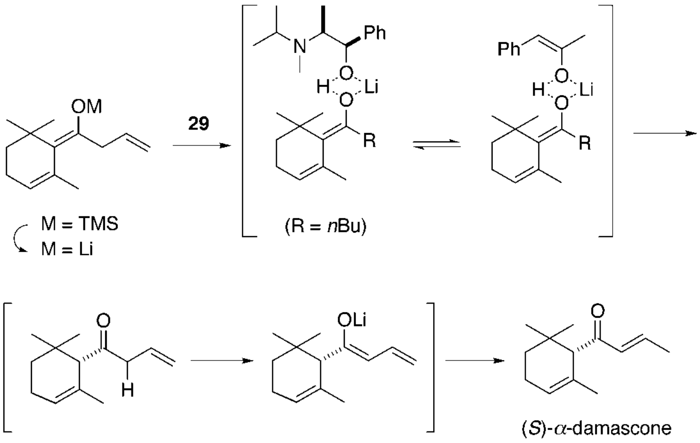
Numerous chiral proton sources such as imides, amides (e.g. **27** derived from Kemp's triacid), phenols, alcohols such as **28**, amino alcohols such as **29**, and amines such as **30**, **31** have been developed (Scheme 25). Among the achiral proton sources, moderately acidic rigid and sterically hindered proton donors usually result in high *ee* values. For this purpose, cyclic imides (such as succinimide, glutarimide, and phthalimide), nonactivated phenol derivatives (such as catechols), dipivaloylmethane, or moderately acidic carbonyl compounds (such as phenyl-2-propanone) were selected. Prochiral substrates are often metal enolates, such as lithium or samarium enolates (generated either from preformed silyl enol ethers or enol acetates, with an excess of organometallic reagents), or they are the products of an organometallic



Scheme 25. Selected organic molecules used in enantioselective catalytic protonation.

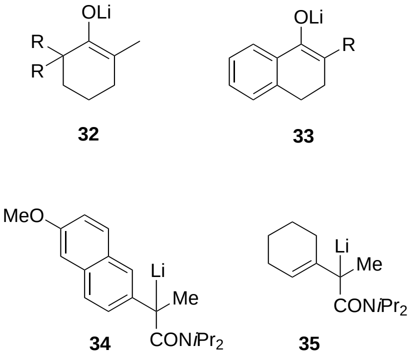
coupling reaction. In some cases, transient enolates or enols can be used as substrates that are generated under the reaction conditions and protonated enantioselectively in situ.[98] Although 0.01 equivalents of chiral catalyst may result in acceptable *ee* values, the enantioselectivity increases with a higher concentration of the catalyst.[99]

The basis of the enantioselective catalytic protonation was laid out in a series of papers on the synthesis of enantiomerically pure (*S*)-*α*-damascone without the addition of any external achiral proton source (Scheme 26).[100] This autocatalytic system is based on the presence of an acidic proton on the protonated intermediate which allows the regeneration of the chiral catalyst **29**. To rationalize the results, a transition-state-like complex was postulated in dynamic exchange with the achiral complex (Scheme 26). According to this hypothesis, the chiral complex affords the product faster than the achiral one.



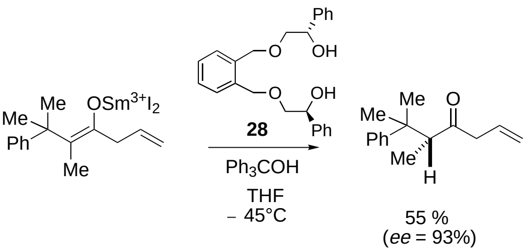
Scheme 26. Synthesis of (*S*)-*α*-damascone by means of enantioselective catalytic protonation. TMS = trimethylsilyl.

Chiral amides such as **27a** and **27b**, which are derived from Kemp's triacid, may serve as catalysts in the asymmetric protonation of lithium enolates such as **32** (Scheme 27).[101] A chiral tetradentate amine such as **30** is another example of a catalyst for enantioselective protonation.[102] In the presence of a stoichiometric amount of an achiral proton source (succinimide) and a catalytic amount (0.2 equiv) of a chiral amine **30**, the protonation of tetralone-derived lithium enolate **33** afforded the desired product with 15–83% *ee*. The LiBr which is present in the reaction mixture, may be part of the structure of the active intermediate. The slow addition of the achiral proton source required for the good *ee* was effected by solid–liquid heterogeneous reaction conditions: the succinimide is weakly soluble in toluene at $-78\,^{\circ}$C, and thus slowly liberates the achiral H^+. Asymmetric protonation is not limited to enolates derived from ketones. The catalytic protonation of lithium enolates of amides such as **34** or **35** by using 10 mol% of **31** as the catalyst results in poor to good *ee* values, depending on the nature of the achiral proton source.[103] The best *ee* values were obtained when $PhCH_2CO_2Et$ and $PhCH_2CO_2t$Bu were used as achiral proton sources (92 and 94%, respectively). On decreasing the amount of catalyst from 10 mol% to 5 mol%, a high *ee* ($\leq$92%) could be maintained.



Scheme 27. Some selected substrates used in enantioselective catalytic protonations.

The enantioselective catalytic protonation of samarium enolates requires more drastic conditions than those of lithium enolates (Scheme 28). The reaction can be catalyzed with **28** as the chiral proton donor.[104] The best result is obtained when the achiral proton source (trityl alcohol) is added very slowly to the reaction mixture. The relatively high temperature ($-45\,^{\circ}$C) and the longer reaction time required is a consequence of the stronger coordination of the oxygen anion to the samarium ion than to the lithium ion. The use of a fluorous biphasic system[105] ensures the very slow diffusion of the achiral proton source into the reaction phase and results in a somewhat higher *ee* than the single-phase reaction.

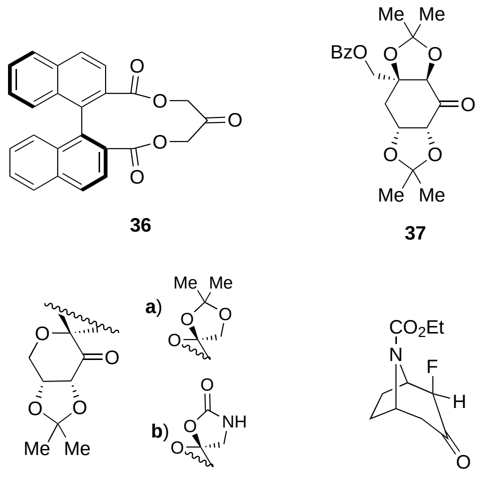


Scheme 28. Enantioselective protonation of samarium enolates.

4.2. Oxidations[106]

4.2.1. Epoxide formation[107]

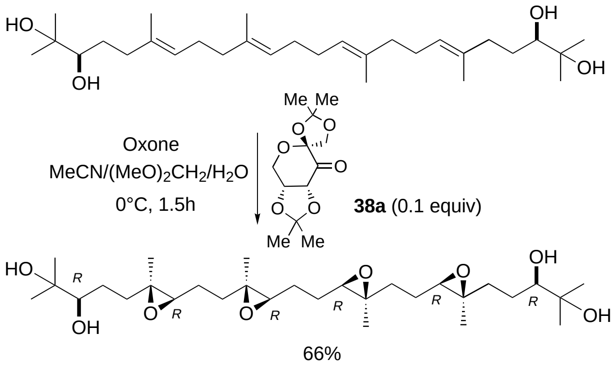
The first powerful highly enantioselective oxidation method of isolated olefins is based on osmium. This reaction remains one of the most general methods in the asymmetric epoxidation and hydroxylation of alkenes. The category of nonmetal-catalyzed, asymmetric epoxidation has only recently emerged as a viable method. New methods are based on the use of chiral ketones,[111] iminium salts,[108a–d] α-amidoketones,[108e,f] and simple imines,[109] as well as a co-oxidant such as H_2O_2 or Oxone, which generates the chiral oxidizing agent in situ (Scheme 29).[109, 110]



Scheme 29. Some selected catalysts for enantioselective catalytic oxidations. Bz = benzoyl.

Chiral ketones that form dioxiranes under the condition of the reaction are probably the most versatile oxidation catalysts with remarkable potential in asymmetric synthesis.[107d, 112] Recent developments in enantioselective catalytic oxidation concern the use of C_2-symmetrical ketones such as **36**,[111] (−)-quinic acid derived cyclitols such as **37**,[112b] and sugar derivatives such as **38**.[112a] Both the structures of the catalysts and the reaction conditions were optimized to minimize the competing Baeyer–Villiger side reaction of the ketone catalyst. These compounds show a great structural diversity (Scheme 29). A strong electron-withdrawing substituent such as fluorine, immonium, or ammonium near the carbonyl group is often a common structural element (Scheme 29). This functionality increases the reactivity of the carbonyl towards the co-oxidant and diminishes the propensity of the catalyst toward Baeyer–Villiger oxidation.

C_2-Symmetrical cyclic ketones such as α,α'-diacyloxyketone **36** provide *ee* values of up to 87% in the epoxidation of nonfunctionalized alkenes that bear large aromatic substituents.[107c] Fructose-derived ketones such as **38a** can epoxidize a large number of *trans*-olefins and trisubstituted alkenes with high *ee*.[113, 107d] However, epoxidation of *cis*-olefins using this ketone led to rather poor enantioselectivity. On the other hand, the spiro-oxazolidine derivative **38b** gave good results for both *cis*- and *trans*-olefins.[114] To minimize the catalyst degradation, a high pH value (pH 10.5 in the case of D-fructose-derived catalyst **38a**) is required.[115] These catalysts must be soluble in water as the reactions are usually performed in a homogeneous CH_3CN/H_2O solvent system to dissolve the co-oxidant. Additional studies have been carried out in a biphasic solvent system. Optimization of the reaction conditions has extended the field of asymmetric epoxidation to dienes, enynes, 2,2-disubstituted vinylsilanes, enol silyl ethers, and esters. A structurally related ketone derived from (−)-quinic acid **37** is also an efficient catalyst for the epoxidation of alkenes.[116] Likewise, the tropinone-derived chiral ketone **39** was described as a good catalyst for the enantioselective epoxidation of alkenes substituted with aromatic groups (33–100% yield, 29–83% *ee*).[117] A recent application in the synthesis of (−)-glabrescol illustrates the scope of this method (Scheme 30).[118]



Scheme 30. Synthesis of a key intermediate in the synthesis of (−)-glabrescol by means of an enantioselective catalytic epoxidation. Oxone = $2\,KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$.

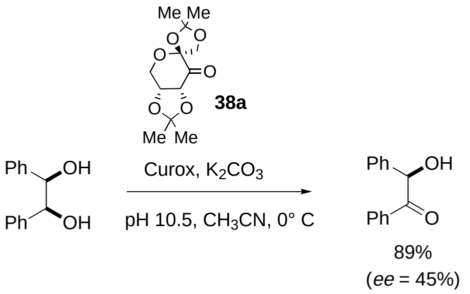
The epoxidation reaction with imine catalysts and Oxone co-oxidant is less developed than the chiral ketone mediated variant.[109] This reaction is believed to proceed via a radical cation intermediate. The side-product found with the desired epoxide is the corresponding diol. The asymmetric induction is usually low when 2-diphenylmethylpyrrolidine **3d** is used as catalyst.[109]

4.2.2. Desymmetrization of Vicinal Diols by Oxidation

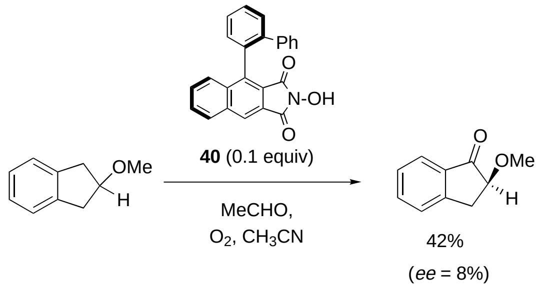
The scope of the oxidation reaction that uses chiral dioxiranes, which are generated in situ, extends beyond the asymmetric epoxidation of isolated olefins. For example, this catalytic system can be used to oxidize vicinal diols into α-hydroxyketones (Scheme 31).[119] The *meso*-hydrobenzoins were desymmetrized at a high pH value (pH 10.5) by using 3 equivalents of fructose-derived ketones such as **38a** (17–60% *ee*).

4.2.3. Oxidation at Benzylic Positions

A conceptually different approach in oxidation allows the use of molecular oxygen as co-oxidant (Scheme 32).[120] A mixture of chiral *N*-hydroxyphthalimide (NHPI; **40**) and acetaldehyde in the presence of O_2 was used to oxidize indane. The yield and selectivity of this transformation is nevertheless



Scheme 31. Desymmetrization of *meso* diols by means of enantioselective oxidation. Curox = potassium monoperoxysulfate.



Scheme 32. Enantioselective oxidation at benzylic positions.

low. The phthalimide *N*-oxyl radical, which is formed by the one-electron oxidation of, was proposed as a key intermediate in the reaction.

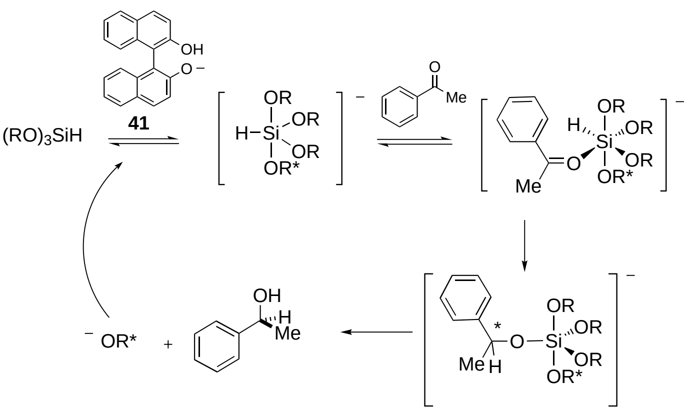
4.2.4. Asymmetric Oxidation of Sulfides to Sulfoxides[121]

The asymmetric oxidation of sulfides to sulfoxides can be realized by using a catalytic amount (10–20%) of chiral sulfonylimines, with potassium percarbonate as co-oxidant.[121c] Yields are high (95–100%) although *ee* values are low (14%).

4.3. Asymmetric Catalytic Reduction

The asymmetric reduction of ketones by using transient hypervalent silicon hydrides is on the borderline of organocatalytic reactions, since the reaction requires the presence of alkoxide anions.[122] However, it is argued that the metal center does not participate in the reaction mechanism (Scheme 33).

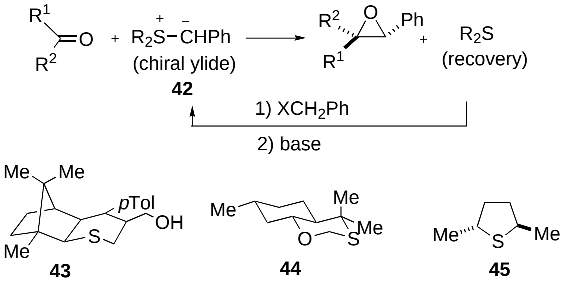
The reaction is based on the activation of trialkoxysilanes by a small amount of a chiral nucleophile (alkoxide). This activated complex undergoes addition to the carbonyl group to form the corresponding silyl-protected alcohols, and liberates the chiral nucleophile. Since the aggregation of organolithium compounds has a strong effect on their reactivity, the use of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as co-solvent not only increases the yield but also enhances the enantioselectivity. Among the tested alcohols, the monolithium salt of 2,2′-dihydroxy-1,1′-binaphthyl (BINOL; **41**) resulted in *ee* values of up to 93%.



Scheme 33. Enantioselective reduction of aromatic ketones by using BINOL-activated silanes.

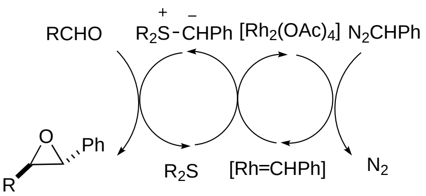
4.4. Asymmetric Ylide Reactions: Epoxidation, Cyclopropanation, Aziridination

Since its discovery, the reaction of sulfur ylides with aldehydes or ketones to give epoxides has received considerable attention and has been extensively developed.[123] Enantiomerically enriched epoxides were prepared either under biphasic/phase-transfer conditions or in homogenous solution by using either alkylation/deprotonation or direct carbene coupling procedures. In the enantioselective catalytic process, the chiral ylide precursor is recovered and is converted back into the ylide reagent **42** under the reaction conditions. The general mechanism of the reaction is depicted in Scheme 34. Among the tested catalysts, conformationally restricted sulfides derived from camphor,[124] **43**, pulegon,[125] **44**, or C_2-symmetrical thiolane,[126] **45**, afforded *trans* stilbene oxide derivatives with high *ee*.



Scheme 34. Some chiral sulfides used in enantioselective catalytic epoxidation reaction. *p*Tol = *p*-tolyl, X = halogen.

It is considered that the formation of the sulfonium salt is the rate-determining step in the catalytic cycle. To assure the required reaction rate, additives such as $AgClO_4$ or $AgBF_4$ salts have been used. An alternative method for the ylide formation is the generation of the sulfonium ylide by carbenes or carbenoids. In this procedure, the sulfonium ylide is formed in a second catalytic cycle from a diazo compound and $[Rh_2(OAc)_4]$ or $[Cu(acac)_2]$ (acac = acetylacetonate; Scheme 35) or by using Simmons–Smith reagents.[127] This variant also allows the preparation of chiral cyclopropanes and aziridines.



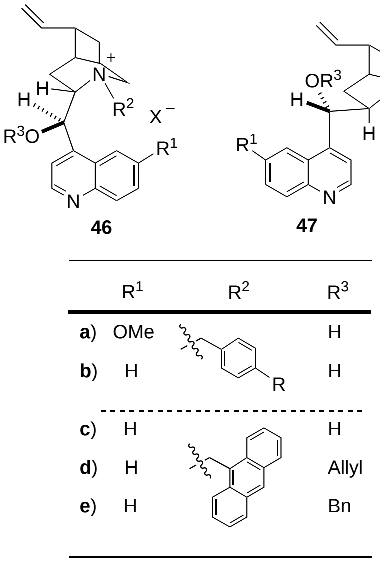
Scheme 35. Enantioselective catalytic epoxidation mediated by chiral sulfides. The catalyst is regenerated by using a metallocarbene in an auxiliary catalytic cycle.

5. Asymmetric Phase-Transfer Catalysis[128]

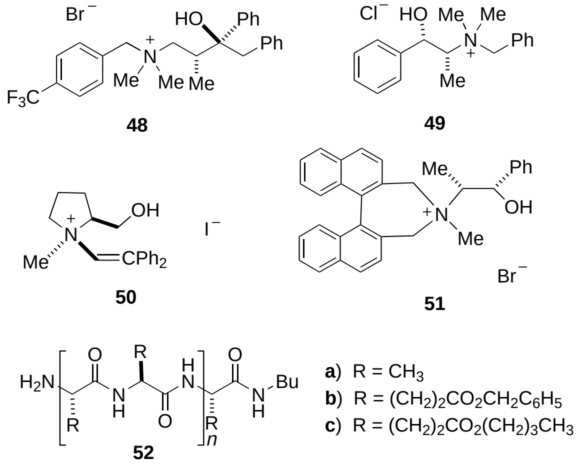
5.1. The Catalysts

Phase-transfer catalysis (PTC) mediated by chiral quaternary ammonium salts represents a unique ion-pair-mediated reaction.[129] The mechanism was determined in 1986, and three main steps were proposed:[130] 1) deprotonation of the active methylene compound with the base generally occurs at the interface of the two layers (either liquid – liquid or liquid – solid phases); 2) extraction of the anion into the bulk organic phase by ion exchange with the cation of the chiral quaternary ammonium salt by forming a lipophilic ion pair; and 3) alkylation of the ion pair with the reagent as well as the concomitant regeneration of the catalyst. Highly enantioselective PTC reactions have been known for many years[131] although some high-induction results were revealed to be erroneous as a result of the high optical rotation of trace impurities.[135b] Among the quaternary ammonium salt catalysts, cinchonium derivatives have been shown to be particularly efficient (Scheme 36).[132]

A number of other chiral ammonium salts that contain the key β-hydroxyammonium structure of the cinchonium derivatives have also been used. The ephedra alkaloid catalysts, for example, **48**, **49**, and **51**, were particularly successful in many reactions. Moreover, oligopeptides such as **52a – c** and polymer catalysts were also used (Scheme 37).[133] The substitution pattern plays a crucial role in the control of the stereoselectivity of the cinchona-catalyzed reactions. A major improvement in the *ee* values was observed by changing the alkyl or benzyl substituent of the quaternary ammonium for the bulkier anthracen-9-ylmethyl (anth) group either in solid – organic or aqueous – organic biphasic systems. This modification resulted in a decisive breakthrough in the application of the enantioselective phase-transfer reactions. The efficiency of the "third generation" catalysts is being exploited increasingly in the synthesis of biologically relevant molecules.



Scheme 36. Selected cinchona-derived quaternary ammonium salts used in the enantioselective catalytic phase-transfer reaction. Bn = benzyl.



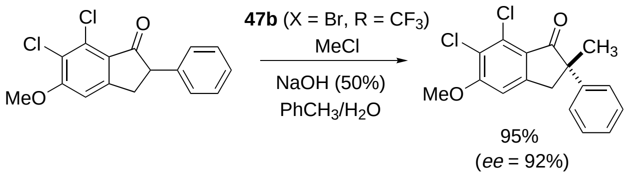
Scheme 37. Selected catalysts for enantioselective catalytic phase-transfer reactions.

Arguably the catalyst forms a well-ordered contact ion pair with the substrate in the organic phase for enantioselective reactions. This mechanistic model is based on the X-ray structure analysis of the catalyst – substrate complex in which the anionic oxygen atom of the enolate and the cationic nitrogen atom form a well-ordered rigid structure. The predominant forces that hold the complexes together are coulombic, and the charges are highly dispersed.[134] The combination of electrostatic and van der Waals interactions results in a tight ion pair in which only one face of the complex is accessible for reaction.[135] The solvents have important effects on the selectivity: nonpolar solvents resulted in higher *ee* values than polar solvents.

5.2. Reactions

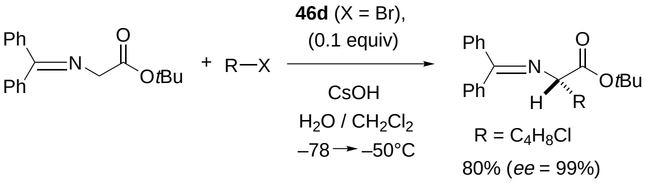
5.2.1. Enantioselective Alkylation

The enantioselective alkylation reaction under biphasic conditions was one of the first examples of chiral PTC transformations.[136] This methodology was already used in the early 1980's when the uricosuric indanone derivative was prepared in an almost quantitative yield and with a remarkably good selectivity (Scheme 38).[137] The "first generation" catalysts with an unsubstituted hydroxy function usually



Scheme 38. Enantioselective alkylation under phase-transfer conditions with a cinchonium-derived catalyst.

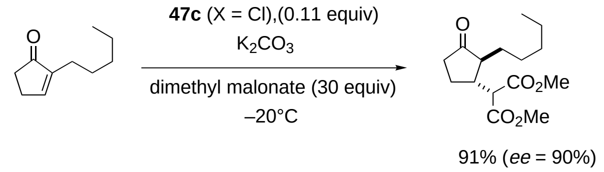
resulted in moderate enantioselectivity even with optimized substrates. Although the free hydroxy function of the catalyst was thought to be indispensable for a high *ee*, it was proposed later that the active catalyst is the *O*-alkyl cinchona salt formed during the alkylation reaction.[138] The "second generation" (*N*-benzyl-*O*-allyl or -alkyl salts) and then the "third generation" (*N*-anth) showed very significant improvements in *ee* values.[139] Furthermore, it was demonstrated that substrates with stronger electron-withdrawing substituents on the adjacent position increase the catalyst selectivity.[140] In particular, the alkylation of the *tert*-butylglycinatebenzophenone Schiff base, [143] which is considered to form a tight catalyst–substrate complex, gave impressive results. A series of natural and unnatural α-amino acid derivatives were prepared with enantioselectivities of up to 400:1 by using catalyst **46d** (Scheme 39).[141]



Scheme 39. The enantioselective alkylation of the *tert*-butylglycinate benzophenone under phase-transfer conditions.

5.2.2. *Michael Additions*

N-Alkylated cinchonium derivatives mediate the enantioselective conjugate addition of carbanions to α,β-unsaturated ketones.[142] However, the addition of thiols and nitroalkanes to similar substrates resulted in low *ee* values using catalyst **46a**, **b** (R = H or NO_2; X = Cl). The use of **47a**, **b** (R = CF_3; X = Br) as catalysts in the enantioselective alkylation reaction was shown to be particularly efficient in the construction of quaternary carbons.[143] The therapeutically useful $GABA_B$ receptor agonist (*R*)-baclofen · HCl was prepared by using the enantioselective Michael addition of nitromethane to the chalcone-derived α,β-unsaturated ketone.[144] Also, 9-anthracenylmethyl-substituted cinchonidium chloride **47c** (X = Cl) mediated the addition of the dimethyl malonate anion to a cyclopentanone derivative in the enantioselective synthesis of methyl-dihydrojasmonate (Scheme 40).[145] The key enantioselective step in the synthesis involves a new system of asymmetric solid–liquid phase-transfer catalysis that uses solvent-free conditions. Vinyloxysilanes can also be used as nucleophiles in the enantioselective Michael addition of cinchona-derived quaternary ammonium salts.[146] The advantages of using enol ethers instead of ketones include faster reactions, higher enantioselectivities and chemical yields, and minimization of the aldol side reaction.



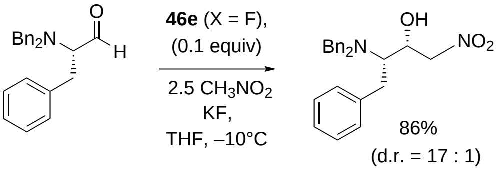
Scheme 40. Application of a chiral quaternary ammonium salt in an asymmetric Michael reaction towards the synthesis of (−)-methyl dihydrojasmonate.

5.2.3. *Aldol and Related Condensations*

As a logical extension of the PTC alkylation, "first generation" catalysts **46b** and **47b** (R = H; X = Cl) were tested in inter- and intramolecular aldol and nitroaldol reactions. A variety of β-hydroxy-α-amino acids were synthesized enantioselectively by using cinchona-derived catalysts.[147] Although the observed enantioselectivities were in the range of 70–90% when simple substrates were used, the *syn*/*anti* ratio varied substantially (from 1:1 to 13:1).[147b]

Catalysts **47b** (R = H) with a fluoride counterion (X = F) were used in the aldol reactions of the enolates of silyl-enol ethers (Mukaiyama–Kuwajima aldol reaction).[148] The advantage of this method is that the use of additional base for the aldol reaction is avoided. Although the diastereoselectivity of the reaction was modest, *ee* values of up to 72% was obtained.

The catalytic asymmetric nitroaldol reaction (Henry reaction) under PT conditions was for a long time compared with the more selective metal complex mediated versions.[149] In a recent variant under solid–liquid PT conditions the reaction of aldehyde with nitromethane catalyzed by **46e** (X = F) afforded the key intermediate of the second generation HIV protease inhibitor amprenavir in good yield and with remarkable stereoselectivity (Scheme 41).[150] The *Re*-face selectivity of the reaction follows mechanistic model discussed in Section 5.1.



Scheme 41. Application of a nitroaldol reaction promoted by a chiral quaternary ammonium salt in the synthesis of amprenavir.

5.2.4. *(1,2)-Addition Reactions*

The nucleophilic trifluoromethylation of carbonyl compounds was realized by using trifluoromethyltrimethylsilane (TMS-CF_3) under PT conditions.[151] The *N*-benzylcinchonium fluoride catalyst **47b** (R = H; X = F) mediates the reaction, and enantioselectivities in the range of 15–51% are observed for simple ketones.

5.2.5. *Olefination Reactions*

The desymmetrization of ketones was mediated by cinchonium salts under PT conditions in catalytic asymmetric Horner–Wadsworth–Emmons reactions.[152] The reaction results in *ee* values of up to 57% when *tert*-butylcyclohexanone was used as a substrate.

5.2.6. *Darzen Reaction*

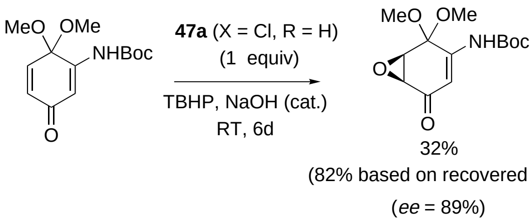
It is difficult to design a catalytic cycle for the metal-promoted Darzen reaction because of the formation of the stable inorganic salt (a metal halide) in the reaction. Therefore a stoichiometric amount of a chiral organometallic reagent is needed. Phase transfer conditions with cinchona-derived catalysts may allow the reaction to be rendered catalytic.[153] Enantiomerically enriched α,β-epoxysulfones were prepared from chloromethyl phenylsulfone with various aromatic aldehydes in the presence of 10 mol% of quinine-derived salt **47b** ($R = CF_3$; $X = Br$). In the optimized case the reaction afforded the *trans* aryl epoxysulfone in up to 81% *ee*.[154] Chiral sulfides can also catalyze the asymmetric Darzen-type epoxidation.[155] The reaction is suitable for the coupling of benzyl halides with aromatic aldehydes. However, this reaction is limited to the formation of stilbene oxides.

5.2.7. *Oxidations*

5.2.7.1. *Epoxide formation*

The enantioselective oxidation of enones with polyamino or resin-supported polyamino acids under tri- and biphasic conditions has been known since the early 1980's.[156] Both the catalyst recycling and the reactivity have been improved considerably over the years. Although the mechanism of the reaction is not well understood, it performs well with remarkable selectivity in a number of cases. Excellent enantioselectivities were obtained on acyclic, and more recently, on cyclic enones.[157] The poly-L-leucine variant epoxidation has been scaled up by SmithKline Beecham in the synthesis of the leukotriene antagonist SK&F104353.[158]

Additionally, cinchona-derived quaternary ammonium salts are efficient in mediating epoxidation under phase-transfer conditions.[159] This reaction was used in the synthesis of different members of the manumycin family (Scheme 42).[160] The use of one equivalent of *N*-benzylchinidinium chloride **47a** ($R = H$; $X = Cl$), and *tert*-butyl hydroperoxide (TBHP) with a catalytic amount of sodium hydroxide gave the desired epoxide with 89% *ee* (Scheme 42). The reaction conditions were also optimized for the oxidation of some chalcone derivatives. Under these conditions 1% of catalyst ($X = Br$) was enough to mediate the epoxidation of α,β-unsaturated ketones in a solution of NaOCl in high dia- and enantioselectivity and in high chemical yields.[161] Likewise, face-selective conjugate additions of ion-paired hypochlorite to an α,β-enone have been realized by using **46e** ($X = Br$) as catalyst.[162] The reaction affords the corresponding epoxide with a remarkably good (up to 130:1) enantioselectivity.



Scheme 42. Enantioselective phase-transfer epoxidation in the synthesis of a key intermediate of (+)-manumycine A. TBHP = *tert*-butylhydroperoxide.

5.2.7.2. *Asymmetric Oxidation of Sulfides to Sulfoxides*

Sulfides can be asymmetrically oxidized to form sulfoxides by using hypervalent iodine compounds in reversed micellar systems that contain a chiral source.[163] Accordingly, $PhIO_2$ (0.5 equiv), in the presence of a catalytic amount of cetyltrimethylammonium bromide (CTAB) as the surfactant, and a catalytic amount of diacyltartaric acid as the chiral source, oxidizes the substrates with moderate to good enantioselectivities (up to 72% *ee*).

5.2.8. *Asymmetric Reductions*

An enantioselective reduction that uses chiral ammonium fluoride catalysts under phase-transfer conditions was described.[164] The reaction is based on silanes such as trialkyloxysilanes, tris(trimethylsiloxy)silane, and polymethylhydrosiloxane, which undergo a hydride-transfer reaction in the presence of F^-. High enantioselectivities were obtained in the reduction of simple ketones such as acetophenone.[164]

5.2.9. *Enantioselective Protonation under Phase-Transfer Conditions*

Enantioselective protonation can be carried out in a fluorous/organic biphasic system (FBS).[105] The reaction conditions were developed in a way to assure the very slow diffusion of the achiral proton source into the reacting phase. In this system, both the chiral and achiral proton sources have a long fluorous chain. Whereas the achiral proton source remains essentially in the fluorous solvent (FC-72), the chiral proton source shuttles between the standard organic solvent and the fluorous phase.

6. Chiral-Cavity-Accelerated Asymmetric Transformations

The selective recognition of substrates followed by chemical transformation with the help of a molecular cavity is a largely documented field in organic chemistry.[165, 166] Although chiral host–guest chemistry is an increasingly important field in asymmetric synthesis, there are few examples in which an enantioselective catalytic transformation occurs. The reason is that the formed host–guest complex is often too stable to allow efficient catalytic turnover. Nevertheless, the chiral-cavity-accelerated asymmetric transformation probably offers the closest analogy to enzyme catalysis. This analogy goes further than it does with simple organic molecules: not only the recognition process but the mode of action, that is, in creation of the transition state analogues, are reminiscent of enzyme activity. Catalytically active chiral cavities were devised either by using polyfunctionalized cyclic molecules such as cyclodextrins, or by using molecular imprinting. For the latter, the term "plastic enzymes" was coined to indicate the use of polymers as supports and the mode of action, which is reminiscent of enzymes.

6.1. Cyclodextrins in Enantioselective Catalytic Synthesis[167]

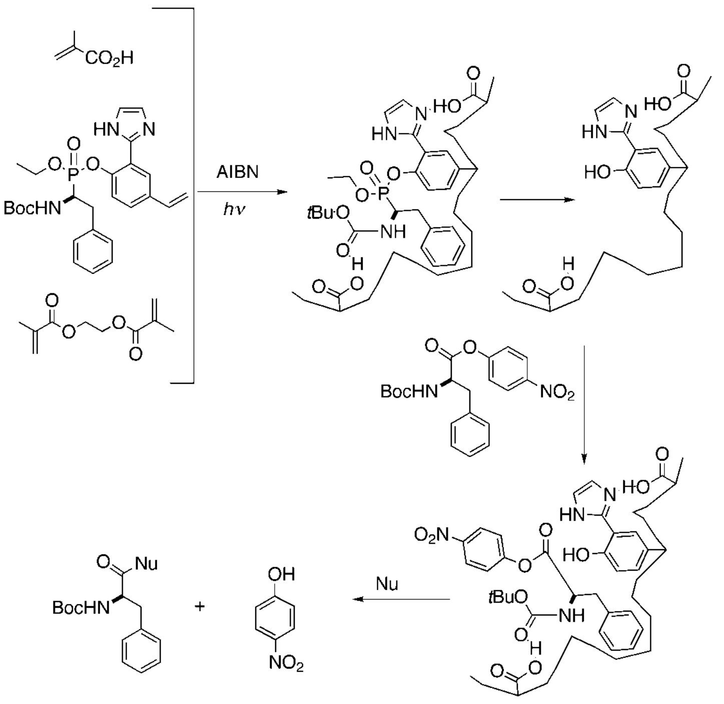
Cyclodextrins form inclusion complexes with a variety of hydrophobic guests based on size, structure, and polarity. Although enantioselective reactions are known, relatively few are amenable to enantioselective catalytic turnover. There are examples of optical induction in the cyanohydrin formation from benzaldehyde, in the asymmetric reduction of ketones, and in the transamination of α-keto acids.[7, 167, 168]

6.2. Molecular Imprinting[169]

When a highly crosslinked network polymer is made in the presence of a template molecule and the template is then liberated, a polymer that contains selective binding sites can be obtained. This technique is called molecular imprinting. This polymer is able to distinguish between a variety of structures in a similar manner to bioorganic catalysts such as enzymes or antibodies. The molecular cavity selectively binds substrates that have similar structures to those of the original template. The molecular recognition arises from a combination of covalent, ion-pairing, and hydrogen bonds. This simple and appealing concept has for more than 50 years attracted chemists from several disciplines and is a promising and important breakthrough in enantioselective catalysis. Highly crosslinked network polymers were developed and exhibit excellent recognition properties for enantiomers of a highly interesting range of substances such as carbohydrates, esters, amino acids and peptides, steroids, and nucleotide bases. Beyond the host–guest complexation ability, some of the bioorganic functions can be mimicked notably by using the binding force energies for chemical reactions and by stabilizing the transition state of the reaction in question (cf. antibodies with enzyme properties, abzymes).

6.2.1. Enantioselective Ester Hydrolysis

Predictable enantioselectivities were obtained in the hydrolysis of different esters by using template-imprinted polymers.[170] The polymeric matrix contained similar catalytic elements that are believed to be responsible for the catalytic action of chymotrypsin (Scheme 43). The esterase site was modeled by mimicking the transition state structure of the hydrolysis reaction by using a template with a similar structure in the ground state. The mechanism of the ester hydrolysis or transesterification is believed to involve a high-energy tetrahedral oxanion transition-state-like intermediate. Rate enhancements caused by esterase enzymes can, to a large extent, be ascribed to the electrostatic stabilization of this structure.[171]



Scheme 43. Enantioselective ester hydrolysis with an imprinted polymer. AIBN = azobisisobutyronitrile.

As stable transition state analogues, phosphonates have been selected as templates. The hydrolytic molecular machinery was modeled around a nucleophilic center in the proximity of the reactive carbonyl group as well as an imidazole and carboxy group within hydrogen bonding distance of the nucleophile. The imidazole group is apparently required for the catalytic activity since only small rate enhancements and no template-induced catalysis were seen when this group was absent. The polymeric catalyst was found to be catalytically active and retains the enantioselectivity over a period of 10 years. Although the reported rate enhancement was modest it can be considered as a first step in the development of imprinted polymers for enantioselective catalysis.

7. Summary

The enantioselective organocatalysis in which the reaction is mediated by a catalytic amount of chiral organic molecule is a an emerging powerful tool in organic synthesis. The interest in this field has increased spectacularly in the last few years and more reactions are expected in the near future. Owing to the sensitive substrate dependency of many of the discussed reactions, only a partial solution has been provided for their practical use. In some cases, the catalyst is very toxic (e.g. the HMPA analogues) and is at odds with potential advantages over metal-catalyzed reactions outlined in the introduction. Although there are important gaps in the understanding of basic factors that control the reactivity and selectivity of the reactions, parallel analyses of the mechanisms help in the rational design of the next generation of catalysts. Despite the fact that the field is in its relative infancy, it offers new perspectives for academic, industrial, economic, and ecological benefit. The scope of reactions is currently restricted, but newly emerging domains pave the way for further developments. Good fortune, intuition, and persistence, as well as the traditional trial and error methods may help in the development of enantioselective catalytic reactions from the almost infinite number of stoichiometric chiral organic transformations.

The CNRS, the city of Paris, the Fondation pour la Recherche Médicale (grant no. 40001838-01), and the Association pour la Recherche contre le Cancer (ARC) (grant no. 7579) are gratefully acknowledged for financial support.

Received: January 2, 2001 [A 441]

---

[1] S. C. Stinson *Chem. Eng. News* **2000**, *78*(43), 55–79.

[2] a) H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433; b) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc. Chem. Commun.* **1972**, 10–11.

[3] For leading references, see: a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**; b) *Asymmetric Catalysis in Organic Synthesis* (Ed.: R. Noyori), Wiley, New York, **1994**; c) *Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., VCH, New York, **2000**; d) "Catalytic Asymmetric Synthesis": *Acc. Chem. Res.* **2000**, *33*, 323–440 (special issue); e) D. Astruc, *Chimie Organométallique*, EDP Sciences, Les Ulis, **2000**; f) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545–548; *Angew. Chem. Int. Ed.* **2001**, *40*, 529–532.

[4] B. Fubini, L. O. Areán, *Chem. Soc. Rev.* **1999**, *28*, 373–382.

[5] a) J.-L. Pierre, *Chem. Soc. Rev.* **2000**, *29*, 251–257; b) B. P. Roberts, *Chem. Soc. Rev.* **1999**, *28*, 25–35.

[6] See, for example: a) M. Yamaguchi, T. Shiraishi, M. Hirama, *J. Org. Chem.* **1996**, *61*, 3520–3530; b) M. Yamaguchi, Y. Igarashi, R. S. Reddy, T. Shiraishi, M. Hirama, *Tetrahedron* **1997**, *53*, 11223–11226; c) M. Yamaguchi, T. Shiraishi, Y. Igarashi, M. Hirama, *Tetrahedron Lett.* **1994**, *35*, 8233–8236.

[7] R. Breslow, *Science* **1982**, *218*, 532–537.

[8] A. J. Kirby, *Angew. Chem.* **1996**, *108*, 771–790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 707–725.

[9] The review focuses on organic catalysts that have no metallic or metalloid components. Accordingly, powerful catalyst classes based on metallocenes (see, for example: a) S. Arai, S. Bellemin-Laponnaz, G. C. Fu, *Angew. Chem.* **2001**, *113*, 240–242; *Angew. Chem. Int. Ed.* **2001**, *40*, 234–236; b) G. C. Fu, *Acc. Chem. Res.* **2000**, *33*, 412–420; c) Y. Ie, G. C. Fu, *Chem. Commun.* **2000**, 119–120; d) B. Tao, C. Ruble, D. A. Hoic, G. F. Fu, *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092) or metalloids such as boron (see, for example: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092–2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986–2013) were excluded, regardless of whether or not the metallic/metalloid center participates in the reaction or is only a spectator. For the same reason organic molecules that form an organometallic/metalloid complex under the reaction conditions, such as crown ethers or some reduction catalysts (for example, see: V. Peper, J. Martens, *Tetrahedron Lett.* **1996**, *37*, 8351–8354; J.-M. Brunel, O. Pardigon, B. Faure, G. Buono, *J. Chem. Soc. Chem. Commun.* **1992**, 287–288) were not selected. A further criteria imposed was that only reactions that form or break covalent chemical bonds were considered. Also, the review concentrates on catalytic reactions. Although in some cases stoichiometric or even excess catalysts were referred too, the main selection criteria was the existence of a catalytic cycle in the reaction, even if inefficient.

[10] G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, New York, **1997**.

[11] C. A. Deakyne, L. C. Allen, *J. Am. Chem. Soc.* **1979**, *101*, 3951–3959.

[12] H. Park, J. Suh, S. Lee, *J. Am. Chem. Soc.* **2000**, *122*, 3901–3908.

[13] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**.

[14] G. Buono, O. Chiodi, M. Willis, *Synlett* **1999**, 377–388.

[15] For a recent review, see: A. Yanagisawa in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 965–979.

[16] S. E. Denmark, D. M. Ce, N. B. Pratt, B. D. Griedel, *J. Org. Chem.* **1994**, *59*, 6161–6163.

[17] a) M. Iseki, Y. Kuroki, M. Takahashi, Y. Kobayashi, *Tetrahedron Lett.* **1996**, *36*, 5149–5150; b) M. Iseki, Y. Kuroki, M. Takahashi, S. Kishimoto, Y. Kobayashi, *Tetrahedron* **1997**, *53*, 3513–3526.

[18] a) K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron Lett.* **1998**, *39*, 2767–2770; b) K. Iseki, S. Mizuno, Y. Kuroki, Y. Kobayashi, *Tetrahedron* **1999**, *55*, 977–988.

[19] I. Chataigner, U. Piarulli, C. Gennari, *Tetrahedron Lett.* **1999**, *40*, 3633–3634.

[20] R. M. Angell, A. G. M. Barrett, D. C. Braddock, S. Swallow, B. D. Vickery, *Chem. Commun.* **1997**, 919–920.

[21] M. Nakajima, M. Saito, M. Shiro, S.-i. Hashimoto, *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420.

[22] One of the referees noticed that the discussion of the Denmark allylation reaction is a little confusing. In his opinion, the coordination of the Lewis base activates the silicon; it is debatable whether or not it makes the Si atom electron deficient. An hypervalent silicon atom may be more electron rich, but allows access to vacant orbitals.

[23] a) K. Ishihara, M. Mouri, Q. Gao, T. Maruyama, K. Furuta, H. Yamamoto, *J. Am. Chem. Soc.* **1993**, *115*, 11490–11495; b) S. Aoki, K. Mikami, M. Terada, T. Nakai, *Tetrahedron* **1993**, *49*, 1783–1792; c) J. A. Marshall, Y. Tang, *Synlett* **1992**, 653–654; d) The crotylation reaction that is catalyzed by the BINAP–Ag(I) complex is *anti*-selective: A. Yanagisawa, A. Ishiba, H. Nakashima, H. Yamamoto, *Synlett* **1997**, 88–90.

[24] S. E. Denmark, J. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 12021–12022.

[25] For recent reviews on catalytic enantioselective aldol reactions, see: a) S. G. Nelson, *Tetrahedron: Asymmetry* **1998**, *9*, 357–389; b) H. Gröger, E. M. Vogl, M. Shibasaki, *Chem. Eur. J.* **1998**, *4*, 1137–1141; c) E. M. Carreira in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), 2nd ed., Springer, Heidelberg, **1999**, pp. 998–1065; d) M. Sawamura, Y. Ito in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, pp. 493–512; e) E. M. Carreira in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, pp. 513–568.

[26] a) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497; c) C. Agami, F. Meynier, C. Puchot, J. Guilhem, C. Pascard, *Tetrahedron* **1984**, *40*, 1031–1038, and references therein.

[27] H. Hagiwara, H. Uda, *J. Org. Chem.* **1988**, *53*, 2308–2311.

[28] S. Danishefsky, P. Cain, *J. Am. Chem. Soc.* **1976**, *98*, 4975–4983.

[29] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) T. Bui, C. F. Barbas III, *Tetrahedron Lett.* **2000**, *41*, 6951–6954.

[30] B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *3*, 573–575.

[31] B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337.

[32] For a recent review on the Mannich reaction, see: S. E. Denmark, O. J.-C. Nicaise in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 923–961.

[33] W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199–201.

[34] a) S. E. Denmark, R. A. Stavenger, K.-T. Wong, *J. Org. Chem.* **1998**, *63*, 918–919; b) S. E. Denmark, R. A. Stavenger, K.-T. Wong, *Tetrahedron* **1998**, *54*, 10389–10402; c) S. E. Denmark, R. A. Stavenger, K.-T. Wong, X. Su, *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991; d) S. E. Denmark, R. A. Stavenger, *Acc. Chem. Res.* **2000**, *33*,

432–440; e) S. E. Denmark, R. A. Stavenger, *J. Am. Chem. Soc.* **2000**, *122*, 8837–8847.

[35] For a recent review on the enantioselective ring opening of epoxides, see: E. N. Jacobsen, M. H. Wu in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1309–1326.

[36] S. E. Denmark, P. A. Barsanti, K. T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428–2429.

[37] J. M. Brunel, O. Legrand, S. Reymond, G. Buono, *Angew. Chem.* **2000**, *112*, 2654–2657; *Angew. Chem. Int. Ed.* **2000**, *39*, 2554–2557.

[38] For recent reviews, see: a) K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1105–1120; b) M. Yamaguchi in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1121–1139; c) M. Kanai, M. Shibashaki in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, pp. 569–592.

[39] a) S. Colonna, H. Hiemstra, H. Wynberg, *J. Chem. Soc. Chem. Commun.* **1978**, 238–239; b) H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *46*, 4057–4060; c) K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2240.

[40] a) R. Helder, R. Arends, W. Bolt, H. Hiemstra, H. Wynberg, *Tetrahedron Lett.* **1977**, *25*, 2181–2182; b) H. Hiemstra, H. Wynberg, *J. Am. Chem. Soc.* **1981**, *103*, 417–430; c) S. Colonna, R. Re, H. Wynberg, *J. Chem. Soc. Perkin Trans. 1* **1981**, 547–552.

[41] A. Sera, K. Takagi, H. Katayama, H. Yamada, *J. Org. Chem.* **1988**, *53*, 1157–1161.

[42] N. Kobayashi, K. Iwai, *J. Org. Chem.* **1981**, *46*, 1823–1828.

[43] T. E. Horstmann, D. J. Guerin, S. J. Miller, unpublished results.

[44] S. Hanessian, V. Pham, *Org. Lett.* **2000**, *2*, 2975–2978.

[45] For reviews on catalytic Diels–Alder reactions, see: a) H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007–1019; b) D. A. Evans, J. S. Johnson in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1177–1235; c) K. Mauroka in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, pp. 467–491; d) K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702–3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558–3588.

[46] O. Riant, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 7403–7405; b) O. Riant, H. B. Kagan, *Tetrahedron* **1994**, *50*, 4543–4554.

[47] M. Koerner, B. Rickborn, *J. Org. Chem.* **1990**, *55*, 2662–2672.

[48] K. A. Ahrendt, C. J. Borths, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.

[49] T. Schuster, M. Bauch, G. Dürner, M. W. Göbel, *Org. Lett.* **2000**, *2*, 179–181; b) T. Schuster, M. Kurz, M. W. Göbel, *J. Org. Chem.* **2000**, *65*, 1697–1701.

[50] For a general review see: Y. Hayashi, K. Narasaka in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1255–1269.

[51] a) H. Wynberg, E. G. J. Saring, *J. Am. Chem. Soc.* **1982**, *104*, 166–168; b) H. Wynberg, E. G. J. Saring, *J. Org. Chem.* **1985**, *50*, 1977–1979.

[52] A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2000**, *122*, 7831–7832.

[53] M. A. Calter, *J. Org. Chem.* **1996**, *61*, 8006–8007.

[54] M. A. Calter, F. C. Bi, *Org. Lett.* **2000**, *2*, 1529–1531.

[55] W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874–9875.

[56] G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.

[57] H. Wack, A. E. Taggi, A. M. Hafez, W. J. Drury III, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 1531–1532.

[58] A. Mori, S. Inoue in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 983–994.

[59] a) G. Bredig, P. S. Fiske, *Biochem. Z.* **1912**, *46*, 7; b) V. Prelog, M. Wilhelm, *Helv. Chim. Acta* **1954**, *37*, 1634–1661.

[60] J.-I. Oku, N. Ito, S. Inoue, *Macromol. Chem. Phys.* **1982**, *183*, 579–589.

[61] R. H. Gregory, *Chem. Rev.* **1999**, *99*, 3649–3682.

[62] a) M. Arend, *Angew. Chem.* **1999**, *111*, 3047–3049; *Angew. Chem. Int. Ed.* **1999**, *38*, 2873–2874; b) L. Yet, *Angew. Chem.* **2001**, *113*, 900–902; *Angew. Chem. Int. Ed.* **2001**, *40*, 875–877; c) D. Enders, J. P. Shilvock, *Chem. Soc. Rev.* **2000**, *29*, 359–373.

[63] M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.

[64] a) J. Oku, S. Inoue, *J. Chem. Soc. Chem. Commun.* **1981**, 229–230; b) K. Tanaka, A. Mori, S. Inoue, *J. Org. Chem.* **1990**, *55*, 181–185; c) H. Danda, *Synlett* **1991**, 263–264; d) H. Danda, H. Nishikawa, K. Otaka, *J. Org. Chem.* **1991**, *56*, 6740–6741.

[65] E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160.

[66] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; b) M. S. Sigman, P. Vachal, E. N. Jacobsen, *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem. Int. Ed.* **2000**, *39*, 1279–1281.

[67] a) P. Langer, *Angew. Chem.* **2000**, *112*, 3177–3180; *Angew. Chem. Int. Ed.* **2000**, *39*, 3049–3052; b) E. Ciganek, *Org. React.* **1997**, *51*, 201–350.

[68] Y. Iwabuchi, M. Nakatani, N. Yokoyama, S. Hatekeyama, *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.

[69] F. Ameer, S. E. Drewes, S. Freese, P. T. Kaye, *Synth. Commun.* **1988**, *18*, 495–500.

[70] T. Hayase, T. Shibata, K. Soai, Y. Wakatsuki, *Chem. Commun.* **1998**, 1271–1272.

[71] F. Roth, P. Grgax, G. Frater, *Tetrahedron Lett.* **1992**, *33*, 1045–1048.

[72] See for example: a) M. Shi, J.-K. Jiang, Y.-S. Feng, *Org. Lett.* **2000**, *2*, 2397–2400; b) M. Ono, K. Nishimura, Y. Nagaoka, K. Tomioka, *Tetrahedron Lett.* **1999**, *40*, 1509–1512; c) T. Iwama, S.-I. Tsijiyama, H. Kinoshita, K. Kanamatsu, Y. Tsurukami, T. Iwamura, S.-I. Watanabe, T. Kataoka, *Chem. Pharm. Bull.* **1999**, *47*, 956–961; d) M. Kawamura, S. Kobayashi, *Tetrahedron Lett.* **1999**, *40*, 1539–1542; e) V. K. Aggarwal, A. Mereu, G. J. Tarver, R. MaCague, *J. Org. Chem.* **1998**, *63*, 7183–7189; f) E. P. Kündig, L. H. Xu, P. Romanens, G. Bernardinelli, *Tetrahedron Lett.* **1993**, *34*, 7049–7052.

[73] For recent review see D. Enders, K. Breuer in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1093–1102.

[74] a) R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726; b) R. Breslow, C. Schmuck, *Tetrahedron Lett.* **1996**, *37*, 8241–8242, and references therein.

[75] a) J. H. Teles, J.-P. Melder, K. Ebel, R. Schneider, E. Gehrer, W. Harder, S. Brode, D. Enders, K. Breuer, G. Raabe, *Helv. Chim. Acta* **1996**, *79*, 61–83, and references therein; b) D. Enders, K. Breuer, G. Raabe, J. Runsink, J. H. Teles, J.-P. Melder, K. Ebel, S. Brode, *Angew. Chem.* **1995**, *107*, 1119–1122; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1021–1023.

[76] a) R. L. Knight, F. J. Leepert, *Tetrahedron Lett.* **1997**, *38*, 3611–3614; b) A. U. Gerhardt, F. J. Leepert, *Tetrahedron Lett.* **1997**, *38*, 3615–3618.

[77] C. A. Dvorak, V. H. Rhawal, *Tetrahedron Lett.* **1998**, *39*, 2925–2928.

[78] D. Enders, K. Breuer, J. Runsink, J. H. Teles, *Helv. Chim. Acta* **1996**, *79*, 1899–1902.

[79] P. Somfai, *Angew. Chem.* **1997**, *109*, 2849–2851; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2731–2733.

[80] a) M. M. Vavon, P. Peignier, *Bull. Soc. Chim. Fr.* **1929**, *45*, 293; b) R. Wegler, *Liebigs Ann. Chem.* **1932**, *498*, 62; c) See also: E. Vedejs, O. Daugulis, S. T. Diver, *J. Org. Chem.* **1996**, *61*, 430–431.

[81] a) J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26; b) E. Vedejs, X. Chen, *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585; c) J. Eames, *Angew. Chem.* **2000**, *112*, 913–916; *Angew. Chem. Int. Ed.* **2000**, *39*, 885–888.

[82] E. Vedejs, E. Rozners, *J. Am. Chem. Soc.* **2001**, *123*, 2428–2429.

[83] s = (rate constant of fast-reacting enantiomer)/(rate constant of slow-reacting enantiomer); see H. B. Kagan, J. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.

[84] T. Kawabata, M. Nagato, K. Takasu, K. Fuji, *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170.

[85] Some powerful metallocene-derived planar chiral catalysts could be noted here as well. See ref. [9a–d]. Although many of these catalysts act as organocatalysts, they can not be strictly considered as organic because of the presence of the metal.

[86] A. C. Spivey, T. Fekner, S. E. Spey, *J. Org. Chem.* **2000**, *65*, 3154–3159.

[87] T. Sano, K. Imai, K. Ohashi, T. Oriyama, *Chem. Lett.* **1999**, 265–266.

[88] a) T. Oriyama, K. Imai, T. Hosoya, T. Sano, *Tetrahedron Lett.* **1998**, *39*, 397 – 400; b) T. Oriyama, K. Imai, T. Hosoya, T. Sano, *Tetrahedron Lett.* **1996**, *37*, 8543 – 8546.

[89] T. Sano, H. Miyata, T. Oriyama, *Enantiomer* **2000**, *5*, 119.

[90] a) S. Kobayashi, M. Horibe, *Tetrahedron: Asymmetry* **1995**, *6*, 2565 – 2570; b) S. Kobayashi, M. Horibe, *J. Am. Chem. Soc.* **1994**, *116*, 9805 – 9806.

[91] M. Calter, T. K. Hollis, L. E. Overmann, J. Ziller, G. G. Zipp, *J. Org. Chem.* **1997**, *62*, 1449 – 1456.

[92] B. Clapham, C.-W. Cho, K. D. Janda, *J. Org. Chem.* **2001**, *66*, 868 – 873.

[93] a) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998**, *120*, 1629 – 1630; b) G. T. Copeland, E. R. Jarvo, S. J. Miller, *J. Org. Chem.* **1998**, *63*, 6784 – 6785; c) G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 4306 – 4307; d) E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, Jr., S. J. Miller, *J. Am. Chem. Soc.* **1999**, *121*, 11 638 – 11 643; e) J. T. Blank, D. J. Guerin, S. J. Miller, *Org. Lett.* **2000**, *2*, 1247 – 1249.

[94] a) R. A. Aitken, J. Gopal, *Tetrahedron: Asymmetry* **1990**, *1*, 517 – 520; b) J. Hiratake, M. Inagaki, Y. Yamamoto, J. Oda, *J. Chem. Soc. Perkin Trans. 1* **1987**, 1053 – 1058; c) C. Bolm, I. Schiffers, C. L. Dinter, A. Gerlach, *J. Org. Chem.* **2000**, *65*, 6984 – 6991.

[95] a) E. Vedejs, O. Daugulis, S. T. Driver, *J. Org. Chem.* **1996**, *61*, 430 – 431; b) E. Vedejs, O. Daugulis, *J. Am. Chem. Soc.* **1999**, *121*, 5813 – 5814; c) E. Vedejs, J. A. MacKay, *Org. Lett.* **2001**, *3*, 535 – 536.

[96] a) C. Fehr, *Angew. Chem.* **1996**, *108*, 2726 – 2748; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566 – 2587; b) A. Yanagisawa, H. Yamamoto in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 1295 – 1306.

[97] a) C. Fehr, I. Stempf, J. Galindo, *Angew. Chem.* **1993**, *105*, 1091 – 1093; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1042 – 1044; b) C. Fehr, I. Stempf, J. Galindo, *Angew. Chem.* **1993**, *105*, 1093 – 1095; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1044 – 1046.

[98] K. Nishimura, M. Ono, Y. Nagaoka, K. Tomioka, *Angew. Chem.* **2001**, *113*, 454 – 456; *Angew. Chem. Int. Ed.* **2001**, *40*, 440 – 442.

[99] A. Yanagisawa, T. Watanabe, T. Kikuchi, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 2979 – 2983.

[100] C. Fehr, J. Galindo, *Angew. Chem.* **1994**, *106*, 1967 – 1969; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1888 – 1889.

[101] A. Yanagisawa, T. Watanabe, T. Kikuchi, H. Yamamoto, *J. Org. Chem.* **2000**, *65*, 2979 – 2983.

[102] P. Riviere, K. Koga, *Tetrahedron Lett.* **1997**, *38*, 7589 – 7592.

[103] E. Vedejs, A. W. Kruger, *J. Org. Chem.* **1998**, *63*, 2792 – 2793.

[104] Y. Nakamura, S. Takeuchi, A. Ohira, Y. Ohgo, *Tetrahedron Lett.* **1996**, *37*, 2805 – 2808.

[105] S. Takeuchi, Y. Nakamura, Y. Ohgo, D. P. Curran, *Tetrahedron Lett.* **1998**, *39*, 8691 – 8694.

[106] M. J. Porter, J. Skidmore, *Chem. Commun.* **2000**, 1215 – 1225.

[107] a) V. K. Aggarwal in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 679 – 693; b) T. Katsuki in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., Wiley, New York, **2000**, pp. 287 – 326; c) S. E. Denmark, Z. Wu, *Synlett* **1999**, 847 – 859, Issue Sup. 1; d) M. Frohn, Y. Shi, *Synlett* **2000**, 1979 – 2000.

[108] Iminium salts: a) X. Lusinchi, G. Hanquet, *Tetrahedron* **1997**, *53*, 13 727 – 13 738; b) V. K. Aggarwal, M. Wang, *Chem. Commun.* **1996**, 191 – 192; c) P. C. B. Page, G. A. Rassias, D. Bethell, M. B. Schilling, *J. Org. Chem.* **1998**, *63*, 2774 – 2777; d) A. Armstrong, G. Ahmed, I. Garnett, K. Goacolou, J. S. Wailes, *Tetrahedron* **1999**, *55*, 2341 – 2352; α-amidoketones: e) A. Armstrong, B. R. Hayter, *Tetrahedron* **1999**, *55*, 11 119 – 11 126; *N,N*-dialkylalloxans: f) A. J. Carnell, R. A. W. Johnstone, C. C. Parsy, W. R. Sanderson, *Tetrahedron Lett.* **1999**, *40*, 8029 – 8032.

[109] M. F. A. Adamo, V. K. Aggarwal, M. A. Sage, *J. Am. Chem. Soc.* **2000**, *122*, 8317 – 8318.

[110] H_2O_2 as the oxidant: a) L. Shu, Y. Shi, *Tetrahedron Lett.* **1999**, *40*, 8721 – 8724; b) L. Shu, Y. Shi, *J. Org. Chem.* **2000**, *65*, 8807 – 8810.

[111] a) D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1996**, *118*, 491 – 492; b) D. Yang, X.-C. Wang, M.-K. Wong, Y.-C. Yip, M.-W. Tang, *J. Am. Chem. Soc.* **1996**, *118*, 11 311 – 11 312; c) C. E. Song, Y. H. Kim, K. C. Lee, S.-G. Lee, B. W. Jin, *Tetrahedron: Asymmetry* **1997**, *8*, 2921 – 2926; d) W. Adam, C.-G. Zhao, *Tetrahedron: Asymmetry* **1997**, *8*, 3995 – 3998; e) D. Yang, Y.-C. Yip, J. Chen, K.-K. Cheung, *J. Am. Chem. Soc.* **1998**, *120*, 7659 – 7660; f) D. Yang, M.-K. Wong, Y.-C. Yip, X.-C. Wang, M.-W. Tang, J.-H. Zheng, K.-K. Cheung, *J. Am. Chem. Soc.* **1998**, *120*, 5943 – 5952; g) D. Yang, Y.-C. Yip, M.-W. Tang, M.-K. Wong, K.-K. Cheung, *J. Org. Chem.* **1998**, *63*, 9888 – 9894.

[112] a) Fructose-derived catalysts: Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806 – 9807; b) ketones derived from (−)-quinic acid: Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1997**, *62*, 8622 – 8623; W. Adam, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1999**, *10*, 2749 – 2755; c) Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11 224 – 11 235; d) Y. Tu, Z.-X. Wang, M. Frohn, M. He, H. Yu, Y. Tang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 8475 – 8485; e) Z.-X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **1999**, *64*, 6443 – 6458; f) halogenated cyclohexanones: A. Solladié-Cavallo, L. Bouérat, *Org. Lett.* **2000**, *2*, 3531 – 3534.

[113] Z.-X. Wang, S. M. Miller, O. P. Anderson, Y. Shi, *J. Org. Chem.* **2001**, *66*, 521 – 530.

[114] H. Tian, X. She, L. Shu, H. Yu, Y. Shi, *J. Am. Chem. Soc.* **2000**, *122*, 11 551 – 11 552.

[115] pH study: a) Z.-X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.* **1997**, *62*, 2328 – 2329; b) Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 3099 – 3104.

[116] a) Epoxidation of silyl enol ethers: Y. Zhu, Y. Tu, H. Yu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 7819 – 7822; W. Adam, R. T. Fell, C. R. Saha-Möller, C.-G. Zhao, *Tetrahedron: Asymmetry* **1998**, *9*, 397 – 401; b) Monoepoxidation of conjugated dienes: M. Frohn, M. Dalkiewicz, Y. Tu, Z.-X. Wang, Y. Shi, *J. Org. Chem.* **1998**, *63*, 2948 – 2953; c) epoxidation of conjugated enynes: G.-A. Cao, Z.-X. Wang, Y. Tu, Y. Shi, *Tetrahedron Lett.* **1998**, *39*, 4425 – 4428; Z.-X. Wang, G.-A. Cao, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7646 – 7650; d) epoxidation of 2,2-disubstituted vinylsilanes: J. D. Warren, Y. Shi, *J. Org. Chem.* **1999**, *64*, 7675 – 7677; e) kinetic resolution of racemic cyclic olefins: M. Frohn, X. Zhou, J.-R. Zhang, Y. Tang, Y. Shi, *J. Am. Chem. Soc.* **1999**, *121*, 7718 – 7719.

[117] A. Armstrong, B. Hayter, *Chem. Commun.* **1998**, 621 – 622.

[118] a) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 4831 – 4832; b) Z. Xiong, E. J. Corey, *J. Am. Chem. Soc.* **2000**, *122*, 9328 – 9329.

[119] W. Adam, C. R. Saha-Möller, C.-G. Zhao, *J. Org. Chem.* **1999**, *64*, 7492 – 7497.

[120] C. Einhorn, J. Einhorn, C. Marcadal-Abbadi, J.-L. Pierre, *J. Org. Chem.* **1999**, *64*, 4542 – 4546.

[121] For a recent review, see: a) C. Bolm, K. Muñiz, J. P. Hildebrand in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Heidelberg, **1999**, pp. 697 – 710; b) H. B. Kagan in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., VCH, New York, **2000**, pp. 327 – 357; see also in c) D. Bethell, P. C. Bulman Page, H. Vahedi, *J. Org. Chem.* **2000**, *65*, 6756 – 6760.

[122] R. Schiffers, H. B. Kagan, *Synlett* **1997**, 1175 – 1178. A similar type of reaction has been devised for the asymmetric addition of trimethylsilylcyanide (TMS-CN) to aldehydes (I. P. Holmes, H. B. Kagan, *Tetrahedron Lett.* **2000**, *41*, 7457 – 7460).

[123] For recent reviews, see: a) V. K. Aggarwal, *Synlett* **1998**, 329 – 336; b) A.-H. Li, L.-X. Dai, V. K. Aggarwal, *Chem. Rev.* **1997**, *97*, 2341 – 2372.

[124] a) N. Furukawa, Y. Sugihara, H. Fujihara, *J. Org. Chem.* **1989**, *54*, 4222 – 4224; b) A.-H. Li, L.-X. Dai, X.-L. Hou, Y.-Z. Huang, F.-W. Li, *J. Org. Chem.* **1996**, *61*, 489 – 493; c) T. Saito, D. Akiba, M. Sakairi, S. Kanazawa, *Tetrahedron Lett.* **2001**, *42*, 57 – 59.

[125] A. Solladié-Cavallo, A. Diep-Vohuule, V. Sunjic, V. Vinkovic, *Tetrahedron: Asymmetry* **1996**, *7*, 1783 – 1788.

[126] K. Julienne, P. Metzner, *J. Org. Chem.* **1998**, *63*, 4532 – 4534.

[127] a) V. K. Aggarwal, J. G. Ford, S. Fonquerna, H. Adams, R. V. H. Jones, R. Fieldhous, *J. Am. Chem. Soc.* **1998**, *120*, 8328 – 8339; b) V. K. Aggarwal, J. G. Ford, R. V. H. Jones, R. Fieldhous, *Tetrahedron: Asymmetry* **1998**, *9*, 1801 – 1808; c) V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lyndon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem.* **2001**, *113*, 1479 – 1482; *Angew. Chem. Int. Ed.* **2001**, *40*, 1430 – 1433; d) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara,

G. Hynd, M. Porcelloni, *Angew. Chem.* **2001**, *113*, 1482 – 1485; *Angew. Chem. Int. Ed.* **2001**, *40*, 1433 – 1436.

[128] a) M. J. O'Donnell in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), 2nd ed., VCH, New York, **2000**, pp. 727 – 755; b) A. Nelson, *Angew. Chem.* **1999**, *111*, 1685 – 1687; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583 – 1585; c) H.-U. Blaser, *Tetrahedron: Asymmetry* **1991**, *2*, 843 – 866.

[129] Chiral crown ethers and some chiral hydroxylated compounds such as (4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (TADDOL), are particularly efficient catalysts in phase-transfer reactions. This review focuses only on quaternary ammonium salts, in which the metal is replaced by the chiral onium counterion under the reaction conditions. Owing to the differences in the mechanism of reactions mediated by crown ethers, which complex the metal ion, this latter topic is beyond the scope of this paper.

[130] M. Rabinovitz, Y. Cohen, M. Halpern, *Angew. Chem.* **1986**, *11*, 958 – 968; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 960 – 970.

[131] See in E. V. Dehmlow, S. S. Dehmlow, *Phase Transfer Catalysis*, 3rd ed., VCH, Weinheim, **1993**.

[132] M. J. O'Donnel, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353 – 2355, and references therein.

[133] P. A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Pulido, S. M. Roberts, L. E. Wu, *Chem. Commun.* **1997**, 739 – 740, and references therein.

[134] K. B. Lipkowitz, M. W. Cavanaugh, B. Baker, M. J. O'Donnell, *J. Org. Chem.* **1991**, *56*, 5181 – 5190.

[135] a) E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13 000 – 13 001; b) for earlier references of this type of reaction, see: M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353 – 2355.

[136] See, for example: a) J. C. Fiaud, *Tetrahedron Lett.* **1975**, 3495 – 3496; b) K. Saigo, H. Koda, H. Nohira, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3119 – 3120; c) S. Julia, A. Ginebreda, J. Guixer, A. Tomás, *Tetrahedron Lett.* **1980**, *21*, 3709 – 3712.

[137] a) U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446 – 447; b) A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowsky, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442 – 443; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476 – 477.

[138] M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507 – 4518.

[139] a) B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2403 – 2409; b) B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2391 – 2402.

[140] D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowsky, *J. Org. Chem.* **1987**, *52*, 4745 – 4752.

[141] a) E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347 – 5350; b) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12 414 – 12 415; c) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595 – 8598.

[142] S. Colonna, A. Re, H. Wynberg, *J. Chem. Soc. Perkin Trans. 1* **1981**, 547 – 552.

[143] R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710 – 4711.

[144] E. J. Corey, F.-Y. Zang, *Org. Lett.* **2000**, *2*, 4257 – 4259.

[145] T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hébrault, *Org. Lett.* **2000**, *2*, 2959 – 2962.

[146] F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 639 – 641.

[147] a) C. M. Gasparsk, M. J. Miller, *Tetrahedron* **1991**, *29*, 5367 – 5378; b) M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843 – 3846.

[148] A. Ando, T. Miura, T. Tatematsu, T. Shiori, *Tetrahedron Lett.* **1993**, *34*, 1507 – 1510.

[149] H. Sasai, N. Itoh, T. Suzuki, M. Shibashaki, *Tetrahedron Lett.* **1993**, *34*, 855 – 858.

[150] E. J. Corey, F.-Y. Zhang, *Angew. Chem.* **1999**, *111*, 2057 – 2059; *Angew. Chem. Int. Ed.* **1999**, *38*, 1931 – 1934.

[151] K. Iseki, T. Nagai, Y. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 3137 – 3138.

[152] S. Arai, S. Hamaguchi, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 2997 – 3000.

[153] a) J. C. Hummelen, H. Wynberg, *Tetrahedron Lett.* **1978**, *12*, 1089 – 1092; b) S. Colonna, R. Fornasier, U. Pfeiffer, *J. Chem. Soc. Perkin Trans. 1* **1978**, 8 – 11.

[154] a) S. Arai, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 2145 – 2148; b) S. Arai, T. Ishida, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 8299 – 8302.

[155] A. H. Li, L. X. Dai, X. L. Hou, Y. Z. Huang, F. W. Li, *J. Org. Chem.* **1996**, *61*, 489 – 493.

[156] S. Juliá, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968 – 969; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 929 – 931.

[157] a) J. V. Allen, S. Bergeron, M. J. Griffiths, S. Mukherjee, S. M. Roberts, N. M. Williamson, L. E. Wu, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3171 – 3180; b) R. W. Flood, T. P. Geller, S. A. Petty, S. M. Roberts, J. Skidmore, M. Volk, *Org. Lett.* **2001**, *3*, 683 – 686.

[158] J. R. Flisak, K. J. Gombatz, M. M. Holmes, A. A. Jarmas, I. Lantos, W. L. Mendelson, V. J. Novack, J. J. Remich, L. Snyder, *J. Org. Chem.* **1993**, *58*, 6247 – 6252.

[159] H. Wynberg, B. Marman, *J. Org. Chem.* **1980**, *45*, 158 – 161.

[160] a) L. Alcaraz, G. Macdonald, J. P. Ragot, N. Lewis, R. J. K. Taylor, *J. Org. Chem.* **1998**, *63*, 3526 – 3527; b) G. Macdonald, L. Alcaraz, N. Lewis, R. J. K. Taylor, *Tetrahedron Lett.* **1998**, *39*, 5433 – 5436.

[161] B. Lygo, D. C. M. To, *Tetrahedron Lett.* **2001**, *42*, 1343 – 1346.

[162] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *1*, 1287 – 1290.

[163] H. Tohma, S. Takizawa, H. Watanabe, Y. Fukukoa, T. Maegawa, Y. Kita, *J. Org. Chem.* **1999**, *64*, 3519 – 3523.

[164] M. D. Drew, N. J. Lawrence, W. Watson, S. A. Bowles, *Tetrahedron Lett.* **1997**, *38*, 5857 – 5860; for earlier reference see: S. Colonna, R. Fornasier, *J. Chem. Soc. Perkin Trans. 1* **1978**, 371 – 373.

[165] For a review on recent developments in asymmetric catalysis with synthetic polymers, see: a) L. Pu, *Tetrahedron: Asymmetry* **1998**, *9*, 1457 – 1477; b) S. Ebrahim, M. Willis, *Tetrahedron: Asymmetry* **1997**, *8*, 3163 – 3173.

[166] The simplest enantioselective catalytic transformation of this type is, indeed, the spontaneous resolution of configurationally labile chiral organic molecules. See, for example: O. Tissot, M. Gouygou, F. Dallemer, J. C. Daran, G. G. A. Balavoine, *Angew. Chem.* **2001**, *113*, 1110 – 1112; *Angew. Chem. Int. Ed.* **2001**, *40*, 1076 – 1078; this topic, however, is beyond the scope of this review.

[167] a) R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997 – 2011; b) K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013 – 2033; c) R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146 – 153.

[168] E. Fasella, S. D. Dong, R. Breslow, *Bioorg. Med. Chem.* **1999**, *7*, 709 – 714, and references therein.

[169] B. Sellergren, *Angew. Chem.* **2000**, *112*, 1071 – 1078; *Angew. Chem. Int. Ed.* **2000**, *39*, 1031 – 1037.

[170] a) B. Sellergren, K. J. Shea, *Tetrahedron: Asymmetry* **1994**, *5*, 1403 – 1406; b) B. Sellergren, R. N. Karmalkar, K. J. Shea, *J. Org. Chem.* **2000**, *65*, 4009 – 4027.

[171] a) A. R. Fersht, *Enzyme Structure and Mechanisms*, Freeman, New York, **1985**; b) T. Bruice, F. C. Lightstone, *Acc. Chem. Res.* **1999**, *32*, 127 – 136.