Review

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*Review*

# Asymmetric Bio- and Organocatalysis. Historical Aspects and Concepts

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## Abstract

To those who did not follow the invention and development of enantioselective catalysis, this mini-review introduces some pertinent historical aspects of the field and presents the scientific concepts of asymmetric bio- and organocatalysis. They are powerful technologies applied in organic laboratories and industry. They realize chiral amplification by converting inexpensive achiral substrates and reagents into enantiomerically enriched products using readily recoverable solvents, if any. Racemic substrates can also be deracemized catalytically. More sustainable fabrications are now available that require neither toxic metallic species, nor costly reaction conditions in terms of energy, atmosphere control, product purification and safety. Nature has been the source of the first asymmetric catalysts (microorganisms, enzymes, alkaloids, amino acids, peptides, terpenoids, sugars and their derivatives). They act as temporarily chiral auxiliaries and reduce reaction activation free enthalpies by changing their mechanisms. Reductions, oxidations, carbon-carbon and carbon-heteroatom bond forming reactions are part of the process panoply. Asymmetric catalyzed multicomponent and domino reactions are becoming common. Typical modes of activation are proton transfers, hydrogen bonded complex formation, charged or uncharged acid/base pairing (e.g., $\sigma$-hole catalysts), formation of equilibria between achiral aldehydes and ketones with their chiral iminium salt or/and enamine intermediates, Umpolung of aldehydes and ketones by reaction with N-heterocyclic carbenes (NHCs), phase transfer catalysis (PTC), etc. Often, best enantioselectivities are observed with polyfunctional catalysts derived from natural compounds, or not. They may combine in a chiral structure nitrogen, phosphorus, sulfur, selenium, iodine functional moieties. Today, man made enantiomerically enriched, if not enantiomerically pure, catalysts are available in both their enantiomeric forms. Being robust, they are recovered and reused readily.

**Keywords:** chiral amplification; enzymes; man made polyfunctional catalysts; natural products; non-metallic catalyzed enantioselective reactions; reaction mechanisms

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## 1. Introduction

The invention and development of catalytic enantioselective reactions [1] are among the most studied topics of stereochemistry and chemical synthesis. Enantioselective catalysis has become routine in the pharmaceutical industry [2–4] and other industries (crop protection, fragrances) [5–8]. Before 2000, asymmetric catalysis relied mostly upon organometallic complexes (not discussed here) and biocatalysis (Chap. 2) [9]. During the last twenty-five years, organocatalysis has dominated the field of asymmetric synthesis (Chap. 3-11) [10–12]. A large number of enantioselective reactions are available. This mini-review presents a selection of them. It has some educational value for chemists with only basic training in stereochemistry.

Early contributions to asymmetric synthesis [13,14] were reported by Emil Fischer [15], Markwald [16], and McKenzie [17] in the early 1900s. Most natural products (terpenes, steroids, alkaloids, lactic acid, tartaric acid, etc.) are chiral and enantiomerically enriched, if not enantiomerically pure. Life's building blocks (amino acids, nucleic acids, carbohydrates, etc.) are chiral and enantiomerically pure (enantiopure). The biopolymers resulting from their combination (e.g., peptides, proteins, oligosaccharides, polysaccharides, glycoproteins, DNA, RNA) are also chiral and enantiopure. Most biomolecules and their biopolymers are homochiral, i.e., they contain only one of two possible enantiomers. Homochirality is a signature of life [18–21]. It has been a dream for chemists to imitate Nature that, through photosynthesis, converts water and carbon dioxide (two achiral reagents) into homochiral compounds such as D-glucose.

(+)-(*R*)-Limonene is responsible for the orange flavor, while its enantiomer, (-)-(*S*)-limonene, is a constituent of the lemon flavor. (+)-(*S*)-Carvone is found in the smell of cumin sheaths, (-)-(*R*)-carvone is a component of spearmint smell. D-Asparagine has a sweet taste, L-asparagine is bitter [22,23]. When a chiral drug interacts with its receptor (e.g., an enzyme), it is no surprise that its two enantiomers interact differently and may lead to different biological effects [24–28]. Your right foot fits better in a right shoe than in a left shoe. In the 1960s, racemic Thalidomide (1:1 mixture of two possible enantiomers) had been administered to pregnant women who gave birth to babies with physical deformations. This disaster is a convincing example of the dependence of pharmacological response toward both enantiomers of a chiral drug. The (*R*)-enantiomer of Thalidomide exhibits desirable analgesic properties; however, the (*S*)-enantiomer does not and is responsible for the terrible teratogenic effects [29]. Metabolite racemates are also present in Nature [30].

### *1.1. Discovery of Biocatalysis and Chirality*

In 1858, Louis Pasteur reacted the racemic mixture of ammonium tartrate with a microorganism called *penicillum* glaucum [31]. An enzyme of this microorganism breaks down the (2*R*,3*R*)-enantiomer of ammonium tartrate (salt derived from L-(+)-tartaric acid) completely and leaves the (2*S*,3*S*)-enantiomer of ammonium tartrate almost unchanged (salt of D-(-)-tartaric acid). This observation has led to a biochemical method of discrimination between two enantiomers widely used today in industry [32–38].

In 1894, Emil Fischer proposed his “lock and key” model for enzyme-catalyzed reactions [39]. A right hand enters a right glove more easily than a left hand. Enzymes display remarkable catalytic activity. This makes them very much used today as catalysts in the industry when mild reaction conditions (temperature, pH) are required [9,40]. After Pasteur's discoveries, the production of enantiomerically enriched compounds from racemic mixtures or achiral substrates was attempted. In 1908, Rosenthaler reported the first example: the addition of HCN to benzaldehyde (PhCHO), which yields mandelonitrile (see below). The chiral catalyst was emulsin, an enzyme isolated from the almond. Today, catalysts made by chemists that are not enzymes or microorganisms are becoming as effective, and often they are easier to use [10]. The enantioselectivities are very high, as are their TON (turnover number: moles of product formed per mole of catalyst) and their TOF (turnover number per unit of time). They can work under conditions (temperature, solvent, nature of reactants) that can be varied much more than with enzymes or microorganisms. Often, an enzyme allows the preparation of only one of the two possible enantiomers. Chemists produce enantiomerically enriched catalysts; they enable us to obtain either one or the other enantiomer of a chiral product. Nevertheless, enzymes and microorganisms remain interesting as catalysts for ecological reasons (no heavy metals, water as solvent, green chemistry).

According to the IUPAC, “asymmetry” in chemistry is a property of three-dimensional objects, such as molecules and crystals, devoid of any symmetry element. These objects belong to the symmetry point group $C_1$ (e.g., (*R*)- and (*S*)-lactic acid: MeCH(OH)COOH). Like your left hand and right hand, the mirror image of a chiral object is not superimposable with itself. Molecules with a two-fold axis of rotation, such as (2*R*,3*R*)- and (2*S*,3*S*)-tartaric acid: HOOC-CH(OH)-CH(OH)-COOH), are also chiral (symmetry point group $C_2$). Objects sharing a plane of symmetry are achiral. “Asymmetric induction” describes the preferential formation in a chemical reaction of one enantiomer or diastereoisomer over the other due to the influence of a chiral feature (chiral promoter) present in the substrate, reagent, catalyst, or environment. “Asymmetric syntheses” are those reactions, or sequences of reactions, which produce chiral non-racemic substances from achiral compounds with the intermediate use of chiral non-racemic materials, but excluding a separation operation [41]. With a chiral promoter, the achiral substrate (single reactant reaction, or multiple reactant reaction, one of the reactant called substrate, the other(s) reactant(s)) enters equilibria with complexes and/or aggregates that are diastereomeric (two diastereomers have different physical and chemical properties, Figure 1.1). This is the case for catalysts that are ion pairs (highly polar species), Brønsted–Lowry acids (protic acids), Lewis acids, bases, enzymes, neutral molecules, or metallic species (less polar systems). The chiral promoter and the complexes it forms also interact with solvent molecules. The chiral promoter can be a soluble substance or a solid interacting with its surface [42]. In 1902, Henri proposed a general theory for the sucrase-catalyzed hydrolysis of sucrose (saccharose) into fructose and glucose (reaction called inversion because the angle of specific rotation of the plane-polarized light changes from a positive to a negative value) in which he recognized that the enzyme equilibrates with a complex containing the substrate (sucrose) [43]. In 1913, Michaelis and Menten proposed their classical mechanism for the enzyme (**E**) catalyzed reaction (eq. (1.1)) which converts substrate **S** into product **P**, via an intermediate **X** [44,45].

$$\mathbf{S} + \mathbf{E} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{X} \xrightarrow{k_2} \mathbf{P} + \mathbf{E} \qquad (1.1)$$

The intermediates complexes or/and aggregates invoked above (correspond to two different intermediates **X** and **X'**) can have different stability or/and rates for their transformation into chiral products that are enantiomers. They evolve to at least two transition states that can be associated with different free enthalpy of activation ($\Delta^{\ddagger}G^{T}$). If the chiral promoter is enantiomerically enriched two enantiomeric products can be obtained in proportion (*er* = enantiomeric ratio) different from 50/50. One defines enantiomeric excess *ee* = [fraction of the major enantiomer - fraction of the minor enantiomer]/[sum of the fractions of major and minor enantiomers]. An enantiomerically enriched product is called scalemic mixture (*er* > 50/50 and *ee* > 0%). An enantiomerically pure compound (*ee* = 100%) does not exist because no analytical method can measure *er* = 100/0. The detection limit for the minor enantiomer cannot be zero, but it can be relatively small. For instance, if the detection limit for a minor enantiomer is 1/1000, *er* > 99.9/0.1, or *ee* > 99.8%. The process becomes catalytic and enantioselective if the enantiomerically enriched promoter is used in sub-stoichiometric quantities. Asymmetric catalysis might be accompanied by chiral amplification (*ee* of the product is higher than that of the catalysts, non-linear effect), chiral loss (*ee* of the product is lower than that of the catalysts), or not [46–51]. Under kinetic control, a racemic chiral promoter leads to a racemic mixture of the product. Its enantiomeric ratio *er* =50/50 and its enantiomeric excess *ee* = 0%.

### *1.2. Kinetic Enantioselectivity*

A large number of catalysts may be soluble in the reaction medium (homogeneous catalysis). Others, such as crystalline quartz, zeolites, or metal surfaces impregnated with chiral molecules, are not (heterogeneous catalysis). Since two enantiomers have the same stability in an achiral environment, the rate of their equilibration (racemization) might compete with the rates of their formation, and thus lead to loss of enantioselectivity. The catalyst catalyzes the forward reaction as well as the backward (opposite) reaction (microscopic reversibility principle). The highest enantioselectivities are obtained under non-equilibrating conditions (exergonic equilibria, $K^{T} > 1$), *i.e.*, under kinetic control. The transition states of these reactions are composed of diastereomeric transition structures. For the addition of achiral HCN (linear structure) to achiral PhCHO (shares a plane of symmetry) to give mandelonitrile (PhCH(OH)CN), one of the two achiral starting materials must be prochiral to lead to chiral products. HCN is not prochiral, but PhCHO is for this reaction. It is also the case for the hydrogenation of PhCHO with deuterium ($D_2$) into chiral PhCH(D)OD, but not for the hydrogenation with $H_2$, giving achiral $PhCH_2OH$. The mandelonitrile contains an asymmetric carbon center and has no symmetry elements. The drawings in Figure 1.1 illustrate this point with two different bars welded together (no symmetry element). Note that dimerization may generate chiral products that have a $C_2$ axis of rotation. An example is the oxidative dimerization of 2-naphthols into 1,1'-binaphthols [52]. Another example of $C_2$-symmetrical chiral compound is (-)-(2*R*,3*R*)-2,3-butanediol ($CH_3$-CH(OH)-CH(OH)-$CH_3$, see reaction (2.6)). If the two bars of the drawings in Figure 1.1 were identical, and if their points or surfaces of binding were in the same location for the two bars, this characteristic would be illustrated.

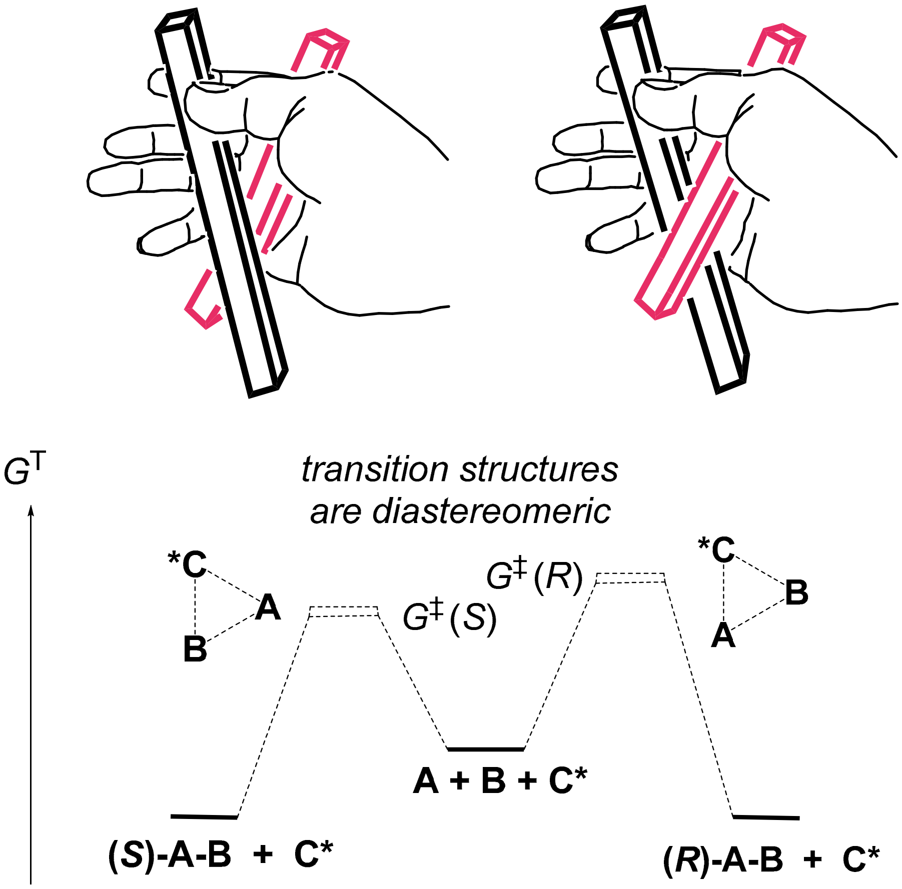

**Figure 1.1.** Representation of enantioselective catalysis for the combination of a substrate **A** (represented by the black bar) with reagent **B** (represented by the red bar) in the presence of a chiral catalyst **C*** (represented by a right hand). The starting materials **A** + **B** are converted into chiral products (*R*)-**A-B** or (*S*)-**A-B**. They have the same stability in a non-chiral environment. All the species that combine **A**, **B**, and **C***, such as short-lived intermediates or transition structures, are diastereomeric and have different stabilities and/or reactivities (reaction rates). Their transition states are associated with different free activation enthalpies ($\Delta G^{‡}(R)$, $\Delta G^{‡}(S)$). The reader may use Lego® bricks (rectangular parallelepipeds) to construct similar objects and illustrate chirality.

### *1.3. Chiral Catalysts Are Temporary Chiral Auxiliaries*

A catalyzed reaction is faster than the same uncatalyzed reaction. The catalyst interacts with the reactants and substrates; it is released at the end of the reaction. It changes the reaction mechanism in several possible ways. We consider the case of a prochiral substrate **A** that combines with achiral reactant **B** to generate products (*R*)-**A-B** and (*S*)-**A-B**. The chiral catalyst **C*** interacts first with **A** and equilibrates with intermediate **A-C***. Several options are considered. In one of them, this intermediate combines with **B** and equilibrates with a complex in which **A** and **B** approach together and are "forced" to react. This situation corresponds to Diels-Alder reactions ((4+2)-cycloadditions) of alkyl-substituted 1,3-dienes adding to $\alpha,\beta$-unsaturated carbonyl compounds (dienophiles) to generate cyclohexene or cyclohexa-1,4-diene derivatives. In the absence of a catalyst, the reaction is a one-step process in which the two new $\sigma$-bonds form in the transition state in concert, not necessarily to the same extent. In 1942, Wassermann observed that protic acids accelerate these reactions [53]. In 1960, Yates reported that $AlCl_3$ accelerates the Diels-Alder reactions of maleic anhydride, dimethyl fumarate and benzoquinone. The protic acid protonates the carbonyl group of the dienophiles, $AlCl_3$ forms Lewis carbonyl/$AlCl_3$ complexes that activate the dienophiles. According to the PMO (perturbation of molecular orbitals) theory the rate of the cycloaddition is dominated by the LUMO(dienophile)/HOMO(diene) interaction (normal electronic demand). The smaller is the energy gap between these frontier orbitals, the faster is the reaction. Upon protonation of the carbonyl group of the dienophile, or formation of a Lewis carbonyl/$AlCl_3$ complex, the energy of the LUMO(dienophile) is reduced, thus accelerating the cycloaddition. This occurs without significant change in the nature (nearly the same chemical functions) and geometry of the dienes and dienophiles compared with the non-catalyzed reaction [54].

In another option, intermediate **A-C*** transforms **A** chemically, generating a second intermediate **A'-C*,** which then combines with **B**. **A'-C*** reacts quickly with **B**, much quicker than **A + B** or **A-C* + B**. The catalyst not only brings **A** and **B** together, but also activates **A** chemically. One speaks here of catalysis by chemical activation. If **B** is prochiral, intermediate **A'-C*** reacts, forming two possible enantiomers (*R*)-**A-B** and (*S*)-**A-B** with two different rates, thus leading to enantioselectivity. Figure 1.2 illustrates an attempt to explain this concept with macroscopic objects. This mini-review describes several examples of this type of catalysis. To illustrate this concept, the reader may consider a chiral catalyst with an amine function that reacts with an aldehyde to equilibrate with a chiral iminium salt, a better electrophile than the starting aldehyde (see e.g., MacMillan's enantioselective Diels-Alder reaction catalyzed by a secondary chiral amine, Section 3.1.5, Figure 3.7). Furthermore, the amine catalyst might react with an aldehyde or a ketone equilibrating with a chiral enamine, which is more nucleophilic than the corresponding enol (see e.g., Section 3.5). Another example is the Umpolung of aldehydes with heterocyclic nucleophilic carbenes into acyl anion equivalents (Breslow intermediates), which then can add to electrophiles such as aldehydes (homo-benzoin condensation, Section 8.1), other carbonyl compounds (cross-benzoin condensation, Section 8.1), aldimines (aza-benzoin condensation, Section 8.2), or Michael acceptors (Stetter reaction, Section 7.3).

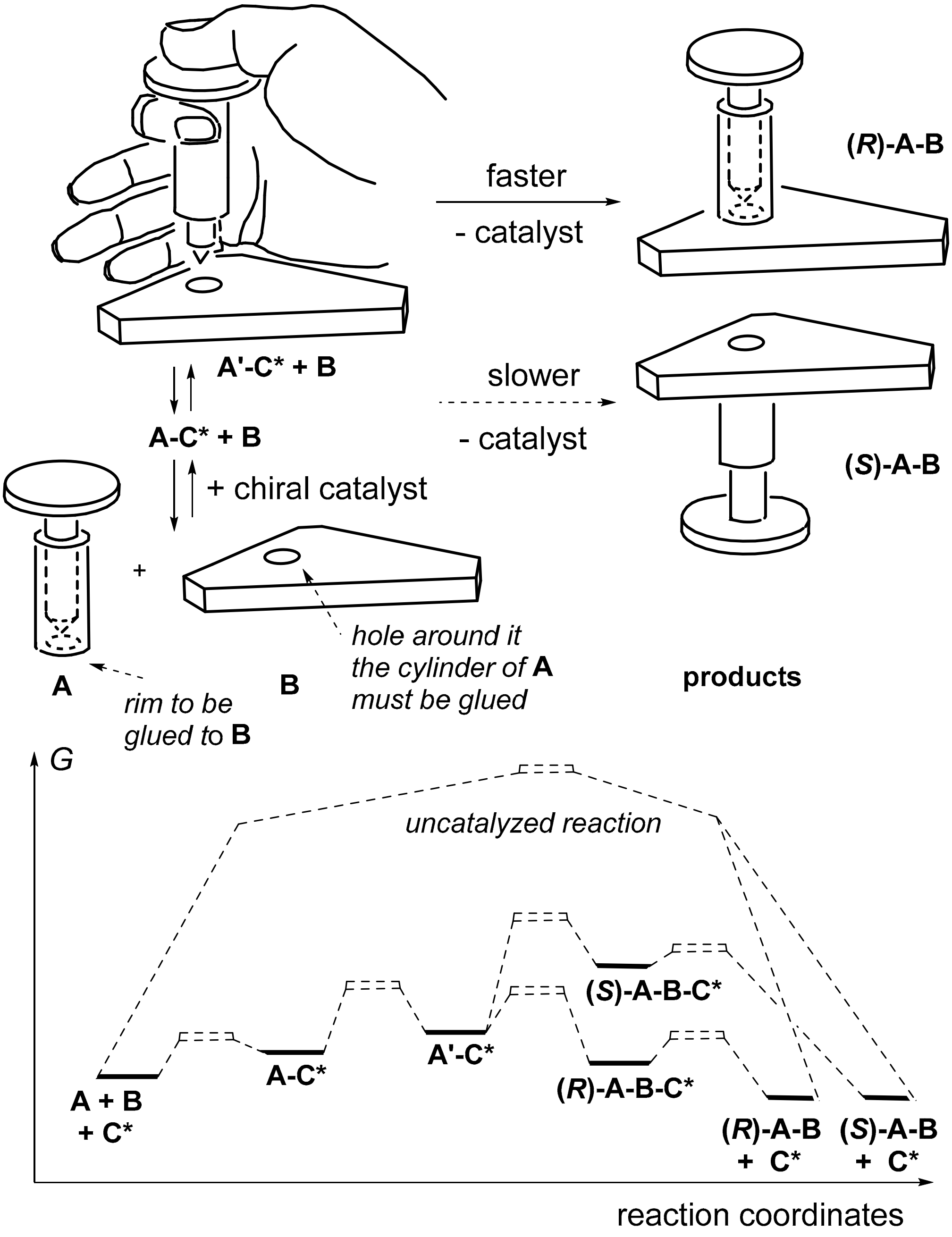

**Figure 1.2.** Representation of a catalyzed asymmetric reaction implying activation of an achiral reactant **A** through a chemical transformation with the chiral catalyst **C***. A chiral intermediate **A-C*** forms first which equilibrates then with the more reactive intermediate **A′-C***. The latter reacts preferentially with one face of the prochiral substrate **B** (represented by an irregular triangle), leading preferentially to enantiomer **(*R*)-A-B** of the product. This implies that intermediate **A′-C*** combines with prochiral **B** forming two possible diastereomeric complexes or intermediates **(*R*)-A-B-C*** and **(*S*)-A-B-C***; they do not have the same stability and/or react with different rates. In the case represented, **(*R*)-A-B-C*** and **(*S*)-A-B-C*** equilibrate with the starting materials, but the concentration of **(*R*)-A-B-C***, which is higher than that of **(*S*)-A-B-C***. The energy barrier for the transformation of **(*R*)-A-B-C*** to product **(*R*)-A-B** is nearly the same as that of the conversion **(*S*)-A-B-C*** into **(*S*)-A-B.** The catalyst is represented by a right hand which grabs first **A** and then activates it into **A′**. The hand does this with its dumb that presses down the piston (change of chemical function), liberating the pointer that help to find the place where **A** has to be attached to **B** (around the hole). Only one of the two faces of **B** can react. Because of its shape (irregular triangle), it can fit into the cavity realized by the bottom of the hand for only one of the two possible orientations. When **A′** of **A′-C*** and **B** have been glued together the hand suppresses the pressure on the piston and let product **(*R*)-A-B** to swim away.

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## 2. Biocatalysis

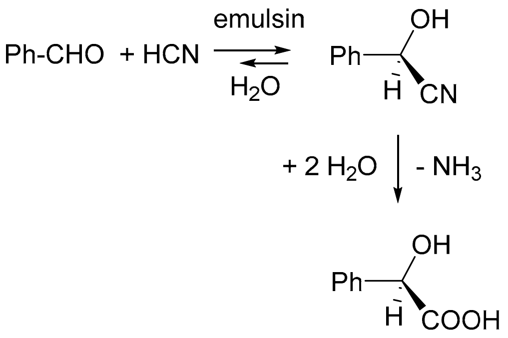
When the catalyst is an enzyme or a microorganism, one speaks of enzymatic catalysis or biocatalysis. Depending on substrates, reagents, and conditions, these reactions might be chemoselective, regioselective, diastereoselective, and enantioselective [55]. They are applied more and more frequently in organic chemistry [56–60] and in industry [9,61–63]. Biocatalysis is a sustainable approach, a green tool (no heavy metals, water as solvent) for the obtainment of enantiomerically enriched substances of high value, such as drugs [64].

Enzymes involved in primary metabolism may accelerate chemical reactions by up to 26 orders of magnitude [65]. In 1975, the Chemistry Nobel Prize was granted to John W. Cornforth for his work on the stereochemistry of enzyme-catalyzed reactions [66], and to Vladimir Prelog for his research into the stereochemistry of organic molecules and reactions [67]. Apart from possible chemical reactions between the catalyst, the reagent, and/or the substrate, the enzyme interacts with them and the solvent through an array of weak and/or strong electrostatic interactions [68]. Their relative importance increases from induced-dipole/induced dipole (London dispersion forces), dipole-induced dipole, dipole-dipole (e.g., hydrogen bonds [69]), ion-dipole ligation, to ion pairing [42]. Enzymes have structural scaffolds with active sites that provide a complementary structural and electrostatic environment to substrates, reactants, and transition structures of their reaction. The catalytic effect results from the fact that enzymes bind and stabilize transition structures better than starting materials, intermediates, and final products [70,71]. Jean-Marie Lehn, [72,73] Charles Pedersen, [74] and Donald Cram [75,76] were awarded the 1987 Chemistry Nobel Prize for their development and use of molecules with structure-specific interactions of high selectivity[77]. Their findings helped chemists to understand biocatalysis and to design new non-enzymatic catalysts [78]. Recently, protein engineering created non-natural enzymes with excellent activity and stereoselectivity [79–81]. Due to their solubility and instability, enzymes are not recovered easily after use. To overcome these problems, they are immobilized by combining them with various possible supports. These biocatalysts can be readily recovered by simple filtration, centrifugation, or other extractive techniques [82,83].

The vigorous development of asymmetric organocatalysis (Chap. 3-11) during the last 25 years was inspired by enzymatic catalysis [84]. Many asymmetric reactions applied enzymes first. Then, much smaller molecules were found to catalyze the same enantioselective reactions. An exception to this rule is the Stetter reaction, which condenses conjugated enones or ene-esters with aldehydes, forming 1,4-dicarbonyl compounds (nucleophilic acylation of Michael acceptors). In 1996, Enders and co-workers reported the first asymmetric version of an intramolecular Stetter reaction. In 2008, they realized enantioselective intermolecular Stetter reactions applying triazolium-derived N-heterocyclic carbenes as chiral catalysts. The Rovis group also contributed to the development of this important C-C bond-forming reaction (see Section 8.3). In 2009, Müller and co-workers reported the first examples of thiamine diphosphate (ThDP)-dependent enzyme-catalyzed asymmetric Stetter reactions [85,86].

### *2.1. Hydroxynitrile Lyases*

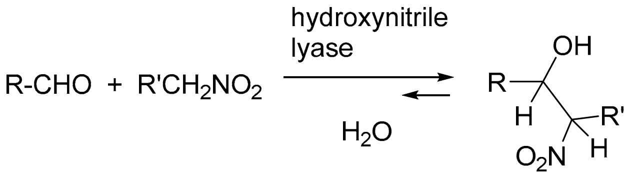
More than 2000 plants possess cyanogenic glycosides that liberate hydrogen cyanide (HCN) upon hydrolysis or under the action of an enzyme (e.g., β-glucosidase). This is the case with bitter almonds. Eating 50 bitter almonds may kill an adult. Fortunately, this is not the case with sweet almonds [87]. In 1837, using an open flask, Wöhler and Liebig applied a crude hydroxynitrile lyase on mandelonitrile (PhCH(OH)CN) to liberate HCN and generate benzaldehyde (PhCHO) (backward reaction of equilibrium (2.1)) [88]. Rosenthaler realized the opposite reaction in 1908 (forward reaction of equilibrium (2.1)). Using a crude enzyme extracted from almonds (emulsin), a relatively high concentration of PhCHO and HCN in water, in a closed flask at 20-30 °C he obtained an optically active cyanohydrin in good yield. Under acidic conditions (HCl/$H_2O$), (+)-(*R*)-mandelonitrile extracted from the reaction mixture with $CHCl_3$ was hydrolyzed into (-)-(*R*)-mandelic acid (reaction (2.2)). These were the first enantioselective syntheses ever from achiral substrates [89].



(2.1)

(2.2)

Today, hydroxynitrile lyases of various sources are available. They allow the enantioselective synthesis of a large number of important industrial intermediates in both enantiomeric forms [90–94]. Furthermore, new enzymes are engineered through directed evolution [95–99], and some of them catalyze different reactions that follow similar mechanisms, or not. For instance, hydroxynitrile lyases catalyze the enantioselective condensation of nitroalkanes to aldehydes to form β-nitroalcohols (equilibrium (2.3)) [100–103].

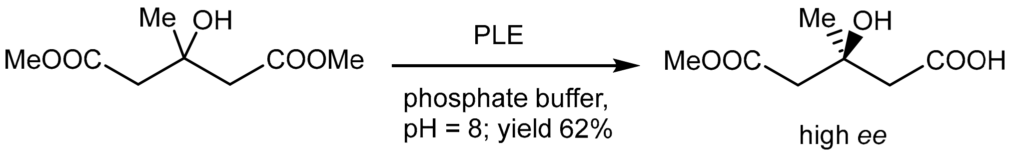


(2.3)

*Arabidopsis thaliana* hydroxynitrile lyase (AtHNL) engineering has uncovered variants with up to 12-fold improved catalytic efficiency compared to the wild type towards asymmetric Henry reaction with up to 99% *ee* [104]. Enzyme promiscuity is the property of enzymes that can catalyze unexpected reactions, and/or transform unexpected substrates, and work under unexpected reaction conditions [105–108].

### 2.2. Esterases

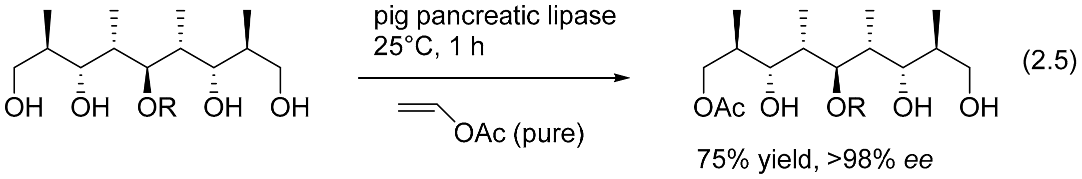
In 1975, Huang and coworkers reported that dimethyl glutarate (meso-compound) was hydrolyzed with PLE (pig liver esterase) in high enantioselectivity into the corresponding monoester (reaction (2.4)) [109]. Several reports on the enzyme-catalyzed desymmetrization of meso-diesters followed [110].



(2.4)

Desymmetrization of malonic esters is predominated by the catalytic hydrolysis using crude pig liver esterase (PLE, EC 3.1.1, enzyme that hydrolyzes esters) to give *α*-quaternary carboxylic acids [111,112]. Very important reactions such as aldol condensation, Knoevenagel condensation, Hantzsch reaction, Michael addition, Canizzaro reaction, Mannich reaction, Morita-Baylis-Hillman (MBH) reaction, Ugi reaction, and oxidation have been catalyzed by lipases (esterases that hydrolyze fat) [113].

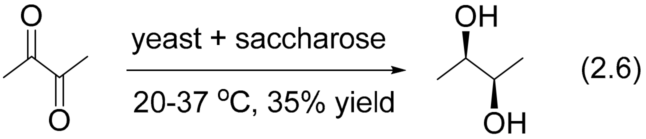
The opposite reaction to esterase hydrolysis is acylation. It requires enol esters as reagents. An example reported by Chênevert is reaction (2.5) that does the desymmetrization of an advanced intermediate in the total synthesis of natural polypropionates [114,115], including Rifamycin S [116].



Enzymatic ester hydrolyses generally proceed by acylation of the enzyme, followed by hydrolysis of the acylated species. With enol esters, this hydrolysis occurs with concomitant acyl group cleavage and C-protonation of the liberated enols. In 1990, Ohta and coworkers reported that the yeast *Pichia farinosa* IAM4682 catalyzes the enantioselective hydrolysis of prochiral enol esters [117]. Since then, carboxylases, esterases, and lipases were shown to catalyze the enantioselective enolate protonation and enol isomerization [118].

### 2.3. Baker's Yeast

The asymmetric reduction of ketones by baker's yeast (*Saccharomyces cerevisiae*) is one of the most used reactions induced by a microorganism. Sometimes it is catalytic; it uses at least one equivalent of a reducing agent such as glucose, sucrose (saccharose), glycerol, or malic acid [119–125]. The asymmetric reduction of diacetyl (2,3-butanedione) into levorotatory 2,3-butanediol ((-)-(2*R*,3*R*)-2,3-butanediol, 35% yield) was reported in 1919 by Neuberg and Nord (reaction (2.6)) [126].



Most yeast-induced reductions of prochiral monoketones ($R^1$-CO-$R^2$, $R^1$ different from $R^2$) are highly enantioselective, leading to the corresponding (*S*)-alcohols. Formally, the reaction adds a molecule of $H_2$ onto the carbonyl (C=O) moiety, giving the corresponding secondary alcohol ($R^1$-CH(OH)-$R^2$). The *re* face of dialkylketones is preferred, giving (*S*)-alcohols (Figure 2.1). Often, formation of ethanol competes (up to 2000 moles per mole of secondary alcohol, which requires up to 1000 moles of glucose) [127,128].

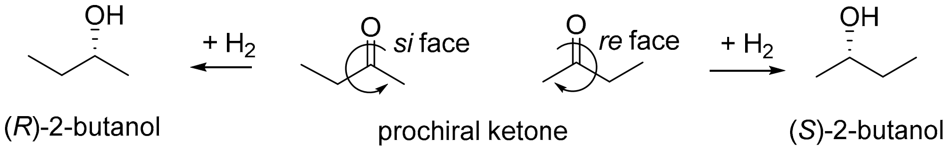
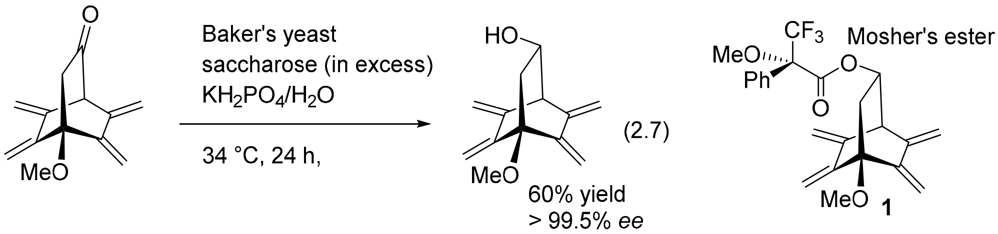


**Figure 2.1.** The prochiral carbonyl compound (2-butanone) has a *re* face, and a *si* face. $H_2$ addition onto the *si* face produces the (*R*)-2-butanol, and the $H_2$ addition to the *re* face gives (*S*)-2-butanol [129].

Baker's yeast reduction of complicated ketones can be highly enantioselective. One example is reaction (2.7) [130]. Mosher's esters (e.g., **1**) permit accurate measurement of the optical purity of alcohols (*er*), through HPLC, $^1$H-NMR, $^{13}$C-NMR or $^{19}$F-NMR (satellite signals $^{13}$C-X of major ester compared with $^1$H, $^{19}$F signals of the minor enantiomer) [131]. Alternatively, HPLC with a chiral stationary phase permits the determination of *er* (chiral column chromatography) [132].



(2.7)

Reductions of C=C double bonds of (*E*)- and (*Z*)-methyl 2-chloro-2-alkenoate by baker's yeast give (*R*)- and (*S*)-2-chloroalkanoic acid in 25-92% *ee* and >98% *ee*, respectively [133]. These reactions show the reaction promiscuity of this microorganism.

### 2.4. Fermentative Oxidation

In 1968, Gibson and coworkers showed that *Pseudomonas putida*, grown with toluene as the sole source of carbon, oxidized chloro, bromo-, iodo-, and fluorobenzenes to their respective 3-halogenated catechol derivatives. They also found that oxidation of 4-chlorotoluene generates (+)-*cis*-4-chloro-2,3-dihydroxy-1-methylcyclohexa-4,6-diene next to 4-chloro-2,3-dihydroxytoluene [134]. Since then, high-yielding whole-cell fermentations of arenes into substituted *cis*-cyclohexa-3,5-dienes have been obtained with high *ee*'s [135–137]. These compounds have been tansformed into all kinds of products of biological interest (see e.g., Figure 2.2) [138–144].

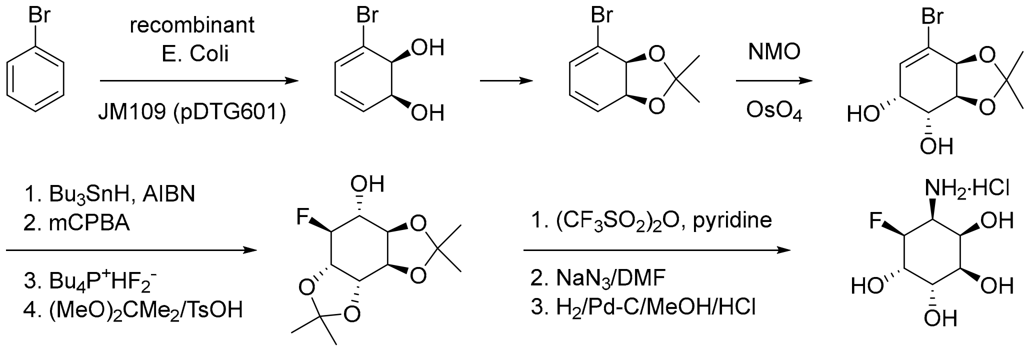


**Figure 2.2.** Example of fermentative oxidation of bromobenzene into a chiral diol, synthetic intermediate in the stereoselective synthesis of a 6-amino-5-fluorocyclohexane-1,2,3,4-tetrol derivative.

### 2.5. Aldolases

In 1934, Meyerhof and Lohmann discovered that aldolases are ubiquitous enzymes in plants and animals [145,146]. They catalyze the backward reaction of aldol equilibrium (2.8) *in vivo* (Figure 2.3). Thus, at high concentrations D-glyceraldehyde 3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP) are condensed to generate fructose 1,6-diphosphate FDP (forward reaction of equilibrium (2.8)). Warburg and Christian first recognized the difference in yeast and muscle aldolase properties [147–149]. Type I aldolases (from higher plants and animals) such as muscle aldolases are not inhibited by metal-chelating agents and do not contain divalent metals, and type II aldolases (e.g., yeast aldolase from microorganisms [150]) are inhibited by divalent metal-chelating agents and contain $Zn^{++}$ [151]. For type I, aldol condensation occurs via a Schiff base resulting from the reaction of the aldehyde and the ε-amino group of a lysine unit of the enzyme (Mech. 1, Figure 2.3). In the case of type II aldolases, the $Zn^{++}$ cation activates the aldehyde via co-coordination with a histidine unit (Mech. 2, Figure 2.3).

An early case of rabbit muscle aldolase (RAMA, E.C.4.1.2.13) catalyzed aldol reaction was reported in 1960 by Jones and Sephton with the synthesis of octulose derivatives through condensation of 1,3-dihydroxy-2-propanone phosphate with pentoses [152]. Then, this biocatalyst was used to catalyze asymmetric aldol condensations with achiral aldehydes. Wide explorations have been carried out by the groups of Whitesides [153,154], Wong, [155–158] and of others [159–161]. The RAMA accepts all aldehydes as electrophilic, except those derivatives congested in the *α* position, the *α*,β-unsaturated aldehydes, or those that easily lead to them by water elimination. The products have the D-threo (3*S*,4*R*) stereochemistry. As a rule, the enzyme accepts DHAP as the privileged nucleophile. This permitted the asymmetric total synthesis of carbohydrates and analogs of biological interest [162,163].

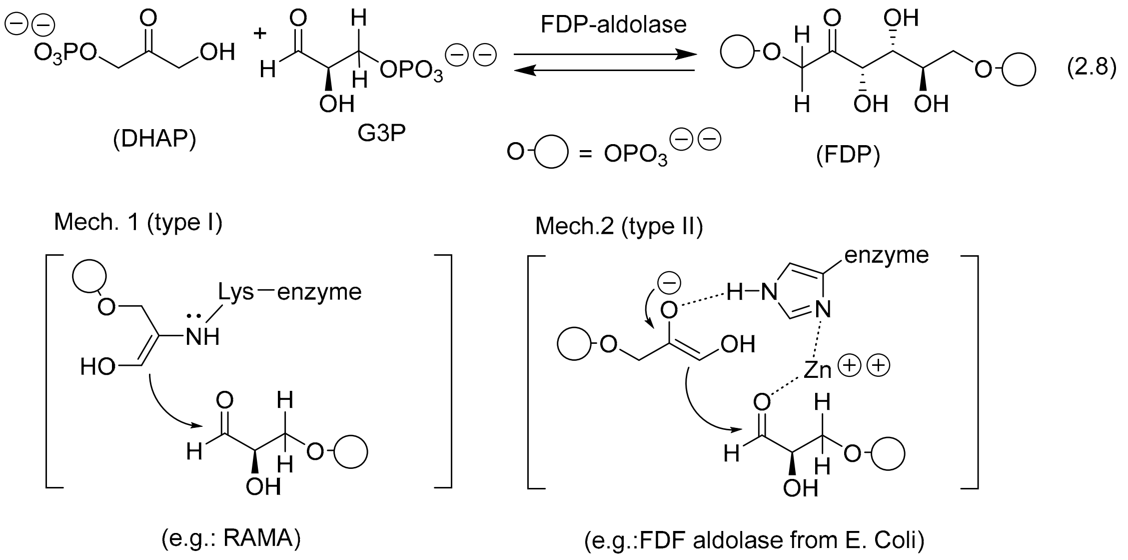


**Figure 2.3.** Mechanism of Type I or Type II aldolase-catalyzed aldol and retro-aldol reactions (2.8). Type I involves the addition of an intermediate enamine onto the carbonyl group. Type II implies the enolate addition onto the carbonyl group activated with an imidazolyl complexed Lewis acid.

In Nature, deoxy-D-ribose-5-phosphate aldolase (DERA, EC 4.1.2.4) is a part of the nucleoside salvage pathway; it catalyzes the retro-aldol reaction, forming glyceraldehyde-3-phosphate and acetaldehyde from 2-deoxy-D-ribose-5-phosphate (sometimes assigned to Type III aldolases) [164]. DERA possesses the unique function to catalyze the aldol reaction between two aldehydes instead of an aldehyde and a ketone [165,166]. It accepts a large variety of aldehydes as electrophiles. In addition, DERA can catalyze sequential addition of acetaldehyde, resulting in the formation of more than one stereogenic center (e.g., equilibrium (2.9), Figure 2.4). The entropically disfavored double condensation is overcome through rapid cyclization, generating stable cyclic hemiacetals (pyranose). The sequential aldol reaction has been applied successfully in industry, for example, in the synthesis of statins (Figure 2.4), cholesterol-lowering agents [167,168]. It also permitted the asymmetric synthesis of key building blocks in the synthesis of epothilone [169]. Enantioselective side-chain intermediates in the statin synthesis rely upon whole-cell systems [170]. For other applications of biocatalysts in the industry, see: [171].

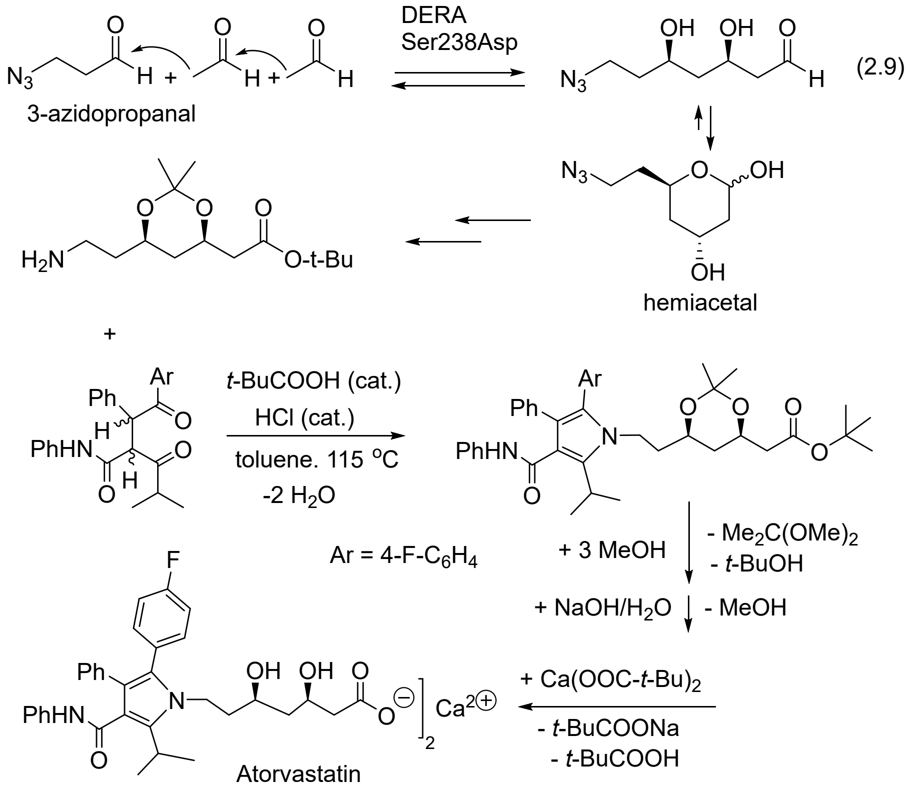


**Figure 2.4.** DERA-induced asymmetric synthesis of the side-chain of Atorvastatin, the drug that has brought the highest financial benefits to the pharma industry.

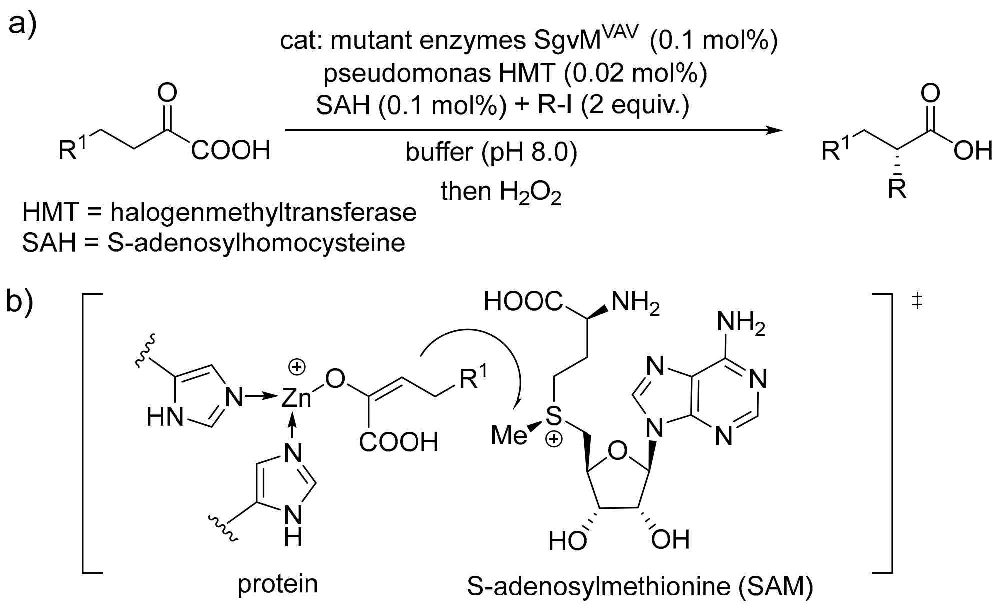
L-Threonine aldolase (LTA) is a 5′-phosphate (PLP)-dependent aldolase that catalyzes the formation of β-hydroxy-$\alpha$-amino acids from glycine (Gly) and aromatic or aliphatic aldehydes [172,173]. β-Hydroxy-$\alpha$-amino acids are chiral building blocks for pharmaceuticals (antibiotics and proteasome inhibitors) [174]. One recognizes four types of LTAs [175–177].

An aldolase called hydratase-aldolase (NahE) catalyzes the stereoselective Michael addition of pyruvate to β-nitrostyrenes. It is a type I aldolase. After oxidative decarboxylation, β-aryl-$\gamma$-nitrobutyric acids can be isolated. They give access to precursors of $\gamma$-aminobutyric acid (GABA) analogues that possess high pharmacological activity [178].

Other efficient aldolases from natural sources, or engineered through directed evolution or/and design are now available [179–185]. Furthermore, enamine catalytic aldolase antibodies developed in the laboratories of Lerner catalyze asymmetric aldol reactions [186–188]. Enzymes have been engineered to catalyze asymmetric Michael additions [189]. As we shall see below, simple chiral amines such as amino acids and small peptides and analogs can be excellent catalysts for the asymmetric intermolecular aldol and Michael reactions.

### *2.6. Other Asymmetric Biocatalyzed C-C Bond-Forming Reactions.*

The introduction of a methyl substituent into medicinal agents can dramatically enhance their bioactivity due to the “magic methyl effect” [190]. Methods allowing for chemoselective, regioselective and stereoselective methylation of carbonyl compounds are precious [191]. More generally, catalyzed $\alpha$-alkylation, $\alpha$-allylation and $\alpha$-propargylation of carbonyl compounds are very much desired reactions. SgvMVAV was engineered as a general biocatalyst for these reactions (2.10). The catalytic system includes a Lewis acidic Zn site that triggers substrate enolization and an adjacent SAM (S-adenosylmethionine) that permits stereoselective methyl transfer (Figure 2.5b) [192].



(2.10)

**Figure 2.5.** a) An example of asymmetric $\alpha$-alkylation of $\alpha$-ketocarboxylic acids catalyzed by a mutant alkyltransferase; b) Proposed transition state for the enzyme-catalyzed $\alpha$-methylation of pyruvates by S-adenosinsylmethionine (SAM).

## 3. Asymmetric Amino-Catalysis: The Queen of Organocatalysis

When the catalyst is a chiral organic compound that is not an enzyme, one speaks of asymmetric organocatalysis [193–200]. Asymmetric organocatalysis is the most innovative field in fine chemistry [10]. Most organocatalysts are robust, non-toxic, and affordable. They imply easy reaction manipulations, simple purification procedures, and do not always require an inert atmosphere. Asymmetric organocatalysis realizes greener chemistry [201] (no toxic metals, less solvent) with atomic economy (fewer co-products and side-products to take care of) [202]. Organocatalysts can be utilized without solvent, or with non-toxic ones such as water, ethanol, ethyl acetate, tetrahydrofuran, methyl *t*-butyl ether, and toluene. They require less energy and produce less waste than organometallic and metal catalysts. Nature provides us with inexpensive enantiomerically pure compounds such as alkaloids, amino acids, terpenes, and carbohydrates. Asymmetric synthesis is also an endless source of new chiral compounds used in the construction of chiral organocatalysts. In 2021, Benjamin List and David W. C. MacMillan received the Nobel Prize in Chemistry for the development of asymmetric organocatalysis [203,204]. When the catalyst is a chiral amine, one refers to asymmetric amino-catalysis [203,205–209].

In 1896, Knoevenagel found that primary and secondary amines, as well as their salts, catalyze the aldol condensation of β-ketoesters or malonic diesters with aldehydes and ketones [210,211]. As we shall see, chiral amines can abstract selectively one or the other proton from enantiotopic C-H or X-H bonds (Section 3.1-1). Protonated chiral amines (ammonium salts) protonate planar enolates and other related π-systems with enantioselectivity (Section 3.1-2). The catalytic effect can also result through other modes of activation [196]. For instance, primary and secondary amines activate aldehydes and ketones through the formation of iminium ion intermediates ($C{=}N^{(+)}R_2$, electrophiles, Section 3.1-4, 3.5), through the formation of enamines ($C{=}C\text{-}NR_2$, nucleophiles, Section 3.1-5, 3.6)), or through the formation of radical ammonium radical-cation intermediates ($R_3N^{(\cdot+)}$, Section 3.7). Moreover, chiral quaternary ammonium salts (e.g.: $R_3N^{(+)}R'\text{-}X^{(-)}$) are enantioselective catalysts in phase transfer reactions (Section 3.2). Enhanced electrophilicity of $\alpha,\beta$ unsaturated acyl chloride is possible through the formation of acylammonium chloride intermediates (Section 3.8). Furthermore, the amine catalyst may work in concert with co-catalysts, or additives that contribute as H-bond donors or acceptors (Chap. 9) [212,213], as halogen (Section 11.6), chalcogen-bonding, staking, or ion-pairing [199,214–216]. Amino-catalysis can be combined with other types of catalysis (synergistic catalysis, see e.g., [217]) such as metal catalysis [218], or with photo-redox processes [219,220] (see Section 3.5-6 for an example). Light brings another dimension to enantioselective organocatalysis [221].

### *3.1. Cinchona Alkaloids and Derivatives as Catalysts*

Asymmetric amino-catalysis dates back to 1912, when Bredig and Fiske added HCN to benzaldehyde (PhCHO) in the presence of cinchona alkaloids (0.3 M). For instance, with (-)-quinine (**2**), the corresponding cyanohydrin (PhC(CN)(OH)H was obtained in 1-2% yield and 2% *ee*. With (+)-quinidine (**4**) as catalyst, *ee* increased to ca. 10% (er < 55/45, forward reaction of equilibrium (2.1)) [222]. This was a groundbreaking report: asymmetric catalysis does not need a microorganism or an enzyme taken from the living world. In 1960, Pracejus added methanol (0.11 M) at - 111 °C to methyl phenylketene (Ph(Me)C=C=O, 0.1 M) in toluene. In the presence of O-acetyl quinine (**3**, 0.001 M), he obtained 2-phenylpropanoic methyl ester (PhCH(Me)-COOMe) in 60-70% yield and 73% *ee* [223]. Following this pioneer work, cinchona alkaloids became the most privileged asymmetry inducers in the area of enantioselective catalysis [224]. As illustrated in Figure 3.1 with derivative **3** (functionalization of the secondary alcohol moiety and exchange of the methoxy substituent for another group), the cinchona alkaloids can be modified easily and generate a large variety of chiral catalysts. They are chiral Lewis base catalysts (Section 3.1-1), hydrogen-bond (HB) donors (Section 3.1-2), chiral protic acids for their conjugate acids (Section 3.1-3), nucleophilic activators (Section 3.1-4), iminium ion activators (Section 3.1-4), and enamine activators (Section 3.1-6). Bifunctional catalysts with halogen-bond (XB) donors (Section 3.1-7) lead to ligand-accelerated catalysis. Quaternized ammonium salts serve as phase-transfer catalysts (Section 3.2) and as activators through hydrogen bridging (Section 3.3). Other derivatives are electron-donating agents (Section 3.4) [225–229].

#### 3.1.1. Cinchona Alkaloids as Chiral Brønsted Bases

In 1980, Whitesell and Felman showed that stoichiometric amounts of a strong base, such as chiral lithium amide, induce the enantioselective conversion of cyclohexene oxide into lithium cyclohex-2-enolate (e.g., with [(*S*)-PhCH(Me)]$_2$NLi, 65% yield, 31% *ee*) [230]. This work demonstrated that a chiral strong base can distinguish between two enantiotopic C-H bonds. The same year, Vogel and Hagenbuch reported the first examples of enantioselective catalyzed isomerization of endoperoxides into the corresponding γ-hydroxy-α,β unsaturated aldehydes (Kornblum-DeLaMare rearrangement [231]) applying cinchona-alkaloids **2-5** (Figure 3.1). For instance, in the presence of 0.0045 molar (+)-quinidine (**4**) a 10% solution of endoperoxide **6** in CH$_3$CN was isomerized at 20 °C (> 95% yield) into **7** with 46% *ee* (reaction (3.1)). A relatively weak base such as (+)-quinidine (**4**) can distinguish between enantiotopic protons that are three carbon centers away from the chiral centers (C(1), C(4)) of the 7-oxanorbornane skeleton [232].

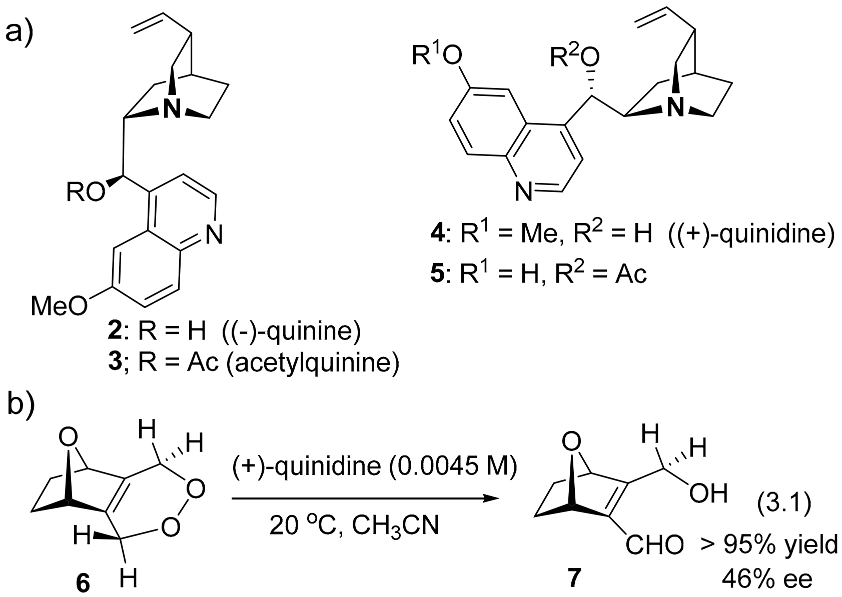
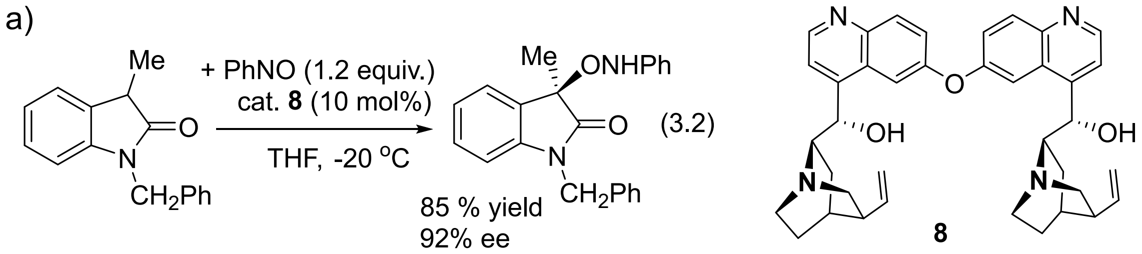


**Figure 3.1.** a) Structures of natural (-)-quinine, (+)-quinidine, and derivatives used as chiral base catalysts; b) First example of an enantioselective amine-catalyzed Kornblum-DeLaMare rearrangement (Vogel, 1980).

In 2006, Toste and co-workers reported the cinchona-alkaloid-catalyzed asymmetric Kornblum DeLaMare rearrangement of endoperoxides resulting from the photooxidation of cyclic dienes and obtained corresponding γ-hydroxycycloenones in good yield and up to 99% *ee*. For instance, the endoperoxides of cycloocta-1,3-diene were isomerized into 4-hydroxycyclooct-2-en-1-one in 99% yield and 99% *ee* in the presence of the quinidine derivative **5** [233].

In 2010, Barbas and coworkers reported that dimeric forms of cinchona alkaloids are better base catalysts than their monomeric forms (Figure 3.2a). For instance, in the presence of catalyst **8**, aminooxydation of 2-oxindoles furnished the corresponding 3-hydroxyoxindole precursors (reaction (3.2)), in good yield and *ee*. This reaction implies the formation of an enolate intermediate (by deprotonation), which forms a chiral ion-pair with the cinchona analogue [234]. In the presence of 3 equivalents of D-diethyl tartrate, asymmetric (4+2)-annulations of isatins (C=O electrophile) with but-3-yn-2-one used a dimeric cinchona-alkaloid organocatalyst (DHQD)2-phthalazine **9** (reaction (3.3)) [235]. These reactions imply the formation of chiral ion-pairs composed of the buty-3-yn-2-one enolate and protonated catalyst **9**. In the same time, the isatins are hydrogen-bridged to D-diethyl tartrate. The first C-C bond forms by the addition of the enolate to the keto group of isatins.



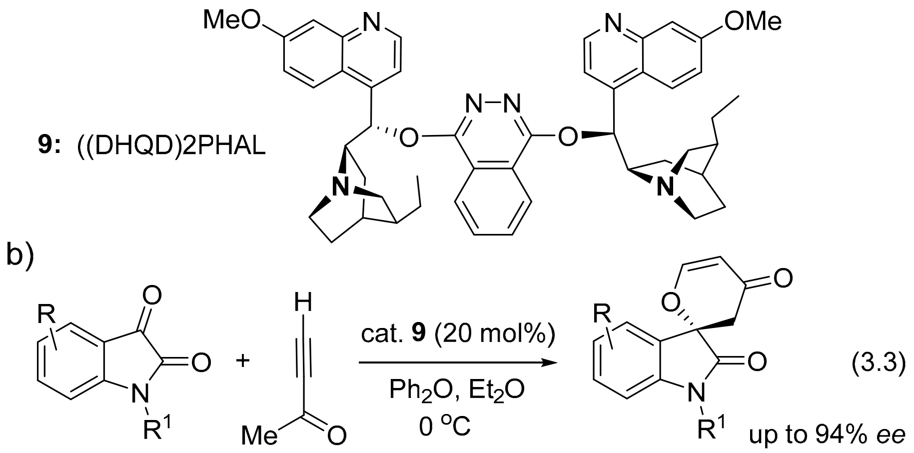


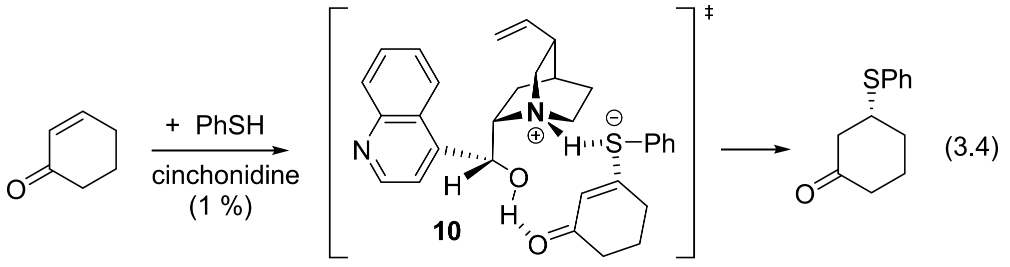
**Figure 3.2.** Typical cinchona alkaloid derivatives used as chiral bases: examples of applications. a) $\alpha$-Amino-oxidation of a ketone (Barbas, 2010); b) (4+2)-annulation of the enol of buty-3-yn-2-one to a highly electrophilic ketone (Xu & Shi, 2013).

(DHQD)2PHAL (**9**, 1,4-bis(9-O-dihydroquinidinyl)phthalazine; other name: dihydroquinidine 1,4-phtalazine diether) and other cinchona alkaloid-based catalysts were developed by Sharpless and co-workers for their enantioselective and catalytic osmylation of alkenes to produce vicinal diols (Sharpless asymmetric dihydroxylation) [236,237]. In 1980, Hentges and Sharpless reported that (-)-quinine (**2**) and (+)-quinidine O-acetylated with their vinyl group hydrogenated are ligands (1 equiv.) for $OsO_4$ (1 equiv.) in the osmylation of alkenes (1 equiv.). They induce enantioselectivity in the formation of vicinal diols [238]. Later, a method using catalytic amounts of toxic $OsO_4$ was developed [239]. For his work on chirally catalyzed oxidation reactions, Barry Sharpless received his first chemistry Nobel award in 2001, which he shared (1/2) with Ryoji Noyori (1/4) and William Standish Knowles (1/4) for their work on asymmetric catalyzed hydrogenation reactions. In 2022, Sharpless received his second Nobel award (1/3) that he shared with Carolyn R. Bertozzi (1/3) and Morten Meldal (1/3) for the development of click chemistry and bio-orthogonal chemistry. (DHQD)2PHAL has been used as a chiral ligand in Pd-catalyzed Suzuki-Miyaura coupling of aryl/heteroaryl halides with aryl boronic acids in aqueous medium and in the absence of phosphine/organic solvent [240], and in Cu(I)-catalyzed azide-alkyne cycloaddition reaction to synthesize 1,2,3-triazoles in water [241]. We shall not discuss these reactions further in this mini-review as they engage metallic species in their catalysts.

Catalytic asymmetric oxidations, most notably dihydroxylation, epoxidation and amino-hydroxylation, are powerful methods for the installation of chiral functionality onto achiral alkene substrates. Halolactonization of unsaturated carboxylic acid is another useful way to install two functionalities on the alkene moiety of unsaturated carboxylic acids. In 2004, Gao and co-workers reported a first catalytic protocol for the iodolactonization of alkenoic acids, whereby trans-5-aryl-4-pentenoic acids were cyclized in the presence of iodine and 30 mol% of a cinchonidine-derived quaternary ammonium salt under phase transfer catalysis (see Section 3.2) [242]. In 2010, Borhan and co-workers reported a first efficient asymmetric chlorolactonization catalyzed (DHQD)2PHAL mixed with benzoic acid [243]. Similarly, enantioselective bromolactonization [244], intermolecular alkene bromoesterification, bromoetherification, bromoamination, and bromohydroxylation [245] have applied the same catalyst. A large number of modern enantioselective organocatalysts contain a Lewis base alone, or a base together with other functions such as hydrogen-bond (HB) or halogen-bond (XB) donors. Examples are presented below.

### 3.1.2. Cinchona Alkaloids and Derivatives Are Capable of Providing Hydrogen Bonding

In 1981, Hiemstra and Wynberg reported that the cinchona alkaloid which bear free OH groups in proximity to the basic quinuclidine nitrogen, catalyze enantioselective conjugate addition reactions to conjugated enones (e.g.: reaction (3.4)). The results were interpreted in terms of a transition structure **10** implying of double hydrogen-bridging [246].

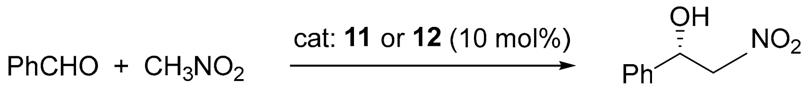


**10**

(3.4)

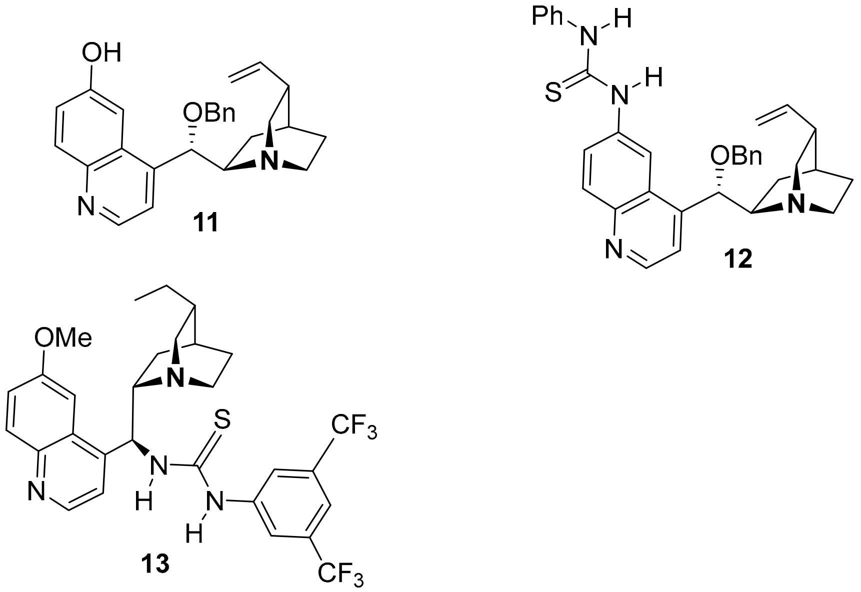
N-H and OH of **10** are H-bond donors

The Henry condensation of aldehydes and nitromethane (e.g., reaction (3.5), Figure 3.3) was little enantioselective in the presence of phenolic catalyst **11**. However, replacing the 6'-phenolic functional group of **11** by a thiourea moiety (see Section 8.1) led to a substantially improved catalyst **12** [247]. Compounds **11-13** are examples of multifunctional catalysts; they interact with substrates and reactants through the basic and nucleophilic amine function and H-bond donors (electrophilic activation, see Chap. 9) [248,249].



(3.5)

with cat. **11**: 90% yield, 6% *ee*
with cat. **12**: 90% yield, 92% *ee*



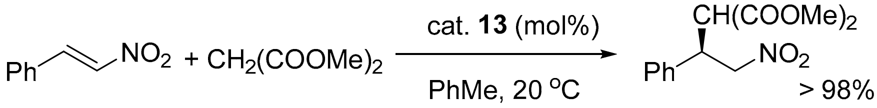
**11**

**12**

**13**

**Figure 3.3.** Examples of cinchona alkaloid-derived catalysts providing H-bonding activation (see Chap. 9). They are examples of multifunctional catalysts (Brønsted base and H-bond donors).

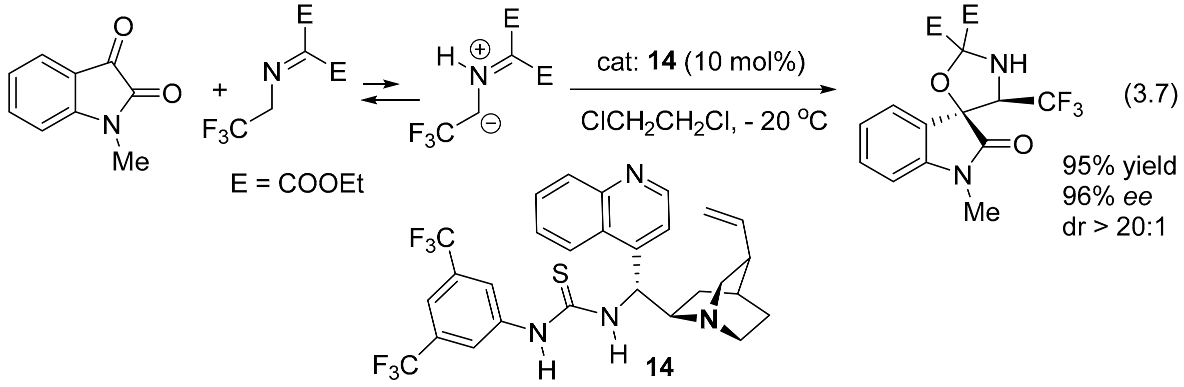
With the quinine analog **13** (Figure 3.3), nucleophilic 1,4-additions of dialkyl malonates to aryl, heteroaryl, and alkyl substituted nitroalkenes are highly enantioselective (e.g., reaction (3.6)) [250].



(3.6)

> 98% conversion
90% *ee*

In 2020, Lu and co-workers reported the catalytic asymmetric oxa-1,3-dipolar cycloaddition (3.7) of *N*-methylisatin with azomethine ylide equilibrating with diethyl 2-(2,2,2-trifluoroethylimino)malonate. It applies cinchona-derived bifunctional thiourea **14** as catalyst [251].



Analogues of **13** and **14** in which the thiourea moieties are exchanged for other H-bond donors such as urea, guanidine, squaramide, and sulfonamide groups are also good asymmetric catalysts (Chap. 9) [252]. Reaction (3.6) is analogous to Michael addition (nucleophilic 1,4-addition). Possible electrophiles are $\alpha$,β-unsaturated aldehydes, ketones, carboxylic esters, carbonitriles, nitroalkanes, and their yne analogues. Possible nucleophiles are enamines, enols of carbonyl compounds, carbonitriles and nitroalkanes, or their carbanions. These reactions can be enantioselective in the presence of chiral amine catalysts [249,253].

### 3.1.3. Conjugate Acids of Cinchona Alkaloids and Simpler Chiral Amines as Enantioselective Protonation Catalysts

In 1976, Lucette Duhamel introduced the concept of deracemization [254]. A racemic chiral $R^1(R^2)(R^3)C$-H compound is deprotonated into the corresponding planar achiral carbanion ion pair $R^1(R^2)(R^3)C^{(-)}$ $M^{(+)}$. The latter is then protonated enantioselectively by an enantiomerically enriched chiral acid, either under thermodynamic or kinetic control [255].

A successful example of asymmetric catalyzed protonation was reported in 1994 by Fehr and Galindo with the enantioselective protonation of the lithium enolate of 1-(2,6,6-trimethylcyclohex-2-enyl)-pentan-1-one in the presence of 20 mol% of (-)-*N*-isopropylephedrine to generate its (*S*) enantiomer in 94% yield and 94% *ee* (compare with Figures 3.4 and 3.5) [256,257]. Fehr also showed that enols are isomerized selectively to one or the other enantiomeric carbonyl compound [258]. In 1991, Kumar, Dike, and coworkers described a synthesis of (*S*)-Naproxen (used to treat pain and inflammation) based on the catalytic enantioselective protonation of an enolate anion intermediate resulting from the Michael addition of PhSH to an acrylic ester catalyzed by quinine (**2**). The counter-ion of the enolate anion is the quininium ion (protonated quinine) which protonates the carbanion enantioselectively (reaction (3.8), Figure 3.4). After desulfurization of the Michael adduct (*S*)-Naproxen was isolated in 85% yield and with 46% *ee*. A single recrystallization gave (*S*)-Naproxen with 85% *ee* [259].

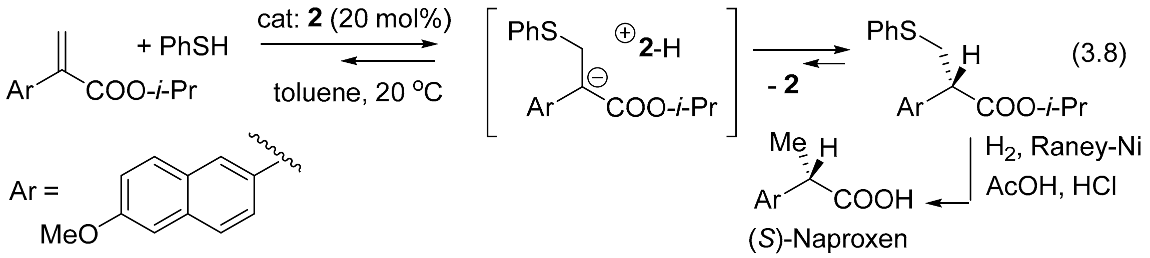


**Figure 3.4.** An early example of asymmetric protonation of a carbanion intermediate with (-)-quinine (**2**) as catalyst (Kumar & Dyke, 1991).

In 2001, Tomioka and co-workers reported a similar asymmetric 1,4-addition, the enantioselectivity (up to 92% *ee*) being induced by a chiral tertiary amine catalyst ((1*R*,2*S*)-($Me_2N$)-CH(Ph)-CH(Ph)-O-$C_6H_4$-2-OMe, 1-2 mol%) [260,261]. Intermolecular oxa-Michael additions are less exothermic than their thia-analog. They are reversible at room temperature [262]. They are difficult to realize in a catalytic enantioselective version. Because cyclization entropy cost is lower than condensation entropy cost, asymmetric intramolecular catalytic alcohol addition to an alkene moiety is possible. An example is the enantioselective cyclization of 4-(2-hydroxyphenyl)-2-butenoates into benzo-2,3-dihydrofuran-2-yl acetates [263]. Related to the conjugate addition of thiols, the asymmetric conjugate addition $(CH_3)_3SiN_3$ + (*E*)-R-CH=$CHNO_2$ → RCH($N_3$)-$CH_2NO_2$ has been catalyzed by cinchona-alkaloids [264].

In 1993, Yasukata and Koga [265] found that one equivalent of a 1:1 mixture of acetic acid and chiral triamine **15** converts 2-methyl-1-tetralone lithium enolate into (*S*)-2-methyl-1-tetralone in 88% yield and 91% *ee*. When the chiral base was used in a catalytic amount (10 mol%), *ee* dropped to 28% (reaction (3.9), Figure 3.5a) [266]. In 2021, Łowicki and co-workers reported that the more elaborated chiral diamine-diphenol **16** is a better catalyst (Figure 3.5b) [267]. Amino acids also catalyze the enantioselective protonation of lithium enolates [268].

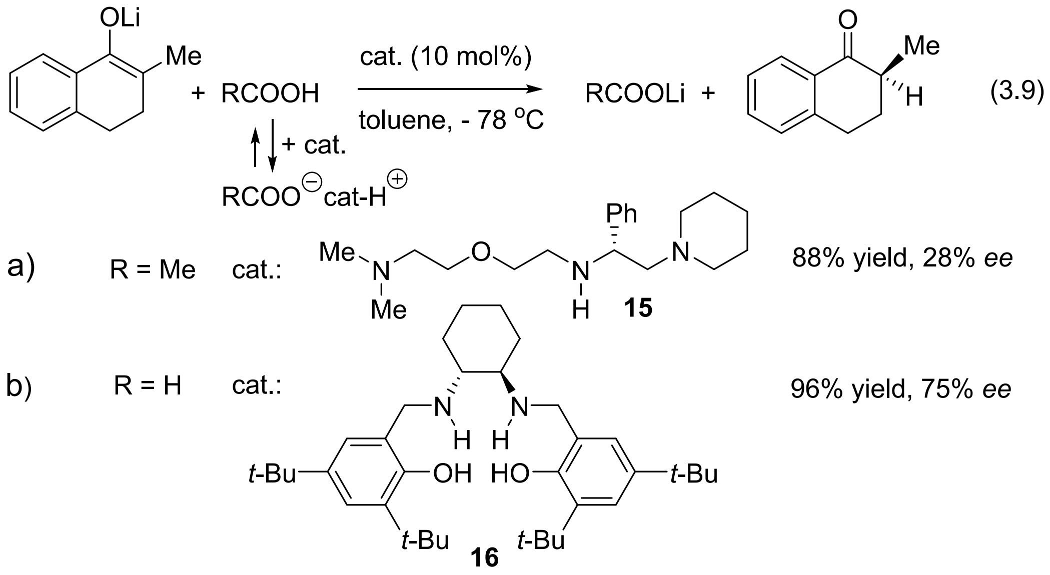


**Figure 3.5.** Example of asymmetric lithium enolate protonation with synthetic polyamines: a) (Koga, 1993); b) (Łowicki , 2021).

Silyl enolates are protonated enantioselectively by HF + cinchona alkaloids as catalysts [269] or betaines derived from cinchona alkaloids [270].

Formally, decarboxylation of malonic acid hemiesters generates planar carbanion intermediates. In the presence of a chiral ammonium ion, their protonation can be enantioselective. For instance, heating (70 °C, THF) 2-*N*-acetylamino-2-ethoxycarbonyl-3-phenylpropionic acid in the presence of 10 mol% *N*-(9-deoxyepicinchonine-9-yl)-4-methoxybenzamide as the chiral base generates ethyl *N*-acetyl-L-phenylalaninate in 70% *ee* [271].

### 3.1.4. Cinchona Alkaloid Derivatives as Nucleophilic Activators

The construction of the medium-sized ring systems, such as eight-membered ones, is difficult compared to five or six-membered rings. One finds eight-membered lactam moiety in natural products and pharmaceutically important substances [272]. Applying a chiral phosphine for the catalysis of a (4+4) annulation reaction, Lu reported, in 2017, a first enantioselective azocane synthesis (Section 5.1, Figure 5.4). Later, Romo and coworkers reported an asymmetric (5+3) annulation via a Michael addition/lactamization cascade catalyzed by tertiary amines [273]. In 2019, the Coquerel group developed an asymmetric Michael addition/four-atom ring-expansion cascade reaction of activated cyclobutanones and 2-amino nitrostyrenes for the synthesis of benzazocinones in a (4+4) annulation manner [274]. In 2020, Chen and coworkers reported an asymmetric (4+4) annulation reaction of 1-azadienes and cyclobutenones under the catalysis of modified cinchona alkaloids. Among several chiral amines assayed cinchona-derived catalyst **9** gave the best yields and enantioselectivities (reactions (3.10), Figure 3.6) [275]. This approach exploits the ability of amine catalysts to add reversibly to unsaturated systems (here the carbonyl group of cyclobutenone **17**), generating zwitterionic intermediates that undergo γ-addition to the electron-poor azadiene **18** permitting the formation of the medium ring final products.

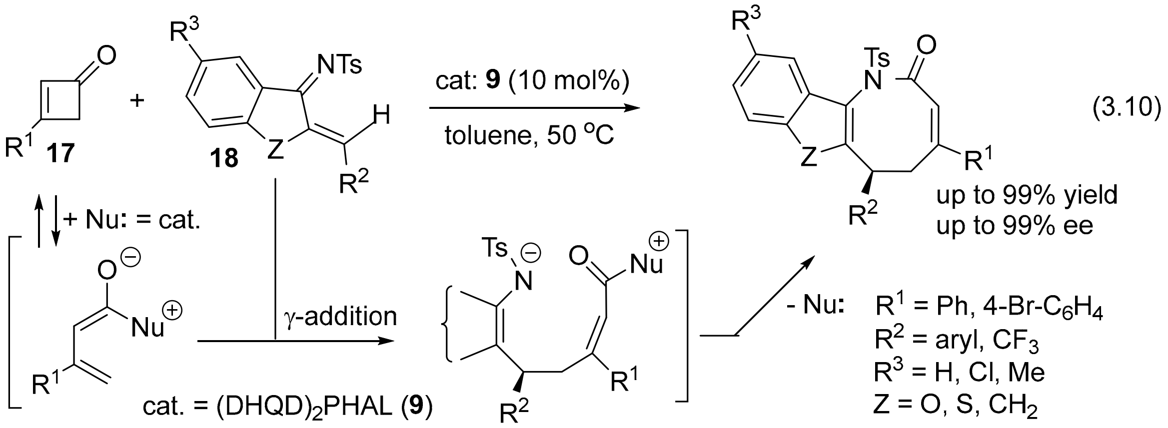


**Figure 3.6.** Asymmetric synthesis of benzazocinones (Chen, 2020).

### 3.1.5. Iminium Ion Mode of Activation by Cinchona Alkaloids

In 2007, the groups of Chen [276] (Figure 3.7a) and Melchiorre [277] (Figure 3.7b) independently introduced 9-amino-9-deoxy-*epi*-cinchona alkaloids (e.g., **19**, **20**) as effective catalysts of the stereoselective functionalization of hindered carbonyl compounds through iminium ion mode of activation. The primary amine of the catalyst reacts with conjugated enones and forms corresponding chiral ene-iminium ion intermediates that are more electrophilic in 1,4-nucleophilic additions than the achiral enones themselves (see also Section 3.5) [278]. In 2008, the List group reported that a variety of cyclic enones are epoxidized with $H_2O_2$ using catalysts such **19**·$(CF_3COOH)_2$ (Figure 3.7c). The tertiary amine acts as a general base to promote the conjugate addition of $H_2O_2$ to the ene-iminium ion intermediate [279].

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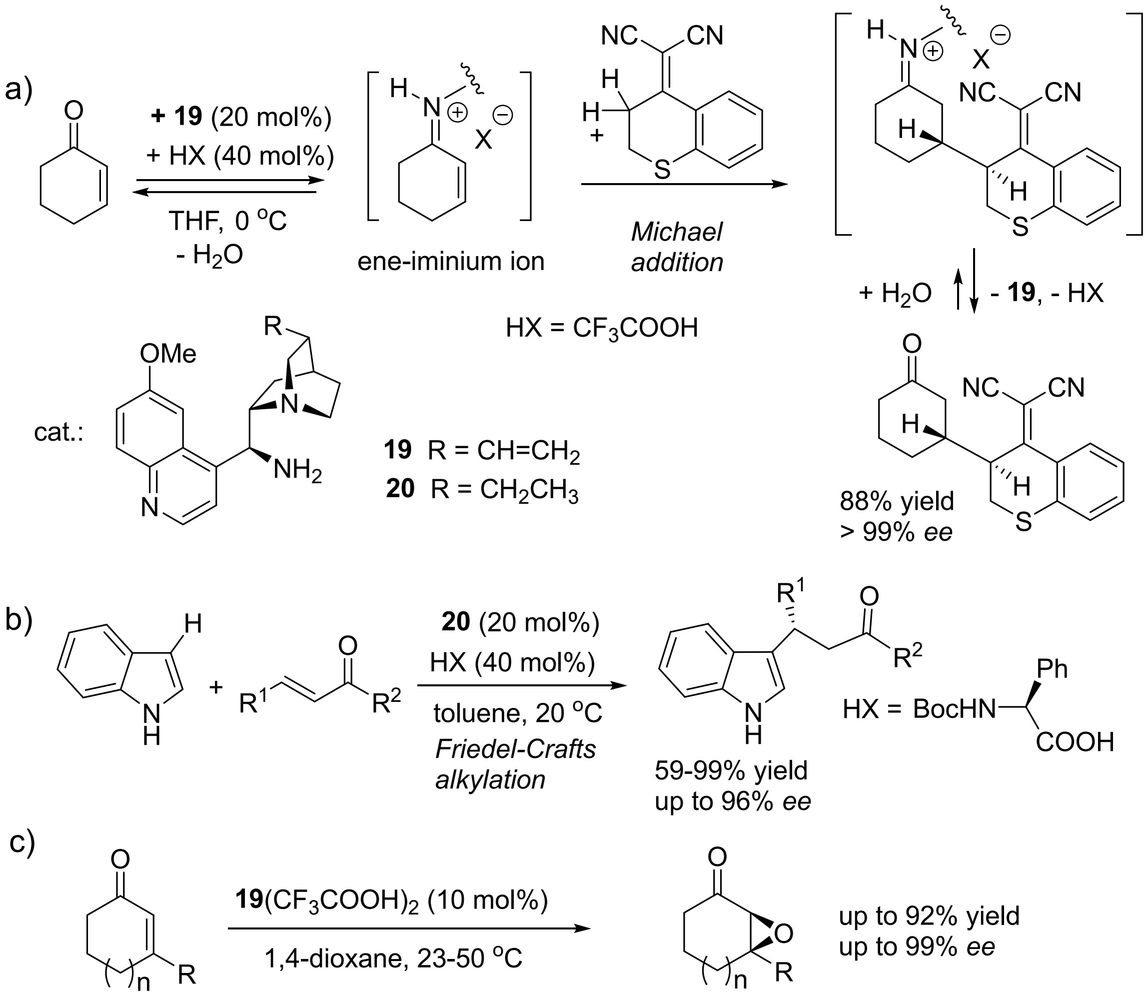
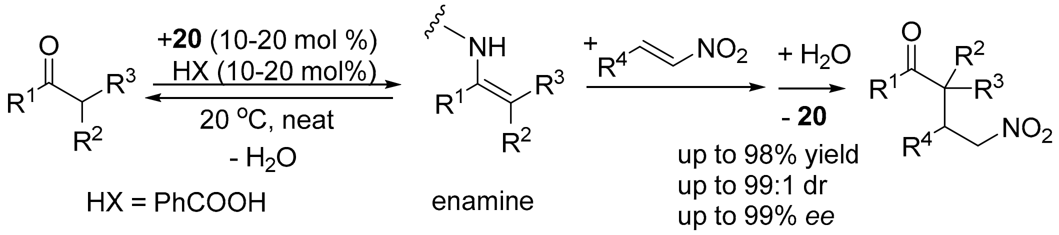


**Figure 3.7.** Examples of iminium mode of activation of α,β-unsaturated ketones. The substrates form ene-iminium ion intermediates with the primary amine of the chiral catalyst. a) Asymmetric Michael addition (Chen, 2007); b) Asymmetric Friedel-Crafts alkylations (Melchiorre, 2007); c) Asymmetric epoxidation of cyclic enones (List, 2008).

### 3.1.6. Enamine Mode of Activation by Cinchona Alkaloids

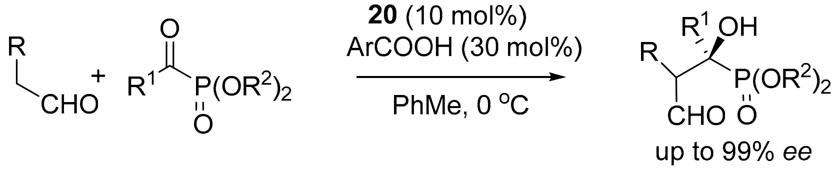
With primary amine **20,** ketones and aldehydes equilibrate with their corresponding enamines, which are more nucleophilic than their corresponding enols (Figure 3.8). Asymmetric reactions (3.11) reported in 2007 by Connon and McCooey illustrate this mode of activation (see also Section 3.6) [280].



(3.11)

**Figure 3.8.** Asymmetric Michael additions of enolizable carbonyl compounds activated through formation of enamine intermediates with the primary amine of the chiral catalyst (Connon, 2007).

In 2011, Perera and coworkers reported the first asymmetric cross-aldol reactions (3.12) of enolizable aldehydes and α-ketophosphonates catalyzed by **20** [281].

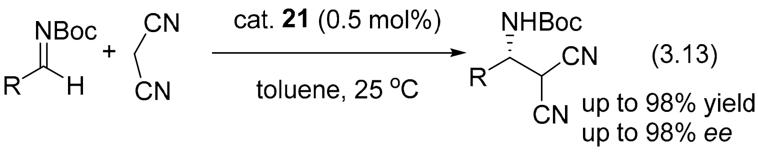


(3.12)

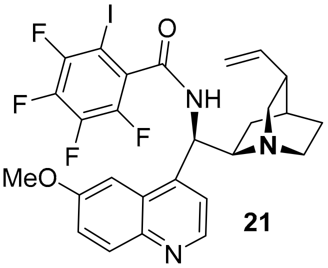
In 2011, MacMillan and coworkers reported the first highly enantioselective *α*-fluorination of ketones. Best yields, diastereoselectivities, regioselectivities, and enantioselectivities (up to 99% *ee*) were obtained using cinchona alkaloid derived primary amine **20** as a catalyst, and NFSI ($(PhSO_2)_2NF$)·as an electrophilic fluorinating agent (see also Section 3.6-4). [282].

### 3.1.7. Cinchona Alkaloid Derivatives with Halogen Bond (XB) Donors

Halogen bonding (XB) has become increasingly relevant in catalytic processes. The halogen bond occurs when there is a net attractive interaction between an electrophilic region (Lewis acid) associated with a halogen atom in a molecular entity, and a nucleophilic region (Lewis base) in another, or the same, molecular entity [283–285]. In 2008, Bolm and co-workers demonstrated the catalytic ability of haloperfluoroalkanes in the reduction of 2-substituted quinolines (activation of type $C{=}(R)N{:}\cdots I\text{-}(CF_2)_nCF_3$) [286]. In 2018, Arai and co-workers found that quinidine-derived iodoarene **21** catalyzes the asymmetric Mannich reaction (3.13) of malononitrile and various *N*-Boc imines with high *ee*. The bifunctional catalyst (amine, C-I) interacts with both the substrate and the reagent. This renders the catalyst highly active, limiting its amount to 0.5 mol% [287,288].



(3.13)



**21**

Noncovalent interactions such as halogen (F, Cl, Br, I), chalcogen (O, S, Se, Te), and pnictogen (N, P, As, Sb) bonding have been known for a very long time. Organic compounds containing these elements have a region with positive electrostatic potential on the heteroatoms (so-called σ-hole; anisotropic distribution of the electron density around these atoms). They mimic metal-containing Lewis acids in electrophilic catalysis [289]. Halogen-bond donors like $ICF_3$ have only one σ-hole, while the chalcogen-bond donor $Te(CF_3)_2$ has two, and the pnictogen-donor $Sb(CF_3)_3$ has three σ-holes. Theoretical investigations show that, besides these electrostatic contributions, charge transfer and dispersion are also important for a proper description of these noncovalent interactions [290]. These σ-hole donors (SHD) exhibit notable catalytic activity accompanied by high tolerance to water and oxygen [285,291].

## *3.2. Cinchona Alkaloid-Derived Ammonium Salts: Enantioselective Phase Transfer Catalysts (PTCs)*

A reagent soluble in water only (e.g., salt $M^{(+)}Nu^{(-)}$, $M^{(+)}$ counter-ion of an anionic nucleophile $Nu^{(-)}$) does not react readily with an electrophile (e.g., R-X) soluble only in an organic solvent that is non-miscible with water. Classically, alkylation of indene requires the formation of indenyl carbanion and its quenching with an alkyl, or an allyl halide under anhydrous conditions. In 1966, Makosza found that indenyl sodium salt obtained from indene with aqueous NaOH is alkylated with alkyl halides if benzyltriethylammonium chloride ($Bn(Et)_3N^{(+)}Cl^{(-)}$) is added to the reaction mixture [292]. In 1971, Starks also found that the addition of a small amount of a tetraalkylammonium salt ($R_4N^{(+)}/Y^{(-)}$) accelerates nucleophilic displacements dramatically [293]. The quaternary ammonium salt is a phase transfer catalyst (PTC) that exchanges its counter-ion $Y^{(-)}$ with the nucleophilic anion $Nu^{(-)}$ and transports it from the aqueous phase to the organic phase, permitting a fast displacement reaction $R_4N^{(+)}/Nu^{(-)} + R\text{-}X \rightarrow R_4N^{(+)}/X^{(-)} + R\text{-}Nu$. Ammonium salts have dominated in the field of ion-pair catalysis.

### 3.2.1. Early Enantioselective Phase Transfer Catalyzed Applications

In 1976, Wynberg and co-workers [294] utilized a cinchona alkaloid-derived quaternary ammonium salt to catalyze the epoxidation of α,β-unsaturated ketones with up to 45% *ee* [295]. Further studies and applications of cinchona-derived catalysts for alkene epoxidation followed this pioneer work [296]. Asymmetric alkene epoxidation is a powerful entry to highly valuable polyfunctional compounds [297]. More methods are represented below. In 1984, a practical asymmetric alkylation of an α-phenylindanone substrate under the influence of *N*-(*p*-trifluoromethylbenzyl)cinchoninium bromide (PTC: **22**, reaction (3.14)) was reported by Dolling and co-workers (Figure 3.9a) [298]. In 1989, O'Donnell and coworkers at Merck presented their synthesis of α-amino acids using various cinchona alkaloid-derived PTCs such **23** (reactions (3.15), Figure 3.9b) [299]. In 1996, Prabhakar and co-workers reported that up to 61% *ee* was obtained for aziridination of methyl acrylate with **24** as catalyst and *N*-aryl hydroxamic acids as nitrogen sources (reaction (3.16), Figure 3.9c). In 2005, Murugan and Siva reported that up to 95% *ee* is realized with the aziridination of *t*-butyl acrylate with PTC **24** [300].

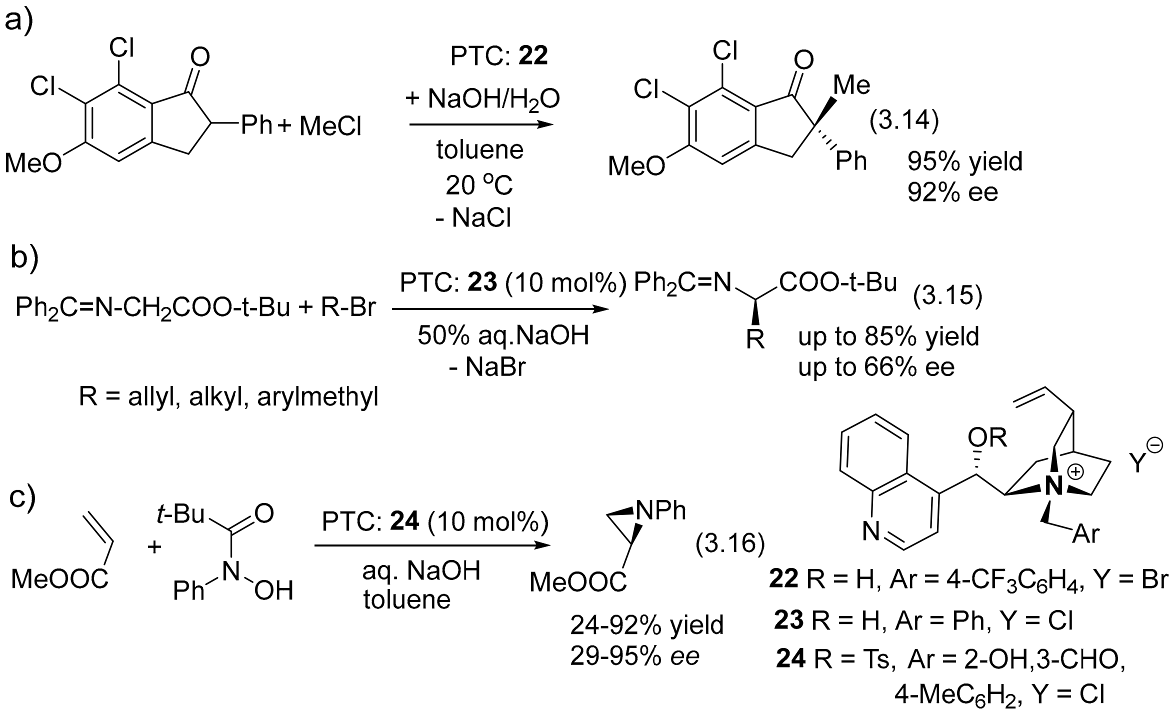
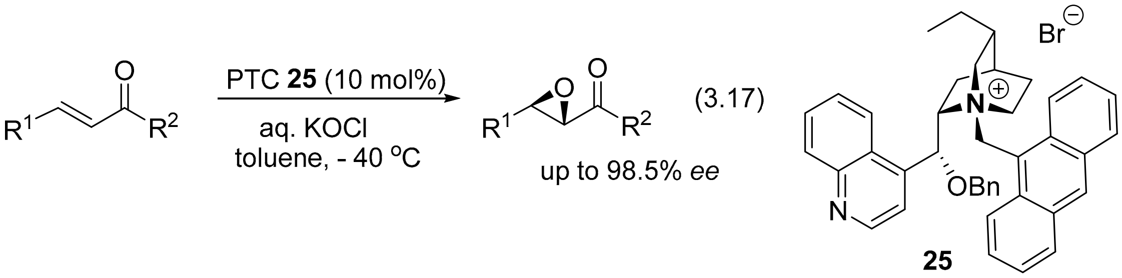


**Figure 3.9.** Examples of asymmetric nucleophilic substitutions catalyzed by phase transfer catalysts. a) Asymmetric α-methylation of a ketone (Dolling, 1984); b) Asymmetric synthesis of α-amino acids (O'Donnel, 1989); formation of chiral carbanion/ammonium ion pairs as reactive intermediates; c) Asymmetric aziridination (Prabhakar, 1996); formation of chiral nucleophilic nitrogen intermediates.

In 1987, and independently of each other, the groups of Lygo [301] and Corey [302] contributed significantly the asymmetric PTC field. When the benzyl group of the quinuclidinium salts is exchanged for an anthracen-9-ylmethyl moiety, higher *ee*'s are observed. In 1999, Corey and co-workers demonstrated high enantioselectivity for epoxidation of enones with catalyst **25** using KOCl as oxidant (reactions (3.17)) [303]. Many more PTCs have then proposed for the same epoxidations [296].



Lyke an enzyme, *N*-9-anthracenylmethyl cinchonidinium chloride (2 mol%) catalyzed the asymmetric hydrolysis of enol esters [304].

### 3.2.2. Industrial Applications of Chiral PTCs

During the last 35 years, asymmetric synthesis using PTCs has become very successful; a large number of chiral ammonium salts have been prepared and used in academia and industry [305–307]. Because the cinchona-derived PTCs are easily prepared, they remain attractive catalysts [308–310]. Their immobilization on polymeric supports has significantly influenced their use in catalysis. Polymer-anchored cinchona alkaloids permit their easy recovery, recyclability, and reusability, and reduce their environmental impact. They have found applications in enantioselective Michael addition, aldol condensation, Henry reaction, dimerization reaction, dihydroxylation, and benzylation. Anchoring cinchona alkaloids onto polymers includes their covalent attachment in the polymer side chain or main chain, and their ionic attachment via quaternization in the main chain or side chain of the polymer [311]. A synthesis of Pregabalin (central nervous system inhibitor, to treat epilepsy and anxiety), which applies the cinchona-derived PTC **26** for an enantioselective Michael addition of nitromethane (reaction (3.18), Figure 3.10) has been developed. The counter-ion of the quaternary ammonium ion is solid polysulfonated polystyrene (beads), which permits the recovery of the catalyst by simple filtration (99% yield of recovery of the catalyst) [312,313].

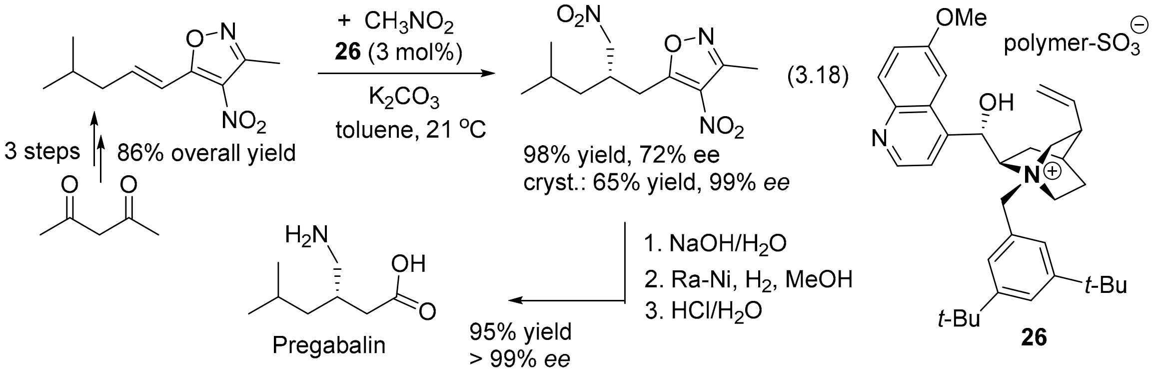
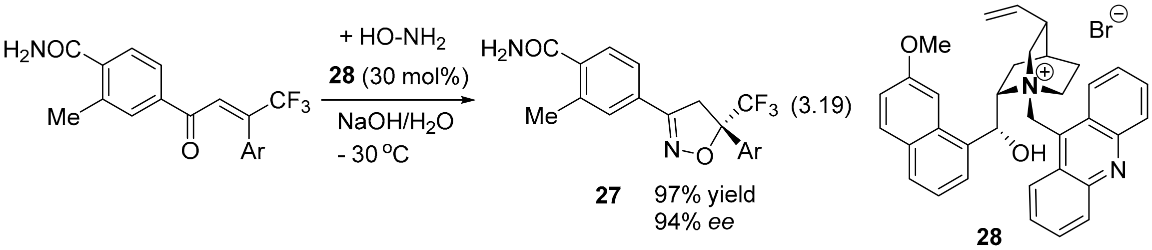


**Figure 3.10.** Asymmetric synthesis of Pregabalin.

In 2013, Toyama and coworkers at Nissan Chemical Industries Ltd. disclosed their asymmetric synthesis of 2-isoxazoline derivative **27** (a pest-control agent), applying the PTC **28** (reaction (3.19); 1,4-addition of hydroxylamine to the enone, formation of imine) [12].



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In 2024, Deng and coworkers presented an asymmetric α-alkylation of N-arylidene-protected alkyl amines (reaction (3.20)). Because of the electron-withdrawing cyano and 4-nitrophenyl groups, substrates **A-H** (Figure 3.11) are acidic enough to be deprotonated by a phenolate, the counter-anion of the PTC **29**. This generates a chiral ion-pair $\mathbf{A}^{(-)}/\mathrm{R^*{}_4N^{(+)}}$ that adds to conjugated enones (Michael addition) with good *trans*-stereoselectivity and *ee* [314].

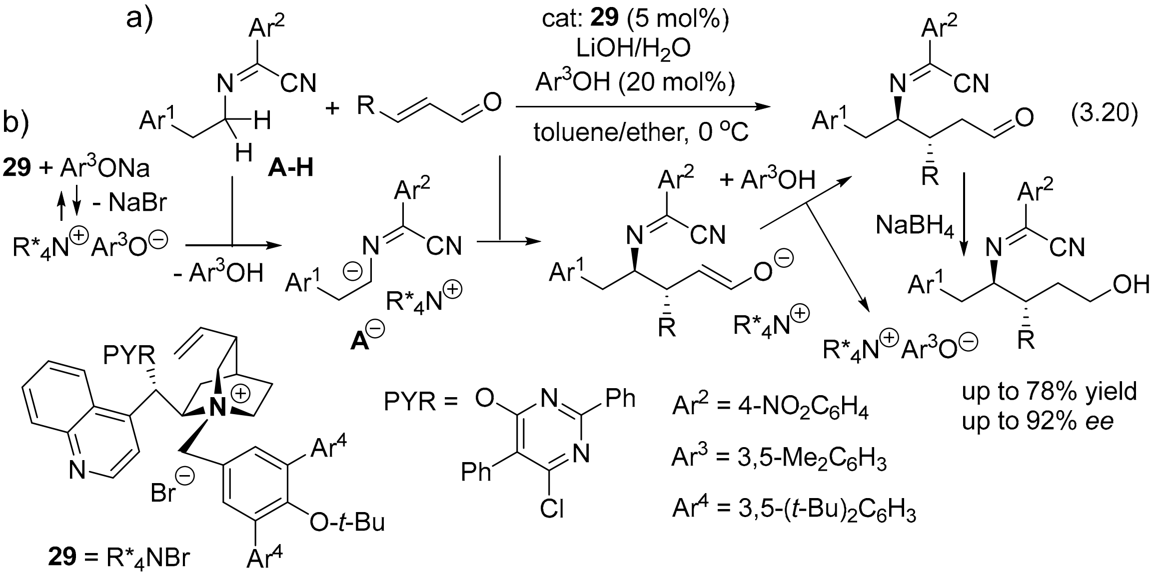
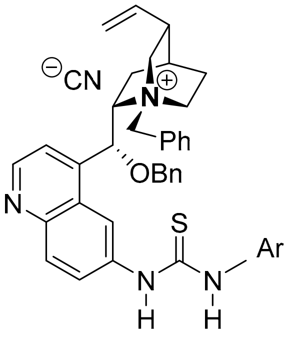


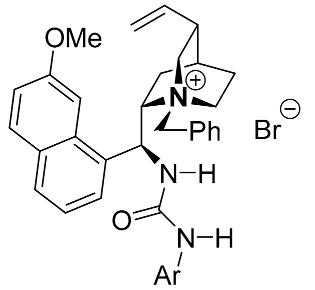
**Figure 3.11.** a) PTC-catalyzed asymmetric α-alkylation of protected amines (Zheng, 2024); b) Possible mechanism.

### 3.2.3. Polyfunctional Cinchona-Derived Polyfunctional PTCs

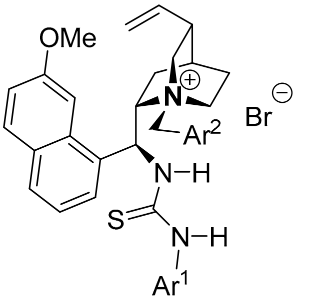
As we shall see below for other type of catalysts, a recent trend has been to add functionalities to the chiral ammonium (or other onium PTCs, see Sections 5.3 and 6.4), generating bi- or polyfunctional PTCs [307,310,315]. Cinchona-derived ammonium salts with a free hydroxy group are bifunctional catalysts as they possess, next to the ammonium ion (ion-pairing catalysis), a hydrogen bond (H-bond) donor that can intervene in the activation process and the chiral recognition (for a better enantioselectivity). Obviously, the invention of cinchona derivatives with more H-bond donors (see Chap. 9) as permitted the development of better yielded and more enantioselective organocatalyzed reactions. The thiourea moiety containing catalyst **30** (10 mol%) reported in 2010 by the group of Fernández and Lasseletta has been applied to the cyanosilylation of nitroalkenes [316]. Catalyst **31** (5 mol%) developed by Dixon and coworkers in 2012 has been applied to the enantio- and diastereoselective nitro-Mannich reaction of amidosulfones [317]. The enantioselective synthesis of quaternary-substituted indolenines via a 5-*endo*-dig cyclization of an α-cyanocarbanion onto an isonitrile applying catalysts **32** (5 mol%) has been reported in 2013 by the group of Smith [318]. In 2018, Duan and co-workers presented an enantioselective aza-Henry reaction of aryl α-ketoester-derived ketimines ($\mathrm{ArC(=NTs)COOR + CH_3NO_2 \rightarrow ArC(-NHTs)(COOR)\text{-}CH_2NO_2}$, 99% yield, 99% *ee*) has been catalyzed by **33** (10 mol%) [319].



**30** Ar = 3,5-$(CF_3)_2C_6H_3$



**31** Ar = 3,5-$(CF_3)_2C_6H_3$
**32** Ar = 4-$NO_2C_6H_4$



**33** $Ar^1$ = 3,5-$(CF_3)_2C_6H_3$
$Ar^2$ = 3,5-(*t*-Bu)$_2C_6H_3$

### 3.2.4. Non-Cinchona-Derived Chiral Ammonium Phase Transfer Catalysts

Chiral quaternary ammonium and diammonium salts catalyze numerous reactions, including enantioselective nucleophilic addition reactions [320]. Early examples derived from tartaric acids (e.g., Figure 3.12a) [321,322] or BINOLs (e.g., **34**, **35**, Figure 3.12b; see Section 9.1 for BINOLs). Other PTCs or ion-pairing catalysts are guanidinium salts such as **36**, **37**, (N-H bond donors) [323,324] pentanidiniums **38** (e.g.: Figure 3.12c) [325] and 1,2,3-triazolium salts (e.g., Figure 3.12d) [326]. PTCs that are chiral phosphonium, sulfonium salts, and crown ethers are introduced in Sections 5.3, 6.4, and 10.3, respectively [310,315].

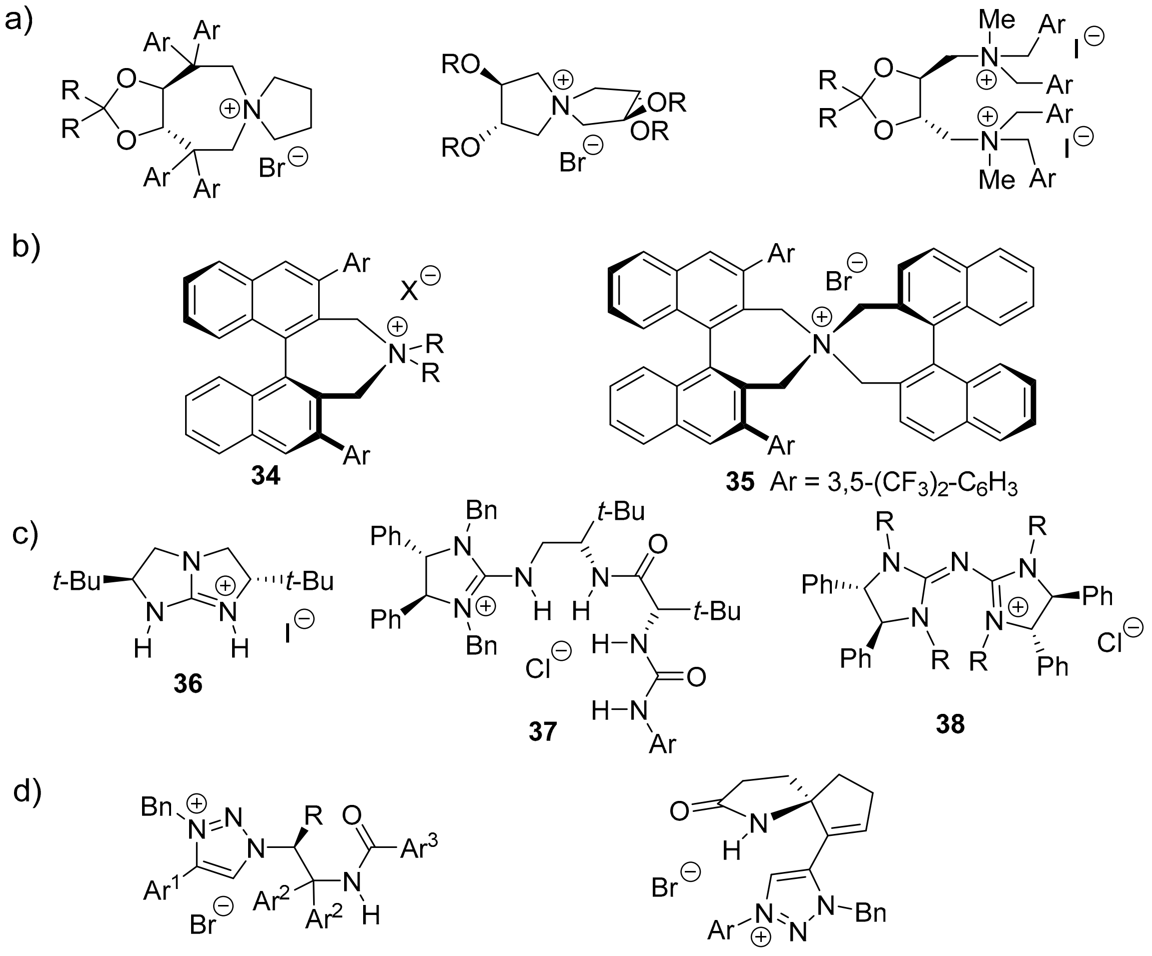
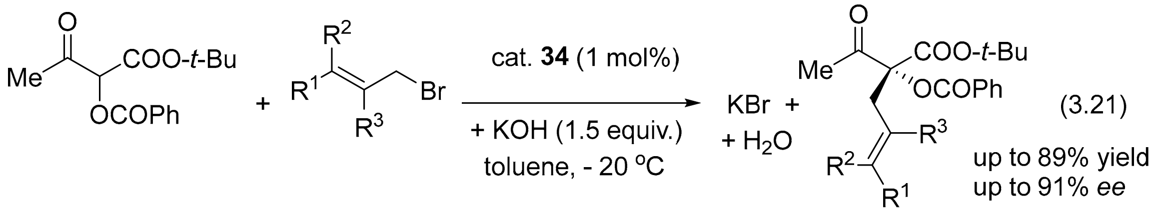


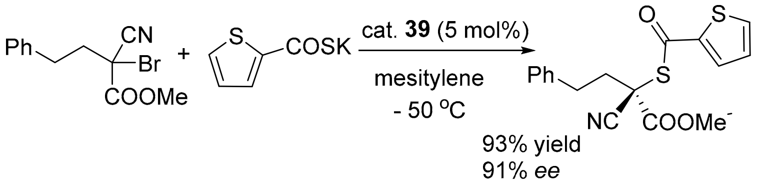
**Figure 3.12.** Examples of non-cinchona-derived PTCs; a) ammonium and bisammonium salts derived from tartaric acids; b) ammonium salts derived from BINOLs; c) guadinidium salts; d) 1,2,3-triazolium salts with one amido N-H bond.

An illustration is the asymmetric allylic allylation (AAA) reported by Maruoka and coworkers in 2003 which applies the Maruoka type of catalyst **34**, a monofunctional PTC (reactions (3.21)) [327]. The method was extended to benzyl and propargyl electrophiles [328–330].



(3.21)

In a typical $S_N2$ displacement reaction ($R_3C\text{-}X + Nu^{(-)} + M^{(+)} \rightarrow R_3CC\text{-}Nu + X^{(-)}/M^{(+)}$) the nucleophile attacks the carbon face opposite the C–X bond, X being the nucleofugal group (leaving group). When $S_N1$ or $S_{RN}1$ processes are not competitive, a less common variant, involves initial nucleophilic attack of the X group from the front in a mechanism noted $S_N2X$. It occurs when steric hindrance retards the backside attack by the nucleophile. Thus, if X = halogen it interacts with the nucleophile ($Nu^{(-)}/M^{(+)}$) to generate a carbanion and a new electrophilic intermediate (Nu–X). The carbanion then displaces X from the Nu–X species to generate the desired substitution product $R_3C$-Nu. In 2019, Lee and co-workers reported an enantioconvergent substitution reaction of activated tertiary bromides by thiocarboxylates or azides. They applied **39** and analogues as PTCs. An example is reaction (3.22). The carbanion intermediate $R_3C^{(-)}/M^{(+)}$ reacts with the pentadinidium salt catalyst $Q^{(+)}/Cl^{(-)}$ and equilibrates with $M^{(+)}/Cl^{(-)}$ + chiral tight-ion pair $R_3C^{(-)}/Q^{(+)}$. One of its faces attacks the Nu-X (2-thiophenyl-COS-Br) intermediate leading to enantioselective $S_N2X$ reaction [331].



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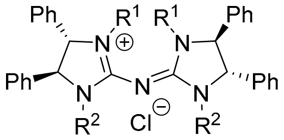


**39** $R^1$ =3,5-($t$-$Bu)_2C_6H_3CH_2$
$R^2$ = 3,5-$(CF_3)_2C_6H_3CH_2$

As for cinchona-derived catalysts, the trend in the recent years has been to develop multifunctional PTCs bearing hydrogen bond donors (HB-PTCs) [310,315,332,333]. Figure 3.13 shows selected examples.

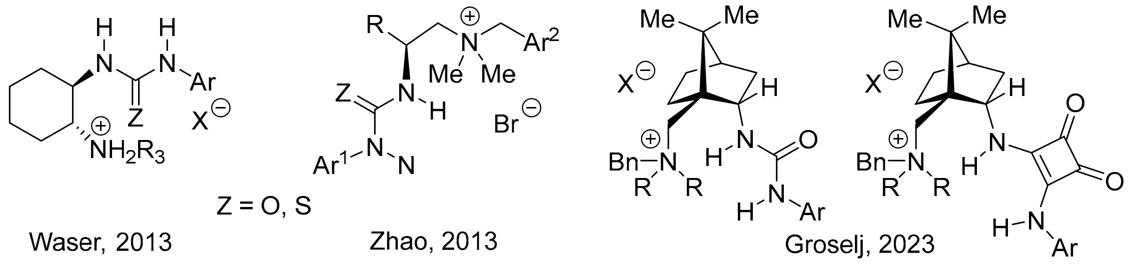


**Figure 3.13.** Examples of non-cinchona-derived ammonium phase-transfer catalysts that are H-bond donors (HB-PTCs).

A new trend is to add halogens in the ammonium salts to make them halogen bond (XB) donors. An example will be presented with the bis(imidazolium) derivative (**228**) catalyzed Mukaiyama aldol reaction (11.12) (Section 11.6) [334].

### 3.3. Asymmetric Hydrogen Atom Abstraction with Cinchona Alkaloid Derivatives

In 2015, MacMillan and co-workers demonstrated that quinuclidinium radical-cations can abstract selectively hydrogen atoms from the C-H bonds of primary ($R^1CH(OH)$-H) and secondary alcohols ($R^1R^2C(OH)$-H). The hydroxyalkyl radical intermediate so-obtained can abstract a hydrogen atom from a hydrogen atom donor, or add to unsaturated compounds making possible the direct C-substitution of alcoholic carbon centers [335]. Phosphate anion as additive enhances the selectivity and yield of the reaction because it forms a strong H-bond with the OH group of the alcohols [336]. Using cinchona alkaloid analogs as catalysts, Phipps and co-workers realized an enantioselective epimerization of meso-1,2-diols (reactions (3.23), Figure 3.14) and meso-1,3-diols. They applied a triple catalyst system including 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (photocatalyst, Act) a cinchona alkaloid derivative as chiral H atom abstractor, and 1-dodecanethiol as an H atom donor catalyst. Electron abstraction from the quinuclidine base to the photocatalyst (Act) is induced under blue light irradiation and tetrabutylammonium dihydrogen phosphate as additive (10 mol%). The enantiomerically enriched radical intermediates **40** could be quenched by Michael acceptors permitting selective alkylation (e.g.: Giese reactions (3.24)) of the C-H moieties of alcohols [229]. For reviews on radical-mediated asymmetric organocatalysis, see: [337,338]. For other processes involving a combination of organo-catalysis and photo-redox catalysis, see: [219,220].

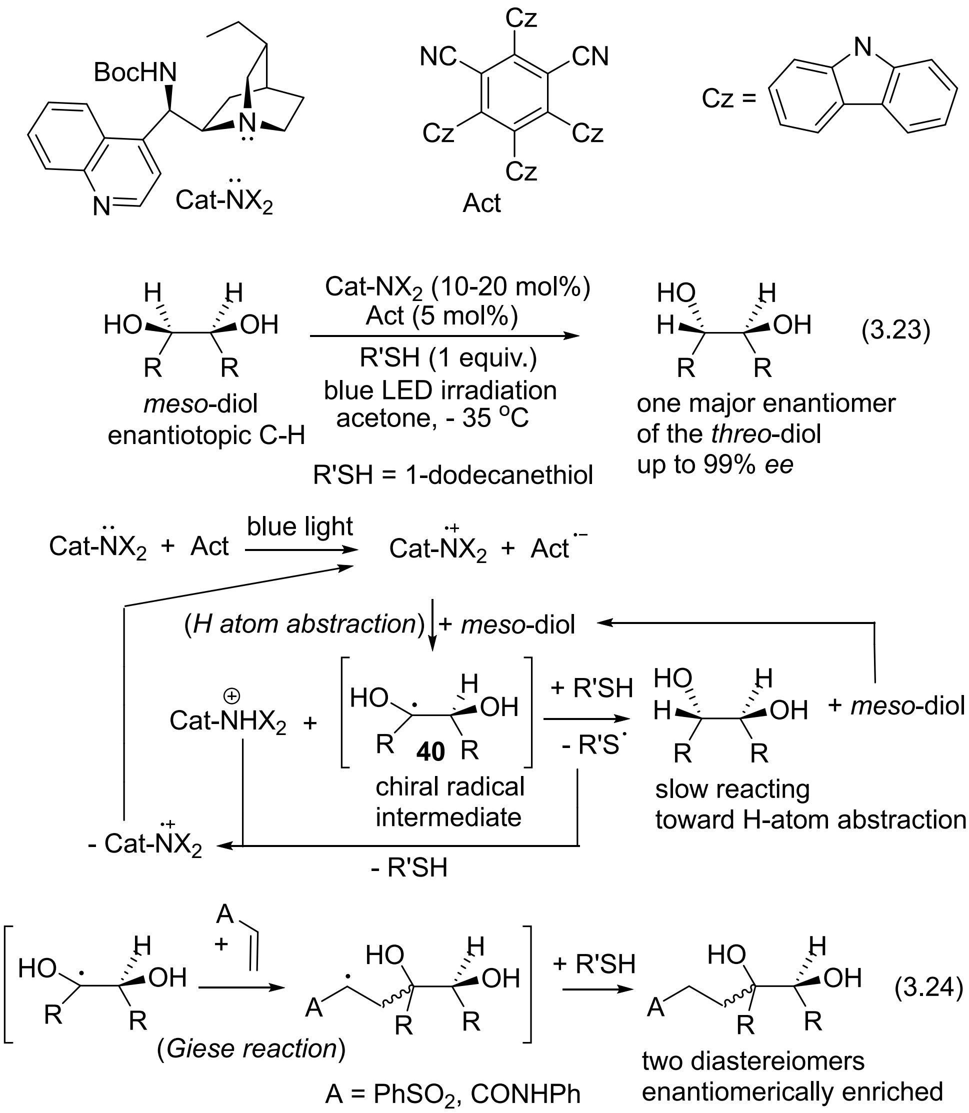


**Figure 3.14.** Phipps' (2024) enantioselective epimerization of *meso*-1,2-diols; application of MacMillan's (2015) enantiotopic H-atom abstraction through activation by ammonium radical-cation intermediates.

### *3.4. Iminium Ion Mode of Activation by Simple Chiral Amines*

In 2000, MacMillan demonstrated that chiral secondary amines (e.g., **41**) can catalyze enantioselective Diels-Alder reactions of dienophiles which are conjugated enals (e.g.: reaction (3.25), Figure 19a) [204]. The enals equilibrate with the secondary amine generating *α*,β-unsaturated iminium ion intermediates (e.g., **42**) that are more electrophilic dienophiles than the starting enals. They add to 1,3-dienes (e.g., Diels-Alder reaction (3.25) producing adduct **43**). As with other electrophilic dienophiles, the kinetic reactivity of **42** (irreversible reactions) depends mostly on the energy (or electron affinity) and shape of their LUMO (Lowest Unoccupied Molecular Orbital). The water formed during the iminium ion generation hydrolyses the iminium ion in the adduct (e.g.: **43**). One speaks here of an "iminium-ion" mode of activation.

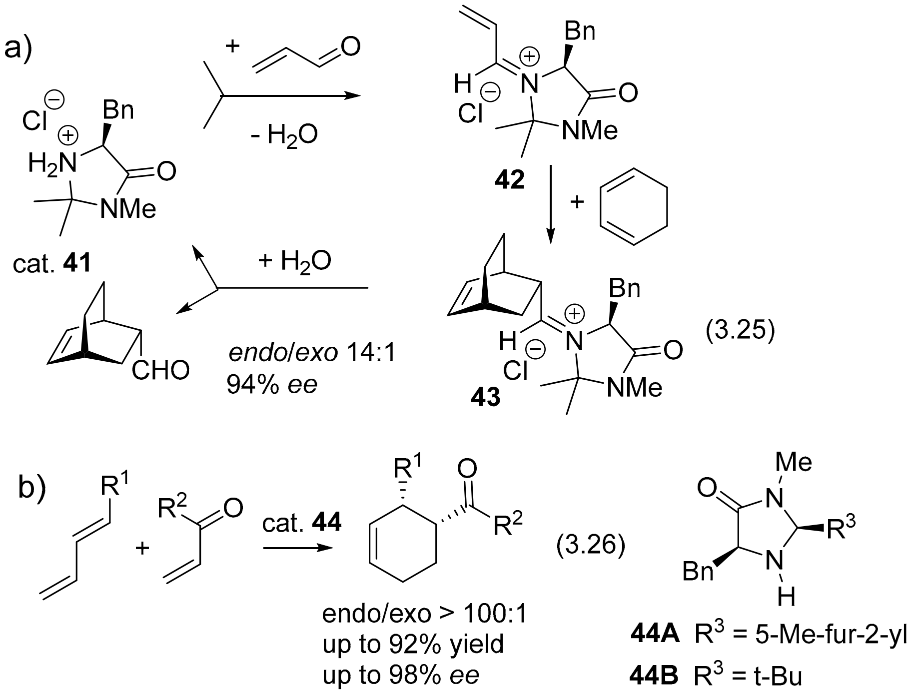
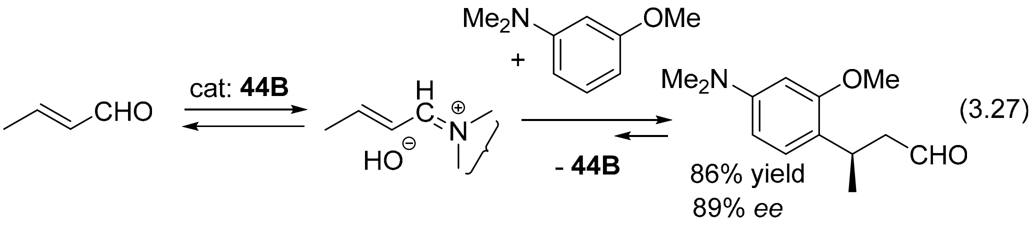
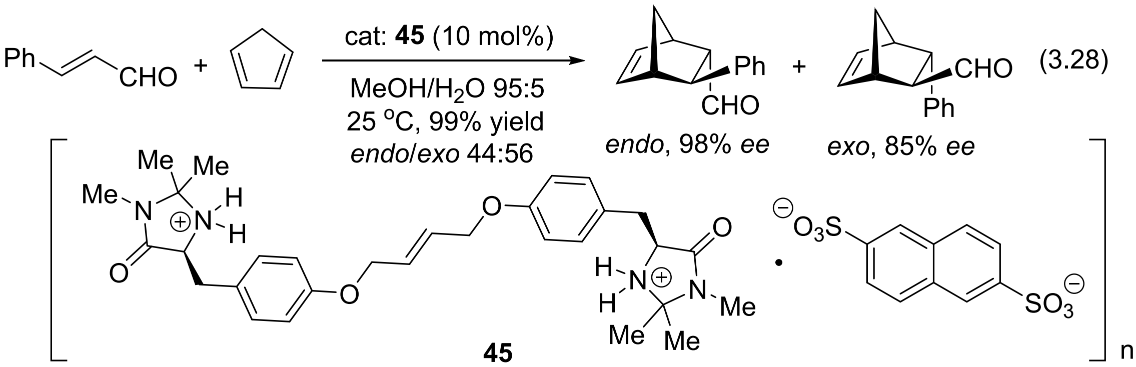


**Figure 3.15.** a) Enantioselective Diels-Alder reaction of cyclohexa-1,3-diene and acrolein catalyzed by chiral secondary amine **41** (MacMillan, 2000); b) Enantioselective Diels-Alder reactions of acyclic 1,3-dienes and conjugated enones, catalyzed by a chiral secondary amine **44.** These catalyzed reactions are iminium ion LUMO driven (MacMillan, 2002).

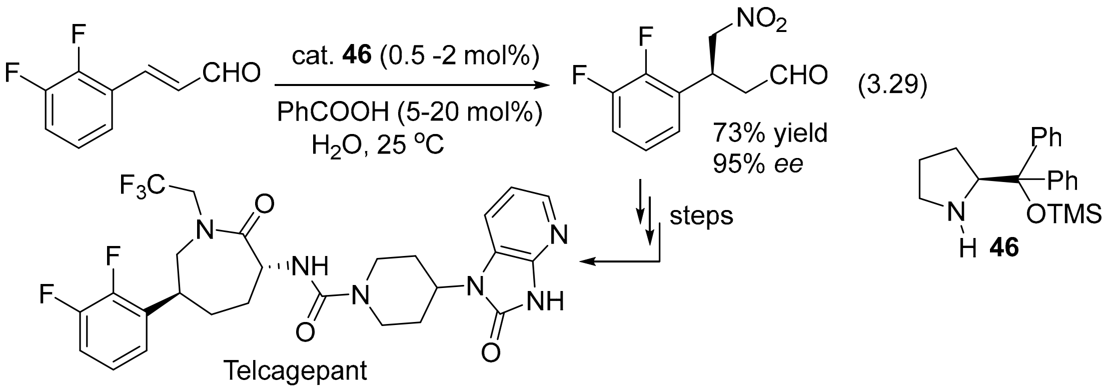
Iminium-ion catalysis is a powerful methodology to activate *α*,β-unsaturated ketones as dienophiles in a similar asymmetric Diels–Alder reactions (3.26) (Figure 3.15b) as shown by Northrup and MacMillan using imidazolidinone **44** as catalyst [339]. The iminium ion intermediates react with nucleophiles generating β-substituted carbonyl compounds (e.g., asymmetric Michael additions of conjugated enals and enones). The iminium-ion mode of activation facilitates Knoevenagel-type condensations, cycloadditions, nucleophilic additions [340–342]. In 2002, Paras and MacMillan reported the enantioselective conjugate addition (3.27) of an electron-rich arene to conjugated (*E*)-but-2-enal, the latter rendered more electrophilic through the formation of a chiral iminium ion intermediate [343].



Iminium activation is also reported for 1,6-additions to conjugated dienones (see Section 3.6). Chiral imidazolidin-4-one derivatives such as **41** and **44** catalyze also 1,3-dipolar cycloadditions [344]. Friedel–Crafts alkylation, indole alkylation, $\alpha$-chlorination of aldehydes, $\alpha$-fluorination of aldehydes, direct aldol reactions, intramolecular Michael reactions, epoxidation, $\alpha$-allylation of aldehydes, $\alpha$-allylation of ketones, and $\alpha$-alkylation of aldehydes. To facilitate the separation, recovery, and reuse of the catalyst, chiral imidazolidinones are grafted to polymeric or inorganic supports. Alternatively a main-chain ionic polymer of a tyrosine-derived chiral imidazolidinone with 1,5-naphthalenedisulfonate with 2,6-naphthalenedisulfonate (**45**) exhibited excellent enantioselectivity for the Diels-Alder reaction (3.28) of (*E*)-cinnamaldehyde and 1,3-cyclopentadiene (98% *ee* for the *endo* isomer). The polymeric chiral organocatalyst was recovered and reused several times, maintaining its high enantioselectivity [345].



A synthesis of a synthetic intermediate in the preparation of Telcagepant, a CGRP receptor antagonist for the treatment of migraine, applies the diphenylprolinol trimetylsilyl ether (**46**; a Hiyashi-Jørgensen catalyst) to catalyze the 1,4-addition of nitromethane to (*E*)-3-(2,3-difluorophenyl)prop-2-enal (reaction (3.29)). The work developed at Merck represents an early (2010) industrial application of iminium organocatalysis. Benzoic acid is a co-catalyst [346].



Melchiorre and coworkers have developed the asymmetric 1,4-additions (3.30) in which electron-rich radical intermediates add to the conjugated enones (Figure 3.16). The catalyst is the primary amine **47** that equilibrates with the iminium ion intermediate **48**. The latter absorbs visible light to generate an electronically excited state **49** that implies an intramolecular electron transfer from the carbazole to the iminium ion moieties. In an initiation step, a silane ($R\text{-}SiMe_2Ph$) undergoes intermolecular electron transfer to **49** and generates intermediate **50** (a relatively stable 1-amino-3-alkylcyclohex-2-en-1-yl radical) next to the corresponding radical-cation $[R\text{-}SiMe_2Ph]^{+\cdot}$. The latter reacts with the medium (benzoic acid or salicylic acid in water) and breaks into radical R and $PhMe_2SiOH/PhMe_2SiOOCAr'$). The electron-rich radical intermediate adds to iminium ion **48** generating radical **51**. The propagating cycle starts now. **51** is converted into radical-cation intermediate **52** by tautomerization and intramolecular electron transfer. Then **52** absorbs an electron from the silane generating imine **53**. This imine is hydrolyzed into the final product with recovery of the catalyst (**47**). Radical-cation $[RSiMe_2Ph]^{(+\cdot)}$ formed in this reaction furnishes radical $R^{\cdot}$ which starts the addition process again [221,347].

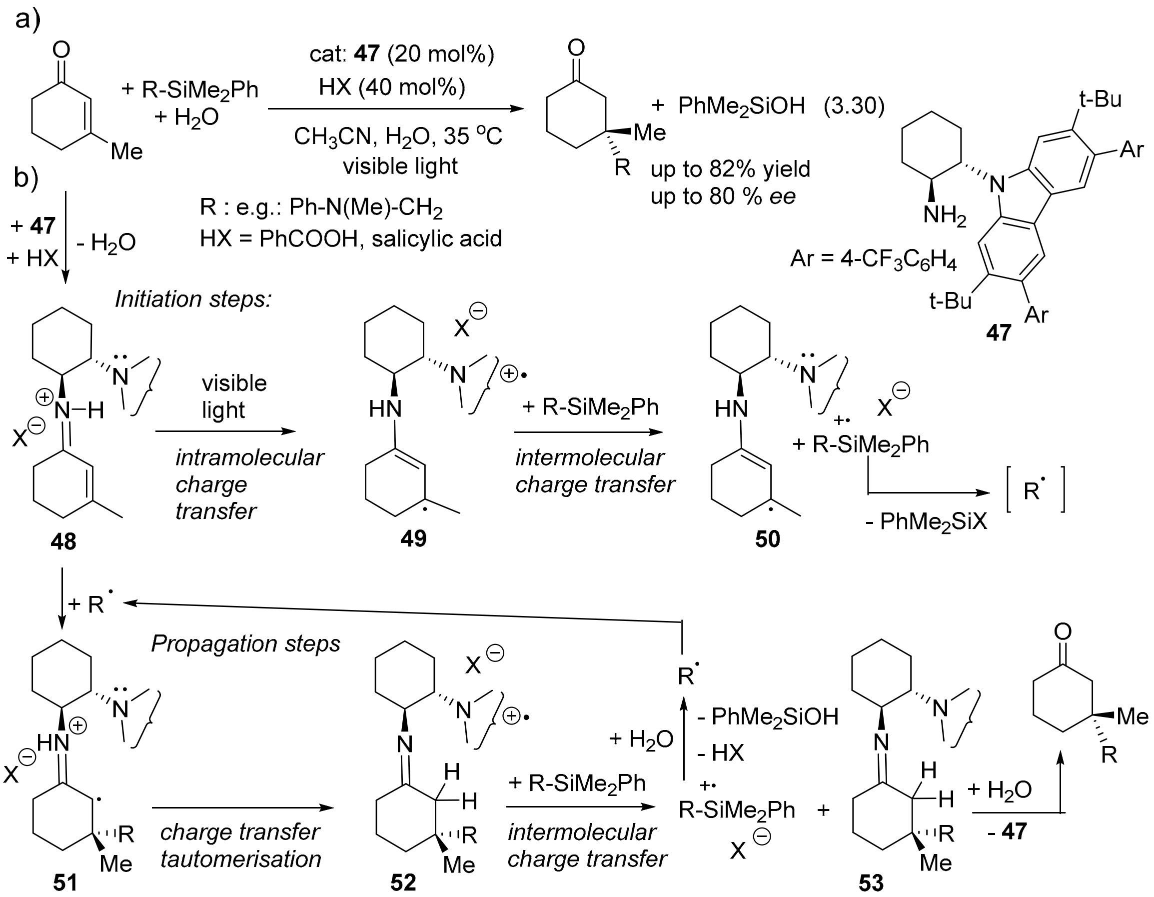


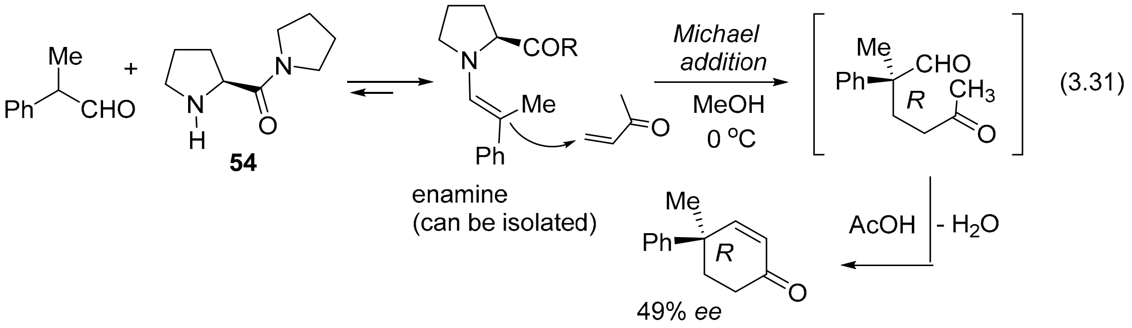
**Figure 3.16.** a) Enantioselective 1,4-alkylation of enones by alkylsilanes induced by visible light (Melchiorre, 2018); b) Possible mechanism implying enantioselective radical conjugate additions driven by a photoactive intramolecular iminium-ion/carbazole complex **48**.

### *3.5. Enamine Mode of Activation by Simple Chiral Amines*

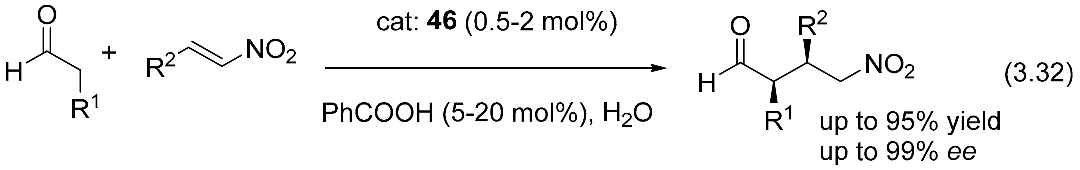
Enamine catalysis involves catalytically generated enamine intermediates resulting from deprotonation of iminium ions. The enamine intermediates are nucleophiles that react with various electrophiles to generate $\alpha$-substituted carbonyl compounds. The enols that add to the carbonyl moieties and other electrophiles in uncatalyzed reactions are exchanged for more nucleophilic, faster-reacting enamines. One speaks here of the “enamine” mode of activation [348,349]. As for other nucleophiles, their kinetic reactivity (irreversible reactions) depends very much on the energy (or ionization energy) and shape of their HOMO (Highest Occupied Molecular Orbital). Several valuable and broadly applicable transformations are asymmetric via enamine catalysis. They include cross-aldol [350,351], Michael reactions (conjugate 1,4-additions of nucleophiles to alkenes activated by an electron-withdrawing substituent), [352–354], Mannich condensations (three-component reactions combining a primary amine with an enolizable carbonyl compound and an aldehyde, or ketone, producing β-amino carbonyl compounds) [355,356]. Diels–Alder reactions ((2+4)-cycloadditions) [357–359], and α-carbon–carbon and α-carbon–heteroatom (C-O, N, S, F, Cl, Br, I) bond formation of aldehydes [360–364].

### 3.5.1. Asymmetric Michael Additions

In 1969, Yamada and Otani reported a first example of enantioselective Michael addition catalyzed by L-proline derivatives (e.g., **54**, reaction (3.31)) [365].

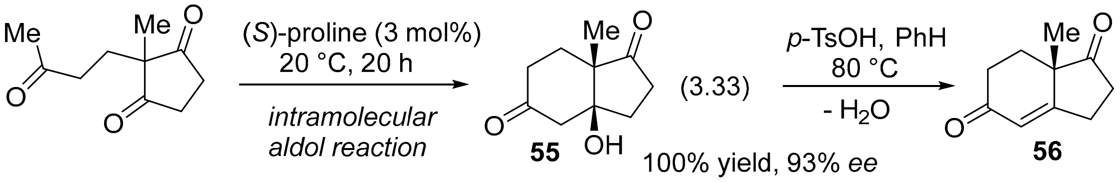


Various effective catalytic systems for asymmetric Michael additions were developed [366]. Reactions (3.32) are examples that apply a Hayashi-Jørgensen catalyst (diarylprolinol trimethyl silyl ether, e.g., **46**) [367,368].

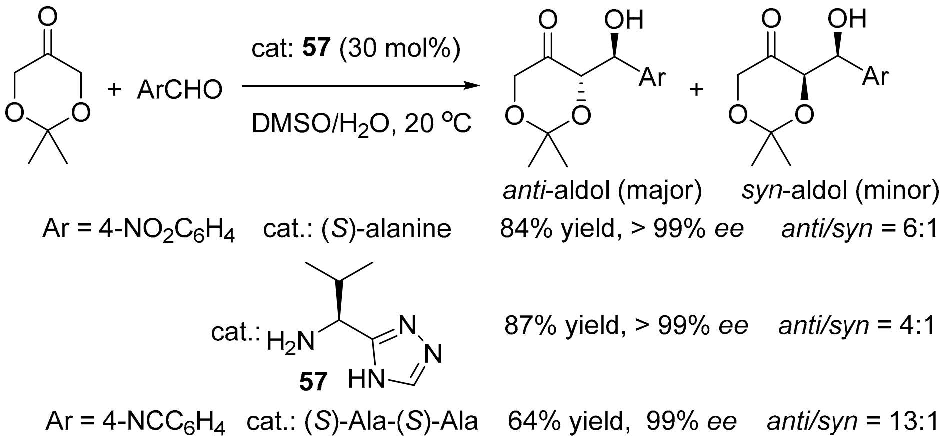


### 3.5.2. Asymmetric Aldol Reactions

In 1971, Hajos and Parrish at Hoffmann-La Roche,[369–371] on one side, and Eder, Sauer, and Wiechert at Schering [372], on the other side, found that a catalytic amount of readily available L-(-) proline (*S*-Pro) catalyzes asymmetric intramolecular aldol reactions (reaction (3.33)) producing bicyclic compound **55**. Crotonization (water elimination from **55**) provides enone **56.**



We had to wait nearly 30 years for the same catalyst to promote enantioselective intermolecular aldol reactions. The intramolecular aldol reactions have an entropy variation of *ca.* -20 eu (entropy units = calK$^{-1}$mol$^{-1}$), which is less negative than the entropy variation of intermolecular aldol reactions for which typically $\Delta S_r^T$ = -35 eu. Because of that, the intermolecular aldol reactions must be run at a temperature low enough to avoid reversibility ($\Delta G_r^T = \Delta H_r^T - T\Delta S_r^T$). At a given temperature $T$, concurrent epimerization may happen in competition with the aldol formation. Indeed, when $\Delta G_r^T$ approaches zero, or becomes positive, equilibration of both enantiomeric aldols occurs. The term $-T\Delta S_r^T$ is positive, and more so for the intermolecular than for the intramolecular reaction. Catalysts for the aldol reaction also catalyze the opposite reaction, the retro-aldol reaction. In order to be successful with the intermolecular amine-catalyzed cross-aldol reaction, conditions must be found that avoid concurrent elimination of water to generate the corresponding $\alpha$,β-unsaturated ketones, and homoaldol reactions. In 2000, List, Lerner, and Barbas reported the first examples of direct, asymmetric intermolecular aldol reactions of acetone with various aldehydes. For instance, acetone and 4-nitrobenzaldehyde were condensed into ($S$)-4-$NO_2$-$C_6H_4$-CH(OH)-$CH_2$-$CH_3$ in the presence of 30 mol% of L-proline, in DMSO and at 25 $^{o}$C (68% yield, 76% *ee*) [203]. The same year, Notz and List reported the catalyzed synthesis of *anti*-1,2-diols. In the presence of 30 mol% of L-proline (DMSO; 25 $^{o}$C) cyclohexanecarboxaldehyde and hydroxyacetone were condensed into *anti*-4-cyclohexyl-3,4-dihydroxybutan-2-one with high regioselectivity (> 20;1), diastereoselectivity (> 20:1) and *ee* > 98% [373]. Since this pioneering work, proline and its derivatives have become the most applied catalysts in asymmetric organo-catalysis [374–377]. In 2024, the group of García-Álvarez reported on the combination of an aerobic and chemoselective Cu-catalyzed oxidation of primary alcohols with a concomitant and compatible enantio- and diastereoselective cross aldol reaction catalyzed by a binary guanidium salt/($S$)-proline system. Under air/moisture and in the absence of any organic solvent, stereodivergent and direct conversion of primary alcohols into asymmetric aldols is possible through an economical one-pot/two-steps process [378]. Other chiral $\alpha$ amino acids, small peptides, chiral amines and diamines, amides, sulfonamides and their combinations, as well as chiral metal complexes and Lewis acids can also catalyze the direct enantioselective aldol reactions [379,380]. Examples reported in 2006 by Córdova and coworkers are presented with reactions (3.34) that applies various catalysts including **57** [381].



(3.34)

The recovery of the soluble organo-catalysts might be a problem. Immobilized organo-catalysts for the heterogeneous asymmetric direct aldol reaction have been proposed [382–384].

The Agami-Houk-List mechanism [385–387] is now widely accepted (Figure 3.17) [388,389]; it has been confirmed by recent high-level quantum calculations [390]. L-proline is a difunctional catalyst as it activates aldol condensations through its amine moiety that forms with aldehydes and ketones (the substrates) ene-amine intermediates that are better nucleophiles than the corresponding enols, and through its carboxylic group, which is a H-bond donor (see Chap. 9) that activates aldehydes (the reactants) by rendering them more electrophilic. Debate exists about which of the transition structures **58** (ketone-derived iminium ion formation), **59** (enamine formation, intervention of a second molecule of L-proline (Agami mechanism [391]), and **60** (enamine addition to the aldehyde, C-C bond formation) shown in Figure 3.17 is associated with the rate-determining step and whether other intermediates form or not [392,393]. This depends on the nature of substrates and reactants and on the reaction conditions (temperature, solvent, concentration). Despite intense interest in amine-catalyzed stereoselective reactions, catalyst loadings > 10 mol% are sometimes necessary as undesired aldol reactions can compete [394].

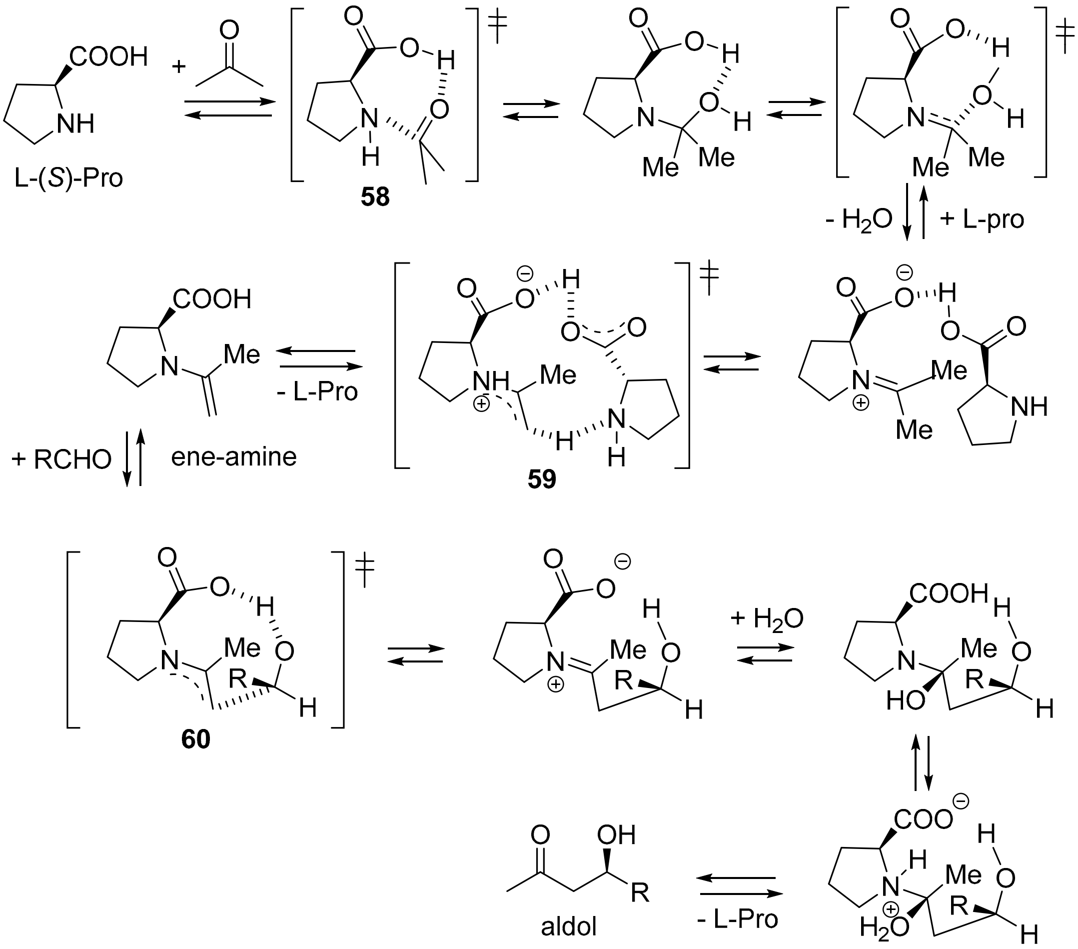
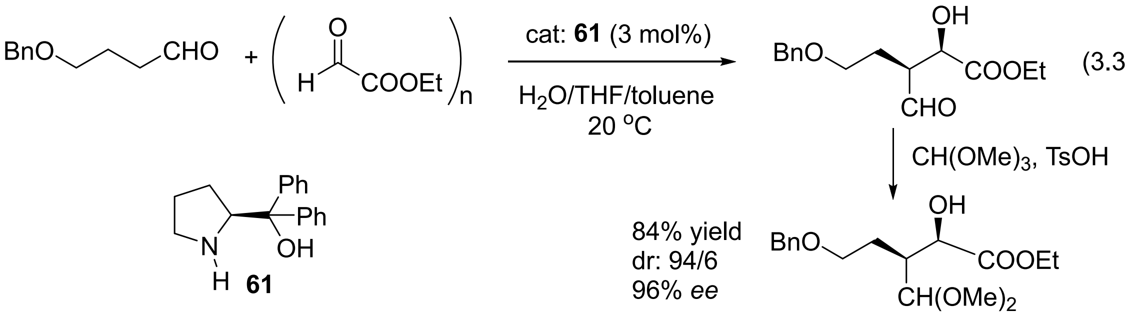


**Figure 3.17.** Simplified Agami-Houk-List mechanism of the proline-catalyzed intermolecular aldol reactions (enamine HOMO driven catalysis).

Reaction (3.35) is an asymmetric organocatalyzed direct cross-aldol reaction that produces a key building block of an HIV protease inhibitor. Its preparation is amenable to industrialization [395]. The catalyst is diphenylprolinol (**61**). Like L-Pro, **61** reacts with 5-benzyloxybutanal to generate an enamine intermediate. The hydroxy group of **61** offers an H-bond to the aldehyde moiety of ethyl glyoxylate. It brings it close to the enamine for a diastereoselective and face-selective addition [396].



(3.35)

### 3.5.3. Asymmetric Mannich Condensations

The direct catalytic asymmetric addition of unmodified carbonyl compounds to preformed or *in situ*-generated imines has emerged as a promising new route to optically enriched $\alpha$- and $\beta$-amino acid derivatives, $\beta$-lactams, and 1,2- and $\gamma$-amino alcohols [397,398]. In 2000, List reported the first example of direct organocatalytic asymmetric three-component Mannich reaction [399,400]. The Mannich reaction of aldehydes, pyruvic esters and 4-methoxyaniline (Figure 3.18) can be either *syn* (e.g., reactions (3.36)) or *anti* selective (e.g., reactions (3.37)) depending on the nature of the amino acid catalyst [208].

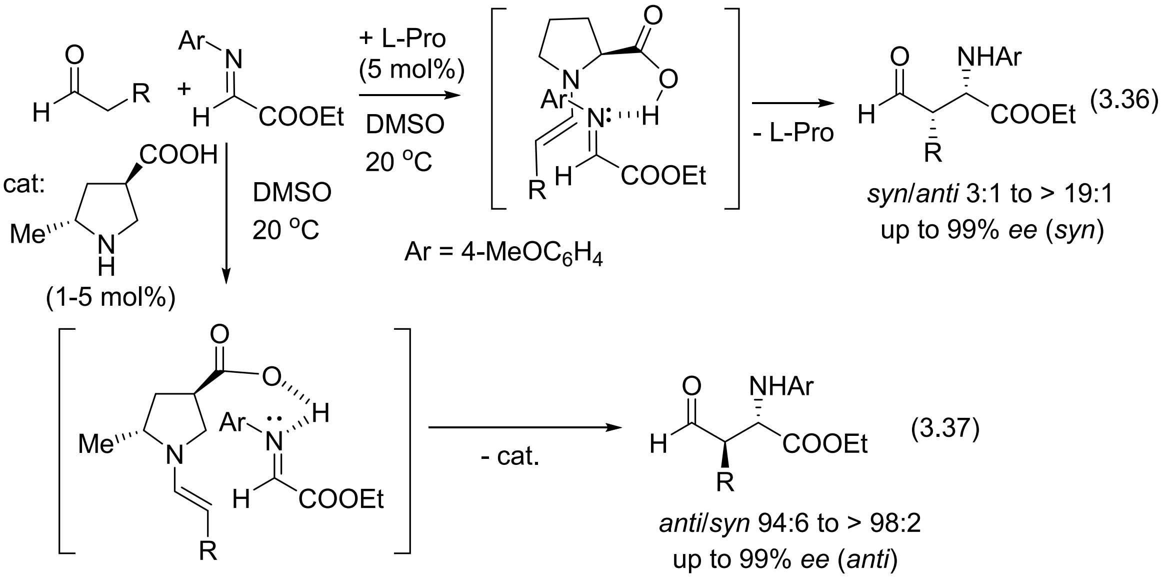
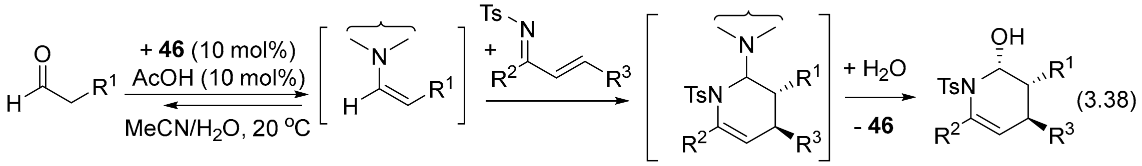


**Figure 3.18.** Examples of asymmetric Mannich condensations catalyzed by amino acids (List, 2000).

### 3.5.4. Asymmetric Diels-Alder Reactions with Inverse-Electron-Demand

Enamine intermediates formed *in situ* between an amine catalyst and enolizable aliphatic aldehydes can act as electron-rich dienophiles in inverse-electron-demand Diels–Alder reactions (reactivity dominated by their LUMO(diene)/HOMO(dienophile) interactions). Examples are reactions (3.38) that apply the Hayashi-Jørgensen catalyst **46** [358].



### 3.5.5. Asymmetric $\alpha$ Halogenations

Amino-catalysis has been successful for asymmetric $\alpha$-fluorination, $\alpha$-chlorination, $\alpha$-bromination, and $\alpha$-iodination of carbonyl compounds [360]. The $\alpha$-fluorination (Figure 3.19a) reported in 2005 by Enders and Hüttl is an early example [401]. On their side and the same year, the groups of Jørgensen [402], Barbas [403], and MacMillan [404] presented their enantioselective $\alpha$-fluorination of aldehydes (see also the asymmetric $\alpha$-fluorination of ketones, Section 3.1.6) [282]. In 2005, Jørgensen and coworkers reported their asymmetric $\alpha$ bromination of aldehydes and ketones (Figure 3.19b) [405]. Reaction conditions that limit the formation of products of $\alpha$-disubstitution were found.

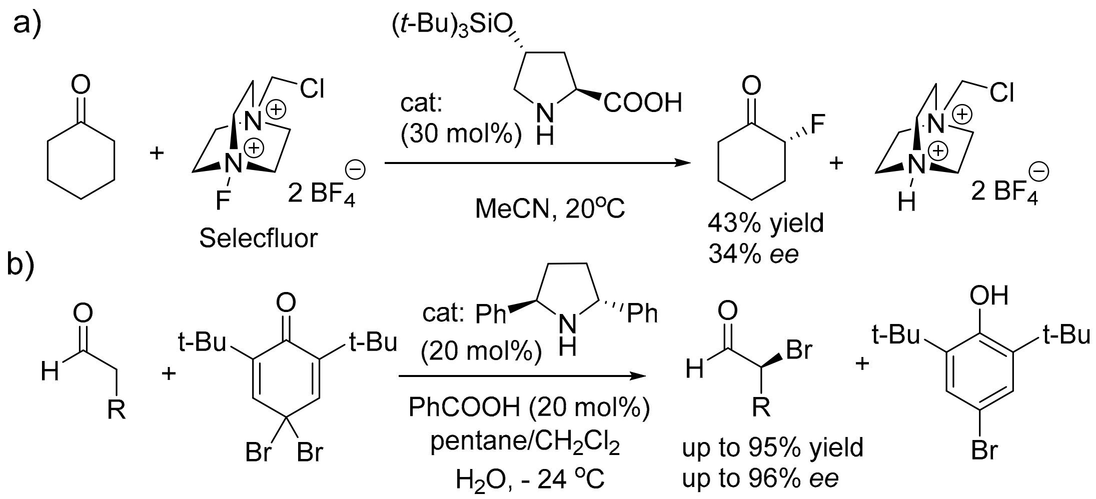


**Figure 3.19.** a) Asymmetric $\alpha$-fluorination of ketones (Enders, 2005); b) Enantioselective $\alpha$-bromination of aldehydes (Jørgensen, 2005).

### 3.5.6. Asymmetric $\alpha$-Benzylation of Aldehydes with Alcohols

An application of the combination of organocatalysis with a photo-redox catalysis is given with the $\alpha$-benzylation of aldehyde (3.39) developed by the group of MacMillan in 2018 (Figure 3.20). Alcohols are cheaper, but much less electrophilic than corresponding chlorides, bromides, iodides, and sulfonic esters. If converted into radical intermediates, the latter adds to activated alkenes such as Michael acceptors (Giese reaction) and electron-rich alkenes like enamines. Iridium(III) complex **62** absorbs a photon, forming the corresponding excited state. The latter takes an electron from the 4-(hydroxymethyl)pyridinium cation, generating an iridium(IV) species and a heterocyclohexadienyl radical that undergoes C-O cleavage of its benzylic alcohol moiety, simultaneously with the formation of water and of a benzylic radical. The latter adds to the imine intermediate resulting from the reaction of the organo-catalyst **41** (Figure 3.15) and the starting aldehyde. A relatively stable amino-substituted radical forms, which is then oxidized by the iridium(IV) complex, restoring the iridium(III) catalyst in its initial state [406]. In 2010, the same group showed that the same double catalytic cycle can be applied to the $\alpha$-benzylation of aldehydes with benzyl bromides [407].

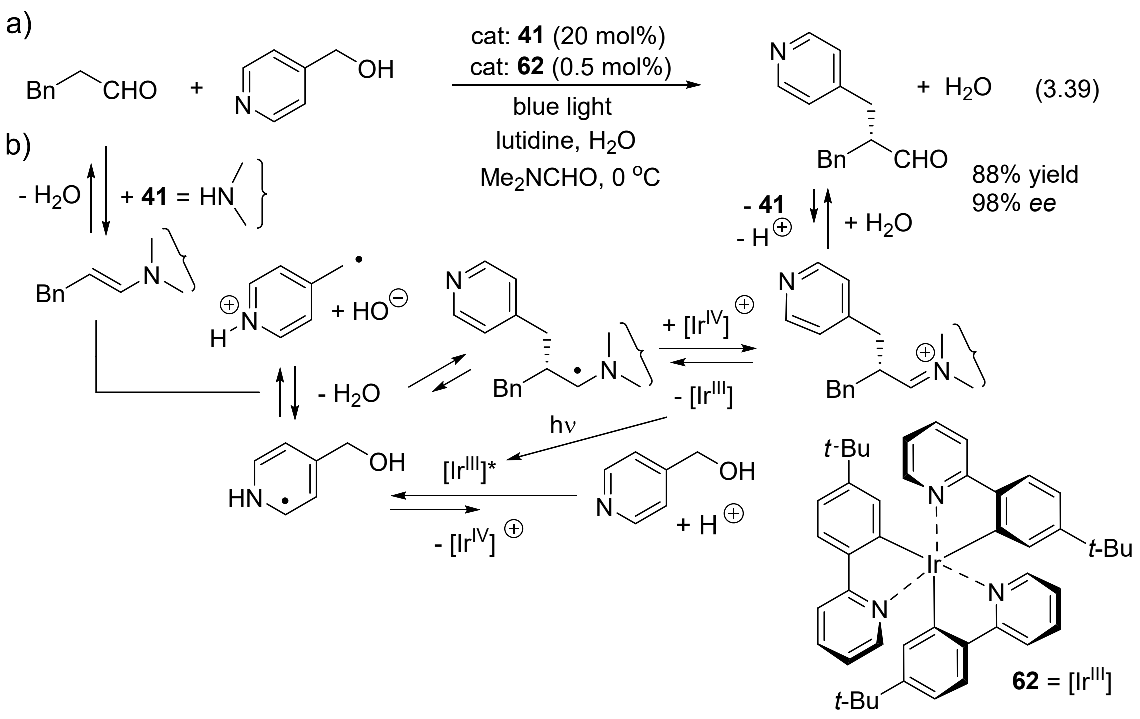


**Figure 3.20.** a) Example of asymmetric benzylation of aldehydes with 4-(hydroxymethyl)pyridine applying the combination of amino-catalysis and photo-redox catalysis (MacMillan, 2018); b) Possible mechanism.

### 3.6. Dienamine and Trienamine Mode of Activation

In 2006, Jørgensen and co-workers presented the concept of asymmetric dienamine catalysis in which a secondary amine converts conjugated enals into γ-substituted enals (e.g., reaction (3.40)) *via* 1-aminoalk-1,3-diene intermediates (Figure 3.21). With diethyl azodicarboxylate as the electrophile, a possible mechanism is the Diels-Alder reaction of the latter (dienophile) with the electron-rich diene resulting from the condensation of the enal with the secondary amine catalyst. Hydrolysis of the adduct liberates the final products [408].

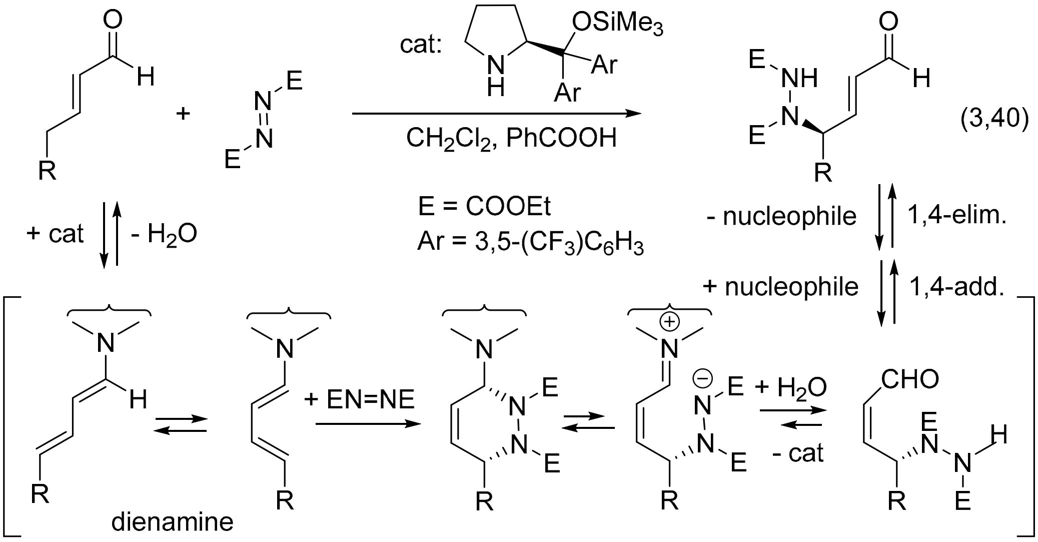


**Figure 3.21.** Example of dienamine mode of activation (Jørgensen, 2006).

In 2011, Jørgensen and co-workers reported that optically active secondary amines and dienenals generate reactive trienamine intermediates, which readily participate in Diels–Alder reactions with different classes of dienophiles (Figure 3.22). For example, the Diels–Alder reactions with 3-olefinic oxindoles (reactions (3.41)) produce spirocyclic oxindoles in high yields, and up to 98% *ee* [409]. A cinchona-based primary amine catalyst enables the extension of this activation mode to a highly selective asymmetric Diels–Alder reaction of dienones with electron-deficient dienophiles [410].

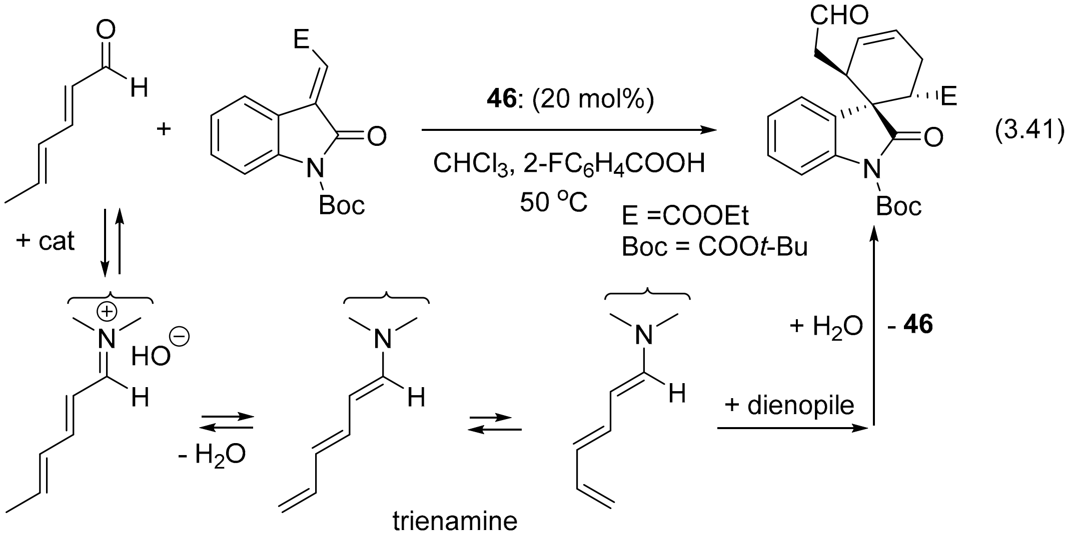
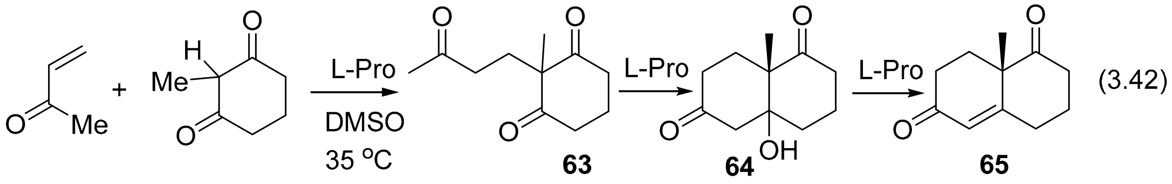


**Figure 3.22.** Trienamine mode of activation (Jørgensen, 2011).

In the presence of chiral amines, 2,4-dienones are activated toward the attack of a nucleophile at the δ position, a mode of activation called vinylogous iminium ion catalysis. Asymmetric and stereoselective 1,6-additions of alkanethiols to β-substituted cyclic dienones are catalyzed by a cinchona-based primary amine [411].

### *3.7. Asymmetric Amine-Catalyzed Domino Reactions*

Domino reactions [412] are two-reactant processes in which two or more successive reactions occur in the same pot. Typically **A** + **B** (starting materials) → **C** (first intermediate, which is not isolated) → **D** (second intermediate, which is not isolated) → **P** (final product). The successive reactions might be catalyzed, or not, by a single catalyst or might require more than one catalyst introduced at the beginning of the process or in sequence. Domino reactions (also called cascade reactions) that form multiple carbon–carbon bonds and stereocenters are powerful and economical routes to construct complex organic compounds; they require no purification of synthetic intermediates, no time and product consuming protection/deprotection steps, and less solvent to recover [413–416]. For reviews see: [417–420,425]. In 2000, Barbas and Bui reported an early example in which L-proline catalyzes the sequence of Michael addition of 2-methylcyclohexa-1,3-dione to methyl vinyl ketone, giving adduct **63**. Follows asymmetric intramolecular aldol reaction generating diketone **64**. Then water elimination provides *S*-(+)-**65** in 49% yield and 76% *ee* (reaction (3.42)) [421]. Racemic **65** is Wieland-Miescher ketone. This sequence of three reactions is the Robinson annulation.



A similar asymmetric intermolecular Michael addition, followed by an intramolecular aldol reaction producing tetrasubstituted cyclohexanones have been catalyzed by (*S*)-1-methyl-4-benzylimidazolidine-2-carboxylic acid [422]. In 2007, the group of Hayashi reported the one-pot enantioselective synthesis of polysubstituted cyclohexanecarbaldehydes (e.g., **68**, reaction sequence

(3.43)) with control of the configuration of four carbon stereocenters (Figure 3.23). The catalyst is the Hayashi-Jorgensen catalyst (**46**) that generates enamine intermediate **66** by condensation with pentanedial (enamine activation). Asymmetric Michael addition of **66** to (*E*)-2-nitrostyrene furnishes adduct **67**. The latter undergoes an intramolecular Henry reaction activated by the formation of an iminium ion intermediate (iminium ion activation). Next to **68**, three other diastereomers form as minor products [423].

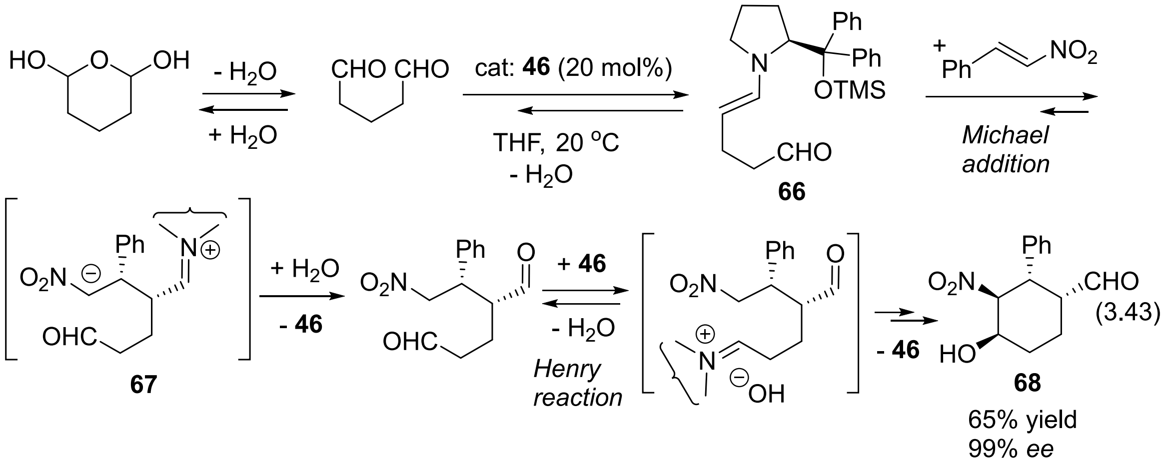
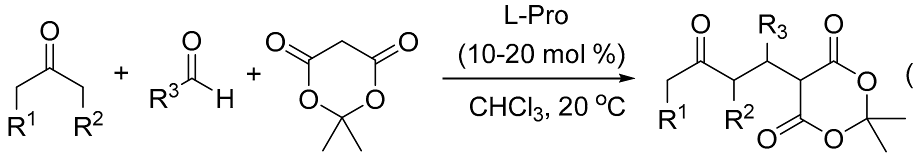


**Figure 3.23.** One-pot asymmetric tandem Michael/Henry reaction through enamine/iminium activation (Hayashi, 2007).

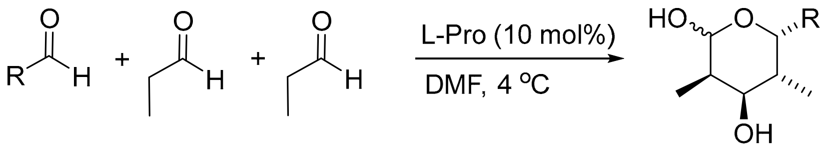
### 3.8. Asymmetric Amine Catalyzed Multicomponent Synthesis

Since the pioneer work of List and coworkers (see Section 3.5-3) [399], several groups have developed asymmetric three-component Mannich reactions [400,424]. The highly chemoselective reactions between two different unmodified aldehydes and one aromatic amine are efficient routes to β-amino aldehydes with diastereoselectivities *syn*/*anti* >19:1 and up to 99% *ee*. In several examples, the two new carbon centers form with absolute stereocontrol [355,425–429]. In 2001, List and Castello reported the asymmetric three-component reaction of ketones, aldehydes and Meldrum's acid (reaction (3.44)) [430].



(3.44)

Imitating enzyme-catalyzed aldol reactions of three aldehydes (see Section 2.5, Figure 2.5) Barbas and co-workers reported in 2002 the L-proline catalyzed asymmetric assembly of three acetaldehyde molecules to provide in a single step, (+)-(5*S*)-hydroxy-(2*E*)-hexenal with *ee* up to 90% [431]. They also reported the asymmetric catalyzed asymmetric synthesis of carbohydrates (hexoses) and polypropionates (reactions (3.45)) [432].



(3.45)

In 2007, Enders and coworkers reported the asymmetric construction of cyclohexene-carbaldehydes **69** with perfect control of the configuration of four carbon stereocenters. The process engages three components (an aldehyde, a conjugated enone, a nitroalkene) and catalyst **46** in the same pot (Figure 3.24). In a first step, enamine activation of the aldehyde permits its Michael addition to the nitroalkene. Then the nitroalkane so-obtained undergoes a Michael addition to the enone activated by formation of an iminium ion intermediate by condensation with catalyst **46**. A dialdehyde is formed which undergoes intramolecular crotonalization providing **70** with a diastereomeric ratio > 100:1 and 99% *ee*. Without purification crude **69** with substituent R = (*E*,*E*)-hept-3,5-dienyl unit undergoes a stereoselective intramolecular Diels-Alder reaction in the presence of $Me_2AlCl$ catalyst in $CH_2Cl_2$. This produces the tricyclic compound **70** that contains eight carbon stereocenters [433].

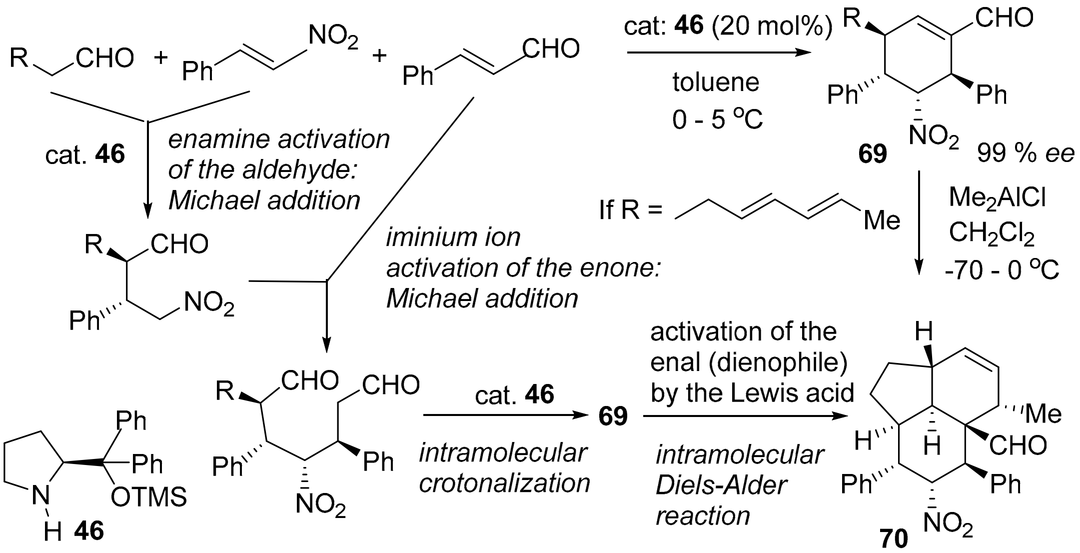


**Figure 3.24.** Asymmetric synthesis of tricyclic compound with eight stereocenters obtained in one-pot from three simple achiral starting materials (Enders, 2007).

### 3.9. Ene-Aminium Radical-Cation Mode of Activation

MacMillan and coworkers have developed the concept of singly occupied molecular orbital (SOMO) catalysis. An electron-rich intermediate such as an ene-amine (nucleophile, the reactivity of which is dominated by their HOMO (highest occupied molecular orbitals) can be oxidized into the corresponding ene-aminium radical cation (electrophilic radical, the reactivity of which is dominated by its SOMO). The latter can react with electron-rich compounds such as enol silyl ethers. By comparison, the LUMO (lowest unoccupied molecular orbitals) controls the reactivity of iminium cation intermediates electrophiles [434]. Using catalysts **44B** and two equivalents of CAN (cerium ammonium hexanitrate) as oxidant they realized the first asymmetric aldehyde $\alpha$-enolation (reaction (3.46), Figure 3.25a). The process combines simple aldehydes and enoxysilanes into enantioenriched $\gamma$-ketoaldehydes. Figure 3.25b shows a simplified, possible mechanism of the process. SOMO activation can also realize enantioselective allylations and arylations of aldehydes and ketones [337,435,436].

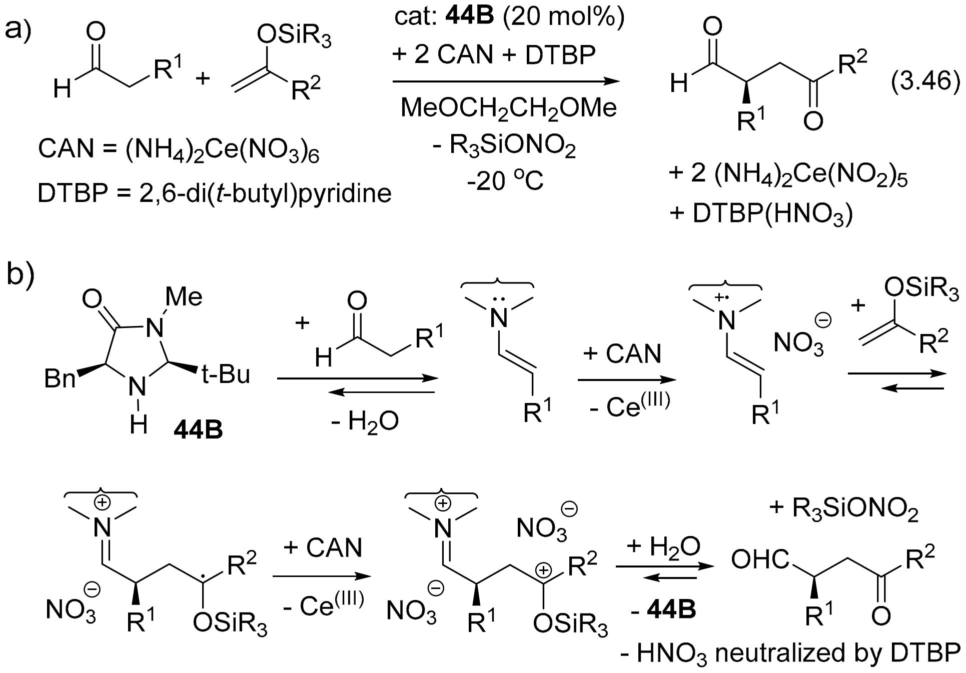


**Figure 3.25.** a) Asymmetric $\alpha$-enolation of aldehydes (ene-aminium radical cation SOMO driven catalysis, MacMillan, 2007); b) Possible simplified mechanism.

### 3.10. Asymmetric Morita-Baylis-Hillman Reactions Catalyzed by Amines

The Morita-Baylis-Hillman (MBH) reaction is an atom-economical coupling reaction of activated alkenes and aldehydes in the presence of a nucleophilic catalyst (Figure 3.26a). It corresponds to the hydrocarbation of the aldehyde with the $\alpha$-C-H bond of the activated alkene. The reaction involves, formally, a sequence of Michael addition of the nucleophilic catalyst, aldol reaction, and a β-elimination with recovery of the catalyst. The reaction was first reported by Morita and coworkers in 1968 [437], and in 1972, by Baylis and Hillman [438]. Phosphines were applied first as nucleophilic activators (Section 5.1). Activated alkenes include acrylic esters, acrylonitriles, vinyl ketones, phenyl vinyl sulfones, phenyl vinyl sulfonates, vinyl phosphates, and acrolein. β-Substituted alkenes require more forcing conditions due to the slow addition of the nucleophilic catalyst. A variety of electrophiles can be used, such as aldehydes, $\alpha$-ketoesters, 1,2-diketones, aldimines, methyl $\alpha$-bromoesters, and arenes [439]. Much effort has been devoted to the development of catalytic enantioselective MBH reactions. The catalyst can be a chiral tertiary phosphine (Section 5.1), a chiral Lewis acid, a chiral Brønsted acid, or a chiral amine [440–442]. In an early example, N-methylprolinol was applied as a catalyst [443]. More recently, MBH reaction (3.47) was catalyzed by L-proline-derived carboxamide **71** (Figure 3.26b) [444].

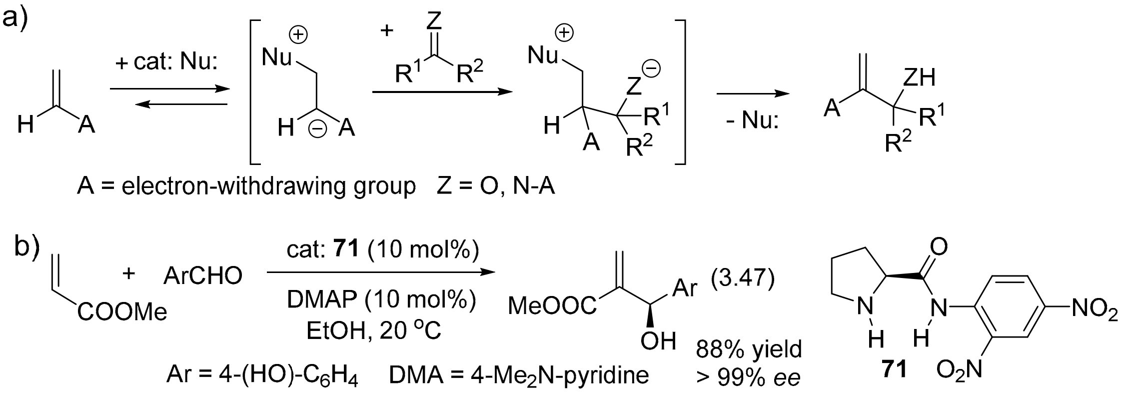


**Figure 3.26.** a) General scheme for MBH and aza-MBH reaction catalyzed by nucleophile; b) Example of asymmetric MBH reaction catalyzed by a L-proline carboxamide (Bhuzare, 2020).

## *3.11. Chiral Lewis Bases That Are Not Amines as Organo-Catalysts*

Free guanidines have found widespread use as strong base catalysts in asymmetric synthesis (Section 3.11.1). Guanidinium and 1,2,3-triazolium salts are employed as weak Brønsted acids, hydrogen-bond donor catalysts, or chiral counterions (PTCs, ion pairing catalysis, Section 3.2-3). Lewis bases, such as chiral phosphines, play a central role in asymmetric catalysis as ligands for transition metal catalysts (topic not treated here). They are also organic catalysts (P-nucleophiles) as outlined in Sections 5.1-2). Catalysts that contain one or several phosphine oxide moieties ($R_3P{=}O$, Section 5.6) or one or several phosphoramide moieties ($R_3NP{=}O$, Section 5.4) are O-nucleophiles that will be presented later. Chiral catalysts containing thioether ($R_2S$, Sections 6.1-2) or thiol (RSH, Sections 6.3-4) functions are S-nucleophiles that will also be presented later together with examples of asymmetric reactions catalyzed by chiral sulfoxides ($R_2S{=}O$, Section 6.6), aminothiocarbonates (Section 8.7), sulfinamides ($R'(R_2N)S{=}O$, Section 6.8) and thiophosphoramides (Section 6.7). Lewis bases that contain selenium, such as diselenides (Section 7.1), selenophosphoramides (Section 7.2), and selenides (Section 7.3), will be presented later. Here we sketch a few examples of reactions catalyzed by chiral Lewis bases such as guadinines, isothioureas, or carbamates.

### 3.11.1. Chiral Guadinines

Since the first report of chiral guanidine-catalyzed Henry (nitroaldol) reaction by the group of Nájera in 1994 [445], various asymmetric reactions applying this type of organo-catalysts have been proposed [324,446–448]. In particular, the Strecker-type reaction developed by Corey represented a significant conceptual advancement in the design of guanidine-catalyzed reactions. Reaction (3.48) utilized a chiral bicyclic guanidine **72** in which two N-H groups interact with cyanide as a nucleophile and with imine as an electrophile to construct the asymmetric environment, as shown for intermediate **73** [449]. Subsequently, Tan and coworkers developed a number of useful and practical reactions catalyzed by chiral bicyclic-type guanidines [450].

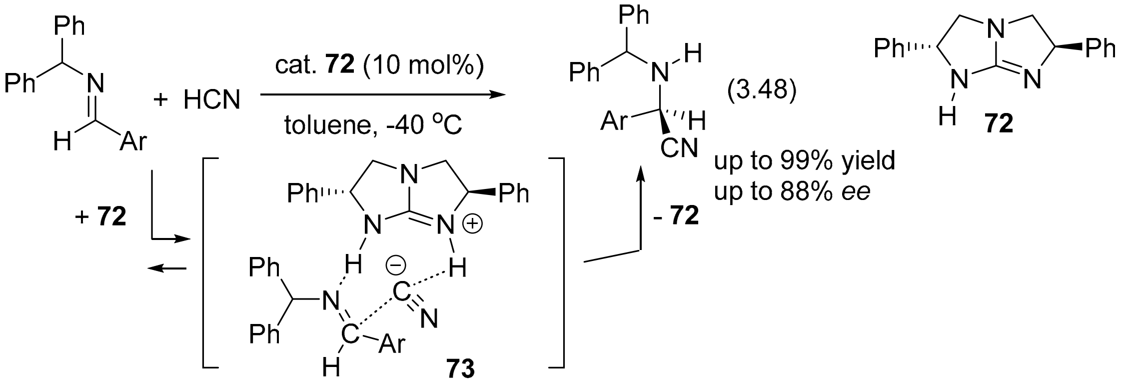


**Figure 3.27.** Example of enantioselective Strecker-type reaction (Corey, 1999).

### 3.11.2. Benzotetramisoles

In 2006, Birman and Li found that the pharmaceutical Tetramisole (**74**, 10 mol%) and its benzo analogue (**75**, 4 mol%) catalyze the enantioselective acylation of secondary alcohols (reaction (3.49)). The imine moiety of the isothiourea backbone serves as the active site, and the chiral center adjacent to this nitrogen atom provides the stereo-control (see **76**) [451].

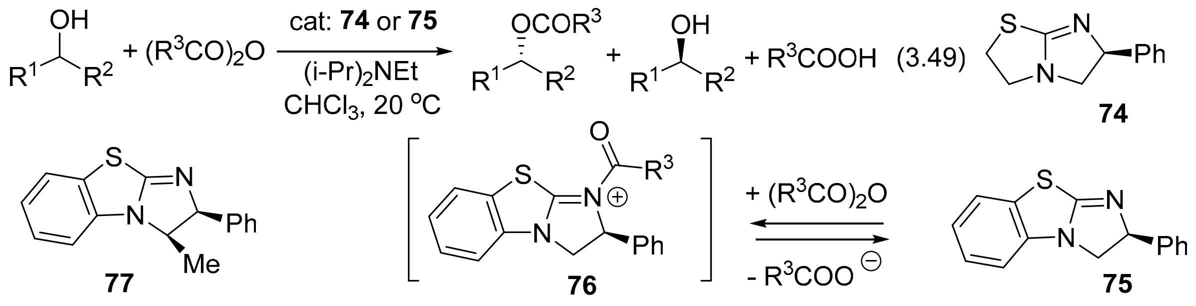
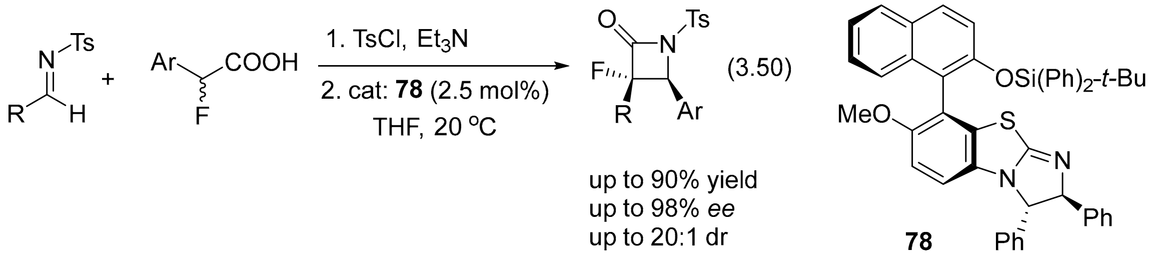


**Figure 3.28.** Isothiourea-catalyzed enantioselective acylation of secondary alcohols (Birman, 2006).

With **77** as a catalyst, Birman and Straub realized the enantioselective (2+2)-cycloaddition of fluoroketene (engendered by elimination of TsOH from the mixed anhydride resulting from the mixing of fluoroacetic acid and *p*-toluenesulfonyl chloride (TsCl)) to imines. The β-lactams so-obtained were alcoholyzed into corresponding *α*-fluoro-β-amino acid derivatives in good yield and high diastereo- and enantioselectivity [452]. In 2024, Zi and coworkers developed a new class of benzotetramisole Lewis base catalysts (e.g., **78**) that have both central and axial chirality. They proved to be better than simpler benzotetramisoles to catalyze (2+2)-cycloadditions of ketenes to imines (reactions (3.50)) [453].



### 3.11.3. Acylammonium Mode of Activation

Several asymmetric catalyzed Diels Alder reactions ((4+2)-cycloadditions) are known and permit the construction of very important polysubstituted carbocyclic and heterocyclic compounds. A first example is MacMillan’s iminium salt-activated dienophiles (Figure 3.15, Section 3.4). Here one describes the work of Romo and coworkers disclosed in 2014 (Figure 3.29). They activated *α*,β-unsaturated acyl chloride dienophiles as acylium ammonium salts. Reaction (3.51) illustrates the concept. Low *ee*’s were observed applying cinchona alkaloid-derived tertiary amines as catalysts. With an isothiourea catalyst such as (-)-benzotetramisole (**75**) good yield and high *ee*’s were obtained [454].

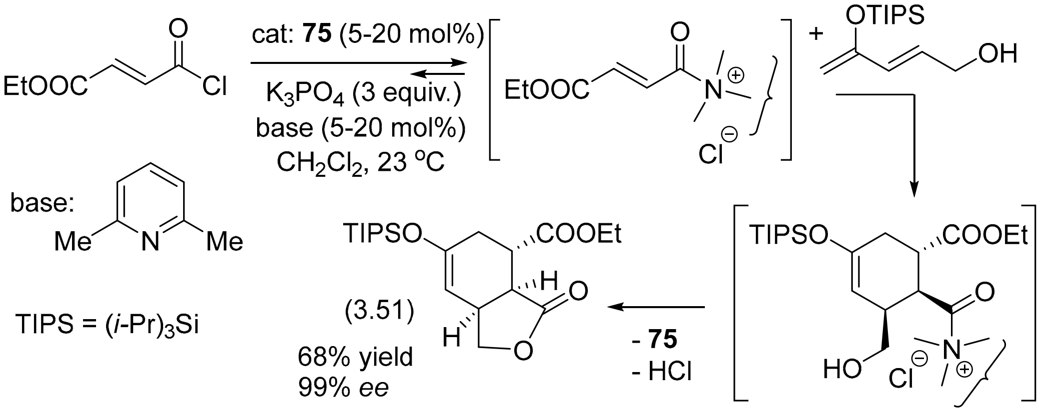


**Figure 3.29.** Acylammonium salt mode of activation of asymmetric catalyzed Diels-Alder reaction (Romo, 2014).

### 3.11.4. Carbamates

In 2015, the Yeung group reported that the enantioselective reaction (3.52) can be catalyzed by a carbamate [455]. Bromolactamization, using a chiral carbamate as a catalyst, resulted in the formation of lactams with up to two stereogenic centers. EtOH additive enhances the reaction rate and enantioselectivity. Reaction (3.52), catalyzed by **79** (Figure 3.30a,b), is a typical example. A switch to the pseudoenantiomeric form of the catalyst led to the formation of the lactam enantiomer. Thiocarbamates catalyze bromo-amino-cyclization of *O*-cinnamyl tosylcarbamates [456].

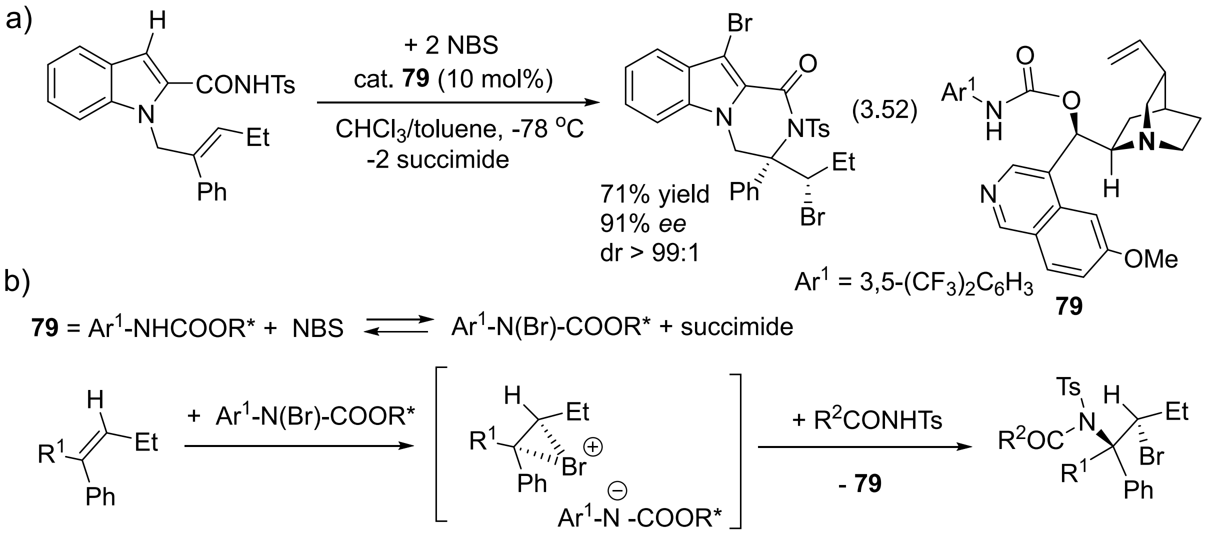


**Figure 3.30.** a) Example of carbamate catalyzed asymmetric bromolactamization (Yeung, 2015); b) Proposed mechanism of reaction; formation of a chiral tight bromonium ion-pair reacting regioselectively with the nucleophile.

## 4. Asymmetric Organo-Catalysis with Peptides

The high rate enhancements and substrate selectivity exhibited by enzymes have stimulated chemists to generate simpler molecules than enzymes with similar chemical properties. With the discovery that natural amino acids like L-proline and analogs can be powerful asymmetric catalysts, a summit was conquered. Often, these catalysts are required in relatively large amounts, and their recovery may be low-yielded as they can form all kinds of secondary products. Peptides combine through peptidic bonds [-C(=O)-N(-H)-] two or more amino acids. They provide a huge diversity in structures and functionality, including arrays of H-bond donors (Chap. 9) and acceptors. With 20 proteogenic amino acids, one can prepare $20^2 = 400$ dipeptides, $20^3 = 8000$ tripeptides, $20^4$, = 160’000 tetrapeptides, etc. The diversity is augmented by the exchange of natural amino acids by non-natural analogs. Moreover, their side chains can be modified chemically to improve their catalytic properties. Combinatorial chemistry has played a key role in establishing effective asymmetric peptidic catalysts [457–459]. They are asymmetric catalysts for enantioselective protonation of enolates (see Sections 2.2; 3.1.2), acylation reactions (Section 2.2), oxidations (Section 2.4), reductions, hydrolytic reactions (Section 2.2), and C–C bond forming reactions such as hydrocyanation (Sections 2.1; 3.1), Michael additions (Sections 3.1.3; 3.5; 3.6), aldol reactions (Sections 2.5; 3.6), the Morita-Baylis-Hillman reactions (Section 3.11), and acyl anion equivalent chemistry (Chap. 8). Many peptides and analogues catalyze the same reactions as simpler chiral amines. Peptides with a functional side chain (e. g.: free $NH_2$ group of lysine, imidazole group of histidine, indole group of tryptophan, guanidinium group of arginine, $CONH_2$ group of asparagine and glutamine, OH group of serine, threonine. and tyrosine, COOH group of aspartic and glutamic acids, SH group of cysteine) can activate substrates and reagents by forming more reactive intermediates. Peptides possess secondary functions and arrays of H-bond donors and acceptors, which provide more specific steric and electrostatic interactions with the substrates and reagents than simpler amines and analogs. Thus, they can lead to higher enantioselectivities using smaller amounts of catalyst and applying milder reaction conditions [460–464]. Simple proteogenic amino acids and peptides are less toxic than catalysts containing transition metals. Since the synthesis of peptide catalysts is costly (production of waste, use of toxic solvents), their recovery and reuse are considered. One method is to immobilize them by cross-linking with hydrophobic polystyrene, hydrophilic TentaGel, polyethylene glycol-polyacrylamide, mesoporous silica, chitosan, or by mixing them with hydroxyapatite or ceria nanocrystals. The recovery of the catalyst requires a simple filtration or centrifugation. Alternatively, the catalysts are grafted onto magnetic nanoparticles. Their recovery applies magnetic separation. Another option is to equip the catalysts with a perfluorinated tag; their recovery relies upon fluorous extraction [465,466].

With the enantioselective conjugate addition of thiols to enones, Inoue and coworkers reported the first example of asymmetric poly-amino acid-catalyzed reaction in 1975. [467–469]. Polyaminoacids have played an important role in the early days of organocatalysis. They probably have been catalysts of prebiotic enantioselective reactions [470–474].

Self-assembly of molecules often results in new properties. Even very short peptides can self-assemble into structures with a variety of physical and structural characteristics. Remarkably, many peptide assemblies show high catalytic activity in model reactions, reaching efficiencies comparable to those obtained with natural enzymes by weight [475]. Foldamers are oligomers with a strong tendency to adopt a specific conformation. They approach principles of enzyme functions. For instance, helical structures provide foldamer families that offer a basis for asymmetric catalysis [476,477]. Despite the great advantages of peptidomimetic scaffolds as potential catalysts, only a few examples of their industrial application have been described [478].

### *4.1. Asymmetric Hydrocyanations*

In 1979, Inoue and coworkers found that diketopiperazine **80** (cyclo(L-phenylalanine-L-histidine) catalyzed the asymmetric addition of HCN to arenecarbaldehydes. For instance, with benzaldehyde (reaction (2.1)), the corresponding cyanohydrin was obtained in 97% *ee* for 87% conversion [479–481].

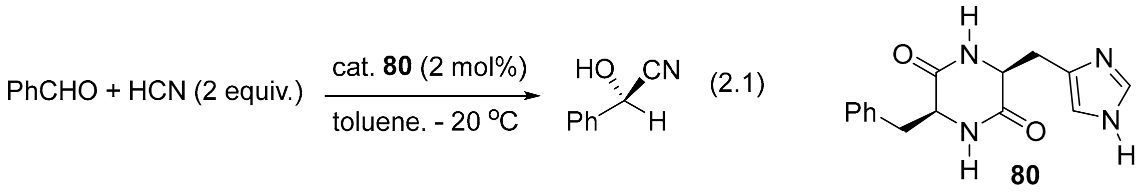


**Figure 4.1.** Inoue's (1979) asymmetric hydrocyanation.

In 1996, Shvo and coworkers found a second-order kinetic dependence on **80** for reaction (2.1), consistent with a mechanism in which two molecules of the catalyst intervene in the transition state, and for which both HCN and the aldehyde are activated by the histidine moiety of **80**. Furthermore, better enantioselectivities are observed when the catalyst forms polymers through hydrogen bonding. This also depends on the solvent, concentration, temperature, and mode of preparation of **80** [482]. In 1996, Lipton and coworkers reported a catalytic enantioselective version of the Strecker amino acid synthesis (reactions (4.1)). Cyclic dipeptide cyclo[(*S*)-His-(*S*)-NorArg] (2 mol%) in methanol catalyzed the addition of hydrogen cyanide to N-alkylimines to afford $\alpha$-amino nitriles in high yield and high *ee*. Acid hydrolysis of N-benzhydryl-$\alpha$-amino nitriles afforded the corresponding $\alpha$-amino acids [483]. In 1998, Jacobsen and coworkers found that **81** is an excellent catalyst for the asymmetric Strecker reaction (4.1) of aromatic and aliphatic aldimines [484–486]. Applying the readily available catalyst **82** (0.5 mol%), Jacobsen described in 2009 scalable asymmetric Strecker reactions that used KCN in AcOH/$H_2O$/toluene (at 0 °C) instead of dangerous HCN for the addition to aliphatic benzyl aldimines. For R = *t*-Bu, 1-methylcyclohexyl, and 3-methylpent-3-yl, yields of the final N-Boc protected amino acids varied between 48-65% with 98-99% *ee* [487].

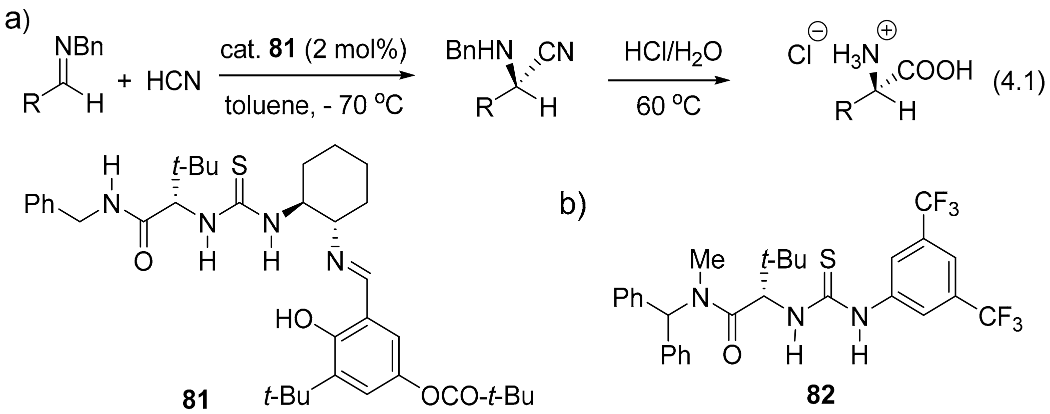


**Figure 4.2.** Examples of asymmetric Strecker reaction catalyzed by short peptide analogues. a) With catalyst **81** (Jacobsen, 1998); b) With catalyst **82** (Jacobsen, 2000).

Other chiral organocatalysts, such as bicyclic guanidine, ureas and thioureas, carbohydrates, *N*-oxides, bisformamides, ammonium salts, Brønsted acids, amino acids, alkaloids, and phase-transfer catalysts and oxazolines (section 11.5) have been applied to the Strecker reaction [488].

### 4.2. *Asymmetric Oxidations*

Asymmetric alkene epoxidation is an extremely powerful entry to highly valuable polyfunctional compounds [297]. In 1980, the Spanish Juliá group reported the enantioselective epoxidation of chalcones using poly-L-alanine as catalyst [489]. In 1983, poly-L-isoleucine (**83**) was found to be a better catalyst as shown with the now called Juliá-Colonna epoxidation of electron-deficient alkenes [490]. It is a triphasic system for which alternative diphasic and monophasic systems have been proposed [491–493]. The latter nucleophilic epoxidation is complementary to other asymmetric organocatalyzed epoxidations [296] and to electrophilic epoxidations, such as the Katzuki-Sharpless [494–496] and Jacobsen-Katzuki epoxidation [497–499].

The stereo-induction of the Juliá–Colonna epoxidation (4.2) depends on the a-helical secondary structure of the poly-leucine catalyst [500]. A 10-mer leucine polypeptide is of sufficient length to provide significant enantioselectivity (Figure 4.3) [501].

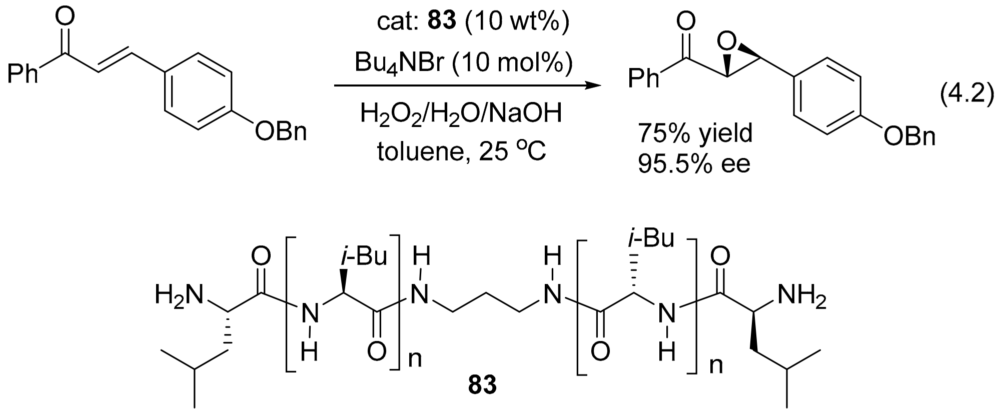
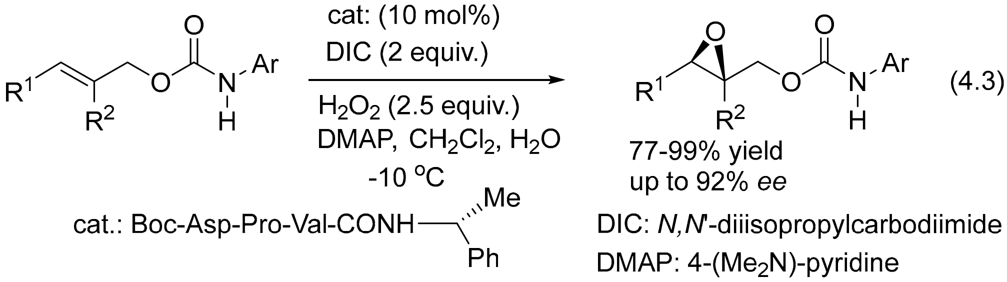


**Figure 4.3.** Example of Juliá-Colonna (1983) asymmetric epoxidation.

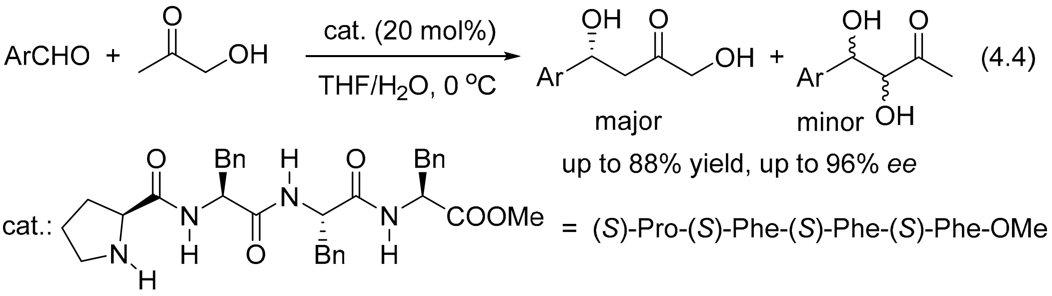
In 1990, Itsuno and coworkers reported the enantioselective epoxidation of chalcones using poly-l-alanine and poly-l-leucine immobilized on cross-linked aminomethyl polystyrene (CLAMPS) resin. Without substantial loss of catalytic activity, the polymer-supported catalyst was recovered and reused several times [502]. Miller and coworkers generated peracids ($RCO_3H$) *in situ* from the carboxylic group of Asp-COOH side moiety of short peptides. They epoxidize allylic carbamates that are not Michael acceptors, as shown with reactions (4.3) [461,503]. Similar Asp-containing peptides permitted enantioselective catalyzed Bayer-Villiger oxidations [504,505].



(4.3)

### 4.3. Asymmetric Intermolecular Aldol Reactions

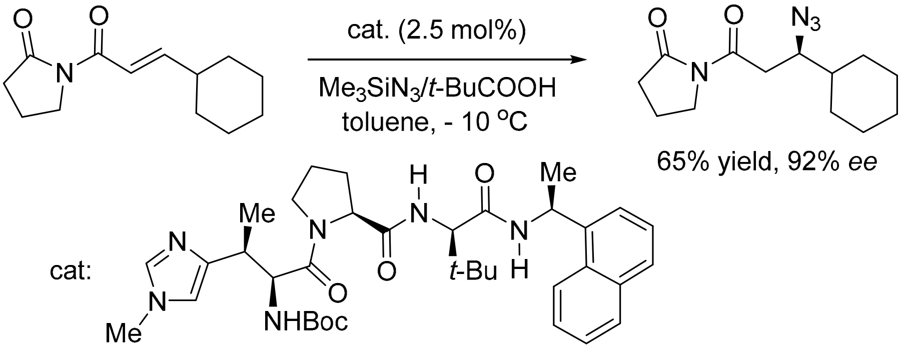
In 2003, the groups of Reymond [506], Gong [507], and List reported that L-proline amides and dipeptides catalyze asymmetric direct aldol reactions. With L-proline or aldolases applied as catalysts, the direct aldol reactions of hydroxyacetone with aldehydes provided mostly 1,2-diols. In contrast, isomeric 1,4-diols are the major products when using L-proline derived tetra- (reactions (4.4)) or pentapeptides as catalysts [509]. Peptide dendrimers also catalyze direct asymmetric aldol reactions [510].



(4.4)

### 4.4. Peptide-Catalyzed Conjugate Additions

In 2000, Miller and coworkers have reported the enantioselective conjugate addition of azide to unsaturated carbonyl compounds. An example is reaction (4.5). The azidocarboxamides so-obtained are converted into β-amino acids and triazoles with conservation of enantiomeric purity [511].



(4.5)

doi:10.20944/preprints202510.1111.v1

Examples of dipeptide-catalyzed Michael additions reported in 2006 (Figure 4.4) are reactions (4.6) [512] and (4.7) [513]. Tripeptides such as H-D-Pro-Pro-Asp-NH2 are efficient catalysts for conjugate addition reactions between aldehydes and nitroolefins (reaction (4.8)) [514].

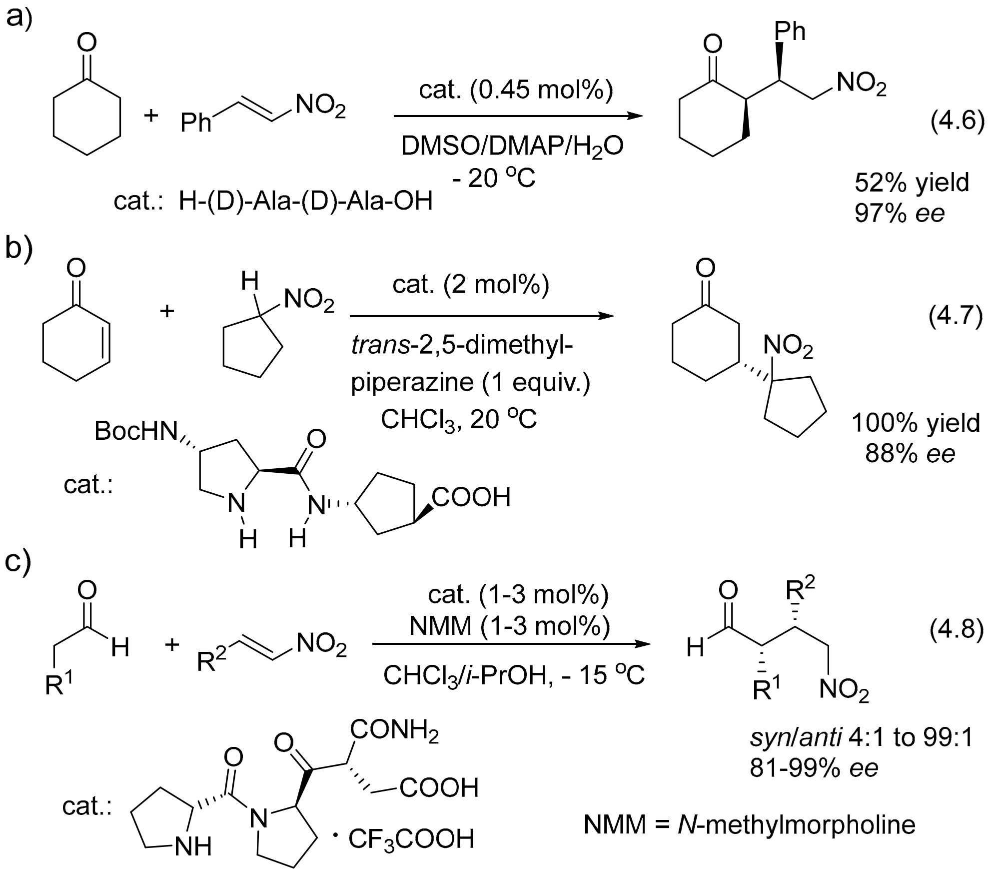
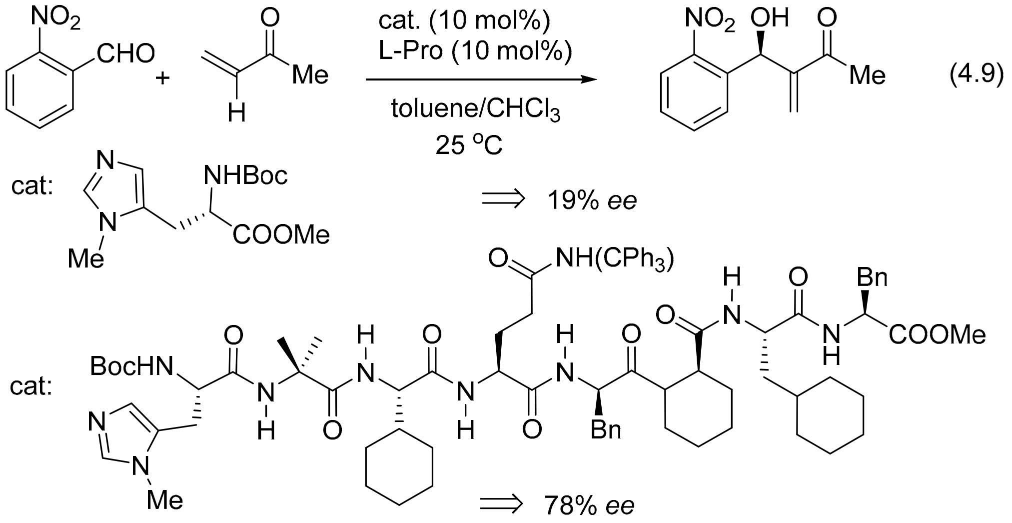


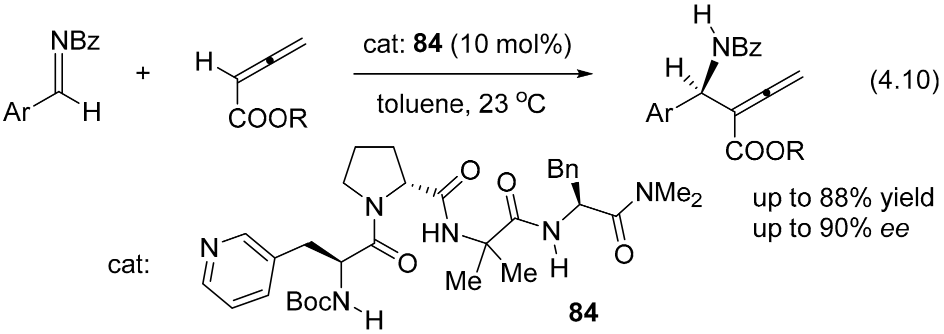
**Figure 4.4.** Examples of asymmetric conjugate 1,4-additions catalyzed by short peptides. a) Córdoba, 2006; b) Tsogoeva, 2006; c) Wennemers, 2007.

### *4.5. Peptide-Catalyzed Morita-Baylis-Hillman Reaction*

In 2003, Miller and coworkers reported the catalyzed asymmetric Morita-Baylis reaction of 2-nitrobenzaldehyde and methyl vinyl ketone (reaction (4.9)). As found earlier by other authors, better yields and enantioselectivities were observed when the peptide catalyst was used with L-proline as co-catalyst. The larger the peptide, the better is the enantioselectivity [515].



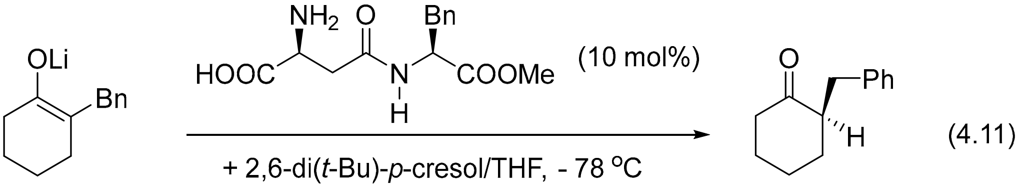
In 2009, Miller also reported enantioselective aza-MBH reactions of N-acyl imines with allenic esters. Reactions (4.10) were catalyzed by peptide **84** containing a Lewis basic pyridylalanine residue [516,517].



**84**

### 4.6. Catalytic Enantioselective Enolate Protonation by Peptides

Nearly three decades after Inoue's work (Section 4.1) on peptide-catalyzed enantioselective protonation, Yanagisawa and coworkers reported in 2006 a complementary strategy for asymmetric peptide-catalyzed protonation of lithium enolates derived from tetralone derivatives. In the presence of stoichiometric amount of achiral acid (2,6-di-*t*-butyl cresol, BHT) and a catalytic amount of dipeptide *N*-β-L-aspartyl-L-phenylalanine methyl ester lithium enolates were protonated furnishing the corresponding ketones with *ee* up to 88%. Under the same conditions, the lithium enolate of 2-benzylcyclohexanone produced the (*R*)-enantiomer in 65% yield and 69% *ee* (reaction (4.11)) [518].



## 5. Phosphorous-Based Catalysis

Phosphines ($R_3P$), phosphine oxides ($R_3P{=}O$), phosphoramides ($(RN)_3P{=}O$) and phosphonium salts ($R_4P^{(+)}X^{(-)}$) are effective organo-catalysts because of their thermal stability, recyclability, and unique catalytic properties [519,520]. Chiral Brønsted acids like diolphosphates and phosphoramides are discussed in Chapter 9.

### *5.1. Nucleophilic Activation by Chiral Phosphines*

Nucleophilic phosphine catalysis implies nucleophilic addition of a phosphine to an electrophilic alkene, allene or alkyne producing a reactive zwitterionic intermediate, generally under mild conditions [519]. Triethylphosphine ($Et_3P$) is less basic, but more nucleophilic than triethylamine ($Et_3N$). In water, pKa($Et_3PH^{(+)}$) = 8.7, pKa($Et_3NH^{(+)}$) = 10.7; quaternization of $Et_3P$ with MeI is 100 times as fast as $Et_3N + MeI \rightarrow Et_3(Me)N^{(+)}I^{(-)}$. Trialkylphosphines burn in the air; they are pyrophoric. Trialkylamines are not. On exchanging their alkyl substituents by aryls the oxidability of phosphines is lower. However, this renders the phosphines much less nucleophilic. For instance, $Et_3P$ reacts with MeI $10^6$ times as fast as $Ph_3P$ [521]. One simple solution to that problem is to use the corresponding phosphonium salts that are air stable together with an appropriate base, for instance: a 1:1 mixture of $(n\text{-}Bu)_3PH^{(+)}/BF_4^{(-)}$ and $(i\text{-}Pr)_2NEt$ [522].

In 1962, Takashina and Price obtained a hexamer of acrylonitrile on treating acrylonitrile with triphenylphosphine (Figure 5.1a) [523]. In 1963, Rauhut and Currier disclosed the trialkylphosphine-catalyzed dimerization of acrylic esters (Figure 5.1b) [524]. The reactions imply the phosphine additions to the activated alkenes, generating zwitterion intermediates that then add (Michael reactions) to another molecule of the alkene. In 1968, Morita reported that the above zwitterion intermediates engendered by the addition of tri(cyclohexyl)phosphine to acrylic esters can be quenched by aldehydes. This was the first example of the now called Morita-Baylis-Hillman or MBH reaction presented in Section 3.10 (see Figure 3.26a for a mechanism) [437].

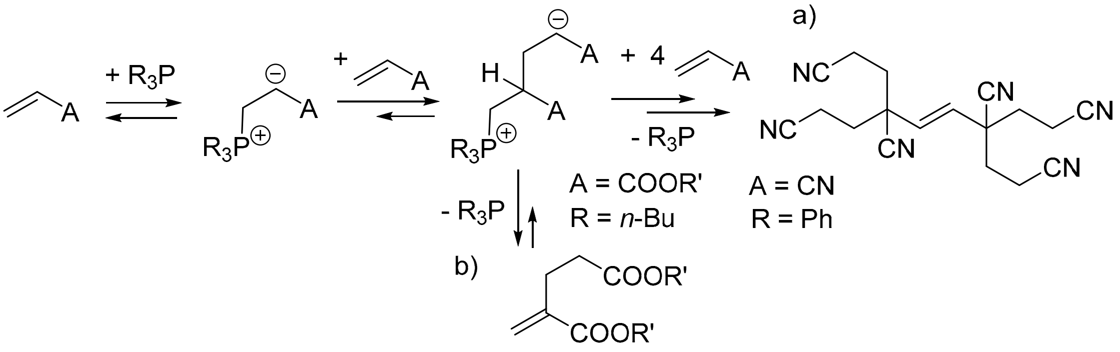


**Figure 5.1.** Phosphine-induced oligomerizations of electro-poor alkenes: a) formation of a hexamer (Price, 1962); b) Formation of a dimer (Rauhut-Currier, 1963).

Chiral phosphines are the most important ligands in asymmetric metal catalysis. [525,526]. Many chiral phosphine catalysts used as ligands in metal catalysis have been explored first in asymmetric organocatalysis. Others were modified known phosphine ligands (for a review, see [527]). In 1995, Lu's group reported phosphine-catalyzed (3+2)-cycloadditions of electron-poor allenes to alkenes that produced cyclopentenes [528]. In 1997, Zhang and coworkers reported the enantioselective phosphine-catalyzed version of these reactions. Reactions (5.1) catalyzed by chiral phosphine **85** (Figure 5.2) are an example [529].

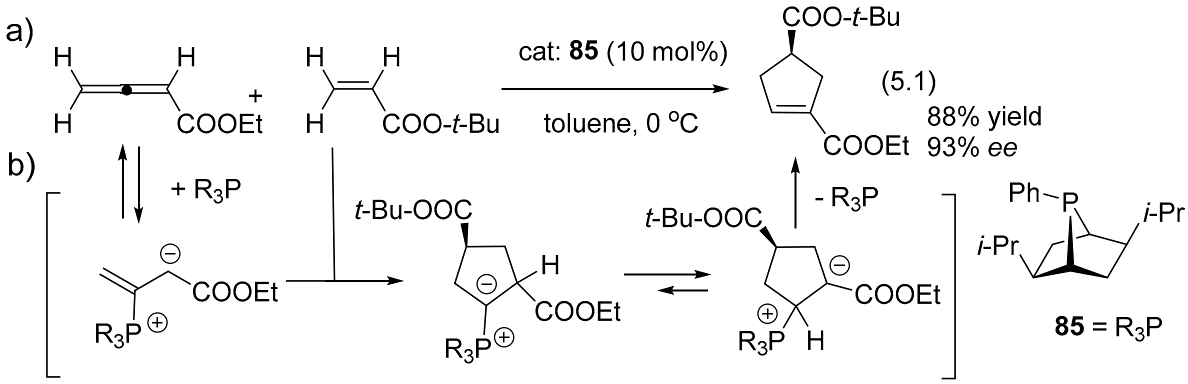


**Figure 5.2.** a) Asymmetric (3+2)-cycloaddition of a 2,3-butadienoate to an acrylic ester catalyzed by a chiral phosphine (Zhang, 1997); b) Possible mechanism.

Applying 7-phosphanorbonane catalysts **85** or **86**, Zhang and coworkers reported in 1998 the first asymmetric γ-addition of dicarbonyl compounds to alkynoates and allenoates (e.g., reactions (5.2), Figure 5.3) [530].

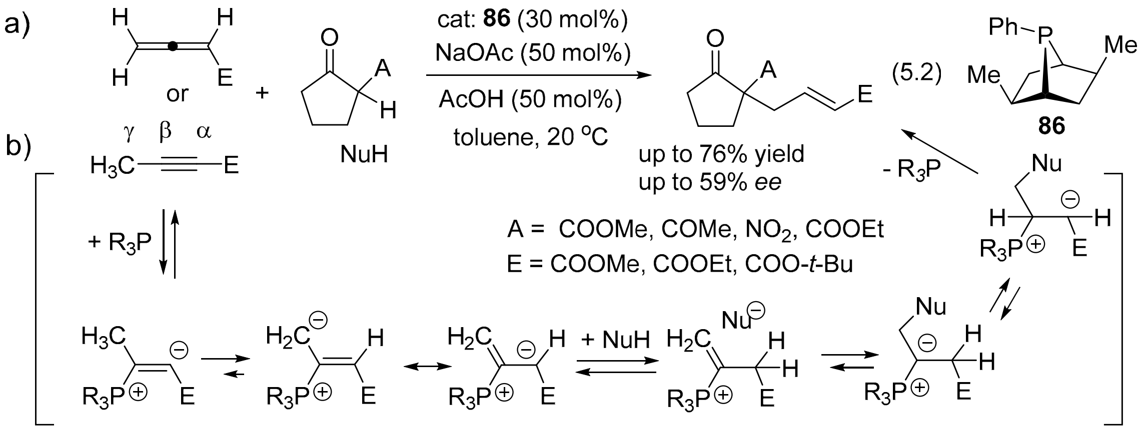


**Figure 5.3.** a) Asymmetric γ-allylation of acidic carbonyl compounds by alkynoate and allenoate esters (Zhang, 1998); b) Possible mechanism.

Following Zhang's reports, several other asymmetric phosphine-catalyzed reactions have been developed, such as (3+2)-, (4+1)-, (4+2)-, and (4+3)-annulations of electron-poor allene and acetylene derivatives, (2+2)-annulation of ketenes, MBH and Rauhut-Currier reactions, and their combinations with other reactions [531]. In 2017, the group of Lu reported an unprecedented example of (4+4)-annulation of allene ketones and 1-azadienes affording azocane derivatives with high enantioselectivity (reaction (5.3), Figure 5.4) [532,533].

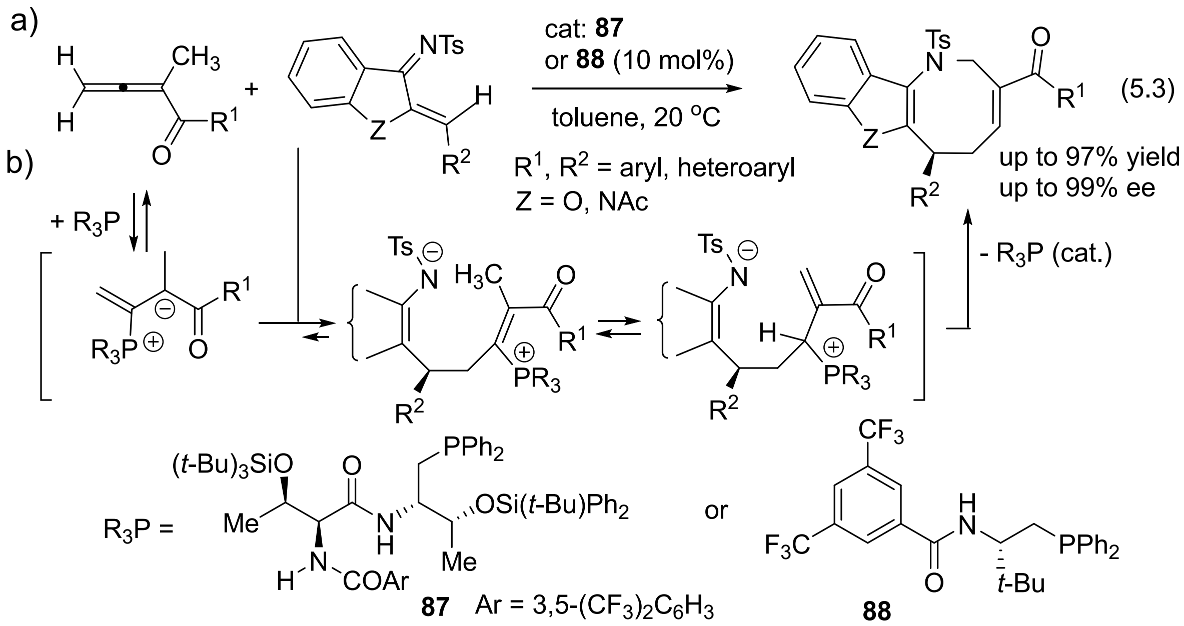


**Figure 5.4.** a) Asymmetric (4+4)-annulations catalyzed by chiral phosphines (Lu, 2017); b) Possible mechanism.

Patureau and coworkers presented a phosphine-catalyzed (3+2)-annulation of benzoxazoles with 1,2-diphenylcyclopropenone (up to 48% *ee*) [534]. In 2025, You and coworkers described similar asymmetric reactions with benzimidazoles and 1,2-diarylcyclopropenone (reaction (5.4), Figure 5.5) catalyzed by diphosphine **89** [535].

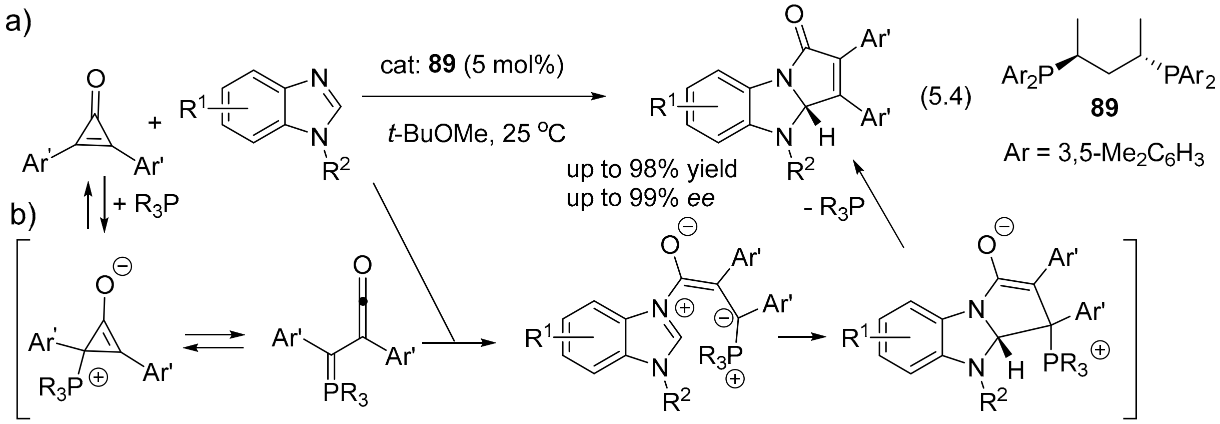
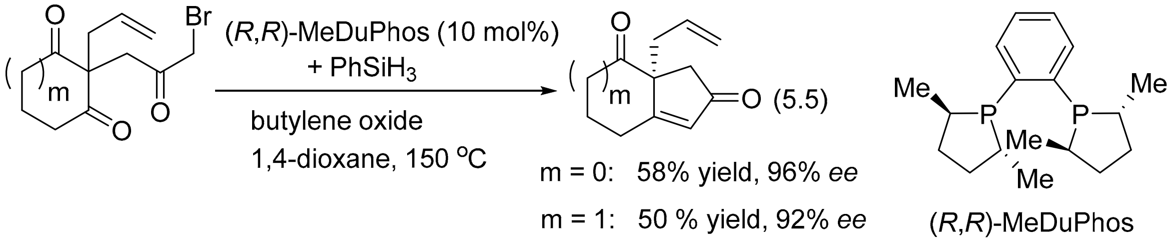


**Figure 5.5.** a) Phosphine-catalyzed asymmetric (3+2) annulation of benzimidazoles with diarylcyclopropenones (You, 2025); b) Possible mechanism.

### *5.2. Enantioselective Wittig and Staudinger-Aza-Wittig Reactions*

Tertiary phosphines are powerful reagents for transforming the C=O bonds of ketones and aldehydes into C=C through Wittig reactions. They also convert carbonyl compounds into imines through Staudinger-aza-Wittig reactions. The development of catalytic $P^{III}/P^{V}=O$ redox processes has transformed the Wittig and Staudinger-aza-Wittig reactions, traditionally plagued by stoichiometric phosphine oxide by-products, into an efficient and more benign method for synthesizing alkenes [536]. In 2014, Werner and coworkers reported the low-yielding, first catalytic asymmetric Wittig reaction through meso-desymmetrization of cyclopentane-1,3-dione with Me-DuPhos as the catalyst and phenylsilane as the terminal reductant (converts the resulting phosphine oxide back into phosphine catalyst, see Figure 5.6) [537]. The Christmann group reinvestigated Werner's asymmetric transformations (5.5) and applied them in the total synthesis of propellanes [538,539].



In 2019, Voituriez and coworkers reported the enantioselective phosphine-catalyzed reactions (5.6) *via* a chemoselective *in situ* phosphine oxide reduction by $PhSiH_3$. Starting with 4,4,4-trifluoroalkane-1,3-diones and dialkyl acetylenedicarboxylates, highly functionalized fluorinated cyclobutenes were obtained applying the HypPhos catalyst **90**. Using the same methodology, $CF_3$-spirocyclobutene derivatives were also synthesized (up to 95% *ee*) [540].

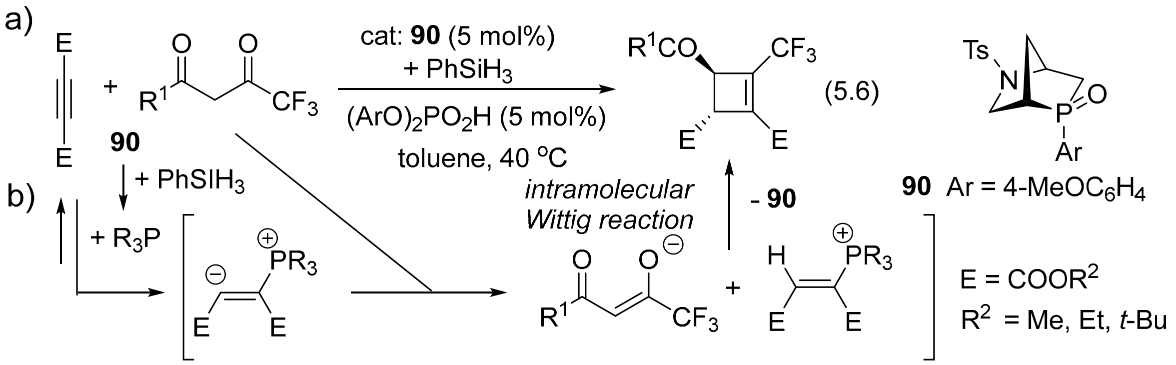
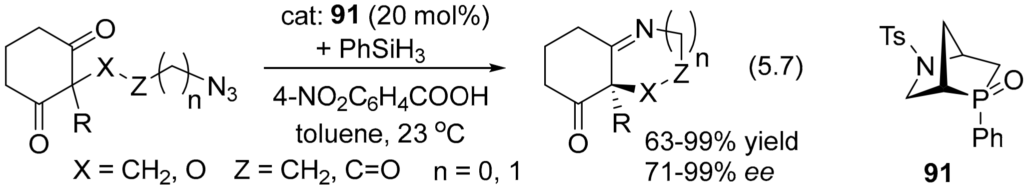


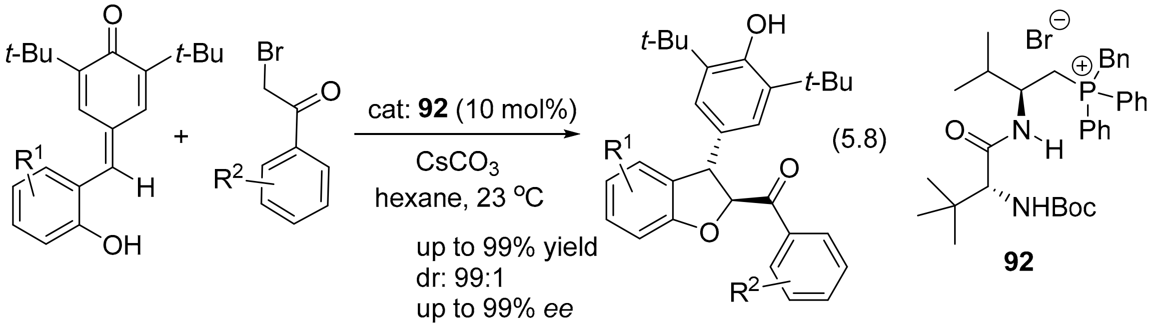
**Figure 5.6.** a) Asymmetric synthesis of fluorinated cyclobutenes (Voituriez, 2019); b) Possible mechanism.

In 1990, Wilson and Pasternak applied their $C_2$-symmetrical (2*R*,5*R*)-1-phenylphospholane to the enantioselective reduction of racemic benzyl azides into primary amines ($R^1$-$N_3$ + $R_3P$ → $N_2$ + $R^1$-N=$R_3$; $R^1$-N=$PR_3$ + $H_2O$ → $R^1$-$NH_2$ + $R_3P$=O) [541]. In 2006, Marsden and co-workers reported the first enantioselective Staudinger–aza-Wittig reaction applying stoichiometric amounts of chiral oxazaphospholane or diazaphospholane derivatives [542]. In 2019, Kwon and co-workers demonstrated that a catalytic, stereoselective Staudinger-aza-Wittig reactions (5.7) could be achieved under mild conditions using a chiral l-hydroxyproline-derived HypPhos catalyst **91** (*endo*-phenyl-HypPhos) [543]. Additives like nitrobenzoic acid promote the $PhSiH_3$ reduction of the phosphine oxide intermediate, permitting to run the reaction at room temperature. In 2022, the Kwon group further demonstrated the synthesis of oxindoles featuring a quaternary carbon center, starting from azidoaryl malonates a catalytic stereoselective Staudinger–aza-Wittig reaction. A bulkier HypPhos oxide catalyst (analogue of **91** oxy-substituted at C(7) and with larger aryl group than Ph), in conjunction with $[Ir(cod)Cl]_2$ as an additive, was employed to achieve high enantioselectivity [544]. Using a $C_2$-symmetric chiral bisphosphine, the Tang group realized recently stereoselective Staudinger–aza-Wittig reactions [545].



### 5.3. Chiral Phosphonium Salts as Phase Transfer Catalysts

In 1998, in a pioneer work, Manabe synthesized chiral phosphonium salts having two NH and two OH groups as hydrogen-bond donors. They were PTCs for asymmetric alkylation of β-keto esters to give the corresponding products with up to 50% *ee* [546]. Since then, many chiral quaternary phosphonium salts have been developped as organocatalysts [547]. In 2007, the group of Ooi developed quaternary tetraaminophosphonium salts [548]. In 2009, Maruoka and co-workers proposed binaphthyl-derived phosphonium salts for asymmetric Michael and Mannich reactions [549]. These phosphonium salts exhibit high stability under strong alkaline conditions and resist attacks by nucleophilic anions. During the last 15 years, the exploration focused on the development and application of amino acid-derived bifunctional phosphonium catalysts [547,550,551]. In 2019, Wang and Xu presented the enantioselective synthesis of benzofuran derivatives (reactions (5.8)). The catalyst **92** was prepared in seven steps from L-valine [552].



### 5.4. Chiral Phosphoramides as Lewis Base Catalysts

The classical catalytic enantioselective allyl addition of aldehydes and ketones that produce allylic alcohols applies a chiral Lewis acid that binds to the aldehyde or ketone (electrophile) and activates it toward nucleophilic attack by an allylmetal reagent [553]. In 1994, Denmark and coworkers found that sub-stoichiometric amounts of chiral phosphoramide **93** induces enantioselective allylation of benzaldehyde with allyltrichlorosilane (reaction (5.9)). In this case, the high oxyplilicity of silicon nucleophile permits its coordination with the P=O bond of the Lewis base (LB) and, in the same time, with the oxygen atom of the aldehyde. A second molecule of LB diplaces a chloride forming a hexacoordinated silicon species **95** that adopts a chair like transition state for the allylation [554]. This mechanism explain the high diastereoselectivity and enantioselectivity observed in many aldehyde allylations with allyltrichlorosilanes (Figure 5.7). Reaction (5.10) that applies the double Lewis base **94** is an example. With its two phosphoramide moieties it reduces the entropy cost of the formation of the hexacoordinated silicon intermediates analogues of **95** [555,556].

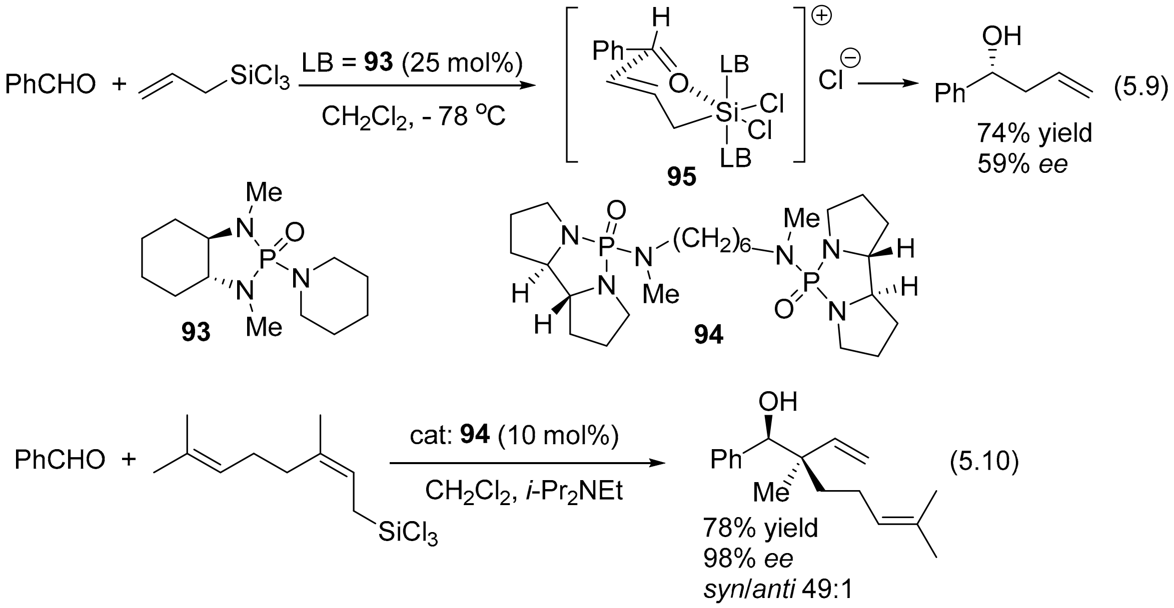


**Figure 5.7.** Early examples of phosphoramide induced enantioselective allylation of benzaldehyde with allyltrichlorosilanes (Denmark, 1994, 2001).

Denmark and Beutner recognized that the combination of Lewis bases with Lewis acids is a general mode of activation of reactants of type $Y_3MX$ (Figure 5.8). These combinations can realize efficient catalysts, including asymmetric ones [557].

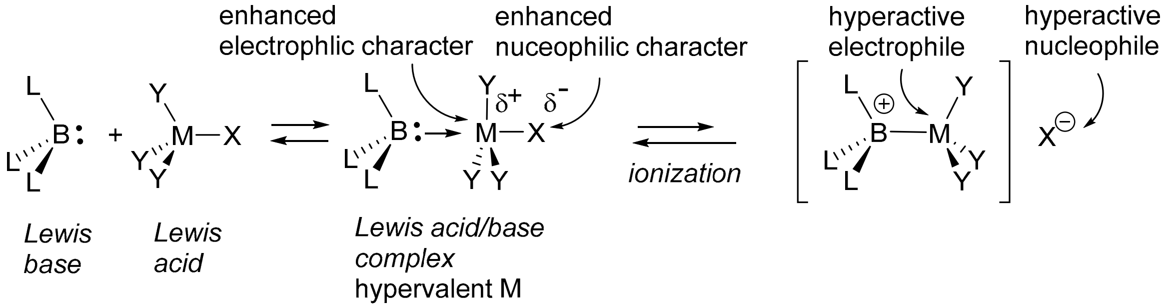
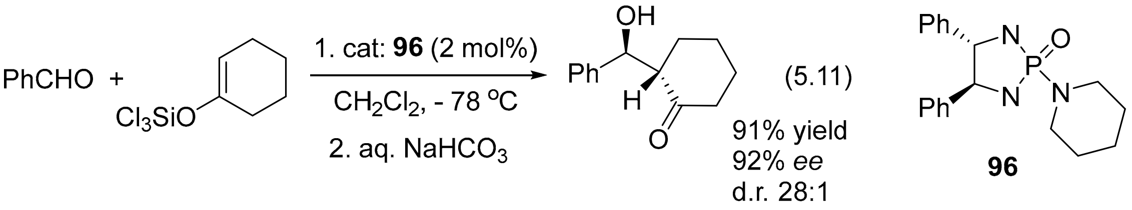
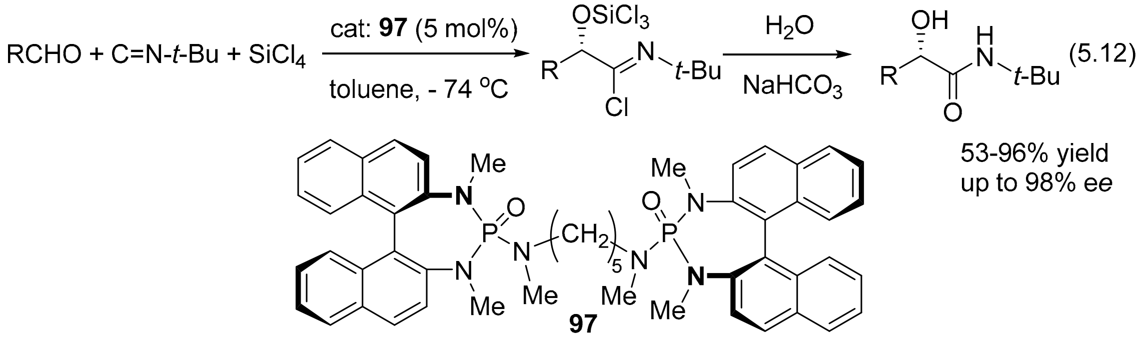


**Figure 5.8.** Electron-pair donors (Lewis bases) can influence chemical reactions by enhancing either (or both) electrophilic or nucleophilic character of reagent $Y_3MX$ (Denmark, 2008).

In 1999, the group of Denmark reported a new approach to the asymmetric aldol reaction. An example is shown with reaction (5.11) that applies phosphoramide **96** as Lewis base to catalyze the condensation of an aldehyde with a trichlorosilyl enol ether [558].

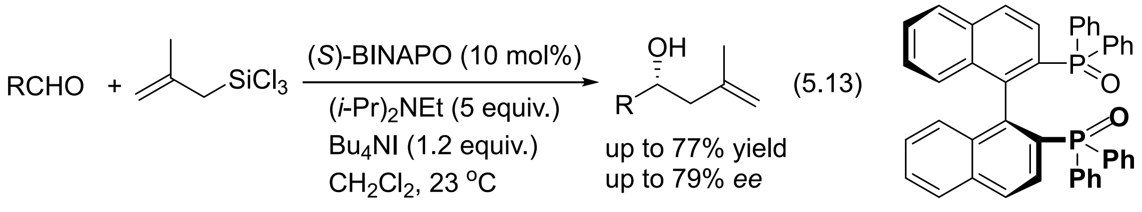


Silicon tetrachloride ($SiCl_4$) is a weak Lewis acid. It can be activated by binding of a strongly Lewis base such a chiral phosphoramide (LB), leading to *in situ* formation of a chiral Lewis acid of type $[(LB)_2SiCl_3]^{(+)}Cl^{(-)}$ (Figure 5.8). This species catalyzes asymmetric aldol additions of acetate-, propanoate-, and isobutyrate-derived silyl ketene acetals to conjugated and nonconjugated aldehydes. Aldol reactions of silyl dienol ethers are also enantioselective in the presence of this species [559,560]. Ring opening of meso-oxiranes with $SiCl_4$ are enantioselective in the presence of chiral phosphoramides and other chiral LB [561]. In 2003, Denmark and Fan described the first, catalytic, enantioselective $\alpha$-additions of isocyanides to aldehydes (reactions (5.12)) that applies Lewis base catalyst **97** [562].



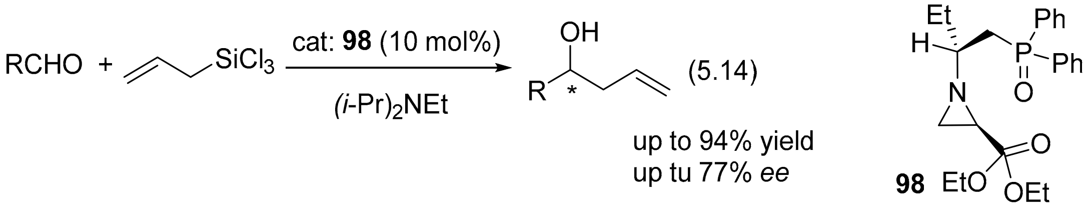
### 5.5. Chiral Phosphine Oxides as Organocatalysts

In 2004, Kobayashi and co-workers reported that stoichiometric amounts of bis-(diphenylphosphanyl)-binaphthyl dioxide (BINAPO, a chiral Lewis base) induces diastereoselective and enantioselective allylation of a-hydrazono esters using allyltrichlorosilanes [563]. With substoichiometric amounts of BINAPO (20 mol%), yield (11%) and *ee* (56%) were low. In 2005, Nakajima and coworkers reported the enantioselective allylation of aldehydes (reactions (5.13)) catalyzed by (*S*)-BINAPO, wherein the combination of diisopropylethylamine and tetrabutylammonium iodide as additives was crucial for accelerating the catalytic cycle [564].



(*S*)-BINAPO

In 2009, the same group showed that (*S*)-BINAPO catalyzes the direct asymmetric aldol reaction of cyclohexanones + ArCHO + $SnCl_4$ [565]. Since then, further phosphine oxides have been developed and applied as chiral catalysts in Lewis base-catalyzed reactions such as aldehyde allylations, aldol reactions, epoxide openings, and halocyclizations [566–569]. An example reported by Dogan and coworkers in 2015 is given with the aldehyde allylations (5.14) catalyzed by **98** [570].



## 6. Asymmetric Organocatalysis by Sulfur Compounds

In this Chapter, we provide a few examples of asymmetric organic reactions catalyzed by S-nucleophiles such as thioethers (RSR') and thiols (RSH), by O-nucleophiles like chiral sulfoxides ($R_2S{=}O$) and sulfinamides ($R'(R_2N)S{=}O$). Chiral sulfonium salts ($R_3S^{(+)}X^{(-)}$) have been applied as asymmetric phase transfer catalysts.

### 6.1. Asymmetric Aldehyde Epoxidations Catalyzed by Chiral Dialkylsulfides

In 1958, Johnson and LaCount reported the first example of a sulfur ylide-mediated epoxidation reaction [571]. Sulfides are nucleophiles that add to aldehydes. Reaction of 9-dimethylsulfonium fluorenylide with 4-nitrobenzaldehyde did not afford an alkene (Wittig-like olefination), but an epoxide instead. In 1965, Corey and Chaykovsky found that simpler dimethyl sulfonium ylide and dimethyloxosulfonium ylide can be used in the epoxidation of aldehydes [572]. In 1989, Furukawa and coworkers reported the first example of a catalytic, asymmetric epoxidation reaction. It features reaction (6.1) and catalyst **99** (Figure 6.1) [573].

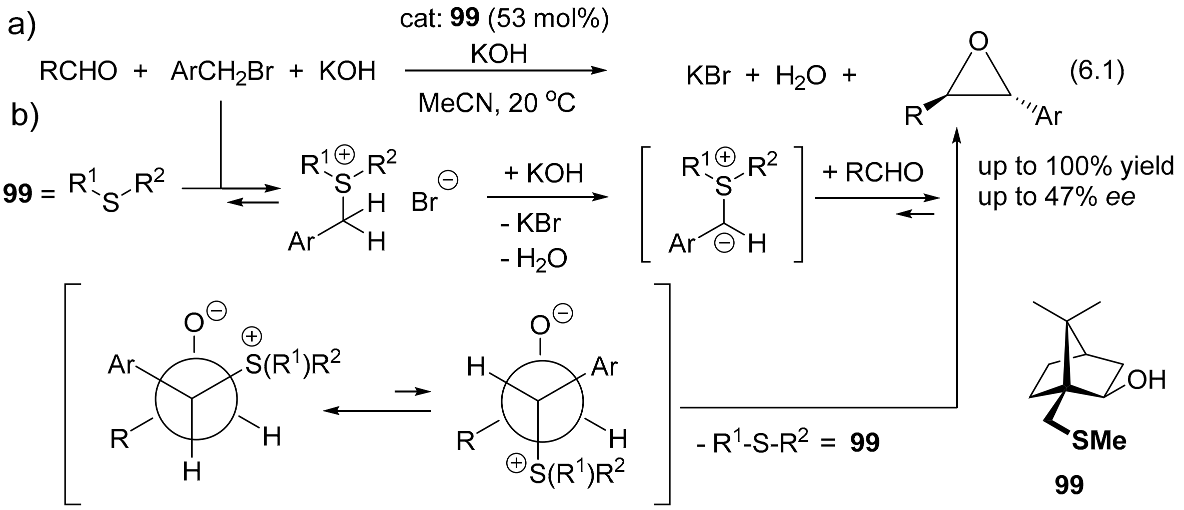


**Figure 6.1.** a) Early examples of sulfur-ylide-mediated asymmetric epoxidation of aldehydes (Furukawa, 1989); b) Possible mechanism.

Then a large number of alternative catalysts have been proposed (Figure 6.2, reaction (6.2)) [574–576].

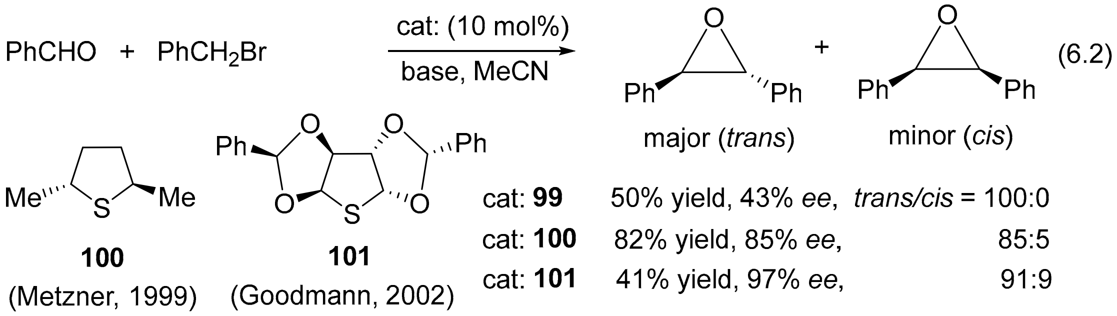


**Figure 6.2.** Asymmetric epoxidation of aldehydes; selected examples of sulfide catalysts for the asymmetric synthesis of *trans*-stilbene epoxide.

### 6.2. Asymmetric Halo- and Chalcolactonization Catalyzed by Sulfides

A wide range of chiral organocatalysts has been developed and applied to enantioselective halolactonization [577]. They include Lewis bases, Lewis acids, Brønsted acids, and phase-transfer catalysts containing basic N-, O-, S-, Se-, and P-heteroatoms. They activate electrophilic halogenating reagents such as NIS, NBS, and NCS (N-I, N-Br, and N-Cl-succinimide). These catalysts interact with the epihalonium ion (haliranium ion) intermediate resulting from the reaction of the alkene with the halonium ion. Good enantioselectivities are observed when this process is irreversible, i.e., when the nucleophilic quenching of the three-membered cyclic intermediate is rapid and irreversible [578]. A recent illustration (Figure 6.3) is bromolactonization (6.3) reported by Shirikawa and coworkers. The sulfide catalyst **102** is polyfunctional. Its phenolic group is essential for good *ee*'s and the diphenylmethanol moiety improves them [579].

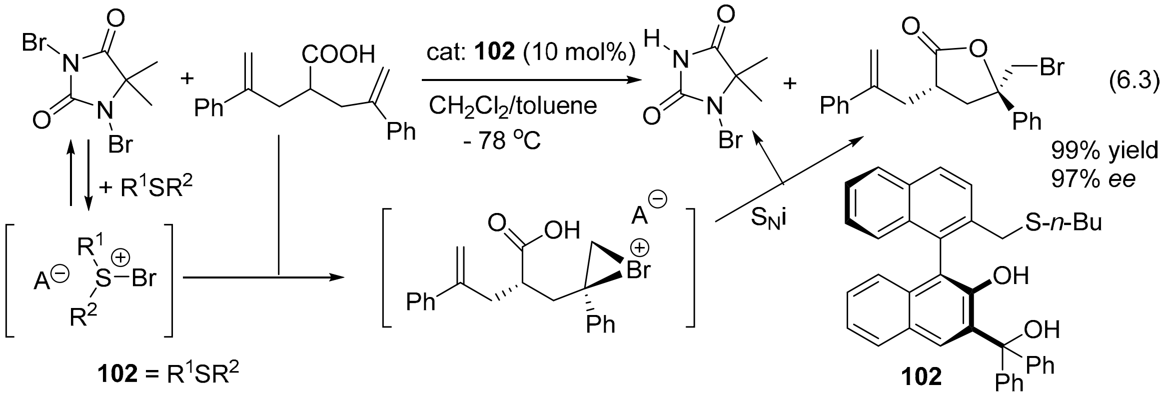
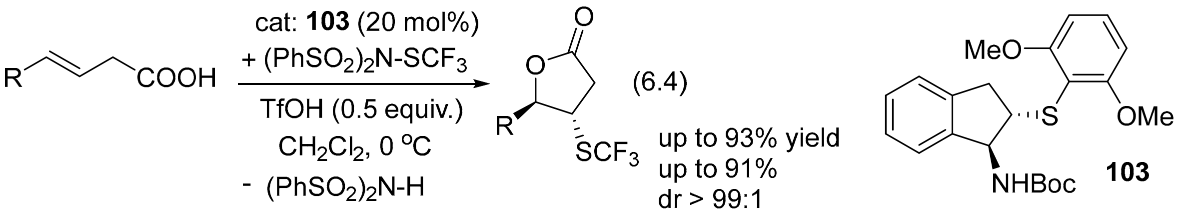


**Figure 6.3.** Example of sulfide-catalyzed enantioselective bromolactonization.

In 2016, Zhao and coworkers reported the first enantioselective trifluoromethylthiolating lactonization of alkenes (6.4) by using an indane-based bifunctional chiral sulfide catalyst **103** [580].



As for other halogen and chalcogen compounds, thioethers are nucleophiles and electrophiles. Their electrophilic property results from their $\sigma$-holes (Section 3.1.7). If halide catalysts are halogen bond (XB) donors, thioether catalysts are chalcogen bond (ChB) donors [581–583].

### *6.3. Enantioselective Hydrogen-Atom Transfer Catalyzed by Chiral Thiols*

In 1998, Roberts and coworkers reported asymmetric radical-chain additions of triphenylsilane and of tris(trimethylsilyl)silane to prochiral alkenes catalyzed by chiral thiols (e.g., reaction (6.5)) [584]. The initiation step of this radical process engages di-*tert*-butyl hyponitrite as an initiator, which abstracts an H atom from the thiol catalyst **104** derived from D-mannose. Then the thiyl radical abstracts an H atom from the silane, forming a silyl radical that adds to the least sterically hindered carbon center of the alkene. The resulting carbon-centered prochiral radical abstracts an H-atom from the chiral thiol with face selectivity, forming an enantiomerically enriched product (Figure 6.4) [585].

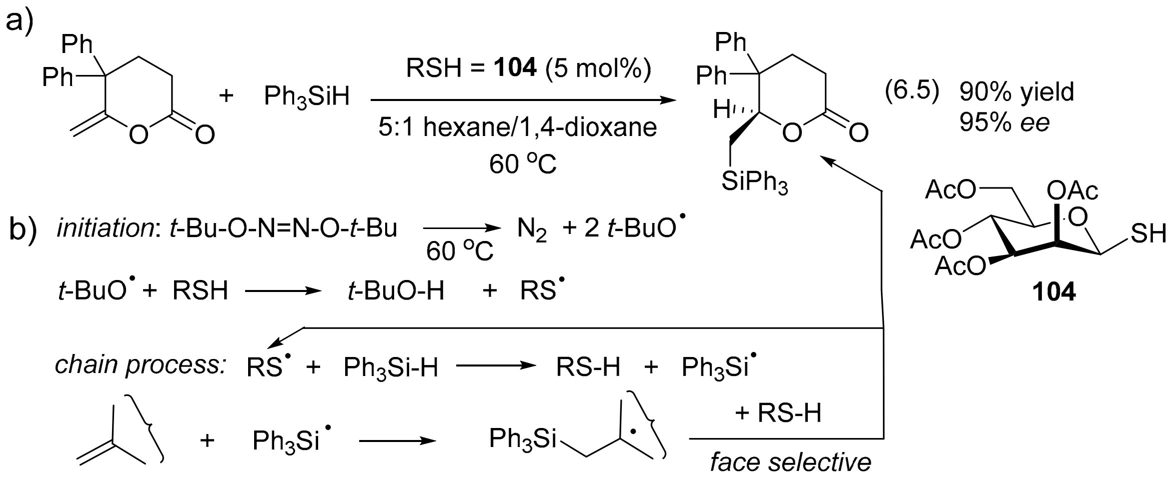


**Figure 6.4.** a) Example of enantioselective radical-chain hydrosilylation of alkenes using chiral thiols as catalysts (Roberts, 1998); b) Possible mechanism.

### 6.4. Asymmetric Rauhut-Currier Reaction Catalyzed by a Chiral Thiols

Aroyan and Miller have found that *N*-acetylcysteine methyl ester catalyzed intramolecular enantioselective Rauhut-Currier reactions, such as reactions (6.6) (Figure 6.5) [586].

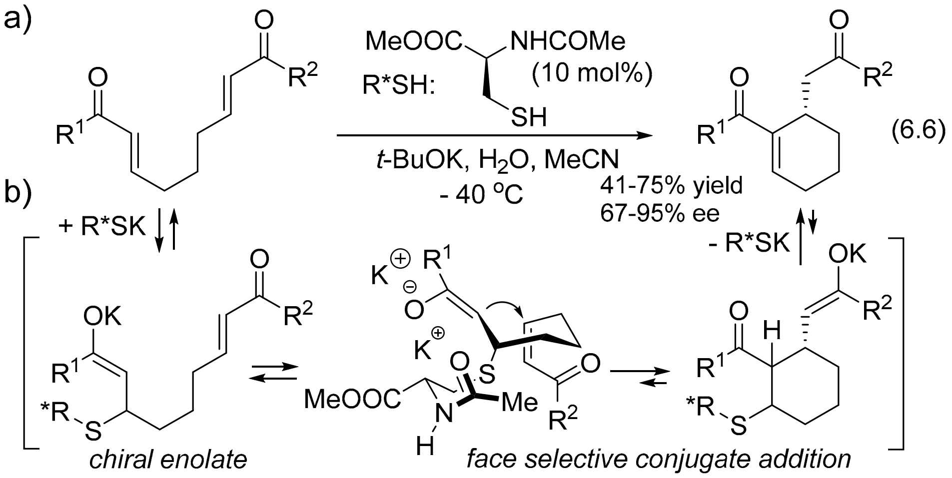
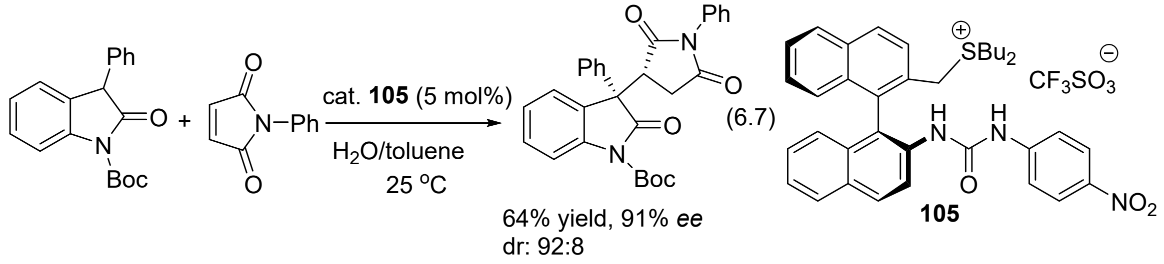


**Figure 6.** 5: a) Asymmetric Rauhut-Currier reaction catalyzed by a thiol (Miller, 2007); b) Possible mechanism.

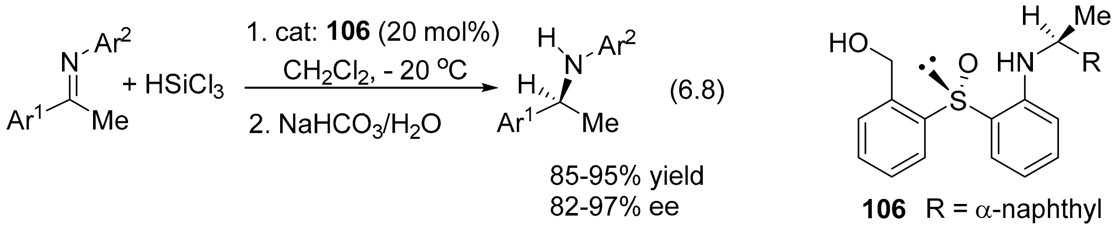
### 6.5. Sulfonium Salts as Chiral PTCs

The formation of sulfonium ylides from sulfonium salts does not occur under base-free, neutral conditions. Under such conditions, chiral sulfonium salt catalysts can efficiently promote asymmetric neutral phase-transfer reactions with a high level of enantioselectivity as demonstrated in 2017 by the group of Shirakawa. An example is given with the enantioselective Michael addition (6.7) catalyzed by **105** [587].



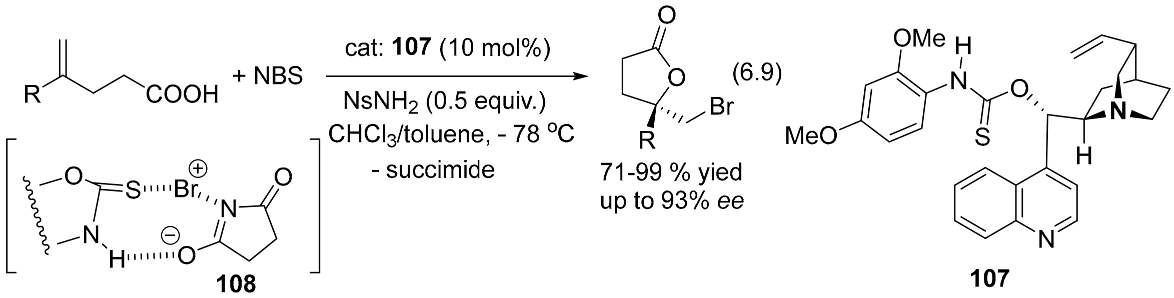
### 6.6. Chiral Sulfoxides

Chiral, enantiomerically pure sulfoxides are easily accessible. A large number of them have been prepared. They are powerful chiral auxiliaries in asymmetric synthesis and as chiral ligands in organometallic complexes [588]. Those possessing various additional functional groups proved to be efficient organocatalysts in asymmetric synthesis [589,590]. The group of Rachwalski developed chiral organocatalysts **106** that possess three functions: the hydroxy group, the stereogenic enantiomerically pure sulfinyl group, and enantiomeric amine moieties. Sulfoxides such as **106** catalyze the enantioselective Henry reaction, aza-Henry reaction, direct aldol condensation, Mannich reaction, and the asymmetric aziridination. They also catalyze the reduction of aromatic ketimines into the corresponding amines, as shown with reaction (6.8) (see also reaction (6.10)) [591].



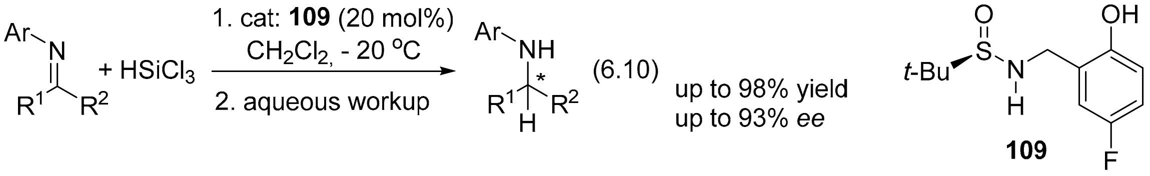
### 6.7. Chiral Amino-Thiocarbamates

In 2010, Yeung and coworkers realized enantioselective bromo-lactonizations (6.9) of 4-substituted pent-4-enoic acids applying the cinchonidine-derived amino-thiocarbamate **107** as a catalyst. The halophilic character of the C=S moiety is expected to promote the N-Br dissociation of NBS. At the same time, the N-H moiety stabilizes the succinimide anion by H-bond donation, forming a chiral brominating reagent as shown with **108** (see also Section 3.11.4) [592]. The enantioselective bromocyclization of olefinic amides into 2-substituted 3-bromopiperidines apply the same catalyst **107** [593].

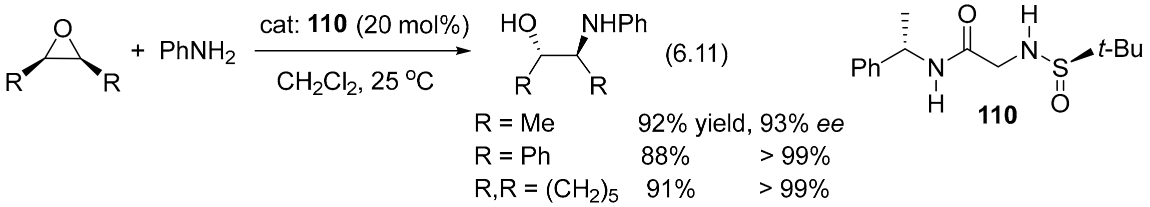


### 6.8. Chiral Sulfinamides

Chiral sulfinamides have emerged as versatile organocatalysts showing both Lewis base and Lewis acid activation modes [594]. In 2006, Sun and coworkers reported the first example of an organocatalytic reaction. They used a *tert*-butanesulfinamide-based organocatalyst **109** (readily obtained from the Ellman's chiral auxiliary *t*-BuS(=O)$NH_2$ [595] ), in which prochiral aromatic ketimines were reduced to amines using trichlorosilane as the hydrogen source (reaction (6.10)). Catalyst **109** must be seen as bifunctional: its S=O moiety is the Lewis base that interacts with the strongly oxyphilic Si center of the reagent $HSiCl_3$, and the phenolic OH group provides a H-bond to the substrate imine moiety of the substrate [596]. In fact, a dimer of **109** was suspected to be the actual catalysts. This led Sun and coworkers to develop S-chiral bissulfinamides as highly enantioselective organocatalysts for the reduction of ketimines [597].

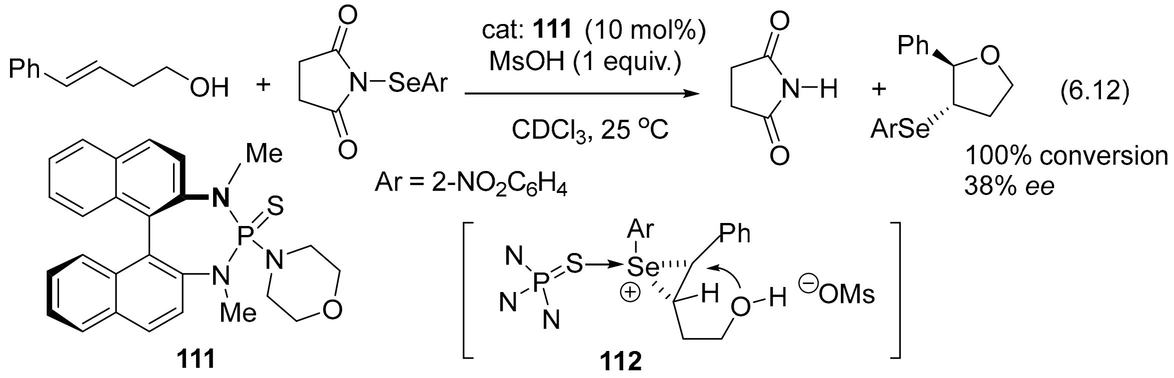


Kureshy and coworkers reported the ring opening reaction of *meso*-epoxides with anilines catalyzed by an easily available enantiomerically pure sulfinamide **110** (reaction (6.11)) [598].



*6.9. Chiral Thiophosphoramides*

In 2010, the Denmark group realized the first enantioselective selenofunctionalization of unactivated olefins (reaction (6.12)) applying thiophosphoramide **111** as a catalyst. A chiral seleniranium ion-pair intermediate is formed, which is coordinated to the P=S base of the catalyst. It undergoes an intramolecular displacement reaction with its alcoholic moiety (transition structure **112**) [599].

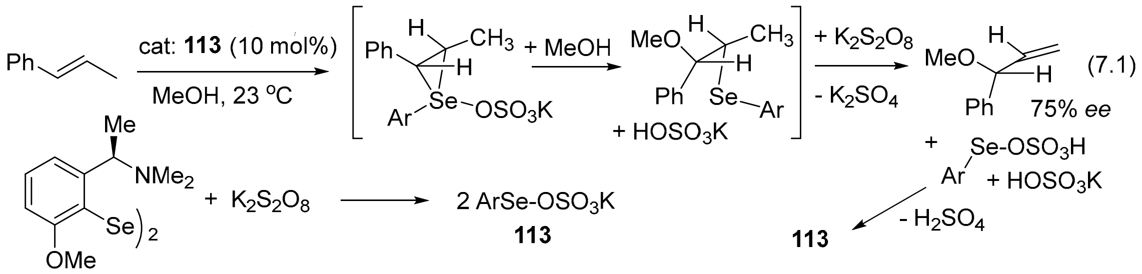


## 7. Asymmetric Catalysis with Organo-Selenium Compounds

Chiral organo-selenium catalysts have been prepared, and several of them have permitted to develop highly enantioselective asymmetric reactions [600–602].

### 7.1. Aminodiselenides as Chiral Pre-Catalysts

In 1998, Wirth and coworkers catalyzed the sequence (7.1) of methoxyselenylation and oxidative β-hydride elimination of *trans*-β-methylstyrene with chiral base **113** resulting from the oxidation of an amino-diselenide with potassium peroxodisulfate [603].



The Se-Se dimer of the natural amino acid L-selenocysteine is responsible for the catalytic activity of glutathione peroxidase. It is a pre-catalyst for the one-pot dihydroxylation of olefins employing $H_2O_2$ as a stoichiometric oxidant and water as a reaction medium. In some cases, the reaction affords enantiomerically enriched 1,2-diols [604]. In 2003, Braga and coworkers prepared chiral aliphatic amino-diselenides. They are pre-catalysts for the enantioselective addition of diethylzinc to aldehydes [605]. Examples of chiral selenium-catalysts developed since then are listed in Figure 7.1. They induce enantioselective hydrosilylation of ketones, addition of diorganozinc to aldehydes, conjugate addition to enones, Pd-catalyzed allylic alkylations, and halocyclization of alkenylamides, alcohols, and carboxylic acids [606,607]. Applying a chiral diselenide catalyst, the Denmark group realized an enantioselective *syn*-dichlorination of alkenes [608].

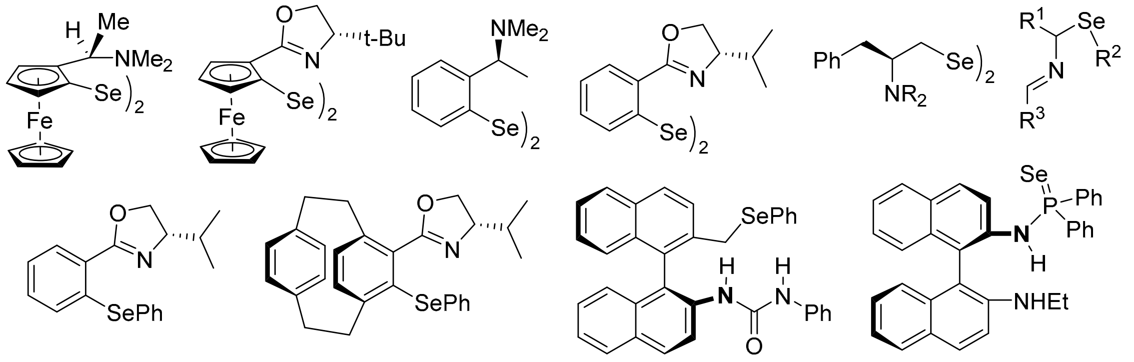


**Figure 7.1.** Examples of diselenides and selenides (Lewis basis) used chiral catalysts.

### 7.2. Selenophosphoramides as Chiral Catalyts

In 2011, the Denmark group reported the first catalytic, asymmetric sulfenylation of simple alkenes using chiral thio- and selenophosphoramide catalysts. Both inter- and intramolecular thiofunctionalizations are possible for a variety of olefins. An example is shown with reaction (7.2) catalyzed by selenophosphoramide**114**. The proposed mechanism (Figure 7.2) involves activation of the sulfur electrophile (*N*-phenylsulfenyl-phthalimide) by the Lewis base catalyst **114** with formation of the chiral and enantiopure selenosulfonium ion intermediate that adds to the prochiral alkene with face selectivity forming a enantioenriched chiral episulfonium ion intermediate (of formal $C_2$-symmetry). Attack of the nucleophile (MeOH) on either one or the other carbon center of the latter give the same final product of *anti*-addition. In 2014, Denmark disclosed an enantioselective intramolecular sulfenamination of the tosylamide of alk-4-enamines applying catalyst **115** (Figure 7.2) [609–611].

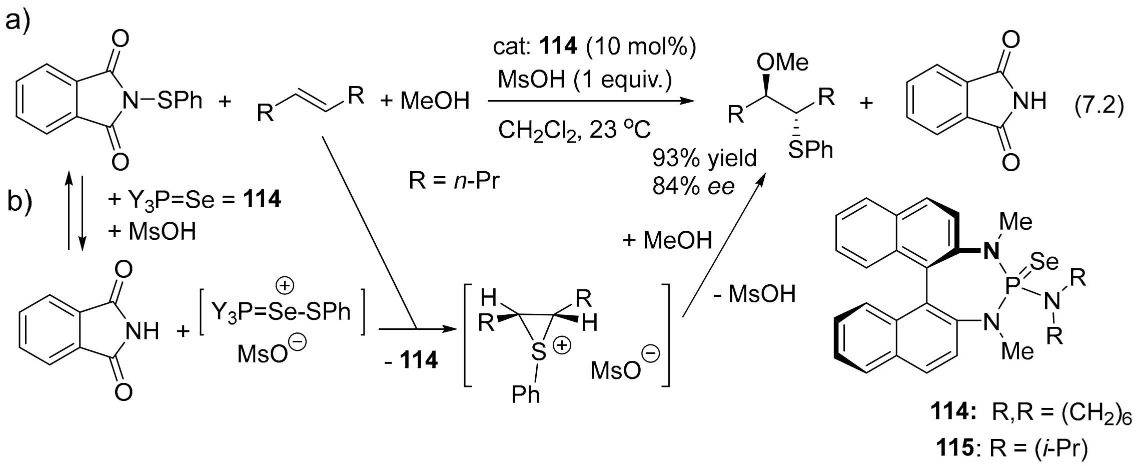
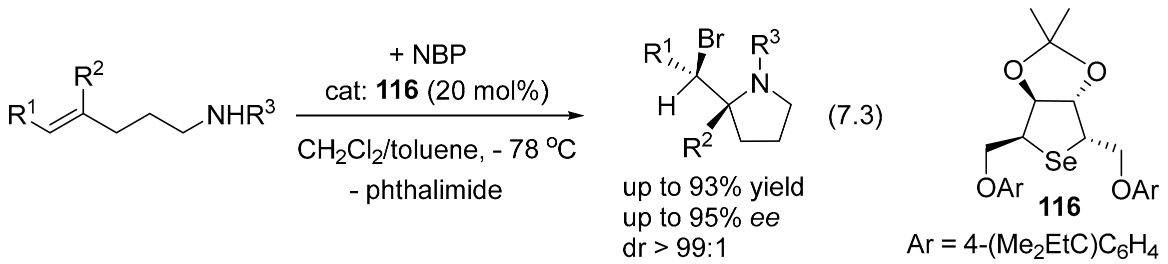


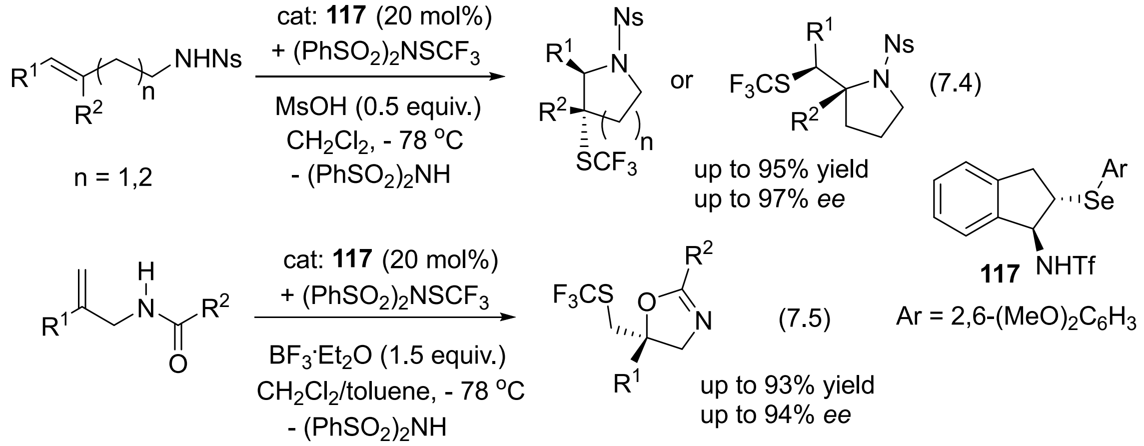
**Figure 7.2.** a) Example of asymmetric thiofunctionalization of unactivated alkene (Denmark, 2011); b) Proposed reaction mechanism.

### *7.3. Selenides as Chiral Catalysts*

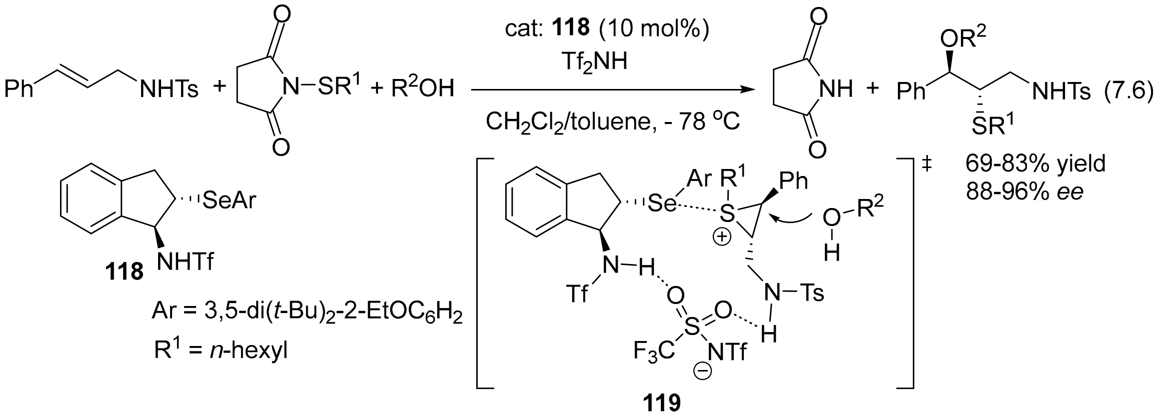
In 2013, Yeung and coworkers catalyzed the asymmetric bromocyclization (7.3) of trisubstituted olefinic amides with the C2-symmetric D-mannitol-derived tetrahydroselenophene **116** [612]. The mechanism of the reaction implies, probably, coordination of the selenide Lewis base with *N*-bromophthalimide (NBP). An activated and chiral electrophilic brominating agent forms as an intermediate that adds to the prochiral alkene with face selectivity. A cyclic epibromonium cation intermediate is generated, which is quenched intramolecularly by the amino moiety.



In 2017, Zhao and coworkers reported the enantioselective CF3S-aminocyclization of internal alkenes to afford saturated azaheterocycles (reactions (7.4)) catalyzed by the bifunctional selenide catalyst **117** [613]. It also catalyzed the enantioselective cyclizations (7.5) [614].

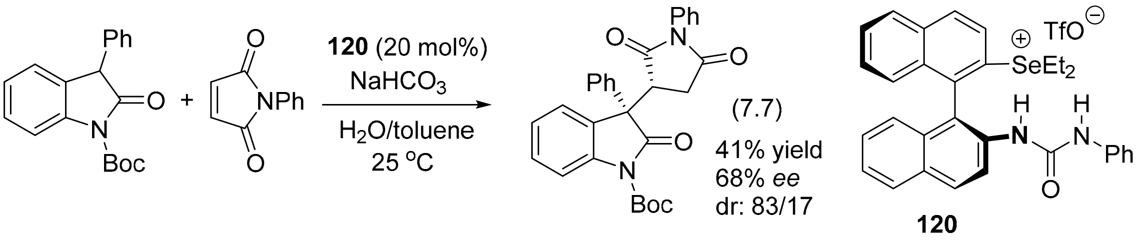


In 2019, the same group reported an efficient protocol for the intermolecular oxysulfenylation (7.6) applying chiral bifunctional selenide **118** as catalyst. Transition state **119** was proposed for these reactions [615].



*7.4. Chiral Trivalent Selenonium Salts as PTCs*

As for sulfonium salts, chiral trivalent selenonium salts are expected to be asymmetric phase transfer catalysts. The Michael addition (7.7) catalyzed by **120** is an example [607].



Trisubstituted selenonium salts are organic Lewis acid catalysts in electrophilic halogenation and aldol-type reactions. Chiral analogues of such catalysts will appear soon [616].

## 8. Asymmetric Organocatalysis with Electron-Rich Carbene Intermediates

In 1943, Ukai reported the first thiazolium salt-catalyzed reaction with the condensation of benzaldehyde into benzoin (2 PhCHO → racemic PhC(OH)H-COPh) [617]. In 1958, Breslow published his mechanism that implies the formation of an electron-rich heterocyclic carbene intermediate. The latter adds to the aldehyde forming an acyl anion equivalent (Breslow intermediate, Figure 8.1b) [618]. Following these seminal works, Stetter [619–621] and several other groups have reported other N-heterocyclic carbene (NHC) precursors including chiral ones (see e.g., Figure 8.1). The latter catalyze enantioselective reactions such as homo- and cross-benzoin, and -acyloin condensations (Section 8.1), cross-aza-benzoin condensations (Section 8.2), Stetter reactions (Section 8.3), aza-Stetter reactions (Section 8.4), cycloadditions (Section 8.5), (3,3)-sigmatropic rearrangements (Section 8.6), Michael acceptor Umpolung (Section 8.7), radical reactions (Section 8.8), and synthesis of atropisomers (Section 8.9).[622–626]. Figure 8.1presents typical NHC precursors (pre-catalysts) used today. The triazolium salts employed first by Enders are dominating the scene. As for other types of organo-catalysts, the trend now is to create polyfunctional NHCs [627].

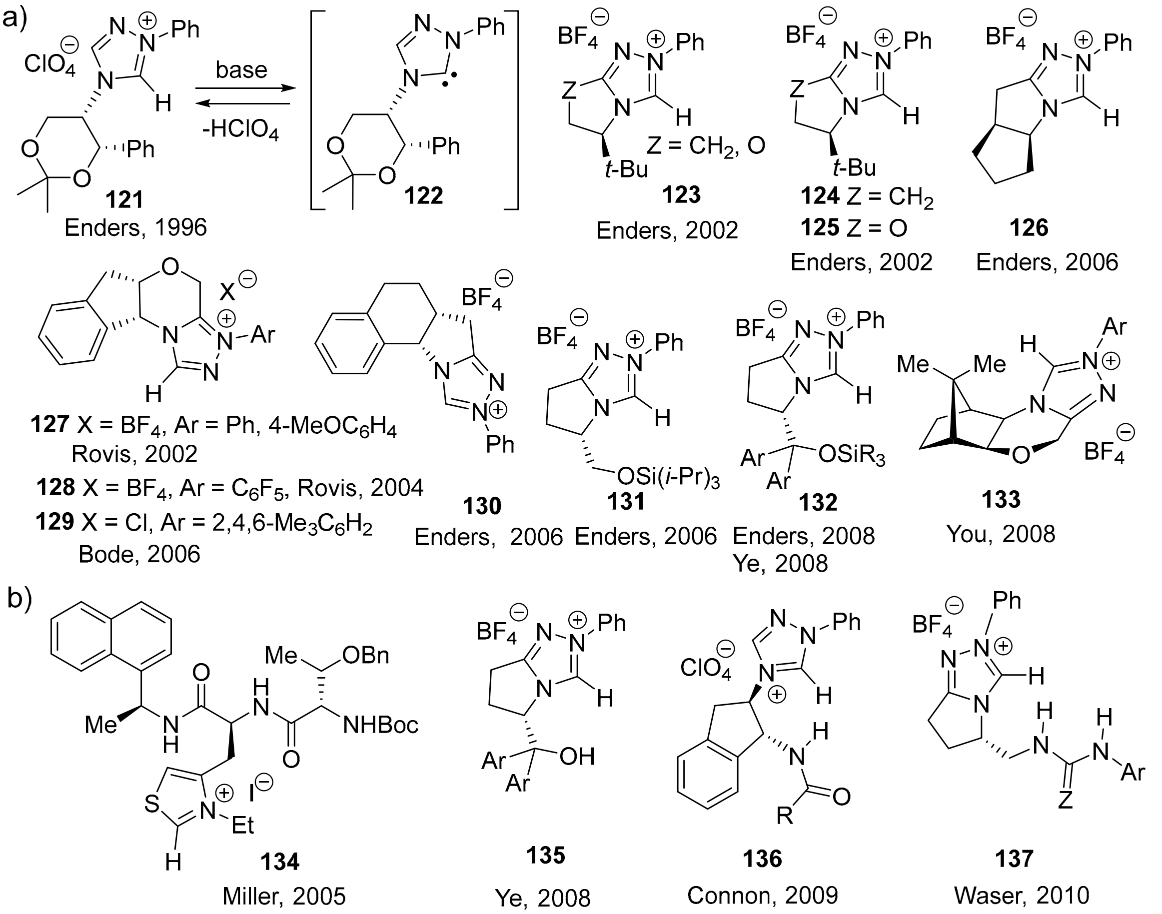


**Figure 8.1.** Typical chiral precursors of NHC catalysts. For many of them both enantiomeric forms are available. a) The NHC generated by pre-catalysts **121**, **123**-**133** induce enantioselectivity because of their shape (steric effects); b) The NHC issued from pre-catalysts such as **134**-**137** are polyfunctional and offer more than steric effects to the reactants (dipole/dipole interactions, H-bond formation, etc.) to realize enantioselective reactions.

NHCs have singlet ground states with a $sp^2$-divalent carbon center. Their stability arises from electronic and steric factors. The lone pair of electrons is stabilized by inductive electron withdrawal by the proximal electronegative atoms ($sp^2$(C:)/$\sigma^*$(C-Z) interactions) and by the mesomeric donation of electron density from the filled p orbitals of the heteroatoms (Z = N, S) to the vacant 2p-orbital at the carbene center (n(Z:)/2p(carbene) interactions). This renders NHCs electron-rich: they are nucleophiles. Figure 8.2 displays typical intermediates generated by reactions of NHCs resulting from triazolium salts. Except for acyl azolium salts, these intermediates are nucleophiles that undergo several possible reactions with electrophiles, as illustrated in the following sections. If NHCs are chiral, these intermediates are also chiral (temporary chiral auxiliary).

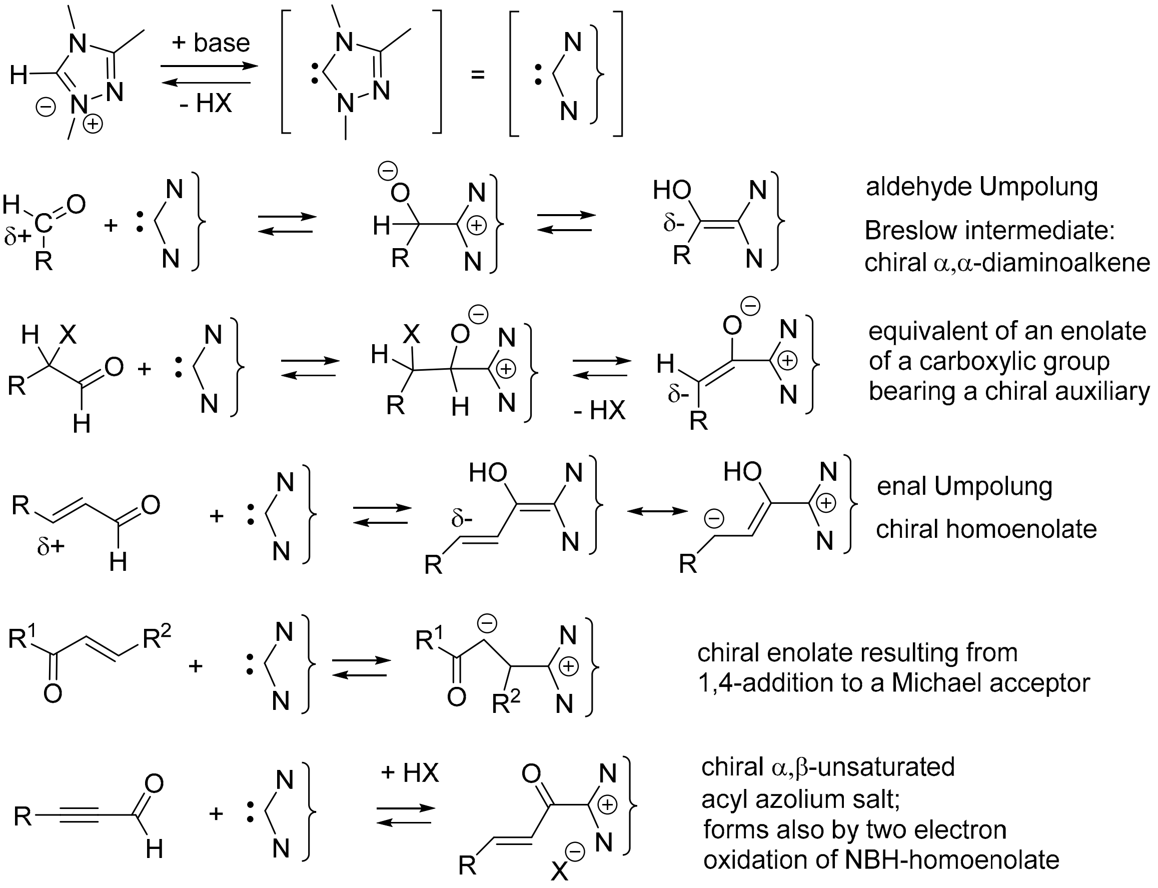


**Figure 8.2.** Typical intermediates formed by reaction of NHCs with carbonyl functions.

### *8.1. NHC-Catalyzed Asymmetric Benzoin Condensations*

In 1966, Sheehan (he had developed the first practical synthesis of penicillin V) and Hunneman reported the first enantioselective asymmetric benzoin condensation (8.1) using zwitterion/carbene intermediates as catalysts generated from chiral thiazolium salts (e.g., **138**, Figure 8.3a, up to 51% *ee*) [628]. Based on the catalytic cycle proposed by Breslow (Figure 8.3b [629]), Sheehan and Hara later studied the stereochemical effect of various enantiopure thiazolium salts on the benzoin condensation. Although the authors did not improve the yield, they observed some *ee* increases [630]. An electrophilic carbonyl moiety becomes a nucleophilic acyl anion equivalent (Umpolung). In analogy to bio-catalysis that uses thiamine (vitamin $B_1$) as a co-factor, under basic conditions, the thiazolium salt **138** (the pre-catalyst) undergoes 1,1-elimination of HBr, generating thiazolylidene carbene **139** (the catalyst) that adds to an aldehyde equilibrating with a zwitterionic intermediate which, after tautomerization, furnishes the crucial Breslow intermediate **140** [631]. The latter is a nucleophile (an enamine). It adds to a second aldehyde molecule and furnishes the benzoin product with regeneration of the active catalyst **139** (Figure 8.3b). Note: cyanide anion also catalyzes the condensation of benzaldehyde into racemic benzoin through a similar mechanism.

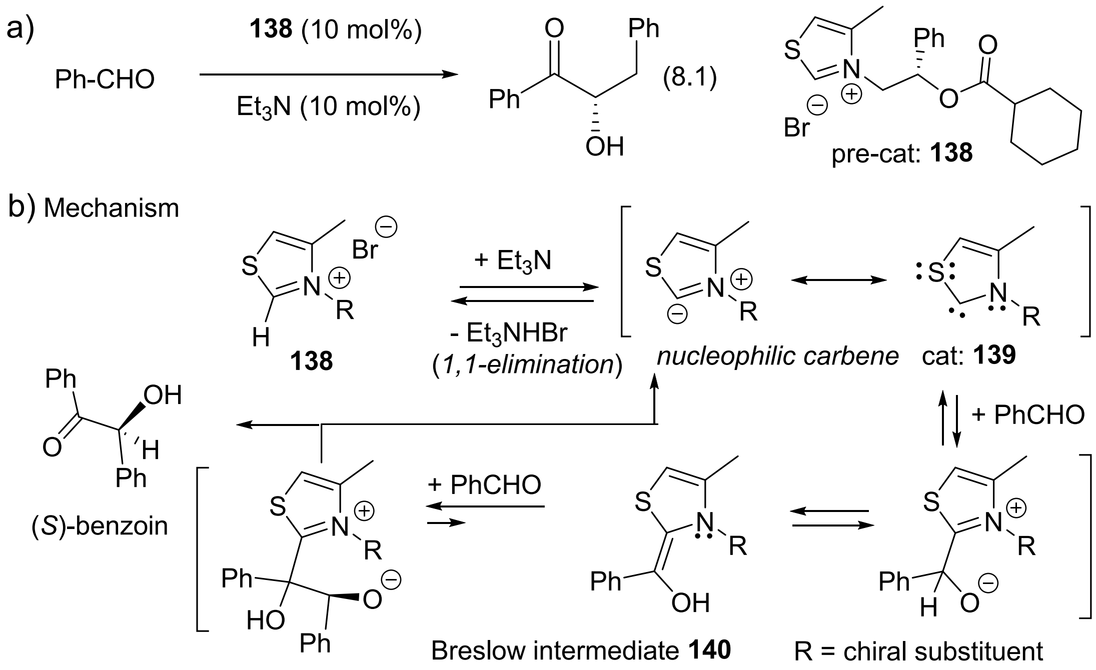
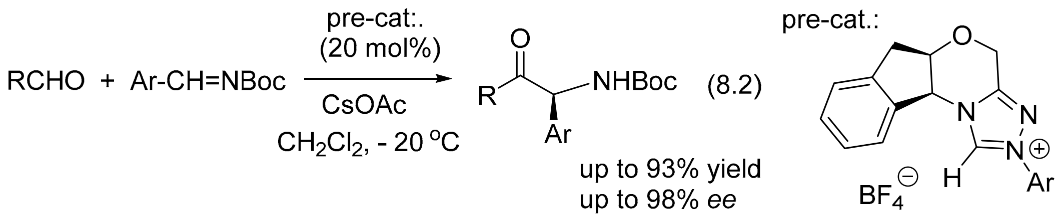


**Figure 8.3.** a) Sheelan's (1966) asymmetric benzoin condensation. b) Breslow's (1958) mechanism: nucleophilic carbene intermediate converts the electrophilic carbon center of an aldehyde into an acyl anion equivalent; the electrophilic carbon center of the carbonyl group becomes a nucleophilic carbon center (Umpolung, polarity inversion).

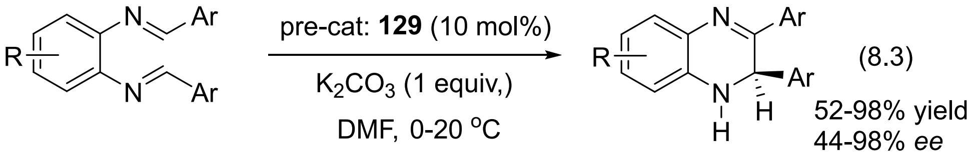
Several reports followed this pioneer work, but with deceiving yields and *ee*'s. In 1996, Enders and coworkers found that NHC **122** (Figure 8.1a) generated on treating triazolium salt **121** (1.25 mol%) with $K_2CO_3$ (THF, 25 °C) is a good catalyst (22-72% yield, 20-86% *ee*) for the asymmetric homo-benzoin condensation of aromatic aldehydes (X-$C_6H_4CHO$, X = H, 3-Me, 4-Me, 3-MeO, 4-MeO,4-$F_3C$. 4-Cl, 4-Br) [632]. With the bicyclic triazolium salt **123** (10 mol%) and *t*-BuOK as a base, up to 95% *ee* was observed for the same reactions [633]. In 2006, the Enders group realized asymmetric intramolecular cross-benzoin reactions of aldehydes and ketones in the presence of tetracyclic triazolium salt **130** as pre-catalyst (10 mol%, THF or toluene, 25 °C). For instance, 2-(3-oxohept-1-yl)benzaldehyde was converted into (*S*)-2-butyl-2-hydroxy-1-tetralone in 85% yield and 98% *ee* [634]. Nearly at the same time, Bode's group reported similar enantioselective intramolecular cross-benzoin reactions [635] applying Rovis pre-catalysts **127** and **128** (Figure 8.1a) [636].

### *8.2. NHC-Catalyzed Asymmetric Aza-Benzoin Condensations*

In 1988, López-Calahorra reported the condensation of iminium salts generated in the reaction of paraformaldehyde, morpholine, or piperidine, and aromatic aldehydes. $\alpha$-Aminoketones were obtained in moderate yields [637]. In 2001, Murry, Frantz, and coworkers reported the first example of an aldehyde-imine cross-benzoin reaction catalyzed by thiazolylidene carbenes, using arylsulfonylamides as imine precursors [638]. In 2005, Miller and coworkers disclosed the enantioselective (up to 87% *ee*) cross-aza-benzoin reaction between aldehydes and N-acylimines. Their pre-catalyst was the peptide-derived thiazolium salt **134** (Figure 8.1b) [639]. In 2012, Rovis and Dirocco reported the direct asymmetric coupling of aliphatic aldehydes and *N*-Boc-protected imines (reaction (8.2)).The cross-aza-benzoin reaction used triazolium salts **141** as pre-catalysts [640]. Asymmetric aza-benzoin condensation with ketimines as substrates is also possible [641].



In 2017, Biju and coworkers reported a NHC-catalyzed enantioselective synthesis of dihydroquinoxalines applying Bode's pre-catalyst (reaction (8.3)). This reaction proceeds *via* Umpolung at one of the imine moieties (electrophilic carbon center C=N) in the substrate, generating a nucleophilic 1,2-diaminoalkene intermediate (aza-Breslow intermediate). The latter reacts with the other imine moiety [642]. The process is a catalytic asymmetric intramolecular aza-aza-benzoin condensation [643]. The first isolation of an aza-Breslow intermediate was made by the group of Douthwaite [644] and later, by Rovis and coworkers [645]. The Biju group has also reported enantioselective intramolecular additions of aza-Breslow intermediates to carbonyl compounds [646].



### 8.3. NHC-Catalyzed Asymmetric Stetter Reactions

In 1974, Stetter and Kuhlmann found that a thiazolium salt in the presence of a base catalyzes the reaction of $\alpha,\beta$-unsaturated ketones, esters, and nitriles with aliphatic, aromatic, and heterocyclic aldehydes (Figure 8.4a). The now-named "Stetter reaction" implies Umpolung of the aldehyde into the corresponding Breslow intermediate that undergoes 1,4-addition (instead of a 1,2-addition as for the benzoin condensation) to Michael acceptors [647]. In 1996, Enders and coworkers reported the first asymmetric intramolecular Stetter reaction. With their pre-catalyst **121**, they obtained modest yields (22-73%) and *ee*'s (41-74%) [648,649]. In 2002, Rovis and coworkers reported a more efficient version (reaction (8.4), Figure 8.4b) [650]. Several alternative pre-catalysts have been proposed for this reaction, as shown with reaction (8.5) (Figure 8.4c) [651].

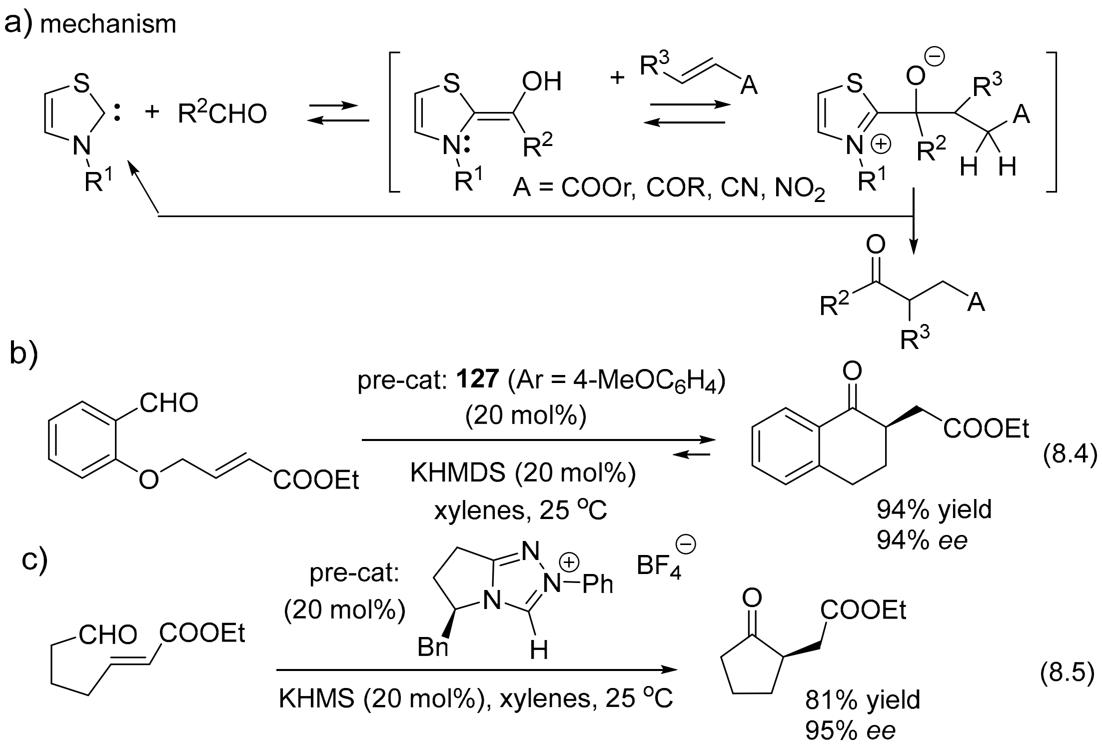


**Figure 8.4.** a) Mechanism of the Stetter reaction; b,c) Examples of intramolecular asymmetric Stetter reactions by Rovis (2002; earlier examples by Enders, 1996).

Before 1999, Enders and coworkers found two examples of catalytic asymmetric intermolecular Stetter reaction utilizing a chiral thiazolium pre-catalyst. Their best overall yields (4%) and *ee* (39%) were deceiving. [652,653]. In 2005, by modifying thiazolylalanine, Miller and coworkers obtained pre-catalysts for the asymmetric intramolecular Stetter reaction (up to 81% *ee*) [654]. In 2008, the Enders group reported better efficiencies for asymmetric intermolecular Stetter reaction between aryl aldehydes and chalcones applying a triazolium pre-catalyst [649,655]. The same year, Rovis and coworkers reported on the combination of glyoxamides with alkylidene malonates to afford Stetter products in high yields and high *ee*, also by applying triazolium pre-catalysts [656]. Further NHC pre-catalysts that permit the efficient asymmetric intermolecular Stetter reaction of nitroalkenes and aldehydes were prepared [657]. In 2011, the same group reported catalytic asymmetric intermolecular Stetter reaction between enals and nitroalkenes [658,659].

### *8.4. NHC-Catalyzed Asymmetric Aza-Stetter Reactions*

In 2019, Lupton and coworkers reported a catalytic asymmetric intermolecular imino-Stetter or aza-Stetter reaction (8.5) that condenses aldimines and 3-methylenechroman-2-ones to afford enantioenriched γ-iminolactones (Figure 8.5) [660]. The process involves the formation of an aza-Beslow intermediate with the protected imine that adds then to Michael acceptors [661].

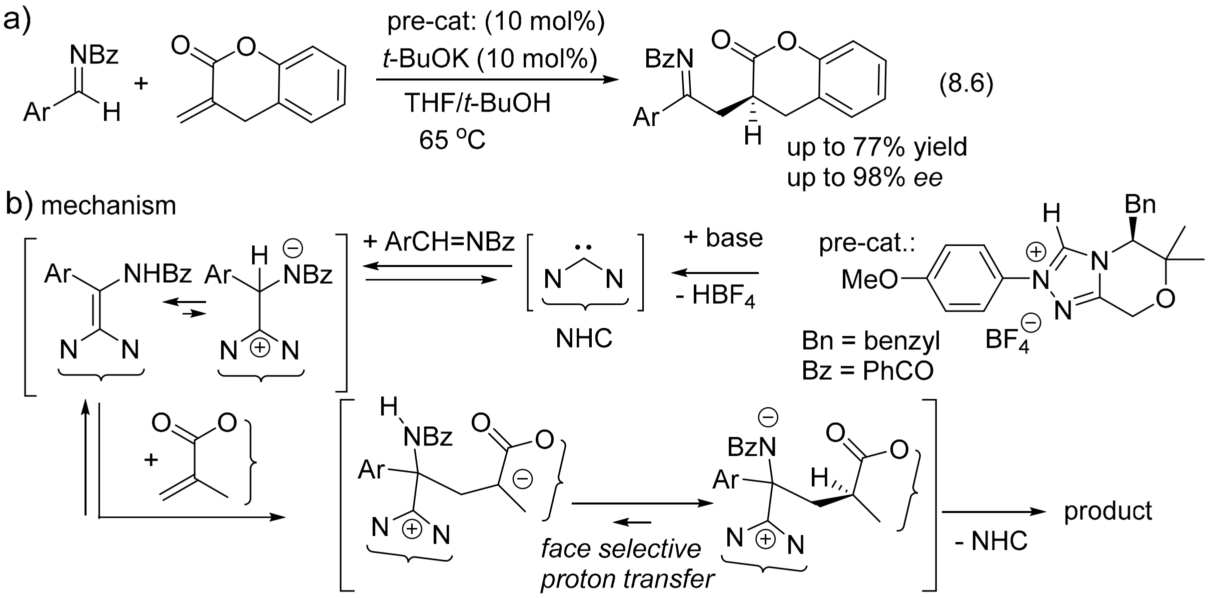


**Figure 8.5.** a) Asymmetric synthesis of γ-iminolactones through NHC-catalyzed imino-Stetter reaction (Lupton, 2019); b) Possible mechanism.

### *8.5. NHC-Catalyzed Asymmetric Cycloadditions*

In 2006, Bode and coworkers reported the first NCH-catalyzed asymmetric aza- and oxo-Diels-Alder reactions (8.7). They applied their pre-catalyst **129**. In the case of azadiene-Diels–Alder reaction (Figure 8.6a), the NHC catalyst adds to β-substituted α,β-unsaturated aldehydes and forms the corresponding alkenyl Breslow intermediates. The latter undergo tautomerization into enolates, the dienophiles that react with alkenyl imines (the aza-dienes) in an *endo* mode of addition. After elimination of NHC (recovery of the catalyst), the cycloadducts are isolated (Figure 8.6b) [662].

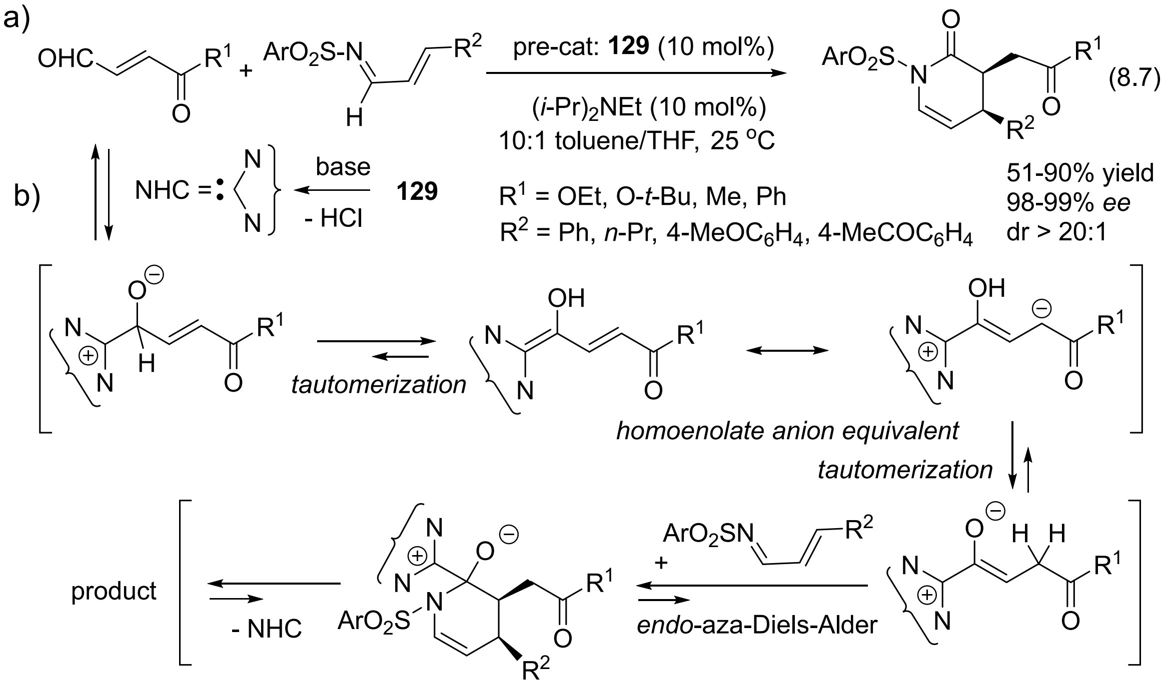


**Figure 8.6.** a) Asymmetric aza-Diels Alder reaction catalyzed by NHC (Bode, 2006); b) Possible mechanism.

The oxa-diene-Diels–Alder reaction reported the same year by the same group occurred in a similar way. In this case, α-chloro-aldehydes and β-substituted α,β-unsaturated ketones or unsaturated α-ketoesters were used as substrates [663]. In 2011, Chi and coworkers reported similar

NHC-catalyzed hetero-Diels-Alder reactions between chalcones (oxa-dienes) and enals (converted into enolate intermediates as dienophiles) [664]. Highly enantioselective formal hetero-Diels-Alder reactions between chalcones and formylcyclopropanes have also been reported by the same group [665].

The first NHC-catalyzed Staudinger cycloaddition (8.8) was presented in 2008 by Ye and coworkers (pre-cat: **141,** Figure 8.7a) [666]. Ketenes react with NHCs giving enolates, nucleophiles that can add to imines forming zwitterions. The latter cyclize into β-lactams. This is a NHC-catalyzed Staudinger reaction, a formal (2+2)-cycloaddition (Figure 8.7b) [667].

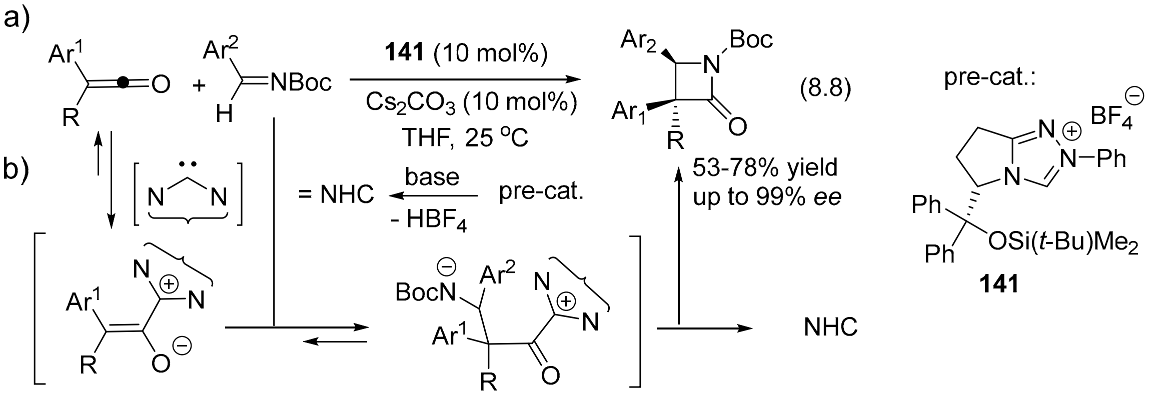


**Figure 8.7.** a) Asymmetric NHC-catalyzed Staudinger cycloaddition (Ye, 2008); b) Possible mechanism.

The same group, the same year, reported a NHC-catalyzed asymmetric (2+2) cycloaddition of alkyl (aryl) ketenes with 2-oxoaldehydes to afford β-lactones (up to 99% *ee*) [668]. In 2009, this group reported a diastereo- and enantioselective synthesis of β-trifluoromethyl-β-lactones bearing two contiguous stereocenters. Chiral NHC-catalyzed formal (2+2)-cycloaddition of alkyl(aryl)ketenes and trifluoromethyl ketones was realized [669].

In 2012, the group of Bode presented highly enantio- and diastereoselective annulations of α- and β,β′-substituted enals with cyclic sulfonylimines as nucleophiles catalyzed by **129**. Reaction (8.9) is an example. The NHC derived from the HCl elimination of **129**. It reacts with the enal forming the corresponding Breslow intermediate that is then oxidized into an acyl azolium chloride. The latter electrophile reacts with the enamine tautomer of the sulfonylimine in a intermolecular N-acylation reaction. Follows a fast oxy-accelerated aza-Cope rearrangement and a final intramolecular N-acylation (Figure 8.8) [670].

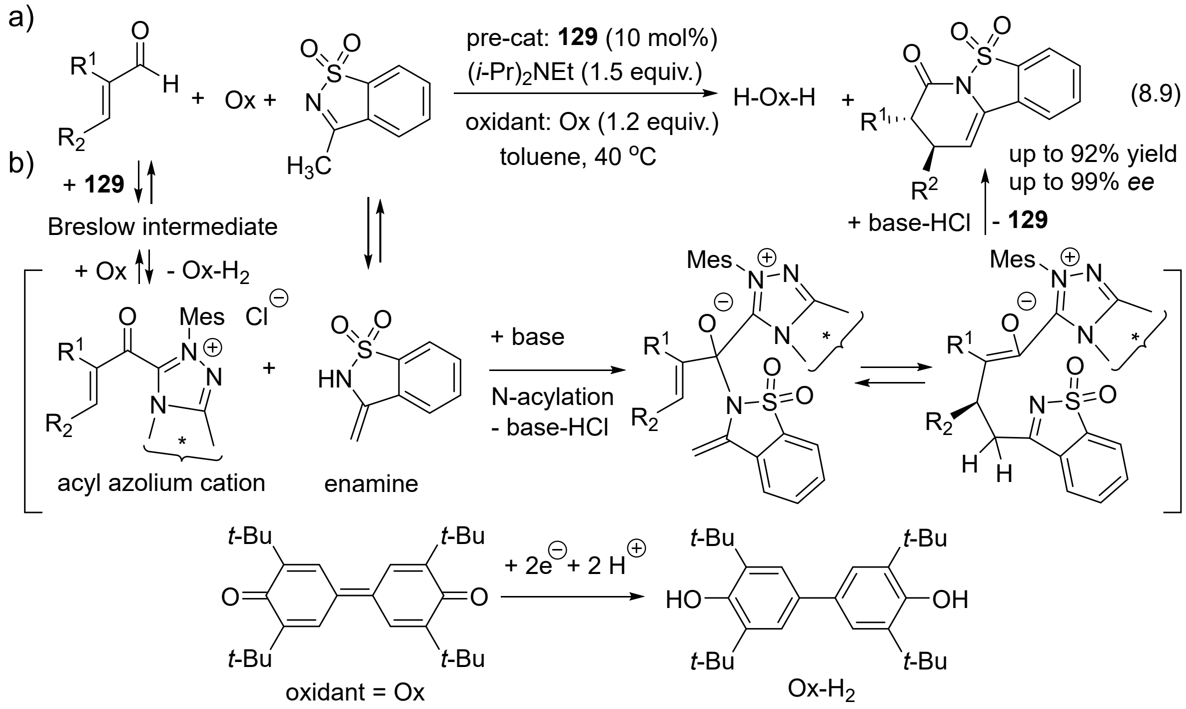


**Figure 8.8.** a) Example of enantioselective oxidative annulation of conjugated enals and a sulfonylimine (Bode, 2012); b) Possible reaction mechanism.

### *8.6. NHC Catalyzed Asymmetric (3,3)-Sigmatropic Rearrangements*

In 2007, Bode and coworkers realized a NHC-catalyzed enantioselective cyclopentene synthesis (reaction (8.10), Figure 8.9a) by condensing cinnamaldehydes and analogues ((*E*)-β-substituted enals) with (*E*)-3-oxo-alk-2-ene-carboxylic esters (chalcones and analogues). As already mentioned, the NHC form first homoenolate equivalents with $\alpha$,β-unsaturated aldehydes (alkenyl-Breslow intermediates). The latter add to the ketone moiety of 3-oxo-alk-2-ene-carboxylic esters (crossed benzoin condensations) forming adducts that are anionic 3,4-dihydroxyhexa-1,5-diene entities ready for oxy-Cope rearrangements furnishing ketones adjacent enolate moieties [671]. Intramolecular aldol reactions, and decarboxylation, provide the final cyclopentenes (Figure 8.9b).

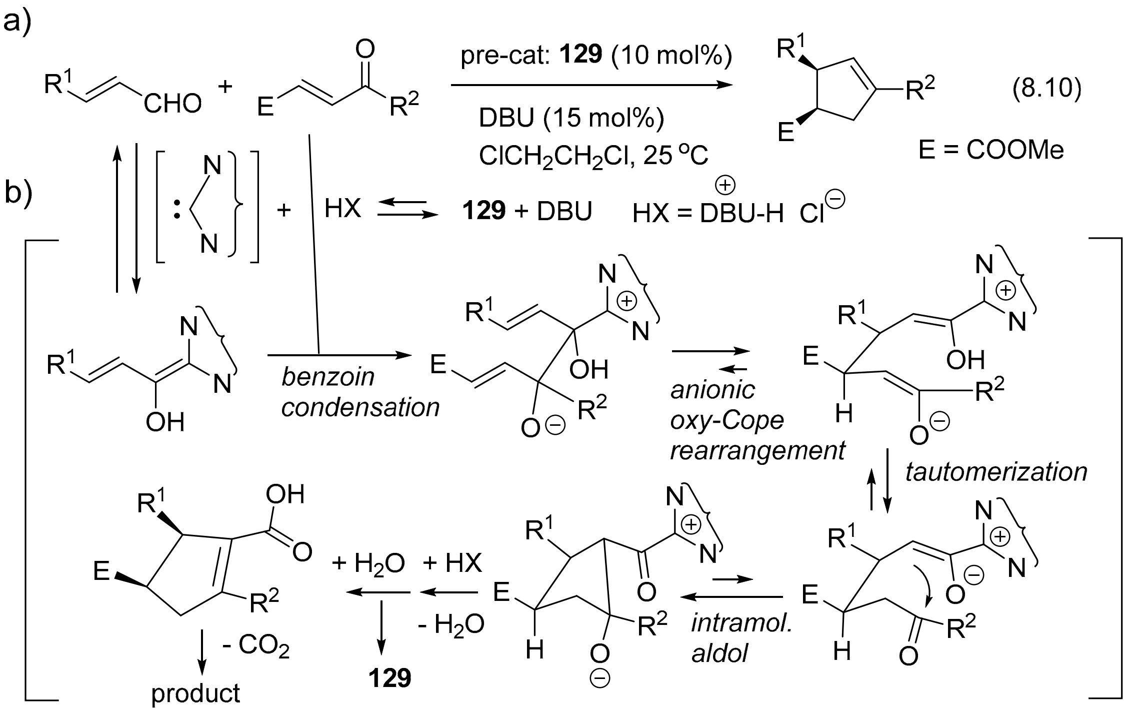


**Figure 8.9.** a) NHC-catalyzed oxy-Cope rearrangement, asymmetric synthesis of 1,3,4-trisubstituted cyclopentenes (Bode, 2007); b) Possible mechanism.

Claisen rearrangements ($R^1CH=CH(A)-CH(B)-O-C(X)=CHR^2 \rightarrow (B)CH=C(A)-CH(R^1)-CH(R^2)-C(=O)-X$) and their variations (nature of substituents A, B, X ) are powerful tools for the stereoselective construction of C-C bonds. Asymmetric versions have been described that use chiral Lewis acids [672–674] and Jacobsen's ureas [675]. In 2010, Bode and coworkers disclosed the enantioselective Coates-Claisen rearrangement (8.11) catalyzed by NHCs [676]. With conjugated ynals, NHCs equilibrate with $\alpha$,β-unsaturated acyl azolium intermediates that react with enols (Figure 8.10), 2-oxopropanoic esters, phenols to produce dihydropyranones [677]. In 2011, the same group reported similar enantioselective synthesis of dihydropyridinones *via* NHC-catalyzed aza-Claisen reactions [678]. Further high yielding and highly enantioselective NHC-catalyzed Coates-Claisen reactions were then reported by the groups of Bode [679] and You [680].

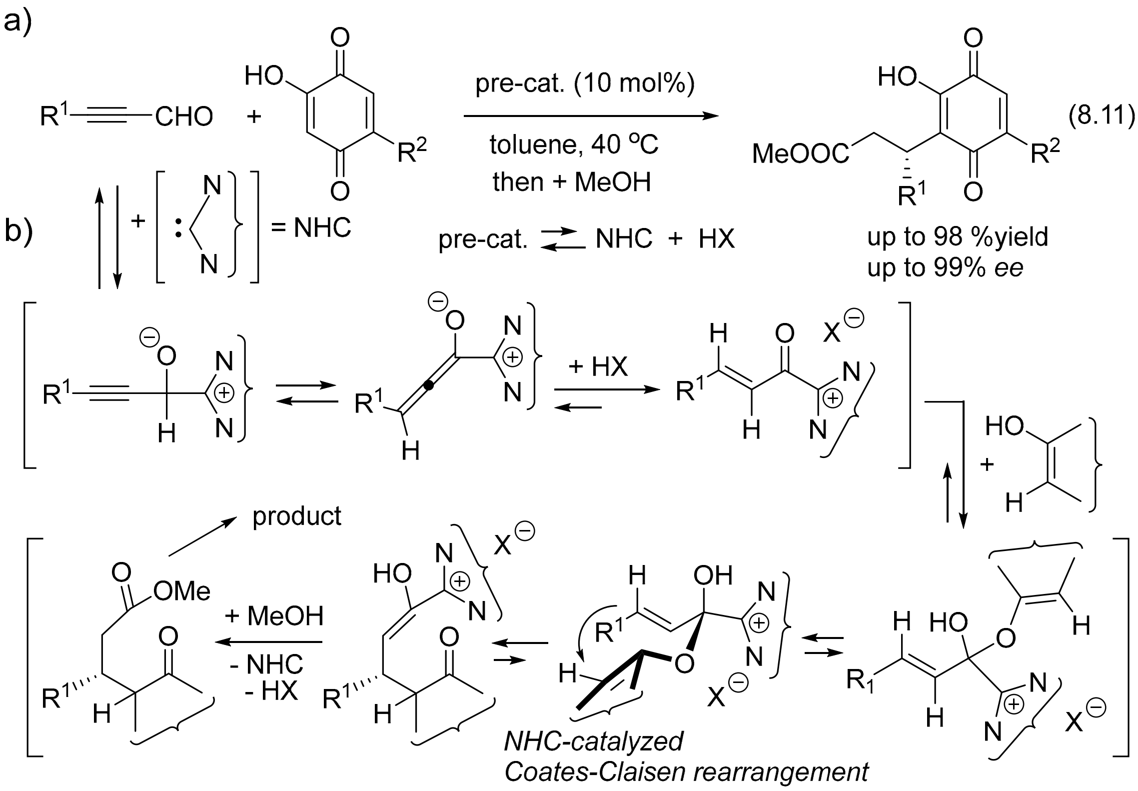


**Figure 8.10.** a) Enantioselective synthesis of dihydropyranones (Bode, 2010); b) Possible mechanism.

### *8.7. Umpolung of Michael Acceptors by NHCs: Conversion of Enones into Homoenolates*

In 2006, Scheidt and coworkers reported the enantioselective of $\alpha,\alpha$-disubstituted cyclopentenes by NHC-catalysed desymmetrization of 2-(4-oxobut-2-en-1-yl)-1,3-diketones. In this work, 1,2-addition of an NHC to the enal moiety generates an alkenyl-Breslow intermediate, which, after protonation, undergoes an intramolecular aldol reaction. Then an intramolecular acylation produces a β-lactone that is decarboxylated into cyclopentenes (up to 94% *ee*) [681]. The Umpolung of Michael by 1,4-addition of NHC acceptors [682] is an unusual activation mode, compared with the more commonly observed 1,2-addition chemistry (formation of alkenyl-Breslow intermediates) [683]. The first example of Umpolung of Michael acceptors by 1,4-addition of an NHC was reported by Fu and co-workers in 2006 for the intramolecular alkylation of $\alpha,\beta$-unsaturated esters to afford cyclopentenes [684].

In 2016, Lupton and coworkers disclosed enantioselective reactions (8.12) based on Michael acceptor Umpolung by NHCs. In the example of Figure 8.11a, a bis-Michael acceptor substrate is cyclo-isomerised enantioselectively to (*S*)-2-aryl propionate esters. The nucleophilic carbene undergoes a 1,4-addition with the conjugated enone, equilibrating with a zwitterion that is composed of an enolate moiety. The latter isomerises into the corresponding homoenolate that is stabilised by the vicinal triazolium cation. The homoenolate adds intramolecularly to the $\alpha,\beta$-unsaturated ester group forming another enolate intermediate that is protonated with face selectivity, the crucial step responsible for asymmetry (Figure 8.11b) [685].

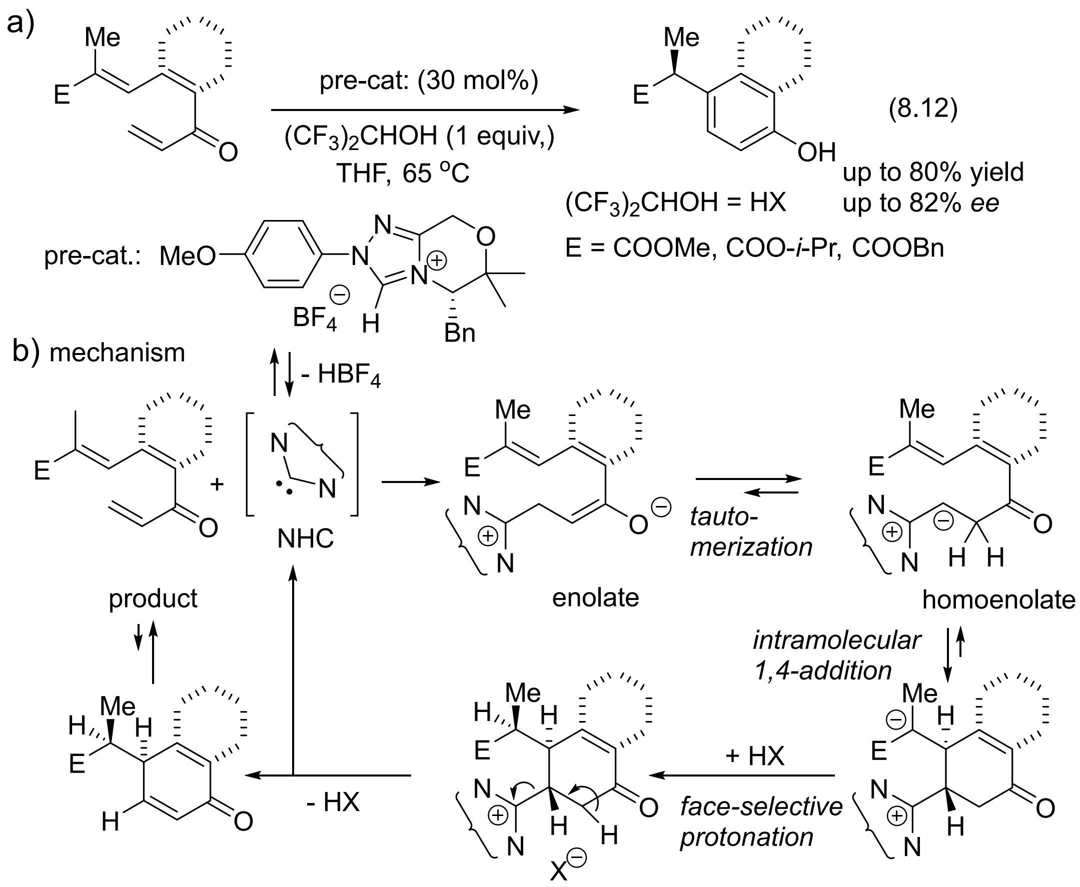


**Figure 8.11.** a) Michael Umpolung forms homoenolates that add intramolecularly to a second Michael acceptor (Lupton, 2016). Asymmetric protonation of the resulting enolate follows. b) Possible mechanism.

Applying the NHC-catalyzed Umpolung to 6-methylidene-(*E*)-hept-2-enedioic esters and 4,4-disubstituted derivatives, Lupton and coworkers developed an enantioselective cyclopentene synthesis [686] and (5+1) annulation reactions [687]. In 2019, Tobisu and co-workers demonstrated the polarity inversion of aryl acrylamides with NHCs [688]. Later, the same group reported a Truce–Smiles rearrangement reaction using the same strategy. [689]. A cross-coupling reaction involving a deoxy-Breslow intermediate was reported in 2022 by the Biju group [690].

### *8.8. Radical Reactions Promoted by NHC Catalysts*

Breslow intermediates are oxidized into acylazolium salts that react with all kinds of nucleophiles, including alcohols, to generate the corresponding carboxylic esters (NHC-catalyzed oxidation of aldehydes) [691]. As seen in the preceding sections, NHCs undergo preferentially 1,2-additions with $\alpha$,β-unsaturated aldehydes, equilibrating with alkenyl-Breslow intermediates that can undergo all kinds of intramolecular or intermolecular reactions. Two-electron oxidation of alkenyl-Breslow intermediates generates $\alpha$,β-unsaturated acylazolium salts that are reactive Michael acceptors useful for many reactions [692–695], including enantioselective ones when applying chiral NHCs [696,697].

Upon deprotonation, Beslow intermediates (enols) equilibrate with Breslow enolates that are oxidised easily (electron-rich enolates). In the presence of an oxidant capable to abstract one electron (single electron transfer: SET) relatively stable radical-cations form that are persistent [698,699]; they can be quenched by other radicals in bimolecular processes [626]. This is also the case for alkenyl-Breslow intermediates. In 2014, Rovis and coworkers used that property to develop an asymmetric oxidation of enals into chiral β-hydroxy carboxylic esters applying pre-catalyst **142** (reaction (8.13), Figure 8.12) [700].

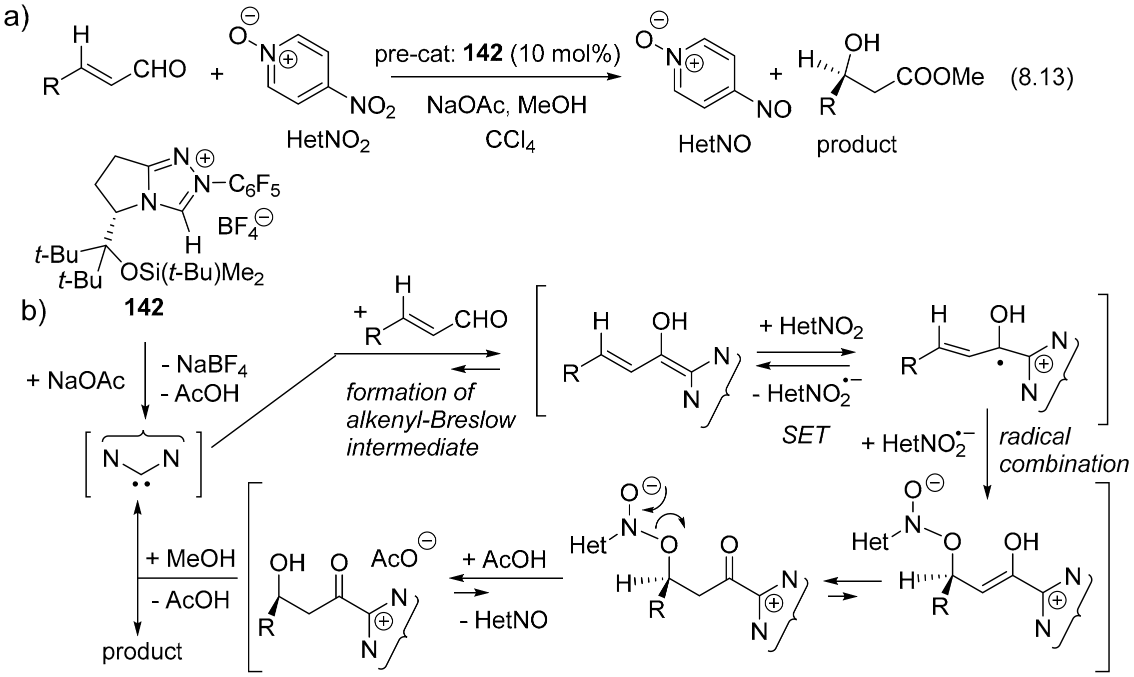


**Figure 8.12.** a) Asymmetric oxidation of enals into β-hydroxyesters (Rovis, 2014); b) Possible mechanism.

In 2022, Hong and coworkers described an NHC-catalyzed radical reaction that converts enals to chiral β-pyridyl esters with excellent pyridyl C(4)-regioselectivity and *ee* (reaction (8.14), Figure 8.13). A pyridinium salt forms a complex with the Breslow enolate resulting from the addition of the NHC-catalyst to the conjugated enal. Under blue light irradiation, a single electron transfer (SET) generates two radicals that combine to form a C-C bond between C(4) of the pyridine moiety and C(β) of the enal [701].

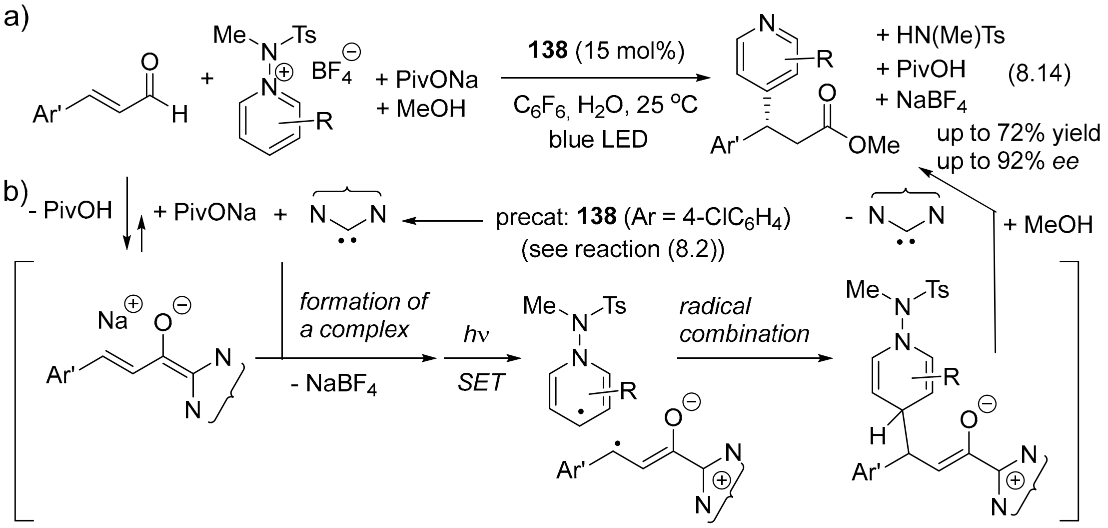


**Figure 8.13.** a) Photocatalyzed enantioselective functionalization at the C(4) position of pyridinium salts through NHC catalysis (Hong, 2022); b) Possible reaction mechanism.

Catalytic enantioselective synthesis of α-aryl ketones includes α-arylation of ketones/enones catalyzed by transition metals, benzylic acylation, and hydroacylation of alkenes *via* either organocatalysis or reductive copper catalysis [702]. Recently, the group of Ye presented (Figure 8.14) a photocatalytic process that does the direct enantioselective oxidative acylation of benzylic C-H's (e.g. reaction (8.15)) applying pre-catalyst **143**. The photocatalyst is 9,10-dicyanoanghracene (DCA).

Under light irradiation, the electronically excited state DCA* is formed. It abstracts an electron from the benzylic substrate ($Ar^1CH_2CH_3$) forming an radical-cation ($Ar^1Et^{(+\bullet)}$) and radical-anion $DCA^{(\bullet-)}$. The benzylic radical cation reacts with face selectivity with the chiral radical-anion generated by electron transfer from $DCA^{(\bullet-)}$ to the acyl azonium salt resulting from the condensation of the chiral NHC catalyst and the acyl fluoride reagent ($Ar^2COF$), and reduction by radical-anion $DCA^{(\bullet-)}$ [702].

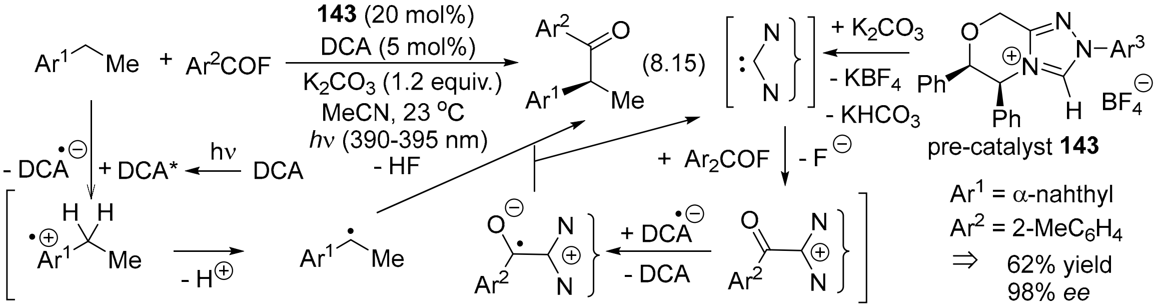


**Figure 8.14.** Cooperative photo-redox and N-heterocyclic carbene catalysis. Enantioselective direct oxidative acylation of benzylic C-H's (Ye, 2025).

### *8.9. NHC-Catalyzed Enantioselective Synthesis of Atropisomers*

Axially chiral molecules are useful ligands in transition metal-catalyzed reactions and powerful organo-catalysts [703,704]. They are present also in Nature [705] and are often bioactive [706]. In 2018, Wang and coworkers reported the first NHC-catalyzed atroposelective (3+3) annulation (8.16) between ynals and cyclic 1,3-diketones that applies **144** as pre-catalyst to provide chiral $\alpha$-pyrone-aryls (Figure 8.15) [707]. Further asymmetric syntheses of atropisomers catalyzed by NHCs have been developped (for a review, see [626]).

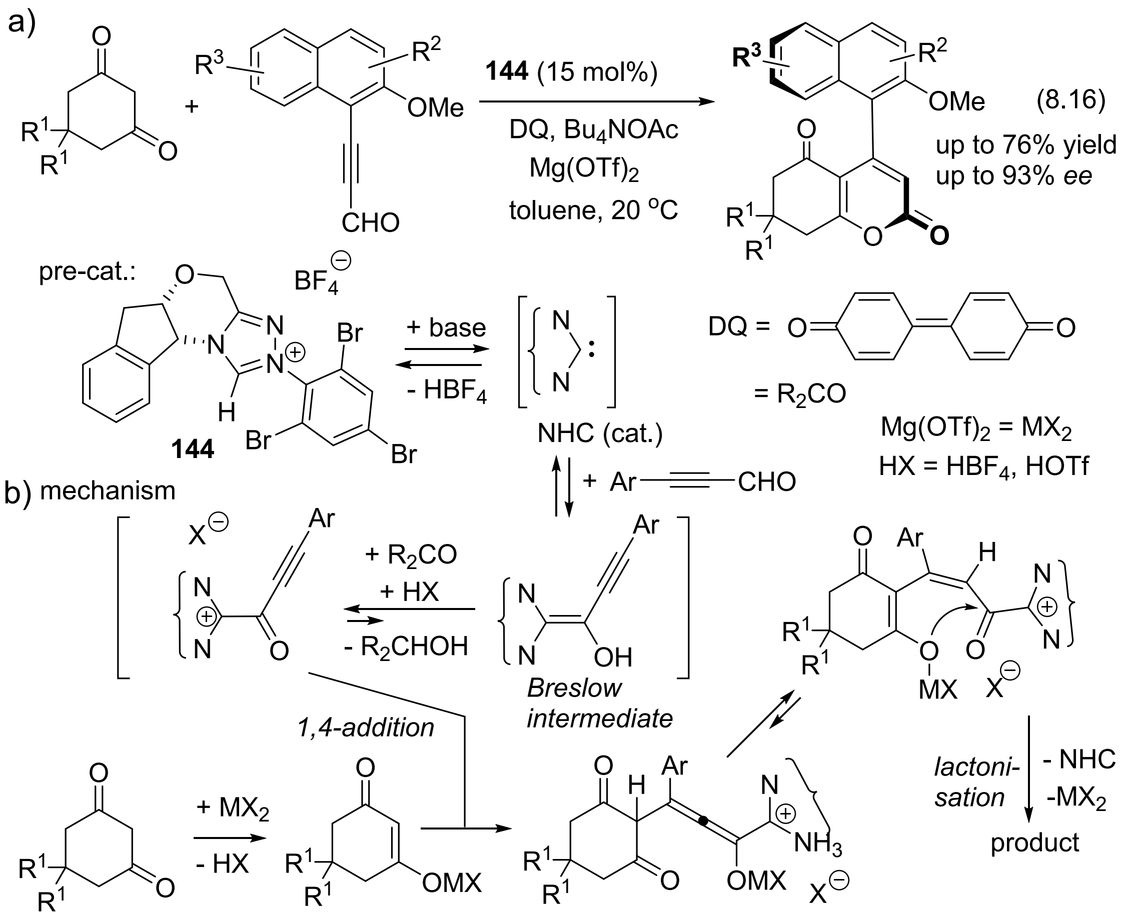


**Figure 8.15.** Enantioselective (3+3)-annulation (Wang, 2918); b) Possible mechanism.

In 2019, Zhu and coworkers reported a formal (4+2)-cyclization of conjugated dienals and α-arylketones catalyzed by chiral NHCs. The enantiomerically enriched products obtained undergo oxidation into atropoisomeric bis-aryls with 90-98% *ee* [708]. In 2022, Chi and coworkers reported the enantioselective preparation (up to 98% *ee*) of axially chiral styrenes bearing a chiral axis between a sterically non-congested acyclic alkene and an aryl ring. The reaction involves ynals, sulfinic acids, and phenols as the substrates with a chiral NHC as the catalyst [709]. Recently, the Biju group have reported NHC-catalyzed amidification leading to N-N axially chiral 3-amino-quinazolinoes (up to 99% yield, up to 98% *ee*) [710].

## 9. Enantioselective Organocatalysis by Hydrogen Bonding

The mechanism of action of various enzymes relies upon hydrogen bonding (H-bond) for the binding of substrates, reactants, and for the binding of transition structures (electrophile activation) [70]. In 1942, Wassermann showed that weak protic acids (carboxylic acids, phenols) accelerate the cycloaddition of cyclopentadiene to benzoquinone (Diels Alder reaction with normal electron-demand, electrophilic dienophiles, Chap. 1) [53]. In 1979, Inoue and coworkers found that a compound smaller than an enzyme like cyclo(L-phenylalanine-L-histidine catalyzes the asymmetric addition of HCN to arenecarbaldehydes (Section 4.1). The cyclic dipeptides possess N-H bonds (H-bond donors). In 1981, Wynberg found that cinchona alkaloids that bear a free OH group in proximity to the basic quinuclidine nitrogen moiety, catalyze enantioselective addition reactions to conjugated enones (Section 3.1.2, reaction (3.4)). In 1984, *N*-alkyl cinchona alkaloid derivatives bearing a free OH group showed to be highly efficient enantioselective PTCs for the alkylation and Michael addition of indanone (Section 3.2.1, Figure 3.9, cat. **22**, **23**). L-proline catalyzed aldol reaction involves the intervention of H-bond from the COOH group (Section 3.5.2). In 1985, Hine and coworkers demonstrated that 1,8-biphenylenediol (a biphenol) is a better catalyst than monophenols of similar Brønsted acidity for the reaction of diethylamine with phenyl glycidyl ether that produces $PhOCH_2C(OH)H-CH_2-NEt_2$. This was explained in terms of double electrophilic activation of the oxirane moiety of glycidyl ether by the two O-H bonds provided by 1,8-biphenylenediol [711]. In 1999, Kita and coworkers reported the asymmetric hypervalent-iodine-mediated oxidation of sulfides to sulfoxides ($ArSMe + 0.5\ PhIO_2 \rightarrow ArSOMe + 0.5\ KI$, up to 72% *ee*) catalyzed by *O,O′*-bis(2-methoxybenzoyl) (2*R*,3*R*)-tartaric acid [712]. In 2010, Terada and coworkers found that *O,O′*-diacyl tartaric acid derivatives catalyze the enantioselective Friedel–Crafts reaction of indoles with an a-imino ester (up to 88% *ee* [713]). (+)-Tartaric acid was found to catalyze enantioselective (4+2)-cycloaddition of isochromeneacetals and vinylboronates furnishing dihydronaphthalenes and dihydrobenzofluorene products with up to 97% *ee* employing 10 mol% of (+)-tartaric acid as the catalyst, in combination with 5 mol% of $Ho(OTf)_3$ [714]. Chiral diols such as TADDOLs ($C_2$-symmetrical tetraaryl-1,3- dioxolane-4,5-dimethanols derived from enantiomerically pure L-(+)-(2*R*,2*R*)-tartaric acids (natural) and its enantiomer) and BINOLs ($C_2$-symmetrical 1,1′-bi-2-naphthol and substituted derivatives, Figure 9.1) [715,716] were available in the 1980’s already. They are H-bond donors. Optically pure 1,1′-bi-2-naphthol (BINOL) (introduced by Noyori in 1980 [717]) and its derivatives (BINOLs) are the most important sources of chirality for organic synthesis and material sciences (Figure 9.1) [718]. In the beginning, they served as diolates of metallic reagents, or as ligands in organometallic catalysts. Their direct use as diols in asymmetric organocatalysis started after 2000. Because of their greater stability and larger variability of their substitution, they have taken a higher importance relative to simpler tartaric acid derivatives. In general, BINOLs and vaulted analogues VANOLs and TADOLs (Figure 9.1) have served as the most efficient catalysts [719].

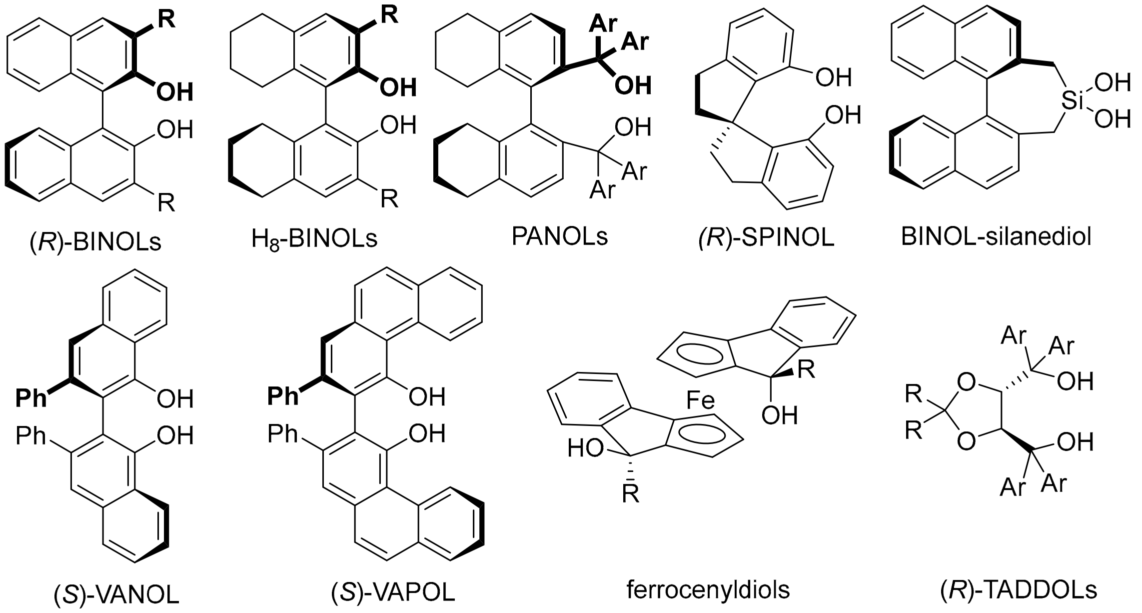


**Figure 9.1.** Typical $C_2$-symmetrical chiral diols. Both their enantiomeric forms are available.

In 1995, Curran and coworkers showed that ureas accelerate Claisen rearrangements. These additives modified the stereoselectiviy of the reactions [720]. In 1998, the group of Jacobsen reported asymmetric Strecker reactions catalyzed by short peptide analogues containing a urea moiety or a thiourea unit (see Section 4.1). This opened a new era to asymmetric organocatalysis with chiral ureas, thioureas and, then with squaramides [69,212,721]. These catalysts are double H-bond donors that activate electrophilic substrates toward nucleophilic reactions (e.g., Figure 9.2b). Alternatively, the catalyst binds strongly to anions and form diastereomeric ion-pair intermediates as suggested by Schreiner and coworkers in 2006 (e.g., Figure 9.2c) [722]. This is asymmetric ion-pairing catalysis [723].

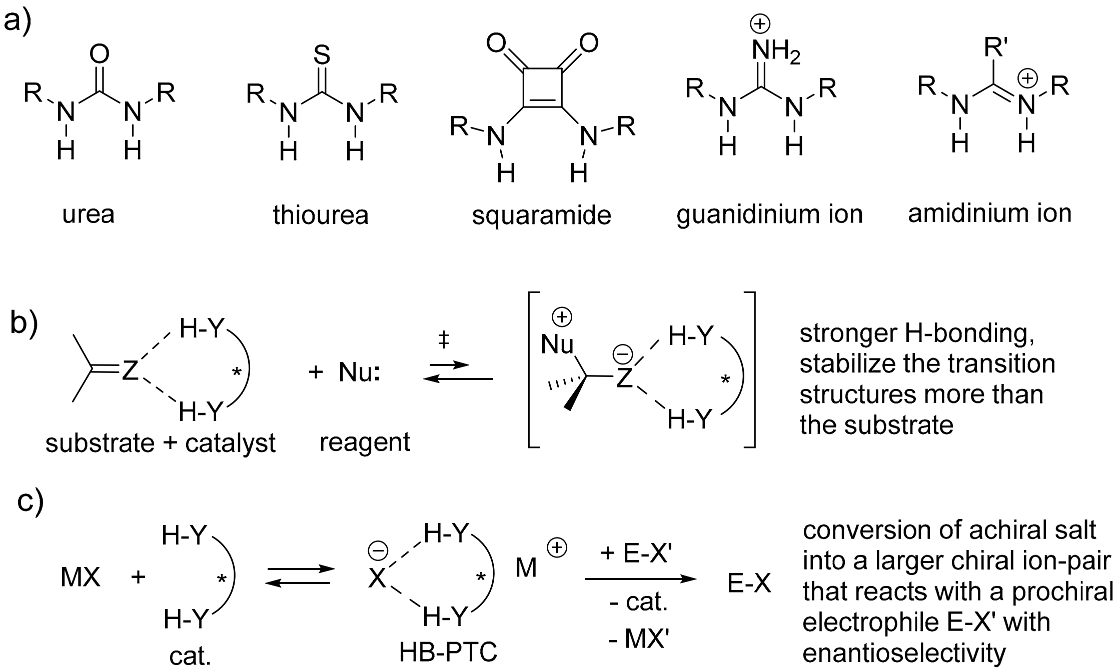


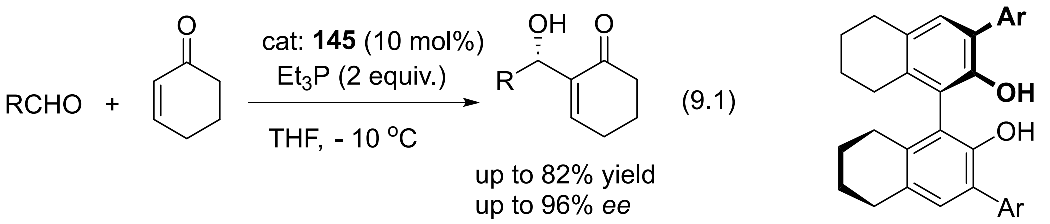
**Figure 9.2.** a) Common chiral donors of two N-H bonds; b) Double activation of nucleophilic additions to carbonyl compounds or imines. The zwitterionic intermediate shown resembles the transition structures of the addition (Bell-Evans-Polanyi principle); c) formation of diastereoisomeric H-bonded complexes with anionic nucleophiles. If MX is a salt insoluble in the organic solvent, the role of the catalyst is to extract the anion $X^{(-)}$ from the salt by H-binding, generating a much larger ion-pair that is soluble in the organic solvent. One speaks of H-binding phase transfer catalysis or HB-PTC.

As already mentioned (Chap. 2) in their ground state and in solution, uncharged (neutral) substrates, reactants, catalysts and solvent molecules are associated through electrostatic forces that include dipole/dipole and dipole/induced dipole interactions. All compounds with A-H bonds possess local dipole moments associated with each A-H moiety. When A is more electronegative than H, the dipole places a partial negative charge on A and a partial positive charge on H. Therefore, a molecule with one, two, three, etc. A-H moieties tends to stick to the negatively charged extremities of another molecule B with its H-atom(s); it forms a complex of type A-H····B. This makes the structural and dynamic properties of living (e.g., enzymes, proteins, glycoproteins, DNA, etc.) and non-living matter (e.g., water, ice, methane/water clathrates, cellulose, etc.). If the dipole/dipole interaction between A-H and B is strong the H-bond between H and B is shorten and partial covalent bonding occurs. At the limit, bonding in complex A-H····B is a covalent three-center four-electron bond [724]. With a weakly acidic catalyst, Y-H, that possesses a single A-H moiety, and a substrate R-X**:** with a partial negative charge on X, an equilibrium of type R-X**:** + Y-H ⇄ R-X···H-Y is realized for which H-bridging is established between X and H without proton transfer. The relative amount of the complex at equilibrium is low if the X···H bond is weak. For an equilibrium constant close to unity ($\Delta G^{T} = 0$) the heat of reaction ($\Delta H^{T}$) must be about -10 kcal mol$^{-1}$ to compensate for the cost of entropy ($-T\Delta S^{T}$) of this equilibrium (condensation) at 25 °C. This is the case only if the solvent does not form competitive H-bonds with R-X**:** and Y-H. If Y-H is a strong Brønsted acid, it may protonate R-X**:** according to equilibrium R-X**:** + Y-H ⇄ R-X$^{(+)}$-H + Y$^{(-)}$ in which a cation and an anion are formed. They form a tight ion-pair implying H-bridging between cation and anion (R-X$^{(+)}$-H····Y$^{(-)}$). If H-Y is chiral, quenching of this ion-pair by a nucleophilic reagent can be enantioselective. One speaks of asymmetric ion-pair catalysis [723] and anion recognition [725–727]. A tight ion-pair may equilibrate with a solvent separated ion-pair or free ion pair for which hydrogen bridging is not possible between cation and anion, but is possible for both of them with the solvent. The relative concentrations of these species depend on solvent and temperature. There is a spectrum of intermediate species between the two above limiting situations. For instance, in their ground state, substrates and reactants make H-bridged complexes with the catalyst Y-H without proton transfer, and only in the transition state, a proton transfers fully. The catalytic effect of Y-H results from the fact that it stabilizes transition structures more than substrates and reactants. A good catalyst must not interact strongly with the final product, otherwise the latter inhibits the catalytic process. What we discussed above for R-X**:** substrates also apply to double-bonded compounds bearing carbonyl (C=O**:**) or imine (C=(R)N**:**) functions. In these cases, the catalytic effect (rate increase and enantioselectivity) arises from extra stabilization of the tetrahedral intermediates resulting from the nucleophilic addition to the carbonyl or imine moiety (Figure 9.2b): The strength of the hydrogen bonding offered by the catalyst increases from substrate + reactant to the transition structures of their reaction. Indeed, the dipole moment in the latter is generally increased. H-Bond donors form relatively stable complexes with anions (e.g., $X^{(-)}$ of Figure 9.2c). Thioureas are often stronger H-bond donors than ureas and diols. Because of the greater electronegativity of the O atom compared with the S atom, one would expect the opposite. The greater size and polarizability of the S atom compared with the O atom explain the observations [728,729]. Squaramides form stronger complexes with halide anions than thioureas. Guanidinium [324] and amidinium ions are stronger H-bond donors because of their higher acidity. Being positively charged, they transfer a proton to a substrate and transition structures more readily.

### *9.1. Applications of Chiral Diols as Organocatalysts*

(*S*)-BINOL forms readily by asymmetric oxidative coupling of 2-naphthol with $CuCl_2$ in the presence of (*S*)-(+)-amphetamine as ligand [730]. When combined with metallic species, BINOLs form diolates that are extremely potent chiral Lewis acid catalysts. One application reported in 2002 by Ding and coworkers is the enantioselective hetero-Diels-Alder reaction of Danishefsky's diene with aldehydes at room temperature, without solvent, in the presence of only 0.1-0.005 mol% catalyst made by mixing Ti(O-*i*-Pr)$_4$ with one or two different BINOLs. The reaction affords dihydropyrones derivatives in high yield (up to 99%) and *ee* (up to 99.8%) [731].

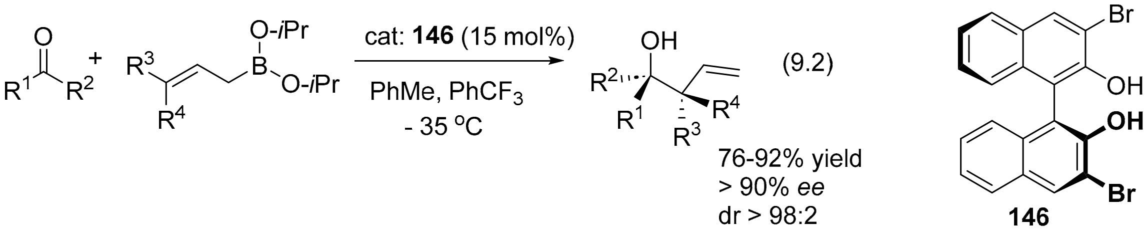
In 2003, McDougal and Schaus reported the first example of a highly enantioselective asymmetric Morita-Baylis-Hillman (MBH) reaction of cyclohexenone with aldehydes using a chiral Brønsted acid **145** (a H8-BINOL) as the catalyst, and triethylphosphine as the nucleophilic promoter (reactions (9.1)) [732].



(9.1)

Ar = 3,5-Me$_2$C$_6$H$_3$ **145**

In 2006, Schaus and coworkers reported the highly diastereo- and enantioselective allylboration of ketones (reactions (9.2)) catalyzed by (*S*)-3,3'-dibromo-BINOL (**146**) [733].

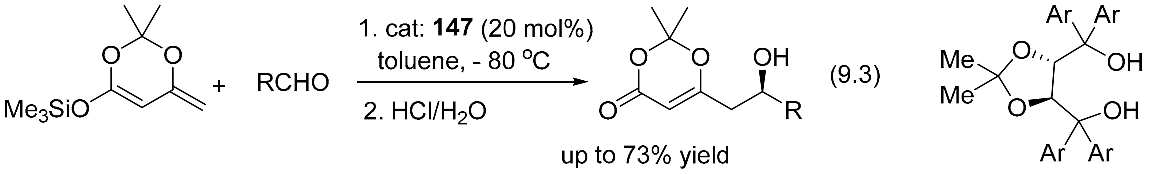


(9.2)

**146**

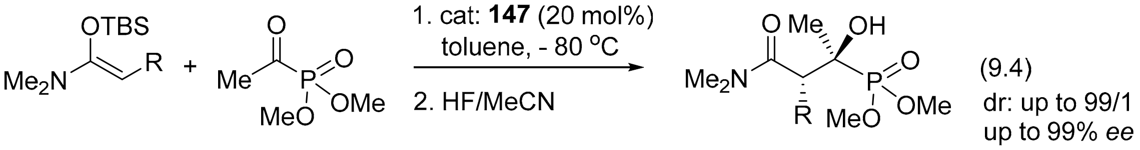
In 2009, the same group found BINOL derivatives that catalyze the enantioselective additions of boronates to acylimines [734]. In 2015, Schaus and coworkers realized enantioselective multicomponent condensation reactions of phenols, aldehydes, and boronates also catalyzed by chiral biphenols. Initial Friedel-Crafts alkylation of the aldehyde and phenol yields an ortho-quinone methide that undergoes an enantioselective boronate addition [735]. Aldehydes and amines are combined with allylboronates in a one-pot two-step procedure to provide chiral homoallylic amines (Petasis-borono-Mannich allylation). In 2017, Jiang and Schaus reported an asymmetric version of this reaction catalyzed by (R)-3,3′-diphenyl-BINOL [736]. For more cases, see [719]. In 1993, the Wulff group introduced vaulted biaryl ligands VANOL and VAPOL (Figure 9.1) as chiral ligands for a metal-catalyzed asymmetric Diels–Alder reaction [737]. They are inexpensive diols that can be prepared on a large scale [738]. The chiral metallic diolates catalyze the enantioselective amidation of imines, iminoallylation of aldehydes, aza-Darzens reaction, *cis*-aziridination of imines, *trans*-aziridination of imines, Baeyer–Villiger reaction, benzoyloxylation of aryloxindoles, desymmetrization of aziridines, Diels–Alder reactions, hetero-Diels–Alder reactions, hydroarylation of alkenes, hydrogenation of alkenes, imidation of imines, Mannich reactions, multicomponent aziridination of aldehydes, Petasis reaction, propargylation of ketones, reduction of imines, chlorination and Michael reactions of oxindoles, hydroacylation of alkenes, pinacol rearrangement, reduction of aminals and Michael addition of alkynes. Many modified VANOL and VAPOL derivatives are crucial chiral ligands for all kinds of catalysts, including Brønsted acids (Chapter 10) [739].

Ferrocene-based diols (Figure 9.1) catalyze asymmetric hetero-Diels-Alder reactions $CH_2=C(OTMS)-CH=CH-NMe_2$, + RCHO achieving up to 92% *ee* when R =1-naphthyl. [740,741]. In 2004, Ding and coworkers reported the enantioselective hetero-Diels-Alder reaction of Brassard's diene ($Me_3SiO(MeO)C=CH-C(OMe)=CH_2$) with aldehydes catalyzed by **147** and other TADDOL derivatives. They realized a one-step synthesis of (*S*)-(+)-dihydrokawain [742]. In 2005, the Rawal group reported that TADDOL derivatives such as **147** are better asymmetric organocatalysts than BINOLs for the enantioselective Mukaiyama aldol reaction of silyl dienol ethers with a range of aldehydes (e.g., reaction (9.3)) [743].

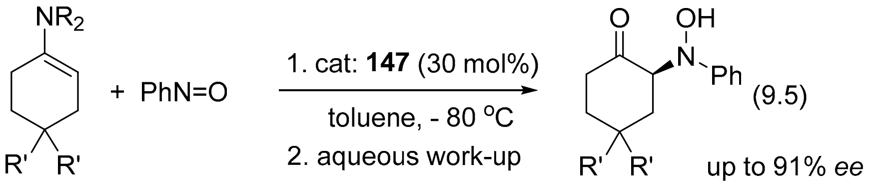


**147** Ar = 1-naphthyl

In 2006, the same group reported the Mukaiyama aldol reactions of *O*-silyl-*N,O*-ketene acetals + RCHO mediated by **147** (up to 96% *ee* for the major *syn* product) or by cyclohexylidene-(1-naphthyl)-TADDOL derivative (up to 98% *ee*) as an organocatalyst [744]. They also found that **147** catalyzes the diastereoselective and enantioselective Mukaiyama reaction (9.4) with acetyl dimethyl phosphonate.



In 2005, Yamamoto and Momiyama reported that carboxylic acids catalyze the reactions of enamines with nitrosobenzene give *O*-nitroso-aldols. In contrast, with **147** as catalyst, *N*-nitroso-aldol were produced (reaction (9.5)) [745].



### 9.2. Silane-1,1-Diols as Chiral Catalysts

In 2006, the group of Kondo reported that silane-1,1-diols recognize anionic species [746]. In 2011, Mattson and coworkers reported on the nitro-group rendered more electrophilic through H-bonding with silane-1,1-diol catalysts [747]. On their side, Franz and coworkers showed that these catalysts are capable to activate electrophiles such as carbonyl compounds [748]. In 2013, the Mattson group exploited silane-1,1-diols such as **148** ((*R*)-3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1′,2′-*e*]silepine-4,4-diol, or BINOL-silanediol) for their ability to bind small anions in asymmetric reactions (9.6) (Figure 9.3) [749]. In 2016, Mattson and Kondo reported similar asymmetric silane-1,1-diol-catalyzed addition of silyl ketene acetals to benzopyrylium triflate intermediates. With the chiral catalyst that binds the triflate anion, diastereomeric ion-pair intermediates form that explain the enantioselectivity [750,751].

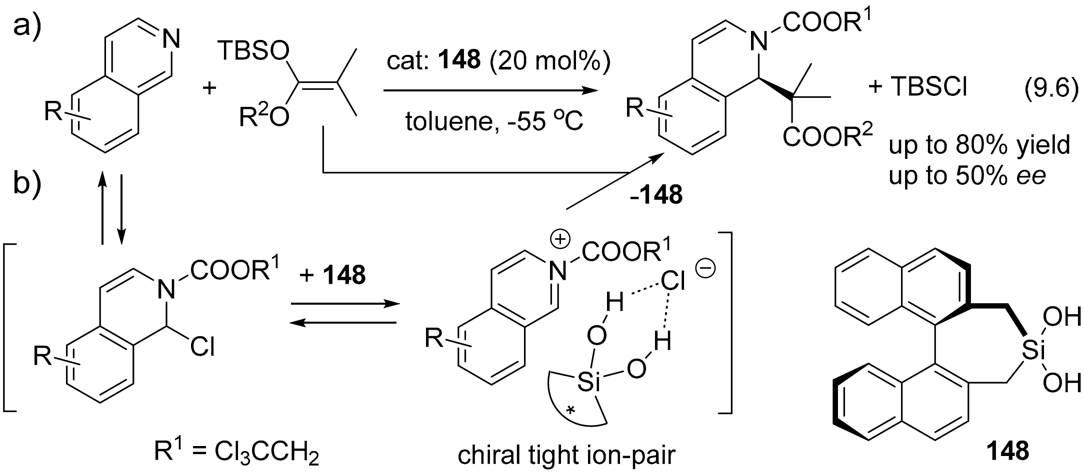
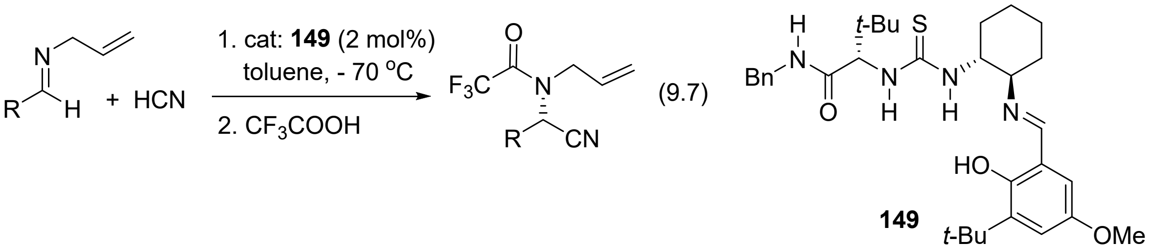


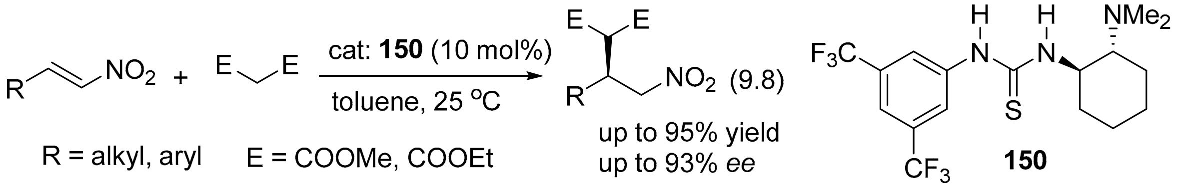
**Figure 9.3.** a) Enantioselective anion-binding catalysis (Mattson, 2013); b) Possible mechanism.

### 9.3. Applications of Chiral Urea and Thiourea Catalysts

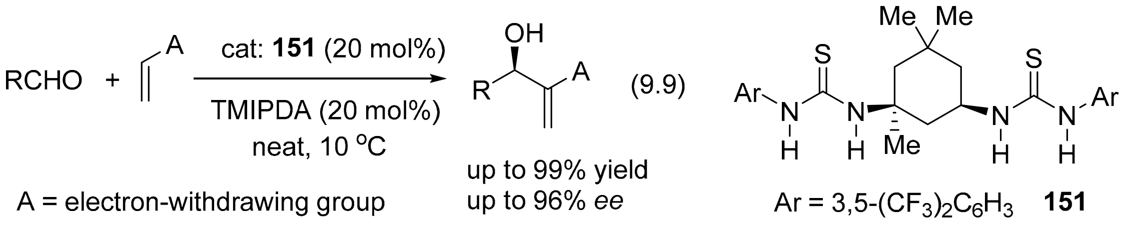
In 1998, Sigman and Jacobsen reported that urea and thiourea derivatives (e.g., **149**) catalyze enantioselective hydrocyanation reactions of imines derived from both aromatic and aliphatic aldehydes (reactions (9.7)) [484].



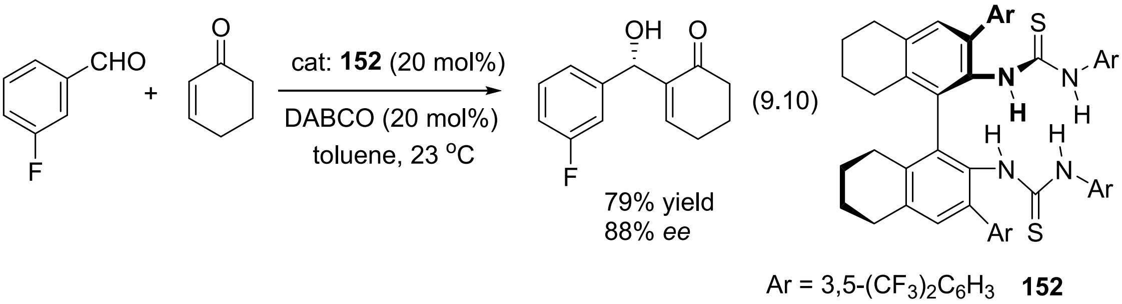
In 2003, Takemoto and coworkers reported a first examples of highly enantioselective 1,4-conjugate addition of malonic esters to nitroalkenes (reactions (9.8)) catalyzed by amino-thiourea derivative **150** [752]. With its amine and thiourea moieties, **150** is an example of bifunctional Brønsted base/H-bonding catalyst (BB catalyst). It catalyzes the enantioselective addition of sulfinates salts to enones [753]. Other reactions apply cinchona-derived thioureas [754,755].



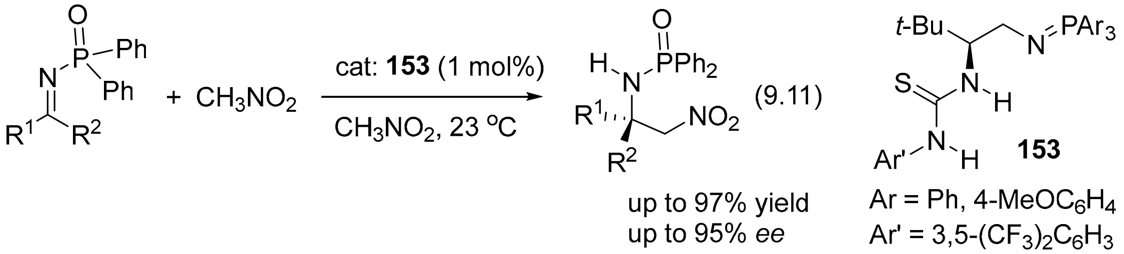
In 2006, Berkessel and coworkers derived the bis(thio)urea catalyst **151** from readiy available isophoronediamine [3-(aminomethyl)-3,5,5-trimethyl-cyclohexylamine, IPDA] produced industrially in a multiton scale. It is also a good catalyst for asymmetric Morita-Baylis-Hillman (MBH) reactions (9.9) together with the base (*N*,*N*,*N*′,*N*′-tetramethylisophoronediamine (TMIPDA) [756].



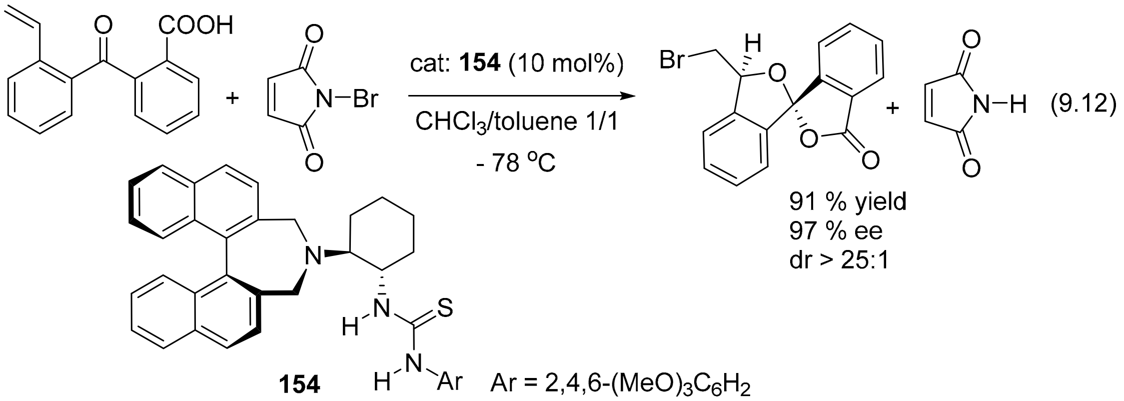
In 2008, Liu and Shi prepared bis(thio)urea organocatalysts from axially chiral (*R*)-(−)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diamine (H8-BINAM). For instance derivative **152** (electrophilic activator) catalyzes the enantioselective MBH reaction of 2-cyclohexen-1-one or 2-cyclopenten-1-one with a wide range of aromatic aldehydes in combination with DABCO (nucleophilic activator). Reaction (9.10) led to the best yields and enantioselectivities [757].



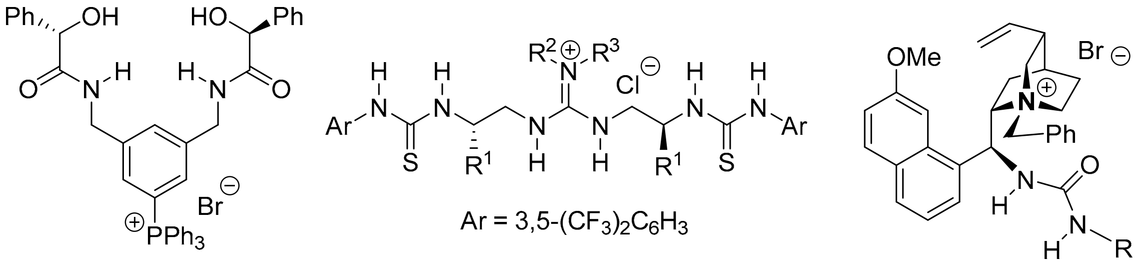
The same year, Wang and coworkers applied a chiral bifunctional multiple hydrogen-bonding-donor amine-thiourea to catalyze a highly *anti*-selective and enantioselective nitro-Mannich reaction ($R^1CH=NBoc + R^2\text{-}CH_2NO_2 \rightarrow R^1\text{-}CH(NHBoc)\text{-}CH(NO_2)\text{-}R^2$) [758]. In 2012 and 2015, Groselj and coworkers prepared several camphor-derived thioureas [759,760]. In 2013, the Dixon group developed bifunctional organocatalysts **153** containing iminophosphorane units (as super bases) and a thiourea moiety (dual H-bond donor). This is an example of bifunctional base (BB) catalyst. They are much better catalysts than analogues possessing only a cinchonine moiety as a base. They catalyze asymmetric additions (9.11) [761].



In 2020, Yeung and coworkers reported the highly enantio- and diastereoselective halocyclization and spiroketalization of olefinic keto-acids (e.g., reaction (9.12)) applying BB-catalyst **154**. The resulting spiro compounds are privileged cores of many drugs and natural products [762].



Phase transfer catalysts (PTCs) that transport anions from a solid or aqueous phase to an organic phase see their efficiency improved by attaching them urea or thiourea units. Figure 9.4 presents early examples of such hydrogen bonding phase transfer catalysts (HB PTC). In 1998, Manabe catalyzed the benzylation of β-ketoesters with phoshonium bromide **155** [763]. In 2005, Nagasawa and coworkers catalyzed the asymmetric Henry (nitro-aldol) reaction with the guanidium-thiourea chloride **156** [764]. In 2014, the Duan group reported a highly enantioselective nitro-Mannich reaction that applies cinchonium-urea **157** as catalyst [765].



**155**, Manabe, 1998 **156**, Nagasawa, 2005 **157**, Duan, 2014

**Figure 9.4.** Early examples of hydrogen bonding phase transfer catalysts (HB PTCs).

Fluorine has become a widespread and important element in drugs [766,767] and agrochemicals [768]. With the number of fluorinated compounds on the market increasing, there is a growing demand for enantioselective fluorination methods, with safe and inexpensive sources of fluorine [769]. Typical mehods apply costly reagents (sources of $F^{(+)}$) which represent a problem for large-scale production (Sections 3.5.5 & 10.3)[361,770]. Alternatively, alkali metal fluorides are safe and inexpensive source of fluoride anion that are available in large amounts [771]. In 2018, Gouverneur and coworkers developed such catalysts for the asymmetric nucleophilic fluorination using safe and readily accessible fluoride salts (Figure 9.5) [772]. Binaphthyl derivative **158** that offers three urea N-H bonds is a good catalyst of reaction (9.13). A racemic product of thiobromination of *cis*-stilbene is ionised into a meso-episulfonium ion intermediate. Its bromide counter-ion is "solvated" by the urea catalyst forming a large anion soluble in the organic phase and capable to exchange its bromide anion with a fluoride anion taken from CsF. This brings the fluoride anion closed to the episulfonium ion forming two possible diastereomeric tight ion-pairs in proportion different from 1/1. They react forming either one or the other enantiomer of the product of fluorination. This metal-free organocatalyzed asymmetric fluorination applied successfully to the synthesis of a *trans*-2-fluorocyclohexan-1-amine motif found in several bioactive pharmaceutical molecules [773,774].

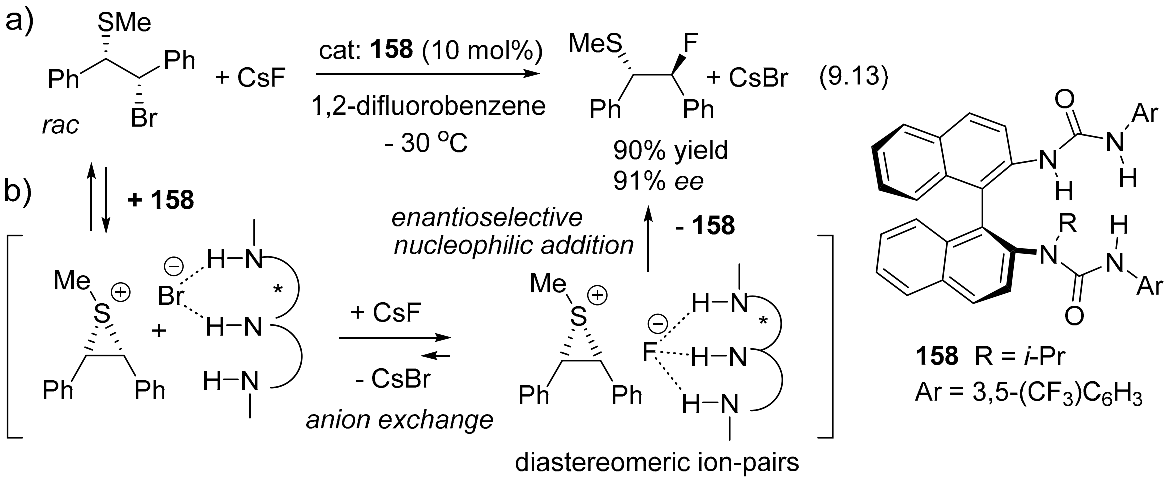
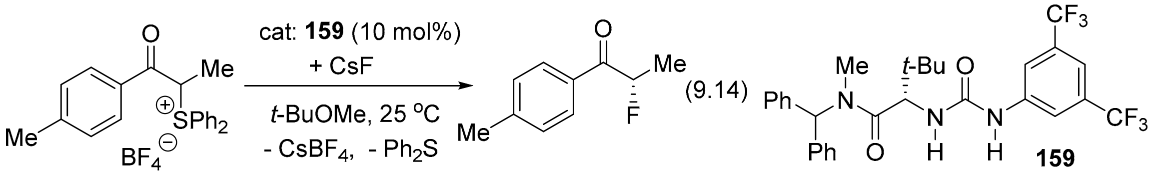


**Figure 9.5.** An example of asymmetric hydrogen bonding phase transfer catalysis that does not contain an onium salt. a) Enantioselective nucleophilic fluorination (Gouverneur, 2018); b) Possible mechanism of the reaction that implies the formation of ion-pairs capable to exchange the bromide (in solution) with the fluoride anion of the solid salt (CsF).

Catalytic synthesis of $\alpha$-fluorinated carbonyl compounds rely primarily on the transition-metal-catalyzed or organocatalytic reaction of a nucleophile (e.g., enolates or enamines) with diverse highly reactive electrophilic fluorinating reagents. In 2025, Sun and coworkers presented the enantioselective nucleophilic displacement reaction (9.14) catalyzed by the thiourea **159** [775].

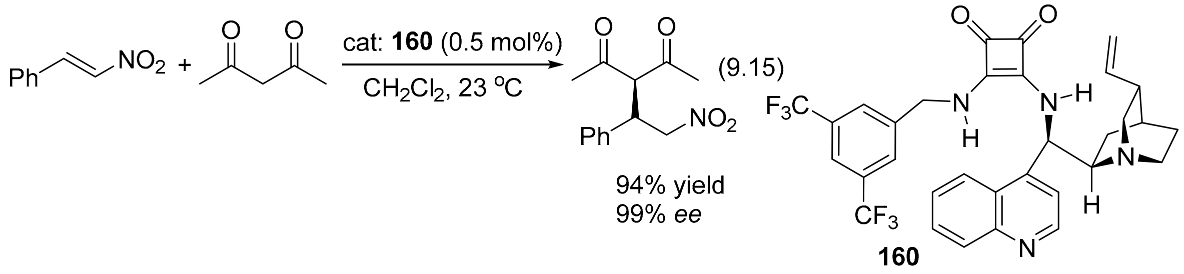


In 2014, Shibata and coworkers presented an iodoarene-catalyzed nucleophilic fluorination of β-dicarbonyl compounds and intramolecular aminofluorination of ω-amino-alkenes using the same reaction conditions. The key for these reactions is the *in situ* generation of a hypervalent iodine compound $ArIF_2$ by hydrogen fluoride, *m*CPBA and a catalytic amount of iodoarene [776]. In 2025, Shi and coworkers realized the first example of enantioselective $\alpha$-flurorination of ketone (47% yield, 46% *ee*) using cyclopropyl malonoyl peroxide as oxidant, pyr·9HF (Olah's reagent) as fluoride anion source, and 2,2′-diiodo-1,1′-binaphthyl as chiral catalyst [777].

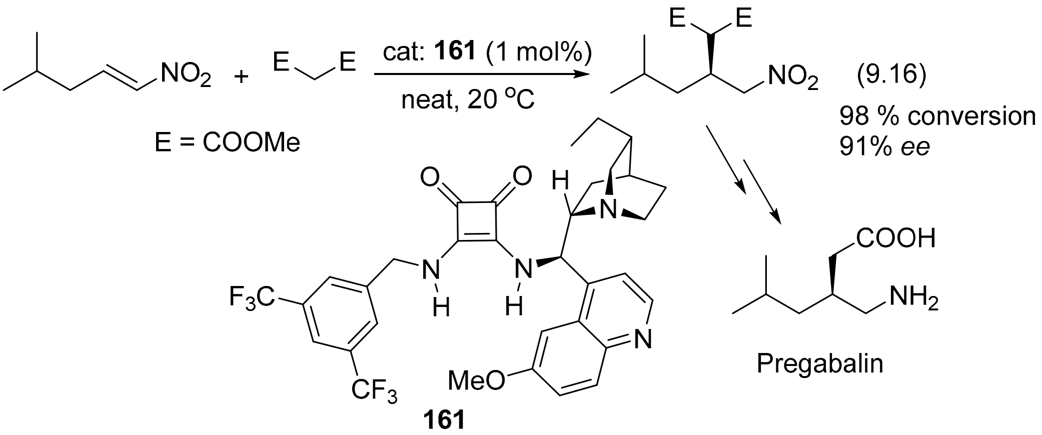
Nowadays, thiourea catalysts play a major role in asymmetric synthesis. Multiple H-bond donors play a significant role in accelerating reactions and improving yields, diastereoselectivities, and enantioselectivities [721,778].

### *9.4. Applications of Chiral Squaramide-Containing Catalysts*

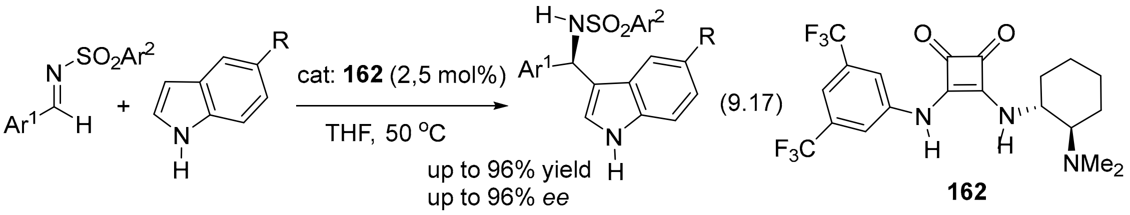
In 2008, Rawal and coworkers presented chiral squaramides as new H-bond donor catalysts. The (−)-cinchonine modified squaramide **160** is easily prepared through a two-step process from methyl squarate. It is an example of a bifunctional base (BB) catalyst. With loadings as low as 0.1 mol% it catalyzes the asymmetric conjugate additions of 1,3-dicarbonyl compounds to β-nitrostyrenes (e.g., reaction (9.15)) [779]. Since then, a large number of thioureas or squaramide BB catalysts have been developed [721,780].



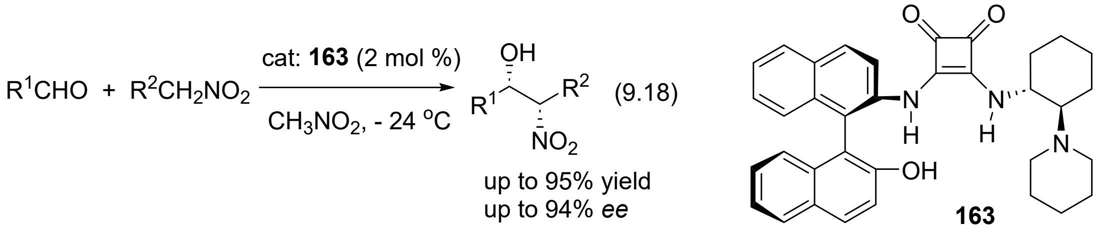
Similar to reaction (9.15), reaction (9.16) catalyzed by **161** starts the synthesis of central nervous system inhibitor Pregabalin (see Figure 3.10, Section 3.2.2 for an alternative synthesis) [781].



Chiral squaramides catalyze enantioselective conjugate additions of diphenyl phosphite to assorted nitroalkenes [782]. They catalyze also enantioselective Friedel-Crafts reactions of indoles with imines (e.g., reactions (9.17) with catalyst **162**) [783].



The trifunctional catalyst **163** catalyzes asymmetric Henry reactions (9.18) [784].



In 2018, Jacobsen and coworkers reported the enantioselective nucleophilic displacement reaction (9.19) catalyzed by **164**. Formation of a tight ion-pair intermediate **165** in which the tertiary carbenium ion resulting from the TNSOTf-promoted SN1 ionization is associated with the counter-ion, which is hydrogen-bridged by the chiral catalyst. Carbocation of intermediate **165** is attacked face-selectively by the nucleophile, explaining the enantioselectivity observed [785].

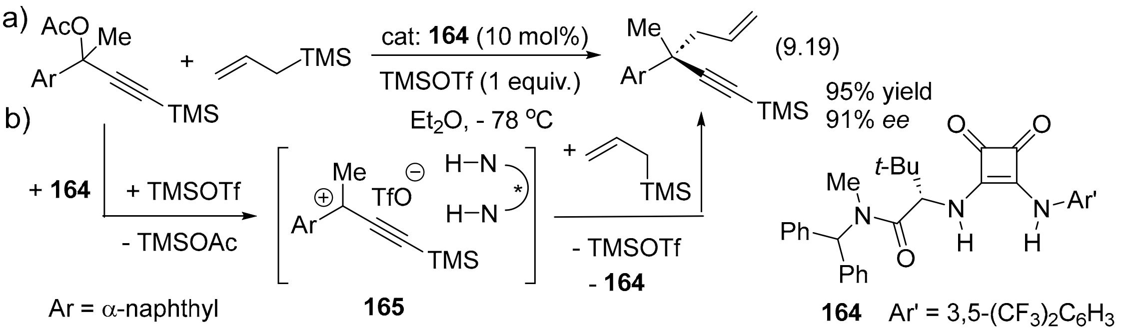
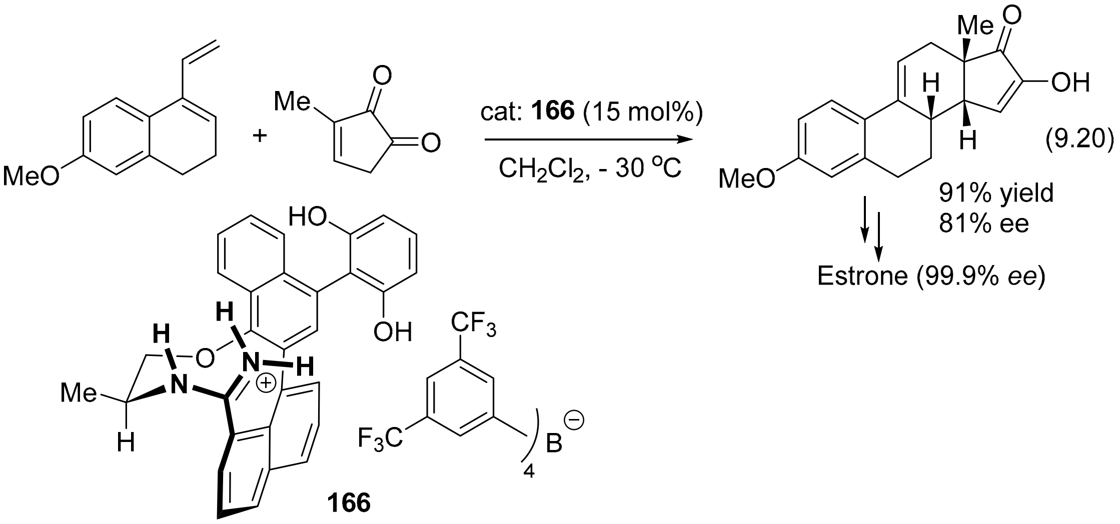


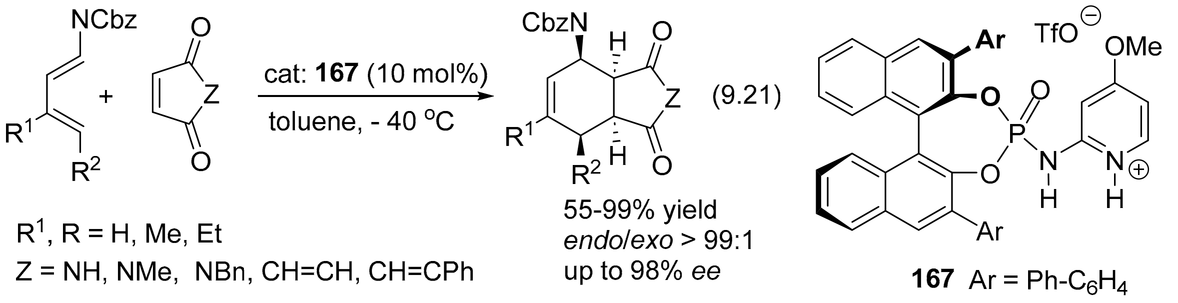
**Figure 9.6.** a) An enantioselective SN1 displacement reaction (Jacobsen, 2018); b) Possible mechanism; formation of a tight ion-pair with a hydrogen bridged chiral anion.

### *9.5. Amidinium Ions as Chiral Organo-Catalysts*

In 2000, Göbel and coworkers showed that a stoichiometric amount of amidinium salt **166** induced an enantioselective Diels-Alder reaction [786]. In 2010, they reported that **166** can be applied in a sub-stoichiometric amount to catalyze reaction (9.20) that produces an advanced synthetic intermediate of estrone [787].

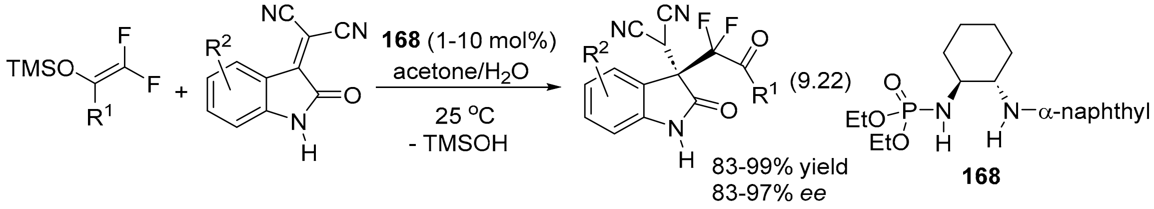


Analogous to amidinium salts H-bond donors are the 2-aminopyridinium salts. The asymmetric Diels-alder reactions (9.21) catalyzed by the pyridinium phosphoramide triflate **167** is an example example in 2016 by Nashikawa and coworkers [788].



*9.6. Other H-Bond Donor Chiral Catalysts*

In 2015, Zhou and coworkers developed the chiral phosphoramide catalyst **168** and applied it to the enantioselective Mukaiyama–Michael addition (9.22) of difluoroenol silyl ethers to tetrasubstituted olefins. The secondary amine moiety of **168** is expected to activate the desilylation of the silyl enol ether through the formation of a hypervalent silicate intermediate. In contrast, the phorphoramide N-H moiety activates a carbonitrile group of the Michael acceptor [789].



## 10. Acid Catalysis by Chiral Brønsted Acids

Akiyama [790] and Terada [791] initiated Brønsted acid organocatalysis in 2004 (Section 10.1.1). Brønsted acids, such as diethyl phosphate, $(EtO)_2P(=O)OH$, pKa = 1.3), are general catalysts to activate electrophiles like carbonyl and imine compounds. Chiral phosphoric acid (CPA) catalysts have permitted many important enantioselective reactions [792]. Other chiral Brønsted acids are also developed, such as borates and boroxinates (pKa($HBF_4$) = - 0.44) [793] and disulfonimides (pKa(benzene-1,2-disulfoimide) = -4.1).

*10.1. Chiral Diol Phosphate Catalysts*

Chiral phosphoric acids are ideal catalysts for the enantioselective activation of basic substrates, including imines and ketimines, through hydrogen bonding or ion pairing in a bifunctional fashion, and for the strongest acids, for the activation of aldehydes and ketones [794,795]. A large number of structurally different chiral phosphoric (CPAs) [792,796] and bisphosphoric acids [797] have been developed (Figure 10.1).

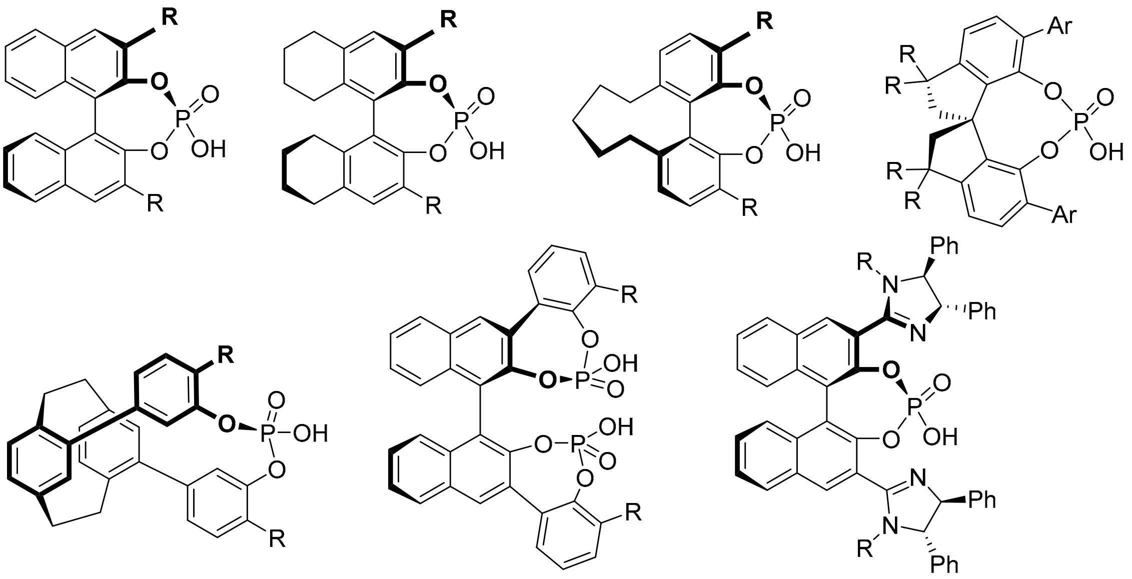


**Figure 10.1.** Typical chiral diarylphosphates (CPAs).

Diol phosphates are bifunctional catalysts that activate electrophiles by a partial or complete proton transfer, forming positively charged intermediates. The latter can be stabilized by the vicinal free phosphoryl moiety (P=O) which is a Lewis base (P=O ↔ $P^{(+)}$-$O^{(-)}$) (Figure 10.2). CPAs transfer chiral information from the catalyst to the products through either double H-bonds or synergistic hydrogen bonding (Figure 10.2a) and ion-pair interactions (Figure 10.2b) [798,799].

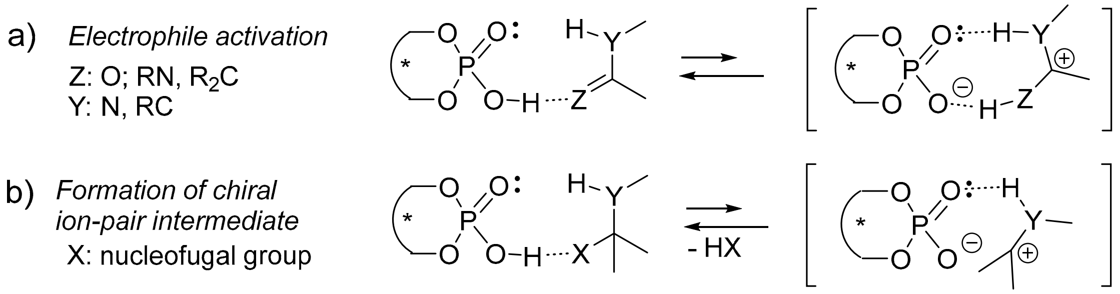


**Figure 10.** 2 Possible modes of activation by chiral diaryl phosphates.

Structural variation of the chiral backbone of the CPA catalyst provides an efficient chiral pocket for almost any achiral electrophilic substrates and their asymmetric reactions. The latter react with face selectivity with a large variety of nucleophilic partners. Today, we dispose of highly enantioselective reactions (see Figure 10.3 for examples) such as enamine additions to imines and carbonyl compounds, electron-rich alkene additions to carbonyl compounds and imines, Friedel–Crafts-type reactions, Strecker reaction, aza-ene, aza-Henry, aza-Diels-Alder reactions, 1,3-dipolar reactions, Pictet-Spengler reactions, transfer hydrogenation and reductive amination, Biginelli reactions, tandem/cascade reactions, multicomponent reactions, conjugate additions, dearomatization reactions. Furthermore, CPA catalysts have also received attention in dynamic kinetic resolution processes. They serve as chiral ligands for metal-catalyzed reactions and have promising prospects as chiral inducers in photocatalytic reactions [800,801]. Enantioselective nucleophilic additions to indole imine 5-methides have been realized recently [802].

### 10.1.1. BINOL Phosphates

In 2004, Uraguchi and Terada reported that phosphoric acid derivatives like **169** (a BINOL phosphate) catalyze the addition of acetyl acetone to *N*-Boc-protected arylimines (reaction (10.1)

[791]. The same year, and independently, Akiyama and co-workers showed that the BINOL-phosphate **170** catalyzes the enantioselective Mannich reaction (10.2) [790]. In 2005, Antilla and coworkers described an asymmetric acylimine amidation catalyzed by (*R*)- or (*S*)-VAPOLphosphate [803]. As already mentioned earlier, the hydrocyanation of imines (Strecker reaction) is a practical and direct method to *α*-amino acids. In 2006, Rueping and coworkers reported on reaction (10.3) catalyzed by the BINOL phosphate **171** [804]. The same group found that TADDOL-catalyzed Strecker reactions are less enantioselective than those catalyzed by BINOL-phosphate [805]. In 2006, Terada and coworkers found that a small amount of **171** accelerates the asymmetric aza-ene-type reaction of *N*-benzoylimines with enecarbamates, providing β-aminoimines (reactions (10.4)) [806]. They also reported on the asymmetric Friedel-Crafts reactions with imines (e.g., reaction (10.5) catalyzed by **172** and/or by **173**) with carbonyl compounds and electron-rich alkenes [796]. In 2016, Nagorny and coworkers reported the asymmetric spiroketalization (10.6). With deuterated enol ethers, chiral phosphoric acid **174** induced a highly diastereoselective *syn*-selective protonation/nucleophile addition, thus ruling out long-lived oxycarbenium intermediates. Calculations supported an asynchronous concerted mechanism with a polar transition state [807].

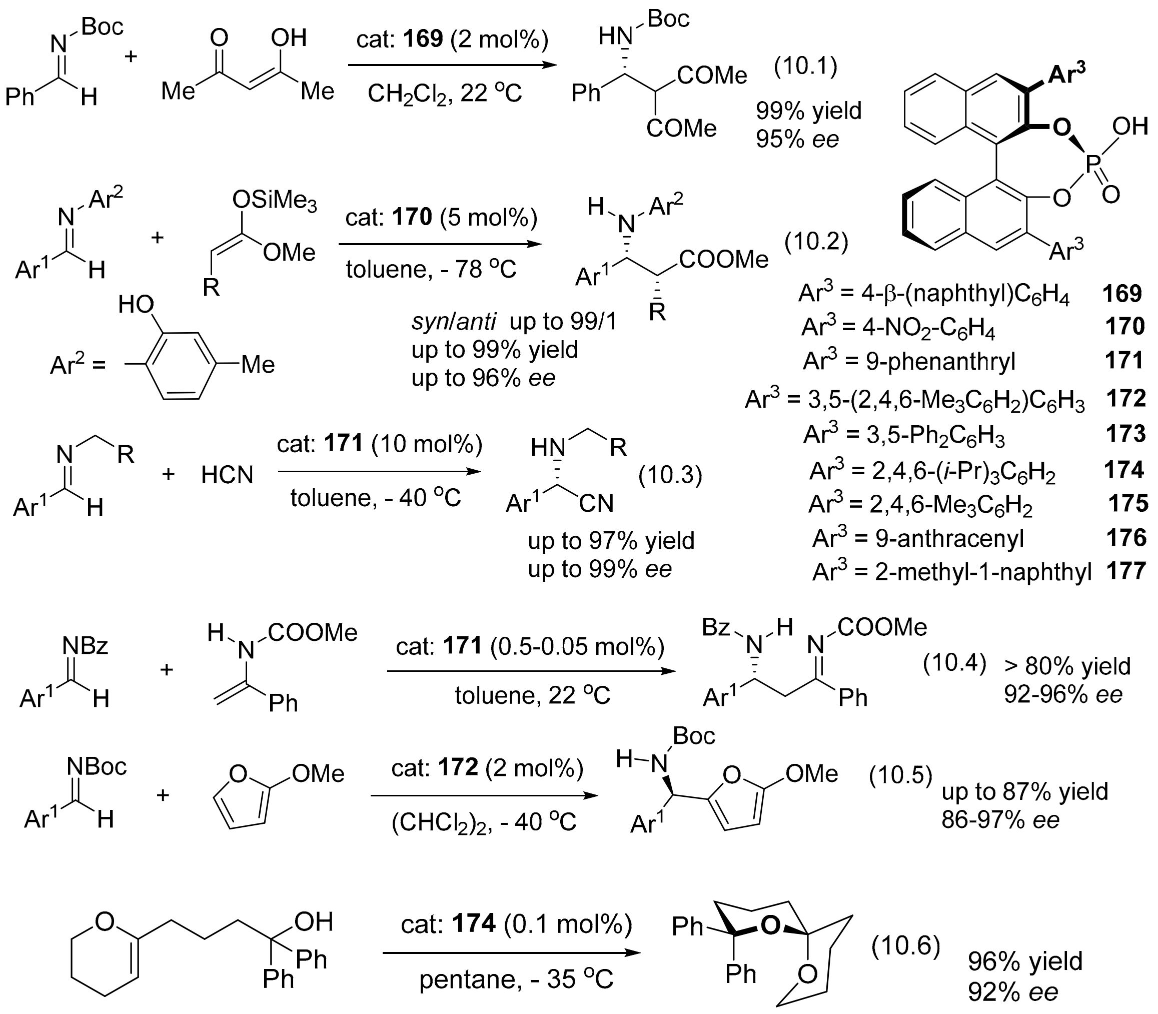


**Figure 10.3.** Examples of asymmetric reactions catalyzed by BINOL-derived CPAs (see below for applications of catalysts **175-177**).

In 2011, Shi and coworkers catalyzed the enantioselective bromocyclization with *N*-bromosuccimide (NBS) of olefins applying chiral phosphoric acid *ent*-**174** as catalyst (10 mol%, $CH_2Cl_2$, 0 °C). Various *cis*-, *trans*-, or trisubstituted γ-hydroxy-alkenes and γ-amino-alkenes are cyclized into 2-substituted tetrahydrofurans and tetrahydropyrroles in up to 91% *ee* [808]. Nearly at the same time, Denmark and Burk demonstrated that the enantioselective bromocycloetherifications of 5-arylpentenols are catalyzed by a combination of chiral Brønsted acid and achiral Lewis base. An example is shown with reaction (10.7) catalyzed by **174** and $Ph_3P=S$. The Lewis base (LB = $Ph_3P=S$:) activates the electrophilic Br of NBS. In the same time the chiral protic acid (HY = **174**) protonates a carbonyl group of NBS and promotes the formation of succimide and ion pair $[LB\text{-}Br]^{(+)}Y^{(-)}$. The latter equilibrates with LB and a chiral hypobromite that adds to the alkene with face selectivity forming a chiral epi-bromonium ion intermediate. The latter undergoes then an intramolecular addition of the alcoholic moiety forming the final bromo-ether and liberating the catalyst **174** (Figure 10.4) [809,810].

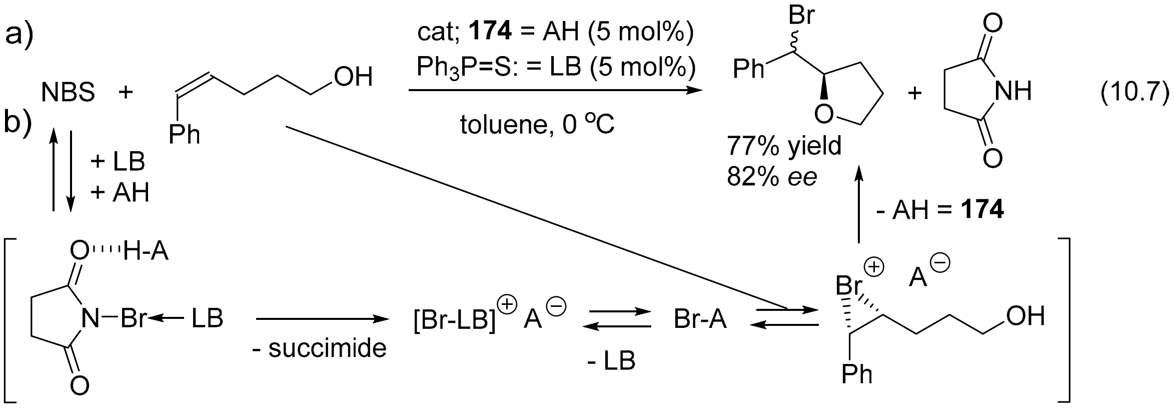


**Figure 10.4.** a) Example of enantioselective bromocycloetherification by Lewis base/chiral Brønsted acid cooperative catalysis (Shi, Denmark, 2011); b) Proposed mechanism.

In 2009, Wang, Zhu, and coworkers presented an organocatalyzed asymmetric version of a three-component reaction combining aldehydes, anilines, and α-isocyanoacetamides. In the presence of CPAs (e.g., **175**), the 5-(1-aminoalkyl)-5-aminooxazole were obtained in excellent yields and moderate to good *ee* (Figure 10.5, reaction (10.8)) [811].

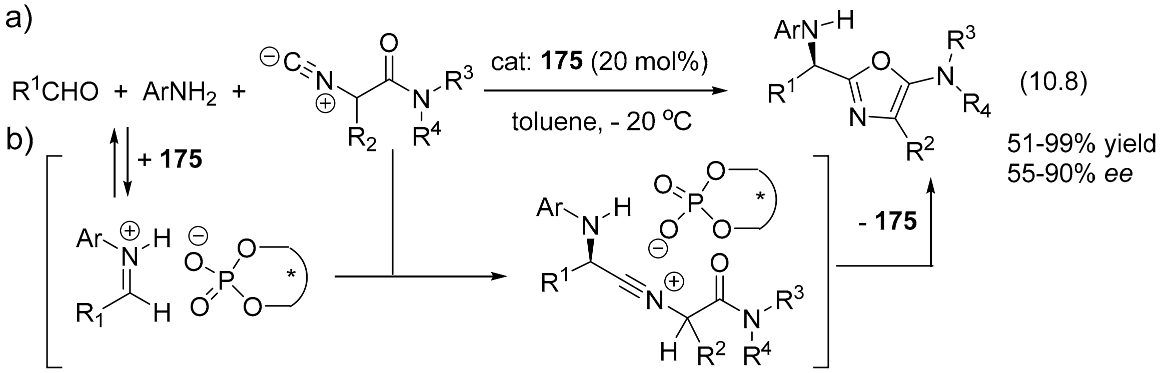


**Figure 10.5.** a) CPA-catalyzed asymmetric addition of isocyanides to aldimines (Wang, Zhu, 2009); b) Proposed mechanism.

In 2015, Tan and coworkers presented the first examples of organocatalyzed asymmetric Passerini reactions (10.9). In this three-component reaction, an isonitrile adds to an aldehyde forming a nitrilium ion that is quenched by the carboxylic acid. Follows an acyl group migration producing the correspond ester of a α-hydroxycarboxamide. In the presence of a CPA such as **176,** chiral transition structure **178** forms. It leads to intermediate **179**. Subsequent acyl group migration is probably also assisted by the CPA (Figure 10.6) [812].

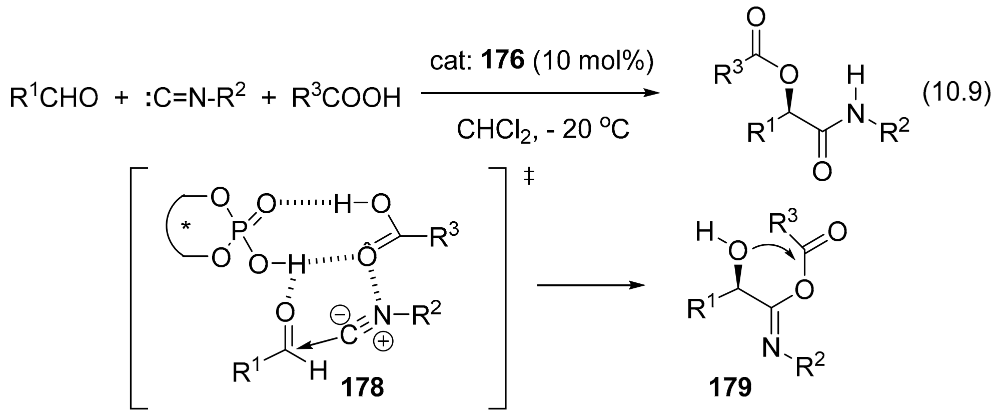


**Figure 10.6.** CPA-catalyzed asymmetric Passerini three-component reaction (Tan, 2015).

Another multi-component reaction is the Biginelli reaction, which permits the quick access to biologically active DHPM (3,4-dihydropyrimidin-2(1*H*)-one or -thione) derivatives. Several catalytic enantioselective versions of the reaction were developed. In 2018, Neto and coworkers combined asymmetric counter-anion-directed catalysis (ACDC) with ionic liquid effect and applied it to the enantioselective Biginelli reactions (10.10) that require no reagent in excess, no solvent, no additive, and permit the easy recovery of the catalyst (Figure 10.7) [813]. All proposed mechanisms of the enantioselective version of the Biginelli reaction described so far imply the iminium mechanism, as reexamined by Kappe [814].

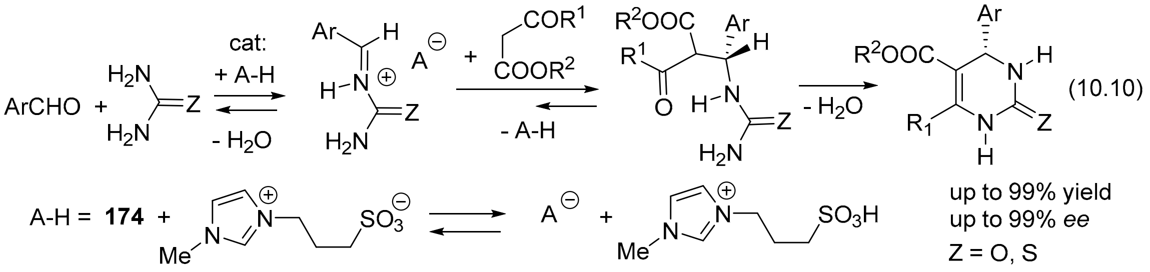


**Figure 10.7.** CPA-catalyzed asymmetric Biginelli three-component reaction (Neto, 2018).

In 2018, List and coworkers realized the first direct and enantioselective $\alpha$-aryloxylation of cyclic ketones with quinones (reaction (10.11)) catalyzed by **177**. Preliminary mechanistic experiments suggest that this reaction proceeds via a proton-coupled electron transfer (PCET) followed by radical coupling (Figure 10.8). This explains why the expected 1,4-addition of the enol to benzoquinone is not observed [815].

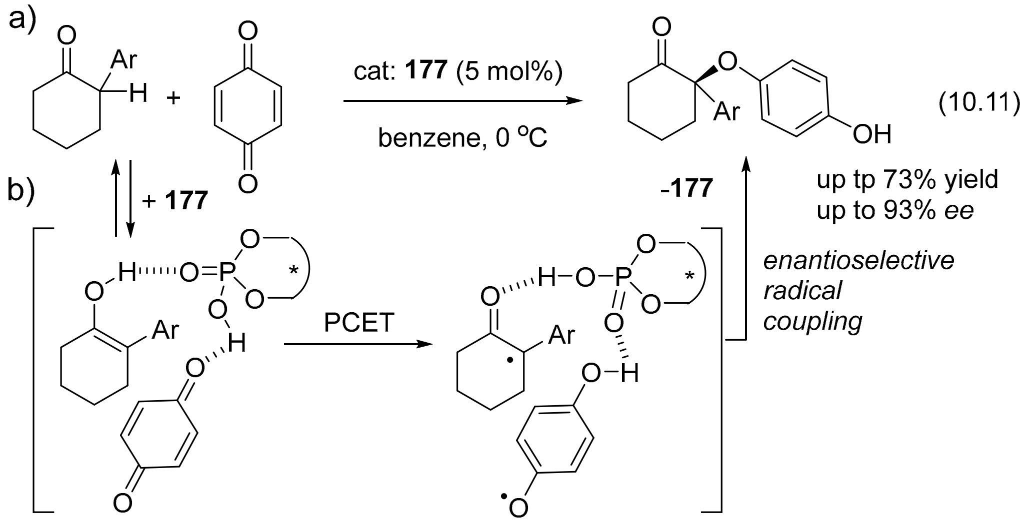


**Figure 10.8.** a) CPA-catalyzed asymmetric 1,6-addition of $\alpha$-arylketones to benzoquinone (List, 2018); b) Proposed mechanism involving proton-coupled electron transfer (PCET) between the enol of the ketone and the Michael acceptor.

In 2024, Shi and coworkers reported an asymmetric (2+4) annulation of achiral furan-indoles with 2,3-indolyldimethanols with uncommon regioselectivity under the catalysis of CPA, thereby generating furan-indole compounds bearing both axial and central chirality in high yields with excellent regio-, diastereo-, and enantioselectivities [816]. In the presence of a Brønsted acid, 2-indolylmethanols and 3-alkyl- (aryl)-2-indolylmethanols are ionized onto carbocationic species *via* dehydration. These intermediates are three-atom building blocks able to enter into (3+n)-cycloadditions with other reaction partners. These reactions can be enantioselective by applying chiral Brønsted acid catalysts such **180**. An example of application reported in 2024 by the Shi group is given in Figure 10.9 with the (3+3)-annulation (10.12) [817].

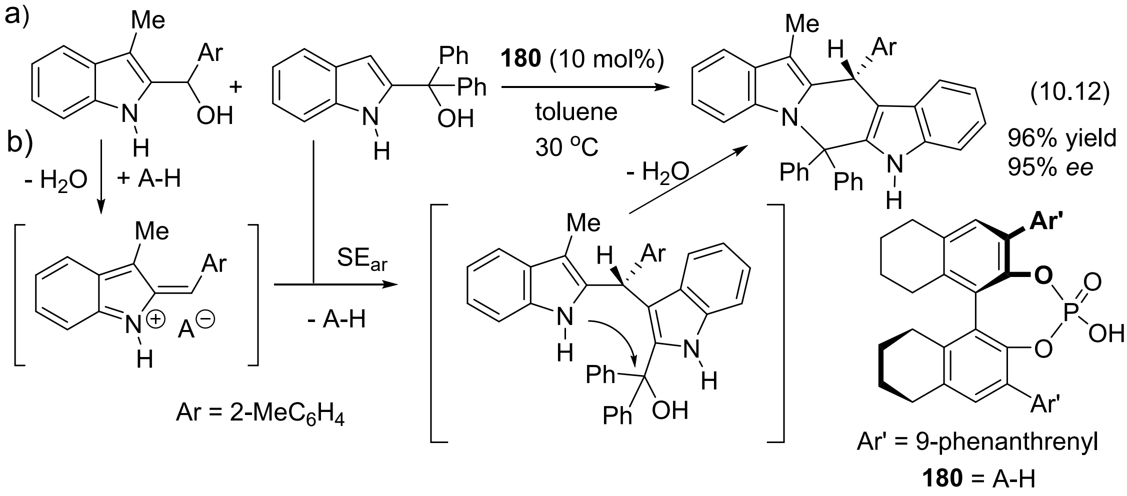
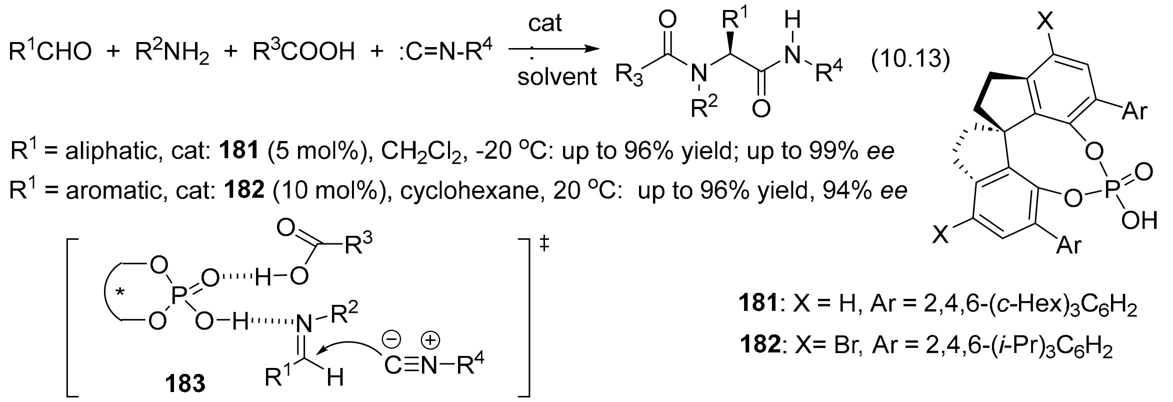


**Figure 10.9.** a) Enantioselective (3+3)-annulation (Shi, 2024); b) Possible mechanism.

### 10.1.2. Other Diol Phosphates

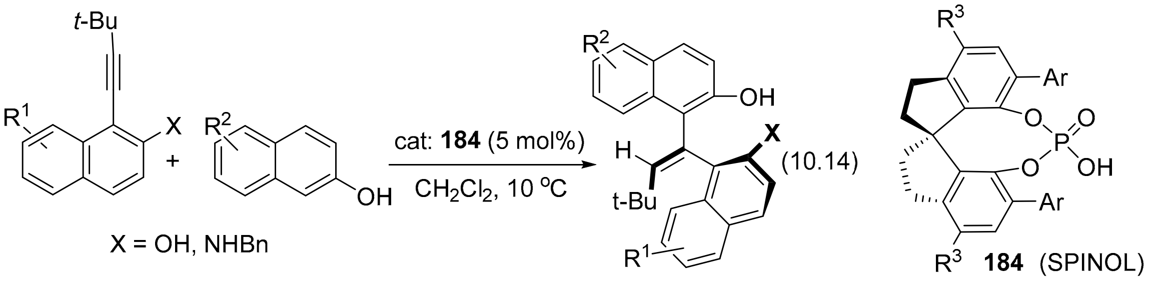
The four-component Ugi reaction is one of the most important multicomponent reactions (MCRs). It produces in one-pot operations $\alpha$-amido amides (dipeptide analogues) carrying four points of diversity as they arise from the combination of four components: an aldehyde, an amine, a carboxylic acid, and an isocyanide. The reaction can be enantioselective when catalyzed by CPAs such as **181** or **182**. In 2018, Tan, Houk and coworkers showed that CPAs catalyze reaction (10.13) with good *ee*. Quantum calculations suggest that a hydrogen-bonded complex **183** involving the phosphoric acid and carboxylic acid sets the stereochemistry for isocyanide attack on an imine intermediate [818].



$R^1$ = aliphatic, cat: **181** (5 mol%), $CH_2Cl_2$, -20 °C: up to 96% yield; up to 99% *ee*
$R^1$ = aromatic, cat: **182** (10 mol%), cyclohexane, 20 °C: up to 96% yield, 94% *ee*

**181**: X = H, Ar = 2,4,6-(*c*-Hex)$_3C_6H_2$
**182**: X= Br, Ar = 2,4,6-(*i*-Pr)$_3C_6H_2$

Alkenylation of arenes (aromatic electrophilic substitution) implies that the direct protonation of an alkyne produces alkenyl-arene derivatives. Arenes and alkynes containing large substituents form separable mixtures of atropisomers. Reactions (10.14) between sterically crowded alkynes and electron-rich naphthalene derivatives catalyzed by the SPINO(spirobiindane)-derived phosphoric acids **184** are enantioselective. They produce EBINOLs (1,1′-(ethylene-1,1-diyl)binaphthyl) and derivatives. Chiral ion pair intermediates of the type 1-naphthylalkylidenyl cation/SPINOLphosphate form [819].



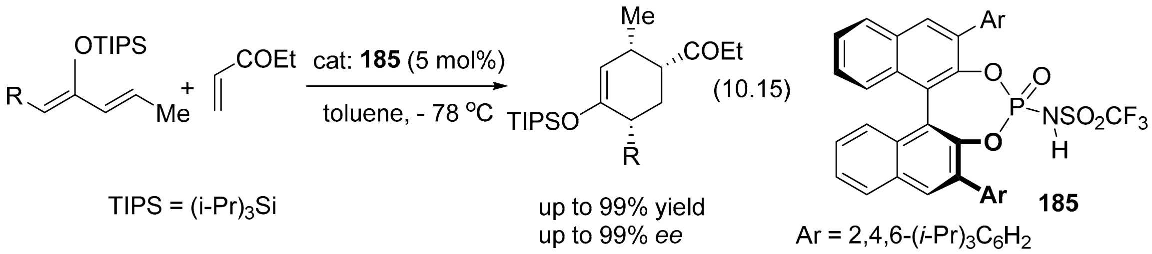
X = OH, NHBn

63-97% yield
96-98% *ee*

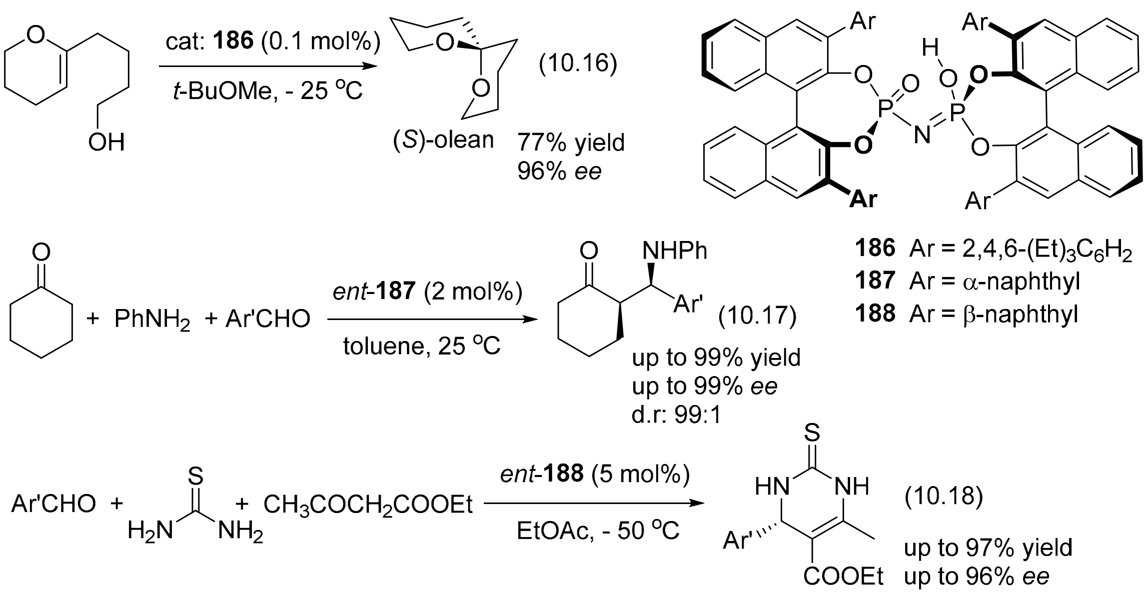
**184** (SPINOL)
Ar = 9-phenanthryl
$R^3$ = Me, Br

*10.2. Stronger Acids Than Diolphosphates*

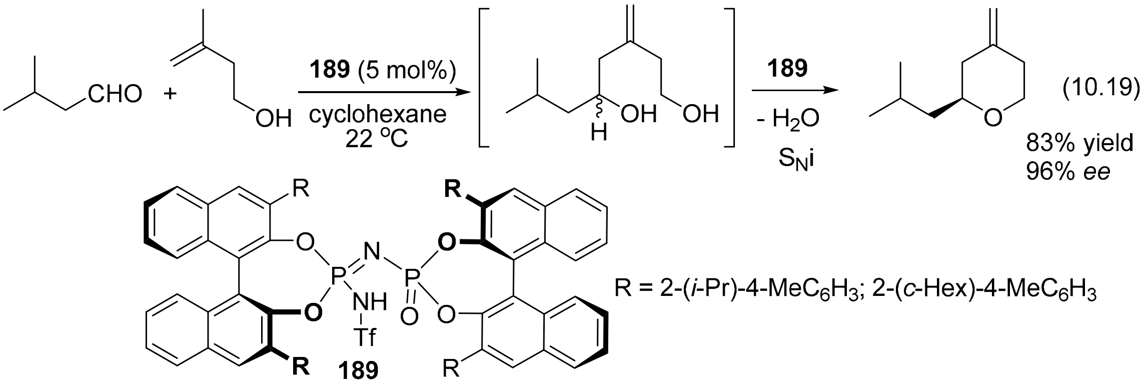
Chiral phosphoric acid catalysts activate basic substrates such as imines or carbonyl compounds. For the functionalization of non-polarized C=C bonds, such as olefins or arenes, stronger acids are necessary [820]. Diaryl phosphates are not acidic enough for a strong activation of carbonyl compounds. The second and third pKa values of *N*-triflyl phosphoramide ($(HO)_2P(=O)$-NHTf) are about 4 and 5 pKa units lower than those of $H_3PO_4$ (7.21 and 12.31, respectively) [821]. This led Yamamoto and Nakashima to develop in 2006 chiral *N*-triflyl phosphoramides. An example is BINOL-derived **185** that catalyzes enantioselective Diels-Alder reactions with normal electronic demand (10.15) [822].



In 2012, List and Coric developed Brønsted acid-promoted asymmetric spiroacetalizations applying various BINOL-derived phosphoric acids and imidophosphoric acids on cyclic enol ethers bearing and alcoholic side-chain. They found that C2-symmetric imidodiphosphoric acid **186** was the best catalyst that permitted the enantioselective synthesis of 6,6- (e.g.: reaction (10.16)), 6,5-, 5,5-, 6,7- and 5,7-spiroacetals [823]. List and coworkers also found that enantioselective oxidation with $H_2O_2$ of sulfides into sulfoxides [824] and acetalization can be catalyzed by imidophosphoric acids such as **186** [825]. In the same years, Zhang and coworkers reported the asymmetric Mannich reactions (10.17) catalyzed by the enantiomer of **187** [826]. They also showed this type of Brønsted acid to catalyze Friedel-Crafts reactions of indoles with imines [827]. In 2014, they reported the enantioselective Biginelli condensations (10.18) [828].



In 2016, the List group reported asymmetric Prins reactions catalyzed by iminoimidodiphosphate Brønsted acids **189**. Reaction (10.19) is an example. It is a sequence of a Prins condensation between the aldehyde and the alkene. Follows a facile cyclization that implies an intramolecular displacement of a homoallylic secondary alcohol by a primary alcohol. At least one of these two reactions must be enantioselective [829].



In 2018, the same group disclosed the enantioselective intramolecular hydroalkoxylation reaction (10.20) which applies Brønsted acid **190** as catalyst (Figure 10.10). The latter protonates the alkene forming an enantioenriched tight ion-pair **191**. Whether this ion-pair equilibrates or not with the covalent species **192**, its intramolecular reaction with the alcoholic moiety is enantioselective [830].

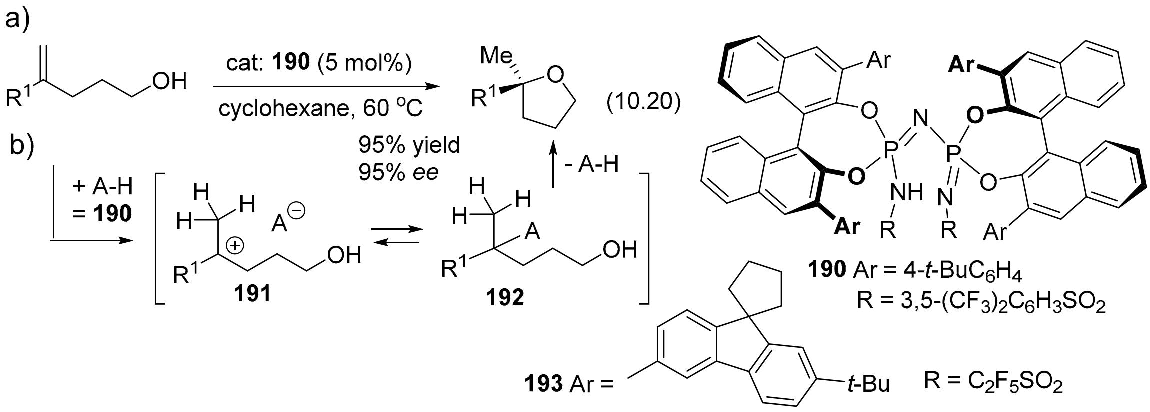


**Figure 10.10.** a) Enantioselective intramolecular hydroalkoxylation (List, 2018); b) Proposed mechanism.

Enantioselective cyclopropanation of alkenes with diazoalkanes are catalyzed both with chiral metal complexes and with engineered metalloenzymes [831]. In 2025, List and coworkers presented a catalytic cycle (Figure 10.11a) in which alkenes are activated as radical cations upon single electron transfer to a photoexcited cationic organocatalyst of type $[\mathbf{A}^{(-)}\mathbf{X}^{(+)}]^*$ associated with an enantiopure counter-anion $\mathbf{A}^{(-)}$. The radical-cation (e.g., **195**) forms an ion-pair with the chiral counter-anion and react enantioselectively and stereoselectivily with the diazoalkanes, to furnish cyclopropane radical cations (e.g., **196**) and loss of $N_2$. A final single electron transfer from the catalyst radical to the cyclopropane radical-cations regenerate the cationic photocatalyst and deliver the desired products (Figure 10.11b). An example is the cyclopropanation of *trans*-anethole with ethyl diazoacetate (10.21) [831]. The photocatalysts $\mathbf{A}^{(-)}\mathbf{X}^{(+)}$ is generated by reaction of acid **193** with the thioxanthylium triflate **194** and $NaHCO_3$ (**193** + **194** + $NaHCO_3 \rightarrow \mathbf{A}^{(-)}\mathbf{X}^{(+)}$ + TfONa + $H_2O$ + $CO_2$).

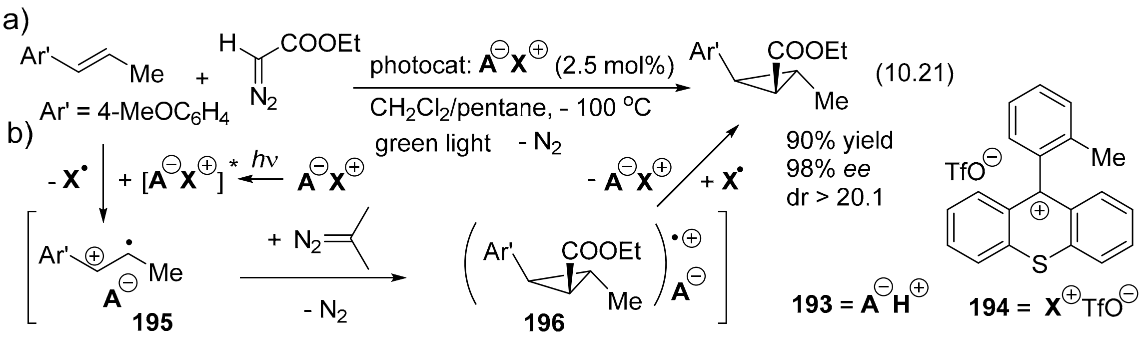
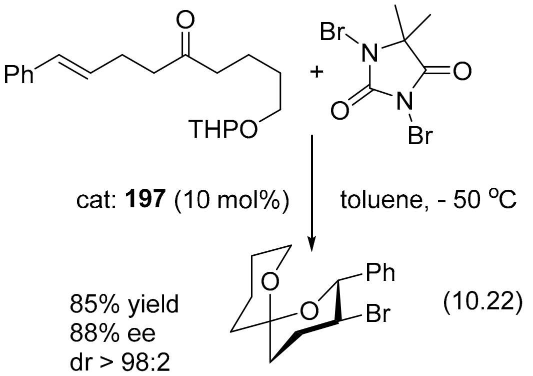
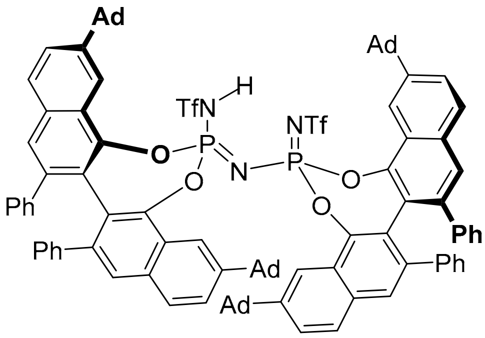


**Figure 10.11.** a) Example of a photo-organo-catalyzed cyclopropanation reaction (List, 2025); b) Proposed mechanism.

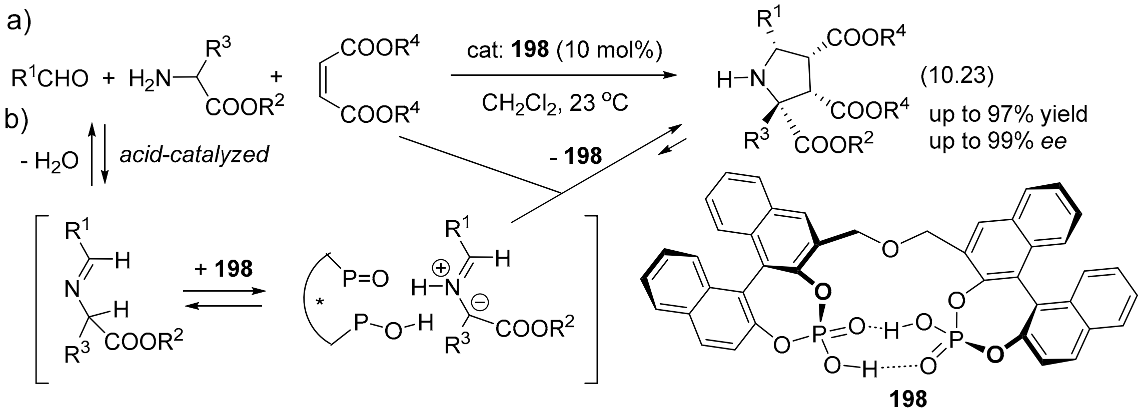
In a recent report Wulff, Borhan and coworkers developed VANOL-imidodiphosphorimidate catalyst **197** and applied it to the asymmetric bromonium ion induced spiroketalyzation (10.22). A large chiral ion-pair is formed between the catalyst and the reagent 1,3-dibromo-5,5-dimethylhydantoin which brominates the olefin with face selectivity producing a β-bromocarbenium ion intermediate that forms a tight ion-pair with the counter-ion of the acid catalyst [832].





**197** Ad = 1-adamantyl

In 2008, Gong and coworkers reported that the bisphosphate **198** is a better catalyst than monophosphoric derivatives such as **170** in the one-pot, three-component dipolar cycloadditions (10.23). This is due to the higher acidity of the bisphosphoric acid compared to monophosphoric acid catalysts (Figure 10.12a). Assisted by the Brønsted acid, the aldehydes and primary amines equilibrate with the corresponding imines, precursors of the azomethine ylid intermediates that are H-bonded with **198** and undergo stereoselective 1,3-dipolar cycloadditions (Figure 10.12b) [833]. In the meantime, bisarylphosphates have been shown to catalyze asymmetric Diels-Alder reactions, aza-Friedel-Crafts reactions, and transfer hydrogenation reactions [797].



**198**

**Figure 10.12.** a) Enantioselective three component dipolar cycloadditions (Gong, 2008); b) Possible mechanism.

On introducing 2,4,6-trimethyl-3,5-dinitrophenyl substituents at C(2) and C(2′) of BINOLphosphate, Zhou and Yamamoto obtained a powerful catalyst for the enantioselective Mukayiama-Mannich reaction [834].

### *10.3. Diolphosphates as Chiral Anionic Phase Transfer Catalysts for Electrophilic Fluorination*

In 2011, Toste and coworkers developed chiral anionic phase transfer catalysts (PTC) and applied them to the electrophilic fluorination of alkenes. An example is reaction (10.24) that uses Selectfluor as electrophilic fluorinating reagent. The latter is insoluble in fluorobenzene, the solvent chosen for this reaction. In the presence of chiral lypophilic diolphosphate **199** and a base (e.g., proton sponge) at least one tetrafluoroborate counter-ion of Selectfluor is exchanged by a phosphate anion generating a species that is soluble and reacts with the alkenes with face selectivity (Figure 10.13) [835].

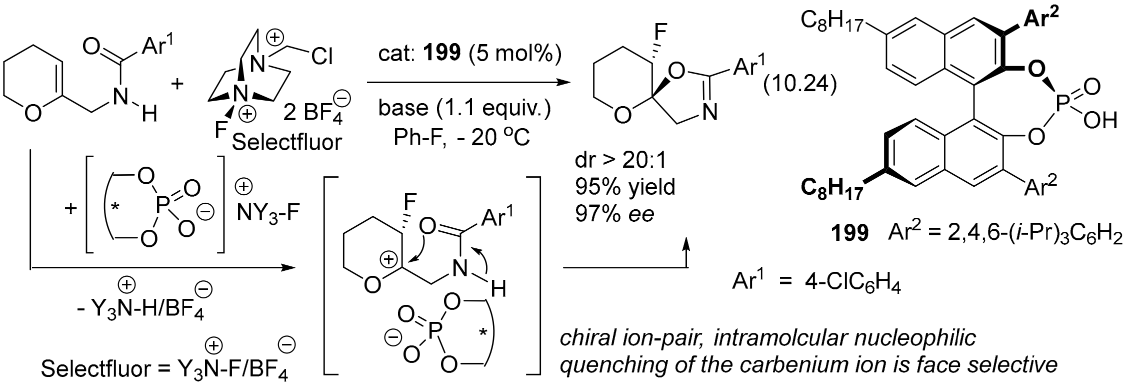
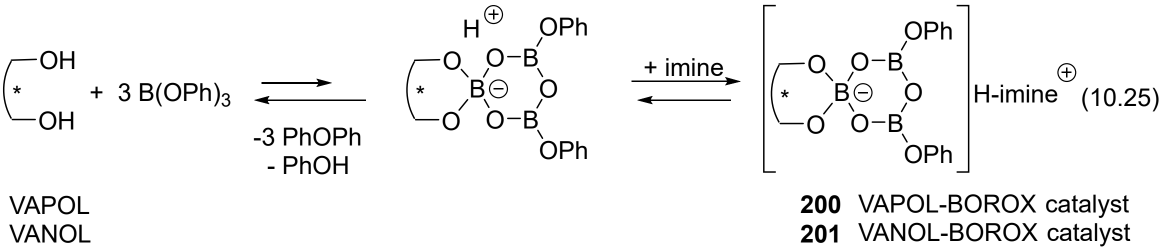


**Figure 10.13.** Asymmetric electrophilic fluorination of alkenes (Toste, 2011).

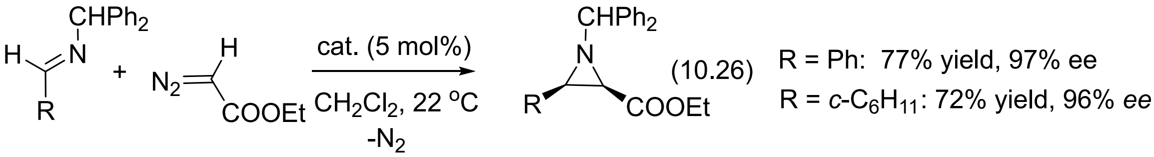
Chiral anion PTC catlayze the enantioselective fluorinative dearomatization of phenols [836]. In 2024, Wang and coworkers presented new chiral bis-phosphate macrocycles that possess cavities with two cooperative phosphate sites. With Selectfluor, they form lipophilic inclusion complexes that are also good catalysts for electrophilic fluorinations [837].

### *10.4. Chiral Borate and Boroxinate Brønsted Acids*

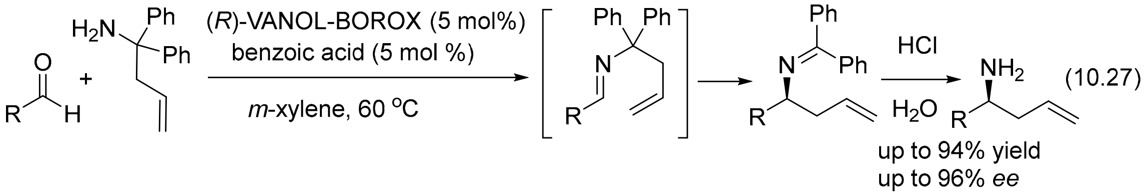
Wulff and coworkers showed that diols such as VAPOL and VANOL (Figure 9.1) formed polyborate anionic catalysts when combined with borates. For instance, the reaction of VAPOL with triphenylborate generates a Brønsted acid of the type boroxinate which, after addition of an imine (or an amine), forms the catalyst VAPOL-BOROX **200** (reaction (10.25)). Similarly, catalyst VANOL-BOROX **201** derives from VANOL [838–840].



An early application is the asymmetric aziridination of imines (reaction 10.26)) reported in 1999 by Antilla and Wulff. In this case, the catalyst resulted from the reaction of (S)-VAPOL with $BH_3{\cdot}THF$ [841]. Later, catalysts of type **200** and **201** have been applied [842–844].

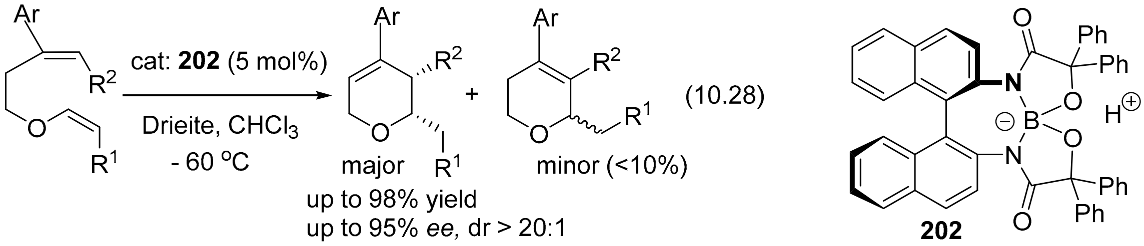


In 2011, Ren and Wulff reported the direct asymmetric aminoallylations of aldehydes (10.27) that implies imine formation and subsequent aza-Cope rearrangement. For good enantioselectivities the benzoic acid additive was necessary. Its role, probably, is to combine with the boroxinate intermediates [845].



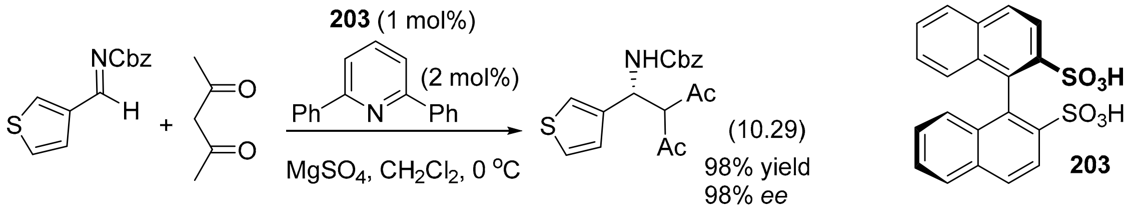
The combination of VANOL or VAPOL with B(OPh)3 catalyzes several other asymmetric reactions. They include: the Diels–Alder, hetero-Diels-Alder, Mannich, Baeyer–Villiger, Michael, aza-Darzens, Petasis and Ugi reactions, the amidation and imidation of imines, the reduction of imines and of aminals, the desymmetrization of aziridines and of diesters, the hydroarylation of alkenes, the *cis*- and *trans*-aziridination of imines and alkenes, the benzoyloxylation of aryloxindoles, the pinacol rearrangement, the hydrogenation of alkenes, the propargylation of ketones, the hydroacylation of alkenes, the α-imino rearrangement, the carbonylative spirolactonization of enallenols, and the controlled switching in a foldamer [793].

In 2020, the group of Ooi presented the robust hydrogen borate **202** as a chiral catalyst for the Prins type of cyclization (10.28) which implies face-selective protonation of the enol ether with formation of a oxycarbenium ion intermediate that is quenched intramolecularly by the arylalkene moiety. The resulting benzylic cation intermediate eliminates then a proton [846].



*10.5. Chiral Disulfonic Acids and Their Ammonium Salts*

In 2008, Ishihara and coworkers prepared chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA, **203**) from BINOL. Mixed with a 2,6-diarylpyridine it forms salts that are catalysts of the direct asymmetric Mannich reaction of 1,3-diketones and of 1,3-ketoester equivalent with arylaldimines. Reaction (10.29) is an example [847,848].



In 2011, Ishihara and coworkers reported a catalytic enantioselective Friedel-Crafts aminoalkylation between aromatic aldimines and *N*-benzylpyrrole applying (*R*)-BINSA-*N*,*N*-dimethylbutylamine, as a dynamic Brønsted acid-Brønsted base catalyst [848,849]. In 2018, the same group described the synthesis of chiral 1,1′-spirobiindane-7,7′-disulfonic acid (SPISA) and 1,1′-spirobiindane-7,7′-disulfonimide from 1,1′-spirobiindane-7,7′-diol (SPINOL, Figure 9.1) in 4 steps. They catalyze the asymmetric aminalization of aromatic aldimines with primary carboxamides [850].

*10.6. Chiral Disulfonimides*

In 2009, Giernoth and coworkers reported the first synthesis of (*R*)-1,1′-binaphthyl-2,2′-bis(sulfon)amide, **204** (BINBAM, more acidic than CPA’s [851]). It was obtained in 4 steps from BINOL [852]. The same year, the List group prepared the 3,3′-dirarylated analogue **205** and found it to be a catalyst of the asymmetric Mukaiyama aldol reaction (10.30) as efficient as BINOL-derived phosphate (Section 10.1.1), N-triflylphosphoramide (Section 10.2), or 1,1′-binaphtlyl-2,2′-disulfonic acid (Section 10.6) [853]. Although TfOH (pKa($H_2O$) = -5.9) is a stronger Brønsted acid than $Tf_2NH$ (pKa($H_2O$) = 1.7), $TMSNTf_2$ is a stronger Lewis acid than TMSOTf [854]. The actual catalyst of the Mukayiama aldol reaction is not the Brønsted acid **205**, but the Lewis acid **206** ⇄ **206′** resulting from the reaction of **205** (pre-catalyst) with the silyl enol ether (Figure 10.14) [855].

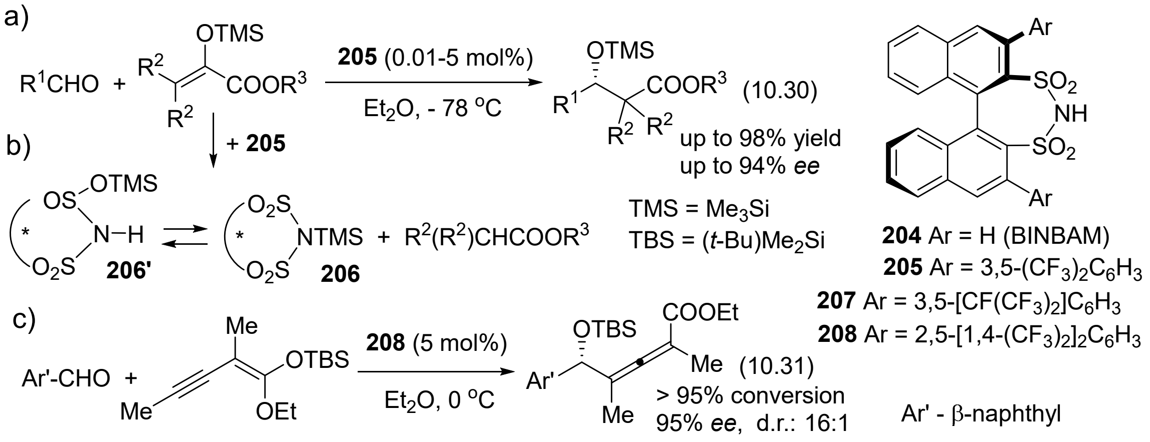


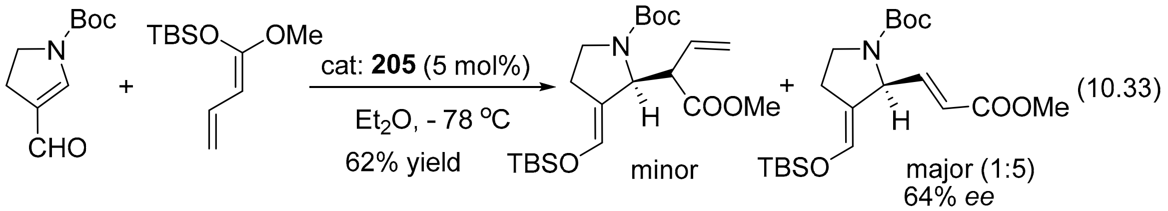
**Figure 10.14.** a,c) Chiral disulfonimides are pre-catalysts of Mukaiyama aldol reactions and related reactions (List, 2009, 2013); c) The actual catalysts are *N*-silyl disulfonimides resulting from the reaction of the catalysts with the silyl enolates.

By pairing a silylium ion equivalent with a chiral enantiopure counter-anion (e.g., **206** ⇄ **206′**), one realizes asymmetric counter-anion-directed catalysis [856,857]. Applications of this concept involve silicon-containing nucleophiles such as silyl ketene acetals (e.g., reaction (10.30), Mukaiyama-Mannich reaction, Danishefsky-type dienes (hetero-Diels-Alder reaction [858]), allylsilanes (Hosomi-Sakurai reaction), silyl phosphites (Abramov reaction), and silyl cyanide. In the latter case, a small amount of catalysts (0.050 – 0.005 mol%) is sufficient. An example is reaction (10.32), which engages 156 g of naphthalene-2-carbaldehyde [859,860].

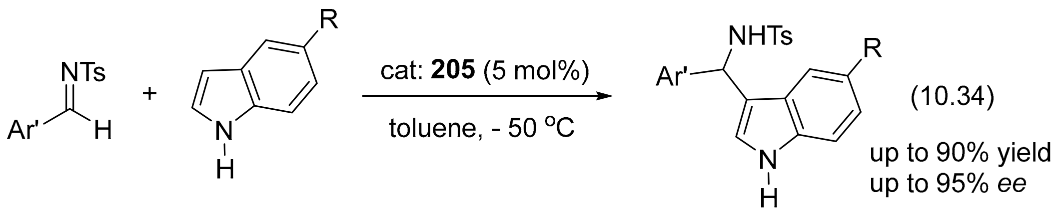
$$\beta\text{-naphthyl-CHO} + Me_3SiCN \xrightarrow[\text{Et}_2\text{O, - 30 °C}]{\text{cat: } \mathbf{207}\text{ (0.05 mol \%)}} \beta\text{-naphthyl-CH(OTMS)CN} \qquad (10.32)$$

97% yield, 92% *ee*

In 2017, Chen and coworkers reported the first example of asymmetric Mukaiyama–Michael reaction (10.33) catalyzed by **205** [861]. In 2018, the List group reported the enantioselective reactions of silyl ketene acetals with Michael acceptors [862].



In 2011, Lee and coworkers demonstrated that disulfonimide **205** is an efficient chiral Brønsted acid catalyst (a DSI catalyst, not a pre-catalyst) as illustrated with the enantioselective Friedel–Crafts reaction (10.34) between a wide range of aldimines and indoles [863].



## 11. Other Asymmetric Organo-Catalysts

Several other functional organic compounds than those presented in the preceeding chapters have been envisonned as asymmetric organocatalysts. We cannot be exhaustive here with them, but we shall concentrate on some of the most useful asymmetric reactions applied that include chiral ketones, imines, amine oxides, oxazolines, and crown ethers. Newly developed halogen bond (XB) donors, such as neutral polyhalogenated compounds and halonium salts, will end this minireview.

### *11.1. Asymmetric Alkene Epoxidation Catalyzed by Chiral Ketones*

Asymmetric alkene epoxidation is a powerful entry to highly valuable polyfunctional compounds [297]. Methods based on organocatalysis are described above (Sections 3.2.1, 4.2) [296]. Those applying ketones as catalysts contribute to green chemistry [864,865]. In 1984, Curci reported the first catalytic dioxirane-promoted alkene epoxidation, but with deceiving enantioselectivities (up to 12.5% *ee*) for (*E*)-β-methylstyrene [866]. Their chiral dioxirane (up to 50 mol%) resulted from the reaction of oxone (potassium hydrogen persulfate, $KHSO_5.KHSO_4.K_2SO_4$) as the oxidant and a chiral ketone (Figure 11.1) [867]. Numerous efforts, such as those of Yang [868,869], Denmark [870], and Armstrong [871,872] have led to better catalysts. In 1996, the Shi group realized highly enantioselective epoxidation of (*E*)-alkenes (reaction (11.1)) with oxone, applying easy-to-prepare D-fructose derivative **209** as the organocatalyst [873]. Catalyst *ent*-**209** is also readily available [874,875]. In 1999, the Shi found that $H_2O_2$ can be utilized as a primary oxidant when pure acetonitrile is used as a solvent [876]. The asymmetric epoxidation of di- and trisubstituted olefins is now possible with ketone **209** as a catalyst. It tolerates different types of substituents, and it can be applied to the epoxidation of conjugated dienes and enynes, of enol silyl ethers or enol esters, of hydroxyalkenes, of vinylsilanes, and of fluoroalkenes. Several other chiral ketones have been proposed as catalysts since then. Shi's ketones **209** and *ent*-**209** apply successfully in the asymmetric synthesis of many drugs, natural products, and analogues of biological interest [296,865] (see also: [877]).

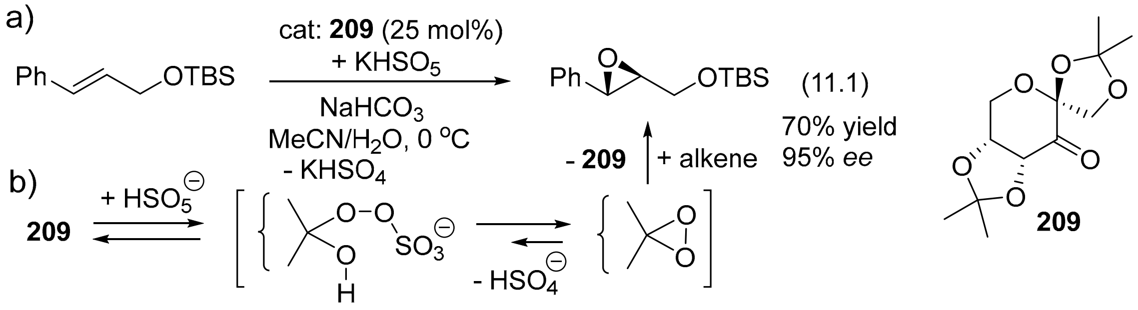
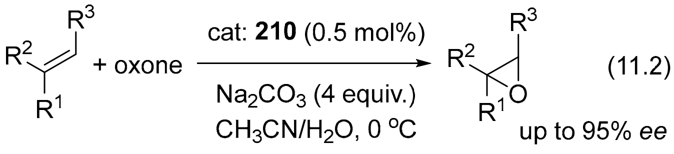
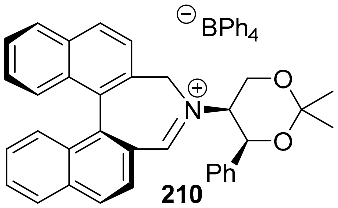


**Figure 11.** 1 a) Asymmetric epoxidation of alkenes (Shi, 1996). b) Mechanism proposed: formation of dioxirane intermediate.

### *11.2. Asymmetric Alkene Epoxidation Catalyzed by Chiral Iminium Salts*

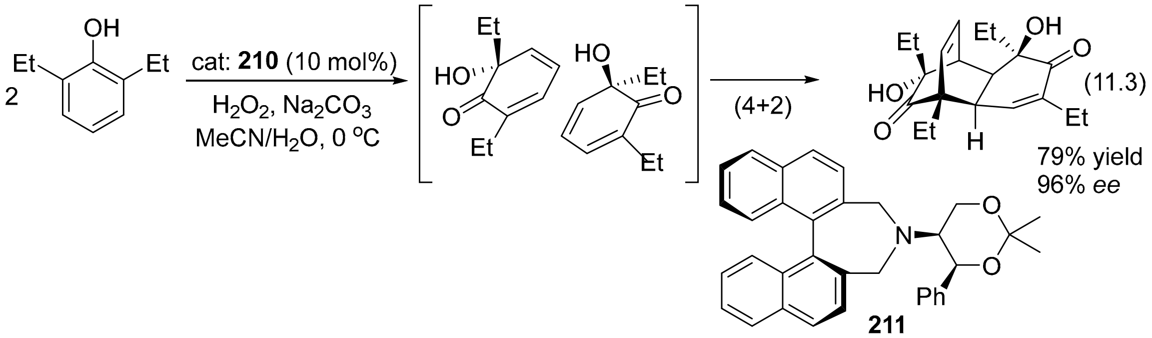
Oxaziridinium salts, first reported by Lusinchi in 1976, [878,879] are also reagents for oxygen transfer to nucleophilic substrates such as sulfides [880] and alkenes, and may be generated catalytically by use of iminium salts in the presence of a stoichiometric oxidant such as oxone. In 1983, Davis and coworkers introduced chiral 2-sulfonyloxaziridines for the stoichiometric asymmetric epoxidation of unfunctionalized alkenes. These reagents transfer an oxygen atom to the alkene in a similar way as dioxiranes [881]. In 2004, Bulman Page and coworkers succeeded in developing a highly enantioselective alkene epoxidation (11.2) with oxone applying their BINOL-derived azepinium salt **210** as catalyst [882,883]. $H_2O_2$ [884] or NaOCl [885] can replace oxone as oxidant in this reaction. In the meantime, more chiral iminium salts have been proposed as catalysts for the enantioselective epoxidation of alkenes [886].





**210**

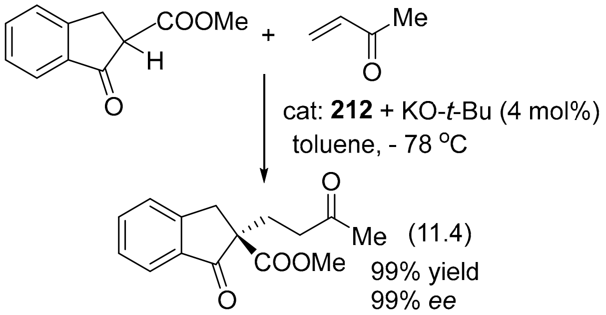
Hydroxylative dearomatization reactions of phenols offer an efficient way to assemble complex, biologically relevant compounds. In 2022, Buckley and coworkers disclosed an enantioselective method applying iminium salt **210** as catalyst for the oxidation of 2,6-dialkylphenol, 2,4,5- and 2,4,6-trialkylphenols. *In situ* oxidation of amine pre-catalysts **211** by $H_2O_2$ generates the catalyst **210**. The reactions (e.g., (11.3)) engender cyclohexa-2,4-dienone intermediates that are (4+2)-cyclodimerized [887].

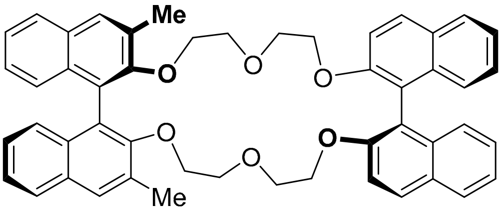


**211**

## 11.3. Crown Ethers

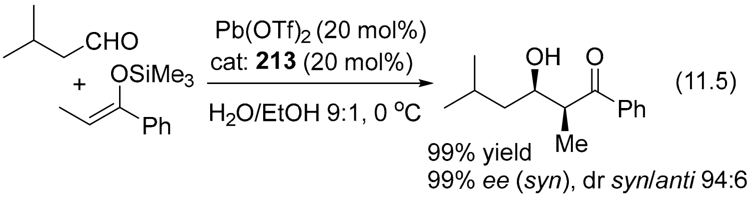
Since their discovery in 1967 by Pedersen [888], macrocyclic crown ethers have been applied in asymmetric transformations in parallel with cyclodextrins and calixarenes [889]. One speaks of asymmetric supramolecular catalysis, which often represents green chemistry. Crown ethers and their derivatives equilibrate with cationic complexes in the presence of alkali cations, ammoniums, and pyridiniums ions. This increases the nucleophilicity of their counter-anions (more "naked" anions, more separated from their cationic partners) [890]. In1981, Cram and Sogah reported the first examples of chiral crown ether-catalyzed Michael additions. Catalyst **212** + *t*-BuOK deprotonates the β-keto-ester forming a chiral enolate anion/cation pair that adds with one of its two faces to methyl vinyl ketone (reaction (11.4)) [891]. Such pioneering work created a new area of asymmetric supramolecular catalysis. Unfunctional crown ethers like **212** and **213** (see below) are chemically stable catalysts that can be engaged in reactions with aggressive reagents and high temperature.

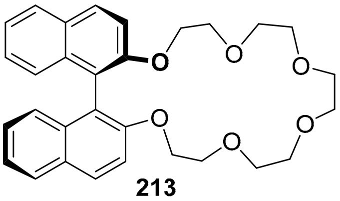




**212**

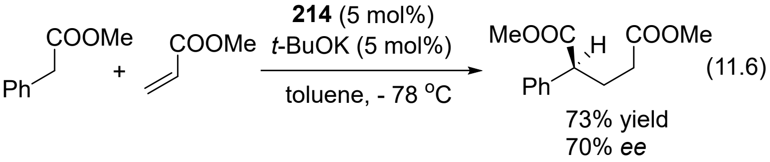
In 2000, Nagayama and Kobayashi reported that complexes of crown ethers and uncommonly used metal ions also serve as asymmetric supramolecular catalysts. They showed that the mixture of $Pb(OTf)_2$ and **213** was an effective chiral catalyst for asymmetric Mukayama aldol reactions of (*Z*)-silyl enol ether of propiophenone with isovaleraldehyde in aqueous solvent (reaction (11.5)) [892].

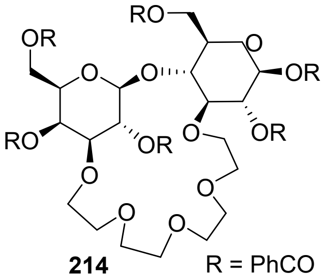




**213**

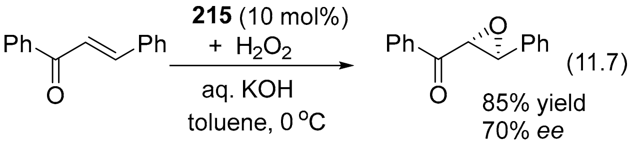
In 1986, the group of Penadés prepared lactose-derived crown ethers such as **214**. The 1:1 mixture of **214** and *t*-BuOK is a PTC that induced the asymmetric Michael addition (11.6) [893]. In the meantime, many more sugar-derived crown ethers have been prepared. Combined with a strong base such *t*-BuOK they catalyze the asymmetric Michael reactions of enones, acrylic esters, acrylonitriles, and α,β-unsaturated nitro compounds as well as alkene epoxidation, cyclopropanation and Darzens condensations [890].

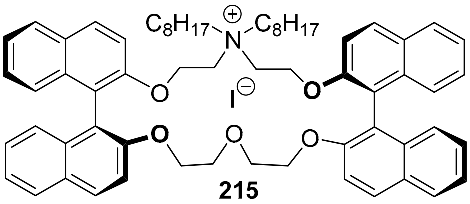




**214** R = PhCO

In 2015, the Kobayashi group catalyzed the direct asymmetric Michael additions of simple amides with α,β-unsaturated carbonyl compounds with a catalyst consisting of potassium bis(trimethylsilyl)amide (KHMDS) and a chiral crown ether [894]. In 2006, epoxidation (11.7) of 1,3-diaryl enones with $H_2O_2$ and azacrown ether-type catalyst **215** was examined by Hori and coworkers [895]. The alkyl groups on the nitrogen were shown to have a significant effect on the epoxidation yield and *ee*.





**215**

*11.4. Chiral N-Amine Oxides*

Following Denmark findings (Section 5.4) that a Lewis base such as phosphoramide **93** catalyzes the enantioselective allylation of benzaldehyde with allyltrichlorosilane (reaction (5.9)), the group of Nakajima in 1998 found that this reaction is catalyzed by *N*-amine oxides. With (*S*)-3,3-dimethyl-2,2′-biquinoline *N,N*′-dioxide (**216**) and in the presence of diisopropylethylamine good yield and enantioselectivity were observed for allylation (11.8) [896]. In 2002, Hayashi and coworkers found that only 0.01-0.1 mol% of 2,2′-bipyridine-*N,N*′-dioxide (MeCN, - 45 °C) was sufficient for a 96% yield and 94% *ee* of reaction (11.8) [897]. Since then, several other chiral *N*-amine oxides such a **217-220** (Figure 11.2**)** have been prepared. They catalyze the asymmetric allylation of aldehydes [898–900].

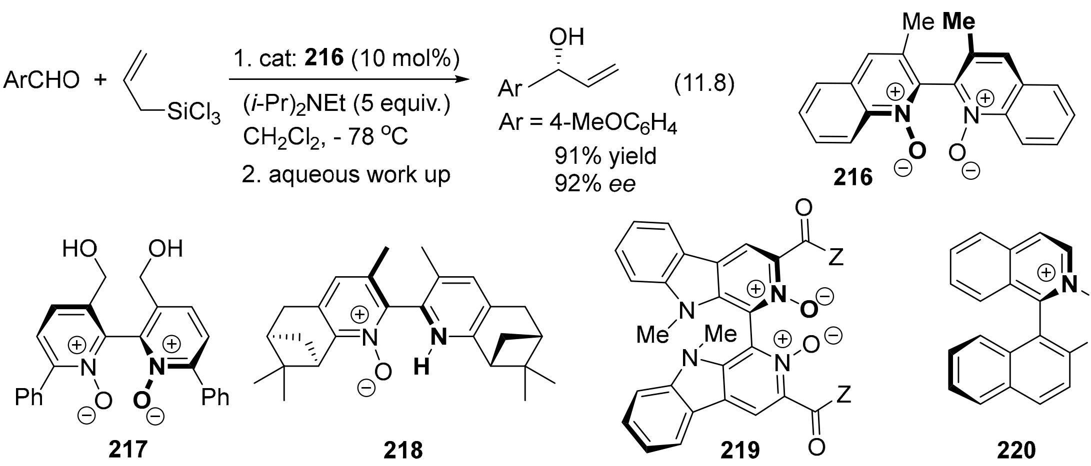
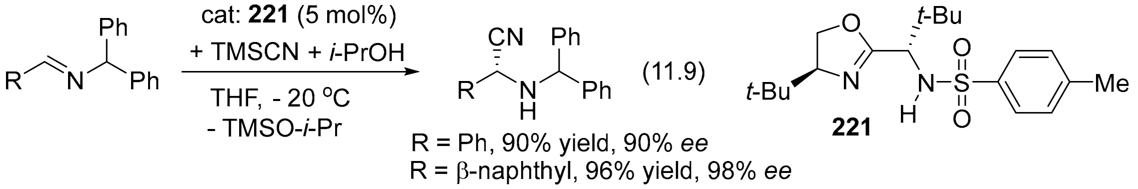


**Figure 11.2.** Examples of chiral *N*-amine oxide catalysts applied to asymmetric allylation of aldehydes (Nakajima, 1998; Hayashi, 2002).

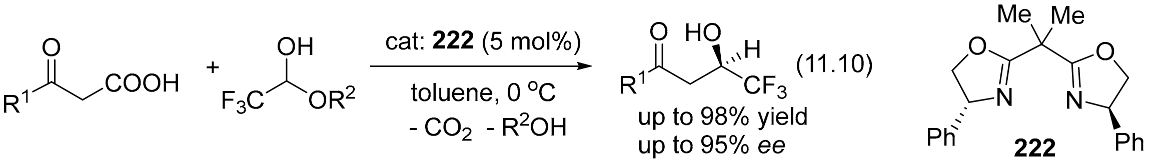
(*S,S*)-*N,N*-Bis (α-methylbenzyl) formamide catalyzes the enantioselective addition of allyl-and crotyltrichlorosilanes to aliphatic aldehydes. [901.]

### *11.5. Chiral Oxazolines and Bisoxazolines*

Chiral oxazolines [902] and bisoxazolines are ligands of metallic species. They play an important role in asymmetric catalysis [903]. In 2013, Ganguly, Khan and coworkers found chiral oxazoline **221** to be a good catalyst of the asymmetric Strecker reaction (11.9) (see also Section 4.1). The catalyst is bifunctional, with an acidic sulfonamide group and a weakly basic N atom of the oxazoline moiety. Activation implies interaction of H-CN (reagent) with the oxazoline (hydrogen bond acceptor) and hydrogen bridging between the imine (substrate) and N-H group of the sulfonamide [488].



In 2018, the group of Ma reported the asymmetric aldol reaction (11.10) catalyzed by the $C_2$-symmetrical bisoxazoline **222**. Activation implies hydrogen bridging between the N atom of **222** and the OH groups of substrate and reactant [904].



The Hofmann-Löffler-Freytag reaction uses N-halogenated amines to construct pyrrolidine rings and other nitrogen-containing heterocycles. It involves a radical-mediated cyclization, where a nitrogen-centered aminyl radical abstracts a hydrogen atom from a carbon atom generating a carbon-centered radical and an amine [905]. Under well-chosen conditions, the carbon-centered radical is converted into the corresponding carbenium ion intermediate by an oxidative radical-polar crossover (ORPC) process. In the presence of bisoxazoline catalysts such as **223**, Lu and coworkers showed in 2025 that the intramolecular quenching of the carbenium ion intermediate by the amine moiety can be enantioselective (Figure 11.3). In their reactions such as (11.11), alkyl benzoyloxycarbamates are converted into oxazolidinones. Blue light irradiation of neutral red (a dye used in biological research and histology, the photocatalyst) generates an electronically excited state that donates an electron to the RNH-OCOAr moiety. The latter splits into benzoyl anion and aminyl radical **224**. This radical is hydrogen-bridged with the catalyst **223**. Follows a (1,5)-hydrogen shift with formation of the carbon-centered radical intermediate **225**. The latter is oxidized by the radical-cation of the dye forming the corresponding carbenium ion intermediate. In the same time, the photocatalyst is recovered. The carbenium ion reacts with the tertiary amine ($R_3N$) giving the corresponding ammonium ion **226**. Intramolecular displacement of the ammonium ion by the bisoxazoline engenders chiral intermediate **227**, which undergoes face-selective intramolecular quenching by the primary amine [906].

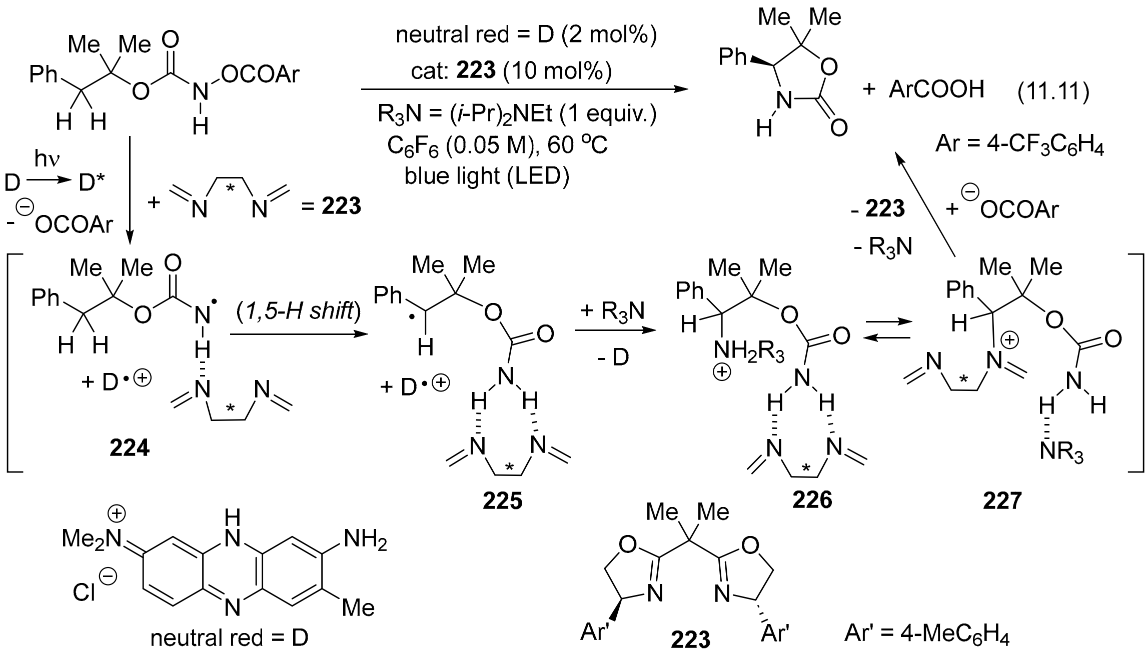


**Figure 11.3.** Example of merging organo-catalysis and photocatalysis. Asymmetric Hoffmann-Löffler-Freytag-type of reaction (Lu, 2025).

### *11.6. Chiral Iodine(I) Lewis Acids (XB Donor, σ-Hole Catalysts)*

Reissert-type dearomatization of quinoline with a silylketene acetal as nucleophile is catalyzed by the helical tetrakis-iodotriazole **228**. The XB donor **228** forms a complex anion **229** with the chloride anion [907]. It equilibrates with a chiral ion-pair containing the iminium ion (electrophile). The latter is attacked face selectively by the nucleophile (silylketene acetal). This is an example of halogen bonding catalysis reported by the group of García-Mancheño in 2023 (Figure 11.4) [908].

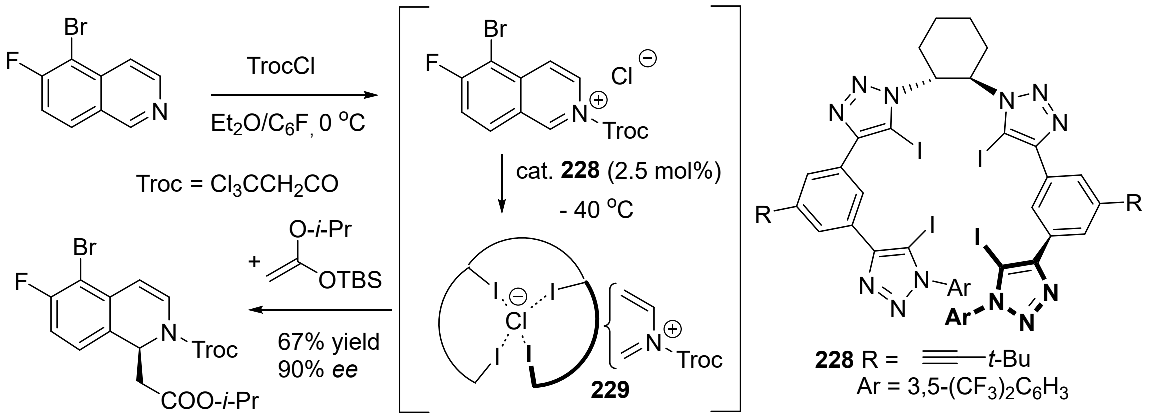
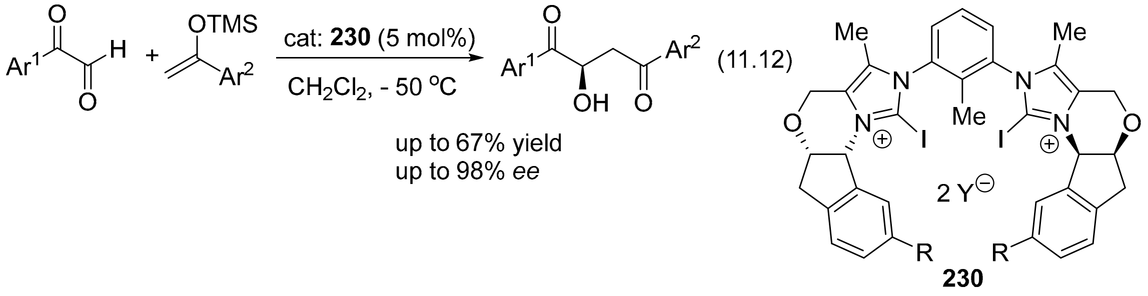


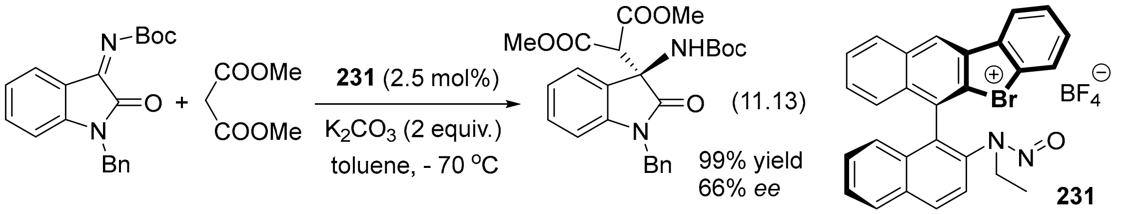
**Figure 11.4.** Example of halogen-bonding enantioselective catalysis applying a neutral tetrakis iodotriazole as catalyst (García-Mancheño, 2023).

Catalyst **228** is an iodine(I) XB donor. Other examples are the bidentate iodine(I) donors **230** prepared by Huber and co-workers. Derivative **230** with Y = $B(C_6F_5)_4$, R = $NHCOCF_3$ catalyzes the asymmetric Muyaiyama aldol reaction (11.12) [909]. In this case, the two C-I groups are $\sigma$-hole Lewis acids activating the carbonyl group of the aldehyde [910].

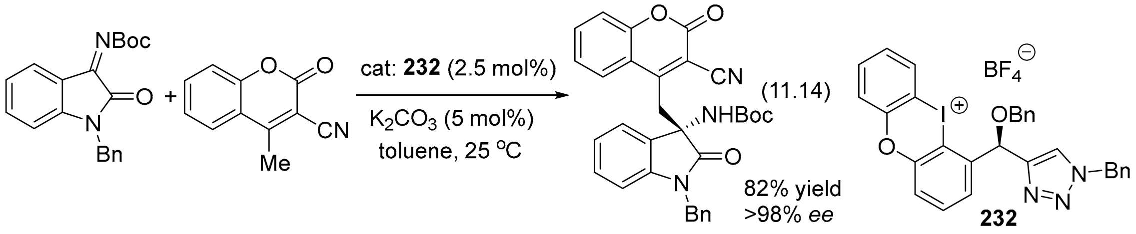


## 11.7. Chiral Halonium Salts as σ-Hole Catalysts

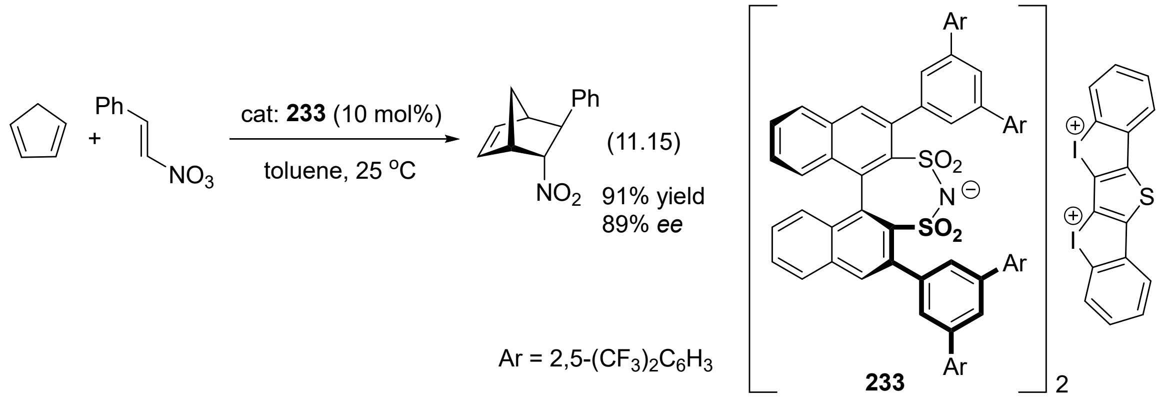
Bromonium and iodonium salts are hypervalent halogen compounds. They are Br(III)- and I(III)-XB donors ($\sigma$-hole Lewis acids). In 2023, Yoshida and coworkers disclosed their synthesis of chiral bromonium salts with N-nitrosamine functionalities as Lewis bases. These catalysts (e.g., **231**) are Lewis acid and Lewis bases in the same time. The enantioselective Mannich reaction (11.13) of malonic esters with ketimines represents an application [911]. In 2022, Yoshida and coworkers had reported the enantioselective formation of N,S-acetals by condensation of thiols to imines catalyzed by a binaphthol-derived iodonium salts similar to **231** [912].



In 2025, Nachstheim and coworkers prepared chiral triazole-substituted iodoniums salts (e.g.: 232) as XB donors. As for reaction (11.13) they catalyze the enantioselective vinylogous Mannich reaction of cyanomethyl coumarin with an isatin-derived ketimine. Nucleophilic additions to imines (e.g., reaction (11.14)) are activated through N···I(III) interactions [913].



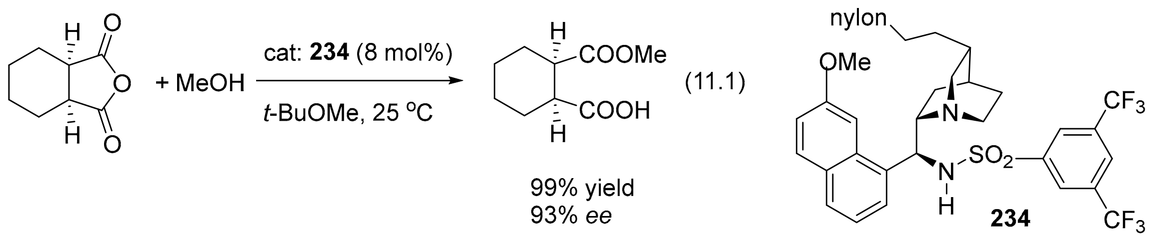
In 2025, the groups of List and Huber found that achiral bidentate iodine(III) based catalyst combined with chiral disulfonimides as counter-anions (e.g., **233**) catalyzes the enantioselective Diels-Alder reaction (11.15) of cyclopentadiene and nitrostyrene. This is an example of halogen bonding (N=O···I$^{(+)}$) with asymmetric counter-anion-directed catalysis [914].



## 12. Epilogue

Asymmetric organocatalysis has kept busy a great number of scientists for the last forty five years. Extremely useful methods of asymmetric synthesis not relying on toxic transition metals, nor on practically demanding biocatalysis, are now available. Both enantiomers of a large number of economically important compounds (drugs, crop protection agents, fragrances, flavours) can be prepared with the same ease and this with high yield and enantioselectivity. The studies have contributed a lot in our understanding of reaction mechanisms. Chemical space (the number of stable compounds that can be constructed with a given number of light atoms (H, B, C, N, O, F, Si, P, S, Cl, Br, I) is huge and probably will never be explored fully for the search of new asymmetric catalysts [915]. Chiral and non-chiral additive to chiral catalysts might have benificial effets on enantioselectivities and yields. This adds another dimension to the structural space to be explored.

The ideal chiral catalyst must be inexpensive (easy to make enantiomerically pure, low molecular weight), nontoxic, and easy to recover. As seen, recovery and recycling of a catalyst can be achieved by immobilization on a high surface solid polymer, such as polystyrene, nylon, chitosan, polymethylhydrosiloxane, glass beads, or magnetic nanoparticles [916]. An example from the List group combines a cinchona alkaloid-derived catalyst with a nylon-6,6 support through UV irradiation. The textile-immobilized organo-catalyst **234** was recycled more than 250 times for the enantioselective mono-addition of MeOH to *meso*-anhydrides (e.g., reaction (11.1)) with no loss in efficiency [917].



Costly catalysts should work in less than 1% (weight) compared with the substrate. Very often the organo-catalyst is nontoxic and thus can be left (e.g., < 0.1% by weight) in the final product to be sold. The reaction should be run in harmless solvent, if any, and under conditions economical in energy (no ccoling below 0 °C, no heating above 60 °C). When a solvent is necessary it must be nontoxic, easy to recover and should be inert (e.g., water, *t*-butyl methyl ether, tetrahydrofuran, pentane, ethanol, ethyl acetate, toluene), *i.e.*, it does not generate side-products by action of the substrate, reagents and catalyst. When the catalytic process furnishes a final product that is crystalline with less than 99.9% *ee,* as required for a drug, its crystallization or co-crystallization with an inert inorganic chemical might improve its enantiopurity [918]. The method might be too costly to develop when a relatively small amount of the compound is required (e.g., for exploratory pharmaceutical or/and medical studies). Thus, chiral chromatographic methods are used instead. If the compound does not crystallize, one makes a solid derivative of it, recrystallize the latter, and do the necessary chemistry to recover the desired compound. Often, racemates crytallize better than enantiopure enantiomers. Alternatively, separation methods that rely upon the formation of crystalline diastereomeric derivatives (salts, complexes, readily hydrolyzable derivatives) with a readily available enantiomerically pure recyclable chiral auxilliary might then be applied.

From what precedes, it is obvious that there is still a lot of opportunities for inventing new catalyts and developing greener and more economical asymmetric processes. The search of new catalysts has contributed a lot in improving our understanding of chemistry in general. Nucleophilic carbenes and $\sigma$-hole catalysts are pertinent examples.

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