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Catalytic Enantioselective Aldol Additions to Ketones

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Enantioselective aldol addition to ketones has received growing attention since the resulting tertiary aldols are valuable building blocks for many biologically active compounds. Recently, several catalytic methodologies have been developed based on the activation of acceptor ketones and/or nucleophile enolates, overcoming problems associated with the lower reactivity and decreased steric discrimination of ketones compared to aldehydes. This microreview presents an overview of the progresses in the catalytic enantioselective aldol additions to ketones.
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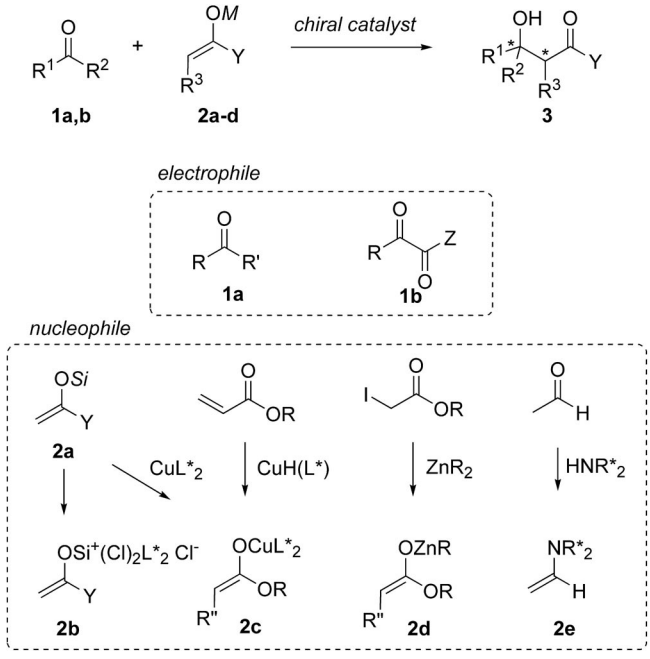
1. Introduction

Chiral tertiary alcohols are important subunits frequently found in biologically active compounds.[1] The catalytic enantioselective construction of the tertiary alcohols through carbon–carbon bond formation constitutes an important research objective in current organic synthesis.[2] Recently, catalytic enantioselective aldol addition to ketones (Scheme 1) has received growing attention since the resulting tertiary aldols are valuable building blocks for the subunits.

In the last decades, remarkable advances have been made in the catalytic enantioselective aldol additions to aldehydes.[3] In sharp contrast, the development of the aldol additions to ketones was quite slow. The difficulty in the ketone-aldol reaction is due to the lower reactivity of ketones and the decreased steric discrimination compared to aldehydes. Recently, several new methodologies have been developed other than the classical chiral Lewis acid catalyzed Mukaiyama-type reaction to overcome the problem.



Scheme 1. Realization of aldol additions to ketones.

The activation of either electrophiles (ketones **1**), nucleophiles (enolates **2**), or both plays a key role in the realization of the aldol additions to ketones. Activated ketones **1b** (Z

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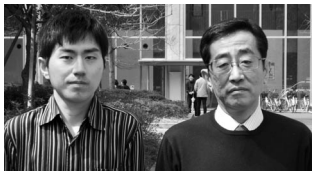

Shinya Adachi (left) was born in Kobe, Japan, in 1980 and received his BSc in 2003 and MSc in 2005 from Kyoto Institute of Technology. Currently, he is working as a doctor course student with Professor Harada at Kyoto Institute of Technology focusing on the development of asymmetric reactions catalyzed by oxazaborolidinones. He is the author of five publications in the areas of catalytic asymmetric synthesis.

Toshiro Harada (right) was born in Kyoto, Japan, in 1952. He graduated from Kyoto University in 1975. He received his Ph.D. from Kyoto University (1980) with Professor Zen-ichi Yoshida. Then he was appointed as a Research Associate in Kyoto Institute of Technology in 1981. He spent the year 1982–1983 as a postdoctoral fellow with Professor W. Clark Still at Columbia University. He was promoted to Full Professor in 2002 in the department of chemistry and materials technology, Kyoto Institute of Technology. His interests are in the development of chiral Lewis-acid catalyzed enantioselective reactions and convergent carbon–carbon bond-forming reactions utilizing carbenoid intermediates.

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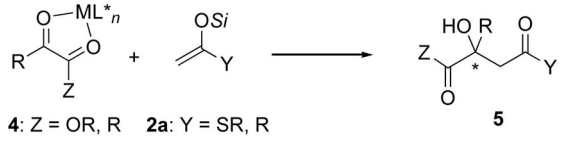
= OR, R) such as α-keto esters and α-diketones have a reactivity comparable to aldehydes and employed in the chiral Lewis acid catalyzed aldol reaction with enolsilanes **2a** and in organocatalytic aldol reaction with an enamine intermediate **2e**. On the other hand, for the less reactive non-activated ketones, catalytic systems involving activated enolates, such as silicate **2b**, copper enolate **2c**, and zinc enolate **2d**, have been developed to realize the more difficult task.

The present review article summarizes the recent progresses in the catalytic enantioselective aldol additions to ketones with an emphasis on how the inherent difficulties in the ketone-aldol reactions have been overcome in each approach.[4]

2. Activated Ketones as Acceptors

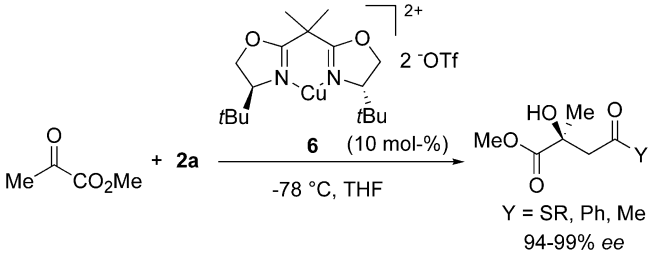
2.1 Lewis Acid Catalyzed Reaction with Enolsilanes

An adjacent electron-withdrawing group notably enhances the reactivity of ketone carbonyl groups such as those in α-keto esters and α-diketones. In addition to the increased reactivity, such dicarbonyl compounds can be coordinated by a Lewis acidic metal atom in a bidentate manner to form a rigid activated complex **4**, ideal for enantioselective reaction with the aid of well-designed chiral ligands (Scheme 2). The resulting tertiary aldol products **5** bears an additional carbonyl groups at the γ position, thus serving as building blocks for the asymmetric synthesis of biologically active molecules.



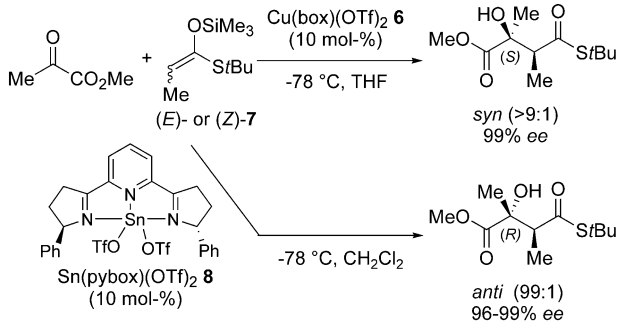
Scheme 2. Chiral Lewis acid catalyzed reaction with enolsilane.

The first successful example of this approach was reported by Evans and co-workers in 1997.[5] The aldol reaction of methyl pyruvate and enolsilanes **2a** were catalyzed by Cu(box)(OTf)$_2$ **6** (10 mol-%) to give α-hydroxy esters in high enantioselectivity up to 99% *ee* (Scheme 3). Not only silyl ketene S,O-acetals (**2a**; Y = SR) but also enolsilanes derived from acetophenone and acetone (**2a**; Y = Ph, Me) could be employed.



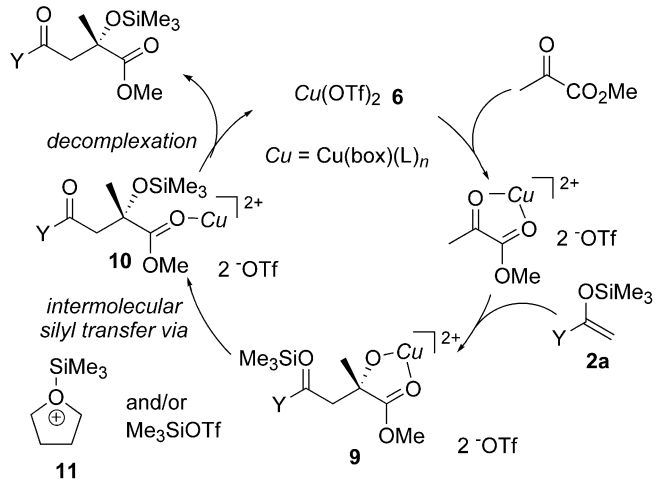
Scheme 3. Cu^{II}(box)-catalyzed reaction of methyl pyruvate.

Both *E* and *Z* isomers of silyl ketene acetal **7** reacted in a stereoconvergent manner providing the *syn* product diastereoselectively (Scheme 4). Interestingly, the reversed high *anti* selectivity was obtained when Sn(pybox)(OTf)$_2$ **8** was used as a catalyst.[6]



Scheme 4. Diastereo- and enantioselective aldol reaction.

A catalytic cycle depicted in Scheme 5 has been proposed.[5b] Although a stoichiometric reaction proceeded more rapidly in CH_2Cl_2 than in THF, the catalytic reaction was faster in THF. The reaction was accelerated by the addition of Me_3SiOTf (1 equiv.) as an external silylating source. These results were rationalized by rate-determining catalyst turnover steps (i.e., intermolecular silyl transfer and decomplexation). THF would associate with the metal center to facilitate silylation of Cu^{II} aldolate **9** and favour product decomplexation from **10**. THF would also accelerate the catalyst turnover by reacting with **9** to form a more accessible silylating species **11**.



Scheme 5. Proposed catalytic cycle for Cu^{II}(box)-catalyzed reaction.

Recently, Bolm and co-workers reported C_1-symmetric amino sulfoximines **12a**,**b**[7] and oxazolinyl sulfoximine **12c**[8] as new ligands effective for the Cu^{II}-catalyzed enantioselective aldol reactions between pyruvates and enolsilanes. The reactions were carried out by using **12**/Cu(OTf)$_2$ (1–10 mol-%) in the presence of 2,2,2-trifluoroethanol (1.2 equiv.) in THF or toluene, affording the corresponding

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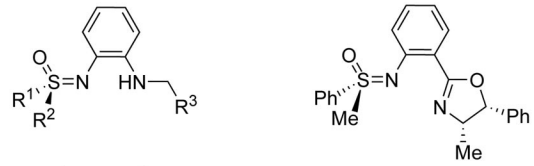
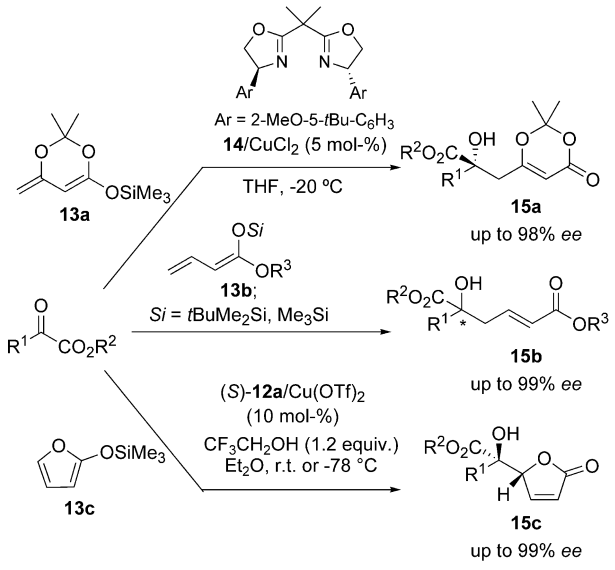
tertiary aldol products with high enantioselectivity up to 98% *ee*. The alcoholic additive is thought to promote the catalytic turnover step of the reaction.[9]



12a: R^1 = Ph, R^2 = Me, R^3 = 2,4,6-*i*Pr$_3$C$_6$H$_2$
12b: R^1 = Me, R^2 = 2-MeOC$_6$H$_4$, R^3 = 2,4,6-Me$_3$C$_6$H$_2$

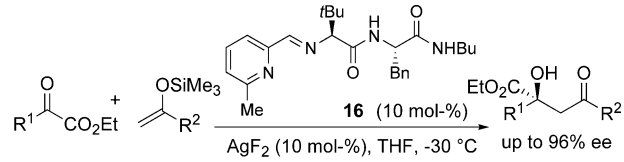
12c

In the presence of a chiral Lewis acid catalyst, dienolsilanes **13a**,**b** react with α-keto esters in a vinylogous manner at the terminal position to give α,β-unsaturated δ-hydroxy diesters **15a**,**b** with quaternary stereogenic centers (Scheme 6). Although enantioselectivity was moderate for Cu(box)(OTf)$_2$ **6**,[10] modified box ligand **14** (5 mol-%) in combination with $CuCl_2$ exhibited high selectivity up to 98% *ee*.[11] Chloride counterions were found to be superior to triflate. Bolm's sulfoximines ligand **12a** also exhibited high enantioselectivity in the reactions with dienolsilanes **13b** and **13c**.[12]



Scheme 6. Vinylogous aldol addition of dienolsilanes to α-keto esters.

Recently, an efficient Ag^I-catalyzed[13] aldol addition to α-keto esters has been reported by Hoveyda, Snapper, and coworkers (Scheme 7).[14] The amino acid-derived, pyridine ligand **16** was discovered after the extensive screening of a series of dipeptide ligands, such as those bearing a phosphane and a salicylic moiety, taking advantage of their relatively simple preparation and the modification of dipeptide backbone to fine-tune the steric and electronic properties of the resulting catalysts.[15] The active catalyst is thought to be a **16**/Ag^{I}F complex, produced in situ by the reduction of Ag^{II}F$_2$ with enolsilanes. The reaction could be carried out in air with undistilled solvent, applicable to sterically hindered substrates (e.g. R^1 = *i*Pr, Cy).

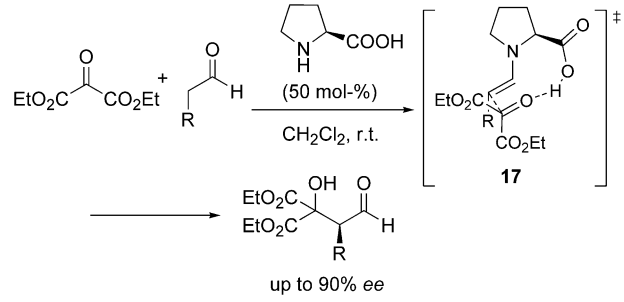


Scheme 7. Chiral Ag^I complex catalyzed reaction of α-keto esters.

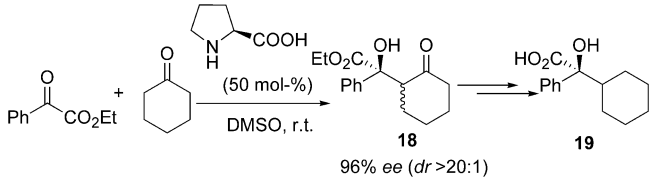
2.2 Direct Aldol Reaction by Organocatalysis

Since the seminal findings that L-proline catalyzes the enantioselective direct aldol reaction,[16] many chiral organocatalysts have been discovered for the reaction.[17] Although most studies focused on the aldol reaction of aldehyde acceptors, advances have been made recently in the reaction of ketone acceptors.

In 2002, Jørgensen and co-workers reported the first direct ketone-aldol reaction.[18] In the presence of L-proline (50 mol-%) in CH_2Cl_2, highly electrophilic diethyl oxomalonate reacted with aldehydes to give the products in up to 90% *ee* (Scheme 8). The reaction is proposed to proceed through transition state **17**, in which the approach of the keto-malonate is directed by the interaction of the incoming carbonyl oxygen atom with the carboxylic acid moiety of the enamine intermediate. Maruoka and co-workers applied the L-proline-catalysis to the reaction of oxophenylacetate and cyclohexanone (Scheme 9).[19] DMSO was found to be an optimal solvent, affording tertiary alcohol **18** in 96% *ee* with high diastereoselectivity. Alcohol **18** was converted to acid **19**, a key intermediate for a widely prescribed muscarinic receptor antagonist (*S*)-oxybutynin.



Scheme 8. Proline-catalyzed reaction of oxomalonate.



Scheme 9. Proline-catalyzed reaction of oxophenylacetate.

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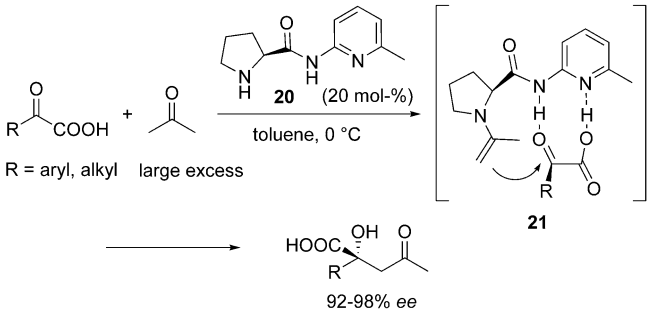
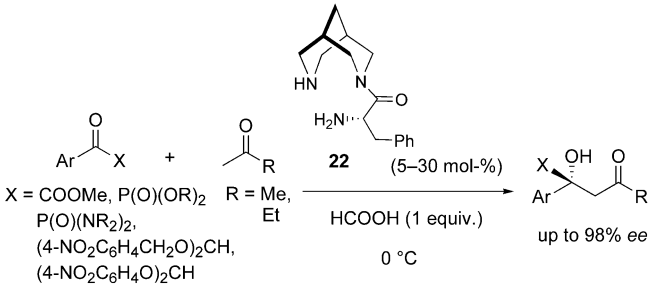
2-Aminopyridine has been widely used in self-assembly and molecular recognition as a good site for the formation of hydrogen bonds with a carboxyl group.[20] Recently, Gong and co-workers have developed L-proline-amide catalyst **20** with a 2-aminopyridine moiety for the aldol reaction between α-keto carboxylic acids and acetone (Scheme 10).[21] Consistent with the proposed assembly **21** wherein two hydrogen bondings cooperatively activate the substrate, **20** exhibited a catalytic activity specifically for α-keto carboxylic acids, but not for an ester derivative.



Scheme 10. L-Proline amide catalyzed reaction of α-keto carboxylic acids.

Very recently, bispidine-based new amine organocatalysts were reported for asymmetric aldol reaction of activated ketones (Scheme 11).[22] Of these, phenylalanine derivative **22** showed a wide scope for activated ketones to give the corresponding aldol products in high enantioselectivities.

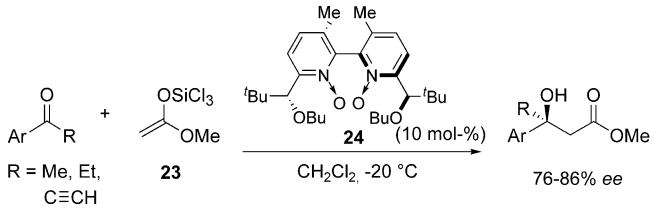


Scheme 11. Bispidine-based chiral amine catalyzed reaction of activated ketones.

3. Non-Activated Ketones as Acceptors

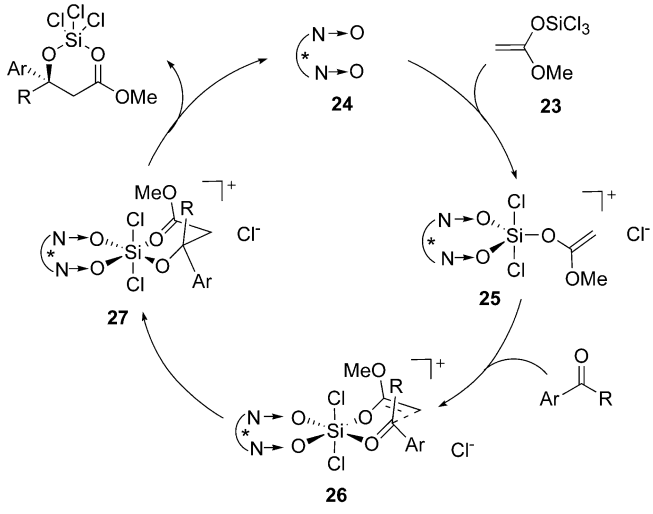
3.1 Lewis Base Catalyzed Reaction with Trichlorosilyl Ketene Acetals

The first asymmetric aldol reaction of non-activated ketones was reported by Denmark and co-workers in 2002 (Scheme 12).[23] The work is based upon their seminal finding of a remarkable Lewis base catalysis[4a] by HMPA in the aldol reaction of a ketone and a trichlorosilyl ketene acetal.[24] Ketene acetal **23** reacts slowly with acetophenone at room temperature, but in the presence of a catalytic amount of HMPA, a rapid addition takes place affording the corresponding aldol product in high yield. After the extensive survey of chiral Lewis bases, axially chiral bis(*N*-oxide) **24** was found to be an optimal catalyst. In the presence of 10 mol-% of **24** in CH_2Cl_2 at –20 °C, simple aromatic ketones reacted smoothly with **23** to give tertiary aldol products enantioselectively (76–86% *ee*) in high yields.



Scheme 12. Chiral base-catalyzed reaction of non-activated ketones.

A mechanism involving a highly reactive cationic silyl enolate **25** has been proposed[23b] based on the previous mechanistic study[25] on relevant phosphoramide-catalyzed aldol reaction of an aldehyde (Scheme 13).[24,26] Cationic silyl enolate **25** generated through the biding of bis-pyridine *N*-oxide **24** to silyl ketene acetal **23** is highly electrophilic, allowing the complexation and activation of a ketone carbonyl group to give a ternary complex **26**. A dual activation of the reaction components is anticipated in this complex:[24] Electron density is drawn away from the carbonyl group, resulting in electrophilic activation of the ketone acceptor and nucleophilic activation of the enoxy moiety. After aldolization, the catalytic cycle is completed by the release of **24** from the resulting aldolate **27** by the attack of the chloride anion.



Scheme 13. Proposed catalytic cycle for chiral Lewis base-catalyzed reaction.

Although being a non-asymmetric reaction, Ishihara and co-workers recently reported the Lewis base catalyzed aldol addition of trimethylsilyl ketene acetals to ketones.[27] In the

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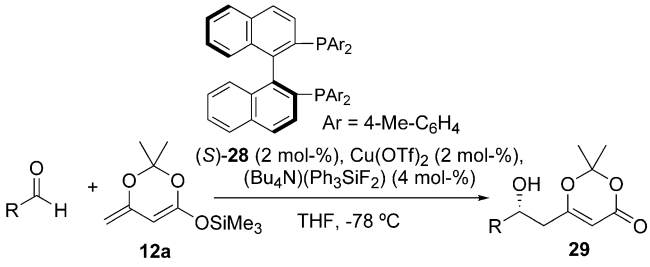
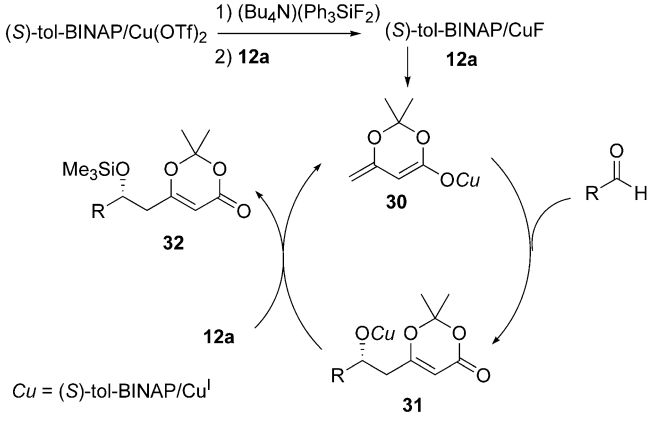
presence of sodium phenoxide and 1,2-$(O{=}PPh_2)_2C_6H_4$ (< 1 mol-%, each), diaryl ketones reacted smoothly at –78 °C in THF to give the corresponding aldol products high yield.

3.2 Cu^I/Phosphane Complex-Catalyzed Reaction with Enolsilanes: Chiral Copper-Enolate Intermediate

In 1998, a conceptually new approach to the catalytic asymmetric aldol reaction of aldehydes was reported by Carreira and co-workers (Scheme 14).[28] In the presence of (*S*)-tol-BINAP (**28**) (2.2 mol-%), $Cu(OTf)_2$ (2 mol-%), and $(Bu_4N)(Ph_3SiF_2)$ (4 mol-%), the reaction of aldehydes with silyl ketene acetal **12a** proceeded at –78 °C to give the vinylogous aldol product **29** in high enantioselectivity. The reaction was demonstrated to proceed through a mechanism involving Cu^I dienolate **30** as a key intermediate (Scheme 15).[28b] The Cu^{II} salt reacts first with $(Bu_4N)(Ph_3SiF_2)$ to form (*S*)-tol-BINAP/CuF_2, which is then reduced by **12a** to give (*S*)-tol-BINAP/CuF as the catalytically relevant species. The Cu^I salt reacts further with **12a** to generate copper dienolate **30**. Aldolization followed by silylation of the resulting copper alkoxide **31** by **12a** gives the silylated adduct **32** with simultaneous regeneration of dienolate **30**.

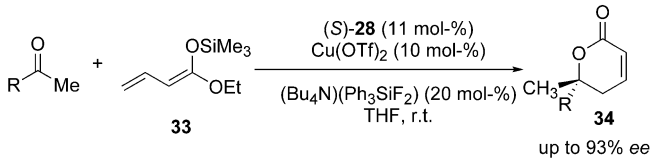


Scheme 14. Cu^I/phosphane complex-catalyzed aldol reaction.



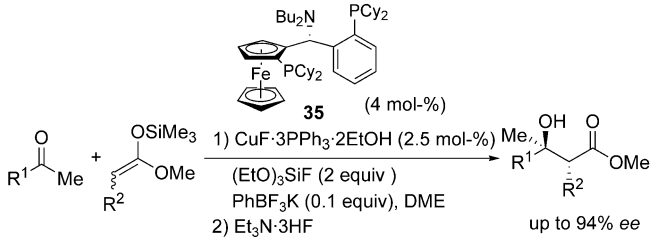
Scheme 15. Catalytic cycle for Cu^I/phosphane complex-catalyzed reaction.

Taking advantage of the high reactivity of copper enolates, Campagne and co-workers successfully applied Carreira's (*S*)-tol-BINAP/CuF catalyst to the asymmetric vinylogous ketone-aldol reaction (Scheme 16).[29] The reaction with silyl ketene acetal **33** gave enantiomerically enriched lactone **34** with a tertiary carbinyl moiety via a copper aldolate intermediate. High enantioselectivities (88–93% *ee*) were reported for the reaction of aliphatic methyl ketones. A formal asymmetric synthesis of taurospongin A,[30] a potent inhibitor of DNA polymerase and HIV reverse transcriptase, was accomplished from lactone **34** [R = $TBSO(CH_2)_2$] (88% *ee*).



Scheme 16. Cu^I/phosphane complex catalyzed vinylogous aldol reaction of ketones.

Shibasaki, Kanai, and co-workers have developed an efficient catalytic aldol addition to ketones, involving a chiral copper enolate intermediate, by using trimethylsilyl ketene acetals (Scheme 17).[31] The reaction was carried out with Taniaphos ligand **35** (4 mol-%), CuF·3PPh_3·2EtOH (2.5 mol-%), $(EtO)_3SiF$ (2 equiv.), and $PhBF_3K$ (0.1 equiv.) in DME at –20 °C to room temp. High levels of enantioselection were reported not only for aryl methyl ketones (83–94% *ee*) but also so for alkyl methyl ketones (79–84% *ee*).[31c] The reaction of silyl ketene acetals derived from propanoate and hexanoate was also enantioselective. The product diastereoselectivity was independent of the *E*/*Z* ratio of the silyl ketene acetals.



Scheme 17. Cu^I/phosphane complex catalyzed aldol additions to ketones.

A catalytic cycle shown in Scheme 18 has been proposed based on the NMR studies of intermediates. $(EtO)_3SiF$ was used both for the generation of an active cationic Cu^I catalyst **36** and for the fluoride exchange of copper-aldolate **37**, leading to the formation of triethoxylsilyl aldolate **38** and regeneration of the catalyst. For the ketone aldol reaction, intermediate **37** is a copper *tert*-alkoxide, which is basic enough to induce the undesirable enolization of a substrate ketone. It was suggested that $PhBF_3K$ as an additive is effective in promoting the rate-determining catalyst-turnover step by generating more electrophilic $(EtO)_2SiF_2$ and/or $(EtO)SiF_3$ in situ.

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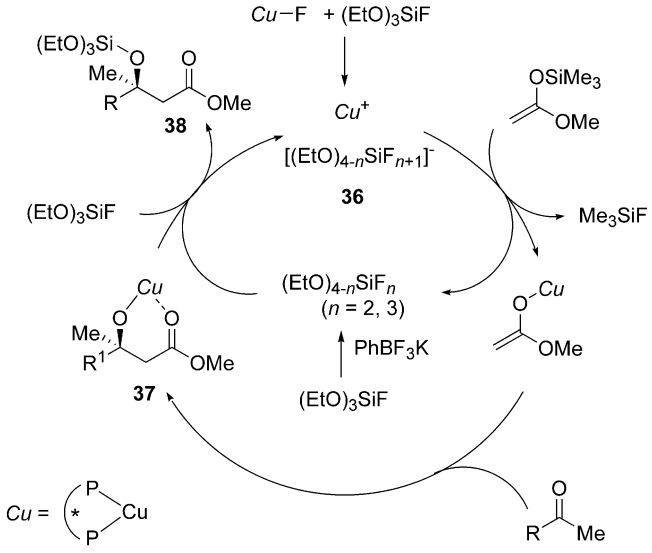
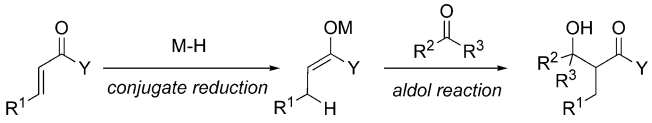


Scheme 18. Proposed catalytic cycle for Cu^I/phosphane complex-catalyzed reaction.

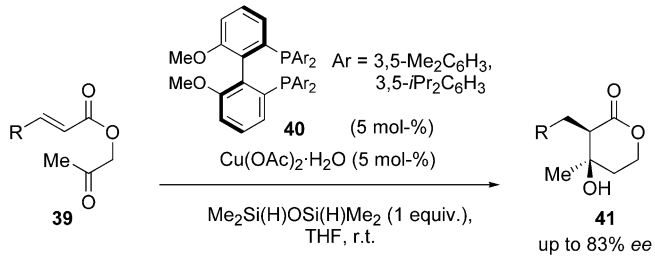
3.3 Reductive Aldol Reaction

The conjugate reduction of an α,β-unsaturated carbonyl compound by a metal-hydride species and subsequent addition of the resulting enolate to carbonyl functions as acceptors afford the α-substituted aldol product (Scheme 19). The reaction sequence is commonly defined as a reductive aldol reaction.[4c] In this approach, enolate intermediates are generated under the mild conditions without using strong bases and asymmetric induction could be achieved both at the α- and β-carbon centers of aldol products. The catalytic enantioselective version of reductive aldol reaction has been extensively studied recently for such benefits of the approach.[32,33]

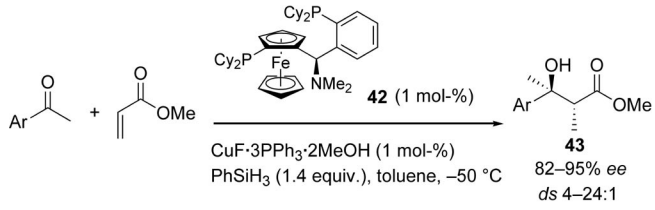


Scheme 19. Reductive-aldol reaction.

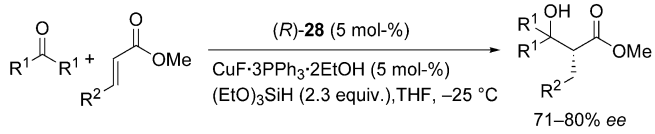
Recently, asymmetric reductive aldol reaction of ketone was reported from three groups. Lam and co-workers[34] used biphenylphosphane ligand **40**/$Cu(OAc)_2$ catalyst system with tetramethylhydrosiloxane as a hydride source to achieve an intramolecular reductive aldol reaction of keto-unsaturated esters **39** (Scheme 20). The reaction provided β-hydroxylactones **41** diastereoselectively with moderate enantioselectivity. Riant and coworkers[35] achieved the intermolecular reaction of methyl acrylate and acetophenone derivatives by employing Taniaphos **42**/[$CuF(PPh_3)_3$]·2MeOH catalyst system with $PhSiH_3$ (Scheme 21). Even with a 1 mol-% of the catalyst, *anti* products **43** were obtained with high diastereo- and enantioselectivity. Shibasaki's group[36] reported the coupling of β-substituted enoates and diethyl ketone with tol-BINAP (*R*)-**28**/[$CuF(PPh_3)_3$]·EtOH catalyst system by employing $(EtO)_3$-SiH as a hydride source (Scheme 22).



Scheme 20. Intramolecular reductive aldol reaction of keto esters.



Scheme 21. Reductive aldol reaction of methyl acrylate and ketones.



Scheme 22. Reductive aldol reaction of conjugate enoates and ketones.

A basis of these reactions was provided by a seminal finding by Mori et al.[37a,37b] and Hosomi et al.[37c] that conjugate reduction of α,β-unsaturated carbonyl compounds proceeds using a hydrosilane and Cu^I salts and by a subsequent progress in a catalytic asymmetric conjugate reduction.[38] In a plausible catalytic cycle (Scheme 23), the conjugate addition of copper hydride phosphane complex **44** generated from CuF/phosphane and a hydrosilane (*Si*–H) gives copper enolate **45**, which then undergoes the aldolization with ketones to give copper alkoxide **46**, as in the reaction starting from silyl ketene acetals (Schemes 15 and 18). In the catalyst turnover step, *Si*–H reacts with **46** to give silylated product **47** with concurrent regeneration of copper hydride species **44**.

When reductive aldol reaction is applied to allenic esters **48**, the putative dienolate **49** may attack the ketone carbonyl group either at the γ or α position to give adduct **50** and **51**, respectively (Scheme 24). Thus, the control of the regioselectivity becomes the additional issue. Recently, Shibasaki, Kanai, and co-workers reported a remarkable ligand effect in the regioselectivity of such reaction (Scheme 25).[39] While SEGPHOS (*R*)-**52** alone with Cu(OAc) gave a mixture the regioisomers (γ/α = 32:18), exclusive formation of γ adduct **50′**, with high *ee* and *cis* selectivity, was obtained in the presence of the achiral phos-

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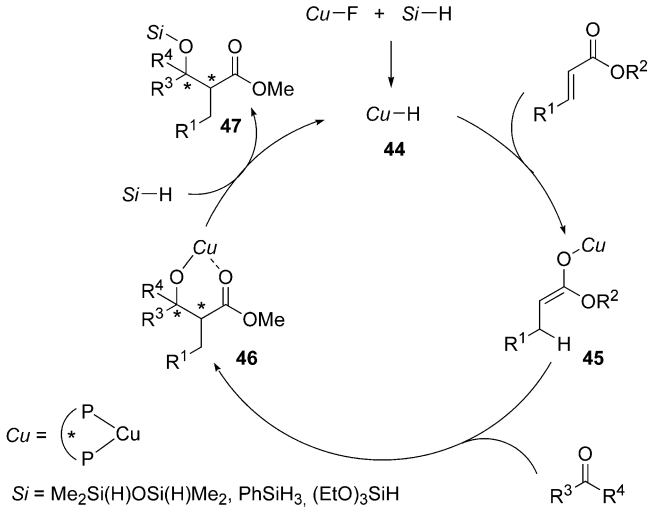
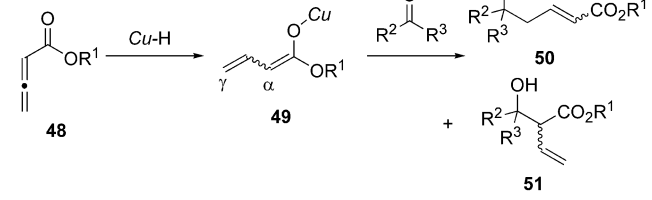
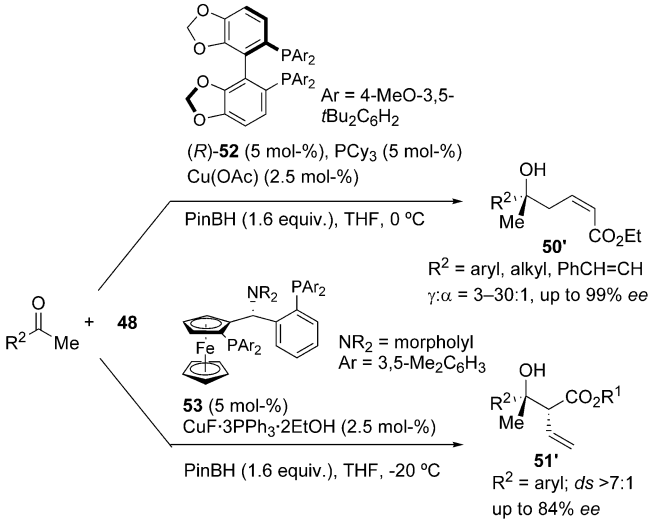


Scheme 23. Plausible catalytic cycle for reductive ketone-aldol reaction.

phane additive (PCy_3). The reaction was demonstrated to be applicable to various methyl ketones including aromatic, aliphatic, and α,β-unsaturated ketones. In sharp contrast to the reaction with SEGPHOS ligand, exclusive formation of α adduct **51′** was obtained with Taniaphos **53** in combination with CuF·3PPh_3·2EtOH. In stead of hydrosilanes, pinacolborane (PinBH) was employed as a hydride source in both reactions.

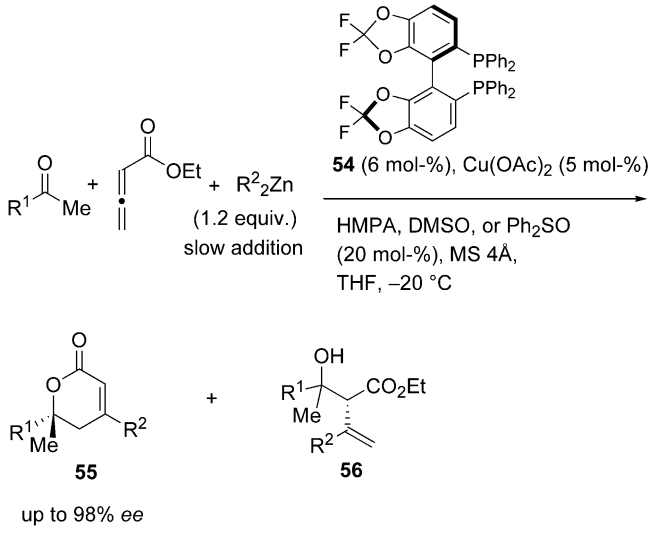


Scheme 24. Reductive aldol reaction of allenic esters.



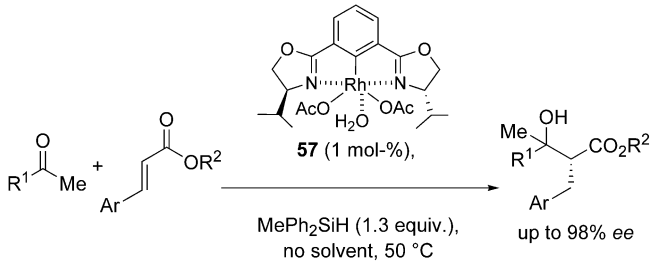
Scheme 25. Regioselective reductive aldol reaction of allenic esters.

Very recently, Shibasaki's group reported a mechanistically relevant asymmetric alkylative vinylogous aldol reaction of ketones that assembles dialkylzincs, allenic esters, and ketones to produce δ-lactones **55** (Scheme 26).[40] In this reaction, $Cu(OAc)_2$/DIFLUORPHOS **54** system exhibited high enantioselectivity. The use of a Lewis base additive, such as HMPA, DMSO, and Ph_2SO, together with molecular sieves (4 Å) was effective in suppressing the byproduct formation of undesirable α adducts **56** to realize the high yields of **55**. Several control and crossover experiments suggested that the addition of the Lewis bases facilitated the retro-aldol reaction of the kinetically favoured copper or zinc α-aldolates, leading to **55** through vinylogous aldolization followed by the irreversible lactonization of the resulting γ-aldolates.



Scheme 26. Alkylative aldol reaction of allenic ester.

So far, a single example of the reductive aldol reaction of ketones catalyzed by a chiral Rh complex has been reported (Scheme 27).[41] Nishiyama and co-workers showed that, even with 1 mol-% of $Rh(Phebox)(OAc)_2$ (**57**), the reaction proceeded efficiently and enantioselectively even under relatively harsh conditions (no solvent at 50 °C). The robustness and high enantioselection of the pincer ligand/Rh^I catalyst system[42] seems to be crucial to the aldol reaction of unactivated ketone.



Scheme 27. Rh-catalyzed reductive aldol reaction of conjugate enoates and ketones.

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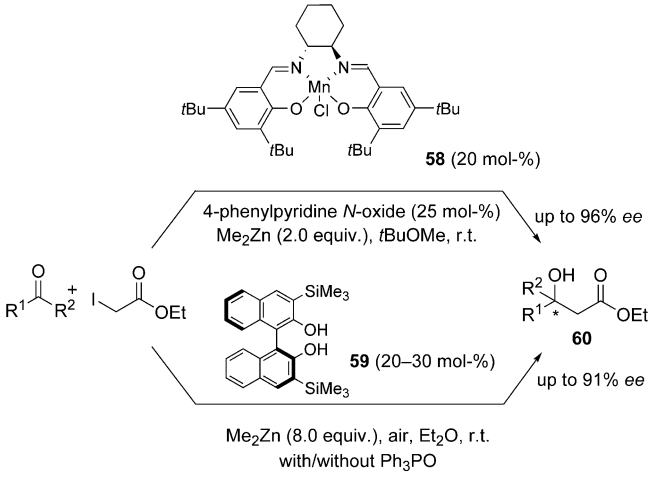
3.4 Reformatsky Reaction

The Reformatsky reaction is among the most useful methods for the formation of β-hydroxy esters by the zinc-induced reaction of α-halo esters and aldehydes or ketones.[43] The reaction is frequently used in organic syntheses as an alternative to the base-induced aldol reaction. In spite of the synthetic potential and the significance of a catalytic asymmetric version of the Reformatsky reaction, its realization has been hampered by its heterogeneous nature and by the in situ generation of reactive zinc enolate species that needs to be tamed by a powerful ligand acceleration. Quite recently, notable progresses have been made on the asymmetric Reformatsky reaction[4d] based on the development of the homogeneous Reformatsky-type reaction by using Me_2Zn or Et_2Zn.[44]

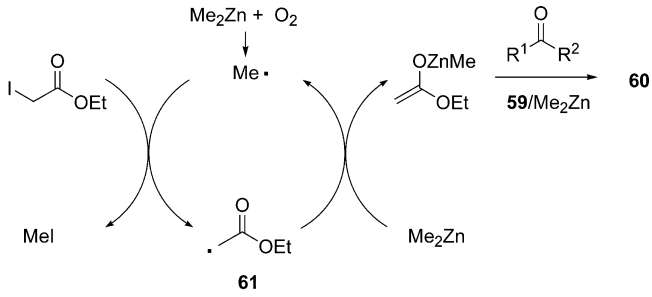
In 2006, Cozzi reported the first example of catalytic asymmetric Reformatsky reaction of ketones (Scheme 28).[45] The reaction was carried out with ethyl iodoacetate and Me_2Zn in the presence of Mn(salen)Cl complex **58** (20 mol-%) and 4-phenylpyridine *N*-oxide (25 mol-%). Enantioselectivities in the range 69–86% was reported for aromatic ketones. Although the highest *ee* of 96% was obtained for 2,2-dimethylcyclopentanone, simple aliphatic ketones exhibited lower selectivity.



Scheme 28. Catalytic reformatsky reaction to ketones.

Very recently, Feringa and co-workers have developed a new catalytic system for the asymmetric Reformatsky reaction of aldehydes[46] and applied it to the reaction of ketones (Scheme 28).[47,48] The reaction was carried out by slowly adding a substrate ketone for 30 min to a Et_2O solution of ethyl iodoacetate (2 equiv.), Me_2Zn (8 equiv.), and BINOL derivative (*S*)-**59** (20–30 mol-%) under air. The reactions of aromatic ketones gave moderate to high enantioselectivities (74–90% *ee*). Interestingly, benzophenone derivatives bearing a substituent, such as Me, Cl, and Br, at the *ortho* position are good substrates for the reaction, affording β,β-diaryl aldol products of around 90% *ee* in the presence of Ph_3PO.[47b] As in the Mn(salen)Cl-catalyzed reaction, lower *ee* was observed for non-aromatic ketones.

The reaction was carried out under air to facilitate the formation of zinc enolates. A radical chain mechanism depicted in Scheme 29 has been proposed for the oxygen-promoted iodine/zinc exchange of the iodoacetate with Me_2Zn.[49] Me_2Zn and oxygen initiates the reaction by releasing a methyl radical,[50] which abstracts an iodine atom from the iodoacetate to generate (ethoxycarbonyl)methyl radical **61**. The zinc enolate intermediate is produced by the reaction of **61** with Me_2Zn. In support for the mechanism, the reaction was completely suppressed by the addition of TEMPO.



Scheme 29. Radical chain mechanism for the formation of zinc enolates.

In the asymmetric Reformatsky reaction, reactive zinc enolates generated in situ should be consumed rapidly by the subsequent enantioselective reaction with ketones (or aldehydes) since the accumulation of the enolates would not only result in undesirable reaction with the starting iodo esters[51] but also induce non-catalyzed background reaction to form racemic products. To circumvent the problem, reaction conditions, such as the rate of the addition of a substrate ketone and the concentration of oxygen, were carefully optimized in the successful reactions.[45–48]

3.5 Lewis Acid Catalyzed Reaction with Dimethylsilyl Ketene Acetal

A number of efficient Lewis acid catalysts have been developed for the asymmetric Mukaiyama aldol reaction of aldehydes.[3] However, for the reaction of ketones, successful examples have been limited to those of highly reactive α-keto esters and α-diketones until very recently. In 2008, the first example of the asymmetric Mukaiyama aldol reaction of non-activated ketones was reported by Adachi and Harada (Scheme 30).[52] The *allo*-threonine-derived oxazaborolidinone (OXB) **63** and its derivatives had been developed for the enantioselective activation of acyclic α,β-unsaturated ketones.[53] The OXB catalysts were reported to be effective to the asymmetric Michael reaction[54] and Diels–Alder reaction.[55] It was demonstrated that OXB **63** is also applicable to the aldol addition to ketones.

The reaction was carried out simply by mixing a ketone, dimethylsilyl ketene acetal **62a** (1.5 equiv.), and OXB **63** (20 mol-%) in toluene at –20 °C. The use of dimethylsilyl derivative **62a** was critical to achieve catalytic reaction and high selectivity.[56] When the conventional trimethylsilyl de-

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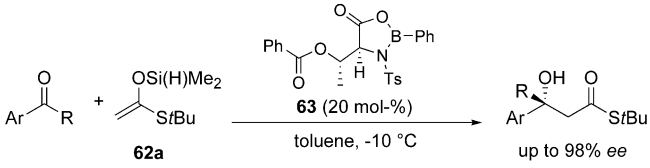
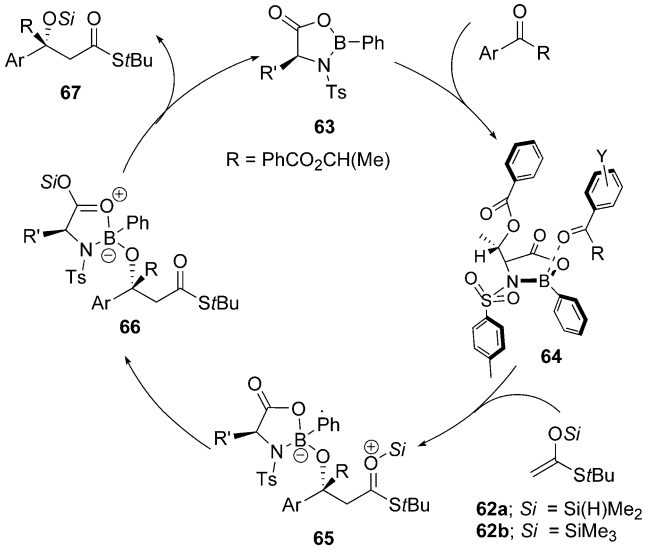


Scheme 30. OXB-catalyzed asymmetric Mukaiyama aldol addition to non-activated ketones.

rivative **62b** was used, the reaction was impeded at about 20% conversion. A variety of acetophenone derivatives, including those bearing ethoxycarbonyl and nitro groups at the *para* position, gave the corresponding tertiary aldol products in high enantioselectivity (91–98% *ee*). High selectivity was also obtained in the reaction of 2-naphthophenone while on the other hand the reactions of aliphatic ketones resulted in lower selectivity.

A catalytic cycle involving a stepwise silyl group migration was proposed (Scheme 31). The attack of **62a**,**b** to a substrate-OXB complex **64** first generates unstable intermediate **65**, which is converted silyl ester intermediate **66**. While **66** (*Si* = $SiMe_3$) serves as a catalyst sink in the reaction using trimethylsilyl derivative **62b**, the second silyl group migration takes place slow but steadily for **66** [*Si* = $Si(H)Me_2$] to give silyl aldolate **67** with regeneration of OXB **63**. The absolute stereochemistry of the tertiary aldol products was rationalized by an activated complex model **64**,[57] being similar to those proposed previously for the reaction of α,β-unsaturated ketones.[54,55]



Scheme 31. Proposed catalytic cycle for OXB-catalyzed aldol reaction.

4. Conclusions

This review describes recent progresses for the catalytic asymmetric aldol reaction of ketone acceptors. The difficulties associated with the lower reactivity and the decreased steric discrimination of ketones have been overcome by catalytic methodologies based on the activation of acceptor ketones and/or nucleophile enolates. Most of them were developed originally for the aldol reaction to aldehydes. However, significant improvements and sophistication have been made in applying them to the ketone-aldol reaction, thus leading to the development of the more robust catalytic systems. In these studies, a precise view on the catalytic cycle often played a crucial role as exemplified by the remarkable acceleration by additives which promote a rate determining catalyst turnover step. The accumulation of such knowledge would provide feedback in the future development of catalytic asymmetric reactions in general.

In spite of the recent advancement, the catalytic asymmetric aldol reaction of unactivated ketones still remains a challenging task. Generally, high enantioselectivities were reported only for aromatic ketones. The scope of the reactions needs to be expanded to be applicable to non-aromatic ketones. In most cases, relatively high catalyst loadings are required to obtain satisfactory product yields and selectivities. More efficient ligands and catalytic systems need to be developed in the future.

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