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# Enantioselective Catalytic Formation of Quaternary Stereogenic Centers

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Enantioselective catalytic formation of tertiary stereogenic centers has nowadays reached an impressive level of maturity, as is reflected in the large variety of available methods that afford high yields and high stereoselectivities. However, the development of stereoselective approaches for the formation of quaternary stereogenic centers still represents an enormous challenge for synthetic chemists. On the other hand, biologically active molecules containing quaternary stereogenic centers provide an incentive for the development of new, selective, and useful processes. Over the last few years, breakthrough work relating to the formation of fully substituted carbon centers has appeared in the literature. In this review we discuss recent highlights of this new direction in catalysis research: the formation of quaternary stereogenic centers by enantioselective catalytic methodologies.



## 1. Introduction

The use of chirotechnology in academia and industry has achieved the goal of successfully generating tertiary carbon atom centers in a highly selective way, by the use of chiral auxiliaries, ligands, or catalysts.[1] However, the preparation of biologically active natural products and drugs bearing quaternary stereocenters still remains a highly demanding task.[2]

Every single new method for the construction of a fully substituted carbon center is a great advance in this challenging field. Over the last few years, new methodologies for the construction of quaternary stereocenters have appeared in the literature. Powerful catalytic methods that enable the enantioselective addition of nucleophiles to the rather unreactive ketones have been discovered. Several new concepts such as, for example, the double activation of both the nucleophile and the electrophile[3] have been introduced by several groups in order to solve the problems posed in the addition of reagents to ketones. Nowadays, the state of the art in this field has reached a new level, and these new methodologies have started to be incorporated in the syntheses of more complex structures.[4] These difficult transformations need the abilities of chemists for the development of new ligands and new promoters, in order to expand the scope of these new exciting reactions.

This overview is directed towards summarizing the best catalytic enantioselective methodologies discovered for the additions of nucleophiles to ketones, introducing some guidelines for the development of new processes. Nucleophilic Michael additions to α,β-unsaturated ketones resulting in the generation of quaternary stereogenic centers are also described, as well as other enantioselective processes. In addition, interesting new methodologies for the formation of quaternary stereogenic centers bearing amino groups are reported. The stereoselective formation of quaternary stereogenic centers has been discussed in some excellent recent reviews.[5] However, there has been a rapid growth of catalytic enantioselective reactions in this field over the last three years, and these new emerging methodologies are the subject of this review.

The definition of quaternary stereocenters sometimes gives rise to some disagreement between scientists, as quaternary stereocenters are normally considered to be quaternary carbon atoms substituted with four carbon atoms bearing four different substituents. However, quaternary stereocenters also include tertiary alcohols or amines, in which one carbon atom is replaced by a functional group or by a heteroatom. We make a distinction between full-carbon quaternary stereogenic centers, which are the most difficult to synthesize, and other "quaternary" stereogenic centers; in the last part of our review we present some strategies for the preparation of fully substituted all-carbon stereogenic centers. Since a Microreview is not intended to be comprehensive nor exhaustive, we have selected work from different authors, and we apologize for the most relevant omissions.

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### 1.1 Enantioselective Control with the Less Reactive Ketones: Problems

The addition of nucleophiles to aldehydes is an important and established process in organic synthesis. New stereogenic centers and C–C bonds are formed in a single step. In cases of the stereoselective catalytic version of this reaction, sets of nucleophiles such as enolsilanes, allylstannanes, -silanes, or -boranes, and zinc reagents can be used.[6] These nucleophiles have been extensively applied in solving difficult problems in the synthesis of natural products, biologically active products, drugs, or special materials. In the addition of chiral or prochiral nucleophiles to achiral or chiral aldehydes, secondary alcohols are obtained as mixtures of enantiomers, single enantiomers, or diastereoisomers. The chemical industry has devoted much effort to the preparation of chiral secondary alcohols by enantioselective hydrogenation methodologies.[7] The generation of tertiary carbon atom stereocenters can in most cases be achieved straightforwardly by use of the appropriate method involving a chiral auxiliary, reagent, or catalyst. However, synthetic access to complex, biologically active molecules containing tertiary alcohols and related systems is still problematic for organic chemists. The best and direct approach for the preparation of chiral tertiary alcohols is the enantioselective addition of organometallic reagents to a ketone.[8] Through the use of chiral organometallic reagents, the diastereoselective addition of the reagent to a ketone could take place. Although there are several reported examples of the addition of Grignard reagents[9] and organolithium[10] compounds to ketones, at least one equivalent of expensive and difficult-to-prepare chiral ligand needs to be used. Sometimes, as in the case of (–)-sparteine, the other enantiomer of the chiral ligand is not available.[11] Generally, chiral auxiliaries are expensive and sometimes multi-step syntheses are required for their preparation. The reduction of the amount of the ligand used for the enantiodiscriminating step is essential for issues of environmental control and cost-related problems. However, catalytic enantioselective additions of nucleophiles to ketones are rather difficult, as ketones are less reactive electrophiles than aldehydes, and the additions do not take place even in the presence of promoters. The higher temperatures required could be deleterious for enantioselectivity. Most of the time either the ketone is recovered unchanged, or byproducts deriving from its reduction, enolization, or dimerization are obtained. Reactions with ketones are normally endothermic,[12] and an organometallic reagent or organocatalyst needs to be able to differentiate the two enantiotopic faces of a carbonyl group, differentiating them through the steric and electronic properties of two quite similar flanking groups in the case of ketones.

### 1.2 Diels–Alder and Hetero-Diels–Alder Reactions of Ketones

Normally, α,β-unsaturated non-chelating ketones are difficult substrates for Diels–Alder reactions, and only recently successful organocatalytic methodologies[13] and the use of extremely active Lewis acids[14] have allowed their use.

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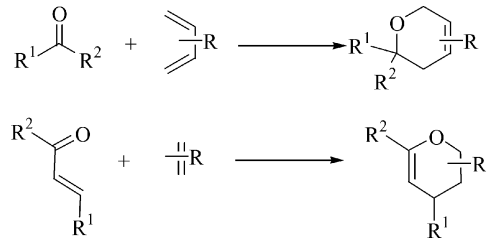
In the other case, the ketone undergoes a direct reaction with a diene, from which two distinctive products might be obtained. In hetero-Diels–Alder reactions of ketones, the carbonyl reacts with a diene, forming a pyran ring. When an electron-poor double bond is used, the pyran could be formed in an electronically inversed Diels–Alder reaction (Scheme 1).



Scheme 1. Hetero-Diels–Alder reactions with ketones.

The majority of recent research into hetero-Diels–Alder reactions of activated ketones has been focussed on asymmetric catalysis. The substrate in these reactions, such as an α-keto ester, is set up for bidentate coordination to a chiral Lewis acid, typically a copper bisoxazoline (CuBOX) complex. The bidentate coordination of the α-keto ester to the chiral Lewis acid activates the keto functionality for reaction, and the tight coordination is more effective in discriminating one of the faces of the ketone functionality. Jørgensen has described enantioselective hetero-Diels–Alder reactions of ketones with Danishefsky-type dienes in the presence of chiral copper(II) complexes. The first catalytic highly enantioselective version of this hetero-Diels–Alder reaction was catalyzed by the $C_2$ *t*Bu-(bisoxazoline)(BOX)-Cu(OTf)$_2$ complex **1** (Figure 1).[15] Remarkably, only 0.05 mol-% of the catalyst was necessary to achieve good enantioselectivity.

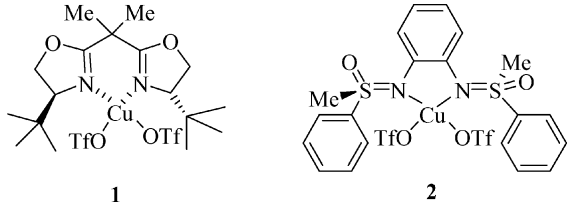


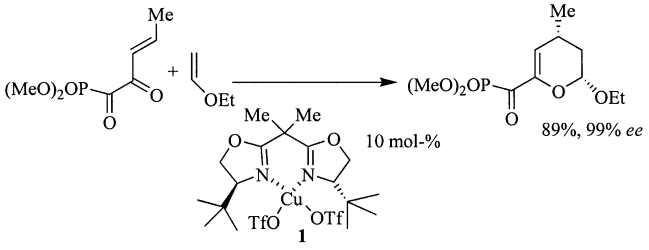
Figure 1. Box- and BiSOX-Cu(OTf)$_2$ complexes.

The reaction is limited to the employment of the reactive Danishefsky diene, while a more reactive electrophilic ketone such as a ketomalonate is necessary for reaction with other dienes.[16] Bolm et al. have successfully applied the chiral bis(sulfoximine) (BiSOX)-Cu(OTf)$_2$ complex **2** as a catalyst for the hetero-Diels–Alder reaction of ketomalonate with cyclohexadiene (Figure 1). This reaction afforded the hetero-Diels–Alder adduct in excellent yield and enantioselectivity.[17]

Later developments by the same group led to the introduction of a new class of quinoline-based $C_1$-symmetric monosulfoximine ligands. These new ligands, in combination with Cu(OTf)$_2$ as the Lewis acid, also afforded hetero-Diels–Alder adducts with high enantiocontrol. The X-ray structure of one of the chiral quinoline-based $C_1$-symmetric ligands, and a mechanistic study, have shown that $C_2$ geometry is not necessary to achieve good enantioselectivity with distorted tetrahedral geometry of these copper complexes.[18] This strategy was also pursued in other catalytic reactions by Bolm and co-workers. Only a few other examples of enantioselective hetero-Diels–Alder reactions with ketones have been published.[15b]

The number of hetero-Diels–Alder reactions in which the ketone functionality is part of a heterodiene is much higher than that of the hetero-Diels–Alder reactions of ketones with dienes discussed above. The first catalytic inverse-electron demand enantioselective hetero-Diels–Alder reactions were reported by Kanemasa, who used titanium derivatives.[19]

In subsequent years, CuBOX complexes were applied for the synthesis of optically active dihydropyrans. The use of activated α,β-unsaturated acyl phosphonates was introduced by Evans (Scheme 2).[20]



Scheme 2. Activated acylphosphonates in the synthesis of dihydropyrans.

Evans and Jørgensen independently reported the use of activated α,β-unsaturated α-keto esters.[21] Good levels of diastereo- and enantioinduction can be achieved for both substrate classes. Wada has also developed a novel catalytic asymmetric tandem-transesterification-intramolecular hetero-Diels–Alder reaction.[22]

## 2. Asymmetric Synthesis of Tertiary Alcohols

### 2.1 Enantioselective Catalytic Alkylation of Ketones

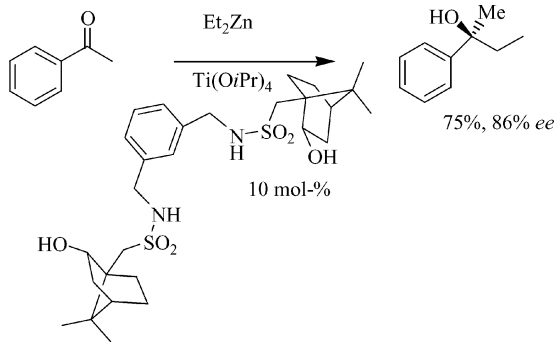
In principle, a variety of organometallic reagents is available for the catalytic enantioselective transfer of alkyl groups. Unfortunately, most of them are particularly reactive, and background reactions are so fast that the design of a catalytic process becomes quite difficult.

In contrast, while organozinc reagents are quite unreactive, they can tolerate the presence of many functional groups, and they are highly selective in nucleophilic addition reactions to carbonyl compounds. Thus, alkyl-, vinyl-, and arylzinc reagents add to aldehydes with excellent chemoselectivities in the presence of Lewis acid catalysts.[23] If a chiral catalyst is used, very high enantioselectivities can be achieved. While hundreds of ligands have been reported

for catalytic enantioselective organozinc additions to aldehydes, now considered a benchmark reaction for evaluating new chiral ligands, much less work on asymmetric organozinc additions to ketones has been reported.

In 1998, Ramón and Yus described the first examples of asymmetric additions of alkyl groups to ketones:[24] the alkylation of ketones with dialkylzinc reagents and a titanium-based catalyst, employing titanium tetraisopropoxide in combination with a camphor-based hydroxysulfonamide ligand. To improve his results further, Yus thought of combining two molecules of the catalyst in one molecule and developed a series of $C_2$-symmetric ligands (Scheme 3).




Scheme 3. $C_2$-symmetric sulfonamide ligand used by Yus in the catalyzed addition of $Et_2Zn$ to acetophenone.

Walsh[25] and then Yus[26] described the most successful ligand to date for the addition of alkylzinc reagents to ketones in the shape of the chiral sulfonamide diol **3** (Figure 2).

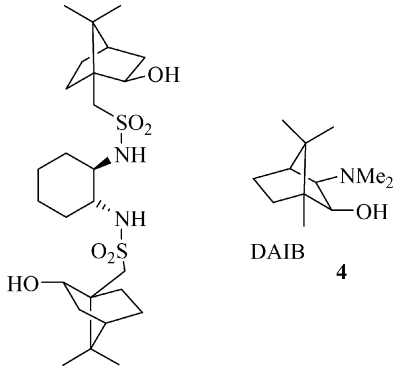



Figure 2. Sulfonamide ligand **3** and DAIB ligand **4**.

The ligand is prepared simply from commercially available camphorsulfonyl chloride and *trans*-diaminocyclohexane; the active ligand is the major diastereoisomer obtained after reduction with $NaBH_4$. Catalyst loading of 2 mol-% was used in conjunction with $Ti(OiPr)_4$ for catalysis of general asymmetric additions of alkyl and functionalized alkyl groups to ketones, with enantioselectivities of up to 99% *ee* being obtained in most cases. In some cases side reactions – this is determined by the steric hindrance of the ketone – are observed. Interestingly, the reaction is easily scalable, and concentrated or neat reaction conditions have been developed, in order to reduce or eliminate the need for solvents in these reactions.[27] Yus has also reported a comprehensive overview of the influence of different chiral or achiral diamines in this reaction.[28]

Another advantage of this ligand is its applicability in consecutive, one-pot reactions. Walsh described the use of this ligand and $Ti(OiPr)_4$ in the catalyzed additions of $Et_2Zn$ and $Me_2Zn$ to cyclic α,β-unsaturated ketones, obtaining good yields and enantioselectivities without any traces of Michael adducts. 2-Substituted enones are good substrates as well, and the products, obtained in enantiomeric excesses of up to 99%, can undergo diastereoselective epoxidation by exposure of the reaction mixture to oxygen (1 atm). In the case of the addition of $Me_2Zn$, it was necessary to add 2 equiv. of $Et_2Zn$ before exposure to oxygen. Functionalized zinc reagents, prepared by the procedure described by Knochel,[23b] were used by Walsh in the synthesis of highly functionalized tertiary alcohols, with impressive enantiomeric excesses for the selected ketones.[29]

In general, with ketones it is necessary to overcome the low reactivity of these substrates by use of the general concept of double activation.[30] Salen metal complexes are well suited to exhibit such behavior, thanks to their distinctive properties (Figure 3).[31] Zn(Salen) complex **5** (Figure 3, M = Zn) was able to activate $Et_2Zn$ in a catalytic reaction with aldehydes.[32]

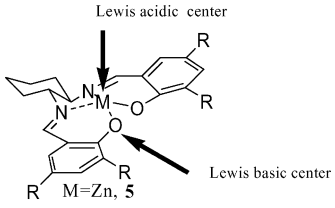


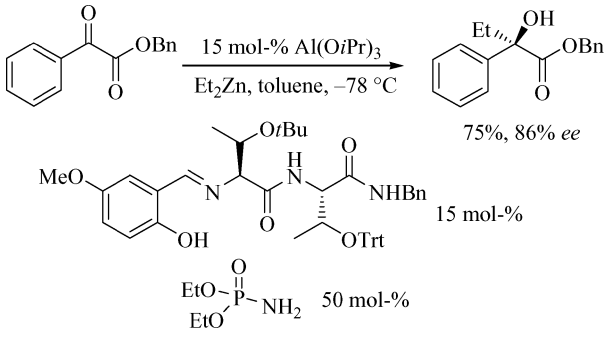

Figure 3. Zn(Salen) metal complex and its distinctive properties.

This concept of double activation was intensely elaborated by Kozlowski, who developed Lewis acid–Lewis base zinc and titanium Salen complexes for the addition of zinc reagents to aldehydes. The addition of dialkylzinc reagents to keto esters was also effectively catalyzed by titanium Salen complexes, while reduction of the keto ester, a side reaction that always accompanies this reaction, was minimized.[33]

Another bifunctional catalyst for the addition of $Me_2Zn$ to α-keto esters was developed by Shibasaki. The catalyst was prepared in two steps from commercially available *cis*-4-hydroxy-D-proline methyl ester;[34] the proline hydroxy group enhances the reactivity of $Me_2Zn$. The background reaction is quite fast, but can be avoided by slow addition of $Me_2Zn$ to the mixture containing the catalyst, while it is also necessary to perform the reaction in the presence of an additive: *i*PrOH used in a precise amount of 27 mol-% was the most successful, leading to good enantioselectivities in reactions with aromatic and heteroaromatic ketones. The role of the *i*PrOH additive was analyzed by nonlinear effects studies, and it was shown that it changes the nature of the catalyst into a monomeric form.

Recently, another publication by Hoveyda and Snapper also described the addition of alkylzinc species to α-keto esters. The use of their Hoveyda–Snapper privileged catalysts,[35] formed from Schiff bases combined with dipeptides,[36] promoted the addition of $Me_2Zn$ and $Et_2Zn$ to α-keto esters. The reaction is performed through the use of catalytic amounts of an aluminium complex that is prepared in situ by treating the Schiff base with $Al(OiPr)_3$, in the presence of additives (Scheme 4). The role of the additive is to occupy a coordination site during the nucleophilic addition, thereby enhancing steric hindrance and the face selectivity of the process.[37]




Scheme 4. Addition of $Et_2Zn$ to keto esters promoted by a peptide-derived ligand.

Another effective and quite simple ligand for the addition of dialkylzinc to ketones was described by Pedro,[38] while in 1998 Fu reported the first example of a catalytic enantioselective addition of a phenyl group to ketones, using Noyori's DAIB ligand **4** (Figure 2).[39] Although the use of $Ph_2Zn$ afforded poor results, the mixed reagents formed by the addition of MeOH improved yields and enantioselectivities. Although good results had been obtained in the addition of phenyl groups to aldehydes,[40] until recently the breakthrough reported by Fu remained an isolated example. Walsh and Yus, however, simultaneously described the use of ligand **3** for the addition of phenyl groups to ketones (up to 99% yield, 80–91% *ee* values).[24,25,41] In both examples aromatic or unsaturated ketones are good substrates, and even dialkyl ketones gave good yields and enantioselectivities.

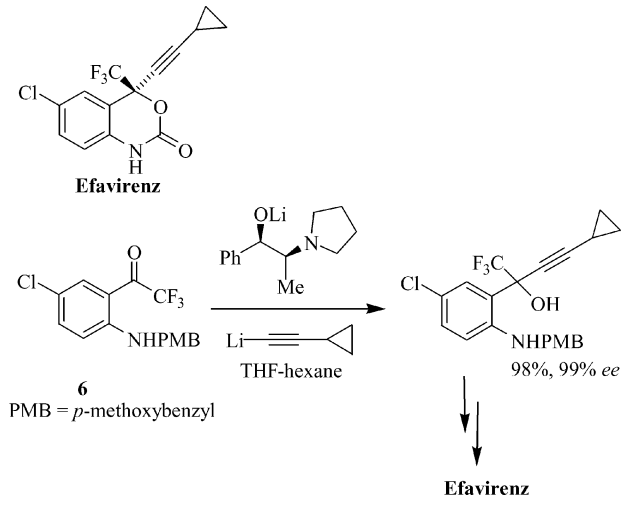
Quite interesting results relating to the use of α-halo ketones in asymmetric phenylation were reported by Walsh. Treatment with $Ph_2Zn$, promoted by 10 mol-% of ligand **3**, gave the desired products, which could subsequently be transformed into chiral epoxides in high yields. On the basis of his observation that 2-substituted α,β-unsaturated ketones were good substrates for the addition of zinc reagents when ligand **3** was used, Walsh investigated the addition of phenyl groups to these substrates. Enantioselectivities of up to 97% and excellent yields were obtained. Among all the substrates investigated, 2-iodo and 2-bromo substituents gave excellent results and are useful products for cross-coupling reaction.

The addition of vinyl groups to aldehydes is a reaction well known from pioneering studies by Oppolzer.[42] The addition of vinyl groups to ketones by the Wipf protocol,[43] which consists of hydrozirconation of alkynes with Schwartz's reagent, followed by transmetalation with $Me_2Zn$, was investigated by Walsh. Through the use of ligand **3** and $Ti(OiPr)_4$ with 5–10 mol-% of catalyst loading, a variety of alkynes and ketones were employed in a straightforward methodology that afforded highly functionalized tertiary alcohols in good yields and with good enantioselectivities.[44] Again, α,β-unsaturated ketones substituted in their 2-positions gave high enantioselectivities in this reaction. To date no other ligand superior to ligand **3** in the enantioselective transfer of alkyl groups to ketones has been designed. Walsh also showed that a ligand derived from *trans*-1,2-diaminocyclopentane afforded slightly lower enantiomeric excesses in the same reaction, probably due to the greater conformational freedom of the cyclopentane ring.[45]

The addition of arylboronic acids to particularly reactive ketones has been reported by Hayashi, who described enantioselective additions of arylboronic acids to isatins promoted by Rh complexes.[46]

### 2.2 Enantioselective Catalytic Additions of Acetylenes to Ketones

Since ketones are less reactive electrophiles than aldehydes, the development of new methods for enantioselective additions of acetylenes to ketones is more challenging. However, the controlled synthesis of quaternary stereogenic centers is important for the preparation of enantiomerically pure natural products and pharmaceuticals, so there is a clear need for such methodologies. The synthesis of such compounds by asymmetric addition of carbon nucleophiles to ketones has so far been met only with limited success. One successful example is represented by the enantioselective synthesis of Efavirenz, a potent nonnucleosidal HIV reverse transcriptase inhibitor that has been approved by the US FDA for the treatment of AIDS (Scheme 5).

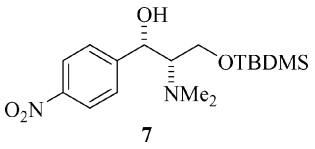



Scheme 5. Efavirenz, a potent nonnucleosidal HIV reverse transcriptase inhibitor.

Thompson and co-workers have described the addition of lithium cyclopropylacetylide to *p*-methoxybenzyl-protected ketoaniline **6** in 98–99% *ee* values.[47,48] However, the successful outcome of the reaction relies on the use of large amounts of (1*R*,2*S*)-*N*-pyrrolydinylnorephedrine as the chiral ligand, and the protection of the aniline moiety. Tan has reported the direct alkynylation of ketoaniline **6** (up to 99.2% *ee*) with use of alkynyllithium or alkynylmagnesium reagents together with stoichiometric amounts of chiral zinc aminoalkoxides, again employing (1*R*,2*S*)-*N*-(pyrrolydinyl)-norephedrine.[49] The reaction has been carried out successfully on a multi-kilogram scale and is probably the most efficient synthesis of Efavirenz to date.[48]

Zinc triflate is able to activate alkynes through coordination to the triple bond. Carreira performed spectroscopic in situ measurements to study this labile coordination, and was able to demonstrate that in the presence of an organic base a reversible deprotonation of the alkyne occurs, resulting in the formation of a reactive zinc acetylide.[50] Carreira has used *N*-methylephedrine as a chiral base, establishing a direct, straightforward procedure for the enantioselective alkynylation of aldehydes.[51] It is worth mentioning that zinc metal is used in catalytic amounts. This reliable procedure was also used in enantioselective syntheses of natural products, but this methodology is not yet applicable for less reactive ketones. Although $In(OTf)_3$ could replace $Zn(OTf)_2$ for alkynylation of ketones by the use of organic bases,[52] no enantioselective variant has yet been published. More strongly activated ketones are reactive enough for the Zn acetylides formed in situ by Carreira's methodology. In fact, Jiang used their catalyst system described above for additions of zinc acetylides to α-keto ester derivatives.[53] He reported that ligand **7** (Figure 4) could be used to catalyze the enantioselective addition of zinc alkynylide to α-keto esters, obtaining the desired products in 73–94% *ee* values.



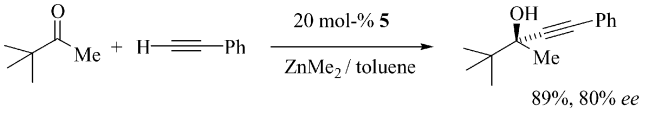

**7**

Figure 4. Jiang's ligand for the catalytic addition of zinc alkynilides to keto esters.

*N*-Methylephedrine was also used in one example. In this case 22 mol-% of *N*-methylephedrine was used and, as reported previously, higher temperatures (70 °C) were critical to ensure high turnover numbers. Base and $Zn(OTf)_2$ were used in catalytic amounts. Hindered aliphatic as well as aromatic α-keto esters as substrates gave tertiary α-hydroxy-β-ynyl esters with excellent enantiomeric excesses of up to 94%.

Jiang and Feng also studied the asymmetric alkynylation of PMB-protected ketoanilines.[54] Excellent *ee* values of up to 99% were obtained with lithium cyclopropylacetylide as nucleophile and $C_2$-symmetric diamino diols as chiral ligands. As alternative zinc sources, commercially available or readily prepared solutions of $Me_2Zn$ or $Et_2Zn$ were suitable for forming the active acetylides. However, $Me_2Zn$ or $Et_2Zn$ are not capable of deprotonating phenylacetylene, and no reaction occurs between these two reagents.[55] In this case, an activation of the $R_2Zn$ reagents towards the deprotonation step is necessary. Although the low reactivity of ketones is well known, zinc acetylides formed in situ by the reaction of phenylacetylene with $Me_2Zn$ can be used for the direct addition of acetylides to ketones. The activation role of $Me_2Zn$ in the subsequent deprotonation is played by the electrophile itself, through coordination to $Me_2Zn$. As soon as the zinc acetylene derivatives are formed, they quickly react with ketones through two possible transition states.[56] Care needs to be taken to avoid low enantiomeric excesses in the alkynylation of ketones caused by inefficient transmission of chiral information in the enantiodetermining step due to the competing and fast noncatalyzed reaction. On the other hand, if the alkynylation is performed with solutions of $Me_2Zn$ or $Et_2Zn$ in the presence of a chiral ligand, the deprotonation step is probably activated by the chiral ligand itself, which also controls the enantiodetermining step.

The first general method that allowed the enantioselective addition of acetylenes to ketones was reported by Cozzi and is based on the Salen framework (Scheme 6 and Figure 3).[57]



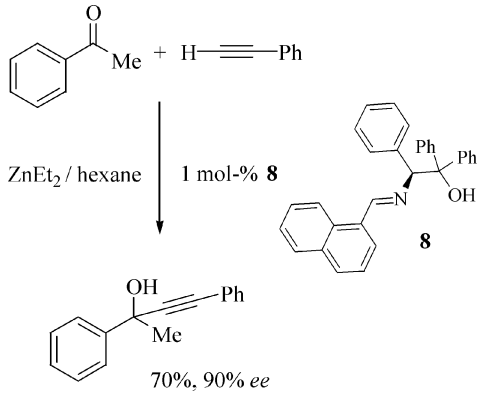

Scheme 6. Addition of phenylacetylene to ketones promoted by Zn(Salen) **5**.

Salen has peculiar properties – its metal complexes are able to act in a cooperative manner[31] and can behave as bifunctional Lewis acid–Lewis base catalysts (Figure 3).[58] The oxygen atoms of Salen metal complexes can coordinate to reactive organometallic fragments.[59] Although only moderate enantioselectivities were obtained, the use of third-generation Salen ligands by Katsuki[60] improved yields and enantioselectivities. Moreover, with these Salen ligands it was possible to reduce the amount of ligands used in the alkynylation to 8 mol-%.[61] Recently, a different Schiff base derived from a sterically hindered amino alcohol was used in the alkynylation of ketones. Wang showed that only 1 mol-% of ligand **8** was sufficient to catalyze the alkynylation of aliphatic and aromatic ketones in hexane (Scheme 7).[62]

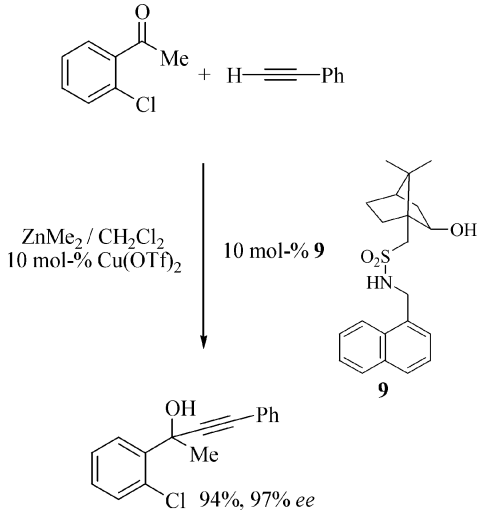
One of the best methods for the addition of alkynes to ketones was reported by Chan.[63] This method is based on the combination of $Cu(OTf)_2$ with camphorsulfonamide ligand **9** (Scheme 8).

This reaction is probably mediated by a $Cu^{I}$ complex formed in situ by the reduction of $Cu^{II}$ with $Me_2Zn$, since the [Cu(OTf)]benzene complex is also an effective catalyst.[63b] Surprisingly, other suitable ligands for copper, such as PyBOX,[64] were completely ineffective, and subtle




Scheme 7. Efficient alkynylation of ketones with ligand **8**.




Scheme 8. Alkynylation of ketones in high *ee* values with the ligand **9** developed by Chan.

changes in the steric hindrance of the camphorsulfonamide caused the failure of the reaction. The bis-camphorsufonamide ligand **3** used for promoting the addition of $R_2Zn$ to ketones is not suitable for catalyzing the addition of phenylacetylene, as was recently reported by Yus.[28] The method described by Chan is well suited for aromatic ketones, and up to 97% *ee* values are obtained, but aliphatic ketones are in general poor substrates. Several effective ligands for the alkynylation of ketones were developed by Wang (Figure 5).[65] In some cases good enantioselectivities could be achieved with aromatic and aliphatic ketones. These ligands are simply prepared chiral amino alcohols derived from phenylalanine and have previously been shown to give good enantioselectivities in the alkynylation of both aldehydes and imines.

Bulky groups introduced near the oxygen atom are likely to be responsible for enhanced stereoselectivity, since they might prevent dimerization of the zinc catalyst in solution.[66] In another example, Wang used easily accessible and inexpensive quinine as chiral ligand for a substoichiometric (80 mol-%) addition of phenylacetylene to ketones.[67] In this case, a combination of $Me_2Zn$ and

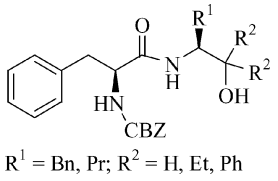



Figure 5. Peptide ligands introduced by Wang.

$AlMe_3$ was used, and the asymmetric alkynylzinc addition to unactivated aromatic ketones proceeded in 70–89% *ee* values.

Cozzi[68] and Wang[69] have found that BINOL (**10**, Figure 6) can be used in enantioselective additions of acetylenes to ketones with promising results in terms of yields and enantiomeric excesses.

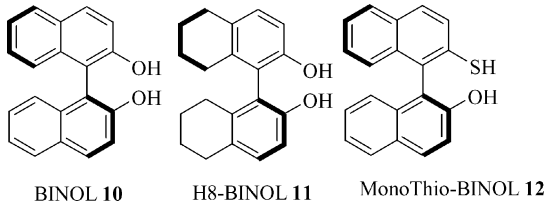



Figure 6. BINOL (**10**), H8-BINOL (**11**), and MonoThio-BINOL (**12**) ligands.

The two procedures, although similar and derived from the same chiral ligand, are based on completely different concepts. Wang carefully examined the ratio between BINOL and $Ti(OiPr)_4$. Contrary to expectations, the use of fewer equivalents of $Ti(OiPr)_4$ was key for promoting the BINOL-catalyzed alkynylation of ketones. This finding can be explained by the fact that stronger Lewis acidic metal complexes need to be used with less reactive ketones. Through the use of 30 mol-% of BINOL, enantioselectivities of up to 92% were obtained for 3-methoxyacetophenone. In the case of the typically more problematic aliphatic ketones, only inferior *ee* values could be achieved. In our titanium-BINOL-catalyzed addition of phenylacetylene to ketones, we started with the idea that titanium acetylides are obtained by equilibrium between $Ti(OiPr)_4$ and $R_2Zn$, as pointed out in careful studies by Gau[70] and Walsh.[71]

Since $Me_2Zn$ is highly flammable and expensive, the direct preparation of titanium acetylide was considered. Titanium acetylides were described by Seebach,[72] and are extremely reactive compounds, storable only at low temperature and stabilized by coordination with electrophiles. To overcome the use of $R_2Zn$ in additions of acetylenes to ketones, we have described the enantioselective catalytic addition of titanium phenylacetylene, prepared in situ, promoted by catalytic amounts of BINOL. The results in terms of yield and stereoselectivity are similar to those reported by Wang. However, the extreme reactivity of titanium acetylides makes the use of low temperature obligatory for this method, and it is therefore not adaptable to the more reactive aldehydes, which react too quickly at –78 °C.

All methods so far described in this section can afford good stereoselectivities but are not general for different kinds of acetylenes. Recently, however, Trost[73] and Shibasaki[52] have described a more general method for the addition of different types of acetylene to aldehydes, although the corresponding reactions with ketones were unsatisfactory. In this context, the admission of additives such as HMPA could be helpful in promoting exchange reactions between $R_2Zn$ and functionalized alkynes[74] when the alkynes were less acidic then phenylacetylene or bore groups that were unstable under the harsh reaction conditions necessary for the deprotonation step.

### 2.3 Enantioselective Allylation of Ketones

Chiral homoallylic alcohols represent a class of compounds that can be widely used in the synthesis of biologically active compounds. Many different organometallic compounds have been shown to catalyze additions of allylorganometallic reagents to aldehydes, as discussed in a recent review.[6] However, far fewer methods in which an organometallic reagent is used to transfer an allylic group to a ketone have been developed. One example is the addition of an allylsilane to a carbonyl group, known as the Sakurai–Hosomi allylation, one of the most reliable methods for providing access to homoallylic alcohols. Nontoxic, stable, and inexpensive allyltrialkylsilanes and allyltrialkoxysilanes are used as nucleophiles in this reaction. However, although excellent examples of asymmetric Sakurai–Hosomi allylations of aldehydes with these reagents have been reported, only a few examples of enantioselective Sakurai–Hosomi reactions with ketones have been described.

Yamamoto reported enantioselective additions of allyltrimethoxysilane to ketones promoted by chiral silver complexes (Scheme 9).[75]

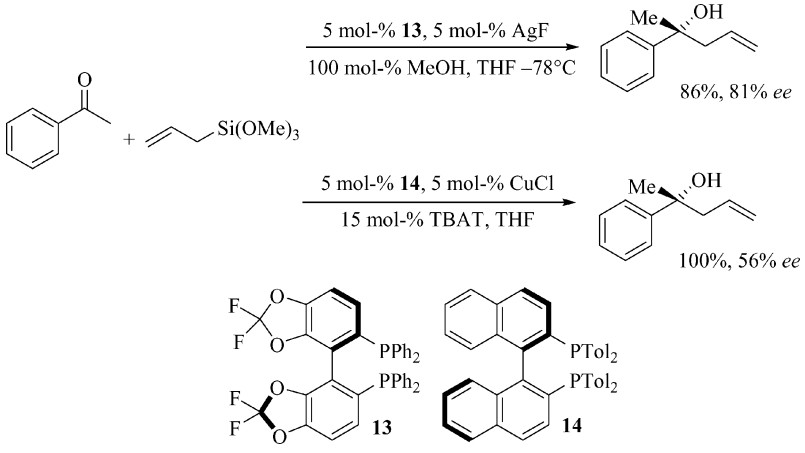
There are several interesting features to this method: the reaction is conducted with a complex of AgF and a chiral phosphane in THF, and MeOH is added in order to dissolve the AgF in THF and to enhance the turnover of the catalyst through protonation of the silver alkoxide intermediate. The chiral phosphane employed is (*R*)-DIFLUORPHOS (**13**),[76] which leads to predominant formation of a monomeric phosphane–AgF complex, due to the poor electron-donation ability of its phosphorus atom. Other phosphane ligands afford mixtures of dimeric phosphorus species. Shibasaki also described a catalytic enantioselective allylation of ketones using TolBINAP (**14**, Scheme 9), with allyltrimethoxysilane as allylating reagent.[77]

However, only moderate enantioselectivities of up to 61% *ee* could be obtained with use of 15 mol-% of TolBINAP. Since allylboronates can be catalytically activated by a Lewis acid,[78] Shibasaki performed the addition in the presence of allylboronate. After intensive screening of chiral ligands and optimization of catalyst preparation methods, a combination of CuF, prepared in situ by reduction of $CuF_2 \cdot 2H_2O$ (15 mol-%), and *i*Pr-DuPHOS (**15**, 30 mol-%) gave the best enantioselectivity in DMF as the reaction solvent (Scheme 10).[79] Addition of 20 mol-% of $La(OiPr)_3$ dramatically accelerated the reaction, led to increased yields, and allowed the catalyst loading to be decreased. The substrate generality of this reaction is broad, and enantiomeric excesses of up to 91% were obtained in short reaction times at –40 °C.

The same allylboronate was also used by Schaus in an organocatalytic allylation methodology promoted by a chiral Brønsted acid.[80] Although the procedure is quite simple and requires BINOL (**10**) derivatives, the scope of the reaction is limited to unsaturated and aromatic ketones.

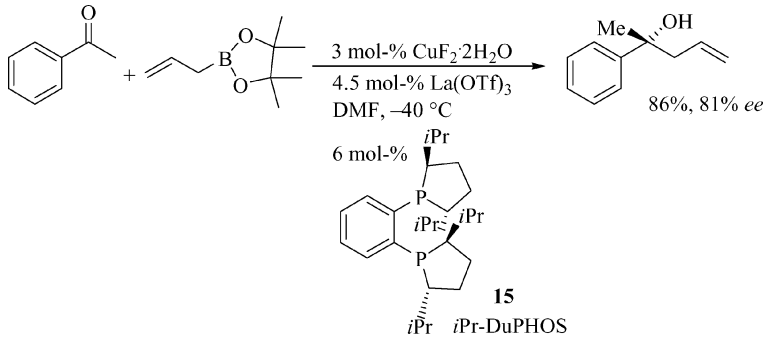
The use of allyltin derivatives in the enantioselective catalytic allylation of ketones was first reported by Tagliavini,[81] who used titanium BINOL derivatives. In order to overcome the reduced reactivity of ketones, tetraallyltin was used in the reactions in conjunction with 20–30 mol-% of a (BINOLate)Ti-based catalyst. The allylation products of the ketones were isolated with up to 65% *ee* values with use of 20 mol-% BINOL and titanium tetraisopropoxide.

The first highly enantioselective catalyst for the asymmetric allylation of ketones was reported by Maruoka and co-workers.[82] The catalyst, based on titanium tetraisoprop-




Scheme 9. Enantioselective allylation of ketones promoted by a silver DIFLUORPHOS (**13**) complex and by TolBINAP (**14**) complexes.

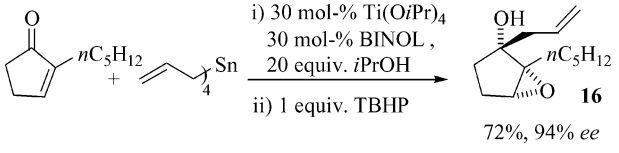
  




Scheme 10. The pioneering studies of allylation of ketones performed by Shibasaki's group.

oxide (60 mol-%), BINOL (60 mol-%), and a diamine ligand (30 mol-%), gave 90 and 92% *ee* values with acetophenone and 2-acetonaphthone, respectively. Unfortunately, the substrate scope of this catalyst was limited, and the authors speculated that the role of the bridging ligand is to form an active bimetallic catalyst, positioning the titanium centers such that they can both activate the substrate and nucleophile simultaneously.

Walsh was able to improve the system described by Tagliavini with his observation that *i*PrOH liberated in the reaction had a beneficial impact on the enantioselectivity of the catalyst.[83] Therefore the catalyst was synthesized with additional propan-2-ol, considerably improving the enantioselectivity (up to 95% *ee*). The scope for the use of different allyltin reagents is limited: Walsh reported that tetramethallyltin gave only low enantioselectivity in the same protocol as used for tetraallyltin. He also found, however, that the reaction conducted in $CH_3CN$ in the presence of H8-BINOL (**11**, Figure 6) afforded a 25% increase in enantioselectivity, opening the window for further improvements to reduce the catalyst loading and to increase the scope of the reaction.[84] If the addition of tetraallyltin is performed with α,β-unsaturated ketones, the derived tertiary alcohols are useful intermediates for further chemical transformations. Walsh used these intermediates with the same titanium catalyst as employed in the asymmetric allylation to conduct a diastereoselective epoxidation reaction. Thus, after ketone allylation, one equivalent of anhydrous *tert*-butyl hydroperoxide (TBHP) was added to the reaction mixture to afford the *syn* epoxy alcohols **16** in good yields (Scheme 11), with the epoxidation reaction readily proceeding at room temperature.




Scheme 11. Multistep transformations accomplished in the presence of BINOL and $Ti(OiPr)_4$.

The reactions between tetraallyltin reagent and ketones can be catalyzed only by a tin complex formed in the presence of catalytic amounts of water. Woodward has proposed the formation of a bimetallic tin complex, in which the two tin atoms are linked together by an oxygen atom. One of the tin atoms is Lewis acidic, while the other one delivers the allyl moiety.[85] The advantage of this reaction is that no titanium catalyst is required, and treatment of $SnCl_4$ with $Sn(CH_2CH{=}CH_2)_4$ in the presence of water and monothiobinaphthol **12** allows the formation of a selective catalyst for the allylation of ketones (up to 94% *ee* values).

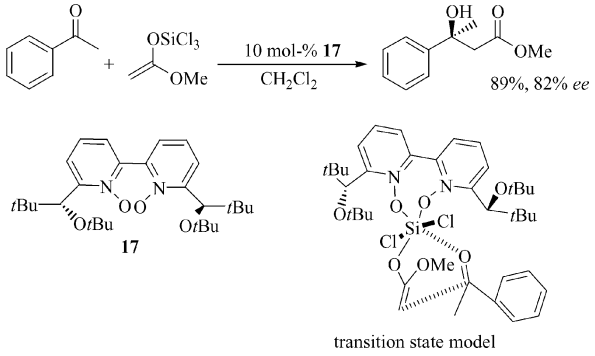
The use of indium complexes in the allylation reaction of ketones was described by Loh, in a reaction promoted by BINOL and $InBr_3$ in the presence of molecular sieves. It is worth noting that the catalytic allylation of ketones with this chiral indium complex can be accomplished simply by using allyltributylstannane, unlike most of the other asymmetric catalytic systems which require tetraallylstannanes.[86] Enantiomeric excesses of up to 92% were obtained, with the reaction showing a broad scope.

### 2.4 Addition of Enolates to Ketones

The catalytic addition of silyl enolates to ketones was reported by Evans[87] and Jørgensen.[88] Different substituted pyruvates reacted with silyl enolates derived from thioacetate with good enantioselectivities. The chelating ketone was coordinated to a BOX copper complex to yield high levels of facial stereoselectivity. Copper PyBOX complexes were effective in aldol reactions with opportune choice of counterion.[89] Contrary to expectation, the best solvent for this catalyzed transformation is THF, but other solvents are also suitable. The copper complexes employed can readily coordinate water, and this changes the geometry of the complex, eroding the stereoselectivity. The color of the copper complex is characteristic, and the presence or absence of coordinated water can be monitored by its color. Catalyst loadings can be as low as 1 mol-%. In addition, non-$C_2$-symmetric ligands have been employed in the addition of silyl enolates to ketones.[90] Although excellent enantioselectivities can be achieved with these methods they are only suitable for chelating ketones. Catalytic enantioselective aldol reactions with simple ketones are among the most synthetically useful reactions for the formation of chiral tertiary alcohols, but the inherent features of this type of reaction make its development rather difficult, in comparison with the catalytic enantioselective aldol reactions of aldehydes. The low reactivities of ketones, relative to alde-

hydes, and retro-aldol reactions usually lead to low levels of conversion. The discrimination of the two enantiofaces is also very difficult with ketones, due to the similar electronic/steric natures of the two substituents linked to the carbonyl group. Therefore, it is not surprising that only a few reports of such reactions have been published. For non-activated ketone acceptors, this problem was partially solved by a diastereoselective addition using chiral auxiliaries attached to both reaction partners.[91] Denmark developed an asymmetric aldol addition reaction through the application of Lewis basic catalysis.[92] The formation of a Lewis acidic enolate, able to coordinate to chiral bases, was extensively used (Scheme 12).

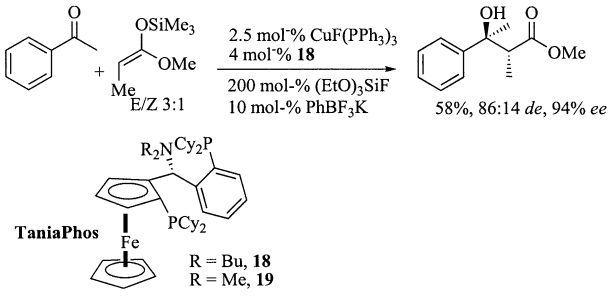



Scheme 12. A breakthrough in the addition of enolates to ketones described by Denmark.

As an acidic enolate, a silyl enolate bearing an electron-withdrawing group was the most suitable. However, although ketone- and aldehyde-derived enoxytrichlorosilanes do not react with ketones, the trichlorosilyl ketene acetal of methyl acetate was shown to be sufficiently reactive and was used in an enantioselectivity study. This enolate is sensitive to hydrolysis, but is readily prepared by transmetalation reaction from the corresponding tributyltin enolate. Of all bases screened, pyridine *N*-oxides such as **17** were found to be superior, and the enantioselective variant of this reaction was developed. Chiral 2,2′-pyridyl bis-*N*-oxides bearing various substituents at their 3,3′- and 6,6′-positions also provided excellent yields of the aldol products, but with variable enantioselectivities ranging from 89% *ee* for aromatic ketones to almost racemic products for aliphatic ketones. From a crystal structure it was shown that one ligand coordinates to $SiCl_4$, and with the aid of extensive computational analysis, Denmark was able to propose a clear rationale for the observed trends in enantioselectivities. The bidentate chiral pyridine *N*-oxide ligands used in these studies are able to bind the electron-poor silyl enolate, as the origin of Lewis base catalysis in this type of aldol reaction comes from ionization of a chloride and reaction via a penta- or hexacoordinate siliconium ion. A stereochemical model has been proposed, in which the aldol addition proceeds through a cyclic, six-membered, boat-like transition state organized around a cationic silicon center. This pioneering work was limited to the highly reactive trichlorosilyl enolate of methyl acetate.

Another concept for aldol reactions of ketones was developed by Carreira.[93] His basic idea was to use the labile fluoride counterion in a soft metal chiral fluoride complex ($Ag^I$, $Cu^{II}$, or $Ni^{II}$) to effect desilylation of an enol silane with concomitant generation of the corresponding chiral enolate. Initial difficulties in the development of such a method were the lack of simple preparative methods for the synthesis of metal fluorides and their limited solubilities in commonly employed organic solvents. Carreira successfully overcame these problems by using TolBINAP-$CuF_2$ complexes, and thereby introduced the use of copper in aldol additions.[94]

On the basis of the CuCl-TBAT (tetrabutylammoniumtriphenyl-difluorosilicate) catalyzed additions of allyltrimethoxysilane to aldehydes, ketones, and imines, Shibasaki proposed that the formation of an active copper fluoride complex is a key requirement for generating a highly active nucleophile. To guarantee a high turnover of the catalyst, the reaction was carried out with 120 mol-% of $(EtO)_3SiF$.[95] An interesting feature of this catalytic system is the employment of the $CuF(PPh_3)_3 \cdot 2\,EtOH$ complex as copper source, as this complex is air-stable and of simple preparation. A preliminary result for a catalytic enantioselective version of this reaction was disclosed in the same paper. A general application of these concepts in catalytic effective aldol reactions to ketones was presented recently by Shibasaki, who used TaniaPhos **18** as chiral ligand (Scheme 13).[96]




Scheme 13. TaniaPHOS–copper-catalyzed additions of silyl enolates to ketones.

In order to develop a general enantioselective $Cu^I$-fluoride-catalyzed addition, the new TaniaPhos ligand **18** was prepared and, more importantly, $PhBF_3K$ was used as additive to overcome the tendency of ketones to give undesired side reactions (i.e., formation of silylenol ethers). This method afforded enantioselectivities of 77–92% and good yields with both aliphatic and aromatic ketones as substrates.[79] Campagne used tol-BINAP (**14**) to develop a catalytic vinylogous Mukaiyama reaction with ketones (17–81% yield, 24–93% *ee*), and applied this reaction for the synthesis of a key intermediate in the total synthesis of taurosponin A.[97] One interesting feature of this work is the simple preparation of the active $Cu^I$ complex by use of $Cu(OTf)_2$, which is reduced to copper(I) by a silyl group or a phosphane.[98] The intermediate of asymmetric conjugate reductions of α,β-unsaturated esters or ketones is a chiral

copper enolate,[99] and could therefore be used in enantioselective aldol reaction to ketones.

The advantage of using this methodology is that it is a one-pot sequential reductive method that does not require the activation and formation of a silylenolate. Shibasaki described catalytic intermolecular reductive aldol reactions to ketones,[100] while an intramolecular process was reported by Lam.[101] Riant described further enantio- and diastereoselective reductive aldol reactions using TaniaPhos **19** as chiral ligand and $PhSiH_3$ as hydride source for reactions of aromatic and heteroaromatic ketones (31–98% yields, 82–95% *ee* values).[102] In all cases the *anti* diastereoisomers were obtained as major products.

Chiral amino alcohol additives were used by Soai in a Reformatsky reaction.[103] Ojida and co-workers discovered through extensive ligand screening that cinchonine is highly effective in controlling the stereochemical outcome of Reformatsky-type reactions with some heteroaromatic ketones.[104] In both examples stoichiometric amounts of chiral ligands were employed.

Recently the first catalytic enantioselective version of a Reformatsky-type reaction with ketones was reported by Cozzi.[105] A controlled and mild formation of the zinc reagent, using the less reactive $Me_2Zn$ in the presence of a chiral zinc metal complex, produced the first catalytic version of the Reformatsky reaction. The concepts used in this approach are the homogeneous version of the Reformatsky reaction, in which $Me_2Zn$ is the zinc source, coupled with a system able to accelerate the exchange between an iodoester and $Me_2Zn$. The exchange reaction was catalyzed by Salen ligands and is probably due to the Lewis base–Lewis acid nature of the metal Salen complex. Among the Salen complexes tested, surprisingly ClMn(Salen)[31] (Figure 3, M = ClMn) emerged as the most effective catalyst, with the reaction showing good enantioselectivity with aromatic and hindered aliphatic ketones in the presence of 4-phenylpyridine-*N*-oxide as additive. Although no radical mechanism is involved in this process, a zinc enolate could also be generated through a radical mechanism, and the catalytic enantioselective addition of these enolates might open a new avenue for catalytic enantioselective Reformatsky reactions.[106]

Organocatalytic methodologies have been successfully applied in the formation of tertiary alcohol derivatives. The addition of acetone to isatin was the first example of an organocatalytic reaction carried out with an activated ketone.[107] In addition, other diketones and keto esters have been shown to react in the addition of acetone promoted by proline or proline derivatives.[108]

### 2.5 Enantioselective Additions of CN to Ketones

In his recent review of the synthesis and application of cyanohydrins[109] North pointed out the difficulties in developing a highly successful methodology for additions of $Me_3SiCN$ to ketones. Belokon reported the best result so far, using Ti(Salen) oxo derivatives (Figure 3, M = TiO) to obtain up to 72% *ee* values in the case of aryl methyl ketones.[110] However, this catalyst gave reduced enantiomeric excesses for ethyl ketones (30% *ee* values) and effectively did not work for aliphatic ketones. Shibasaki explored the application of bifunctional ligands to enhance enantioselectivities in this reaction further. First he described a new design of the ligand that was able to enhance the reactivity of ketones through bifunctional behavior.

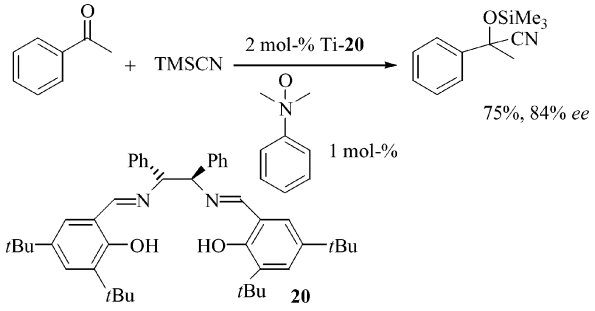
The catalyst prepared in situ in the presence of $Ti(OiPr)_4$ was able to control the addition of TMSCN to ketones.[111] The ligand design was simplified and ameliorated very recently.[112] Moreover, the use of other metals was considered with the same ligands, and lanthanide salts were used for solving a key step problem in a total synthesis of a natural product. Deng reported an organocatalytic approach for the first highly enantioselective cyanosilylation of ketones catalyzed by a chiral Lewis base. The advantage of this methodology is the employment of a recyclable modified cinchona alkaloid, but the reaction is quite limited, to acetal ketones.[113] In spite of these important advances, several problems remain unresolved. Among these are the relatively low levels of enantioselectivity obtained with acyclic aliphatic ketones, and the long routes required for the synthesis of some of the more effective chiral ligands (up to thirteen linear steps).

Hoveyda has reported a new Al-catalyzed asymmetric cyanation of ketones that utilizes a peptidic chiral ligand and delivers high enantioselectivity with both aromatic and aliphatic ketones. The peptide ligand was identified by a systematic screening study, taking advantage of the modularity of peptide-based chiral ligands. The treatment of acetophenone with TMSCN in the presence of a dipeptide Schiff base ligand (20 mol-%), $Al(OiPr)_3$ (20 mol-%), and as additives MeOH (20 mol-%), and 3 Å molecular sieves (2 equiv.) afforded the desired products in good yield and enantioselectivity.[114]

Acyclic aliphatic and unsaturated ketones can also be used in these Al-catalyzed additions, from which the corresponding cyanohydrins are isolated with high enantioselectivities. Most of the recent advances in this reaction have been published by Feng.[115] Firstly, he studied the employment of chiral pyrrolidine *N*-oxides derived from proline in this reaction.[116] He then investigated the cyanosilylation of ketones using *N*-oxides in three different ways: in a catalytic double activation method, as additives in the reaction, and as bifunctional catalysts (Scheme 14).

An efficient method for the enantioselective cyanosilylation of ketones by a double activation method was also described by Feng. A Ti(Salen) complex prepared with ligand **20** was combined with a Lewis base in a one-pot fashion, and these activated the electrophile and the nucleophile, respectively. A series of Ti(Salen) complexes was evaluated, together with different achiral *N*-oxides.[117] Cyanohydrins were obtained in the range from 59 to 86% *ee* and in high yields. The authors have recently started to consider other Salen metal complexes and have described the same reaction with use of chiral Salen aluminium complexes and *N*-oxides for the enantioselective cyanosilylation of ketones.[118] Different substituted salicylaldehydes were

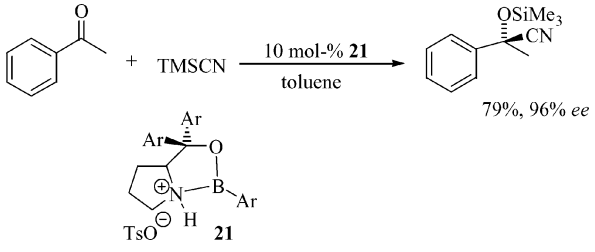



Scheme 14. Addition of $Me_3SiCN$ to ketones promoted by a Ti-(Salen) complex.

evaluated in the process, and the best catalyst derived from 5′-bromo-substituted salicylaldehyde exhibited the highest enantioselectivity (93% *ee*) in the presence of an *N*-oxide derived from 3,5-di-*tert*-butylaminophenol. This catalyst system is remarkably active, as only 0.5 mol-% of the catalyst in the presence of 0.25 mol-% of the *N*-oxide are used. In addition, excellent yields (80–99%) and enantioselectivities (79–94% *ee* values) were recorded with a broad range of ketones.

The use of phenolic *N*-oxides and titanium catalysts has also been described in additional publications by Feng,[119] who has reported the use of a multifunctional catalyst containing a Lewis acid moiety, capable of activating an electrophile, and a Lewis base moiety, able to activate the nucleophile. The ligand was prepared in a few, simple steps from commercially available diphenylprolinol, Corey's catalyst for CBS reductions, the *N*-oxides being introduced on the alkylated nitrogen. However, the enantiomeric excesses obtained were strongly dependent on the ketones used.[120]

Two remarkable results were published in 2005. Firstly, Corey reported that the oxazaborolidinium salt **21** (Scheme 15) is a good catalyst for the cyanosilylation of methyl ketones in the presence of phosphane oxides as co-reactants, providing good yields and high enantioselectivities (up to 95% *ee* values).[121]




Scheme 15. Corey's proline ligands applied in the addition of $Me_3SiCN$ to ketones.

Feng then reported a straightforward approach for the enantioselective cyanosilylation of ketones, showing that simple amino acid salts, in the presence of *i*PrOH as an additive, can promote additions of TMSCN to ketones with up to 92% *ee* values.[122] Other authors have explored the properties of different Salen metal complexes in cyanosilylation reactions, and ClMn(Salen) can afford up to 85% *ee* values in the presence of $Ph_3PO$ as additive.[123]

### 2.6 Recent Miscellaneous Methodologies

An organometallic methodology for the alkylation of ketone enolates was described by Jacobsen. Tributyl ester enolates were alkylated with a range of reactive primary halides through the employment of catalytic quantities of ClCr(Salen) (Figure 3, M = CrCl). The reaction is a remarkable example of transition metal-catalyzed α-alkylation of carbonyl compounds with electrophiles, providing access to quaternary stereogenic centers with high selectivities.[124] This new reaction affords functionalized, optically active compounds bearing quaternary stereocenters with high enantioselectivities, in excellent yields, and with high atom economy, using simple operations and mild and environmentally benign reaction conditions.

The first example of a Mo-catalyzed asymmetric alkylation used for the generation of quaternary stereocenters was reported recently,[125] while a highly efficient catalytic enantioselective fluorination of oxindole derivatives (such as aryl- and alkyloxindoles) was achieved with use of catalytic amounts of a chiral Pd complex (2.5 mol-%, 96% *ee*). In addition, when the aryl substituent was Ph, enantioselective fluorination followed by solvolysis gave a monofluorinated ester with 93% *ee*.[126]

## 3. Total Syntheses of Natural Products through Enantioselective Catalytic Additions to Ketones

Catalytic methodologies have been applied for the formation of quaternary stereogenic centers to overcome difficult synthetic steps in total synthesis. Selected examples of recent literature are presented in this section. Trost's group has demonstrated that the Pd-catalyzed asymmetric allylic alkylations (AAA reaction) of prochiral nucleophiles can be used as an effective strategy for the construction of quaternary stereocenters, giving excellent yields and enantioselectivities for β-keto esters, ketones, and 3-aryloxindoles.[127] This methodology could not be successfully applied to 3-alkyloxindoles. As the mechanism of the Mo-catalyzed AAA reaction involves nucleophiles precoordinating to the metal followed by reductive elimination, this system was applied to generate quaternary stereocenters, and the formal synthesis of physostigmine (**22**, Figure 7) was accomplished.[128]

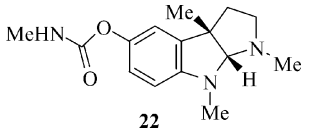
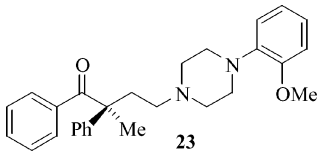



Figure 7. Physostigmine (**22**).

The first example of the use of an organocatalytically mediated Diels–Alder reaction in total synthesis, including the formation of a quaternary center, was presented by Kerr.[129] The total synthesis of (+)-hapalindole Q has been achieved; MacMillan's organocatalyst was used in a key step in a Diels–Alder reaction to provide the desired intermediate with high enantioselectivity (93% *ee*).

Overman used a catalytic enantioselective Heck reaction in his total synthesis of trispyrrolidinoindoline alkaloids such as idiospermuline.[130] The first enantioselective total syntheses of bisorbicillinolid, bisorbicillinol, and bisorbibutenolide were accomplished by Deng and co-worker in 10/11 steps and 12–19% overall yields, by use of a modified cinchona alkaloid-catalyzed cyanosilylation as the stereochemistry-defining step.[131] Romo has used a catalytic enantioselective CuBOX-mediated reaction in his studies directed towards the total synthesis of the marine toxin (–)-gymnodimine.[132] Recently, Denmark has reported the application of a catalytic enantioselective allylation catalyzed by a chiral phosphoramide in the asymmetric synthesis of serotonin antagonist LY426965 (**23**, Figure 8).

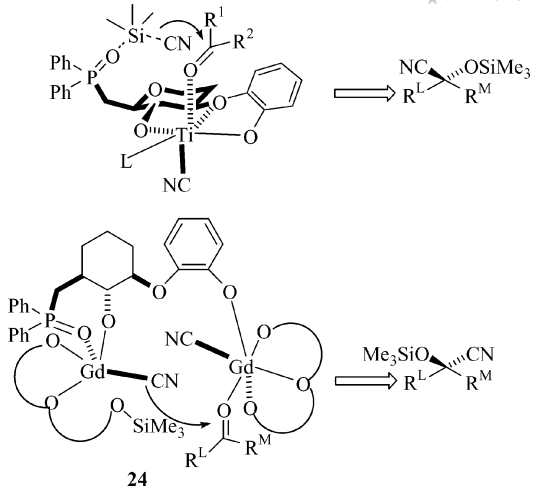



**23**

Figure 8. Serotonin antagonist LY426965 **23**.

These syntheses demonstrated not only the efficiency of these allylation methods in the generation of quaternary centers but also the versatile functionality provided in such allylation adducts. The challenges posed in performing such a reaction are the following: a) the synthesis of geometrically pure 3,3-disubstituted allylmetal reagents, b) correlation of the geometrical purity of allylmetal reagents to the diastereomeric composition of the product, and c) control of asymmetric induction with external chiral catalysts.[133] Catalytic asymmetric synthesis of the natural antibiotic fostriecin (CI-920) and its analogue 8-epifostriecin was described by Shibasaki, who used four catalytic asymmetric reactions to construct all of the stereogenic centers of fostriecin and 8-epi-fostriecin. In particular, a catalytic enantioselective cyanosilylation of a ketone produced the chiral tetrasubstituted carbon center. The enantiomers of the cyanohydrin product were obtained with high enantioselectivity by using the catalyst **24** and switching the coordinated metal of the catalyst from titanium to gadolinium (Figure 9).[134]

Shibasaki has also described the enantioselective construction of a quaternary stereocenter through a Reissert-type reaction. This new reaction should allow for the efficient synthesis of many intermediates. He demonstrated the utility of this reaction through an efficient catalytic enantioselective synthesis of MK801, the anticonvulsant phenytoin, and of a biosynthetic intermediate of the dopamine-derived alkaloid salsolinol.[135] Shibasaki has also reported the catalytic enantioselective synthesis of a key intermediate for the (20*S*)-camptothecin family. One interesting feature of this work was the switching of enantiofacial selectivities while using only one chiral source. In the key step the enantioselective catalytic cyanosilylation of a ketone was used.[136]




**24**

Figure 9. Switching the coordinated metal of the catalyst from titanium to gadolinium.

A short-step synthesis of versatile chiral building blocks for triazole antifungal agents such as ZD0870 and Sch45450 with catalytic enantioselective cyanosilylation of electron-deficient ketones as the key step has been developed. High enantioselectivity was achieved by use of a catalyst prepared from $Gd(HMDS)_3$ and ligand in a 2:3 ratio. This new catalyst preparation method was superior to the previous method that had used $Gd(OiPr)_3$ as a metal source.[137] A new method for the catalytic enantioselective Diels–Alder reaction using polysubstituted silyl enol ethers as dienes has been described. High enantioselectivity (up to 92% *ee*) was achieved with a catalyst generated from $FeBr_3$ and $AgSbF_6$ in a 1:2 ratio and aryl-PyBOX (aryl = Ph or *p*-ethoxyphenyl). This reaction should facilitate the enantioselective synthesis of polycyclic acylphloroglucinols such as hyperforin or garsubellin A.[138]

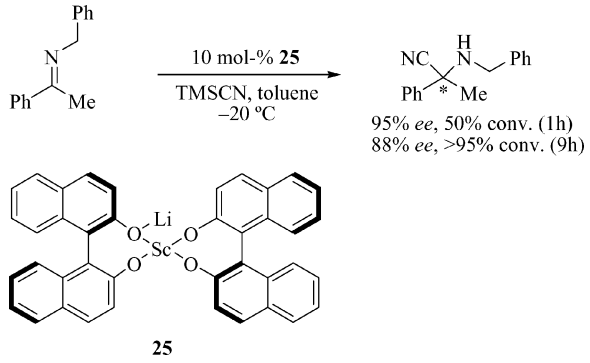
## 4. Asymmetric Synthesis of Tertiary Amines

### 4.1 Enantioselective Metal-Catalyzed Additions to Ketoimines

The classical Strecker reaction (cyanation of imines) is one of the most convenient methods for the preparation of α-amino acids. Catalytic enantioselective Strecker reactions using ketoimines as substrates provide easy access to chiral α-disubstituted amino acids. Vallée reported the first examples of metal-catalyzed asymmetric additions of TMSCN or HCN to *N*-benzyl-phenylmethylimine, catalyzed either by titanium-based complexes[139] or, more successfully, with chiral heterobimetallic complex $Sc(BINOL)_2Li$ **25**, which affords enantiomeric excesses of up to 95% (Scheme 16).[140]

In a series of publications, Shibasaki describes the use of chiral gadolinium complexes for the enantioselective Strecker reaction of ketimines.[141] The active catalyst is prepared from $Gd(OiPr)_3$ and D-glucose-derived ligand **26**[142] in a 1:2 ratio, the preferred protecting group on the imine



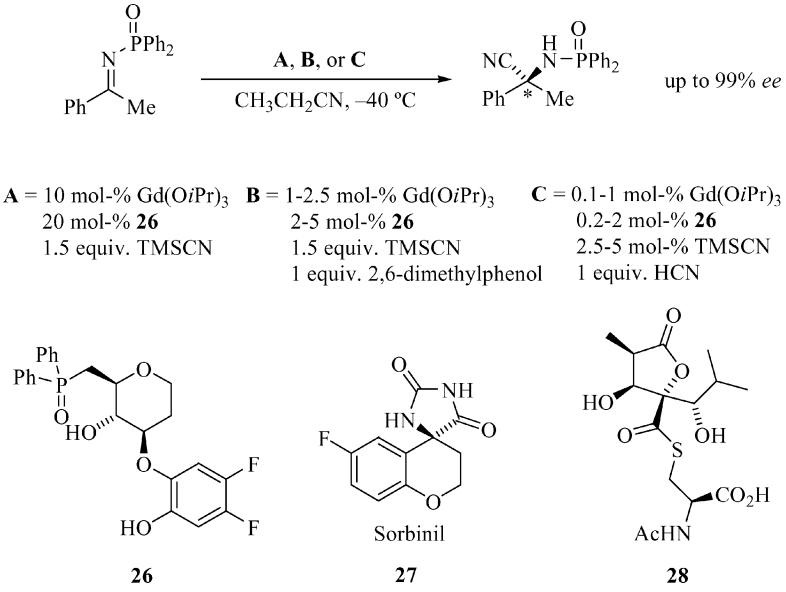

Scheme 16. Addition of TMSCN to ketimines.

*N*-atom being a diphenylphosphanylyl group (Scheme 17). Enantioselectivities of up to 99% *ee* can be achieved for additions of TMSCN to acetophenone-derived ketoimines with use of 10 mol-% of $Gd(OiPr)_3$ and 20 mol-% of **26** (Method A).[143] A significant improvement in substrate generality and catalyst activity can be achieved by performing the reaction in the presence of 2,6-dimethylphenol (DMP) as an additive: the catalyst loading can be lowered to 1–2.5 mol-% $Gd(OiPr)_3$ and 2–5 mol-% of **26**, and high enantioselectivity for heteroaromatic and cyclic ketoimines can be achieved (Method B).[144] This improved method has been successfully applied for the catalytic, asymmetric synthesis of sorbinil (**27**), a therapeutic agent developed by Pfizer for the treatment of chronic complications of diabetes mellitus, and for the synthesis of the proteasome inhibitor (+)-lactacystin (**28**).[145] ESI-MS studies revealed that the beneficial role of the protic additive DMP stems from the generation of a proton-containing active catalyst species.

The same active catalyst can also be generated by using stoichiometric HCN as an additive, only catalytic amounts of TMSCN being necessary in this case (Method C).[146] Catalyst amounts can be lowered to as little as 0.1 mol-% while high enantioselectivity is maintained. In a recent publication, Shibasaki investigated the higher-order modular assembly of these Gd complexes with three-dimensional structure elucidation, and found that the enantioselectivity of an artificial asymmetric catalyst is tunable, depending on the assembly mode of the chiral modules.[147]

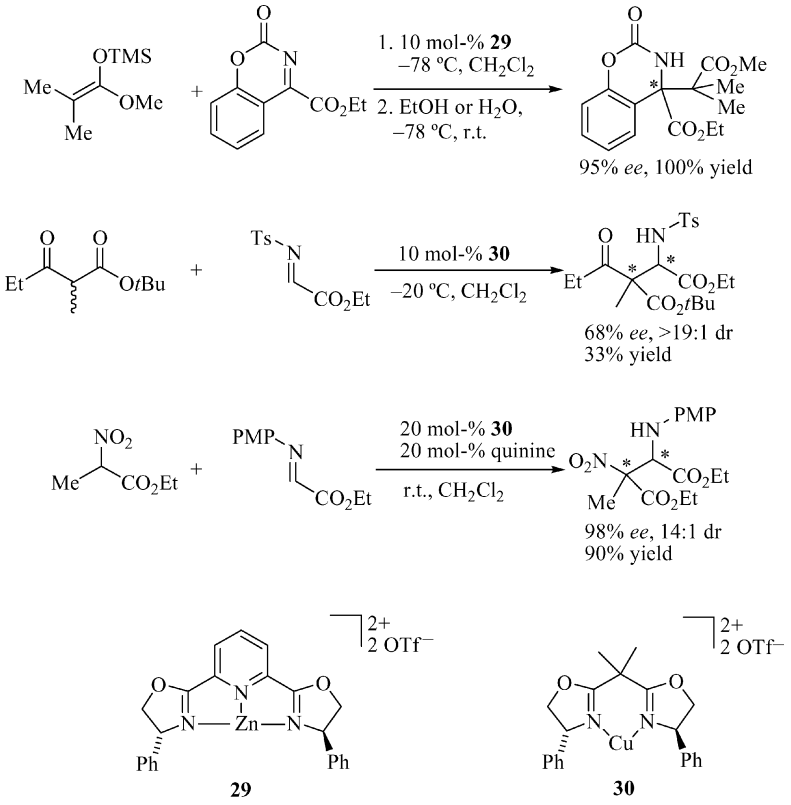
The Mannich reaction is an important C–C bond-forming reaction in which enols or enolates react with imines to form β-aminoesters or ketones. In 2003, Jørgensen reported the first catalytic enantioselective Mannich reaction of silylketene acetals with ketimines possessing intrinsic anchoring protective groups (Scheme 18).[148]

Complex **29**, consisting of $Zn(OTf)_2$ and (*R*,*R*)-Ph-pybox, catalyzes the formation of the corresponding chiral quaternary α-amino acid derivatives in up to 95% *ee* values. In addition, Jørgensen and co-workers developed the first direct asymmetric Mannich reactions of β-keto esters with activated *N*-tosyl-α-imino esters catalyzed by chiral (*R*)-Ph-bisoxazoline/$Cu(OTf)_2$ complex **30**.[149] The best results in terms of yield and diastereo- and enantioselectivities are obtained when *tert*-butyl esters of β-keto esters are used as the substrates. The same catalyst system can also be successfully applied for the addition of β-ketophosphonates to activated *N*-tosyl-α-imino esters.[150] In a recent publication, Jørgensen describes the combined use of complex **30** with the cinchona alkaloid quinine for the formation of quaternary centers through aza-Henry reactions. This represents a new approach in asymmetric synthesis, using dual chiral activation based on molecular recognition by a chiral organocatalyst and a chiral Lewis acid. The enantioselectivity of the aza-Henry reaction is controlled by the chiral Lewis acid and the diastereoselectivity by the cinchona alkaloid.[151] In a recent publication, Shibasaki reported the first catalytic enantioselective Mannich reactions of simple ketimines through the use of a CuOAc–DTBM–SEGPHOS



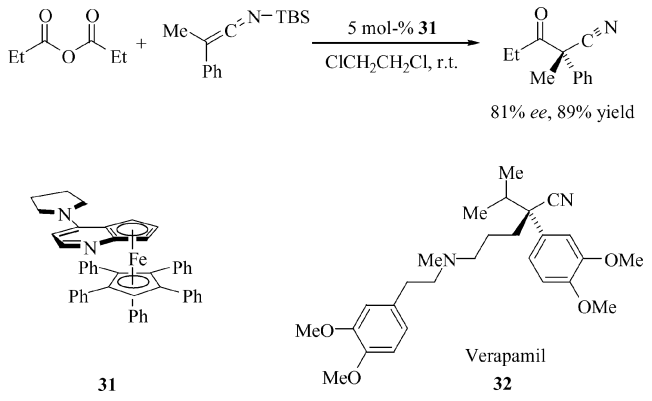

Scheme 17. Addition of TMSCN to ketoimines promoted by Gd complexes of ligand **26**.




Scheme 18. Jørgensen's reported Mannich reaction with silyl enolates.

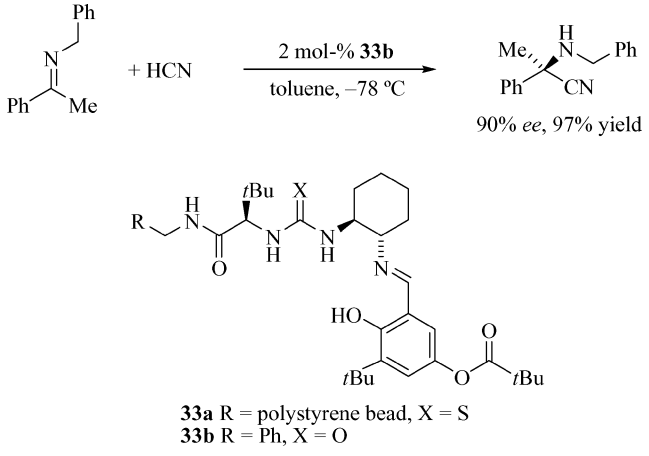
(or DuPHOS) system and a silicon trapping reagent.[152] Sodeoka's chiral Pd aqua complexes **45** catalyze not only Michael reactions (see Scheme 26) but also Mannich-type reactions of β-keto esters with various imines, including not only imino esters but also other imines derived from simple aldehydes, with high enantioselectivities.[153] Another feature of these complexes is that they are tolerant to water, so that reactions can be conducted without the exclusion of air and moisture. Moreover, three-component coupling reactions between aldehydes, amines, and β-keto esters are possible, in which stoichiometric amounts of water molecules are generated during the in situ imine formation. Silyl ketene imines react with anhydrides through a chiral-nucleophile-catalyzed pathway in the presence of Fu's 4-(pyrrolidino)pyridine derivative **31** (Scheme 19).[154] This method has been applied for the enantioselective synthesis of the drug verapamil (**32**), a calcium channel blocker used for the treatment of hypertension and angina.




Scheme 19. Silyl ketene imines react with anhydrides in the presence of the chiral nucleophilic catalyst **31**.

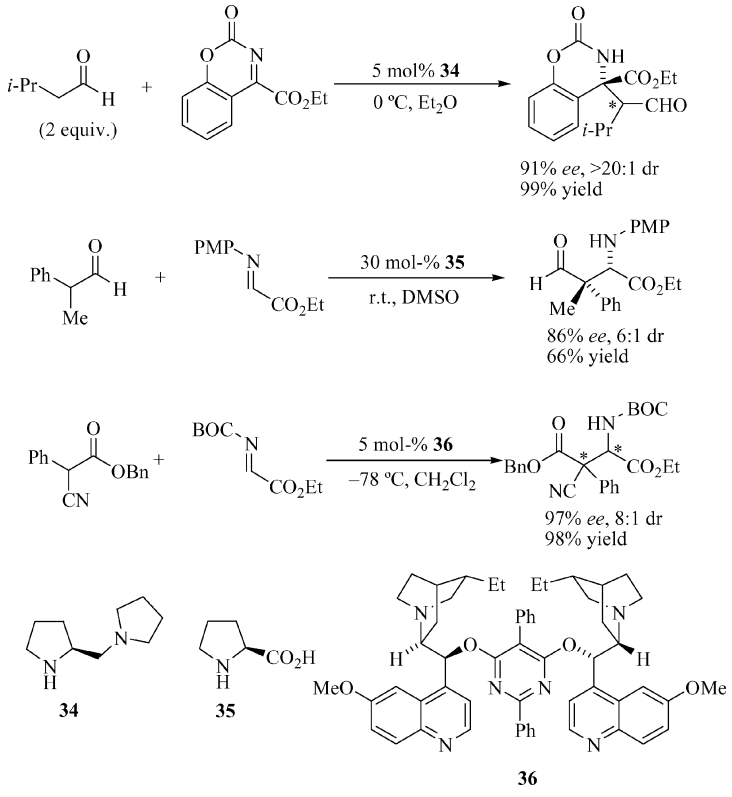
## 4.2 Enantioselective Organocatalytic Additions to Imines

Schiff base **33** is a remarkably general catalyst for the hydrocyanation of ketimines, producing Strecker adducts in >90% *ee* values for a variety of substrates (Scheme 20).[155]




Scheme 20. Strecker reaction performed in the presence of the thiourea catalyst **33b**.




Scheme 21. Organocatalytic additions of aldehydes and cyanoesters to imines.

A parallel library synthesis and screening approach led to the discovery and optimization of resin-bound catalyst **33a**, which can be recycled repeatedly. Slightly higher enantioselectivities and reactivities can be achieved with its soluble analogue **33b**.[156] The resulting α-aminonitrile adducts can be converted into the corresponding α-quaternary α-amino acids by a formylation/hydrolysis sequence. Detailed NMR studies and computational modeling provided more structural and mechanistic insight into the role of the catalyst in this reaction and allowed for the rational design of a second generation of Schiff bases with a broader substrate scope.[157]

Chiral amine bases are efficient catalysts for Mannich-type reactions: Jørgensen and co-workers reported the first organocatalytic direct Mannich reaction of ketimines and unmodified aldehydes based on the concept of intrinsic protecting group anchoring (Scheme 21).[158]

L-Proline-derived diamine **34** is the catalyst of choice, affording optically active quaternary α-amino acid derivatives in high yields and with excellent diastereo- and enantioselectivities. Depending on the choice of catalyst, either diastereomer of the Mannich adduct can be prepared: reactions occur at the *si* face of the imine and the *si* face of the enamine formed in situ with diamine **34**, whereas use of L-proline (**35**) results in reaction at the *si* face of the imine and the *re* face of the enamine. Barbas et al. demonstrated that L-proline (**35**) also catalyzes direct Mannich reactions of *N*-PMP-protected α-imino ethyl glyoxylates with various α,α-disubstituted aldehydes containing alkyl, aryl, benzyl, and heteroaryl substituents.[159] The resulting β-formyl α-amino acid derivatives are formed with high *syn* diastereoselectivities and enantioselectivities of up to 99% *ee*. These Mannich adducts can be further oxidized, providing a straightforward asymmetric route to quaternary α- and β-amino acids and β-lactams. It is noteworthy that these reactions can be performed without the requirement for an inert atmosphere or anhydrous solvents. Cinchona alkaloid $(DHQD)_2PYR$ (**36**) is an efficient organocatalyst for the addition of α-substituted cyanoacetates and a β-keto ester to *N*-Boc-protected imines, generated in situ by dehydrobromination of Boc-protected α-bromoglycine esters.[160] The natures of the cyanoester groups are critical for the stereochemical outcomes of the reactions, with the benzyl group giving optimal results. Cinchona alkaloids have also been reported to be excellent bifunctional catalysts for asymmetric Mannich reactions of cyclic 1,3-dicarbonyl compounds with acyl imines[161] and of 2-substituted malonate esters with *N*-Boc and *N*-Cbz aldimines.[162] Feng described enantioselective Strecker reactions of *N*-diphosphanylyl ketoimines by use of a chiral *N*,*N*′-dioxide catalyst prepared in situ and derived from L-piperidinamide and *m*-CPBA.[163]

## 5. Synthesis of Quaternary All-Carbon Centers

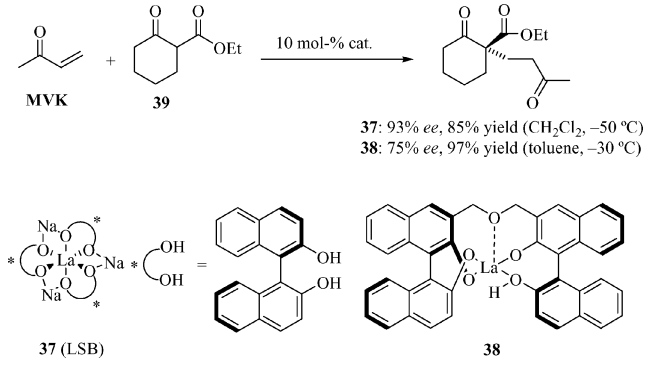
### 5.1 Enantioselective Metal-Catalyzed Michael Reactions

Over the last decade, the asymmetric Michael reaction catalyzed by chiral metal complexes has been established as one of the most efficient methods for enantioselective carbon–carbon bond formation. Most research in this area has

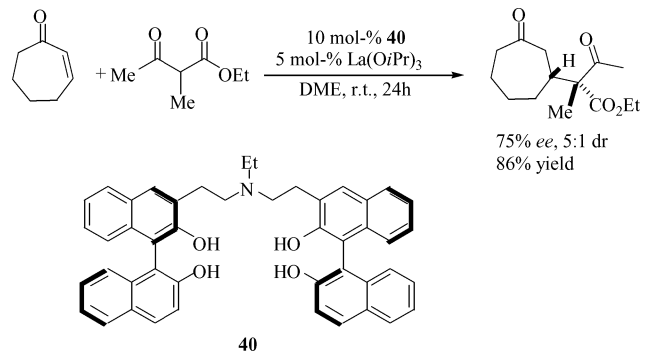
focused on the construction of tertiary carbon centers, but much progress in the construction of all-carbon quaternary stereogenic centers has recently been achieved.

Shibasaki's bifunctional La-Na-BINOL complex **37** (LSB) affords high enantiocontrol in additions of acyclic and cyclic β-keto esters to methyl vinyl ketone (MVK), of up to 93% *ee* (Scheme 22).[164] Slow addition of β-keto ester and the use of dichloromethane as solvent are crucial to achieving high enantiomeric excesses in the Michael adducts. In search for a stable and reusable non-polymer-supported catalyst for this reaction, Shibasaki developed alkali-metal free La-linked-BINOL complex **38**, in which lanthanum metal acts as Lewis acid and the lanthanum naphthoxide moiety acts as Brønsted base.[165]




Scheme 22. Shibasaki's bifunctional La-Na-BINOL complexes **37** (LSB) and **38** in the addition of acyclic and cyclic β-keto esters to methyl vinyl ketone.

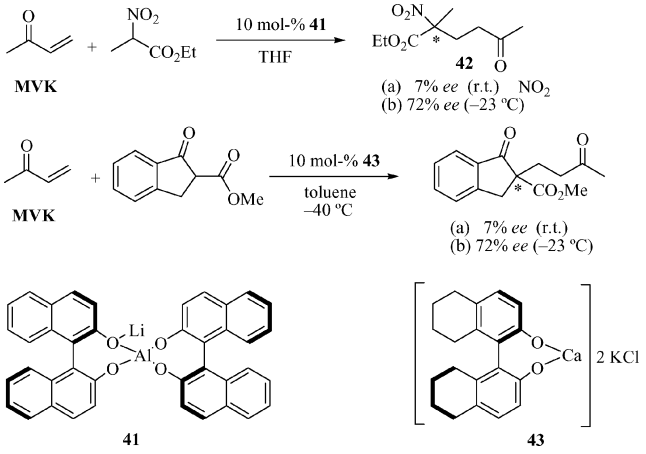
In contrast to other Lewis acid catalysts, complex **38** is air- and moisture-stable and can be stored at ambient temperature for several weeks. There is a slight decrease in enantiocontrol in the reaction of β-keto ester **39** with MVK catalyzed by complex **38** in comparison with LSB **37** (75% *ee* vs. 93% *ee*, respectively). In a recent publication, Shibasaki reports the construction of vicinal quaternary and tertiary carbon centers through catalytic Michael additions of α-substituted β-keto esters to cyclic enones.[166] In this case, NR-linked-BINOL ligand **40** is the catalyst of choice, and tuning of the linker length and the *N*-substituent was critical to achieve high reactivities and good stereoselectivities (Scheme 23).




Scheme 23. Linked BINOL in Michael reactions.

In addition, a new and more convenient method for the preparation of La complexes, in which air- and moisture-stable $La(OTf)_3$ and Huenig-base ($iPr_2NEt$) are used, was described. Shibasaki's LSB and linked BINOL complexes are also efficient catalysts for asymmetric Michael additions of thiols to α,β-unsaturated carbonyl compounds[167] and for direct Zn-catalyzed Michael reactions of hydroxy ketones.[168]

Feringa and co-workers reported the first examples of metal-mediated enantioselective Michael additions of α-nitroesters to β-unsubstituted enones through the use of chiral "Al-Li-BINOL" complex **41** as a heterobimetallic catalyst (Scheme 24).[169]

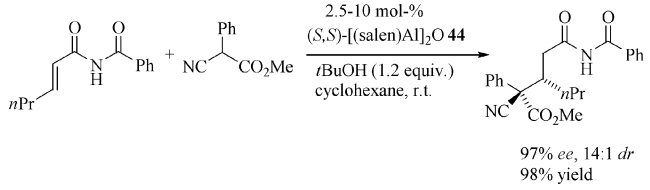



Scheme 24. Al- and Ca-BINOL complexes for Michael additions to MVK.

The catalyst is prepared in situ from $LiAlH_4$ and 2.45 equiv. (*R*,*R'*)-BINOL, and consists of a mixture of different aluminium complexes in solution, as shown by $^{27}Al$ NMR studies. The enantioselectivity of the Michael addition is extremely temperature-dependent: Michael adduct **42** shows 7% *ee* when the reaction is performed at room temp. whereas 72% *ee* of the opposite enantiomer is found when the 1,4-addition is performed at –23 °C. Interestingly, no enantioselectivity is found either with the La-Li-BINOL complex or with the alkali metal-free La-BINOL complex. More recently, Kumaraswamy showed that monometallic enantio-enriched calcium-octahydro-BINOL (H8-BINOL) complex **43** can also function as a bifunctional catalyst: treatment of methyl 1-oxoindan-2-carboxylate with MVK in the presence of 10 mol-% of catalyst **43** in toluene at –40 °C afforded up to 72% *ee* values with good yields (Scheme 24).[170] A further expansion of the scope of the asymmetric Michael reaction is the addition of trisubstituted cyanoacetate derivatives to acyclic α,β-unsaturated imides catalyzed by Jacobsen's chiral (Salen)-aluminium complex **44** (Figure 3, M = Al–O–Al; Scheme 25).[171] High diastereo- and enantioselectivities can be achieved with aryl, heteroaryl, and unbranched alkyl cyanoacetates.

In a recent communication, Jacobsen reported the total synthesis of the proteasome inhibitor (+)-lactacystin through the use of an Al-Salen-catalyzed conjugate addition of an aminocyanoacetate derivative to a β-silyl imide




Scheme 25. Al(Salen) complex for the addition of trisubstituted cyanoacetates to α,β-unsaturated imides.

substrate as the key step.[172] The same catalyst system can also be applied for conjugate additions of cyanoacetates to acyclic α,β-unsaturated ketones.[173] In one example a quaternary stereocenter was formed by addition of methyl phenylcyanoacetate to hept-3-en-2-one with high diastereo- and enantiocontrol (89% *ee*, >30:1 *dr*).

A chiral *N*,*N*′-dioxide/scandium trifluoromethanesulfonate complex developed by Nakajima et al. catalyzes Michael additions of β-keto esters to MVK and acrolein.[174] High enantioselectivities can only be achieved with 1-oxoindan-2-carboxylic esters as Michael donors, and enantioselectivities increase with the bulkiness of the ester substituent. The best result was obtained with a *tert*-butyl ester, which afforded 84% *ee* in the addition to MVK. A transition state model shown in Figure 10, in which the scandium trifluoromethanesulfonate forms a complex with the *N*-oxide ligand and the β-keto ester, might explain the importance of the indan-2-carboxylate skeleton in directing the enantiocontrol, as well as the beneficial effect of bulkier ester substituents: the bulky *tert*-butyl ester moiety is located on the *si*-face of the keto ester plane in order to avoid steric repulsion with the quinoline moiety, which causes MVK to attack the *re*-face preferentially. This model is consistent with the predominant formation of the (*R*)-configured product.

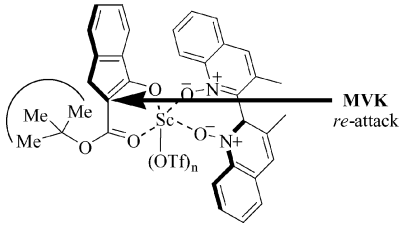
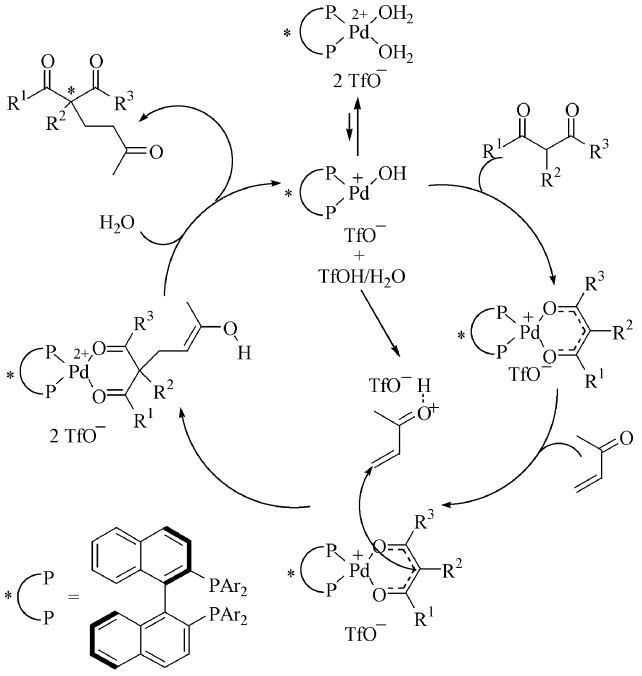



Figure 10. Transition state of Sc-promoted Michael reactions.

Sodeoka and co-workers developed chiral Pd(BINAP)- and Pd(tol-BINAP)-aqua complexes **45a** and **45b**, which are highly enantioselective and general catalysts for Michael reactions of a variety of Michael donors with vinyl ketones (Scheme 26).[175]

These Pd complexes function as acid–base catalysts to activate both Michael donors and acceptors: chiral palladium enolates are generated as key intermediates that are inherently basic and act cooperatively with a strong protic acid (TfOH) to activate the Michael acceptors for promotion of the carbon–carbon bond-forming reaction; Scheme 26 shows the proposed catalytic cycle. The substrate scope of this catalyst system ranges from various β-keto esters to β-substituted enones for the formation of vicinal

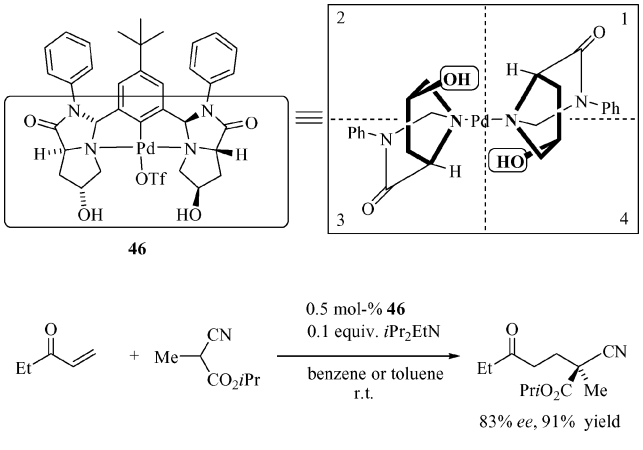



**45a** Ar = 4-Me-$C_6H_4$; (*R*)-Tol-BINAP
**45b** Ar = Ph; (*R*)-BINAP

Scheme 26. Sodeoka's palladium-catalyzed Michael reactions.

tertiary and quaternary centers, and from 1,3-diketones to α,β-unsaturated aldehydes as Michael donors. These Pd complexes can also be immobilized by use of ionic liquids while affording results comparable to those obtained in organic solvents, and the catalyst can be reused up to five times.[176]

Another example of the use of a palladium catalyst in asymmetric Michael reactions is that of Uozomi's chiral Pincer Pd complex, bearing two hexahydro-1*H*-pyrrolo[1,2-*c*]imidazolone groups **46** (Scheme 27).[177] Enantioselectivities of up to 83% *ee* can be achieved in the addition of α-cyanocarboxylates to vinyl ketones.




**46**

Scheme 27. Pincer palladium complex in Michael reactions.

Molecular modeling studies indicate that the hydroxy substituents on the pyrrole rings might play an essential role in asymmetric induction. As can be seen in Scheme 27, the

hydroxy substituents are situated in close proximity to the metal center in the regions of the second and fourth quadrants (from the viewpoint of the metal side) to provide effective chiral surroundings. Chemical yields are strongly affected by the anionic ligand of the pincer complex, with triflate being preferred.

Rhodium complexes represent another class of efficient catalysts for the construction of quaternary centers through Michael reactions. The first example of a Rh-catalyzed Michael addition was reported by Ito and co-workers. α-Methyl-substituted cyanoacetates and their corresponding Weinreb amides react with vinyl ketones or acrolein in the presence of 0.1–1 mol-% of Rh catalyst **47** with high enantiomeric excesses of up to 94% and in high yields (Figure 11).[178] Rh catalyst **47** is prepared in situ from $Rh(acac)(CO)_2$ and a *trans*-chelating chiral diphosphane ligand (PhTRAP). The same catalyst system can also be applied for the synthesis of optically active phosphonic acid derivatives containing a phosphorus-substituted quaternary asymmetric carbon center.[179] Takaya et al. developed Rh-catalyst **48**, which also contains a *trans*-chelating chiral diphosphane ligand system. Enantioselectivities of up to 73% *ee* can be achieved in the addition of α-substituted cyanoacetates to MVK and methyl acrylate.[180]

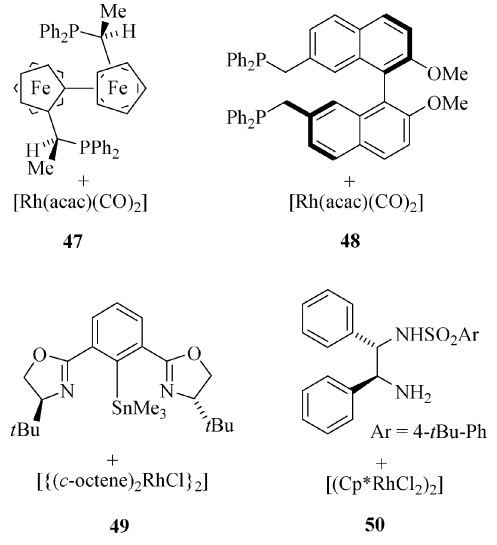
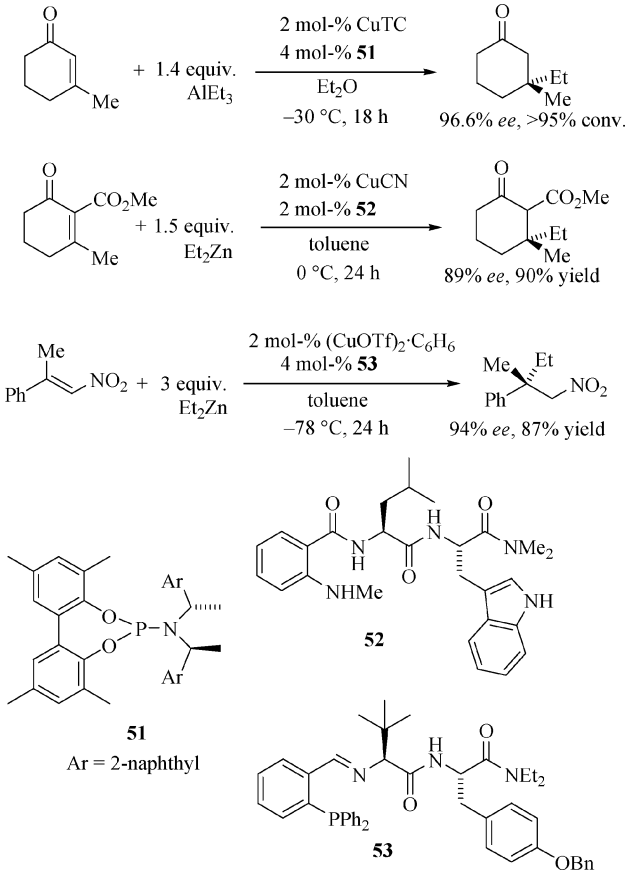



Figure 11. Chiral rhodium complexes employed in Michael reactions.

Rh-catalyst **49** containing a Pincer-type ligand (Phebox) was reported by Motoyama and Nishiyama to afford high enantiomeric excesses in Michael additions of α-substituted cyanoacetates to acrolein.[181] The active catalyst is a chiral $Rh^{III}$ complex $[(Phebox)Rh^{III}(SnMe_3)Cl]$, generated in situ by oxidative addition of $[\{RhCl(c\text{-octene})_2\}_2]$ to the stannyl compound $[(Phebox)SnMe_3]$.

The nitrile group of the Michael donor is necessary for the Michael addition to proceed and is believed to coordinate to the Rh metal: no product is obtained on treatment of β-keto esters and α-nitro compounds with acrolein. Chiral diamine-based Rh complex **50** catalyzes Michael additions of β-keto esters and MVK in up to 75% *ee* values.[182] Carretero described Rh-catalyzed, Chiraphos-mediated conjugate additions of alkenylboronic acids to β,β-disubstituted α,β-unsaturated 2-pyridylsulfones with *ee* values of up to 99%.[183] Recently, Hayashi reported Rh-catalyzed asymmetric 1,4-additions of arylboronic acids to 3-substituted maleimides, furnishing 3,3-disubstituted succinimides with high regio- and enantioselectivities.[184]

The scope of Cu-catalyzed asymmetric conjugate additions of alkylmetals to Michael acceptors has been substantially extended over the last two years, providing access to quaternary carbon centers. The groups of both Alexakis and Hoveyda have developed catalyst systems that tolerate substrates known for their low reactivity in these reactions, such as β-trisubstituted enones. Alexakis and co-workers demonstrated that trialkylaluminium reagents can be added to 3-substituted cyclohexenones through the use of 2 mol-% of copper thiophenecarboxylate (CuTC) and 4 mol-% of biphenol-based phosphoramidite ligand **51** in up to 96.6% *ee* values (Scheme 28).[185] Another example of the use of chiral phosphoramidite ligands in Cu-catalyzed asymmetric conjugate additions, in which dialkylzinc reagents react with acyclic aryl-substituted alkylidine β-keto esters derived from Meldrum's acid, was reported by Fillion.[186] In a recent communication, Alexakis demonstrated a novel approach for asymmetric conjugate additions to trisubstituted enones, in which Grignard reagents associated

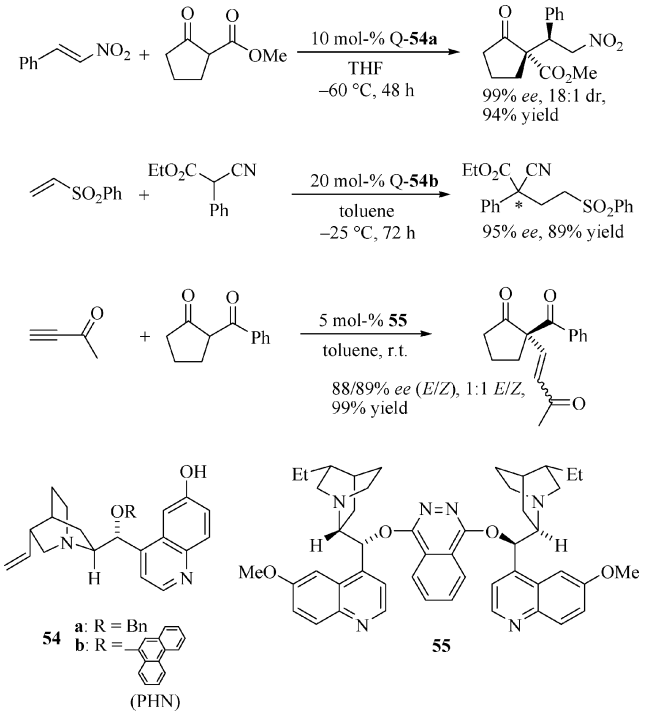



Scheme 28. Copper-catalyzed Michael additions.

with a copper catalyst and a chiral diaminocarbene ligand are used.[187]

Enantioselectivities are moderate at this point, but might be improved with second-generation ligands. Clear advantages of the use of these more reactive Grignard reagents are increased reaction scope, due to their easy or commercial availability, and the lack of any requirement to use specially activated enones. Hoveyda et al. screened ca. 90 chiral amino acid-based ligands and identified ligand **52**, which promotes the addition of dialkylzinc reagents to both five- and six-membered tetrasubstituted enones in the presence of catalytic copper cyanide, with excellent enantioselectivities of up to 98%.[188] It is noteworthy that both Cu salt and ligand are air-stable, and that reactions can be carried out on the benchtop with undistilled toluene. Structurally related phosphane-based ligands such as ligand **53**, developed by Hoveyda's group, are efficient catalysts for asymmetric conjugate additions of dialkylzinc reagents to nitroalkenes. In the presence of 4 mol-% **53** and 2 mol-% $(CuOTf)_2{\cdot}C_6H_6$, enantiomeric excesses of up to 98% can be achieved (Scheme 28). Recently, Hoveyda reported examples of Cu-catalyzed asymmetric conjugate additions of alkyl- and arylzinc reagents to simple unactivated β-substituted cyclic enones by use of chiral bidentate *N*-heterocyclic carbene ligands.[189] Cyclic ketones with all-carbon quaternary stereogenic centers can be obtained in excellent yields and with 54–97% *ee* values.




Scheme 29. Organocatalytic Michael reactions.

### 5.2 Enantioselective Organocatalytic Michael Reactions

Chiral bifunctional organocatalysts have become attractive alternatives to metal catalysts for enantioselective Michael reactions over the last few years. Deng and coworkers identified cinchona alkaloids as effective catalysts for enantioselective conjugate additions of trisubstituted Michael donors to nitroalkenes, constructing adjacent quaternary and tertiary stereocenters (Scheme 29).[190]

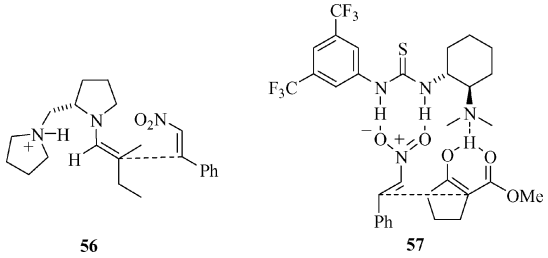
Excellent diastereoselectivity and enantioselectivity can be obtained with various cyclic and acyclic β-keto esters and β-dicarbonyl compounds. In addition to the wide scope for Michael donors, cinchona catalysts such as **54a** also tolerate a wide range of nitroalkenes as Michael acceptors bearing aryl, heteroaryl, or alkyl groups with varying electronic and steric properties. Deng reported the successful application of the same organocatalyst system for the addition of α-aryl- and α-alkyl-α-cyanoacetates to vinyl sulfones.[191] Catalyst **54b** afforded up to 97% *ee* values in this reaction, and the products could easily be converted into optically active α,α-disubstituted amino acids. More recently, Deng successfully applied his cinchona alkaloid organocatalysts for conjugate additions of α-substituted β-keto esters to α,β-unsaturated ketones.[192] A wide range of substrates that include cyclic and acyclic β-keto esters as donors and vinyl ketones bearing alkyl and aryl substituents of varying steric and electronic properties as acceptors afforded excellent yields and enantioselectivities. High diastereo- and enantioselectivities can also be achieved in the challenging conjugate additions of keto esters to β-substituted enones, successfully creating adjacent all-carbon quaternary and tertiary stereocenters.

Bella and Jørgensen developed the first cinchona alkaloid-catalyzed organocatalytic enantioselective conjugate additions of β-dicarbonyl compounds to alkynones.[193] The best results were obtained with $[DHQ]_2PHAL$ **55** as catalyst for both aromatic and aliphatic alkynones, giving high yields and good to high enantioselectivities. A one-pot procedure using catalytic tributylphosphane allows for the isomerization of the initial *E*/*Z* product mixture to the more stable (*E*) isomers while maintaining the enantiomeric excesses of the addition products. In another publication, Jørgensen described organocatalytic allylic C–C bond-forming additions of activated alkylidenes to acrolein with good yields and enantioselectivities.[194] Chiral tertiary amines in the form of cinchona alkaloid catalysts were used to give allyl intermediates that exhibit unusual α-selectivity in the C–C bond-forming step. There are several recent reports on the use of polymer-supported cinchona alkaloid catalysts for asymmetric Michael reactions.[195]

Direct asymmetric Michael reactions of α,α-disubstituted aldehydes with (*E*)-β-nitrostyrenes can be performed by using the chiral diamine 1-(2-pyrrolidinylmethyl)pyrrolidine **56** in combination with TFA as a bifunctional catalyst.[196] Figure 12 illustrates the proposed transition state, in which the diamine/TFA complex catalyzes a *si*-facial attack on the β-nitrostyrenes via an enamine intermediate. The α,α-dialkyl-γ-nitroaldehyde Michael products can be obtained in up to 96% yields with up to 91% *ee* values and are useful precursors for the synthesis of γ-aminobutyric acid neurotransmitters[197] and unusual γ-amino acids. Similarly to

Barbas' findings above, Alexakis reported direct Michael additions of aldehydes to vinyl sulfones catalyzed by the chiral diamine *N*-*i*Pr-2,2′-bipyrrolidine (iPBP).[198] However, reactions with α,α-disubstituted aldehydes used for the construction of quaternary centers afford only low enantioselectivities (up to 12% *ee* values). Another example of chiral bifunctional organocatalysts is provided by amine thiourea catalysts in which a thiourea moiety is linked to an amino group on a chiral scaffold.



**56** **57**

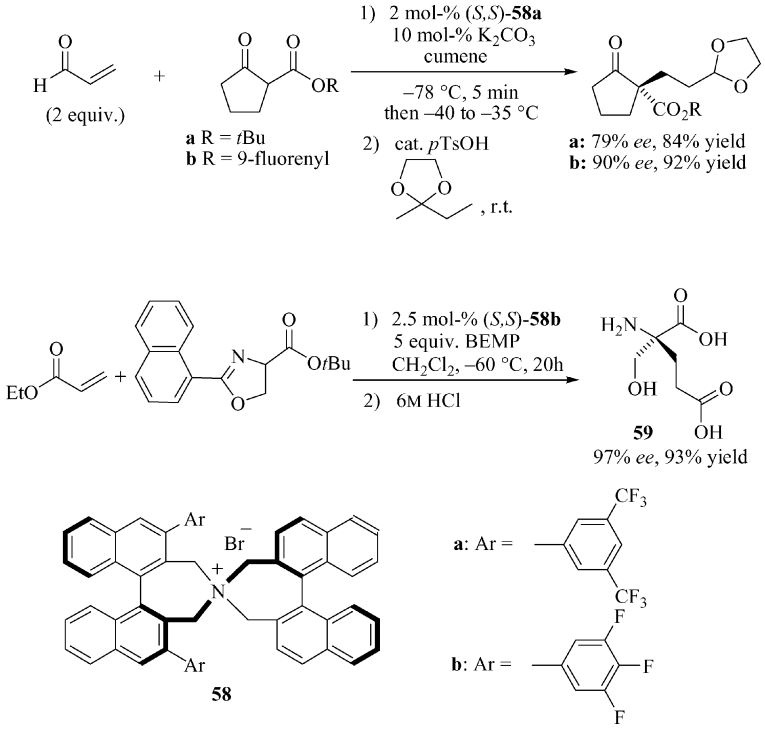
Figure 12. Proposed transition states in two different organocatalytic Michael reactions.

The first example of such a catalyst was reported by Takemoto.[199] Thiourea **57**, bearing 3,5-bis(trifluoromethyl)-benzene and dimethylamino groups, catalyzed Michael additions of a number of five- to seven-membered, as well as bicyclic α-substituted, β-keto esters to differently substituted β-nitrostyrenes with high enantio- and diastereoselectivities. Chen and co-workers demonstrated that the Michael additions of α-substituted cyanoacetates and vinyl sulfones could be promoted by bifunctional thiourea/tertiary amine organocatalysts.[200] Excellent enantioselectivities (72–96% *ee* values) could be achieved, and biologically important β[2,2]-amino acids could be easily prepared from the addition products. Jacobsen identified primary amino thiourea derivatives as effective and general catalysts for enantio- and diastereoselective conjugate additions of α,α-disubstituted aldehydes and nitroalkenes, providing an attractive solution to the challenging problem of generating chiral building blocks with contiguous quaternary and tertiary stereogenic centers.[201]

Chiral phase-transfer catalysts represent another successful organocatalyst class for Michael reactions. Maruoka developed *N*-spiro $C_2$-symmetric chiral quaternary ammonium salt **58a**, which catalyzes Michael additions of β-keto esters both to acrolein and to MVK with high enantiocontrol under solid–liquid phase-transfer conditions (Scheme 30).[202] Park and Jew applied catalyst **58b** for the synthesis of (2*S*)-α-(hydroxymethyl)-glutamic acid (HMG, **59**), a potent antagonist of metabotrobic glutamate receptor mGluR2.[203] The Michael reaction was carried out with use of 2.5 mol-% **58b** and 5 equiv. phosphazene base BEMP in $CH_2Cl_2$ at –60 °C, and the Michael adduct was converted into HMG (**59**) by acid hydrolysis. In a recent publication, Maruoka described a second-generation chiral phase-transfer catalyst that catalyzed asymmetric conjugate additions of various α-substituted α-cyanoacetates to acetylenic esters.[204]

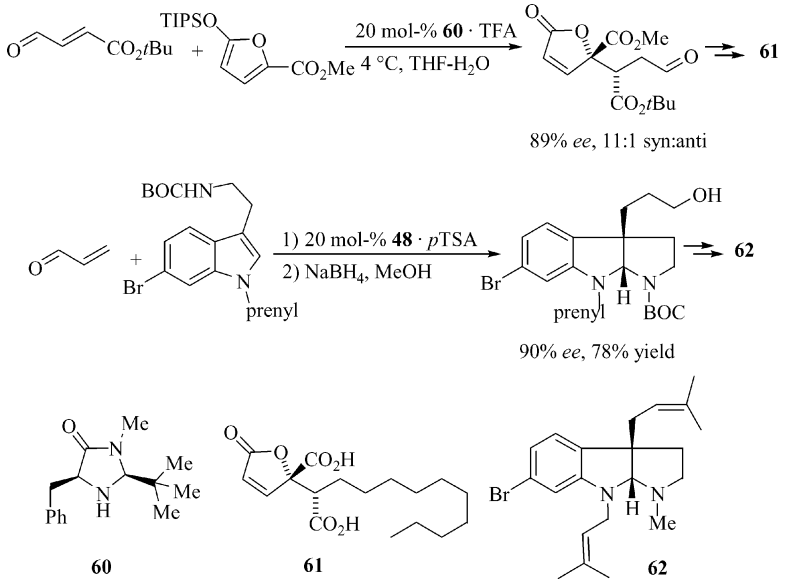
Iminium organocatalysis with chiral imidazolidinone **60** was reported by MacMillan as the first enantioselective Mukaiyama–Michael reaction (Scheme 31).[205]

Addition of silyloxy furans to simple α,β-unsaturated aldehydes provides a new synthetic strategy directed towards chiral γ-butenolides. The synthetic utility of this new



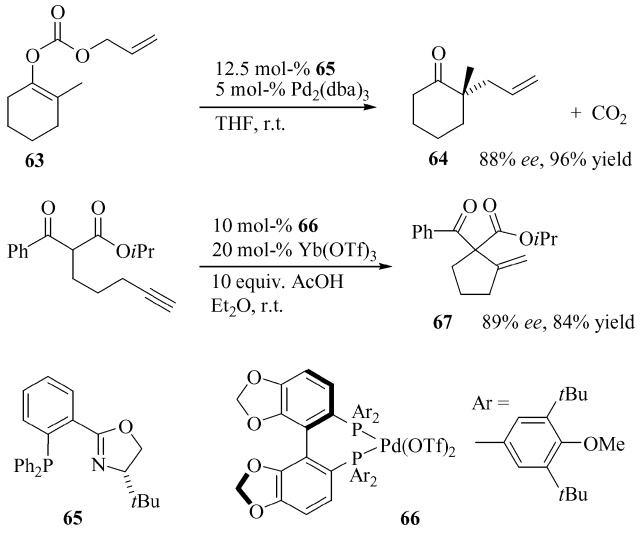

Scheme 30. $C_2$-symmetric chiral quaternary ammonium salts for Michael additions of β-keto esters to acrolein and MVK.




Scheme 31. Application of MacMillan's catalyst **60** in Michael reactions.

method was demonstrated by the synthesis of the biosurfactant spiculisporic acid (**61**). The Mukaiyama–Michael adduct was obtained in 89% *ee* and with 11:1 *syn*/*anti* selectivity, and could be elaborated to spiculisporic acid in a three-step procedure. Imidazolidinone **60** also catalyzed cascade Michael addition-cyclization reactions between tryptamines and α,β-unsaturated aldehydes.[206] This method provided easy access to the pyrroloindoline scaffold, an alkaloid structural motif, and has successfully been applied for the enantioselective synthesis of the marine alkaloid (–)-flustramine B (**62**). Bartoli and Melchiorre have reported interesting additions of 1,3-dicarbonyl compounds to maleimides. The enantioselectivities of these reactions are the highest reported to date for this class of Michael acceptors.[207]




Scheme 32. Enantioselective Tsuji allylation by Stoltz and stereoselective Conia-Ene reaction by Toste.

### 5.3 Miscellaneous Reactions for the Catalytic Formation of Quaternary all-Carbon Centers

The first examples of asymmetric Tsuji allyl enol carbonate and silyl enol ether allylations, which provide unprecedented access to important cyclohexanone derivatives in a highly enantioenriched form, was reported by Stoltz.[208] Both P,O- and P,P-ligands showed good reactivities but low enantioselectivities in these transformations. The ligands of choice are P,N-ligands, specifically phosphanyloxazolines (PHOX): enol carbonate **63** could be transformed into cyclohexanone **64** in 96% yield and with 88% *ee* by use of (*S*)-*t*Bu-PHOX ligand **65** and $Pd_2(dba)_3$ (Scheme 32). Simple enol ethers could also be used as the nucleophilic components for this reaction. In addition, Stoltz and coworkers have successfully applied this new methodology for an enantioconvergent decarboxylative allylation of racemic β-keto esters.[208b]

The thermal cyclization of ketones into alkynes (Conia-Ene reaction) provides access to α-vinylated ketones. In the case of ε-acetylenic carbonyl compounds, the Conia-Ene reaction provides easy and atom-economical access to methylenecyclopentanes. Toste and co-workers reported the first example of a transition metal-catalyzed version for this reaction, employing phosphanegold(I) complexes as catalysts.[209] However, probably because of the linear geometry of gold(I) complexes and thereby poor transmission of ligand chirality, no enantioselectivity was observed for this catalyst system. By switching to the dual $Pd^{II}/Yb^{III}$–DTBM-SEGPHOS catalyst **66**, high enantiocontrol of 89% *ee* could be achieved in 89% yield in the synthesis of Conia-Ene adduct **67** (Scheme 32).[210]

## 6. Conclusion and Outlook

In conclusion, we present an updated overview of catalytic methodologies applied to the formation of quaternary stereogenic centers. In most of the cases reported, the results obtained are far from optimal, and more efficient ligands and/or catalytic systems still need to be discovered in the future. Additions of nucleophiles to ketones remain a fascinating and highly challenging area of asymmetric catalysis.[211] The results obtained are often good, in terms of enantioselection, but poor in terms of catalytic efficiencies. Recent reports have shown that the design of new chiral catalysts has become more tailored toward ketonic substrates.[212] In this review we present both metal-mediated and organocatalytic reactions. A future challenge for chemists will be taking the advantages of the opportunities and potential offered by both of these two quite different areas, and combining organocatalytic reactions with organometallic transformations, with the aim of achieving low-cost and environmentally friendly multiple sequential transformations.

## Acknowledgments

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