Recent Progress in the Catalytic Synthesis of Tertiary Alcohols from Ketones with Organometallic Reagents

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Abstract: Efficient tertiary alcohol synthesis is currently one of the most rapidly advancing fields in organic chemistry, and recent powerful catalytic methodologies can provide versatile tertiary alcohols, even with enantioselective properties. This review summarizes work on the highly efficient catalytic synthesis of tertiary alcohols from ketones and organometallic reagents. New trends in the catalytic synthesis of tertiary alcohols, including functionalized ones, such as tertiary cyanohydrins and tertiary aldols, are examined from the frontier viewpoints that use typical or transition-metal catalysts, organocatalysts, and metal ate complexes, among others.

1 Introduction

Tertiary alcohols are versatile building blocks for the synthesis of natural products and pharmaceuticals. One major advanced strategy for synthesizing tertiary alcohols is a carbon–carbon bond-forming reaction between ketones and organometallic reagents. Organolithium, organomagnesium (Grignard reagents), organoaluminum, organosilicon, organocopper, organozinc, and organotin reagents have been developed over the past century, and they are still powerful reagents for constructing a carbon–carbon bond with carbonyl compounds. However, these organometallic reagents often cause the enolization of substrates (i.e., ketones) due to their strong basicity or competitive reduction via β-H transfer to give secondary alcohols. Therefore, it is still a challenge to obtain the desired tertiary alcohols in high yield without undesired side products. This is in sharp contrast to the synthesis of secondary alcohols, especially from aldehydes and organometallic reagents, with regard to conspicuous steric and electronic constraints between ketones and organometallic reagents. In particular, the catalytic enantioselective addition of organometallic reagents to ketones is problematic because of their extremely low reactivities and the difficulty of controlling the enantiofacial stereoselectivity. Recently, however, to overcome these essential problems in ketones and organometallic reagents, some excellent catalytic methods for synthesizing tertiary alcohols have been developed, including a highly efficient synthesis of optically active derivatives through catalytic enantioselective carbon–carbon bond formation to ketones. These methods include three types of processes; (a) substrate activation with a Lewis acid catalyst, (b) reagent activation with a Lewis base catalyst, and (c) dual activation of the substrate and reagent with a bifunctional Lewis acid–Lewis base catalyst (Scheme 1). In these methods, carbonyl activation and/or carbon–metal bond activation, and carbon–carbon bond formation are observed. In this review, we discuss recent progress in the highly efficient catalytic synthesis of tertiary alcohols, including functionalized tertiary cyanohydrins and tertiary aldols, from ketones and organometallic reagents. In particular, new trends are considered through an examination of the use of typical and transition-metal compounds, organocatalysts, metal ate complexes, and others.

2 Synthesis of Simple Tertiary Alcohols with Grignard Reagents

While organomagnesium reagents (i.e., Grignard reagents) remain the most popular choice for carbon–carbon bond formation in organic chemistry, their reactions with ketones can often give rise to reduction products or aldol addition adducts/starting ketones due to competing eno-
lization problems. Owing to the strong reactivity of Grignard reagents, the catalytic control of these reactions has been difficult. Thus, Imamoto et al. and Knochel et al. developed efficient stoichiometric organocerium(III) and organolanthanum(III) reagents, respectively (section 2.1). Ishihara et al. developed stoichiometric trialkylmagnesium(II) ate complexes (section 2.2). Stoichiometric chiral organozinc(II) ate complexes were also developed by Gosselin et al. (section 2.3). Moreover, Ishihara et al. recently developed highly efficient and practical zinc(II)-catalyzed Grignard reactions of ketones by a method that uses catalytic trialkylzinc(II) ate complexes for the first time (section 2.4). For a diastereoselective reaction, Yamamoto et al. developed a novel sequential aldol–Grignard reaction protocol (section 2.5).

2.1 Stoichiometric Organocerium(III) and Organolanthanum(III) Reagents

Imamoto and co-workers reported that suspended heterogeneous organocerium(III) reagents, which were prepared by the reaction of Grignard reagents with cerium(III) chloride, undergo exclusive nucleophilic addition to ketones at 0 °C in tetrahydrofuran within one hour. Even substrates that are susceptible to enolization can be used in this system. Reference experiments involving the reaction of readily enolizable 1,3-diphenyl-2-propanone (1) with n-butylmagnesium bromide (1.5 equiv), with no added cerium(III) chloride, showed poor results and gave 2 in yields of 18–36% (Scheme 2). In sharp contrast, in the presence of cerium(III) chloride (1.5 equiv), the reaction proceeded smoothly and adduct 2 was obtained in 98% yield. Moreover, the reaction of Grignard reagents with α,β-unsaturated enones, which is often accompanied by undesirable 1,4-addition, was dominated by 1,2-addition in the presence of cerium(III) chloride. 1,2-Addition to

**Biographical Sketches**

**Manabu Hatano** was born in Tokyo, Japan, in 1975, and received his PhD from the Tokyo Institute of Technology in 2003 under the direction of Professor Koichi Mikami. He was a JSPS Fellow under the Japanese Junior Scientists Program from 2000 to 2003. In 2003, he joined Professor Kazuaki Ishihara’s group at Nagoya University as an assistant professor, and became associate professor in 2007. He has received the Tejima Research Award for Young Scientists (2004), the TORAY Award in Synthetic Organic Chemistry, Japan (2006), the Lectureship Award of the Young Generation Special Forum from the Chemical Society of Japan (2007), and the Encouragement Prize from the Tokai Branch of the Society of Synthetic Organic Chemistry, Japan (2007). His research interests include asymmetric catalysis of carbon–carbon bond-forming reactions with chiral acid–base salt catalysts, the chemistry of ate complexes for efficient catalytic asymmetric reactions, and the design of chiral self-assembled complexes toward supramolecular asymmetric catalysts.

**Kazuaki Ishihara** was born in Aichi, Japan, in 1963, and received his PhD from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for three months in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After he completed his postdoctoral studies with Professor E. J. Corey at Harvard University (15 months beginning in 1991), he returned to Japan and joined Professor Hisashi Yamamoto’s group at Nagoya University as an assistant professor in 1992, and became associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. He has received the Inoue Research Award for Young Scientists (1994), the Chemical Society of Japan Award for Young Chemists (1996), the Thieme Chemistry Journal Award (2001), the Green and Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science and Technology (2003), the JSPS Prize (2005), the BCSJ Award (2005), the 1st International Conference on Cutting-Edge Organic Chemistry in Asia Lectureship Award (2006), Japan/UK GSC Symposium Lectureship (2007), and the IBM Japan Science Prize (2007). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis toward green and sustainable chemistry, and acid-base combination chemistry.
benzylideneacetone (3) with isopropylmagnesium chloride (1.5 equiv) and cerium(III) chloride (1.5 equiv) proceeded with a minimum generation of 1.4-adduct 5, and the desired product 4 was obtained in 91% yield (Scheme 3). In the cerium(III) chloride promoted Grignard addition to ketones, a cerium center has strong oxophilic character and can activate a carbonyl moiety by coordination. The fact that the strong basicity of Grignard reagents is weakened by mixing with cerium(III) chloride is also an important factor.

The activity of the lanthanide(III) salt in these reactions strongly depends on its complicated drying procedure and its solubility, although few lanthanide salts are soluble in organic solvents. Knochel and co-workers developed a method for preparing tetrahydrofuran-soluble LaCl₃·2LiCl, which may be suitable for complexation with Grignard reagents for the addition reaction to carbonyl compounds. A solution of LaCl₃·2LiCl promoted the addition of Grignard reagents to various types of hindered and/or enolizable ketones to lead to tertiary alcohols. With a considerable minimization of side reactions, α-tetralone (6) reacted quantitatively with isopropylmagnesium chloride, which led to the tertiary alcohol 7 in 95% yield (Scheme 4). In the absence of lanthanide salts, 7 was obtained in only 30% yield, whereas Imamoto’s method provided 7 in 73% yield. Similarly, the addition of 2-pyridylmagnesium chloride to camphor (8) gave the corresponding tertiary alcohol 9 as a sole diastereomer in 92% yield (Scheme 5). In the case of α,β-unsaturated enones such as cyclohex-2-enone (10), the addition of cyclopentylmagnesium chloride proceeded exclusively in the presence of LaCl₃·2LiCl to give the desired tertiary allylic alcohol 11 in 93% yield (Scheme 6). In the absence of lanthanum(III) salt, the only product was the allylic alcohol 12 via a reduction process.

### Scheme 1
Catalytic synthesis of tertiary alcohols from ketones and organometallic reagents

### Scheme 2
Tertiary alcohol synthesis with organocerium(III) reagents

### Scheme 3
Selective 1,2-addition with organocerium(III) reagents

Grignard and alkyllithium reagents are very popular in alkylation reactions of aldehydes. However, their reactions with ketones often give undesired reduction products, self-aldol condensation products, and/or the starting ketones together with the desired alkylated tertiary alcohols. To avoid these problems, highly nucleophilic but weakly basic alkylation reagents are required for the selective alkylation of sterically bulky ketones. However, Grignard reagents are relatively weak bases and are not sufficiently nucleophilic, while alkyllithium reagents are highly nucleophilic but too basic. Recently, Ishihara and co-workers found that trialkylmagnesium ate complexes (R₃MgLiX), which were easily prepared from Grignard...
reagents (1 equiv) and alkyllithium (2 equiv), were significantly effective for alkyl-selective addition to ketones. The enhanced nucleophilicity and the suppressed Brønsted basicity of alkylation reagents were controlled in trialkylmagnesium(II) ate complexes. The reactivities of n-BuLi, n-BuMgBr, n-Bu3Mg, and n-Bu3MgLi·LiCl were compared with regard to the addition of the n-butyll group to acetophenone under the same conditions (Scheme 7). Lithium chloride that was released via mixing from n-BuMgCl and n-BuLi, leading to n-Bu3MgLi·LiCl, was obviously effective for giving the desired alkylation. However, n-Bu3MgLi without lithium chloride, prepared from n-Bu3Mg and n-BuLi, showed lower performance than n-Bu3MgLi·LiCl.

![Scheme 7 Tertiary alcohol synthesis with trialkylmagnesium(II) ate complexes](image)

With regard to the atom-economy of alkylation, the alkyl source R in trialkylmagnesium ate complexes of R3MgLi·LiX is not completely consumed during the reaction and the remaining R source would be sacrificed. Fortunately, Hatano and Ishihara et al. found that RMe2MgLi·LiX selectively gave the R adduct. The reactivities of RMe2MgLi·LiBr and RMgBr were compared in the addition of R to benzophenone under the same conditions (Scheme 8). Alkylations with EtMe2MgLi·LiBr, i-PrMe2MgLi·LiBr, n-PrMe2MgLi·LiBr, and n-BuMe2MgLi·LiBr showed high yields and high selectivities for the corresponding R adducts. Comparable Grignard reagents were totally ineffective and gave significant amounts of the reduced byproducts. In particular, dramatic results were observed with n-BuMe2MgLi, where the yield was improved from 0% to 92%.

![Scheme 8 Addition to benzophenone with RMe2MgLi·LiBr reagents](image)

2.3 Stoichiometric Chiral Organozinc(II) Ate Complexes

Gosselin, Britton, et al. reported the stoichiometric enantioselective addition of organozinc(II) ate complexes to ethyl 2,2,2-trifluoropyruvate. The reaction of ethyl 2,2,2-trifluoropyruvate with one equivalent each of diethylzinc, ethylmagnesium chloride, and (R)-1,1’-bi-2-naphthol ([R]-BINOL) in dichloroethane at −40 °C for 24 hours gave the desired ethylation adduct in >95% yield with 64–72% ee (Scheme 9). Interestingly, the reagent obtained from a stoichiometric mixture of diethylzinc, EtLi, and (R)-BINOL gave the same adduct with the opposite sense of stereochemistry (52% ee). For other alkyl and aryl additions to ethyl 2,2,2-trifluoropyruvate, some reagents were prepared from diethylzinc, RMgCl, and (R)-BINOL in dichloroethane–tetrahydrofuran, and the adducts were obtained in low to moderate yields with moderate to high enantioselectivities (up to 83% ee).

![Scheme 9 Stoichiometric enantioselective addition of organozinc(II) ate complexes to ethyl 2,2,2-trifluoropyruvate](image)

2.4 Catalytic Trialkylzinc(II) Ate Complexes

Very recently, Ishihara and co-workers developed a highly efficient alkylation of ketones with Grignard reagents in the presence of catalytic trialkylzinc(II) ate complexes (R2ZnMgCl) derived from zinc chloride in situ. Instead of stoichiometric alkylithium reagents to form R2ZnLi, the catalytic use of simple and inexpensive zinc chloride without purification should offer a significant advantage over existing technologies. Although alkylation to biaryl ketones, such as benzophenone, with Grignard reagents often gives reduction products in considerable yields, the presence of zinc chloride (10 mol%) improved the yield of desired alkylated products 13 and suppressed the yield of undesired side adducts 14 (Table 1). Interestingly, isopropylation to not only aromatic but also aliphatic ketones with isopropylmagnesium chloride (1.3 equiv) proceeded smoothly in the presence of 10 mol% of zinc chloride, even though sec-RMgX often favors reduction over the desired alkylation (Table 2).

As a specific example, the alkylation product of 2-adamantanone, 2-alkyl-2-adamantanol, is a useful photoresistant material, but when only Grignard reagents are used, reaction occurs in preference to the desired alkylation. In Ishihara’s method, a 100-mmol-scale reaction of 2-adamantanone with 1.3 equiv of (R)-1,1'-bi-2-naphthol in dichloroethane–tetrahydrofuran gave the desired adduct in >95% yield with 64–72% ee (Scheme 9). Interestingly, the reagent obtained from a stoichiometric mixture of diethylzinc, EtLi, and (R)-BINOL gave the same adduct with the opposite sense of stereochemistry (52% ee). For other alkyl and aryl additions to ethyl 2,2,2-trifluoropyruvate, some reagents were prepared from diethylzinc, RMgCl, and (R)-BINOL in dichloroethane–tetrahydrofuran, and the adducts were obtained in low to moderate yields with moderate to high enantioselectivities (up to 83% ee).
mantanone produced 2-ethyl-2-adamantanol (17) in 81% yield (14.6 g) (Scheme 10).

A plausible catalytic cycle including the transition-state assembly in this zinc chloride catalyzed alkylation of ketones with Grignard reagents is shown in Scheme 11. This unique catalytic system is based on the trialkylzinc(II) ate complexes, R$_3$ZnMgCl. First, R$_3$ZnMgCl is generated via R$_2$Zn from ZnCl$_2$ and RMgCl. R$_3$ZnMgCl coordinates to ketones at the [MgCl]$^+$ moiety in a six-membered ring with a chair conformation, and then [R$_2$Zn–R]$^–$ attacks the activated substrate followed by release of the corresponding adduct and the regeneration of R$_3$ZnMgCl. The key to promoting this catalytic system is careful control of the R$_3$ZnMgCl reagents with regard to decreased basicity and increased nucleophilicity compared to the original Grignard reagents.

Scheme 11 Proposed catalytic cycle and transition-state assembly

2.5 Sequential Aldol–Grignard Reaction

Very recently, Yamamoto and co-workers developed the highly diastereoselective Lewis acid catalyzed sequential aldol–Grignard reaction. In a simple one-pot sequential aldol reaction protocol, tris(trifluoromethanesulfonyl)amine (HNTf$_2$) within five minutes, and phenylmagnesium bromide (2 equiv) was subsequently added dropwise at –78 °C (Scheme 12). The corresponding product was obtained in 85% yield with excellent diastereoselectivity giving the anti product as the major diastereomer (dr = 95:5). The observed sense of stereoinduction results from nucleophilic addition on the p-face of the carbonyl opposite to that of their previously reported sequential aldol–Grignard reaction utilizing the acetalddehyde TTMSS enol ether. Wide general applicability of TTMSS enol ethers, aldehydes, and Grignard reagents was observed, and the corresponding tertiary alcohols were obtained in high diastereoselectivities. They also established the sequential aldol–aldol–Grignard reaction, and the four-component products such as 21 were obtained in one pot in moderate yields with high diastereoselectivities.

3 Catalytic Enantioselective Alkylation, Arylation, and Alkenylation Reactions with Organozinc Reagents

For carbon–carbon bond-forming reactions on carbonyl compounds, organozinc reagents (R$_2$Zn) are the most popular species, and can be easily prepared or obtained commercially as a solution, neat liquid, or solid. In general, organozinc reagents show little reactivity toward many electrophilic substrates, even those that are aldehydes. The most competitive catalytic enantioselective reaction in organic synthesis is the addition of diethylzinc to alde-
hydes, since chiral secondary amines are readily obtained in good to excellent yields.14,15 However, the catalytic enantioselective addition of organozinc reagents to ketones is still a challenging field. A few catalytic enantioselective examples in ketones have been reported, owing to their extremely low reactivities and the difficulty of controlling the enantiomeric stereoselectivity.16 In particular, organozinc reagents are much less reactive than organolithium or organomagnesium reagents, but organozinc reagents are preferred since they tolerate the presence of many functional groups in substrates.

Fu and Dosa published the first catalytic enantioselective addition of organozinc reagents to ketones in 1998.17 In this pioneering work, the addition of diphenylzinc (3.5 equiv) to ketones was promoted by 15 mol% of 3-exo-dimethylaminoisoborneol (DAIB; 22), and the corresponding chiral tertiary alcohols were obtained in good to high enantiomeric excesses of up to 91% (Scheme 13). Methanol (1.5 equiv) was essential for improving both the yields and enantioselectivities of the desired tertiary alcohols.

Scheme 13 First catalytic enantioselective addition of Ph2Zn to ketones using a DAIB–Zn(II) catalyst

Around the same time as Fu’s publication, Yus and Ramón reported the first catalytic enantioselective addition of alkylzinc reagents to ketones.18 Although an equimolar amount of titanium(IV) isopropoxide was required, some substrates exhibited high enantioselectivities (up to 89% ee) in the presence of 20 mol% of chiral camphorsulfonamide ligand 23 (Scheme 14).

Walsh et al. developed C2-symmetric bis(camphorsulfonamide) ligand 24, derived from cyclohexane-1,2-diamine.19 This ligand was an excellent chiral auxiliary for the highly enantioselective diethylzinc addition to a series of aromatic and aliphatic ketones (Table 3). While only 2 mol% catalyst loading was necessary, an equimolar amount of titanium(IV) isopropoxide was required. Moreover, this catalyst could be applied to a large-scale synthesis. For example, 2 mol% of 24 catalyzed the enantioselective addition of ethyl to 3'-methylacetophenone (5 g) to give the corresponding tertiary alcohol with perfect enantioselectivity (99% ee) in 73% yield (4.5 g). At almost the same time as Walsh’s publication, Yus and co-workers independently devised chiral ligand 24 after they had found that chiral ligand 25 was effective.20 Chiral ligand 25 required not only 10 mol% catalyst loading but

Table 3 Catalytic Enantioselective Addition of Diethylzinc to Ketones Using a Bis(camphorsulfonamide)–Titanium(IV) Catalyst

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Ligand 24 (mol%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCOMe</td>
<td>2</td>
<td>71</td>
<td>96</td>
</tr>
<tr>
<td>3-MeC6H4COMe</td>
<td>2</td>
<td>78</td>
<td>99</td>
</tr>
<tr>
<td>a-tetralone</td>
<td>10</td>
<td>35</td>
<td>&gt;99</td>
</tr>
<tr>
<td>PhCOBu</td>
<td>2</td>
<td>79</td>
<td>88</td>
</tr>
<tr>
<td>PhCH2CH2COMe</td>
<td>10</td>
<td>68</td>
<td>71</td>
</tr>
<tr>
<td>1-cyclohexenylCOMe</td>
<td>2</td>
<td>56</td>
<td>96</td>
</tr>
</tbody>
</table>
also an equimolar amount of a titanium(IV) complex (Scheme 15). Recently, Wang and co-workers reported that a similar ligand, based on L-tartaric acid, could catalyze the diethylzinc addition to ketones with almost the same level of enantioselectivity as 25.22

Kozlowski and DiMauro reported the first catalytic enantioselective addition of organozinc reagents to \( \alpha \)-ketoesters (Scheme 16).23 The \( \alpha \)-ketoester structure is regarded as an activated ketone, and thus a high reactivity is expected. They designed the bifunctional diaminosalen–titanium(IV) catalyst 26 with a Lewis acid moiety in the titanium(IV) center to activate the ketoester, and a Lewis base part in the piperidines to activate the organozinc reagents (see the proposed transition-state assembly 27). The reactions proceeded in toluene at \(-40^\circ\text{C}\) in two hours without further addition of titanium(IV) isopropanoxide beyond the 5 mol% of the centered titanium(IV). The resultant \( \alpha \)-alkyl-\( \alpha \)-hydroxyesters were obtained in high yields, but with low to moderate enantioselectivities (up to 78% ee).

Shibasaki and co-workers reported the first example of a catalytic enantioselective addition of dimethylzinc to \( \alpha \)-ketoesters with an acid–base bifunctional system.24 Chiral ligand 28, which contains arranged multicenters such as alcohols and an amine, promoted the reaction (Scheme 17). In particular, both high yields and high enantioselectivities were observed with aromatic and heterocyclic \( \alpha \)-ketoesters in the presence of 28 (10 mol%). Interestingly, slow addition (30 h) of dimethylzinc and the use of protic additives such as propan-2-ol (27 mol%) positively affected both the yield and enantioselectivity. With regard to the disappearance of nonlinear effects in the presence of propan-2-ol, propan-2-ol changes the actual catalyst into a monomeric structure by mixed aggregate formation.

Walsh and co-workers also reported that chiral ligand 24 catalyzed a highly enantioselective phenylation to ketones (Table 4).25 Significant improvements, such as a low catalyst loading (10 mol%) and use of only 1.6 equiv of diphenylzinc, were made. Extremely high enantioselectivities and chemical yields were observed in a variety of aromatic and aliphatic ketones. \( \alpha,\beta \)-Unsaturated enones were also acceptable for diphenylzinc addition in high yields with high enantioselectivities.26 The wide scope of this method using a readily available ligand (24) was attractive from the viewpoint of a practical asymmetric catalysis, although 60 mol% of titanium(IV) isopropanoxide was used.

Walsh and Li developed a highly efficient catalytic enantioselective alkenylation and dienylation of ketones in the presence titanium(IV) compounds and 24 (Scheme 18).27 A variety of alkynes could be used for the in situ preparation of alkylzinc species that were suitable for the
asymmetric alkenylation reaction. The key to success was a combination of hydrozirconation/transmetallation to the organozinc reagent (Me₂Zn). The corresponding optically active tertiary allylic alcohols were successfully obtained within 24 hours in high yields and with high enantioselectivities.

[Chemical Structures]

Scheme 18 Catalytic enantioselective alkenylation of ketones using 24

Ramón, Yus, and co-workers reported that chiral 1,2-bis(sulfonamide) derivatives, such as 29, could catalyze the enantioselective addition of organozinc reagents to ketones. The reaction between acetophenone and diethylzinc proceeded smoothly in the presence of 5 mol% of 29, which is the first example of the highly efficient ethylation of inactive ketones under mild conditions without titanium(IV) compounds achieved by the simple mixing of substrate, diethylzinc, and the chiral ligand in a solvent. In the phenylation of 4'-chloroacetophenone, the corresponding tertiary alcohol was obtained on a one-gram scale in 91% yield with 93% ee by using 3 mol% of (S)-30 (Table 5). In particular, this is the first example of the highly efficient ethylation of inactive ketones under mild conditions without titanium(IV) compounds achieved by the simple mixing of substrate, diethylzinc, and the chiral ligand in a solvent.

Scheme 20 Solvent-free catalytic enantioselective addition of organozinc reagents to ketones using 24

tones using a conjugate Lewis acid–Lewis base phosphoramidate–zinc(II) catalyst. The chiral zinc(II) catalyst was derived from an inexpensive natural amino acid, L-valine. From a variety of aromatic and aliphatic ketones, optically active tertiary alcohols were obtained in high yields and with high enantioselectivities (up to 98% ee) by using 10 mol% of (S)-30 (Table 5). In particular, this is the first example of the highly efficient ethylation of inactive ketones under mild conditions without titanium(IV) compounds achieved by the simple mixing of substrate, diethylzinc, and the chiral ligand in a solvent.

Table 5 Catalytic Enantioselective Organozinc Addition to Ketones

<table>
<thead>
<tr>
<th>Ar</th>
<th>(Ar = 4-BrC₆H₄)</th>
<th>(4.8 equiv)</th>
<th>2 mol% of 24</th>
<th>toluene, 24 h</th>
<th>78%, 99% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO(C₆H₄)₂S-NH-S-NH₂</td>
<td>(5 mol%)</td>
<td>10 mol% of 24</td>
<td>toluene, solvent-free, 38 h</td>
<td>55%, 94% ee</td>
<td></td>
</tr>
<tr>
<td>MeO(C₆H₄)₂S-NH-S-NH₂</td>
<td>(5 mol%)</td>
<td>2 mol% of 24</td>
<td>heptane, r.t.</td>
<td>83%, 95% ee</td>
<td></td>
</tr>
<tr>
<td>MeO(C₆H₄)₂S-NH-S-NH₂</td>
<td>(5 mol%)</td>
<td>0.5 mol% of 24</td>
<td>heptane, r.t.</td>
<td>80%, 93% ee</td>
<td></td>
</tr>
</tbody>
</table>

* For phenylation, 1 equiv of Ph₂Zn and 2 equiv of Et₂Zn were used. For ethylation, 3 equiv of Et₂Zn was used.
key intermediate in the synthesis of the antihistamine drug clemastine (Scheme 21).

In the plausible transition states shown in Figure 1, \((S)-30\) and diethylzinc would form the N,N-chelated EtZn(II) center as a Lewis acid to activate the ketone \((R_1COR_2, R_1 > R_2)\). The \(P=O\) moiety, as a Lewis base which is electro-donatively activated through conjugation among Zn–N–P=O bonds, would coordinate to the diethylzinc reagent, leading to six-membered chelation in a chair conformation with a ketone. The isopropyl moiety (‘up’ in Figure 1) might relay the direction of the two bulky 1-naphthyl moieties, ‘down’ and ‘up’, respectively. Therefore, the six-membered cyclic transition state which leads to the \(S\)-configured product via \(s\)-face attack would be stabilized without steric repulsion.

For the enantioselective synthesis of efavirenz (31), the Merck and Dupont Research groups developed the addition of lithium cycloproplylacetylide to \(p\)-methoxybenzyl-protected ketoaniline with 96–98\% ee (Scheme 22). However, large amounts of the reagents and chiral amino alcohol salt (32) were necessary. Moreover, the same group also developed the highly enantioselective alkynylation of a ketone mediated by chiral zinc(II) aminokoxides, in which a stoichiometric amount (1.3 equiv) of chiral auxiliary was used.

Jiang and co-workers reported that an inexpensive chiral amino alcohol (33) could be used to catalyze the enantioselective addition of zinc(II) acetylides to \(\alpha\)-ketoesters to prepare tertiary \(\alpha\)-hydroxy-\(\beta\)-ynyl esters. The reactions proceeded smoothly in the presence of 33 (22 mol\%), zinc(II) trifluoromethanesulfonate (20 mol\%), and triethylamine (30 mol\%) in toluene at 70 °C for two days, and the desired adducts were obtained in high yields with high enantioselectivities (81–94\% ee) (Scheme 23).

Cozzi achieved the first general catalytic enantioselective addition of terminal alkynes to unactivated ketones. To overcome the low reactivity of the substrates, his approach involved the concept of double activation (i.e., Lewis acid–Lewis base), especially the use of a chiral salen–zinc(II) complex (Scheme 24). For a range of aromatic and aliphatic ketones, 20 mol\% of \((R,R)-N,N'\)-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine (34) in toluene at room temperature effectively provided...
the desired products with moderate to high enantioselectivities.

Chan and co-workers established a highly enantioselective addition of phenylacetylene to aromatic ketones with camphorsulfonamide ligand \( \text{23,40} \) which was devised by Ramón and Yus. \( \text{18} \) The reaction of a variety of aromatic ketones with phenylacetylene (2.6 equiv) in the presence of dimethylzinc (3 equiv) was catalyzed by 10 mol\% each of copper(II) trifluoromethanesulfonate and \( \text{23} \) in dichloromethane at 0 °C for 48 hours. The corresponding optically active tertiary propargyl alcohols were obtained in good to high yields with excellent enantioselectivities of up to 97% ee (Scheme 25). Chan’s examples are highly efficient with regard to low catalyst loading and excellent enantioselectivities, since selective addition to ketones is difficult. Substitution at the \( \text{ortho} \) position of the substrates favorably affected the enantioselectivities, since the steric hindrance of the ortho substituents restricts the orientation of the substrates.

Saito and Katsuki reported the salen–zinc(II) catalyzed enantioselective alkynylation of ketones. \( \text{41} \) They used 8 mol\% of an in situ generated zinc(II) complex with chiral salen ligand \( \text{35} \) (Scheme 26). For a range of ketones and terminal acetylenes, the alkynylated products were obtained in moderate to good yields with high enantioselectivities.

Cozzi et al. also reported that titanium(IV)–BINOLate catalyzed the enantioselective addition of titanium phenylacetylide to ketones (Scheme 27). \( \text{42} \) Titanium(IV) phenylacetylides were readily prepared from 1.5 equiv of chlorotitanium(IV) isopropoxide and lithium phenylacetylide without organozinc reagents. Aromatic ketones provided good results with moderate yields and good enantioselectivities. Around the same time, Wang and co-workers demonstrated that an (S)-BINOL ligand combined with a catalytic amount of titanium(IV) isopropoxide effectively catalyzed the enantioselective addition of alkynylzinc to give unactivated aromatic and aliphatic ketones (Scheme 28). \( \text{43} \) The corresponding tertiary propargyl alcohols were obtained with 85–92% ee. A 1:1 ratio of (S)-BINOL and titanium(IV) isopropoxide (20 mol\% each) was critical for activating ketones so that the corresponding highly acidic titanium(IV)–BINOLate was formed.

Wang and co-workers reported the enantioselective phenylacetylene addition to aromatic ketones catalyzed by cinchona alkaloid \( \text{36} \)–aluminum(III) complexes (Scheme 29). \( \text{44} \) This is the first chiral aluminum(III) catalyst to allow the enantioselective alkynylzinc addition to unactivated ketones to proceed with 70–89% ee under optimized conditions. However, the amount of chiral aluminum(III) catalyst (40 mol\%) with cinchona alkaloid (80 mol\%) was inappropriate for a practical catalysis.
REVIEW

Catalytic Tertiary Alcohol Synthesis

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Scheme 29 Aluminum(III)–cinchona alkaloid catalyzed enantioselective addition of phenylacetylene to aromatic ketones

Wang and co-workers reported the enantioselective addition of phenylacetylene to aromatic ketones catalyzed by chiral oxazolidine ligands.45 In the presence of chiral oxazoline ligand 37 (20 mol%), the desired tertiary propargyl alcohols were obtained with 68–88% ee (Scheme 30).

Scheme 30 Catalytic enantioselective addition of phenylacetylene to aromatic ketones using a chiral oxazolidine ligand

Wang and co-workers reported that a chiral copper(II) complex was effective in the highly enantioselective addition of phenylacetylene to a series of simple ketones (Table 6).46 The chiral copper(II) complex was prepared from copper(II) trifluoromethanesulfonate (5–8 mol%) and a bis(hydroxycamphorsulfonamide) ligand (25) (5–8 mol%) which had been designed by Yus and co-workers.20,21 For aromatic ketones, electron-donating and electron-withdrawing substituents had little effect on the enantioselectivities of the products. However, a substituent at the ortho position had a favorable effect on the ability to achieve high enantioselectivities. With aliphatic ketones, the reaction proceeded smoothly with high enantioselectivities (91–94% ee).

Wang and co-workers also developed the highly efficient catalytic enantioselective addition of phenylacetylene to aromatic ketones with chiral Schiff base amino alcohol 38 derived from L-phenylglycine (Scheme 31).47 When 1 mol% of 38 was used, the desired products were obtained from aromatic ketones in good yields with >90% ee. Moreover, when 0.1 mol% of 38 was used, high enantioselectivity (up to 85% ee) was still achieved. This is one of the most practical methods for synthesizing optically active tertiary propargyl alcohols from simple aromatic ketones and phenylacetylene. Very recently, this catalytic system was used to achieve the enantioselective addition of 1-ethynylcyclohexene to aromatic ketones (Scheme 31).48

Very recently, Shibasaki and co-workers developed a general method for the direct alkylation of trifluoromethyl ketones by using CuO\textsubscript{t}-Bu–XANTPHOS or phenanthroline complexes as catalysts.49 In particular, a wide range of substrates scope with regard to trifluoromethyl ketones was observed under practical catalytic conditions with Cu(OTf)\textsubscript{2}–2KOH–1,10-phenanthroline (10 mol%) in toluene at 100 °C, and the desired tertiary propargyl alcohols were obtained in good to excellent yields (Table 7). Various alkynes, including phenylacetylene, alkylacetylene, and synthetically useful silylacetylene, were applicable. They also discribed their preliminary results in a catalytic enantioselective trifluoromethyl-substituted tertiary propargyl alcohol synthesis. By using a chiral bidentate phosphine or pybox ligand, moderate enantioselectivities (42–52% ee) were achieved. They proposed that the reaction likely proceeds via copper(I) alkynides, which are generated in situ by copper(I) alkoxide (Scheme 32). Thus, the selective activation of alkynes by soft copper(I)–soft alkyne π-orbital interactions and the enhanced nucleophilicity of the resulting copper(I) alkynide by the ligands were the key to the success of this catalytic cycle.

Table 6 Catalytic Enantioselective Addition of Phenylacetylene to Ketones with Bis(hydroxycamphorsulfonamide)–Copper(II) Complexes

<table>
<thead>
<tr>
<th>Ketone (R)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>90</td>
<td>88</td>
</tr>
<tr>
<td>2-FC\textsubscript{6}H\textsubscript{4}</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>2-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>93</td>
<td>95</td>
</tr>
<tr>
<td>4-MeOC\textsubscript{6}H\textsubscript{4}</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>4-ClC\textsubscript{6}H\textsubscript{4}</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>i-Pr</td>
<td>94</td>
<td>92</td>
</tr>
</tbody>
</table>

Scheme 31 Catalytic enantioselective addition of acetylene compounds to aromatic ketones using chiral Schiff base amino alcohols
Proposed catalytic cycle

Scheidt and Lettan reported that trialkoxysilylalkynes acted as alkynyl nucleophiles in the reaction with ketones to afford tertiary propargyl alcohols in the presence of a Lewis base catalyst. The combined use of 20 mol% of potassium ethoxide and 18-crown-6 in tetrahydrofuran at 0 °C promoted the reaction without giving undesired aldol products from enolizable ketones (Scheme 33). The addition of a small amount of 18-crown-6 allowed for the use of catalytic potassium ethoxide. In their mechanistic description, the addition of Lewis base (EtO–) to trialkoxysilylalkynes would lead to the formation of a hypervalent silicate, which could mediate the transfer of an alkynyl nucleophile to activated ketone via a hexacoordinate organization.

Kanai, Shibasaki and co-workers were the first to develop a catalytic enantioselective alkenylation of trifluoromethyl ketones. High enantioselectivities were established in the alkenylation of aryl trifluoromethyl ketones using a CuF–(R)-DTBM-SEGPHOS complex as a chiral catalyst (5–10 mol%) and alkenylsilanes (2 equiv) as nucleophiles (Scheme 34). To improve the yields and enantioselectivities, (MeO)2MeSi(CH=CH2) was found to be a better vinyl source than (MeO)3SiCH=CH2 for simple vinylation. Although the enantioselectivity was moderate, the same reaction conditions were be used for the catalytic phenylation of trifluoromethyl ketones using (MeO)2SiPh2.

Catalytic enantioselective alkenylation of trifluoromethyl ketones using a CuF–(R)-DTBM-SEGPHOS complex

Recently, Gau and co-workers reported the first example of catalytic enantioselective aryl additions of organoaluminum reagents to aromatic ketones. In the presence of (S)-BINOL (10 mol%), Ph3Al(thf) (2.5 equiv), and titanium(IV) isopropoxide (5 equiv), the reactions with aromatic ketones were carried out. The use of (MeO)2R2Si (2 equiv) as a vinyl source resulted in the best yields and enantioselectivities. The reactions were performed at 0 °C, and the yields and enantioselectivities are listed in Table 8.

Table 8 Enantioselective Triarylaluminum Addition to Ketones Catalyzed by a Ti(IV)–BINOL Complex

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-NaphCOMe</td>
<td>Ph</td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>2-CIC6H4COMe</td>
<td>Ph</td>
<td>73</td>
<td>97</td>
</tr>
<tr>
<td>4-MeOCH2COMe</td>
<td>Ph</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>1-cyclohexenylCOMe</td>
<td>Ph</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>2-furylCOMe</td>
<td>Ph</td>
<td>95</td>
<td>84</td>
</tr>
<tr>
<td>PhCOMe</td>
<td>2-Naph</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>PhCOMe</td>
<td>4-TMSCH2</td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>PhCOMe</td>
<td>4-MeOCH2</td>
<td>87</td>
<td>78</td>
</tr>
</tbody>
</table>
ic ketones proceeded smoothly in toluene at 0 °C to give the corresponding tertiary alcohols in high yields with >90% ee (Table 8). The addition of different aryl groups, such as 2-naphthyl or 4-(trimethylsilyl)phenyl, to aromatic ketones also gave the desired products in high yields with high enantioselectivities (90–93% ee). α,β-Unsaturated ketones and heterocyclic ketones could also be used with 20 mol% of (S)-BINOL.

6 Catalytic Enantioselective Reformatsky Reaction

The Reformatsky reaction consists of the zinc-induced synthesis of β-hydroxy esters from α-haloesters with aldehydes and ketones. Over the past century, milder reaction systems have been achieved step by step using, for example, Rieke zinc, copper–zinc couple, or zinc–silver–graphite. Recently, efficient stoichiometric or catalytic Reformatsky reactions have been developed with chromium(II), samarium(II), indium(I), and iron(II) compounds under heterogeneous conditions. Remarkably, Honda and co-workers reported a homogeneous Reformatsky reaction that used diethylzinc in the presence of a rhodium(I) complex (i.e., Wilkinson’s catalyst) (Scheme 35). In this method, inter- and intramolecular Reformatsky reactions proceeded under simple and mild reaction conditions. Moreover, highly efficient nickel(II)-catalyzed imino-Reformatsky reactions have been developed by Snapper and Cozzi.

Scheme 35 Rh(I)-catalyzed Reformatsky reaction

Steady progress has been made on the development of an enantioselective Reformatsky reaction. However, a truly catalytic enantioselective Reformatsky reaction or imino-Reformatsky reaction was not available before 2006. Recently, Cozzi and co-workers reported the first practical catalytic enantioselective Reformatsky reaction with ketones, which was based on the chiral salen–manganese(III) catalyst 40 (Scheme 36). Zinc(II) enolates could be prepared by the direct exchange of iodo esters with dimethylzinc (2 equiv). The enantioselectivities were substantially improved in the presence of 4-phenylpyridine N-oxide (25 mol%), an additive that is often used in selen–manganese(III)-catalyzed epoxidation. Aromatic ketones gave enantioselectivities in the range of 69–86% ee, and 2,2-dimethylcyclopentanone gave the highest enantioselectivity and good yield for a simple aliphatic ketone.

7 Catalytic Enantioselective Allylation Reaction

Catalytic enantioselective allylation to carbonyl compounds is one of the most important synthetic methods in asymmetric synthesis. However, the reported processes for the catalytic enantioselective synthesis of secondary homoallylic alcohols from aldehydes usually fail to give any product when applied to ketones. Efforts to develop a catalytic enantioselective synthesis of tertiary homoallylic alcohols from ketones and allylmetal compounds such as tin, boron, and silicon began in 1999.

Tagliavini and co-workers developed the first catalytic enantioselective allylation of ketones with tetraallyltin by using BINOL–titanium(IV) catalysts. The catalyst was prepared from (R)-BINOL (20 mol%), dichlorotitanium(IV) isopropoxide and allyltributyltin (40 mol%), and the reactions of aromatic and aliphatic ketones with tetraallyltin (1.5 equiv) proceeded in dichloromethane at room temperature with moderate enantioselectivities of up to 65% ee (Scheme 37).

Scheme 37 First catalytic enantioselective allylation of ketones using a BINOL–Ti(IV) complex

Maruoka and co-workers developed a chiral bis-titanium(IV) catalyst (41) derived from (S)-BINOL/4,6-bis(tritylaminodibenzo[b,furan]/titanium(IV) isopropoxide for the enantioselective allylation of ketones. Treatment of ketones with tetraallyltin (1.5 equiv) in the presence of 41 (10–30 mol%) in dichloromethane at room temperature gave rise to the corresponding products in high yields and with high enantioselectivities of up to 92% ee (Scheme 38).

Scheme 38 Catalytic enantioselective allylation of aryl ketones with mixed allyltin reagents in the presence of monothiobinaphthol (42). The most efficient allylation source was obtained from a mixture of tetraallyltin (0.7 mol fraction) and alkyltriallyltin (0.3 mol fraction). Interestingly, the presence of water (40 mol%) with the mixed allyltin reagent (1.2 equiv) and 42...
(20 mol%) promoted allylation with inhibition of the racemic background reaction, and the desired products were obtained with 82–89% ee (Scheme 39).

Scheme 39 Catalytic enantioselective allylation of ketones using chiral monothioinaphthol with water as a promoter

Walsh and co-workers developed a practical chiral BINOL–Ti(IV) catalyst in the presence of propan-2-ol to provide a variety of tertiary homoallylic alcohols from ketones. They found that the beneficial effect on enantioselectivity reached a maximum when 20 equiv of propan-2-ol was added. With a combination of BINOL (20–30 mol%), titanium(IV) isopropoxide (20–30 mol%), propan-2-ol (20 equiv), and tetraallyltin (1.5 equiv), the allylation of ketones proceeded smoothly in dichloromethane, and the desired products were obtained in good to excellent yields and with high enantioselectivities (up to 96% ee) (Table 9).

More recently, these authors reported the first catalytic enantioselective methallylation of ketones using an H8-BINOL–Ti(IV) complex (Scheme 40). Very recently, they established the highly enantioselective allylation of ketones under concentrated conditions. Without any solvents, the reactions proceeded smoothly in the presence of BINOL (10 mol%), titanium(IV) isopropoxide (20 mol%), propan-2-ol (3 equiv), and tetraallyltin (1.5 equiv) (Table 10).

Loh and co-workers also reported the enantioselective allylation of ketones catalyzed by chiral In(III)–PYBOX complexes. In the presence of 20 mol% of the chiral catalyst prepared from indium(III) trifluoromethane-sulfonate, the desired tertiary homoallylic alcohols were obtained with good enantioselectivities (up to 92% ee) not only with aromatic ketones but also with aliphatic and cyclic aromatic ketones.

Loh, Lu and co-workers also reported the enantioselective allylation of ketones catalyzed by chiral In(III)–PYBOX complexes. In the presence of indium(III) trifluoromethanesulfonate, the desired tertiary homoallylic alcohols were obtained with good enantioselectivities (up to 92% ee) not only with aromatic ketones but also with aliphatic and cyclic aromatic ketones.
sulfonate (20 mol%) and the PYBOX ligand (44) (22 mol%), allyltributyltin (1.2 equiv) reacted with ketones to afford the corresponding tertiary homoallylic alcohols with moderate to high enantioselectivities (54–95% ee) (Scheme 42). They found that chlorotrimethylsilane (1.2 equiv) played a crucial role in the reaction, and its absence resulted in a dramatic decrease in both the yield and enantioselectivity of the products.74

Very recently, Feng and co-workers reported the enantioselective allylation of ketones using chiral N,N'-dioxide 45–In(III) catalyst.75 In the presence of 30 mol% of indium(III) bromide and 60 mol% of 45, the desired homoallylic alcohols were obtained with good enantioselectivities (up to 83% ee), although an unsatisfactory amount of chiral catalyst was needed (Scheme 43).

So far, only toxic allyltin reagents could be used as allylating reagents in an enantioselective fashion, and these reactions require high catalyst loading (10–30 mol% in most cases). In contrast, the catalytic Sakurai–Hosomi alkylation to ketones is one of the most reliable methods for obtaining tertiary homoallylic alcohols and has the advantage of using inexpensive, nontoxic, and stable allyltin reagents, which overcome the above-mentioned hurdles in allylation of ketones.79 In the presence of silver(I) fluoride and (R)-DIFLUORPHOS (47) (5 mol% each) in tetrahydrofuran at −78 °C, the highly enantioselective allylation of a variety of ketones was demonstrated (Table 12). Interestingly, the catalyst turnover was increased by the addition of methanol (1 equiv), and the products obtained were tertiary homoallylic alcohols, not the silylated products. Remarkably, γ-substituted allyltrichlorosilane gave branched syn products with high diastereoselectivities and high enantioselectivities, regardless of the chirality of the starting allylsilane.

With regard to other mild allylmetal reagents, instead of toxic allyltin reagents with high catalyst loadings, Kanai, Shibasaki, and co-workers developed the first catalytic enantioselective allylboration and crotylboration of ketones, which overcome the above-mentioned hurdles in optically active tertiary homoallyl alcohol synthesis.80 Under optimized conditions, 3 mol% of CuF–i-Pr-DuPHOS (48), as a chiral catalyst, and 4.5 mol% of lanthanum(III) isopropoxide, as a cocatalyst, were used. Thus, the enantioselective allylation of various ketones, including aromatic, heterocyclic, α,β-unsaturated, and aliphatic ketones proceeded smoothly, and the corresponding tertiary homoallylic alcohols were obtained in high to excellent yields (Table 11). Moreover, they achieved the first example of the catalytic enantioselective allylation of ketones using allylsilane in the presence of CuCl–(R)-tol-BINAP (46)–TBAT (15 mol%), although the enantioselectivity was moderate (Scheme 44).

Table 11  Catalytic Allylation of Ketones Using CuCl–TBAT Catalysts with Allyltrimethoxysilane

Yamamoto and Wadamoto developed the silver(I)-catalyzed enantioselective Sakurai–Hosomi allylation of ketones.79 In the presence of silver(I) fluoride and (R)-DIFLUORPHOS (47) (5 mol% each) in tetrahydrofuran at −78 °C, the highly enantioselective allylation of a variety of ketones was demonstrated (Table 12). Interestingly, the catalyst turnover was increased by the addition of methanol (1 equiv), and the products obtained were tertiary homoallylic alcohols, not the silylated products. Remarkably, γ-substituted allyltrichlorosilane gave branched syn products with high diastereoselectivities and high enantioselectivities, regardless of the chirality of the starting allylsilane.

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ketones, proceeded smoothly at room temperature in \(N, N\)-dimethylformamide at \(-40^\circ C\) for one hour using commercially available pinacol 2-propenylboronic ester (49) (1.2 equiv) (Table 13). In addition, the catalytic enantioselective crotylboration of ketones with 50 using a chiral Cu(I)–\(i\)-Pr-DuPHOS catalyst was accomplished (Scheme 45). The success of their catalysis depends on a unique facilitation effect of lanthanum(III) isopropoxide in the dynamic ligand exchange between boron and copper atoms.

Schaus and co-workers developed a highly enantioselective and diastereoselective allylboration and crotylboration of ketones catalyzed by 3,3′-Br₂-BINOL (51).\(^8^1\) In the presence of 15 mol% of 51, catalytic enantioselective allylboration of a variety of aromatic and heteroaromatic ketones (1.5 equiv) with allyldiisopropoxyborane (1 equiv) or crotyldiisopropoxyborane proceeded in toluene–(trifluoromethyl)benzene at \(-35^\circ C\) for 15 hours (Scheme 46). In all cases, the desired tertiary homoallylic alcohols were obtained in high yields (76–93%) and with high to excellent stereoselectivities (96–98% de and 90–99% ee).

Table 12 Catalytic Enantioselective Sakurai–Hosomi Allylation of Ketones Using a Chiral Ag(I)–DIFLUORPHOS Catalyst

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>OH</th>
<th>Si(OMe)₃ (2 equiv)</th>
<th>THF, –78 °C, 12 h</th>
<th>92%, 90% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>HO</td>
<td>HO</td>
<td>HO</td>
<td>F₃C</td>
<td>92%, 90% ee</td>
<td></td>
<td></td>
</tr>
<tr>
<td>92%, 90% ee</td>
<td>89%, 91% ee</td>
<td>97%, 96% ee</td>
<td>97%, 94% ee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>74%, 92% ee</td>
<td>95% (syn/anti = 90:10)</td>
<td>93% ee</td>
<td>97% (syn/anti = 99:1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 13 Catalytic Enantioselective Allylboration of Ketones Using a Chiral Cu(I)–i-Pr-DuPHOS Catalyst

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>OH</th>
<th>R₁</th>
<th>R₂</th>
<th>CuF₂·2H₂O (3 mol%)</th>
<th>La(Oi-Pr)₃ (4.5 mol%)</th>
<th>94%, 82% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO</td>
<td>HO</td>
<td>HO</td>
<td>HO</td>
<td>F₃C</td>
<td>92%, 90% ee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>94%, 82% ee</td>
<td>84%, 65% ee</td>
<td>87%, 90% ee</td>
<td>96%, 67% ee</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Scheme 45 Catalytic enantioselective crotylboration of ketones using a chiral Cu(I)–\(i\)-Pr-DuPHOS catalyst

(Scheme 46). In all cases, the desired tertiary homoallylic alcohols were obtained in high yields (76–93%) and with high to excellent stereoselectivities (96–98% de and 90–99% ee).

Very recently, Sigman and co-workers reported the first example of a chiral chromium-catalyzed enantioselective addition of allyl bromides to aryl ketones.\(^8^2\) In the presence of 52 (a chiral peptide ligand with an oxazoline moiety), chromium(III) chloride (10 mol% each), triethylamine (20 mol%), chlorotrimethylsilane (4 equiv), and manganese(0) (2 equiv) in tetrahydrofuran at 0 °C,\(^8^3\) allylation of aryl ketones with allyl bromide (2 equiv) proceeded with high enantioselectivity (Scheme 47). Other allylic halides, methallyl bromide and crotyl bromide, were successfully added to acetophenone with similar enantioselectivities (70–91% ee).

Table 14 Catalytic Enantioselective Allylboration of Ketones Using a Chiral Cu(I)–i-Pr-DuPHOS Catalyst

<table>
<thead>
<tr>
<th>Ar</th>
<th>R</th>
<th>Br</th>
<th>R</th>
<th>OH</th>
<th>Ar</th>
<th>R</th>
<th>Br</th>
<th>R</th>
<th>OH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>82%, 92% ee</td>
<td>Ph</td>
<td>Me</td>
<td>83%, 99% ee</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3-CF₃C₆H₄</td>
<td>Me</td>
<td>63%, 91% ee</td>
<td>3-CF₃C₆H₄</td>
<td>Me</td>
<td>77%, 93% ee</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Scheme 46 Catalytic enantioselective allylboration of ketones using 51

Scheme 47 Enantioselective chiral Cr(III)-catalyzed addition of allyl bromide to ketones

\(\text{CuF}_2\cdot2\text{H}_2\text{O} (3 \text{ mol%})\) \(\text{La(Oi-Pr)}_3 (4.5 \text{ mol%})\) \(\text{DMF, \(-40^\circ C, 1 \text{ h}\)}\)

\(\text{CuF}_2\cdot2\text{H}_2\text{O} (6 \text{ mol%})\) \(\text{La(Oi-Pr)}_3 (6 \text{ mol%})\) \(\text{DMF, \(-40^\circ C, 1 \text{ h}\)}\)

\(\text{CrCl}_3 (10 \text{ mol%})\) \(\text{Et}_3\text{N (20 mol%)}\) \(\text{TMSCl (4 equiv)}\) \(\text{Mn(0) (2 equiv)}\) \(\text{THF, \(-40^\circ C, 1 \text{ h}\)}\)

\(\text{Ar} = \text{Ph, } R = \text{Me}: 82\%, 92\% \text{ ee}\) \(\text{Ar} = 3\text{-CF}_3\text{C}_6\text{H}_4, R = \text{Me}: 63\%, 91\% \text{ ee}\) \(\text{Ar} = \text{Ph, } R = \text{Et}: 77\%, 93\% \text{ ee}\)
8 Catalytic Enantioselective Aldol Reaction with Organosilicon Reagents

The aldol reaction is one of the most important reactions for synthesizing a \( \beta \)-hydroxy carbonyl structural scaffold, one that is often found in natural products and pharmaceuticals. Several methods have been developed for the catalytic diastereoselective and/or enantioselective aldol addition of enolates, derived from ketones, esters, and their derivatives, to aldehydes. In particular, organosilicon reagents are quite useful in this area. The Mukaiyama aldol reactions between aldehydes and trimethylsilyl enolates to give secondary aldols have been investigated with regard to the use of achiral and chiral Lewis acid catalysts, while Lewis base catalysts have also been found to be applicable in secondary aldol synthesis. Recently, Mukaiyama and co-workers also developed a landmark Lewis base catalyzed enolate aldol reactions between aldehydes. In sharp contrast, practical methods for the catalytic aldol reaction of ketones with silyl enolates have been limited. However, during the ten years since the pioneering work with ketones, using chiral bis(oxazoline)-copper(II) catalysts, some powerful methods for synthesizing tertiary aldols, including enantioselective processes, have been developed. In fact, due to the occurrence of the retro aldol reaction, the synthesis of tertiary aldols from ketones and enolates is very difficult. Moreover, in addition to the attenuated reactivity of ketones, the facial selectivity of a ketone is still quite a challenge in enantioselective catalysis. Here we review the simple catalytic aldol reactions between inactivated ketones and silyl enolates to give tertiary aldols, except for reductive aldol reactions with ketones and \( \alpha,\beta \)-unsaturated enones that are currently being developed.

In 2002, Denmark and co-workers were the first to develop the catalytic enantioselective aldol reaction with ketones, using chiral Lewis base organocatalysts. To overcome the unfavorable kinetics and thermodynamics of the addition to ketones, they used a highly reactive trichlorosilyl enolate of methyl acetate (Table 14). Indeed, the spontaneous uncatalyzed addition of 53 to acetophenone took place even at 0 °C. Nonetheless, chiral bisquinoline-based bis-N-oxide (54) was found to be highly effective as a Lewis base catalyst. In the presence of 10 mol% of 54, the reaction between aromatic ketones and 53 (1.2 equiv) was carried out in dichloromethane at room temperature for two hours, and the corresponding optically active tertiary aldols were obtained in good to excellent yields with high enantioselectivities (80–86% ee). Other ketones, such as heterocyclic and aliphatic ketones and \( \alpha,\beta \)-unsaturated enones, gave high yields but low to moderate enantioselectivities. In their proposed catalytic cycle (Scheme 48), the binding of 54 to 53 leads to the ionization of chloride and generates cationic silyl enolate 55. The enhanced electrophilicity of 55 overrides the steric repulsion of the ketone in complexation to 56. After carbon–carbon bond formation, an ester moiety is generated, and the internal coordination of this group to the trichlorosilyl unit in 57 likely facilitates the release of 54 and completes the catalytic cycle.

In 2003, Shibasaki and co-workers developed a new method for the catalytic aldol reaction of ketones. The reaction between a wide range of ketones and trimethylsilyl enolates (2 equiv) proceeded smoothly in the presence of 2.5 mol% of CuF·3Ph3P·2EtOH and 1.2 equivalents of fluorotriethoxysilane in tetrahydrofuran at room temperature (Table 15). In every case, the presence of fluorotriethoxysilane was essential for the desired tertiary aldols to be obtained in high yields. Based on the results of NMR experiments, the authors found that triethoxysilicate was generated, from trimethylsilyl enolate and the active copper(I) species. Copper(I) enolate 60 reacts with a ketone to give copper(I) alkoxide 61, and then reacts with fluorotriethoxysilane to give silicate 62. Finally, fluoride exchange

**Table 14** Catalytic Enantioselective Aldol Addition to Ketones with a Chiral Lewis Base Organocatalyst

<table>
<thead>
<tr>
<th>X</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>96%, 82%</td>
<td></td>
</tr>
<tr>
<td>CF3</td>
<td>Ph</td>
<td>Ph</td>
<td>91%, 76%</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>Pr</td>
<td>Et</td>
<td>90%, 80%</td>
<td>ee</td>
</tr>
</tbody>
</table>

**Scheme 48** Proposed catalytic cycle

---

between 62 and fluorotriethoxysilane produces the triethoxysilyl-protected tertiary aldol product 63 and active silicate 58 to complete the catalytic cycle.

Shibasaki and co-workers extended this methodology to the catalytic enantioselective version of the reaction.95,96 For example, in the presence of 2.5 mol% of CuF·3PPh3·2EtOH–(S)-tol-BINAP complex, the aldol reaction between pentan-3-one and the (E)- or (Z)-trimethylsilyl enolate with 1.2 equivalents of fluorotriethoxysilane gave the corresponding product with up to 82% ee (Scheme 50).

Campagne and co-workers reported a tol-BINAP (46)–copper(II) trifluoromethanesulfonate catalyzed enantioselective vinylogous aldol reaction of ketones with a silyldienolate in the presence of 20 mol% of tetrabutylammonium triphenyldifluorosilicate (TBAT) (Scheme 51).97 Enantiomerically enriched lactones with tertiary alcohols were obtained in moderate to high yields. As a specific example, these authors achieved a formal enantioselective synthesis of taurospongin A via this key catalytic enantioselective lactonization.

<table>
<thead>
<tr>
<th>Table 15</th>
<th>Catalytic Aldol Addition to Ketones with Copper(I) Catalysts via Catalytic Triethoxy Silicates and Copper(I) Enolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>+</td>
</tr>
<tr>
<td>R1</td>
<td>R2</td>
</tr>
<tr>
<td>1) CuF·3PPh3·2EtOH (2.5 mol%)</td>
<td>(EtO)3SiF (1.2 equiv)</td>
</tr>
<tr>
<td>THF, r.t.</td>
<td>2) Et3N·3HF</td>
</tr>
<tr>
<td>X = H: 95% (2 h)</td>
<td></td>
</tr>
<tr>
<td>X = Cl: 85% (4 h)</td>
<td></td>
</tr>
<tr>
<td>X = OMe: 85% (35 h)</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 49  Proposed catalytic cycle

Scheme 50  Catalytic enantioselective aldol reaction using chiral phosphine–copper(I) complexes

Scheme 51  Formal catalytic enantioselective synthesis of taurospongin A

Kanai, Shibasaki, and co-workers developed a highly enantioselective aldol reaction of ketones using a chiral copper(I) fluoride–phosphine complex (2.5 mol%).98 As the chiral phosphine ligand, TANIAPHOS (64), which bears a ferrocene skeleton, was remarkable. From various aromatic, aliphatic, and heterocyclic ketones, the desired optically active tertiary aldols were obtained in excellent yields with high enantioselectivities (Table 16). As in their previous system, a copper(I) enolate generated through transmetallation was the actual nucleophile in this system, and the addition of a stoichiometric amount of (EtO)3SiF (2 equiv) to facilitate the rate-determining catalyst turnover was essential. Moreover, they found that the addition of 10 mol% of potassium phenyltrifluoroborate (PhBF3K) significantly improved the yield without affecting the enantioselectivity. In their proposed catalytic cycle, the results of an NMR study showed that the beneficial effect of PhBF3K was attributable to the generation of highly nucleophilic (EtO)3SiF2 and (EtO)SiF3, which promote the release of the product and the active catalyst to complete the catalytic cycle (Scheme 52).
Very recently, Ishihara and co-workers developed the combination of sodium phenoxide (65) and 1,2-phenylene bis(diphenylphosphine oxide) (66) as an extremely active in situ homogeneous Lewis base catalyst for the practical Mukaiyama aldol reaction with ketones (Table 17). In their method (i.e., the actual Mukaiyama aldol reaction), highly useful and common trimethylsilyl enolates (1.2 equiv) were used directly without transmetallation, and the corresponding aldolates were rapidly protected with a trimethylsilyl group to prevent a serious retro-aldol reaction. The desired tertiary aldols with, in particular, a trimethylsilyl group to prevent a serious retro-aldol reaction, were obtained in high yields from a variety of aromatic ketones, heterocyclic ketones, ketoesters, and diketones in the presence of 0.5–10 mol% of 65-66 in tetrahydrofuran at −78 °C.

**Table 16** Catalytic Aldol Addition to Ketones Using a Chiral Copper(I) Catalyst

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1OEt + R1OEt</td>
<td>93%</td>
<td>92% ee</td>
</tr>
<tr>
<td>(EtO)₃SiF + (EtO)₃SiF</td>
<td>92%</td>
<td>90% ee</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn+1</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

**Table 17** Mukaiyama Aldol Reaction Using a Sodium Phenoxide–Phosphine Oxide Combination as an Extremely Active Lewis Base Catalyst

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1OEt + R1OEt</td>
<td>93%</td>
<td>92% ee</td>
</tr>
<tr>
<td>(EtO)₃SiF + (EtO)₃SiF</td>
<td>92%</td>
<td>90% ee</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn+1</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>(EtO)₄-nSiFn</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

* 1 mol% of catalyst was used.
* 5 mol% of catalyst was used.
* 10 mol% of catalyst was used.

Under the optimized reaction conditions, a 100 mmol-scale reaction produced the desired tertiary aldol, with an α-quaternary carbon center, from benzophenone and methyl trimethylsilyl dimethylketene acetal in 97% yield (34.8 g) with 0.5 mol% of 65-66, in tetrahydrofuran at −78 °C for six hours (Scheme 53).

**Scheme 52** Proposed catalytic cycle

**Scheme 53** Gram-scale synthesis of a tertiary aldol with an α-quaternary carbon center

In their proposed catalytic cycle, a catalytic amount of PhO⁻ was essential for promoting the reactions. In 65-66, the Na⁺ moiety wrapped by 66₂ makes the counter anion (i.e., PhO⁻) naked, and hypervalent silicate 67 is generated (Scheme 54). Thus, activated enolate 67 ultimately increases the nucleophilicity enough to attack even ketones. Presumably, the naked PhO⁻, as 65-66, could be regenerated from PhOTMS in continuous catalytic cycles. Ishihara’s method is so practical because highly useful and chemically stable trimethylsilyl enolates can be used directly, unlike other methods that employ trichlorosilyl enolates or trialkoxysilyl enolates.
Mikami and co-workers developed a dicaticonic chiral palladium(II)-catalyzed ketoester-ene reaction, between a silyl enol ether and ketoesters, that constructs highly enantioselective β-hydroxy silyl enol ethers. By using 0.01 mol% of palladium(II) chloride/(R)-SEGPHOS (68)/AgSbF6 (S/C = 10 000), the desired ene product (71) was obtained quantitatively with 90% ee from TIPS enol ether and ethyl pyruvate (70) (Scheme 55). Other silyl protecting groups on the enol ether, such as tert-butyldimethylsilyl and tert-butyldiphenylsilyl, were also effective; interestingly, however, the trimethylsilyl enol ether gave the Mukaiyama aldol product instead of the ene product in moderate yield with high enantioselectivity.

Shibasaki and co-workers developed a bifunctional chiral D-glucose-derived ligand (73)–Ti(IV) catalyst, which was derived from an effective aluminum(III) complex for the catalytic enantioselective cyanation of aldehydes. In the presence of 10 mol% each of 73 and titanium(IV) isopropoxide in tetrahydrofuran at –20 °C, a broad applicability for reactions of various ketones with high enantioselectivities was shown for the first time (Scheme 58). The actual catalyst should be a complex composed of titanium(IV) monocyano monoisopro- poxide, in which the titanium(IV) center would activate the carbonyl moiety of a ketone as a Lewis acid, and the phosphine oxide would activate trimethylsilyl cyanide as a Lewis base. Later, the authors improved the enantioselectivity and catalyst turnover by ligand tuning; excellent enantioselectivity (up to 97% ee) was observed with lower catalyst loadings (1 mol%). This pioneering work by Shibasaki and co-workers is a remarkable contribution in catalytic enanti-
While planning the synthesis of the key intermediate 76 for the (20S)-camptothecin family of compounds, Shibasaki and co-workers also devised chiral bifunctional catalysts with lanthanide complexes.111 Interestingly, a switch in enantioselectivity (from R to S) was observed, as well as a higher activity of the bifunctional chiral D-glucose-derived ligand (5 mol%) on a 50-gram scale without any difficulty (Scheme 59).

Scheme 59 Catalytic enantioselective tertiary cyanohydrin synthesis using a bifunctional chiral ligand–Ti(IV) catalyst

nucleophile is the lanthanide metal cyanide, not trimethylsilyl cyanide itself. Shibasaki and co-workers developed a practical method for synthesizing an important pharmaceutical, (S)-oxybutynin, which acts as a muscarinic antagonist.112 The chiral center of the core tertiary α-hydroxy carboxylic acid was constructed by the catalytic enantioselective cyanosilylation of ketone 75 using 1 mol% of Gd(III)–73 complex as a key step. Despite the expected difficulty due to the steric demands of the phenyl and cyclohexyl groups in 79, the reaction on a 100-gram scale proceeded smoothly, and the corresponding adduct was obtained quantitatively with 94% ee (Scheme 62).

Feng, Jiang, and co-workers investigated the application of bifunctional catalysis with chiral N-oxide–titanium(IV) complexes in the enantioselective cyanosilylation of ketones,113 In the presence of 20 mol% of 80 and 24 mol% of titanium(IV) isopropoxide, the reaction with ketones

Scheme 62 Formal catalytic enantioselective synthesis of oxybutynin using a bifunctional chiral ligand–Gd(III) catalyst
and trimethylsilyl cyanide (2 equiv) proceeded with moderate enantioselectivities up to 69% ee (Scheme 63).

Snapper, Hoveyda, and co-workers developed a chiral peptide (81)–Al(III) complex as an easily accessible and recyclable Lewis acid catalyst. The addition of trimethylsilyl cyanide (2 equiv) to a variety of aromatic and aliphatic ketones gave the products in high yields and with high enantioselectivities (80–95% ee) (Scheme 64).

Feng and co-workers reported the enantioselective cyanosilylation of ketones by a catalytic double activation method that uses a chiral salen–Al(III) complex as an easily accessible and recyclable Lewis acid catalyst. In the presence of 2 mol% of Al(O–Pr)₃ (10–20 mol%) in toluene, good yields and enantioselectivities (83%, 94% ee) were observed for a variety of methyl ketones (Scheme 65). Later, a similar method using chiral aluminum(III) catalysts was also achieved, and a variety of tertiary cyanohydrins were obtained in high yields with high enantioselectivities. Based on this pioneering work, other chiral salen–metal complexes with triphenylphosphine oxide have also been reported by Kim and co-workers.

Deng and co-workers developed a highly enantioselective cyanosilylation of ketones catalyzed by a modified cinchona alkaloid as a chiral Lewis base. Their strategy involves the catalysis of ketones bearing a functional group, followed by transformation of the functional group into a wide range of structures. Specifically, excellent enantioselectivities and yields were obtained with α-α-dialkoxy ketones (i.e., acetal ketones) bearing a wide range of aryl, alkenyl, alkynyl, and alkyl substituents in the presence of 2 mol% of 84 (Scheme 66). Especially noteworthy was the synthesis of 85, which contains a quaternary stereocenter bearing two substituents that are analogous to each other in terms of both steric and electronic properties (Scheme 67).

Corey and Ryu reported the catalytic enantioselective cyanosilylation of ketones using the chiral oxazaborolidinium salt. Under the optimized conditions with (S)-86 (10 mol%) and methyl diphenylphosphine oxide (11 mol%) in toluene, good yields and enantioselectivities were observed for a variety of methyl ketones (Scheme 68). The predominant enantiomers obtained with (S)-86 were the R-configured products, which were formed by addition of the cyano moiety to the si-face of the coordinated methyl ketones. The key to explaining the transition-state assembly (87) was the α-C–H···O hydrogen bonding and an attractive interaction between the coordinated methyl ketone carbonyl, especially with an electron-withdrawing substituent, and the neighboring π-electron-rich 3,5-xylyl group of 86.
Jacobsen and co-workers developed the enantioselective cyanosilylation of ketones using chiral thiourea as organocatalyst. The chiral bifunctional thiourea–amine catalyst, which should promote the simultaneous activation of both nucleophile and electrophile, proved to be general for the highly enantioselective cyanosilylation of a wide variety of ketones (Scheme 69). The addition of trifluoroethanol (1 equiv) with trimethylsilyl cyanide (2 equiv) (Scheme 70) proved to be general for the highly enantioselective cyanosilylation of ketones using chiral thiourea catalyst.121 The chiral bifunctional thiourea–amine salt. In the presence of L-phenylglycine sodium salt (Scheme 71), Feng and co-workers reported the catalytic enantioselective tertiary cyanohydrin synthesis using a chiral tetraaza ligand–Ti(IV) catalyst.124 The reactions proceeded in the presence of 30 mol% of –Ti(Oi-Pr)4 and 2.5 equiv of trimethylsilyl cyanide, and the corresponding products were obtained with up to 94% ee (Scheme 72).

Feng and co-workers also reported a catalytic enantioselective cyanosilylation of ketones was achieved using a chiral N,N'-dioxide–titanium(IV) complex with an achiral N-oxide (Scheme 71). The reactivity was improved when a new class of proline-derived N,N'-dioxide, 90 (2.5 mol%), was used in place of an N-monooxide. Achiral phenolic N-oxide 91 as an additive (2.5 mol%) was effective for improving the enantioselectivity.

Feng and co-workers developed chiral tetraaza ligand 92 for the titanium(IV)-catalyzed enantioselective cyanosilylation of ketones. The reactions proceeded in the presence of 30 mol% of –Ti(Oi-Pr)4 and 2.5 equiv of trimethylsilyl cyanide, and the corresponding products were obtained with up to 94% ee (Scheme 72).
11 Catalytic Enantioselective Trifluoromethylation Reaction

The synthesis of chiral trifluoromethylated compounds has an important role in organofluorine chemistry. In particular, $\alpha$-trifluoromethyl-substituted tertiary alcohols provide chiral building blocks in the design of drug candidates.\(^\text{126}\) Trifluoromethylation with trifluoromethyl-metal reagents is attractive because nonfluorinated prochiral substrates (i.e., ketones) can be directly transformed into chiral $\alpha$-trifluoromethylated tertiary alcohols. Despite their importance, to date only a few methods have been reported regarding the asymmetric addition of a trifluoromethyl group to ketones. In these examples, readily available chiral quaternary ammonium salts of cinchona alkaloids have been used.

Catalytic enantioselective trifluoromethylation of ketones with (trifluoromethyl)trimethylsilane was initially examined by Iseki, Nagai, and Kobayashi in 1994.\(^\text{127}\) The reactions were carried out by the addition of (trifluoromethyl)trimethylsilane (1.3 equiv) to a mixture of ketone and the $N$-benzylcinchonium fluoride 94 (20 mol\%) in toluene at $-78^\circ$C, and the corresponding products were obtained in high yields with up to 51% ee (Scheme 74).

Caron and co-workers reported the modified cinchonine catalyst 95, which was effective for the trifluoromethylation of 96 with (trifluoromethyl)trimethylsilane (1.5 equiv) in dichloromethane (Scheme 75).\(^\text{128}\) The protecting group in 96 affected the enantioselectivity of 97 significantly, and 97 was finally obtained in 97% yield with 92% ee in the presence of 4 mol\% of 95.

Very recently, Mukaiyama and co-workers developed a catalytic enantioselective trifluoromethylation of ketones with (trifluoromethyl)trimethylsilane (1.4 equiv) in the presence of 10 mol\% of cinchonidine-derived quaternary ammonium phenoxide.\(^\text{129}\) The reaction of a variety of aryl ketones proceeded smoothly in toluene–dichloromethane, and the corresponding products were obtained in high yield with 51–87% ee (Scheme 76). In a particular example, sterically demanding substituents on the nitrogen atom of cinchonidine, such as 98, where Ar = 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl, were effective at improving the enantioselectivity.

Also very recently, Shibata, Toru, and co-workers reported a highly enantioselective trifluoromethylation of ketones catalyzed by a combination of monocinchoninium derivatives and tetramethylammonium fluoride (TMAF).\(^\text{130}\) Based on a preliminary examination of a combination of monocinchoninium derivatives and tetramethylammonium fluoride, they developed a combination of biscinchoninium derivatives, such as 99, with tetramethylammonium fluoride (Scheme 77). In the presence of 10 mol\% each of 99 and tetramethylammonium fluoride, enantioselective trifluoromethylation proceeded on a broad range of alkyl aryl ketones with enolizable protons, as well as those with functional groups such as halogenyl and methoxy moieties. In particular, cyclic $\alpha$-trifluoromethylated tertiary alcohol 100 was obtained from $\alpha$-tetralone in 75% yield with 94% ee.
12 Catalytic Cyanomethylation Reaction

β-Hydroxy nitriles are known as useful building blocks since they are readily converted into β-hydroxy carboxylic acids or γ-amino alcohols. Mukaiyama and co-workers developed the Lewis base catalyzed cyanomethylation of ketones using (trimethylsilyl)acetonitrile (101) (Scheme 78). In the presence of 10 mol% of lithium acetate, the reaction between aromatic ketones and 101 (1.4 equiv) proceeded smoothly, and the corresponding β-hydroxy nitriles were obtained in high yields.

\[
\text{R}^1 \text{R}^2 + \text{MeSICF}_3 \rightarrow \text{R}^1 \text{HO} + \text{CF}_3 \text{S} \text{R}^2
\]

Scheme 78 Lewis base catalyzed 1,3-dithiane addition reaction of ketones

13 Catalytic 1,3-Dithiane Addition Reaction

The addition of 1,3-dithiane is one of the most important umpolung reactions in synthetic organic chemistry. The dithiane anions are widely known as masked acyl carbanions that react with carbonyl compounds to afford the protected α-hydroxy aldehydes. Very recently, Mukaiyama and Michida developed a Lewis base catalyzed 1,3-dithiane addition to ketones using 2-trimethylsilyl-1,3-dithiane (102) (Scheme 79). α-Hydroxy dithianes were obtained in good yields in the presence of 30–50 mol% of tetrabutylammonium phenoxide in polar solvent such as N,N-dimethylformamide. Not only aromatic ketones, but also aliphatic ketones, were suitable substrates. Also, a 1,2-addition product was obtained from an α,β-unsaturated ketone in good yield.

\[
\text{R}^1 \text{R}^2 + \text{TMSCH}_2CN \rightarrow \text{R}^1 \text{HOCH}_2CN \text{R}^2
\]

Scheme 79 Lewis base catalyzed 1,3-dithiane addition reaction of ketones

was reviewed. Despite the expected and/or unexpected difficulties with ketones and organometallic reagents, this area may be one of the most rapidly advancing fields in current organic chemistry. The practical catalytic methodologies reviewed here provide versatile tertiary alcohols with enantioselective properties. New trends in the catalytic synthesis of tertiary alcohols will likely include the use of more functionalized tertiary alcohols under milder reaction conditions with possibly minimized amounts of organometallic reagents and catalysts.

Acknowledgment

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References


Catalytic Tertiary Alcohol Synthesis

(54) Wessjohann, L.; Gabriel, T.
(56) Kanai, K.; Wakabayashi, H.; Honda, T.
(60) Cozzi, P. G.
(69) (a) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(b) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(70) Kim, J. G.; Camp, E. H.; Walsh, P. J.
(71) Wooten, A. J.; Kim, J. G.; Walsh, P. J.
(72) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P.
(73) (a) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(b) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(74) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P.
(b) Yamamoto, Y.; Asao, N. Chem. Rev. 1993, 93, 2207.
(d) Denmark, S. E.; Fu, J. Chem. Rev. 2003, 103, 2763.


