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Catalytic enantioselective aldol reactions

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Recent developments in catalytic asymmetric aldol reactions have been summarized. Enantioselective aldol reactions are important methods to synthesize β -hydroxy carbonyl compounds in optical pure form, and as such, numerous successful chiral catalysts were designed and applied for asymmetric aldol reactions. This review article is organized under the categories of: (1) catalytic enantioselective aldol reactions of preformed enolates, (2) catalytic enantioselective direct-type aldol reactions using chiral metal catalysts, (3) catalytic enantioselective direct-type aldol reactions using organocatalysts, (4) catalytic enantioselective aldol reactions in aqueous media. Examples of the aldol reactions that employ simple carbonyl compounds will be also the focus of this review.

1. Introduction

The preparation and supply of useful organic materials for society is an important obligation of synthetic organic chemists. For example, medicines, plastics, dyes, cosmetics, and perfumes, which make our lives more comfortable, are prepared from organic molecules. Carbon–carbon bond forming reactions are one of the most important reactions to construct the basic frameworks of such organic compounds.^{1,2} On the other hand, from the viewpoint of green sustainable chemistry, the development of environmentally benign methods, which are efficient,

safe, economical, energy-saving, and harmless, is required to realize ideal organic transformations. An important concept in sustainable chemistry is catalysis, in which the desired reactions can be promoted under milder reaction conditions by using a small amount of a catalyst, and consequently the development of catalytic carbon–carbon bond forming reactions is currently an important area of research.

Biologically active molecules, such as drugs, are often complex molecules that contain many stereocenters, where changes to the stereocenters of the molecule can significantly change their biological activities. Therefore, stereoselective synthesis is required for the efficient supply of drugs and other related biologically active compounds. It is especially important to control the stereochemistry of chiral centers to obtain the

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Yasuhiro Yamashita

Yasuhiro Yamashita studied Chemistry at the Graduate School of Pharmaceutical Sciences, The University of Tokyo, and received his MsD in 1998 (supervisor, the late Professor Kenji Koga) and then his PhD in 2001 (supervisor, Shū Kobayashi). He started his academic career as an assistant professor in 2001 at the Graduate School of Pharmaceutical Sciences, the University of Tokyo. He then joined Professor John F. Hartwig's group at Yale University as a postdoctoral fellow (2005–2006). He returned to the University of Tokyo and was promoted to an associate professor in the Department of Chemistry, School of Science (2007).



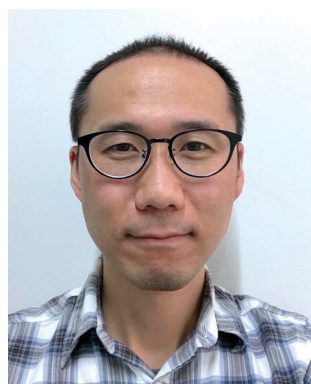
Tomohiro Yasukawa

Tomohiro Yasukawa was born in Kanagawa, Japan, in 1987 and studied at the University of Tokyo, receiving his PhD degree in 2015 working under the direction of Prof. Shū Kobayashi. At present, he is a project assistant professor in a group of Green & Sustainable Chemistry Social Cooperation Laboratory in The University of Tokyo. His research interests include the development of heterogeneous catalysts for environmentally benign organic synthesis.

optically active form since different biological activities are observed between enantiomers of chiral compounds. There are several methods that provide optically pure products in chemical synthesis. The resolution of racemic products is one method to access enantiopure compounds, but is wasteful since only one half of the molecule is used. Therefore, asymmetric synthesis is the desired methodology to obtain chiral compounds. The chiral pool method, in which the absolute configuration of the chiral molecule is derived from the diastereoselective synthesis of enantiopure natural sources, such as sugars, amino acids, and terpenes, is a reliable strategy to access enantiopure molecules. However, the limited availability of chiral molecules from natural sources makes this approach unattractive. The most attractive approach to obtain chiral molecules is through enantioselective synthesis from achiral or racemic starting materials using optically active reagents and catalysts. The advantages of enantioselective synthesis are: (1) the chiral center can be introduced at the desired position at any stage of the synthetic plan, (2) the target product can be

synthesized from non-natural and achiral or racemic compounds, and (3) catalytic reactions are possible by using chiral catalysts. Among these, the possibility of performing catalytic reactions is very important since only small amounts of expensive chiral and optically active catalysts are needed, which makes the asymmetric synthesis more efficient and economical. Therefore, the development of catalytic enantioselective reactions is highly desirable.

The aldol reaction is a carbon–carbon bond forming process between two carbonyl compounds that results in the formation of β -hydroxy carbonyl compounds, and is one of the most widely used methods to access complex organic molecules in a stereoselective fashion.^{3,4} Traditionally, aldol reactions have been conducted by using acidic or basic species, and in many cases, in catalytic amounts. When aldehydes or nonsymmetric ketones are used as a carbonyl acceptor, a new stereocenter is introduced on the β -carbon atom, and the asymmetric synthesis of β -hydroxy carbonyl compounds is realized by controlling the absolute configuration of the β -carbon atom during the carbon–carbon bond formation event. Therefore, asymmetric aldol reactions have been investigated as one of the most reliable asymmetric carbon–carbon bond forming reactions.⁵ The earliest examples of utilizing the aldol reaction to access enantiopure β -hydroxy carbonyl compounds relied on the chiral pool method, in which aldol donors bearing chiral auxiliaries underwent diastereoselective addition reactions with the aldol acceptors to generate optically active intermediates for natural products.^{6,7} Carbonyl donors bearing chiral oxazolidinones and their analogs, prepared from α -amino acids, are often employed as reliable chiral auxiliaries for asymmetric aldol reactions.^{8,9} However, the need to use stoichiometric amounts of the chiral auxiliaries makes it an inefficient asymmetric process, and instead catalytic enantioselective aldol reactions offer the most ideal method for providing enantiopure β -hydroxy carbonyl compounds.¹⁰ This review article focuses on the development of catalytic enantioselective aldol reactions over the last three decades and is organized under the categories of: (1) catalytic



Woo-Jin Yoo

Woo-Jin Yoo obtained his BSc and MSc degrees in 2003 and 2005, respectively, at the University of Guelph under the direction of Prof. William Tam. He then studied with Prof. Chao-Jun Li at McGill University and earned his PhD degree in 2009. He later joined the research laboratory of Prof. Shū Kobayashi at the University of Tokyo as a JSPS postdoctoral fellow, and was subsequently appointed as an assistant professor in 2011 in the same group. He is broadly interested in the development of new synthetic methods and catalysts for sustainable organic synthesis.



Taku Kitanosono

Taku Kitanosono earned his BSc and MSc degrees from the University of Tokyo under the supervision of Prof. S. Kobayashi. After receiving PhD degree in 2015, he was appointed assistant professor in the Department of Chemistry at the University of Tokyo. His research interests include the unusual application of catalysis in aqueous environments, such as chiral heterogeneous catalysis, micellar catalysis, and artificial metalloenzymes.



Shū Kobayashi

Shū Kobayashi studied at the University of Tokyo, receiving his PhD in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as an assistant professor, he was promoted to lecturer then associate professor at the Science University of Tokyo. In 1998, he moved to the Graduate School of Pharmaceutical Sciences, The University of Tokyo, as a full professor. In April 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, within the Faculty of Science of The University of Tokyo.

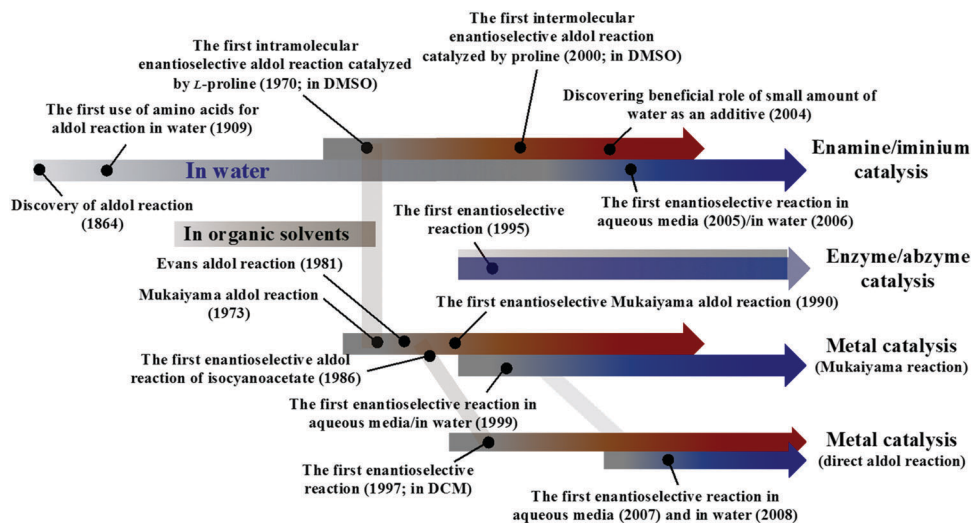
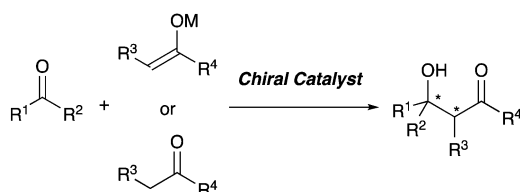


Fig. 1 Timeline of the development of the asymmetric aldol reaction. Orange: in organic solvents, blue: in aqueous media. Some monumental works are highlighted.



Scheme 1 Catalytic enantioselective aldol reactions.

enantioselective aldol reactions of preformed enolates, (2) catalytic enantioselective direct-type aldol reactions using chiral metal catalysts, (3) catalytic enantioselective direct-type aldol reactions using organocatalysts, (4) catalytic enantioselective aldol reactions in aqueous media (Fig. 1). Examples of the aldol reactions that employ simple carbonyl compounds will be the focus of this review (Scheme 1), and enantioselective aldol-type reactions using other related nucleophiles, such as vinylogous aldol reactions, nitro-aldol reactions, and cyanoaldol reactions, will not be covered.

2. Catalytic enantioselective aldol reactions of preformed enolates

Although the catalytic aldol reaction is a powerful carbon-carbon bond forming process, aldol reactions involving two different carbonyl moieties can lead to several side reactions, such as self-condensations, overreactions, and the dehydration of products, to limit the yields, and the regio- and stereoselectivities of the desired products. One solution to solve these issues is to use a preformed reactive metal or metalloid enolates in aldol reactions. This process comprises two steps: (1) one of the carbonyl compounds is converted into a metal or metalloid enolate, and then (2) it is introduced with the other carbonyl compounds for the desired aldol addition reaction. Preforming the enolate prior to the aldol addition event can

prevent serious undesired side reactions. There are two main methods for this process: (1) the use of unstable, but highly reactive metal enolates, such as enolates derived from lithium or boron, which can normally react with the aldol acceptor without the need for any activator, even at a very low reaction temperature, (2) the use of a less reactive, but stable and isolable metal or metalloid enolates, such as silicon enolates, which do not react directly with the aldol acceptor in the absence of some activating reagents. The advantage of these methods is that the regio- and geometrically controlled-formation of the corresponding enolates, under kinetic conditions, can easily undergo stereoselective aldol reactions. It should be noted that in the first method, the reactivity of the enolates is usually too high, and it is difficult to control the stereoselectivity of the aldol reaction. On the other hand, the use of a less reactive preformed enolate is more amenable for controlled reactions since the use of additional activating reagents can modulate the reactivities of the aldol reactions. Furthermore, in the latter method, catalytic enantioselective aldol reactions can be realized when the chiral activating reagents function catalytically. Therefore, catalytic enantioselective aldol reactions using preformed metal or metalloid enolates have been widely adopted as a reliable method to access chiral β -hydroxy carbonyl compounds.

2.1. Catalytic enantioselective Mukaiyama aldol reactions of trialkyl silicon enolates

The Mukaiyama aldol reactions, which are aldol reactions of carbonyl compounds with silicon enolates that use Lewis acids as activators, is one of the most fundamental methods to enable efficient cross-aldol reactions.^{11–13} Normally, the Lewis acids activate the carbonyl acceptors to enhance their electrophilicity for the addition reactions of the silicon enolates. The Lewis acids can be employed as catalysts *via* silicon atom transfer to the hydroxyl group on the formed product. This is conceptually important for asymmetric synthesis since catalytic asymmetric aldol reactions can be realized by using chiral Lewis acids.

Based on this concept, many chiral Lewis acids were developed and successfully applied for catalytic enantioselective Mukaiyama aldol reactions.

2.1.1. Chiral Lewis acid-catalyzed reactions

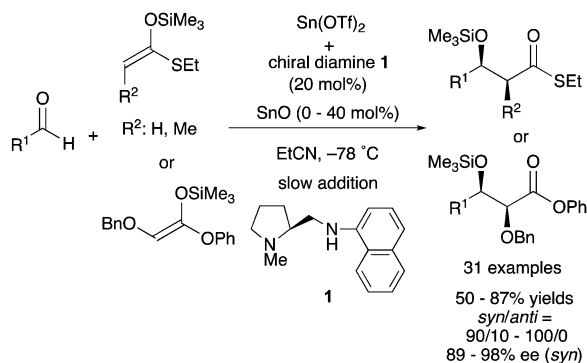
2.1.1.1. Chiral tin-diamine complex-catalyzed enantioselective Mukaiyama aldol reactions. In the early 1990s, the first catalytic enantioselective aldol reaction with preformed silicon enolates was reported by Mukaiyama and co-workers (Scheme 2).^{14–22}

Prior to this work, they demonstrated that Mukaiyama aldol reactions with high enantiopurities could be promoted by a stoichiometric amount of chiral tin Lewis acid complex derived from $\text{Sn}(\text{OTf})_2$ and a chiral diamine. They found that by further developing the reaction conditions, they were able to achieve a truly catalytic process for this reaction. By using chiral diamine **1**, bearing a 1-naphthyl group, the catalytic Mukaiyama aldol reactions of alkyl, alkenyl, and alkynyl aldehydes with silicon enolates, derived from *S*-ethyl ethanethioate and propanthioate, preceded well to afford the desired adducts with high *syn*- and enantioselectivities. In the aldol reaction with a silicon enolate derived from phenyl α -benzyloxy acetate, tin oxide (SnO) was found to be an effective catalyst that could lead to higher enantioselectivities. It was found that the slow addition of the silicon enolates was essential to achieve high selectivities.

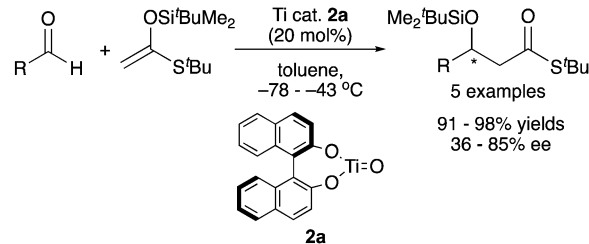
2.1.1.2. Chiral titanium and zirconium complexes-catalyzed enantioselective Mukaiyama aldol reactions. After the initial report by Mukaiyama, other research groups disclosed the use of chiral Lewis acids for asymmetric aldol reactions with silicon enolates. One of the earliest chiral Lewis acids employed for the asymmetric Mukaiyama aldol reactions were those derived from titanium modified by 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) derivatives.

In 1990, Mukaiyama and co-workers reported a catalytic enantioselective Mukaiyama aldol reaction using a chiral oxo-titanium catalyst (Scheme 3).²³ The titanium complex **2a**, prepared from BINOL and $\text{Ti}(\text{O})(\text{O}^i\text{Pr})_2$, was able to catalyze the asymmetric aldol reactions with various aldehydes and a silicon enolate, prepared from *S*-*tert*-butyl ethanethioate, with moderate to good enantioselectivities obtained in most cases.

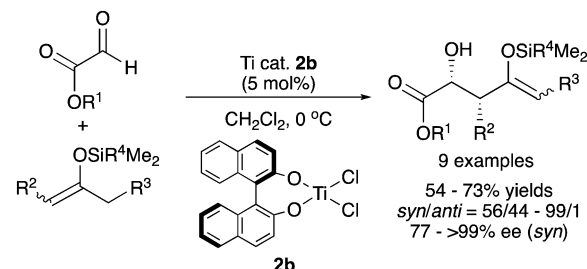
In 1993, Mikami and co-workers reported Mukaiyama aldol-type reactions of glyoxylate with silicon enolates, derived from



Scheme 2 Chiral tin-diamine Lewis acid-catalyzed enantioselective Mukaiyama aldol reactions.



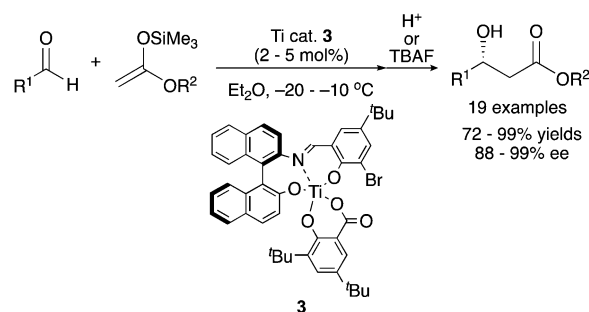
Scheme 3 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral titanium Lewis acid derived from BINOL and $\text{Ti}(\text{O})(\text{O}^i\text{Pr})_2$.



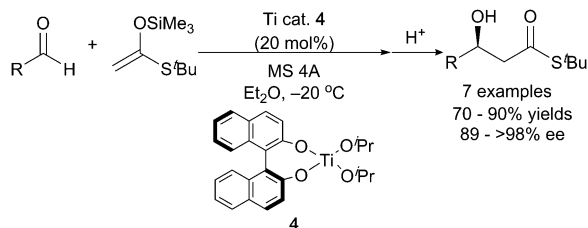
Scheme 4 Enantioselective Mukaiyama aldol-type reactions catalyzed by a chiral titanium Lewis acid prepared from BINOL and $\text{TiCl}_2(\text{O}^i\text{Pr})_2$.

ketones, using a chiral titanium complex **2b** prepared from BINOL and $\text{TiCl}_2(\text{O}^i\text{Pr})_2$ (Scheme 4).²⁴ The reaction was found to proceed not through an addition reaction, but by an ene reaction mechanism, and the resulting products were obtained as silicon enolates with high *syn*- and enantioselectivities. Furthermore, when an excess amount of the glyoxylate was used, the resulting silicon enolate intermediates could undergo additional aldol condensation to form the double adducts with high diastereoselectivities.²⁵ In addition, trifluoroacetaldehyde was also employed as an aldol acceptor in this catalyst system.²⁶

In 1994, Carreira and co-workers developed a chiral titanium catalyst **3**, prepared from 2-amino-2'-hydroxy-1,1'-binaphthyl, 3,5-bis-*tert*-butylsalicylaldehyde, $\text{Ti}(\text{O}^i\text{Pr})_4$, and 3,5-bis-*tert*-butylsalicylic acid, for enantioselective Mukaiyama aldol reactions (Scheme 5).^{27,28} It was found that the salicylic acid moiety promoted the intramolecular silyl transfer process, which dramatically enhanced the reaction rate and led to high yields and high enantioselectivities of the aldol adducts. In addition,



Scheme 5 Chiral tridentate-ligated titanium Lewis acid-catalyzed enantioselective Mukaiyama aldol reaction.



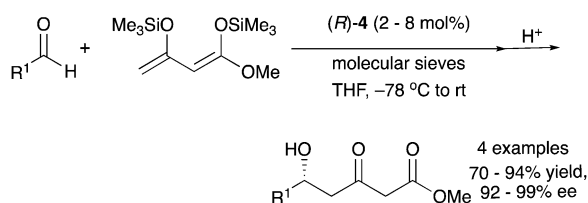
Scheme 6 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral titanium Lewis acid derived from $\text{Ti}(\text{O}^i\text{Pr})_4$ and BINOL.

this catalyst system was successfully applied for the synthesis of (*R*)-epinephrine. Moreover, methoxypropene was also applicable as an enolate equivalent for the aldol-type reactions using a similar catalyst.²⁹

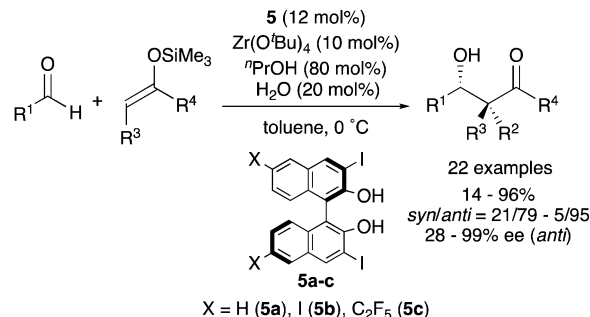
In 1995, Keck and co-workers reported catalytic enantioselective Mukaiyama aldol reactions using a chiral titanium complex **4**, prepared from $\text{Ti}(\text{O}^i\text{Pr})_4$ and BINOL (Scheme 6).³⁰ The aldol reactions between aldehydes and a silicon enolate derived from *S*-tert-butyl ethanethioate proceeded smoothly in the presence of MS4A, with the aldol adducts obtained in good to high yields with high enantioselectivities. The reaction system was further optimized for aliphatic aldehydes, and phenol was also found to be effective as an additive for the catalyst system.³¹ In addition, Scettri and co-workers reported that this chiral titanium–BINOL complex **4** could be employed for enantioselective Mukaiyama aldol-type reactions of silicon dienolates (Scheme 7).³² The titanium complex was effective at creating an asymmetric environment to enable obtaining high enantioselectivities.

Recently, the catalytic asymmetric Mukaiyama aldol reaction was used for the synthesis of pitavastatin calcium (Livalo[®]),³³ which is a cholesterol-lowering drug belonging to the statin class of drugs. Livalo[®] is an inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, and is one of the more potent statins on the market.

Not only titanium–BINOL derivatives complexes, but chiral metal complexes from the related group IV metal zirconium have also been successfully applied to enantioselective Mukaiyama aldol reactions. In 2000, Kobayashi and co-workers developed a chiral zirconium catalyst system for the aldol reactions of silicon enolates derived from esters and thioesters (Scheme 8).^{34,35} Zirconium complexes prepared from 3,3'-diiodo-BINOL derivatives **5** and zirconium tetraalkoxides were found to be effective catalysts for the enantioselective Mukaiyama aldol reaction, with good to high yields and good to high *anti*- and enantioselectivities observed for the aldol adducts. A key additive for



Scheme 7 Asymmetric Mukaiyama aldol-type reactions with silicon dienolates using chiral titanium catalysts.



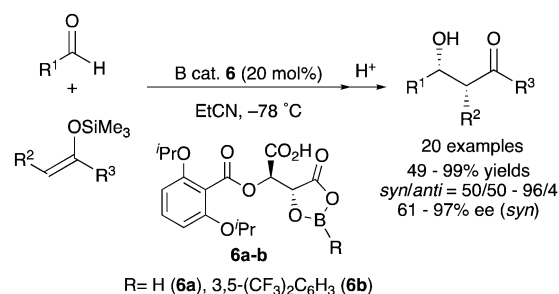
Scheme 8 Chiral zirconium complexes-catalyzed enantioselective Mukaiyama aldol reactions.

this catalyst system was propanol, which could intercept the silyl cation formed *in situ* to promote the catalytic cycle. Furthermore, the addition of water was crucial to creating a highly stereoselective catalyst. The introduction of an electron-withdrawing group at the 6,6'-positions of the BINOL ring system was found to improve the catalytic activity of the zirconium catalyst. These zirconium complexes were bench-stable and could be stored for a long period of time without any loss in catalytic activity and selectivity.^{36,37} Moreover, this catalytic system was shown to be applicable for the aldol reactions of silicon enolates derived from a glycine derivative.^{38,39}

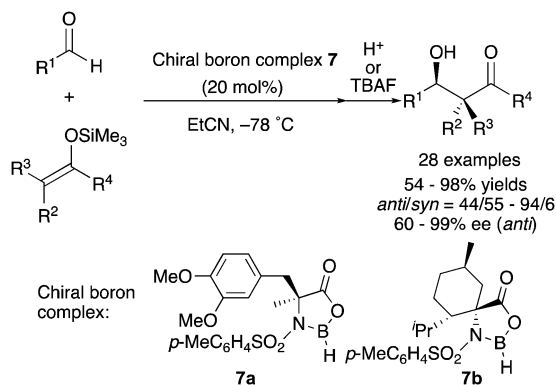
2.1.1.3. Chiral boron complexes-catalyzed enantioselective Mukaiyama aldol reactions. Chiral boron-based Lewis acids have been successfully employed in catalytic enantioselective Mukaiyama aldol reactions. Chiral ligands prepared from tartaric acid or chiral α -amino acids were successfully employed to modify the boron center for high enantioselection.

In 1991, Yamamoto and co-workers reported catalytic enantioselective Mukaiyama aldol reactions using a chiral boron complex **6** prepared from a tartaric acid derivative and BH_3 –THF complex (Scheme 9).^{40,41} Silicon enolates derived from ketones and esters reacted with aromatic and aliphatic aldehydes with moderate to high diastereoselectivities and good to high enantioselectivities. By employing 3,5-bis(trifluoromethyl)phenylboronic acid instead of the BH_3 –THF complex, the catalyst activity was improved without reducing the enantioselectivities.⁴²

Masamune and co-workers reported catalytic enantioselective Mukaiyama aldol reactions using a chiral boron complex **7** prepared



Scheme 9 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral boron Lewis acid derived from tartaric acid.



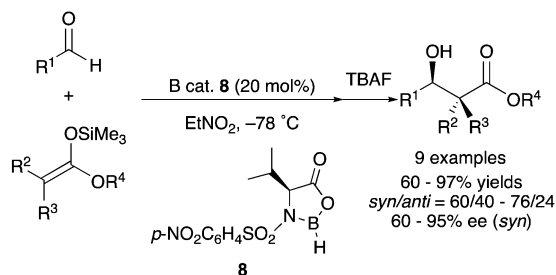
Scheme 10 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral boron Lewis acids derived from α,α -disubstituted amino acid derivatives.

from α,α -disubstituted amino acid derivatives and a BH_3 -THF complex (Scheme 10).^{43,44} They revealed that the aldol reactions with silicon enolates derived from esters and thioesters proceeded in moderate to high yields with moderate to high enantioselectivities. In aldol reactions involving silicon enolates derived from propionates, good to high *anti*-selectivities were observed.

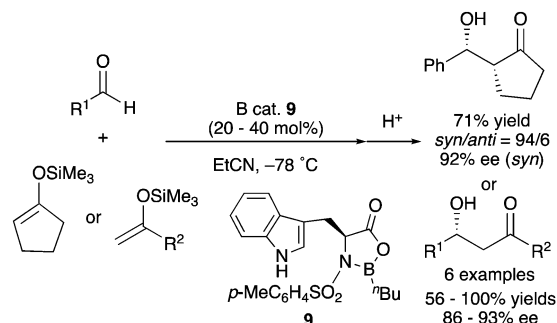
In 1992, Kiyooka and co-workers also developed a modified valine-derived chiral boron complex **8** for catalytic enantioselective Mukaiyama aldol reactions (Scheme 11).⁴⁵ The aldol reactions with silicon enolates derived from esters proceeded in nitroethane at -78°C to provide the aldol adduct in moderate to high yields with moderate to high stereoselectivities.

In 1992, Corey and co-workers also developed a chiral boron complex **9**, derived from modified tryptophan, as a catalyst for enantioselective Mukaiyama aldol reactions (Scheme 12).⁴⁶ The reaction of benzaldehyde with a silicon enolate derived from cyclopentanone led to the desired β -hydroxy ketone in a good yield with high *syn*- and enantioselectivities. Moreover, silicon enolates derived from acyclic ketones were found to be good aldol donors, with high enantioselectivities obtained in the presence of aromatic and aliphatic aldehydes. The structure of Corey's boron catalyst was further optimized by Yamamoto and co-workers, who found that by introducing a 3,5-bis(trifluoromethyl)phenyl group on the boron center, the catalyst loading could be reduced.^{47,48}

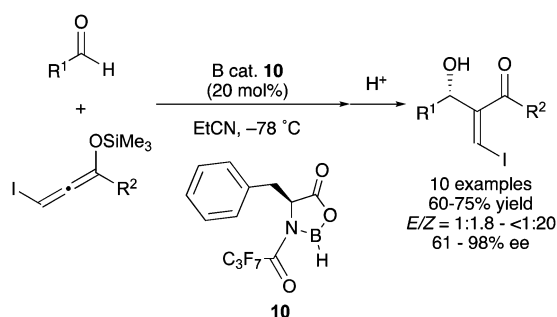
In 2001, Li and co-workers reported enantioselective Mukaiyama aldol reactions with silicon allenolates using a chiral boron complex **10** derived from phenylalanine (Scheme 13).⁴⁹ The



Scheme 11 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral boron Lewis acid derived from modified valine.



Scheme 12 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral boron Lewis acid derived from modified tryptophan.

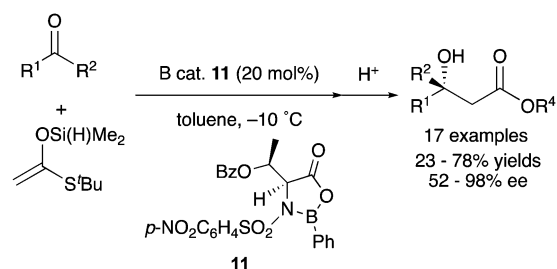


Scheme 13 Enantioselective Mukaiyama aldol reactions with silicon allenolates catalyzed by a chiral boron complex derived from phenylalanine.

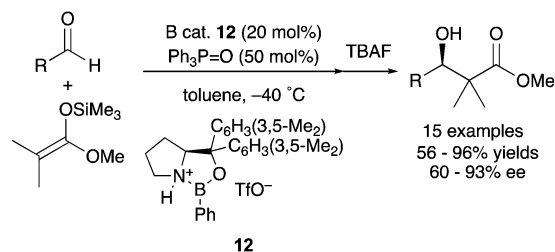
desired β -halo Baylis-Hillman-type adducts were obtained in good to high enantioselectivities. The fluoroacetyl group of the catalyst was crucial for control of the enantioselectivity.

In 2008, Harada and co-workers revealed that catalytic enantioselective Mukaiyama aldol reactions of ketones proceeded smoothly when using a chiral boron complex **11** derived from allo-threonine derivative (Scheme 14).⁵⁰ Using a dimethylsilyl enolate derived from *S*-tert-butyl ethanethioate as the aldol donor, the desired reactions proceeded in good yields with high enantioselectivities.

In 2010, Hwung, Ryu and co-workers reported chiral oxazaborolidinium ion **12** catalyzed enantioselective Mukaiyama aldol reactions with a silicon enolate derived from methyl isobutyrate (Scheme 15).⁵¹ Triphenylphosphine oxide was employed as an additive to suppress the undesired silyl cation-mediated racemization pathway. By using this method, (–)-inthomycin C was successfully synthesized.



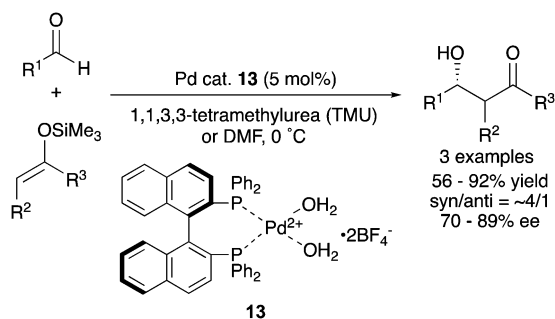
Scheme 14 Chiral boron Lewis acid, derived from modified allo-threonine, as a catalyst for enantioselective Mukaiyama aldol reactions of ketones.



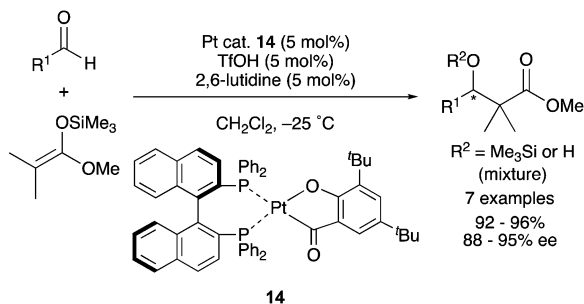
Scheme 15 Enantioselective Mukaiyama aldol reactions catalyzed by a chiral boron Lewis acid derived from a prolinol derivative.

2.1.1.4. Chiral palladium, platinum, and silver complexes-catalyzed enantioselective Mukaiyama aldol reactions. Although the initial reports of enantioselective Mukaiyama aldol reactions involved hard chiral Lewis acids, the use of softer metals in the asymmetric aldol reaction have been shown to be equally effective. In 1995, Shibasaki and co-workers reported that the chiral palladium complex **13** could catalyze enantioselective Mukaiyama aldol reactions (Scheme 16).^{52–54} Unlike typical Lewis acids, which activate the aldol acceptors *via* coordination to the carbonyl moiety, NMR studies indicated that a palladium enolate was formed, *via* transmetalation, under the reaction conditions. Water was found to be essential to generate the active catalyst species, while urea-type solvents with high polarity were effective to enhance the enantioselectivities of the Mukaiyama aldol reaction.

In 1998, Fujimura reported enantioselective Mukaiyama aldol reactions using a chiral bisphosphine platinum acyl complex **14** as a catalyst (Scheme 17).⁵⁵ Oxygen and water were required to



Scheme 16 Chiral aqua-palladium complex as a catalyst for enantioselective Mukaiyama aldol reactions.



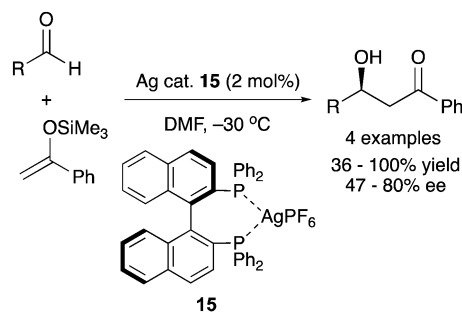
Scheme 17 Chiral platinum complex-catalyzed enantioselective Mukaiyama aldol reactions.

generate the highly enantioselective catalyst species, with the formation of a C-bound platinum enolate in the reaction system supported by NMR studies. Kiyooka and co-workers further investigated chiral palladium-BINAP complexes for enantioselective Mukaiyama aldol reactions.⁵⁶ They also employed (–)-sparteine as a ligand in the catalyst system.⁵⁷ Similarly, they also demonstrated that platinum-BINAP complexes were effective for asymmetric aldol reactions.⁵⁸

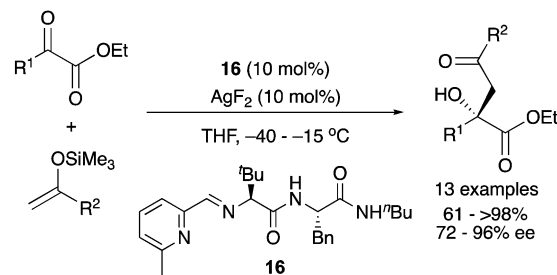
In 2000, Yamagishi and co-workers reported that the AgPF₆-BINAP catalyst **15** promoted the Mukaiyama aldol reactions to furnish the aldol adducts in moderate to good enantioselectivities (Scheme 18).^{59,60} They also investigated the AgOAc-BINAP complex as a chiral catalyst, and found that the opposite enantiomers were obtained as major products when compared to the reactions with AgPF₆-BINAP **15** with the same absolute configuration.

In 2006, Hoveyda and co-workers, reported a chiral silver complex, prepared from an amino acid-based chiral ligand **16**, as a catalyst for enantioselective Mukaiyama aldol reactions (Scheme 19).⁶¹ α -Ketoesters were employed as carbonyl acceptors, and good to high yields and enantioselectivities were achieved. Interestingly, the aldol reactions could be carried out easily in air and with undistilled solvent. Although catalytic amounts of AgF₂ were employed, it was believed to undergo *in situ* reduction by the silicon enolate to generate the catalytically active AgF species.

2.1.1.5. Chiral metal-box or pybox complexes-catalyzed catalytic enantioselective Mukaiyama aldol reactions. Chiral bisoxazoline compounds are privileged multidentate ligands that have been



Scheme 18 Chiral silver complex-catalyzed enantioselective Mukaiyama aldol reactions.

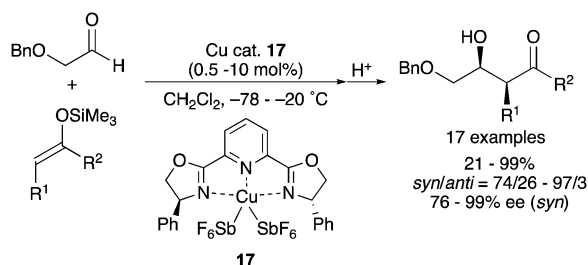


Scheme 19 Chiral silver complex-catalyzed enantioselective Mukaiyama aldol reactions.

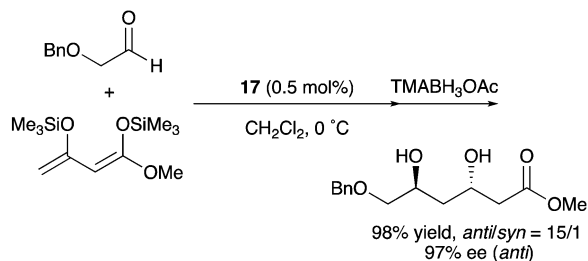
well-established to coordinate with various metal Lewis acids to generate effective chiral catalysts. In particular, methylene-tethered chiral bisoxazolines (box) and chiral pyridine-2,6-bisoxazolines (pybox), which can be easily prepared from commercially available amino acids, are often employed as ligands in various asymmetric processes.

In 1996, Evans and co-workers examined a chiral copper-pybox complex **17** as a catalyst for the enantioselective Mukaiyama aldol reactions of α -benzyloxyacetaldehyde (Scheme 20).^{62,63} The reactions of silicon enolates, prepared from esters, thioesters, and ketones, proceeded smoothly to afford the desired products in moderate to high yields with good to high *syn*- and enantioselectivities. Bidentate coordination of the aldehyde to the copper center was found to be crucial, and aldehydes that lacked a benzyloxy group did not generate any aldol adducts with any significant enantioselectivities. In addition, the *syn*-selectivity was found to be independent of the *E/Z* geometry of the α -monosubstituted silicon enolates. Also, two different chiral α -benzyloxyaldehydes were employed as aldol acceptors, but only one optically active aldehyde showed high selectivity, which suggested that matching the structure of the aldehyde in the transition state of the reaction was important to achieve high selectivity. They also reported enantioselective Mukaiyama aldol-type reactions of silicon dienolates using chiral copper catalysts related to their works covering aldol reactions using silicon enolates (Scheme 21). The desired reactions of α -benzyloxyacetaldehyde or methyl pyruvate proceeded at -78°C to afford the desired products in high yields with high enantioselectivities.

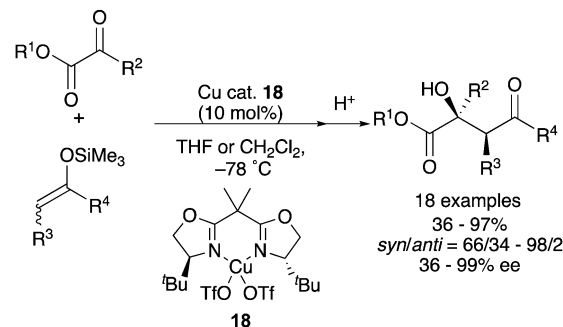
Evans and co-workers also reported enantioselective Mukaiyama aldol reactions of pyruvates catalyzed by a chiral copper complex



Scheme 20 Enantioselective Mukaiyama aldol reactions of α -benzyloxyacetaldehyde catalyzed by a chiral copper Lewis acid prepared from $\text{Cu}(\text{SbF}_6)_2$ and pybox.



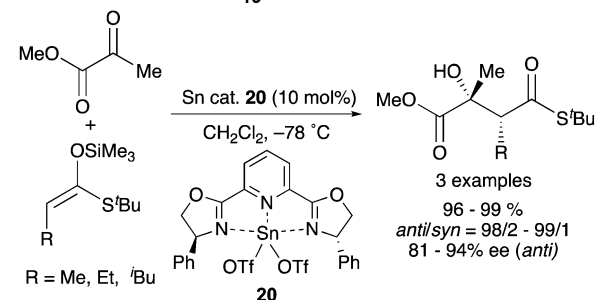
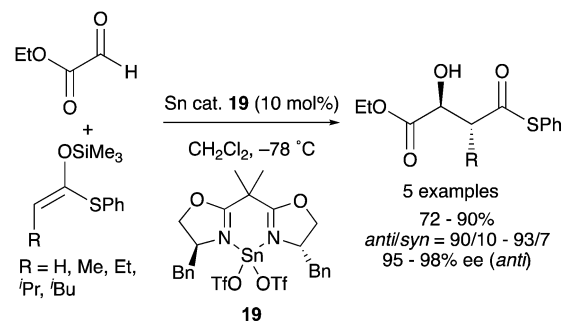
Scheme 21 Enantioselective Mukaiyama aldol-type reactions with a silicon dienolate using chiral copper catalysts.



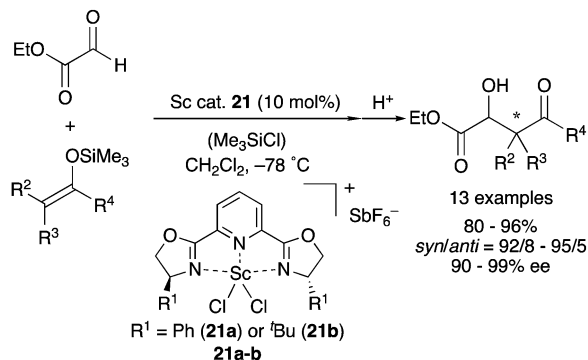
Scheme 22 Enantioselective Mukaiyama aldol reactions of pyruvates catalyzed by a chiral copper Lewis acid derived from $\text{Cu}(\text{OTf})_2$ and a box ligand.

18 prepared from $\text{Cu}(\text{OTf})_2$ and a chiral box ligand (Scheme 22).⁶⁴ They found that the enantioselective reactions proceeded at -78°C to afford the desired products in high yields with moderate to high *syn*- and enantioselectivities. Similar to the reactions of α -benzyloxyacetaldehyde, bidentate coordination to the copper center by the two carbonyl groups was believed to be important to create an excellent asymmetric environment. The *syn*-selectivity was independent of the *E/Z* geometry of the α -monosubstituted silicon enolates, and the aldol acceptors could be extended to 1,2-diketones to obtain products in high regio-, *syn*-, and enantioselectivities. Immobilized chiral copper catalyst systems were also developed and applied in enantioselective aldol reactions.^{65,66}

Evans and co-workers reported that chiral box and pybox ligands could coordinate with $\text{Sn}(\text{OTf})_2$, to generate active chiral tin Lewis acid catalysts (**19** and **20**) for Mukaiyama aldol reactions (Scheme 23).⁶⁷ The reactions of α -ketoaldehyde or α -ketoester with silicon enolates derived from thioesters



Scheme 23 Chiral tin-box and pybox complexes as catalysts for enantioselective Mukaiyama aldol reactions.



Scheme 24 Chiral scandium complex-catalyzed enantioselective Mukaiyama aldol reactions.

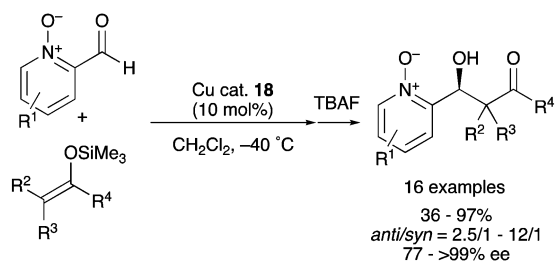
proceeded at $-78\text{ }^{\circ}\text{C}$ to afford β -hydroxy thioesters in high enantioselectivities.

In 2002, Evans and co-workers also reported a chiral scandium complex **21** for the enantioselective Mukaiyama aldol reactions of ethyl glyoxylate (Scheme 24).^{68,69} The chiral pybox ligand was found to be effective for creating an asymmetric environment around the scandium center, and the choice of the counter anion was determined to be important to achieve high enantioselection.

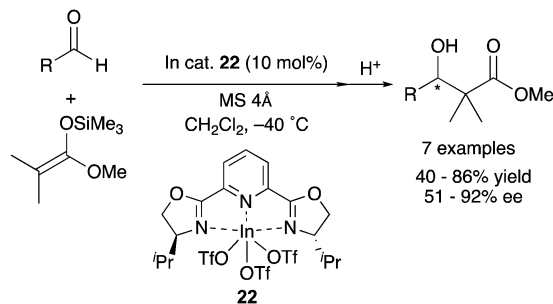
Jørgensen and co-workers reported the enantioselective Mukaiyama aldol reactions of 1-oxypyridine-2-carboxyaldehyde derivatives using a chiral copper catalyst **18** (Scheme 25).⁷⁰ The reaction proceeded smoothly to afford the desired adducts in high yields with good to high *anti*- and enantioselectivities. The *N*-oxide moiety was successfully reduced to generate *N*-free pyridine derivatives without any loss of the enantiopurity of the product.

In 2006, Loh and co-workers also reported a $\text{In}(\text{OTf})_3$ -chiral pybox **22** system for enantioselective Mukaiyama aldol reactions (Scheme 26).⁷¹ A silicon enolate, derived from methyl isobutyrate, smoothly reacted with various aldehydes to furnish β -hydroxy esters in moderate to high enantioselectivities.

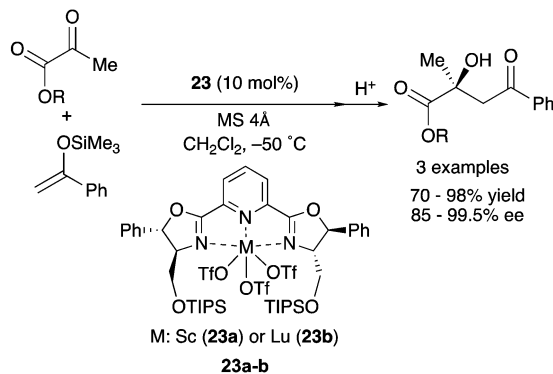
In 2006, Desimoni and co-workers investigated enantioselective Mukaiyama aldol reactions of pyruvates with a silicon enolate, prepared from acetophenone, using a chiral Lewis acid **23** derived from lanthanide triflates and a chiral pybox ligand (Scheme 27).⁷² After screening various metals, scandium and lutetium ions were found to provide the aldol adducts with the highest enantioselectivities.



Scheme 25 Chiral copper complex-catalyzed enantioselective Mukaiyama aldol reactions of 1-oxypyridine-2-carboxyaldehyde derivatives.

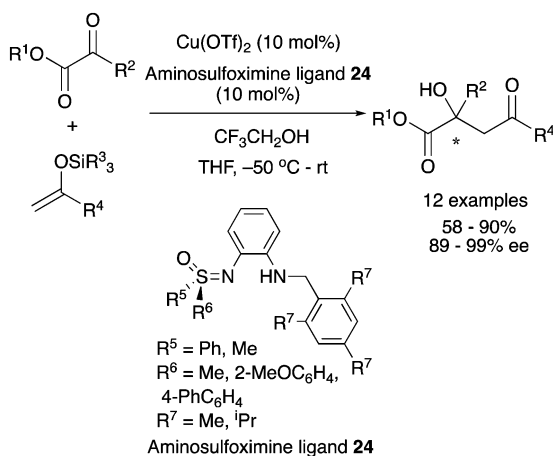


Scheme 26 Chiral indium complex-catalyzed enantioselective Mukaiyama aldol reactions.

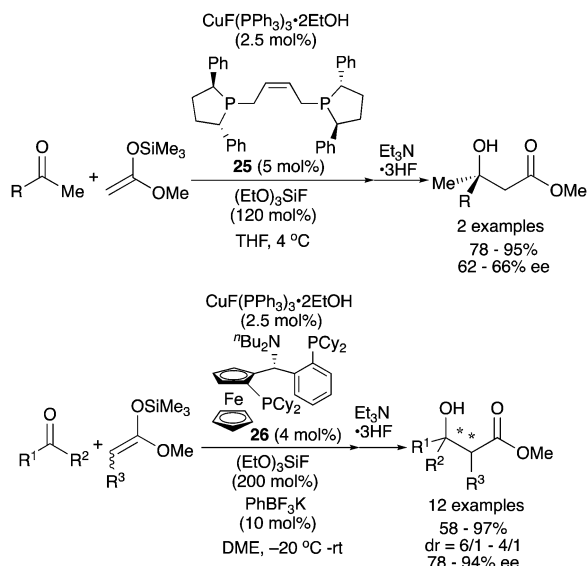


Scheme 27 Chiral scandium or lutetium complex-catalyzed enantioselective Mukaiyama aldol reactions.

2.1.1.6. Miscellaneous chiral metal complexes-catalyzed catalytic enantioselective Mukaiyama aldol reactions. Chiral Lewis acids derived from other classes of ligands have been successfully employed in various enantioselective Mukaiyama aldol reactions. In 2004, Bolm and co-workers reported enantioselective Mukaiyama aldol reactions of pyruvates using chiral copper catalysts prepared from C_1 -symmetric aminosulfoximines **24** (Scheme 28).^{73,74} They found that 2,2,2-trifluoroethanol was an effective solvent for promoting the aldol reactions, with moderate



Scheme 28 Catalytic enantioselective Mukaiyama aldol reactions using copper-chiral aminosulfoximine complexes.



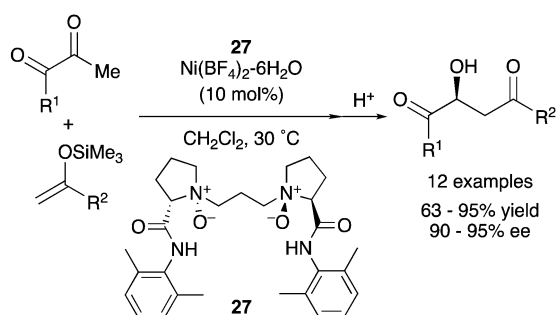
Scheme 29 Chiral CuF complexes as catalysts for the enantioselective Mukaiyama aldol-type reactions of simple ketones.

to high yields and high enantioselectivities observed for the aldol products.

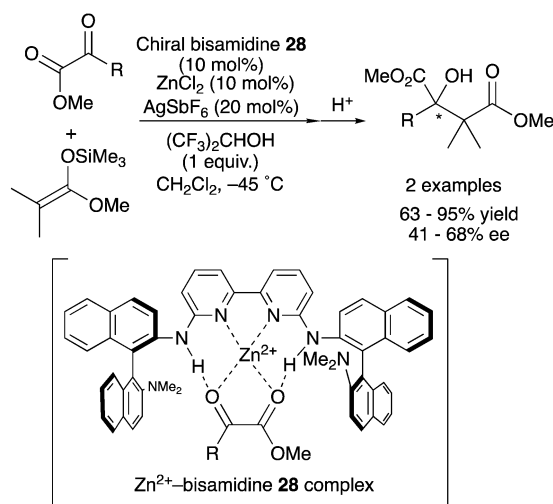
In 2005, Kanai, Shibasaki, and co-workers developed catalytic enantioselective Mukaiyama aldol reactions of ketones by using a chiral copper catalyst system (Scheme 29).^{75,76} In these reactions, the formation of chiral copper enolates was crucial, and high enantioselectivities were obtained for β-hydroxy ester. They also determined that having a stoichiometric amount of (EtO)₃SiF and a catalytic amount of PhBF₃K played an important role in promoting the catalytic process.

In 2011, Feng, and co-workers reported enantioselective Mukaiyama aldol reactions of glyoxal derivatives (Scheme 30).⁷⁷ By using a nickel Lewis acid and chiral *N,N'*-dioxide ligand 27, the reactions proceeded in good to high yields with over 90% enantioselectivities.

Yamanaka and co-workers designed and applied a chiral cationic metal-bisamidine ligand 28 for enantioselective Mukaiyama aldol reactions (Scheme 31).⁷⁸ In the proposed catalyst structure, the Lewis acidic metal and the Brønsted acid sites were situated in a manner that enabled multiple coordination to the carbonyl moieties to effectively activate α-ketoesters. They also



Scheme 30 Chiral nickel complex-catalyzed enantioselective Mukaiyama aldol reactions.

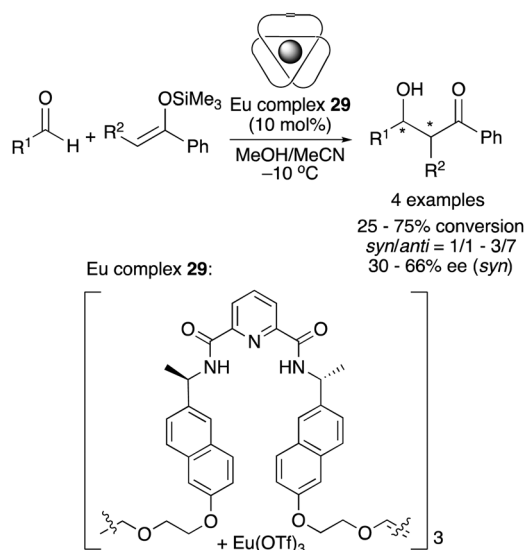


Scheme 31 Chiral zinc-bisamidine complex-catalyzed enantioselective Mukaiyama aldol reactions.

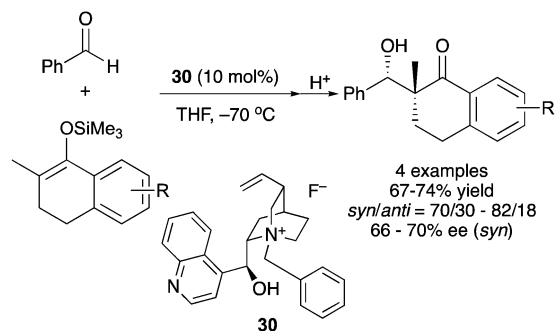
found that the use of 1 equivalent of hexafluoroisopropanol led to an improvement in the enantioselectivity of the aldol reaction.

In 2016, Leigh and co-workers reported that a chiral trefoil knot 29, derived from a tris(2,6-pyridinecarboxamide) oligomer with six chiral centers, could complex with an europium ion to generate an effective catalyst for enantioselective Mukaiyama aldol reactions (Scheme 32).⁷⁹ The oligomer was believed to fold around the europium ion to generate an overhand knot complex with a single handedness. They found that this supra-molecular complex enabled the Mukaiyama aldol reaction to proceed and could deliver the aldol adducts in good yields with moderate enantioselectivities.

2.1.2. Chiral organocatalyst-promoted reactions. While chiral metal catalysis is broadly employed in enantioselective



Scheme 32 Chiral europium trefoil knot-catalyzed enantioselective Mukaiyama aldol reactions.



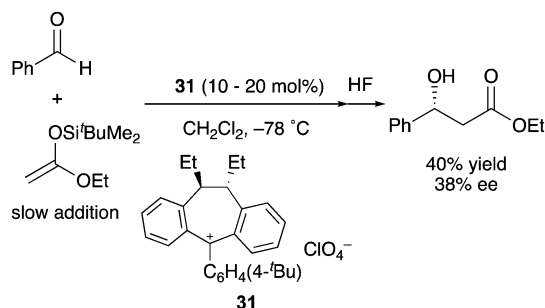
Scheme 33 Enantioselective Mukaiyama aldol reactions catalyzed by a cinchonidine-derived quaternary ammonium fluoride.

Mukaiyama aldol reactions, the use of chiral organocatalysts has gained some attention. In 1993, Shioiri and co-workers reported that a cinchonidine-derived quaternary ammonium salt **30** promoted the enantioselective Mukaiyama aldol reactions of silicon enolates derived from 2-methyl-1-tetralone derivatives with benzaldehyde (Scheme 33).⁸⁰ The desired products were obtained in good yields with good enantioselectivities.

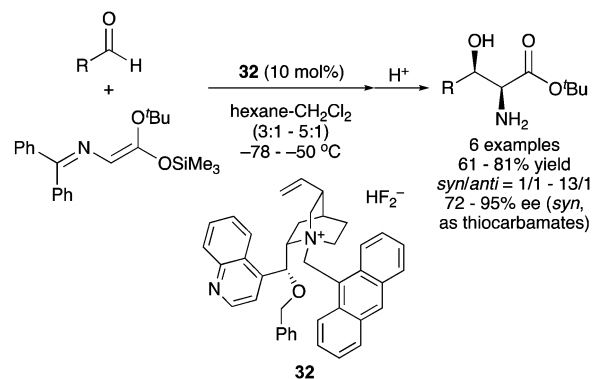
In 1997, Chen and co-workers reported the chiral triaryl-carbenium ion **31** as a catalyst for enantioselective Mukaiyama aldol reactions (Scheme 34).⁸¹ Although the enantioselectivity obtained was not high, this was an important example of a chiral triarylcarbenium ion-catalyzed enantioselective Mukaiyama aldol reaction.

In 1999, Corey and co-workers employed a cinchonidine-derived quaternary ammonium salt **32** for catalytic enantioselective Mukaiyama aldol reactions using a silicon enolate derived from a glycine Schiff base (Scheme 35).⁸² A mixed solvent system, prepared from hexane and dichloromethane, was found to be effective for the reaction, and moderate to good *syn* and good to high enantioselectivities were obtained in the reactions with aliphatic aldehydes.

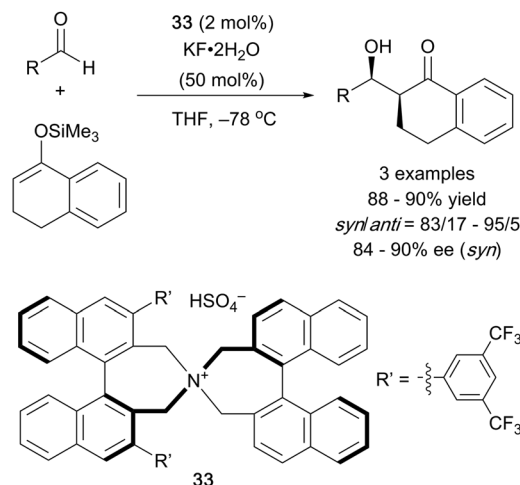
In 2001, Maruoka and co-workers applied a chiral quaternary ammonium fluoride, bearing binaphthyl skeletons as a catalyst, for enantioselective Mukaiyama aldol reactions (Scheme 36).⁸³ A silicon enolate prepared from 1-tetralone reacted with aromatic aldehydes to afford the desired adduct with good to high enantioselectivities. The active fluoride species was prepared from KF·2H₂O and the chiral quaternary ammonium hydrogen sulfate **33** *in situ*.



Scheme 34 Chiral triarylcarbenium ion-catalyzed enantioselective Mukaiyama aldol reactions.



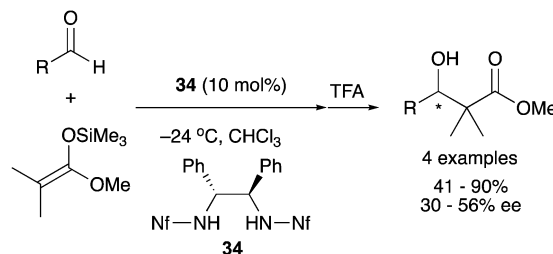
Scheme 35 Chiral quaternary ammonium salt-catalyzed enantioselective Mukaiyama aldol reactions.



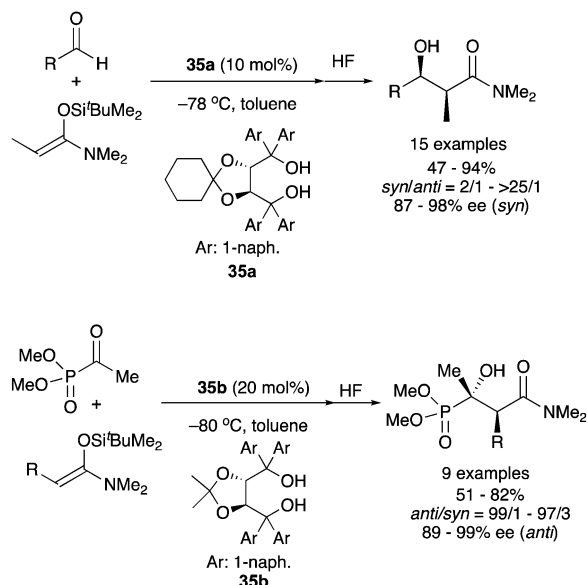
Scheme 36 Enantioselective Mukaiyama aldol reactions catalyzed by chiral quaternary ammonium fluoride.

In 2005, Jørgensen and co-workers developed enantioselective Mukaiyama aldol reactions using a chiral acid capable of undergoing hydrogen bonding as an organocatalyst (Scheme 37).⁸⁴ The chiral bis-sulfonamide derivative **34** was found to promote the reaction to afford the desired adducts in moderate to high yields with moderate enantioselectivities.

In 2006, Rawal and co-workers developed a $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL) derivative for enantioselective Mukaiyama aldol reactions (Scheme 38).⁸⁵ TADDOL



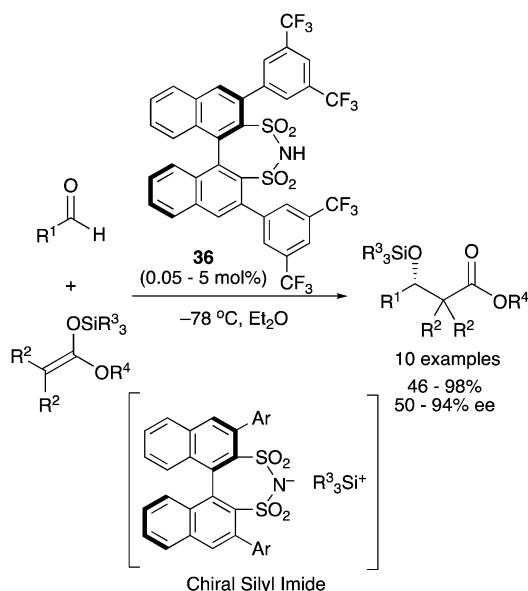
Scheme 37 Chiral bis-sulfonamide-catalyzed enantioselective Mukaiyama aldol reactions.



Scheme 38 TADDOL-catalyzed enantioselective Mukaiyama aldol reactions.

catalyst **35a** was found to activate several aldehydes *via* hydrogen bonding and promoted enantioselective aldol reactions with a silicon enolate derived from *N,N*-dimethylpropionamide. The reactions were shown to proceed at $-78\text{ }^{\circ}\text{C}$ to afford the desired *syn*-aldol adducts in good to high diastereo- and enantioselectivities. Also, they applied the catalyst **35b** with enantioselective aldol reactions with α -ketophosphonate as the aldol acceptor (Scheme 38).⁸⁶

In 2009, List and co-workers developed a chiral bis-sulfonamide **36** with a BINOL backbone as a chiral Brønsted acid for enantioselective Mukaiyama aldol reactions (Scheme 39).⁸⁷ The aldol reactions proceeded smoothly in high yields with



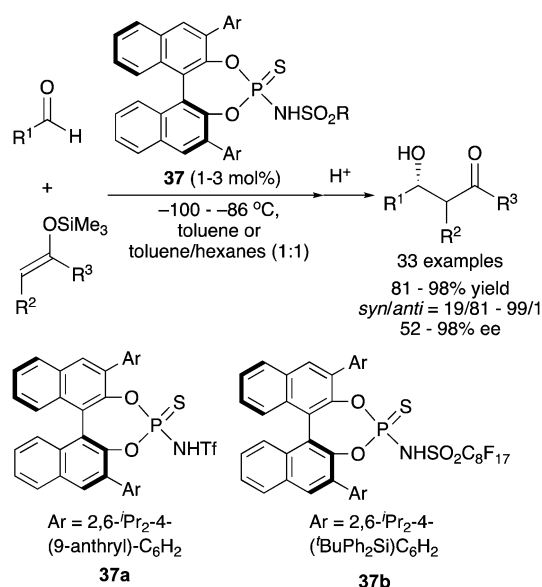
Scheme 39 Enantioselective Mukaiyama aldol reactions mediated by a chiral bis-sulfonamide with a BINOL motif.

high enantioselectivities. In the proposed mechanism, the chiral bis-sulfonamide initially reacted with the silicon enolate to produce *N*-silyl imide species, and then the resulting silyl cation species activated the aldehyde, with the enantioselection determined by the counter chiral imide anion *via* a chiral counter-anion effect.

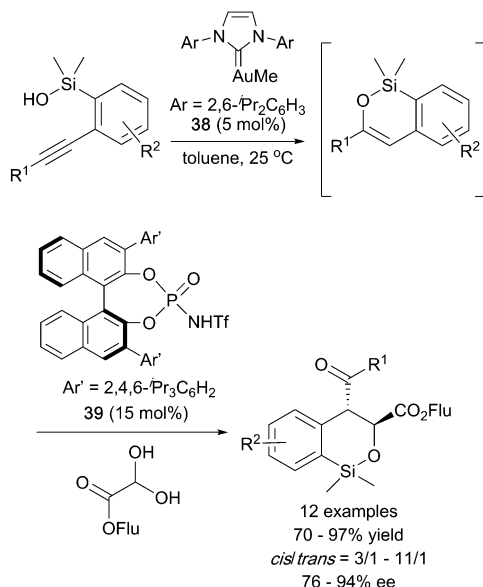
In 2010, Yamamoto and co-worker reported that the chiral triflylthiophosphoramidate **37a** could catalyze enantioselective Mukaiyama aldol reactions. By using a strong chiral acid, the desired reactions proceeded at very low temperatures to afford the aldol adducts in high yields with moderate to high enantioselectivities (Scheme 40).⁸⁸ Mechanistic studies indicated that the actual catalyst was a Brønsted acid species, not silylated species as reported by List.⁸⁷ They further optimized the catalyst structure (**37b**), and found that introducing a perfluoroalkyl group on the sulfonamide and *tert*-butyldiphenylsilyl groups on the 3,3'-positions of the aromatic groups led to significantly improved reactivities and higher enantioselectivities for the Mukaiyama aldol reaction.⁸⁹

In 2013, Gong and co-workers reported enantioselective Mukaiyama aldol reactions using *in situ*-formed silicon enolates, which were prepared by the intramolecular hydrosilylation of alkynes mediated by a gold complex **38** (Scheme 41).⁹⁰ In the presence of a chiral triflylphosphoramidate catalyst **39**, enantioselective aldol reactions with a glyoxylate equivalent proceeded smoothly to afford the desired products in good to high yields with good to high enantioselectivities.

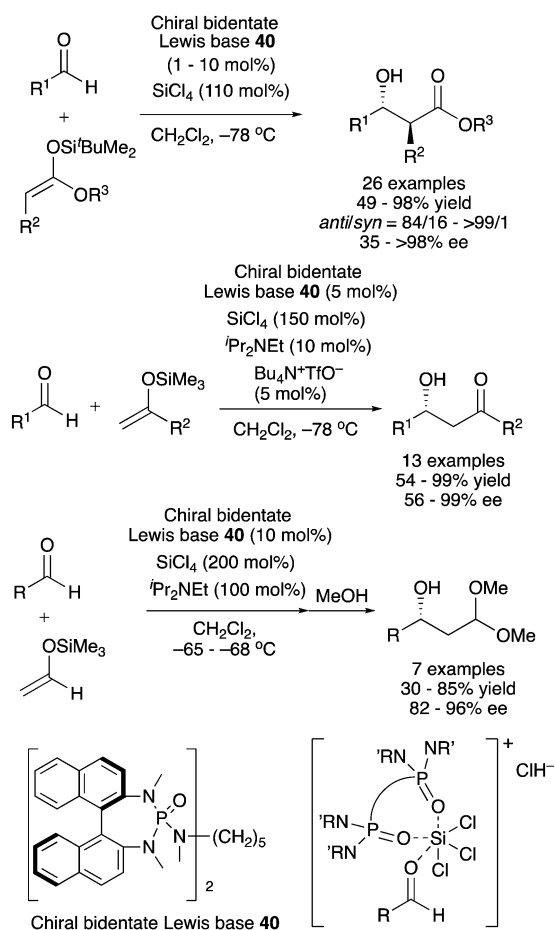
2.1.3. Chiral Lewis base-activated Lewis acid-mediated reactions. In 2002, Denmark and co-workers reported enantioselective Mukaiyama aldol reactions using optically active Lewis base **40**-activated Lewis acids as a chiral promoter (Scheme 42).⁹¹⁻⁹⁴ Different from typical chiral Lewis acid catalyst systems, they employed a stoichiometric amount of an achiral Lewis acid and a catalytic amount of a chiral Lewis base **40**. In this catalytic



Scheme 40 Enantioselective Mukaiyama aldol reactions mediated by chiral phosphoramidates with a BINOL backbone.



Scheme 41 Enantioselective relay catalytic cascade involving intramolecular hydrosilylations and Mukaiyama aldol reactions.



Scheme 42 Enantioselective Mukaiyama aldol reactions using chiral Lewis base-activated Lewis acids.

system, the chiral Lewis base formed an adduct with the weak Lewis acid to generate a stronger chiral Lewis acidic moiety that could act as the true catalyst for the Mukaiyama aldol reaction. Previously, Denmark developed chiral Lewis base catalysts for the activation of trichlorosilyl enolates for enantioselective aldol reactions (*vide infra*), and, in this work, they applied the chiral Lewis base **40** as a catalyst for this aldol reaction. They found that the desired reactions proceeded well, in the presence of amine bases, to provide aldol adducts in moderate to high yields with moderate to high enantioselectivities. Not only silicon enolates prepared from esters, but also those derived from methyl ketones and aldehydes were also shown to be compatible aldol donors.

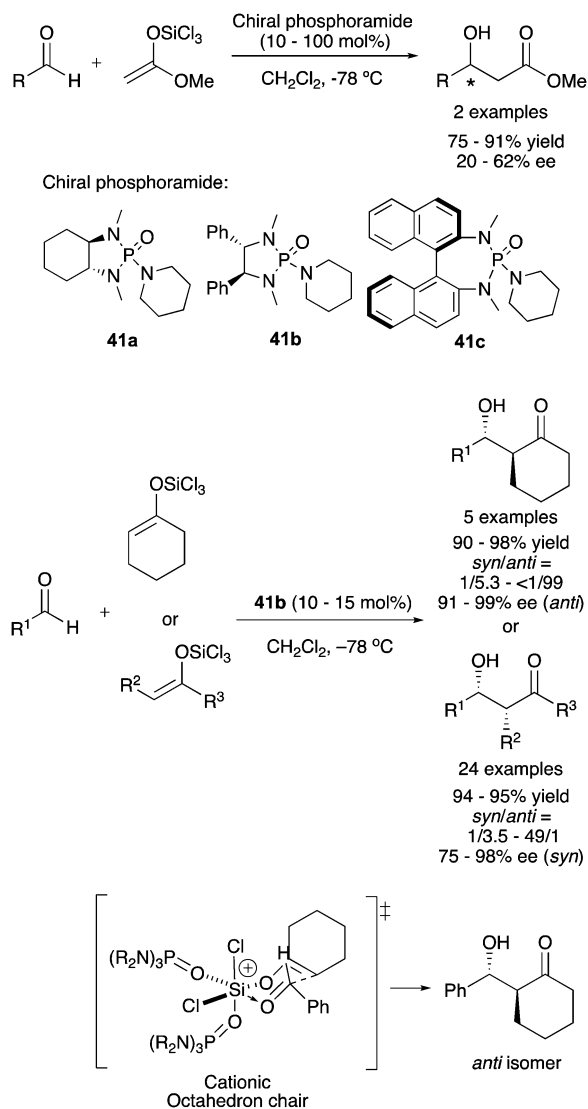
2.2. Catalytic enantioselective Mukaiyama aldol reactions of trihalo- and trialkoxy silicon enolates

Compared with the trialkylsilyl group, trihalo- and trialkoxysilyl groups are less stable, but they are more amenable to undergo coordination with Lewis bases. Therefore, it was anticipated that the coordination of a chiral Lewis base moiety to trihalo- and trialkoxysilicon enolates would generate chiral enolates with higher nucleophilicity for addition reactions.

In 1996, Denmark and co-workers developed various catalytic enantioselective Mukaiyama aldol-type reactions with trichlorosilicon enolates in the presence of chiral Lewis base organocatalysts **41a–c** (Scheme 43).^{95–108} They proposed that silicon enolate moieties capable of expanding its valence, by forming a complex with one or two chiral Lewis bases, were essential for catalytic enantioselective processes and consequently designed various optically active phosphoramidates as potential chiral Lewis base catalysts. The aldol reactions of reactive trichlorosilicon enolate, derived from acetates, were investigated, but insufficient enantioselectivities were obtained due to the background reactions occurring even at –80 °C. On the other hand, by utilizing trichlorosilicon enolates derived from ketones, the aldol reactions proceeded with high enantioselectivities. In their proposed reaction mechanism, they suggested that the aldol reactions proceeded through a cyclic transition state and that the *E*-enolate resulted in *anti*-adducts as the major products, while the *Z*-enolate led to the *syn*-adducts as the major products. They revealed that two chiral Lewis bases were coordinated to the silicon atom, and controlled the stereoselectivities in the higher catalyst loading reactions. In addition, the aldol reactions were investigated using optically active chiral aldehydes or ketone enolates, and high diastereoselectivities were observed.

Denmark and co-workers also reported catalytic, diastereoselective, and enantioselective cross-aldol reactions between aldehydes and silicon enolates derived from aldehydes (Scheme 44).^{109–112} Both *E*- and *Z*-trichlorosilyl enolates of aldehydes provided the *anti*- and *syn*-cross aldol products, respectively, in moderate to high yields with moderate to high enantioselectivities. It was noteworthy that the use of a chiral bidentate Lewis base **40** as the catalyst was critical for achieving useful enantioselectivities.

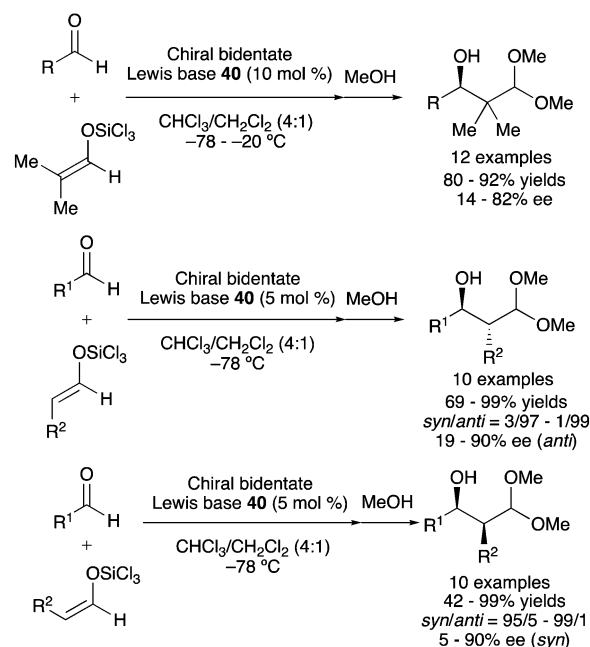
In 2003, Nakajima and co-workers reported enantioselective Mukaiyama aldol-type reactions of trichlorosilicon enolates



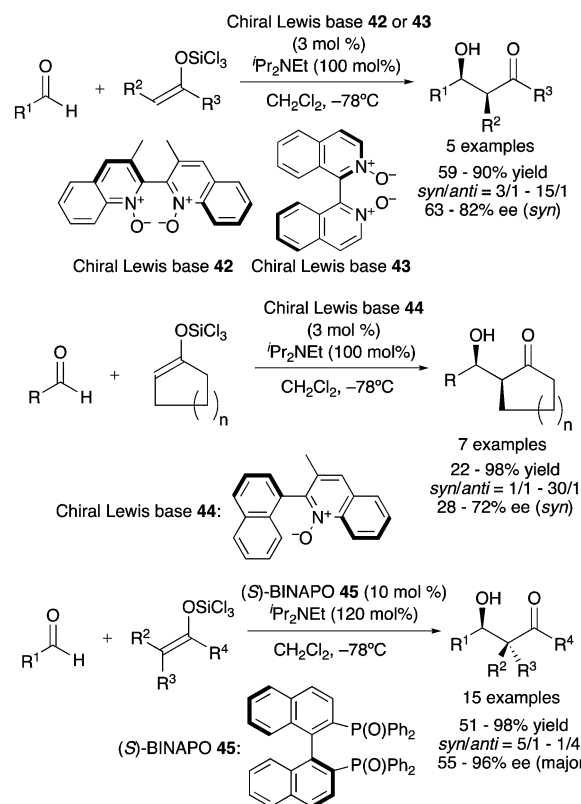
Scheme 43 Enantioselective Mukaiyama aldol reactions of trichlorosilicon ester and ketone enolates using chiral monodentate Lewis base catalysts.

with aldehydes using chiral Lewis bases as the catalysts. The chiral monodentate *N*-oxide **44** or bidentate *N*-oxides **42–43** were effective for the aldol reactions, with good enantioselectivities obtained in most cases (Scheme 45).^{113–115} They also found that the BINAP oxide (BINAPO) **45** was a good chiral bidentate Lewis base catalyst, whereby the aldol reactions proceeded in moderate to high yields with moderate to high diastereo- and enantioselectivities.

Related to the aldol reactions of trichlorosilicon enolates, catalytic enantioselective Mukaiyama-type aldol reactions of trimethoxysilicon enolates have also been reported. In 2000, Yamamoto and co-workers developed tol-BINAP-AgF **46**-catalyzed Mukaiyama-type aldol reactions using trimethoxysilicon enolates, in which the desired reactions proceeded to provide the aldol adducts in moderate to good yields with moderate to high *syn*- and enantioselectivities (Scheme 46).¹¹⁶ In their proposed reaction mechanism, they suggested the reaction proceeded *via* a cyclic transition state, in which the fluoride anion of the

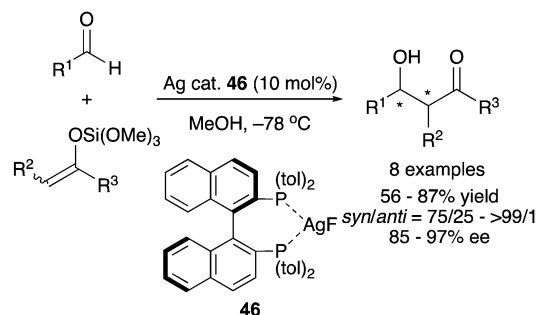


Scheme 44 Enantioselective Mukaiyama aldol reactions with trichlorosilicon aldehyde enolates using a chiral bidentate Lewis base catalyst.



Scheme 45 Enantioselective Mukaiyama aldol reactions with trichlorosilicon enolates using chiral *N*-oxide and *P*-oxide catalysts.

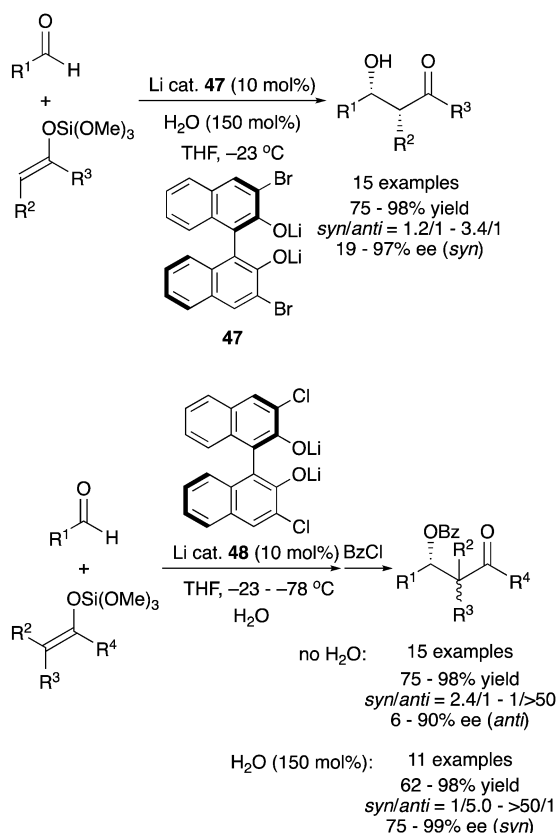
chiral silver catalyst activated the trimethoxysilyl group, while the silver atom acted as a Lewis acid to activate the aldehyde oxygen. They further reported that a BINAP/AgOTf/KF/18-crown-6



Scheme 46 Enantioselective Mukaiyama aldol reactions with trimethoxy-silicon enolates using a chiral silver fluoride catalyst.

ether system could be utilized for asymmetric aldol reactions.¹¹⁷ In this reaction, the BINAP–AgOTf complex and KF–18-crown-6 system worked independently, and the reactions proceeded *via* a similar transition state, but with the *E*-enolate resulting in *anti*-isomers as the major products.

In 2004, Nakajima and co-workers reported catalytic enantioselective Mukaiyama-type aldol reactions of trimethoxysilicon enolates using lithium binaphtholates **47** and **48** as chiral catalysts (Scheme 47).^{118,119} They found that the addition of water to the reaction system improved the *syn*-selectivity, while under anhydrous conditions, *anti*-isomers were obtained as the major products. Moreover, they investigated the aldol reactions

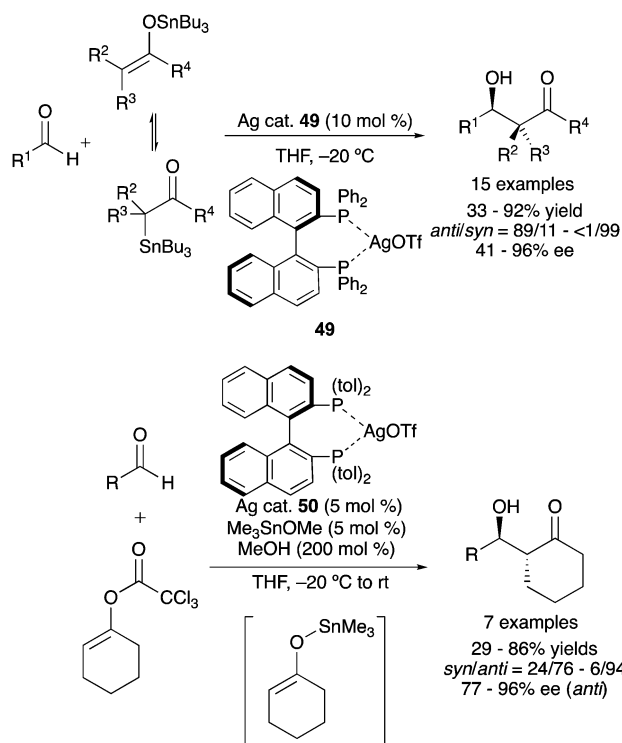


Scheme 47 Enantioselective Mukaiyama aldol-type reactions with trimethoxysilicon enolates using lithium binaphtholates.

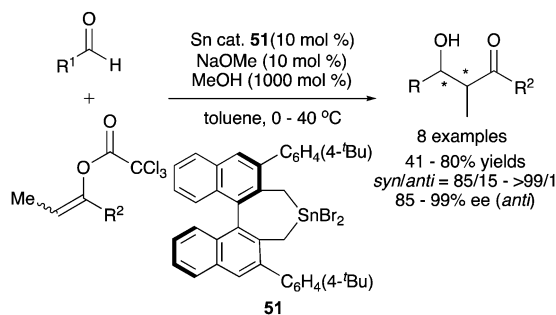
to construct quaternary carbon centers, and observed high enantioselectivities in these cases (Scheme 47).¹²⁰

2.3. Catalytic enantioselective aldol reactions of tin, boron, and other enolates

Not only silicon enolates, but also other stable metal or metalloid enolates have been shown to be suitable aldol donors for Mukaiyama-type aldol reactions. In 1997, Yamamoto and co-workers reported catalytic enantioselective aldol-type reactions of tin enolates with aldehydes in the presence of a AgOTf–BINAP complex **49** (Scheme 48).¹²¹ The two different enolates, *O*- or *C*-tin enolates, were prepared from enol acetate and Bu₃SnOMe in the absence of a solvent. In the presence of the chiral silver complex, the Mukaiyama-type aldol reactions proceeded at –20 °C to provide the corresponding optically active β-hydroxy ketones in good yields with good diastereo- and enantioselectivities. The reaction was believed to proceed *via* a cyclic 6-membered transition state, with the geometries of the enolates significantly influencing the *syn*- and *anti*-selectivities of the aldol products. Furthermore, they reported the first example of an aldol-type reaction using a catalytic amount of tin enolate in an asymmetric version with the BINAP–silver(I) complex **50** as a catalyst (Scheme 48).^{122,123} They observed a rapid formation of the tin enolate from enol trichloroacetate following treatment with Bu₃SnOMe at –20 °C in THF, which indicated that the catalytic use of trialkyltin methoxide to activate enol trichloroacetates was possible. Finally the introduction of Me₃SnOMe as a co-catalyst led to higher reactivity. They also reported that Bu₂Sn(OMe)₂ was a more effective co-catalyst for the aldol reactions of aliphatic aldehydes.¹²⁴



Scheme 48 Enantioselective aldol reactions with tin enolates using chiral silver Lewis acid catalysts.

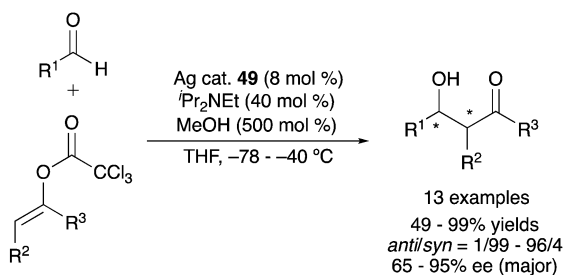


Scheme 49 Enantioselective aldol reactions with enol trichloroacetate using a chiral tin catalyst.

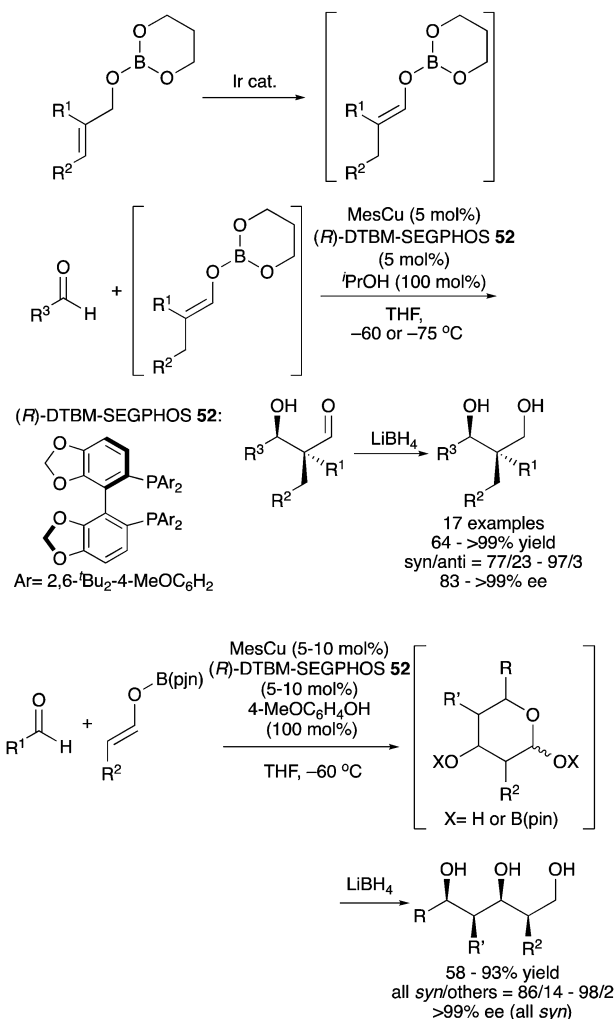
In 2009, Yanagisawa and co-workers developed chiral tin catalysts for Mukaiyama-type aldol reactions between aldehydes and enol trichloroacetates (Scheme 49).¹²⁵ They found that the BINOL derived-tin compound **51** was an effective catalyst for the enantioselective aldol reaction, and they proposed that the enol trichloroacetates underwent transmetalation with the catalyst to generate the reactive chiral tin enolate, which then underwent addition with the aldehyde to provide aldol adducts in moderate to high yields with high *syn*- and enantioselectivities. An isatin derivative was also found to be an effective aldol acceptor for this catalytic enantioselective aldol reaction.

In 2014, Yanagisawa and co-workers further developed a chiral silver complex as a catalyst for Mukaiyama-type aldol reactions with enol trichloroacetate without the need to use catalytic amounts of tin species (Scheme 50).¹²⁶ It was suggested that the enol trichloroacetate underwent transmetalation with the AgOTf-BINAP complex **49**, with the aid of methanol, to form a chiral silver enolate, which then further reacted with aldehydes to furnish the aldol adducts in good to high enantioselectivities.

In 2015, Kanai, Matsunaga, and co-workers developed catalytic enantioselective aldol reactions using boron enolates obtained from allylic alcohols (Scheme 51).¹²⁷ The cross-aldol reactions proceeded with good to high diastereoselectivities and high enantioselectivities when a chiral copper complex, prepared from a bulky bisphosphine ligand, DTBM-SEGPHOS **52**, was used as the catalyst. Furthermore, an enantioselective double-aldol reaction was possible using this catalyst system, and chiral triol products were obtained with high stereoselectivities. Catalytic stereoselective aldol reactions of optically



Scheme 50 Enantioselective aldol reactions with enol trichloroacetate using a chiral silver catalyst.



Scheme 51 Enantioselective aldol reactions with *in situ*-formed boron enolates using a chiral copper catalyst.

active aldehydes were also possible, and it was found that utilizing the opposing enantiomer could lead to a change in the diastereomeric outcome of the aldol products.

3. Catalytic enantioselective direct-type aldol reactions using metal catalysts

Although the use of preformed enolates overcomes the selectivity issues faced in cross-aldol reactions, direct-type aldol reactions represent the ideal organic transformation from a viewpoint of atom economy. However, overcoming these issues by careful control of the reaction conditions and catalyst design have enabled chemists to achieve catalytic enantioselective direct aldol reactions.

The use of metal complexes to catalyze direct aldol reactions, including enantioselective variants, has been an area of intense study since the 1980s. The inspiration for the design of artificial metal catalysts for direct aldol reactions may have originated from type II aldolases, which possess a zinc ion cofactor to facilitate deprotonation.¹²⁸ The early development

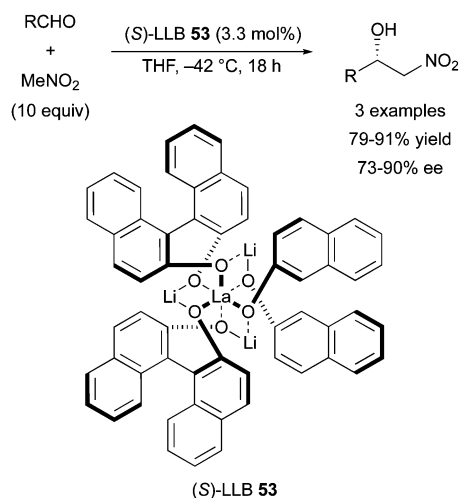
of chiral metal catalysts for direct enantioselective aldol reactions focused on Lewis acidic metal complexes. These metal catalysts are designed to activate the electrophile and/or facilitate enolate formation from an aldol donor, with the chiral environment surrounding the metal–ligand complex controlling the enantioselectivity of the aldol reaction. On the other hand, one of the most important factors for direct aldol reactions is undoubtedly the efficient formation of active enolate species. The function of the metal catalysts for direct aldol reactions is not limited to a simple Lewis acidic activation of substrates, and many unique strategies to generate active enolates by metal catalysts are possible.

3.1. Reaction of non-activated ketones and aldehydes

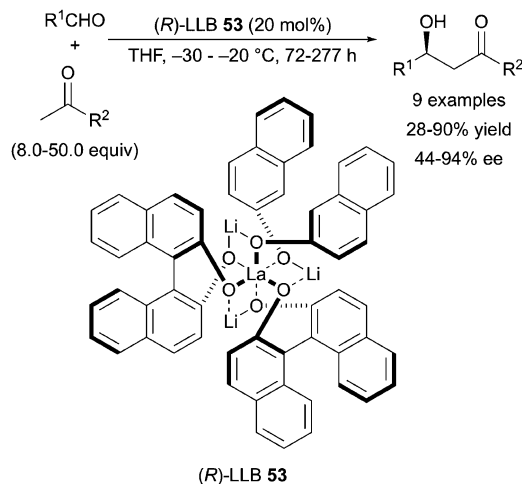
In this section, enantioselective direct aldol reactions of unactivated ketones, such as acetone, cyclohexanone, and acetophenone, are described. The substrate structures are rather simple, and so they were mainly studied during the early stage of development of catalytic enantioselective direct aldol reactions. This chapter focuses on the use of chiral metal complexes as catalysts, whereby the chiral environment is created around the active metal center and the chiral metal complex directly influences the stereo-determining step.

3.1.1. Chiral metal complex-based catalysts. An important advance in chiral metal complexes for direct aldol reactions was the work by Shibasaki and co-workers, who in 1992, demonstrated that the lanthanum–lithium–tris(binaphthoxide) (LLB) complex **53**, possessing both Lewis acidity and Brønsted basicity, could act as an efficient catalyst for enantioselective nitro-aldol reactions (Scheme 52).¹²⁹

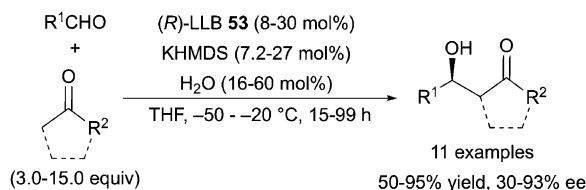
Subsequently, Shibasaki and co-workers reported the first example of enantioselective direct aldol reactions of unactivated ketones and aldehydes catalyzed by (*R*)-LLB **53** (Scheme 53).¹³⁰ Although a high enantioselectivity was achieved for the aldol reaction between *tert*-butyl aldehyde and acetophenone, other substrates gave moderate selectivities, and very long reaction times were required.



Scheme 52 Chiral rare earth metal alkoxide-catalyzed nitro-aldol reactions.



Scheme 53 Heterobimetallic complex-catalyzed aldol reactions of unactivated ketones and aldehydes.

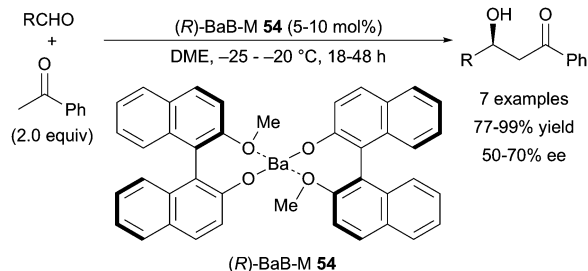
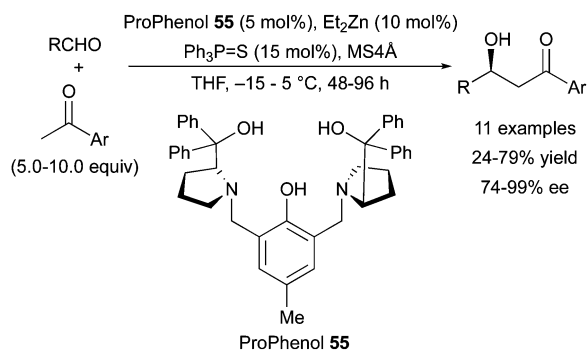


Scheme 54 Improved LLB catalyst for aldol reactions.

The same group improved their LLB **53** catalyst systems by the addition of catalytic amounts of KHMDS and H₂O (Scheme 54).¹³¹ The self-assembly of LLB **53** and KOH, generated *in situ* from KHMDS and H₂O, was believed to have occurred, and this new catalyst system successfully improved the reaction conditions by decreasing the catalyst loading, the equivalent of ketones needed, and the reaction time, compared with the previous LLB **53** system. The substrate generality of aliphatic aldehydes was surveyed and they found that tertiary aldehydes gave excellent enantioselectivities, while secondary and primary aldehydes led to low enantioselectivities. In the case of ketones, acetone, methylethyl ketone, and cyclopentanone were shown to be suitable substrates. In the case of cyclopentanone, the *syn*-product was obtained in a high yield and diastereoselectivity (93:7). These protocols were also applied to the synthesis of natural products, such as epothilone A and B.¹³²

In 1998, Shibasaki and co-workers reported the (*R*)-2-hydroxy-2'-methoxy-1,1'-binaphthyl (BINOL-Me)-based Ba(II) complex (BaB-M **54**) as a catalyst for the enantioselective aldol reactions of acetophenone (Scheme 55).¹³³ They found that the amount of the ketone could be successfully reduced to 2.0 equivalents when the aldol reaction was performed with several aliphatic aldehydes. However, the enantioselectivities of the aldol adducts were moderate. They determined the catalyst structure by LDI-TOF-MS and NMR, which suggested the Lewis acidic nature of the catalyst.

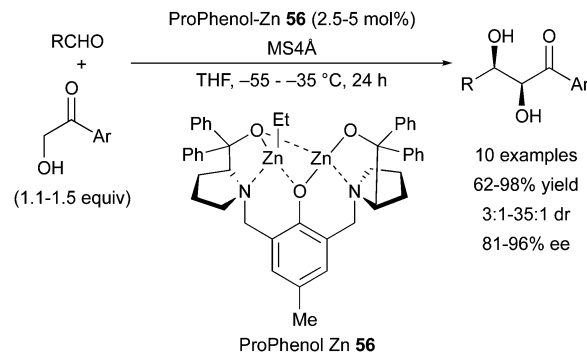
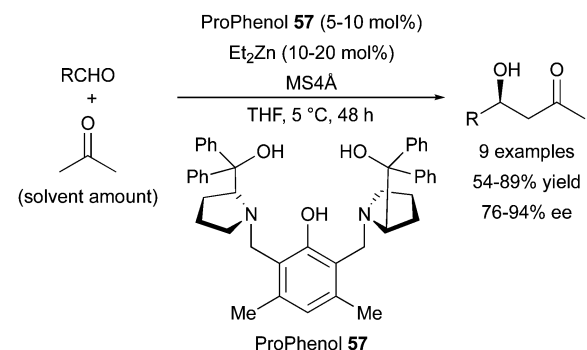
In 2000, Trost and co-workers reported a dinuclear zinc(II) complex that was able to catalyze enantioselective aldol

Scheme 55 Ba(II) complex **54**-catalyzed aldol reaction of acetophenone.

Scheme 56 Dinuclear zinc(II)-catalyzed aldol reactions of methyl aryl ketones and aliphatic aldehydes.

reactions of methyl aryl ketones and aliphatic aldehydes (Scheme 56).¹³⁴ They designed a ligand that incorporated a phenoxide moiety as a base and a semicrown structure to facilitate a facile catalyst turnover to overcome potential product inhibition. The proline-based chiral ligand, ProPhenol **55**, was then synthesized and examined for enantioselective direct aldol reactions. The *in situ*-prepared zinc complex provided the highest enantioselectivity in the presence of a phosphine sulfide additive, which may have helped with catalyst turnover by displacing the product from the catalyst intermediate. They demonstrated that reactions with various branched aldehydes could be achieved with excellent enantioselectivities, while a linear aldehyde led to a low yield and moderate enantioselectivity (24% yield, 74% ee). The stoichiometry of the metal to ligand was determined by the evolution of ethane gas and, based on their studies, a bimetallic structure was proposed.

In 2001, the same group applied the ProPhenol–zinc complex **56** as a catalyst for enantioselective aldol reactions of aromatic α -hydroxyketones and aliphatic aldehydes (Scheme 57).¹³⁵ The reactions of α -hydroxyketones proceeded smoothly with a low catalyst loading (2.5 mol%) and in the absence of a phosphine sulfide additive. Under the optimized conditions, various aldehydes, including primary aldehydes, were converted to the corresponding *syn*-diols in high yields, good to high diastereoselectivities, and high enantioselectivities. The excellent selectivity was rationalized by the proposed model of the enolate of the α -hydroxyketone, which acted as a bidentate ligand to bridge the two zincs, while the proposed structure of the zinc complex **56** was supported by ESI-MS analysis. This catalyst was

Scheme 57 Dinuclear zinc(II)-catalyzed aldol reactions of aromatic α -hydroxyketones.

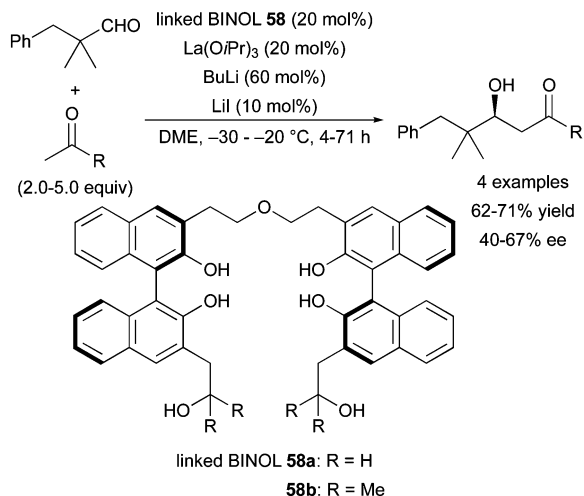
Scheme 58 Dinuclear zinc(II)-catalyzed aldol reactions of acetone.

also applied for the synthesis of a polyhydroxylated natural product, boronolide.¹³⁶

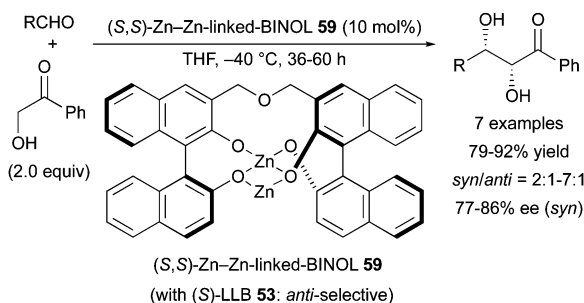
In the same year, the same group reported ProPhenol–zinc complex-catalyzed enantioselective cross-aldol reactions between acetone and aldehydes (Scheme 58).¹³⁷ A modified ligand, 3,5-dimethylphenol-based ProPhenol **57**, was examined and the resulting zinc complex demonstrated, in most cases, greater performance than the catalyst derived from the previous ligand **55**. Various aldehydes, including linear aldehydes and aromatic aldehydes, were applied for the reaction with acetone to afford β -hydroxy ketones in high yields and enantioselectivities.

In 2001, Shibasaki and co-workers developed linked-BINOL-based heterobimetallic catalysts for enantioselective aldol reactions (Scheme 59).¹³⁸ These designed catalysts possessed a metal center as a Lewis acid and a covalently attached alkoxide as a Brønsted base, which could be varied without changing the framework of the complexes. The catalyst prepared from $\text{La}(\text{O}^i\text{Pr})_3$, $n\text{-BuLi}$, and ligand **58a** was found to be a good catalyst for enantioselective aldol reactions of a tertiary aldehyde, and they also found that the addition of LiI slightly improved the enantioselectivities of the aldol adducts. For the aldol reaction with 3-pentanone, the catalyst prepared from linked BINOL **58b** provided better results, with an *anti*-product obtained in moderate selectivities.

In the same year, the same group reported the enantioselective aldol reactions of 2-hydroxyacetophenone to access either *syn*- or *anti*- α,β -dihydroxy ketones (Scheme 60).¹³⁹ In the presence of

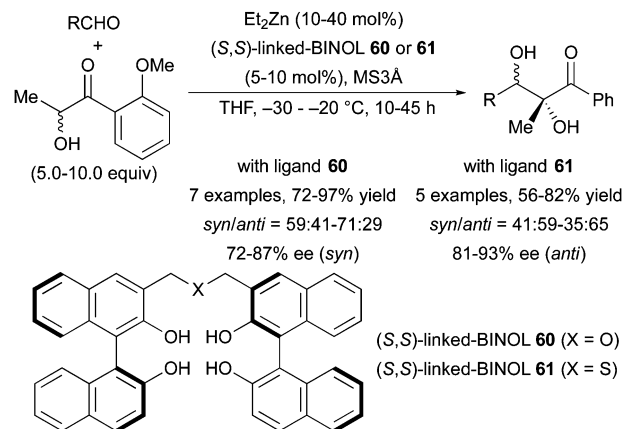


Scheme 59 Linked BINOL–lanthanum/lithium-catalyzed aldol reactions.

Scheme 60 Linked BINOL–zinc-catalyzed aldol reactions of α -hydroxyketones.

$(S)\text{-LLB } 53$ modified with KHMDs and H_2O , *anti*-diols were obtained in excellent enantioselectivities (90–95% ee) when primary aldehydes were utilized as substrates. They found that secondary or tertiary aldehydes led to unsatisfactory results using $\text{LLB } 53$ as a catalyst. However, a zinc–zinc-linked-BINOL complex **59**, prepared from Et_2Zn , as a catalyst enabled the aldol reaction to occur with various aliphatic aldehydes, including primary and secondary aldehydes, to provide *syn*-diols in good diastereo- and enantioselectivities. When substituents were introduced on the benzene ring of 2-hydroxyacetophenone, the enantioselectivities were improved, and it was found that enantioselective aldol reactions with 2-hydroxy-2'-methoxyacetophenone proceeded with excellent enantioselectivities (87–99% ee) when zinc–zinc-linked-BINOL **59** was used as a catalyst.^{140,141} Shibasaki proposed that the chelation between the methoxy group, zinc, and substrate could explain the improvements observed for the selectivity of the aldol reaction.

In 2003, detailed mechanistic studies of the linked-BINOL chiral zinc catalyst were investigated.¹⁴² These revealed that a complicated oligomeric zinc-rich complex, such as a hepta-nuclear zinc complex, could be the actual active species. Based on these results, the catalyst system was improved further and a second-generation catalyst, derived from Et_2Zn /linked-BINOL **60** 4/1 with MS3A , was developed. With the improved system,

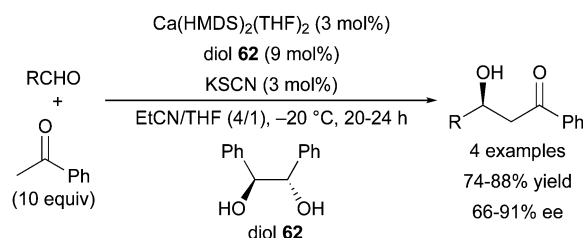


Scheme 61 Linked BINOL–zinc-catalyzed aldol reactions of 2-hydroxy-2'-methoxypropiophenone.

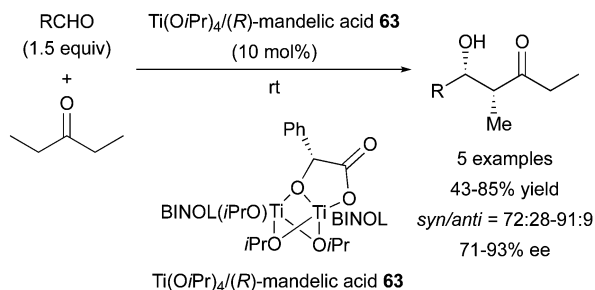
using as little as 0.1 mol% of ligand and 0.4 mol% of Et_2Zn efficiently promoted the asymmetric aldol reaction. Moreover, the new systems were applied for the enantioselective aldol reactions of 2-hydroxy-2'-methoxypropiophenone, and various *syn*-diols with a chiral tetrasubstituted carbon centers were obtained in good enantioselectivities (Scheme 61). A sulfur-linked BINOL **61** was then examined, and the corresponding *anti*-diols were obtained in high enantioselectivities. However, it was noted that the diastereoselectivities were still low in both systems.

In 2001, Noyori and co-workers reported a calcium(II)–chiral hydrobenzoin **62** complex as a catalyst for the enantioselective aldol reactions of acetophenone (Scheme 62).¹⁴³ The addition of KSCN was necessary to increase the enantioselectivity of the aldol reaction. Branched aliphatic aldehydes provided the aldol adducts in good enantioselectivities, although a linear aldehyde showed poor reactivity and selectivity. Based on CSI-MS analysis, a highly aggregated chiral complex consisting of three catalytic components was proposed.

In 2002, Mahrwald reported a titanium(IV) alkoxide/mandelic acid/racemic BINOL complex **63** as a catalyst for the enantioselective aldol reactions of 3-pentanone (Scheme 63).¹⁴⁴ Several aldehydes, including an aromatic aldehyde, a linear aliphatic aldehyde, and an ynol, were found to be suitable substrates to afford the corresponding *syn*-adducts in good to high diastereo- and enantioselectivities. The structure of complex **63** was postulated based on X-ray analysis of the $\text{Ti}(\text{O}i\text{Pr})_4$ /mandelic acid complex.



Scheme 62 Calcium(II)-catalyzed aldol reactions of acetophenone.



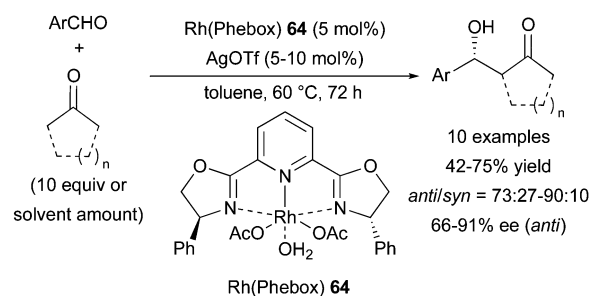
Scheme 63 Titanium(IV)-catalyzed aldol reactions of 3-pentanone.

In 2003, Calter reported a chiral tetramethyldiaminocyclohexane- $\text{Zn}(\text{NO}_3)_2$ complex for the enantioselective aldol reaction of *p*-nitro benzaldehyde and acetone.¹⁴⁵ Unfortunately, the product was obtained in a low yield and enantioselectivity (37% yield, 22% ee).

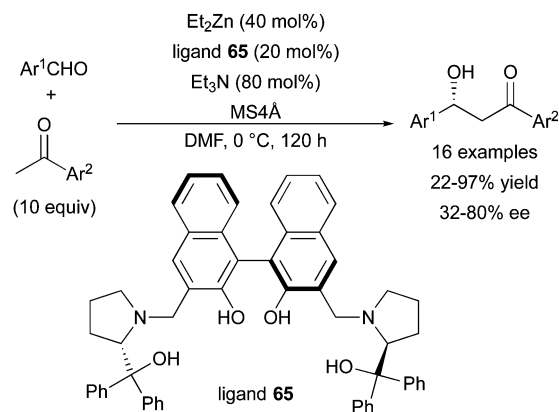
In 2008, Nishiyama and co-workers reported bis(oxazoliny)-phenyl-rhodium (Phebox Rh) **64** as a catalyst for enantioselective aldol reactions with aromatic aldehydes (Scheme 64).¹⁴⁶ It was assumed that the acetate ligand on the rhodium complex could act as a Brønsted base to promote facile enolate formation, and they also found that the addition of AgOTf improved the diastereoselectivity of the reaction with cyclic ketones. They found that several aldehydes bearing electron-withdrawing moieties were converted to their corresponding *anti*-adducts in moderate yields, good diastereoselectivities, and high enantioselectivities. In addition, the reactions of acetone also proceeded with moderate yields and good enantioselectivities.

In 2008, Da and co-workers reported the chiral zinc complex-catalyzed enantioselective aldol reactions of aromatic aldehydes and aryl methyl ketones (Scheme 65).¹⁴⁷ The semicrown chiral ligand **65**, which was synthesized from BINOL and (*S*)-diphenylprolinol, was mixed in a ratio of 1:2 with diethyl zinc with a tertiary amine to provide the most selective catalyst for the asymmetric aldol reaction. Under optimized conditions, various aromatic aldehydes were shown to react with acetophenone to afford the corresponding products in moderate enantioselectivities. Naphthyl methyl ketones could be utilized to provide the desired products in moderate yields and enantioselectivities. In all cases, a relatively long reaction time was required.

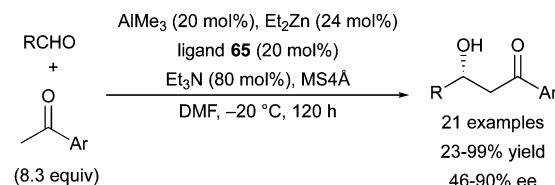
In 2016, Li and co-workers reported an aluminum/zinc heterobimetallic complex, prepared from the semicrown chiral



Scheme 64 Rhodium complex-catalyzed aldol reactions of aromatic aldehydes.



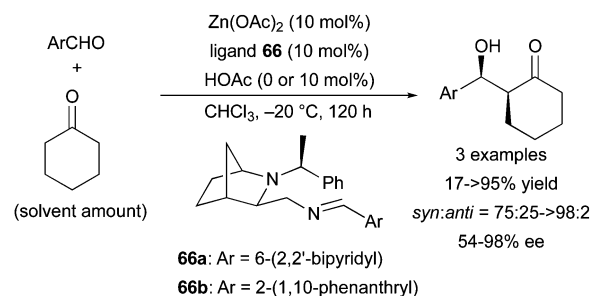
Scheme 65 Zinc-catalyzed aldol reactions of aromatic substrates.



Scheme 66 Zinc/aluminum-catalyzed aldol reactions of aryl methyl ketones.

ligand **65**, AlMe_3 , and ZnEt_2 (1:1:1.2), as a catalyst for the enantioselective aldol reactions of aryl methyl ketones (Scheme 66).¹⁴⁸ They hypothesized that the aluminum site acted as a Lewis acid and that the zinc alkoxide acted as a Brønsted base. The catalytic performance was found to be better than that previously reported for zinc-ligand **65** complex systems, and a wide variety of aldehydes, including aliphatic aldehydes, could be converted to the corresponding products in moderate to high enantioselectivities. However, a high catalyst loading and long reaction time were still required.

In 2016, Wojaczyńska and co-workers developed zinc(II)-2-azabicyclo skeleton-based ligand complexes as catalysts for the enantioselective aldol reactions of cyclohexanone (Scheme 67).¹⁴⁹ The designed ligand possessed a rigid chiral bicyclic skeleton with an additional tertiary amine and a bipyridine moiety appended by an imine linkage. Experimental and computational analyses revealed that two types of complexes were formed, $[\text{ZnLX}_n]^{(2-n)+}$ and $[\text{ZnL}_2]^{2+}$, and that the $[\text{ZnLX}_n]^{(2-n)+}$ species was the active catalyst for the enantioselective aldol reactions. When 4-nitrobenzaldehyde

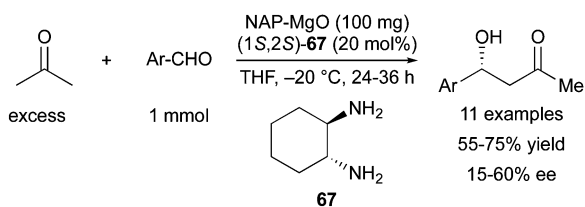


Scheme 67 Zinc(II)-catalyzed aldol reactions of cyclohexanone.

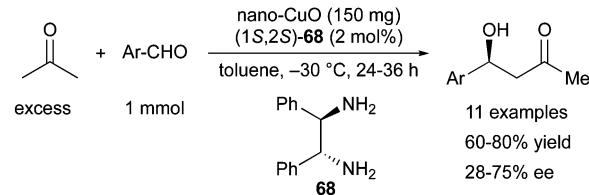
was used as a substrate, the complex derived from ligand **66a** provided the desired aldol adduct in a high yield and moderate enantioselectivity, while for the aldol reaction with *p*-nitrobenzaldehyde, the complex derived ligand **66b** provided the aldol product in a high yield and moderate enantioselectivity. For the asymmetric aldol reaction with 4-chlorobenzaldehyde, excellent diastereoselectivity and enantioselectivity were observed, despite the poor yield. In all cases, *syn*-adducts were obtained as the major products.

3.1.2. Metal-amine cooperative catalysis. In this section, the combination of metal catalysts and organocatalysts, mainly enantiopure primary and secondary amine catalysts, is discussed. Here, chiral amines generate enamine intermediates to activate the aldol donor and typically play a central role in controlling the enantioselection. When non-chiral metal salts are added to chiral amine catalysis, the metal may interact with an electrophile to tune the reactivity^{150,151} or may play other roles, such as inhibiting side reactions,^{152–155} to facilitate the aldol reaction. There are also examples involving the use of a non-chiral metal co-catalyst that may activate an aldol donor in iminium catalysis¹⁵⁶ and hydrogen bond catalysis.¹⁵⁷ However, the metal itself sometimes does not (or is not expected to) form any chiral species through complexation with the chiral amine species. Such catalysis should not be categorized as “chiral metal catalysis” and therefore we do not cover these here in detail. On the other hand, when the complexation of a metal to a chiral amine occurs, it is difficult to judge how the ligated metal species will contribute to the control of enantioselection, even if enamine catalysis is proposed. In contrast, there are cases in which metal complexes, derived from chiral amines, are the actual species that determine the enantiocontrol or where the unligated chiral amine itself may be responsible for stereocontrol. Here, we introduce such “possibly chiral metal complex catalysis” and focus on the designed amine-based chiral ligands, though the true role of the chiral metal species may not be clear.

In 2006, Choudary, Kantam, and co-workers reported aerogel-prepared nanocrystalline MgO (NAP-MgO), which possessed a large surface area (590 m² g^{−1}) and a three-dimensional (3D) polyhedral structure, as a heterogeneous catalyst for enantioselective aldol reactions acetone with aromatic aldehydes (Scheme 68).¹⁵⁸ In the presence of a chiral diamine **67**, the reaction with various aldehydes proceeded to afford the products in low to moderate enantioselectivities. The NAP-MgO could be reused up to four times, after heating the recovered catalyst at 250 °C for 1 h under a nitrogen atmosphere, without changes in the yield and enantioselectivities of the aldol products. In 2008,



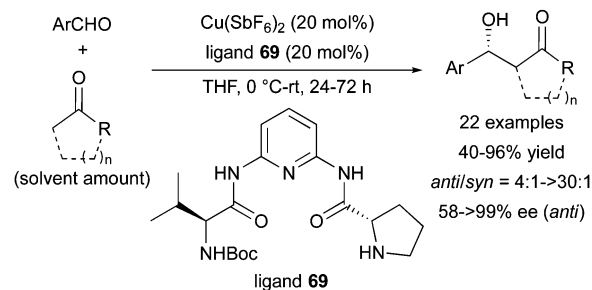
Scheme 68 Nano-MgO-catalyzed aldol reactions of acetone and aromatic aldehydes.



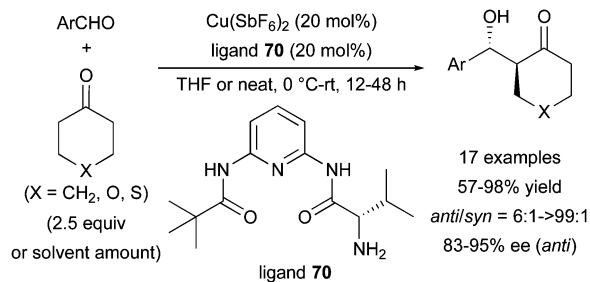
Scheme 69 Nano-CuO-catalyzed aldol reactions of acetone and aromatic aldehydes.

Kantam and co-workers reported nanocrystalline CuO (nano-CuO) as a heterogeneous catalyst for the enantioselective aldol reactions of acetone with aromatic aldehydes in the presence of a chiral diamine **68** (Scheme 69).¹⁵⁹ Nano-CuO, which possessed a larger surface area (136 m² g^{−1}) than commercial CuO, showed a higher catalytic activity and various aromatic aldehydes could be utilized to generate aldol adducts with moderate enantioselectivities. The metal catalyst could be reused for up to four cycles without a significant loss of activity, with XRD analysis confirming that no structural or morphological changes occurred after the reaction.

In 2009, Wang and co-workers reported a Lewis acid/enamine catalyst combination for the enantioselective aldol reactions of aromatic aldehydes (Scheme 70).¹⁶⁰ A tridentate ligand, tethered with a chiral secondary amine, was designed, and they hypothesized that the tridentate ligand intercepts the metal to prevent the coordination of the secondary chiral amine to the metal center to ensure that the chiral amine could act as an organocatalyst. Though the organocatalyst **69** enabled the reaction to occur, the addition of the metal catalyst improved the enantioselectivity of the aldol process. The combination of ligand **69** and copper salt was found to be a good catalyst system and various aromatic aldehydes, bearing electron-withdrawing groups, were coupled with acetone, cyclic ketones, or 2-butanone to deliver the aldol adducts in good to excellent yields and enantioselectivities. The same group further tuned the ligand structure by the changing amino acid components, and developed ligand **70** (Scheme 71).¹⁶¹ Not only acetone and cyclohexanone, but also six-membered heterocyclic ketones were viable substrates for the aldol reaction to afford the corresponding *anti*-aldol products in high to excellent diastereo- and enantioselectivities. In this system, an aromatic aldehyde with an electron-donating group (*p*-tolyl aldehyde) was also utilized without a significant loss



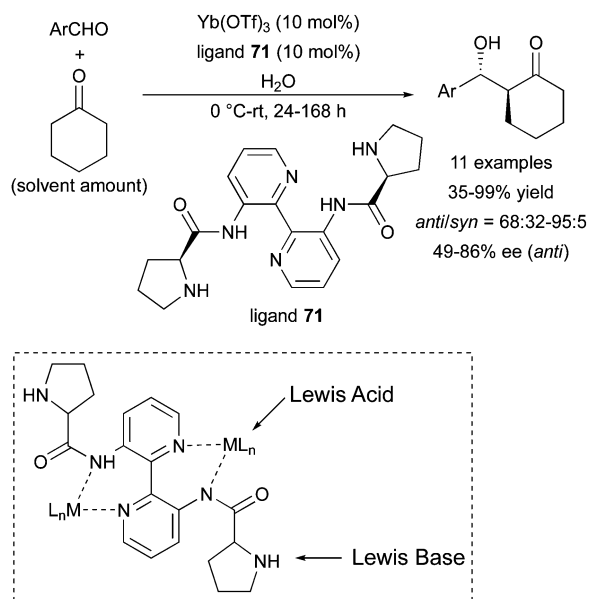
Scheme 70 Copper(II)/enamine catalyst system for direct asymmetric aldol reactions with aromatic aldehydes.



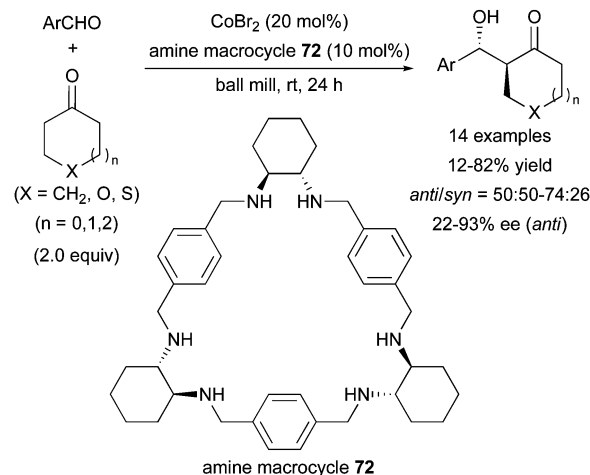
Scheme 71 Copper(II)/enamine catalyst for the aldol reactions of cyclic ketones.

of selectivity. Unlike ligand **69**, ligand **70** was unable to catalyze the reaction, and the authors speculated that the coordination of the metal salt with the chelating ligand led to a rigid chiral structure that acted as a bifunctional catalyst, in which the Lewis acidic component activated the aldehyde and the pyrrolidine moiety generated an enamine intermediate with the ketone.

In 2012, Zhao and co-workers developed 3,3'-disubstituted 2,2'-bipyridine-based chiral ligands for enantioselective aldol reactions (Scheme 72).¹⁶² The authors found that the ytterbium(III) catalyst system promoted the reactions between cyclohexanone with several electron-deficient aromatic aldehydes, and aldol adducts with high diastereo- and enantioselectivities were obtained. On the other hand, the direct enantioselective aldol reactions of acetone and cyclopentanone, as donors, led to aldol products with low yields and moderate selectivities. The authors performed control studies and found that ligand **71** could catalyze the reaction (10% yield, 59% ee), while the addition of Yb(OTf)₃ and water dramatically improved the results. Interestingly, although the optimized reaction conditions included a 1:1 mixture of Yb(OTf)₃ and ligand **71**, ¹H NMR analysis revealed that



Scheme 72 Ytterbium(III)/amine-based ligand as a catalyst for the aldol reactions of cyclohexanone.

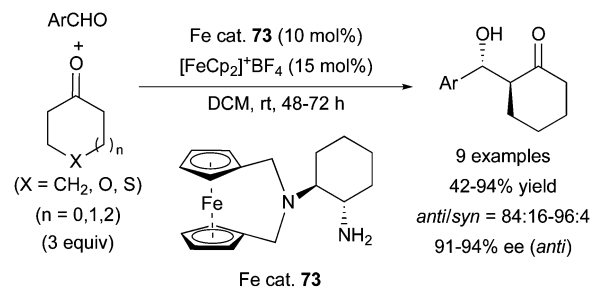


Scheme 73 Cobalt(II)/amine macrocycle catalyst for the aldol reactions of cyclic ketones.

a 2:1 mixture was formed, in which two Yb species were coordinated in a bidentate fashion with **71**.

In 2013, Tanaka and co-workers reported a chiral amine macrocyclic ligand for the enantioselective aldol reactions of cyclic ketones in a ball mill (Scheme 73).¹⁶³ When CoBr₂ and the macrocycle **72** were utilized in catalytic amounts, several aromatic aldehydes and cyclic ketones were shown to undergo direct aldol reactions, but the resulting products were obtained in poor diastereoselectivity with moderate to good enantioselectivities. Although the optimized conditions revealed that a 1:2 mixture of **72** and copper salt was the best, where the complex was formed as a 1:3 complex, as characterized by X-ray analysis. However, the use of a mixture of 1:3 macrocycle **72** and Cu(OAc)₂ did not improve the results of the aldol reaction.

In 2015, Cui, Luo, Wu, and co-workers reported a ferrocene-based chiral primary amine as a redox-tunable catalyst for the enantioselective aldol reactions of cyclic ketones (Scheme 74).¹⁶⁴ The ferrocene was introduced as a redox moiety, which could be easily oxidized to its ferrocenium form, which was more Lewis acidic. The authors hypothesized that ferrocenium could serve as a Lewis acid to activate the aldol acceptor, while the chiral primary amine could generate the enamine intermediate with the aldol donor. In the presence of [FeCp₂]⁺BF₄⁻ as an oxidant, the bifunctional catalyst **73** enabled the enantioselective aldol



Scheme 74 Redox-tunable iron/amine catalyst for the aldol reactions of cyclic ketones.

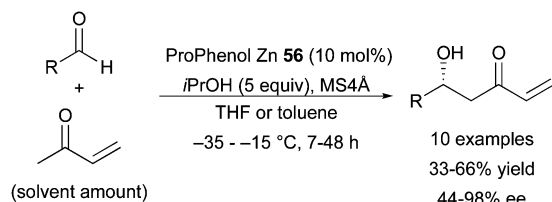
reactions of several electron-deficient aromatic aldehydes to afford the corresponding *anti*-adducts in excellent enantioselectivities. Control studies revealed that in the absence of the oxidant, a poor reactivity and selectivity of the aldol reaction was observed. The authors also demonstrated that the catalyst could be recovered by precipitation and reused for five cycles with only a slight decrease in the yield and selectivities of the aldol reaction.

3.2. Reactions of α,β -unsaturated ketones

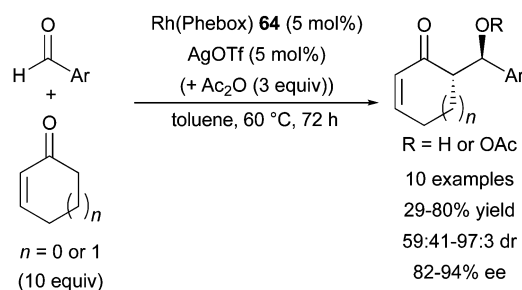
The selective enantioselective aldol reactions of α,β -unsaturated carbonyl compounds is of interest due to the ability of the resulting aldol adducts to undergo further organic transformations with the unsaturated moiety. However, there are several challenges when utilizing unsaturated carbonyl compounds for aldol reactions, such as the potential for undesired Michael reactions and retro-aldol reactions.

3.2.1. Reactions of enones. In 2005, Trost and co-workers reported the first example of enantioselective aldol reactions between an enone and aldehydes (Scheme 75).¹⁶⁵ They found that the dinuclear chiral zinc complex **56**, prepared from ProPhenol and Et_2Zn , was an excellent catalyst for the direct enantioselective aldol reactions between aldehydes and methyl vinyl ketone, and several types of aliphatic ketones could be converted to the corresponding β -hydroxy vinyl ketones in moderate yields and high enantioselectivities.

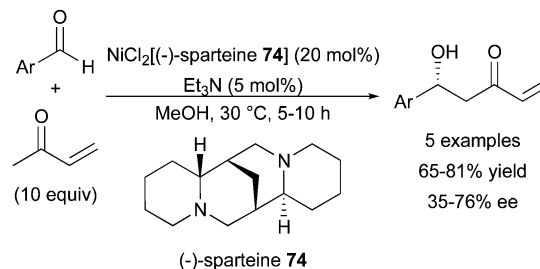
In 2009, Nishiyama and co-workers reported a chiral rhodium-(bis-oxazolinyphenyl) complex **64** as a catalyst for the enantioselective direct aldol reactions of cyclic enones and aldehydes (Scheme 76).¹⁶⁶ In their initial studies, the retro-aldol reaction was observed and this led to a decrease in the diastereoselectivity of the reaction. They found that an excess amount of acetic anhydride could be used to trap the aldol adduct, and obtained



Scheme 75 Dinuclear zinc complex-catalyzed aldol reactions with methyl vinyl ketone.



Scheme 76 Rhodium(Phebox)-catalyzed direct aldol reactions of enones and aldehydes.



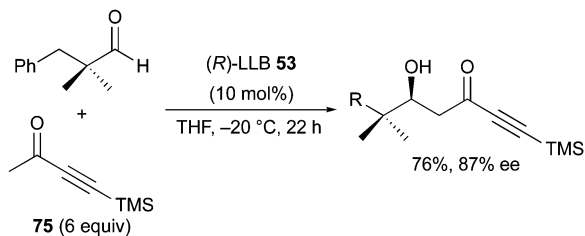
Scheme 77 Nickel-sparteine as a catalyst for direct asymmetric aldol reactions with methyl vinyl ketone.

the corresponding acetylated product in a high yield with good diastereo- and enantioselectivities for the model substrate. Several aromatic aldehydes bearing an electron-withdrawing group were examined and the desired acetylated products could be obtained in moderate yields with high regio- and enantioselectivities. When the reactions were performed with cyclopent-2-enone, the acetylation did not proceed well and low regioselectivities were observed.

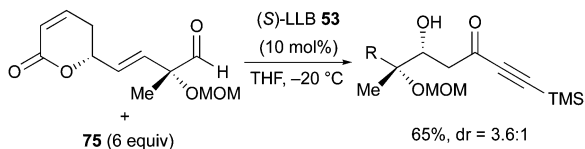
In 2010, Maheswaran reported that $\text{CuCl}_2[(-)\text{-sparteine } 74]$ and $\text{NiCl}_2[(-)\text{-sparteine } 74]$ complexes could catalyze the enantioselective aldol reactions between methyl vinyl ketone and aromatic aldehydes (Scheme 77).¹⁶⁷ Although $(-)\text{-sparteine } 74$ was used to generate both complexes, the copper catalyst provided the (*R*)-isomer, while the use of the nickel catalyst led to the (*S*)-isomer. Several aromatic aldehydes bearing an electron-withdrawing group were examined with both catalyst complexes, and the desired aldol adducts were obtained in good yields and moderate enantioselectivities with a concomitant enantio-reversal phenomenon. In general, the use of the nickel catalyst provided aldol adducts with higher yields in shorter reaction times compared to with the chiral copper complex. Based on the X-ray structural data, the innate stereochemical differences in the molecular structure of the catalysts were found to be the basis for the enantio-reversal phenomenon.

3.2.2. Reaction of ynones. In 2003, Shibasaki and co-workers reported the first example of direct catalytic enantioselective aldol reactions with ynones.^{168,169} However, since the acidity of the α -proton of ynones is higher than that of phenyl ketones, the enolate concentration becomes higher and the background reaction can be more problematic. Therefore, a weakly basic condition is needed to obtain a high selectivity. By using a Lewis acid, Brønsted base two-center asymmetric catalyst, such as (*R*)-LLB **53**, the model reaction with the α,α -disubstituted aldehyde proceeded to provide the aldol product in a high yield and high enantioselectivity (Scheme 78). The same catalyst system was utilized as a key step for the synthesis of a fragment for Fostriecin (Scheme 79).

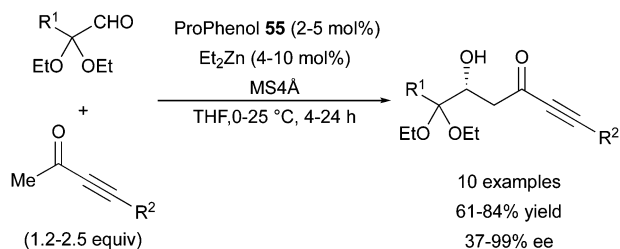
In 2004, Trost and co-workers reported the zinc-ProPhenol-catalyzed direct enantioselective aldol reactions of methyl ynones and α -ketal aldehydes (Scheme 80).¹⁷⁰ Initially, a silyl protected alkyne was examined and they found that their zinc catalyst system worked well for several α -ketal aldehydes to afford the products in excellent enantioselectivities. Moreover, they found that a terminal alkyne and an alkyl ynone were also viable



Scheme 78 LLB-Catalyzed aldol reaction of alkynyl ketone.



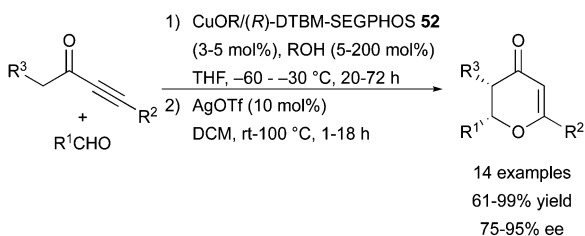
Scheme 79 Diastereoselective synthesis of the fragment of Fostriecin.



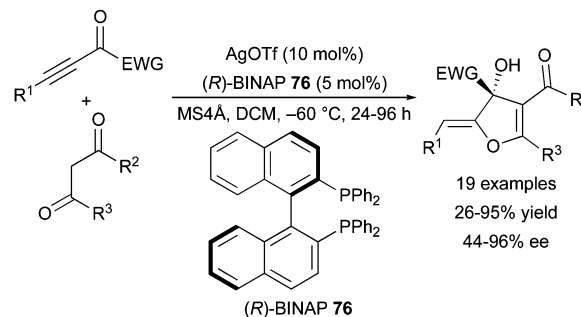
Scheme 80 Zinc-ProPhenol-catalyzed aldol reactions with ynones.

reaction partners, with the products obtained in a slightly decreased yield and enantioselectivity. Based on several control studies, enantioselective autoinduction was shown to be in operation, and it was also shown that a new, highly selective catalyst derived from the enantiopure aldol product may be formed during the course of the asymmetric aldol reaction. In addition, this catalyst system was also applied for the formal enantioselective synthesis of Fostriecin.¹⁷¹

In 2012, Kanai, Shibasaki, and co-workers reported a tandem process, in which a chiral copper(i) alkoxide was used as a catalyst for enantioselective aldol reactions between aldehydes and ynones, which were then followed by silver(i)-catalyzed oxy-Michael reactions of the resulting aldol adducts to afford dihydropyranones (Scheme 81).¹⁷² A chiral copper(i) complex, which is a soft Lewis acid that interacts with the alkyl triple bond, was utilized as a catalyst since: (1) the strong interaction



Scheme 81 Sequential catalytic asymmetric aldol-oxy-Michael reaction for the asymmetric synthesis of dihydropyranones.



Scheme 82 Enantioselective aldol-cycloisomerization cascade reactions with ynones catalyzed by a chiral silver(i) phosphine complex.

between the copper catalyst and ynones facilitates the selective deprotonation, even in the presence of enolizable aliphatic aldehydes, under weakly basic conditions, (2) the copper aldolate intermediate is stabilized by the metal- π interaction to prevent the undesired retro-aldol reaction, and (3) the activation of the alkynyl triple bond facilitates the intramolecular oxy-Michael reaction.

The balance between the basicity and the amount of alcohol additive was shown to be important for achieving good enantioselectivities as excess alcohol minimizes the retro-aldol reaction by decreasing the concentration of metal aldolate. Under optimized reaction conditions, the sequential one-pot aldol/oxy-Michael reactions of aliphatic aldehydes afforded the corresponding dihydropyranones in good to high yields and enantioselectivities. In the case of the reactions using aromatic aldehydes, which generate aldol products more sensitive to the retro-aldol reaction and dehydration, aqueous workup after the aldol reaction using dilute aqueous H₂O₂ to oxidize the phosphine ligand was necessary to achieve the following oxy-Michael reactions.

In 2015, Singh reported a chiral BINAP 76-silver(i) complex as a catalyst for enantioselective aldol-cycloisomerization cascade reactions with ynone to synthesize dihydrofuran heterocycles (Scheme 82).¹⁷³ They found that ynones, bearing electron-withdrawing groups, could undergo enantioselective aldol reactions with 1,3-diketones, followed by a tandem 5-*exo*-dig cyclization of the resulting aldol adducts to afford the corresponding chiral dihydrofuran in moderate to high yields and enantioselectivities. Unfortunately, acyclic diketone, such as acetylacetone, and cyclopentane-1,3-dione were found to be unreactive under the optimized reaction conditions.

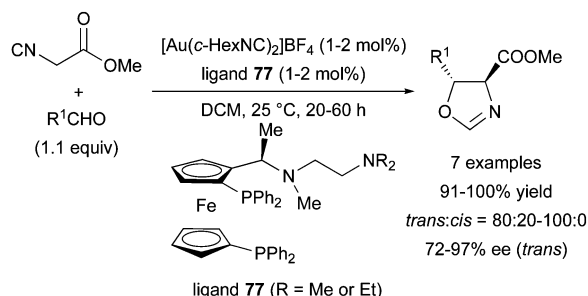
3.3. Reactions of active methylene compounds

Esters are generally less reactive than ketones for direct aldol reactions due to the lower acidity of the α -protons of esters and the thermal instability of the corresponding enolates. One of the typical solutions to these problems is the use of aldol donors bearing an electron-withdrawing group at the α -position to increase the acidity of the α -protons and to enhance enolization. Several types of activating group have been investigated and most are transformable to versatile structures after the aldol reaction.

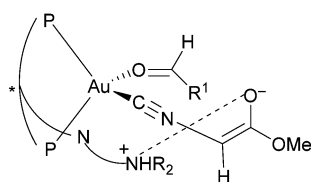
3.3.1. Reaction of isocyanoacetates. Isocyanoacetates have broad synthetic potential due to their multi-reactive groups: an acidic C–H fragment, an ester, and isocyanide group. As such, isocyanoacetates can be used for multicomponent reactions, nucleophilic additions, and can coordinate with metals.¹⁷⁴ In aldol-type reactions with isocyanides, aldol adducts tend to easily cyclize to generate the corresponding oxazoline products. Moreover, oxazoline derivatives can undergo ring-opening under mild hydrolytic conditions to afford β -substituted α -amino acids. This section introduces various types of soft transition metal-based catalysts that are able to undergo complexation with the isocyano group and enhance the acidity of the α -hydrogen atom and are known to promote the aldol reactions with isocyanides. On the other hands, some Lewis acid catalysts promote a different pathway, namely the α -addition of isocyanides to aldehydes to afford oxazole products, which is not a covered topic in this review.^{175–177}

In 1986, Ito, Hayashi, and co-workers reported the first example of enantioselective aldol reactions of aldehydes with methyl isocyanoacetate (Scheme 83).¹⁷⁸ A chiral ferrocenylphosphine 77-gold(i) complex was found to catalyze the reactions to provide the corresponding 4-(methoxycarbonyl)-2-oxazolines in excellent yields and with high diastereo- and enantioselectivities. To explain the high efficiency of the catalyst, they proposed that a transition state is formed, in which the terminal dialkylamino group on the ligand participates in the formation of the enolate of isocyanoacetate (Scheme 84). The participation of the terminal amino group in the enolate formation was supported by their NMR studies.¹⁷⁹

The distance between the amino group and the ferrocene moiety was shown to be crucial for the selectivity and when ferrocene-based ligands, bearing short side chains, were utilized, poor enantioselectivities were observed. To improve the catalyst, the ligand was further tuned by changing the dialkyl



Scheme 83 Chiral gold(i)-catalyzed aldol reactions of aldehydes with isocyanoacetate.

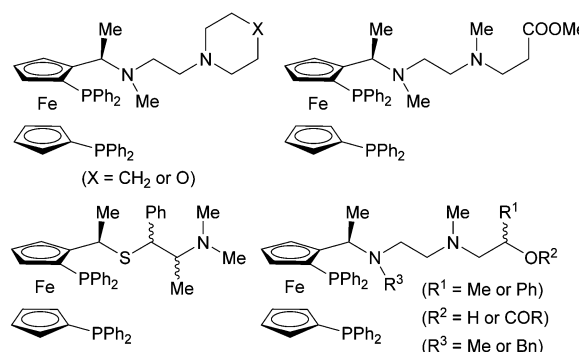


Scheme 84 Assumed transition state in the gold-catalyzed asymmetric aldol reaction with isocyanoacetate.

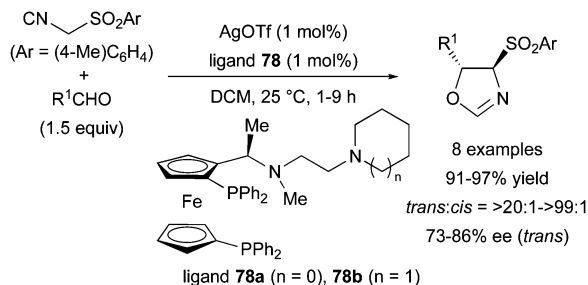
amino group at the end of the ferrocene side chain.^{180,181} It was found that the introduction of morpholinyl or piperidinyl groups improved the stereoselectivities of the gold catalysts, and the substrate scope was thus expanded to include less hindered aliphatic aldehydes,¹⁸⁰ paraformaldehyde,¹⁸² α -ketoesters,¹⁸³ and fluorinated benzaldehydes^{184–186} as electrophiles and substituted α -isocyanocarboxylates,^{182,187} α -isocyanoacetamides,^{185,188} isocyanomethyl phosphonates,¹⁸⁹ and α -isocyano Weinreb amides¹⁹⁰ as nucleophiles.

The effect of the ligand structure was further studied by Togni, Pastor, and co-workers. The planar and central chiralities in the ferrocenylphosphine ligand were varied to examine their effect on the stereoselectivity of the aldol reaction.¹⁹¹ It was found that the central chirality strongly affected the resultant product stereochemistry and the mismatched conformation led to a lower enantioselectivity, indicating that the internal cooperative chirality influenced the product diastereo- and enantioselectivity.¹⁹² Togni and co-workers also developed a variety of ferrocenylphosphine ligands, such as a ligand with a modifiable ester group,¹⁹³ sulfur-containing ligands with additional stereogenic centers,¹⁹⁴ and amino alcohol derivatives containing ligands with additional stereogenic centers,^{195,196} and studied the influence of the distant chiral centers on the enantioselective aldol reaction (Scheme 85). They proposed a mechanistic model for the transition state of the stereoselective step and suggested that the sterics play an important role in the observed cooperative chiral.

In 1990, Ito and co-workers reported silver(i)-catalyzed enantioselective aldol reactions of aldehydes with tosylmethyl isocyanide (Scheme 86).¹⁹⁷ While they initially studied this



Scheme 85 Various structures of ferrocenylphosphine ligands.



Scheme 86 Silver-catalyzed aldol reactions of aldehydes with tosylmethyl isocyanide.

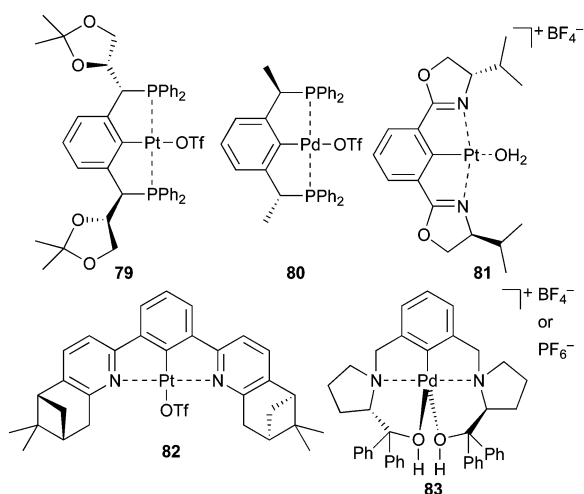
process with a gold(i) complex, the poor enantioselectivity (*ca.* 20% ee) they observed prompted them to study other chiral metal complexes. They found that metal complex prepared from AgOTf and the chiral ferrocenylphosphine ligands **78a** or **78b** led to more effective catalysts, and the corresponding *trans*-4-tosyl-2-oxazolines were obtained from various types of aldehydes in excellent yields, and with excellent diastereoselectivities and good enantioselectivities.

In 1991, Hayashi, Ito, and co-workers developed a chiral metal complex comprising AgClO₄ and a ferrocenylphosphine ligand **78a**, and found that it was an effective catalyst for the enantioselective aldol reactions of isocyanoacetate with aldehydes.¹⁹⁸ In order to understand the mechanistic differences between the gold and silver catalysts, they performed IR analysis and found that while the gold(i) complex adopted a tri-coordinated structure with two phosphorus atoms of the bidentate ligand and one molecule of isocyanide, two molecules of isocyanide were coordinated to the silver(i) catalyst to form a tetra-coordinated complex. However, they found that the 4-coordinated silver complex was in equilibrium with the corresponding 3-coordinated species and that the 3-coordinated silver species was assumed to be the key intermediate for the stereoselective pathway. Thus, the slow addition of the isocyanide was essential to achieve high enantioselectivities (up to 88% ee).

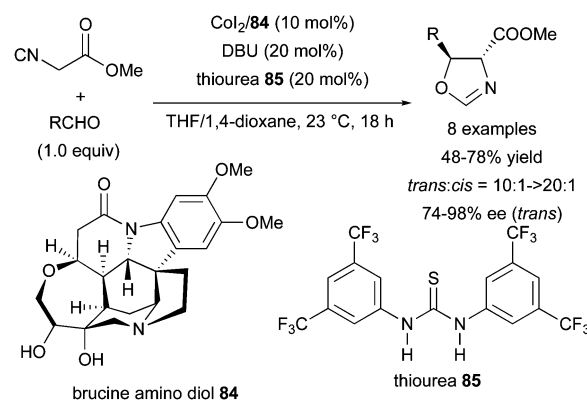
Other precious metal catalysts, such as palladium, rhodium, and platinum, were studied for the enantioselective aldol reactions of isocyanide using tridentate chiral ligands (Scheme 87). In 1994, Venanzi and co-workers discovered that a platinum(ii) complex **79**, containing a chiral tridentate P-C-P ligand, could catalyze the enantioselective aldol reactions of methyl isocyanoacetate.¹⁹⁹ Although high yields were obtained for a wide variety of aldehydes, poor to moderate enantioselectivities were observed in all cases (up to 65% ee). In 1998, Zhang and co-workers developed a palladium(ii) complex **80**, containing a chiral tridentate P-C-P ligand, for the enantioselective aldol reactions of methyl isocyanoacetate.²⁰⁰ They found that when the

trans-adducts were obtained as major products, the enantioselectivities were low (up to 31% ee), while the enantioselectivities for the *cis*-adducts were moderate (42–77% ee). In 2002, Motoyama and co-workers developed a platinum(ii) complex **81**, derived from a bis(oxazolinyl)phenyl-based chiral tridentate N-C-N ligand, for the enantioselective aldol reactions of isocyanides and aldehydes.²⁰¹ These reactions proceeded smoothly in the presence of a base to afford the products as almost exclusively the *trans*-adducts and moderate enantioselectivities were observed (up to 75% ee). In 2006, Anh and co-workers developed a platinum(ii) complex **82**, containing an (*S*)-(-)- β -pinene-derived chiral tridentate N-C-N ligand, and examined this complex as a catalyst for the enantioselective aldol reactions of methyl isocyanoacetate.²⁰² Whereas high yields and *trans*-selectivities were observed, the platinum complex was shown to be a poor enantioselective catalyst (0–12% ee). In 2008, Gebbink developed a chiral NCN-pincer palladium(ii) complex **83**, derived from chiral ligands bearing bulky diphenylhydroxymethyl pyrrolidinyl moieties.²⁰³ When the catalytic enantioselective aldol reactions of isocyanoacetate with various aromatic aldehydes were studied with this complex, the observed enantioselectivities of the *cis*-adducts (35–42% ee) were found to be higher than those of the *trans*-adducts (17–26% ee). Unlike other reported catalyst systems, the *cis*-adducts were obtained as the major product for some substrates, although the diastereoselectivities were often poor.

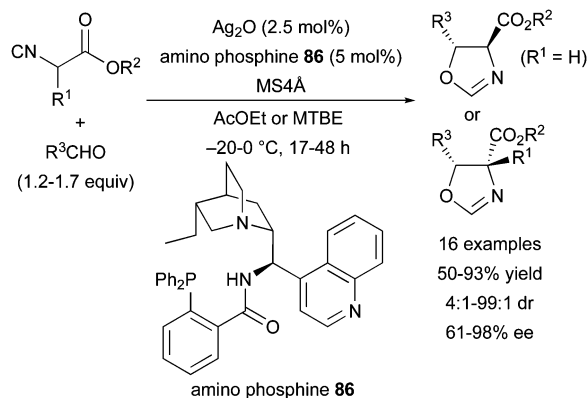
In 2011, Oh and co-workers developed a cooperative catalyst system between chiral cobalt(ii) complexes and achiral organo-catalysts for the enantioselective aldol reactions of methyl α -isocyanoacetate (Scheme 88).²⁰⁴ They envisioned that the anion-binding interactions between thiourea **85** and methyl α -isocyanoacetate assisted the coordination of the enolate to the chiral metal center in an organized fashion. The combination of **85** and the cobalt(ii) complex, derived from brucine amino diol **84**, achieved excellent enantioselectivity in a mixed solvent system, which increased the solubility of the chiral cobalt catalyst. Both aromatic and aliphatic aldehydes could be converted to the corresponding *trans*-oxazolines in high yields and with high diastereo- and enantioselectivities. The diol moiety of ligand **84** was assumed to be crucial for the cooperative



Scheme 87 Examples of palladium or platinum complexes examined as catalysts for enantioselective aldol reactions with isocyanide.



Scheme 88 Cobalt(ii)/thiourea-catalyzed aldol reactions of methyl α -isocyanoacetate.



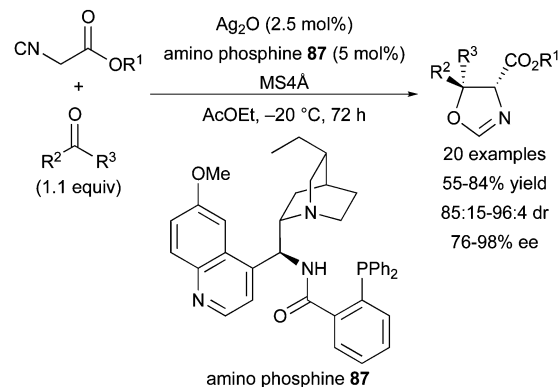
Scheme 89 Silver(I)-amino phosphine-catalyzed aldol reactions of isocynoacetates with aldehydes.

catalysis since with it, there existed the possibility of a secondary hydrogen-bonding interaction between the enolate and the hydroxy group of the chiral metal complex.

In 2011, Dixon and co-workers reported a cooperative Brønsted base/Lewis acid catalyst system for the enantioselective aldol reactions of isocynoacetates with aldehydes (Scheme 89).²⁰⁵ A new class of chiral amino-phosphines was prepared by functionalizing the amino group of 9-amino(9-deoxy) epincinchona alkaloids with appropriately spaced diaryl phosphine ligands. The authors hypothesized that the differential in the hard/soft character of the two Lewis bases in these amino-phosphines would allow for selective binding of the phosphine to an appropriate soft metal ion, while the cooperative effect between the phosphine-ligated metal ion and the basic nitrogen would enhance the acidity of the α -hydrogen of isocynoacetates *via* coordination with the soft transition metal component, with deprotonation of the activated nucleophilic component enabled by the tertiary amine. The combination of Ag_2O and the amino phosphine **86** was found to create an efficient cooperative catalyst system for the aldol reactions of isocynoacetates. Various aldehydes and isocynoacetates, including α -substituted isocynoacetates, were smoothly converted to the corresponding oxazoline products in good to high yields, diastereoselectivities, and enantioselectivities. Asymmetric aldol reactions with α -substituted isocynoacetates resulted in facial selectivity opposite to the non-substituted isocynoacetate, while facial selectivity on the aldehyde was the same. This catalyst system has also been applied for the synthesis of a broad spectrum of antibiotics, such as chloramphenicol.²⁰⁶

In 2015, the same group examined Ag_2O -amino phosphine catalyst systems for the enantioselective aldol reactions of isocynoacetates with ketones (Scheme 90).²⁰⁷ A binary catalyst system, consisting of a cinchona-derived aminophosphine **87** and Ag_2O , worked well for the aldol reactions with various kinds of aromatic ketones to afford the corresponding *trans*-oxazolines, with a fully substituted stereogenic center at the β -carbon atom, in good to excellent diastereo- and enantioselectivities. On the other hands, aliphatic ketones afforded the corresponding oxazoline products with poor enantioselectivities.

3.3.2. Isothiocyanates. Similar to isocyanides, isothiocyanate-substituted carbonyl compounds are useful glycine equivalents

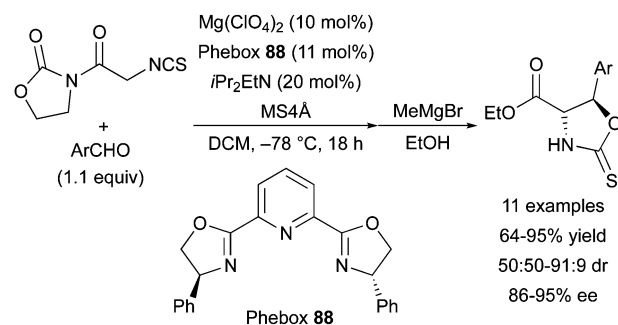


Scheme 90 Silver(I)-amino phosphine-catalyzed aldol reactions of isocynoacetates with ketones.

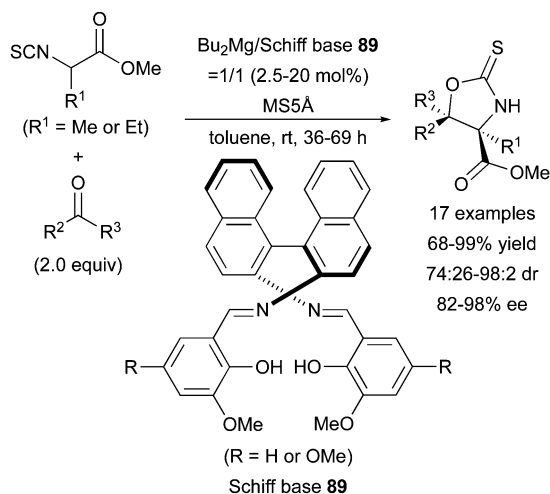
for aldol-type reactions since the *in situ*-formed aldol adducts can be irreversibly trapped by the isothiocyanate group to yield oxazolidinethione products. The oxazolidinethione moiety can be easily converted into an oxazolidinone to afford unprotected chiral β -hydroxy- α -amino acid derivatives.²⁰⁸

In 2005, Willis and co-workers reported magnesium(II) complex-catalyzed enantioselective aldol reactions of isothiocyanate-substituted oxazolidinones with aromatic aldehydes (Scheme 91).²⁰⁹ Initially, the reactions with an isothiocyanate-substituted ester were examined in the presence of a chiral magnesium(II) catalyst and Hünig's base. However, the enantioselectivities were uniformly low, although the asymmetric process could be improved by introducing an oxazolidinone moiety to the isothiocyanate and by utilizing the tridentate chiral ligand Phebox **88**. Consequently, ester-substituted oxazolidinethiones were obtained in high enantioselectivities after the cyclized products were treated with a Grignard reagent.

In 2009, Matsunaga, Shibasaki, and co-workers reported a magnesium(II) complex as a catalyst for the enantioselective aldol reactions of α -substituted α -isothiocyanato esters with ketones (Scheme 92).²¹⁰ A 1:1 complex of Bu_2Mg /Schiff base **89**, derived from vanillin and a binaphthyldiamine derivative, effectively catalyzed the asymmetric reaction at room temperature, while other metal sources, such as Et_2Zn , $\text{Sr}(\text{O}^i\text{Pr})_2$, $\text{Ba}(\text{O}^i\text{Pr})_2$, and $\text{La}(\text{O}^i\text{Pr})_3$, resulted in poor selectivities or reactivities. They found that the substrate generality was broad and various aldol



Scheme 91 Magnesium(II)-catalyzed aldol reactions of isothiocyanate-substituted oxazolidinone with aromatic aldehydes.

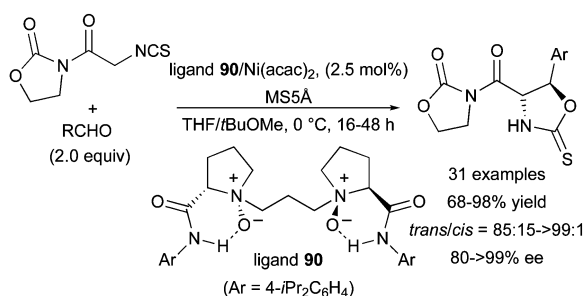


Scheme 92 Magnesium(II)-catalyzed aldol reactions of α -substituted α -isothiocyanato esters with ketones.

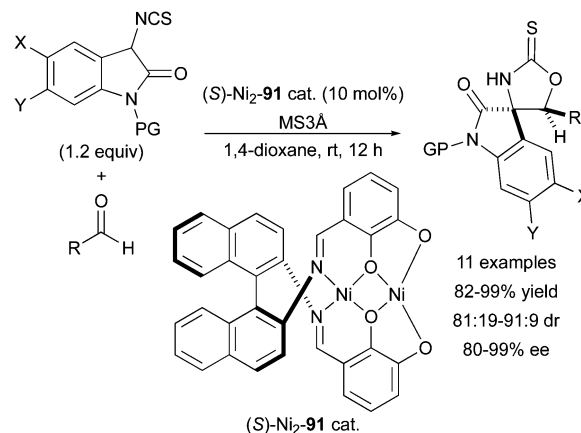
acceptors, including aromatic ketones, heteroaromatic ketones, cyclic ketones, and linear aliphatic ketones, were all viable substrates to generate the corresponding protected α -amino- β -hydroxy esters, bearing contiguous tetrasubstituted chiral carbon stereocenters, in excellent enantioselectivities.

In 2010, Feng and co-workers reported a nickel(II) complex-catalyzed enantioselective aldol reactions of isothiocyanate-substituted oxazolidinone with aromatic aldehydes (Scheme 93).²¹¹ They found that a chiral complex composed of $\text{Ni}(\text{acac})_2$, a cheap and air-stable nickel source, and the N,N' -dioxide ligand **90** led to an excellent catalyst that enabled the asymmetric process to occur with a wide range of aldehydes, including aromatic, heteroaromatic, and aliphatic aldehydes, to deliver the corresponding oxazolidinethiones in high to excellent yields and selectivities. Control experiments revealed that the N -oxide moiety of the ligand played a key role in the enantioselective inductivity, while X-ray analysis of the nickel complex showed that both the carbonyl oxygen atoms and the N -oxide oxygen atoms were coordinated with nickel.

In 2013, Kanai, Matsunaga, and co-workers reported a dinuclear nickel(II) complex as a catalyst for the enantioselective aldol-type reactions of 3-isothiocyanato oxindoles to aldehydes (Scheme 94).²¹² The authors examined various homodinuclear metal/Schiff base complexes as chiral catalysts and



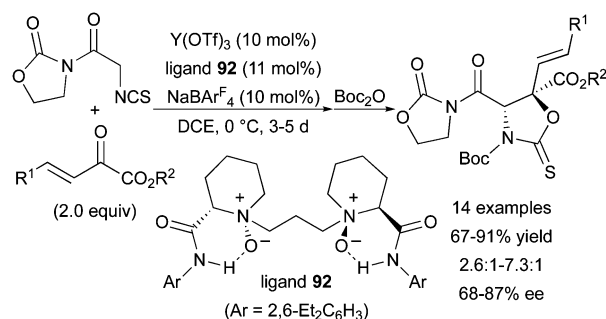
Scheme 93 Nickel(II)-catalyzed aldol reactions of isothiocyanate-substituted oxazolidinone with aldehydes.



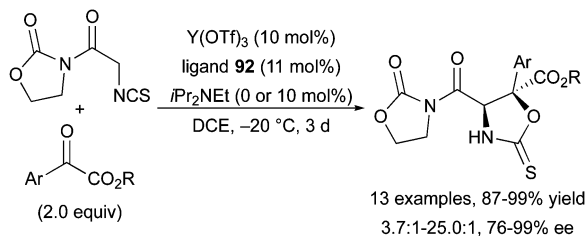
Scheme 94 Dinuclear nickel(II) complex-catalyzed aldol-type reactions of 3-isothiocyanato oxindoles to aldehydes.

found that the $\text{Sr}(\text{O}^i\text{Pr})_2$ /Schiff base complex, which was suitable for the reaction of 3-isothiocyanato oxindoles with aldimine,²¹³ resulted in poor enantioselectivity, while the dinuclear nickel(II) complex (Ni_2 -**91**) acted as an excellent catalyst and led to high stereoselectivity of the desired product. The authors demonstrated that various aliphatic aldehydes could be converted to the corresponding spirooxindole products in high to excellent yields and stereoselectivities, while reactions with aromatic aldehydes afforded poor results. In addition, when the catalyst loading was reduced to 0.1 mol%, a high yield of the desired product could be obtained with high enantioselectivity, but with a decrease in the diastereoselectivity.

In 2013, Feng and co-workers reported a yttrium(III) complex as a catalyst for the enantioselective aldol reactions of α -keto esters with isothiocyanate-substituted oxazolidinone (Scheme 95).²¹⁴ They found that a yttrium(III)- N,N' -dioxide **92** complex, in conjugation with a non-coordinating anion source (NaBAR^F_4), enabled various aromatic β,γ -unsaturated α -keto esters to undergo an asymmetric aldol reaction to afford the corresponding 1,2-adducts in high yields and with good diastereo- and enantioselectivities. In addition, a challenging γ -alkyl-substituted unsaturated keto ester was also found to be a viable substrate, providing the aldol adduct with moderate selectivity. The yttrium(III) complex was also found to efficiently catalyze the aldol reactions with aryl-substituted α -keto esters, and higher stereoselectivities were



Scheme 95 Yttrium(III)-catalyzed 1,2-addition of β,γ -unsaturated α -keto esters with an α -isothiocyanato imide.

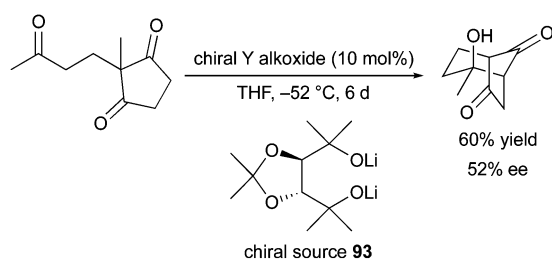


Scheme 96 Yttrium(III)-catalyzed 1,2-addition of aryl-substituted α -keto esters with an α -isothiocyanato imide.

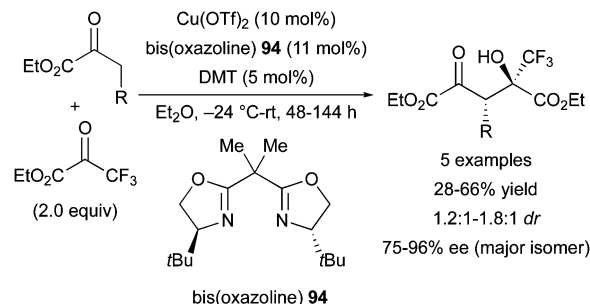
observed for various substrates compared to the reaction with unsaturated keto esters (Scheme 96). Interestingly, the asymmetric aldol reactions of β,γ -unsaturated α -keto esters and aryl-substituted α -keto esters exhibited different diastereoselection under the reaction conditions yet control studies ruled out the possibility of epimerization. To understand this phenomenon, the authors performed nonlinear effect analysis and found that the reaction of the aryl-substituted α -keto ester exhibited a significant positive nonlinear effect, which suggested the existence of a catalytically active oligomeric species. On the other hand, the reaction of the β,γ -unsaturated α -keto ester showed a slightly positive nonlinear effect, indicating a monomeric catalyst species was involved in the asymmetric aldol reaction. The substrate dependence on the catalyst composition indicated that the binding strength of the substrate affects the equilibrated catalyst mixture. Based on these results, activation models of the α -isothiocyanato imide for the reaction of the two types of keto esters were proposed to explain the discrepancy in the observed diastereoselectivity. While the reaction of aryl-substituted α -keto ester might prefer the *Re-Re* face approach, this approach may be unfavorable when the β,γ -unsaturated α -keto ester is used as a substrate due to the steric repulsion between the styryl moiety of the keto ester and the oxazolidinone moiety of the imide.

3.3.3. Reaction of dicarbonyl compounds. Dicarbonyl compounds, such as β -ketoesters, have a highly acidic α -proton and can easily enolize. However, the use of these substrates in aldol reactions is relatively limited due to the potential for the retro-aldol reaction to occur under the proton-transfer conditions. Despite this, examples of dicarbonyl compounds in asymmetric aldol reactions have been reported.

In 1992, Shibasaki and co-workers reported an yttrium(III)-catalyzed enantioselective intramolecular aldol reaction of a triketone (Scheme 97).¹²⁹ They found that the chiral yttrium(III)



Scheme 97 Yttrium(III)-catalyzed intramolecular aldol reaction of triketone.

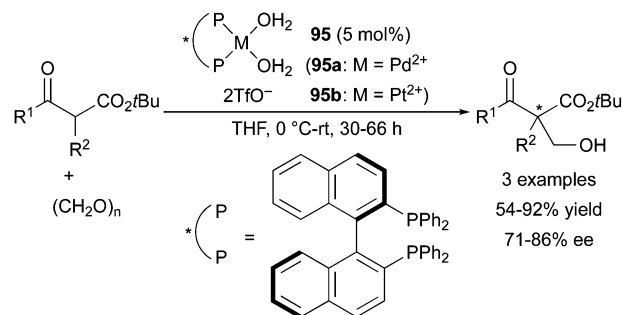


Scheme 98 Copper(II)-catalyzed aldol reactions of α -keto esters with ethyl trifluoropyruvate.

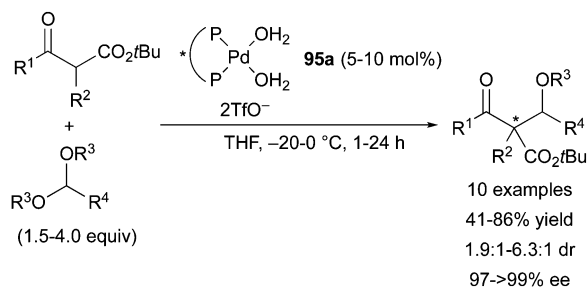
alkoxide, prepared from YCl_3 , NaO^tBu , and chiral diol-based lithium alkoxide **93**, catalyzed the intramolecular aldol reaction of a *meso*-triketone and the bicyclic product was obtained in a moderate yield and enantioselectivity.

In 2004, Gathergood, Jørgensen, and co-workers reported a copper(II) complex as a catalyst for the enantioselective aldol reactions of α -keto esters with ethyl trifluoropyruvate (Scheme 98).²¹⁵ Initially, they studied the homo-aldol reaction of ethyl pyruvate and found that a $\text{Cu}(\text{OTf})_2$ /bisoxazoline ligand **94** complex catalyzed the aldol reaction in the presence of an amine base to produce diethyl 2-hydroxy-2-methyl-4-oxoglutarate with an excellent enantioselectivity (96% ee). The asymmetric reaction was then expanded to cross-aldol reactions, and it was found that the copper catalyst system worked well in the presence of *N,N*-dimethyl-*p*-toluidine (DMT) as a base to enable several α -keto esters to undergo the aldol process to generate 2-hydroxy-2-trifluoromethyl-4-oxoglutarates with high enantioselectivities, but low diastereoselectivities.

In 2007, Sodeoka and co-workers reported the first example of the enantioselective hydroxymethylations of α -substituted β -ketoesters with paraformaldehyde catalyzed by chiral palladium(II)- and platinum(II)-BINAP complexes (Scheme 99).²¹⁶ They assumed that the active methine compounds reacted with the palladium complex **95a** to generate chiral palladium enolates and release water and TfOH, which plays an important role in the generation of formaldehyde from paraformaldehyde. To support this hypothesis, they found that the neutral $\text{Pd}(\mu\text{-OH})$ complex did not efficiently promote the hydroxymethylation reaction. By choosing the appropriate catalyst (palladium or platinum),



Scheme 99 Palladium(II) or platinum(II)-bisphosphine complexes as catalysts for the aldol reactions of β -keto esters with paraformaldehyde.



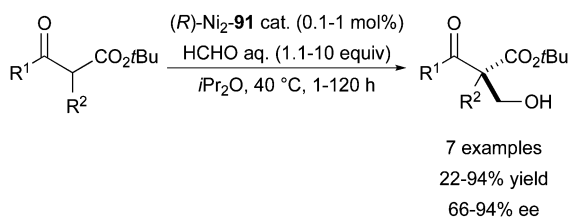
Scheme 100 Palladium(II)–bisphosphine complex as a catalyst for the aldol-type reactions of β -ketoesters with acetals.

both cyclic and acyclic α -substituted β -ketoesters were converted to the corresponding products with good enantioselectivities.

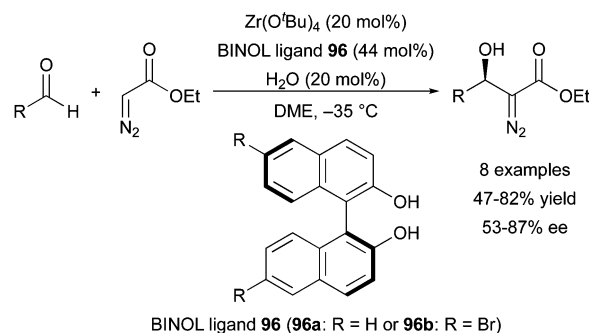
In 2008, the same group reported the application of their palladium(II)– and platinum(II)–bisphosphine complex catalysts **95** for enantioselective aldol-type reactions of α -substituted β -ketoesters with acetals (Scheme 100).²¹⁷ The neutral $\text{Pd}(\mu\text{-OH})$ –BINAP catalyst **95a** efficiently catalyzed the reaction with cyclic ketoesters and various acetals, including acetals derived from benzaldehyde and α,β -unsaturated aldehyde, to generate the corresponding aldol adducts with outstanding enantioselectivities. An acyclic ketoester was found to be less reactive with the palladium complex **95a** as a catalyst since the complexation with the acyclic ketoester was slow and, as a result, the palladium complex **95a** tended to be reduced by the alcohol derived from the starting acetals. The platinum(II) complex **95b**, which was more resistant to enolate decomposition, was then employed to address this issue, and the corresponding product was obtained in a good yield with high diastereo- and enantioselectivity.

In 2009, Matsunaga, Shibasaki, and co-workers reported a dinuclear Ni_2 –Schiff base complex **91** as a catalyst for the enantioselective aldol reactions of β -keto esters with formaldehyde (Scheme 101).²¹⁸ Since these homodinuclear transition metal–Schiff base complexes were bench-stable solids,²¹⁹ they hypothesized that these catalysts could be suitable for reaction with aqueous formaldehyde solution. They found that a high catalytic turnover (TON = up to 940) could be achieved when complex **91** was used as a catalyst, and showed the reaction could even proceed with catalyst loadings as low as 0.1–1 mol% for several substrates to provide aldol products in good to high yields and enantioselectivities.

3.3.4. Reaction of diazo acetates. Direct aldol reactions with diazoacetate are attractive since α -diazo carbonyl compounds are useful intermediates that can undergo diverse transformations.²²⁰



Scheme 101 Dinuclear nickel complex-catalyzed aldol reaction of β -keto esters with formaldehyde.

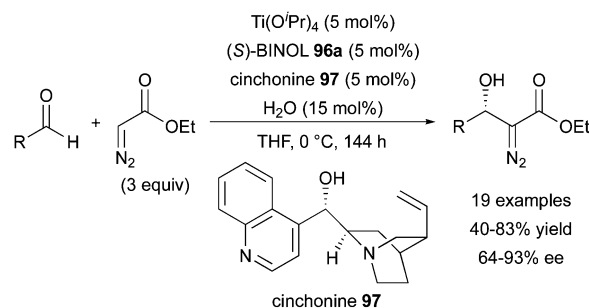


Scheme 102 Zirconium–BINOL-catalyzed aldol reactions with diazoacetate.

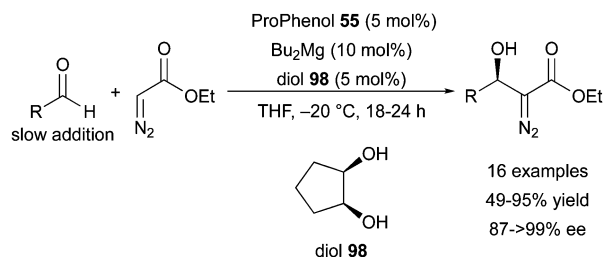
In 2003, Wang and co-workers reported the first example of enantioselective aldol-type reactions of aldehydes with ethyl diazoacetate (Scheme 102).²²¹ They found that Kobayashi's zirconium(IV) catalysts,²²² prepared from $\text{Zr}(\text{O}^t\text{Bu})_4$ and the BINOL derivative **96**, with a catalytic amount of water, enabled the asymmetric aldol reaction. However, they found that the asymmetric aldol reaction with heteroaryl and aliphatic aldehydes proceeded very slowly, and required the use of more than a stoichiometric amount of MgBr_2 to accelerate the reactions to obtain the desired products in moderate to good enantioselectivities. They assumed that the resulting aldol adducts possessed a strong affinity for the catalyst and that MgBr_2 was utilized to facilitate the catalyst turnover. They also demonstrated that the obtained β -substituted α -diazo carbonyl compounds could be transformed into β -hydroxy α -keto esters by direct oxidation with oxone and could then be further reduced to α,β -dihydroxy esters using NaBH_4 in good *anti*-selectivity.

In 2009, Feng and co-workers reported a bifunctional titanium(IV) complex as a catalyst for the enantioselective aldol reactions of aldehydes with ethyl diazoacetate (Scheme 103).²²³ The catalyst, which was prepared from a 1:1:1 mixture of $\text{Ti}(\text{O}^i\text{Pr})_4$, BINOL **96a**, and cinchonine **97**, was shown to enable the asymmetric aldol reaction with aromatic aldehydes to provide aldol products in high enantioselectivities, but only moderate yields. However, the asymmetric aldol reaction with an aliphatic aldehyde gave only a moderate enantioselectivity (64% ee).

In 2009 and 2012, Trost and co-workers reported a chiral dinuclear magnesium complex, formed from Bu_2Mg and



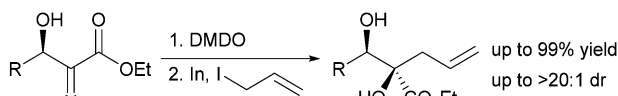
Scheme 103 Titanium–BINOL complex as a catalyst for aldol reactions with diazoacetate.



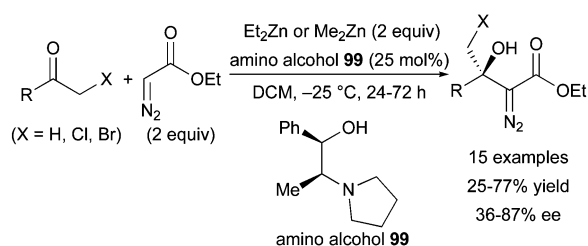
Scheme 104 Magnesium–ProPhenol as a catalyst for aldol reactions with diazoacetate.

ProPhenol **55**, as a catalyst for enantioselective aldol reactions with diazoacetate and aldehydes (Scheme 104).^{224,225} This chiral catalyst was demonstrated to effectively promote the asymmetric aldol reaction of a wide range of aldehydes, including aliphatic substrates and an unsaturated aldehyde. The authors demonstrated several transformations of the aldol products, such as oxidation by the aldol adduct with DMDO to generate β-hydroxy α-keto esters, which were then subjected to an indium-mediated allylation reaction to afford a chiral 1,2-diols bearing a tertiary alcohol with high enantio- and diastereomeric purities (Scheme 105). This structural motif is important in the synthesis of natural products, and was also applied in the synthesis of a polyketide fragment. In 2013, the same group further demonstrated the conversion of β-hydroxy α-diazo esters to β-amido-α-diazoesters *via* a highly stereospecific C–O to C–N exchange with retention of the configuration.²²⁶

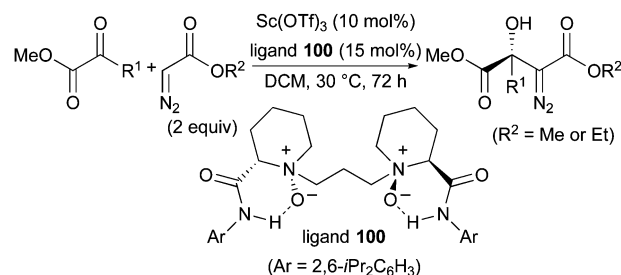
In 2009, Cozzi and co-workers reported the first example of enantioselective aldol-type reactions of ethyl diazoacetate to ketones (Scheme 106).²²⁷ Using excess amounts of diethyl zinc and catalytic amounts of chiral amino alcohol **99**, the desired aldol adducts were obtained with moderate enantioselectivities. A relatively high loading of the chiral source was required due to the fast background reactions, while for the less reactive dimethyl zinc, $\text{Ph}_3\text{P}=\text{S}$ was utilized instead as an additive. Under these conditions, various ketones, including aliphatic ketones, could be converted to the corresponding products in



Scheme 105 Indium-mediated allyl transfer reaction with β-hydroxy α-keto esters.



Scheme 106 Zinc-mediated aldol reaction of ethyl diazoacetate to ketones.

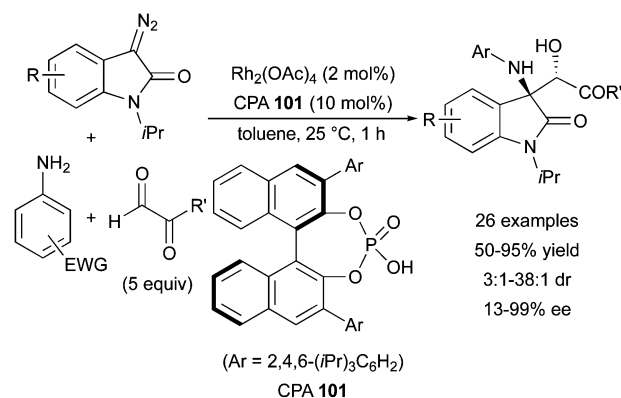


Scheme 107 Scandium(III) complex-catalyzed aldol reaction of diazoacetate esters to α-ketoesters.

moderate to good enantiomeric excess. They found that a longer reaction time could improve the yields for several substrates, but also diminished the enantiopurity of the final product.

In 2009, Feng and co-workers reported a C_2 -symmetric N,N' -dioxide **100**–scandium(III) complex as a catalyst for enantioselective aldol-type reactions of α-ketoesters and diazoacetate esters (Scheme 107).²²⁸ The reaction was found to proceed at ambient temperature and various aromatic α-ketoesters were converted to the corresponding products in good yields and with excellent enantioselectivities. However, both the yield and enantioselectivity were poor when an aliphatic α-ketoesters was used as the substrate.

The above-mentioned examples directly utilized diazoacetate as a nucleophile for aldol-type reactions. On the other hand, transition metals, such as rhodium, can generate metal carbene species, which are the reactive intermediates for a broad spectrum of transformations, from diazo compounds.²²⁹ In 2013, Gong and co-workers reported the combination of rhodium(II) acetate and a chiral Brønsted acid as a cooperative catalyst system for enantioselective three-component aldol-type reactions between 3-diazoindoles, anilines, and glyoxylates (Scheme 108).²³⁰ The reaction proceeded *via* following two steps: (1) rhodium-catalyzed generation of ammonium ylides from 3-diazoindoles and anilines, and (2) chiral Brønsted acid-catalyzed enantioselective addition of the ylides to glyoxylates. The chiral phosphoric acid (CPA) **101** was found to be the best co-catalyst for the multi-component reaction, with the desired products obtained in



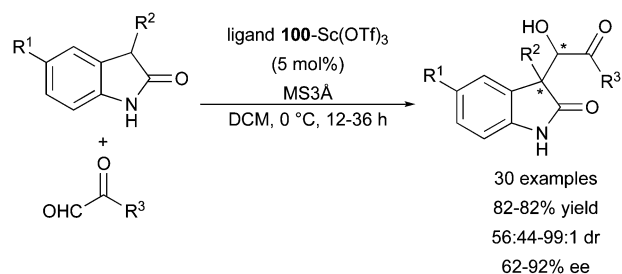
Scheme 108 Brønsted acid/rhodium(II)-catalyzed enantioselective three-component aldol-type reactions.

high diastereoselectivities and enantioselectivities. Various types of substituted 3-diazoindoles and anilines, bearing electron-withdrawing substituents, could be converted to the corresponding products in high yields and selectivities.

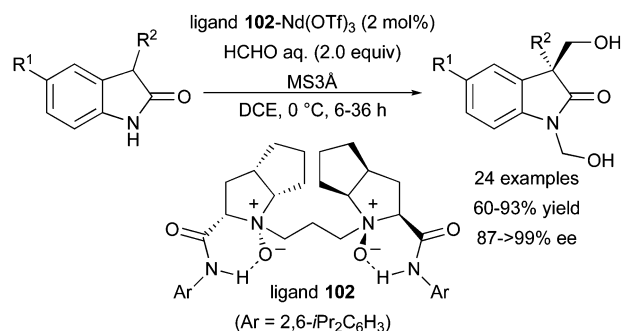
3.3.5. Reaction of oxindoles. Oxindoles with a quaternary stereogenic center at the C3 position are of potential medicinal interest due to the unique biological activities of natural products possessing this structural motif.²³¹

In 2010, Feng and co-workers reported a C_2 -symmetric N,N' -dioxide **100**-scandium(III) complex as a catalyst for the enantioselective aldol-type reactions of 3-substituted 2-oxindoles with glyoxals (Scheme 109).²³² The chiral scandium catalyst worked well for a wide variety of α -keto aldehydes and substituent oxindoles, and in most cases, high yields and excellent enantioselectivities of the desired products were obtained. Interestingly, reactions with methyl- or boc-protected oxindoles hardly proceeded, indicating that the free NH group of oxindoles is necessary for the aldol reaction. In addition, they observed the corresponding peaks of ligand **100**-Sc-based enolate species and dimeric species by ESI-MS analysis. The observation of dimeric species was consistent with the results from their nonlinear effect study, which showed a positive nonlinear effect.

Feng's group also reported the C_2 -symmetric N,N' -dioxide **102**-neodymium(III) complex as a catalyst for the enantioselective hydroxymethylation of 3-substituted 2-oxindoles with formalin (Scheme 110).²³³ The addition of formaldehyde occurred not only on the C3 position, but also on the nitrogen atom, to provide bis hydroxymethylated products. Interestingly, they found through their screening studies of rare earth metal triflates that Sc(OTf)₃, Yb(OTf)₃, and Lu(OTf)₃, which have smaller ionic radii



Scheme 109 Scandium(III) complex-catalyzed aldol reaction of 2-oxindoles.



Scheme 110 Neodymium(III) complex-catalyzed hydroxymethylation of 2-oxindoles.

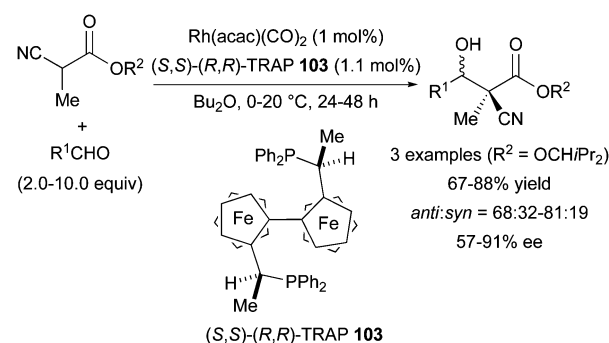
and stronger Lewis acidities among the rare earth metals, generally gave lower enantioselectivities, while Nd(OTf)₃ provided the highest enantioselectivity. Using the chiral Nd(III) complex as a catalyst, numerous oxindoles were examined as substrates and the desired aldol products were obtained in high yields and high enantioselectivities. They demonstrated that the *N*-hydroxymethyl group could be easily removed by treatment with NaOH and also demonstrated the application of these reactions for the formal synthesis of bioactive compounds.

3.3.6. Reactions of other activated methylene compounds.

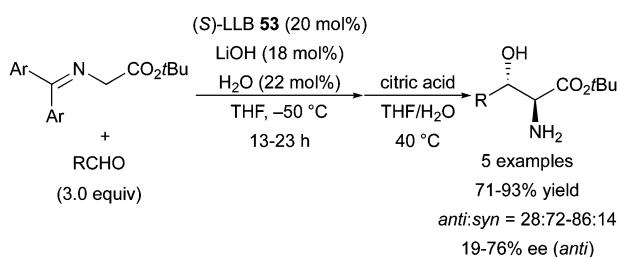
In 1998, Ito and co-workers reported a *trans*-chelating chiral diphosphine ligand TRAP **103**-rhodium(I) complex as a catalyst for the enantioselective aldol reaction of 2-cyanopropionates (Scheme 111).^{234,235} They found that the aldol reaction between 2-cyanopropionate and paraformaldehyde (10 wt% in water) led to the product in a high yield and enantioselectivity, while other aliphatic aldehydes provided the desired products in moderate to good diastereo- and enantioselectivities only when bulky esters on the aldol donor was used as a substrate. On the other hand, the asymmetric aldol reaction did not proceed with benzaldehyde as a substrate.

In 2002, Shibasaki and co-workers reported enantioselective direct aldol reactions of glycinate Schiff bases by utilizing a chiral lithium complex, prepared from LLB **53**, LiOH, and water, as a catalyst (Scheme 112).²³⁶ They found that the aldol reactions proceeded smoothly to afford *anti*- β -hydroxy- α -amino acid esters in moderate to good diastereoselectivities and enantioselectivities after the intermediates underwent hydrolysis with aqueous citric acid.

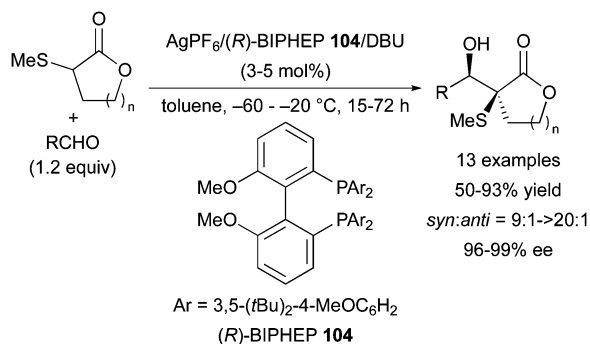
In 2012, Kumagai, Shibasaki, and co-workers reported a chiral silver/DBU binary catalyst system for the direct enantioselective



Scheme 111 Diphosphine-rhodium(I) complex-catalyzed aldol reaction of 2-cyanopropionates.



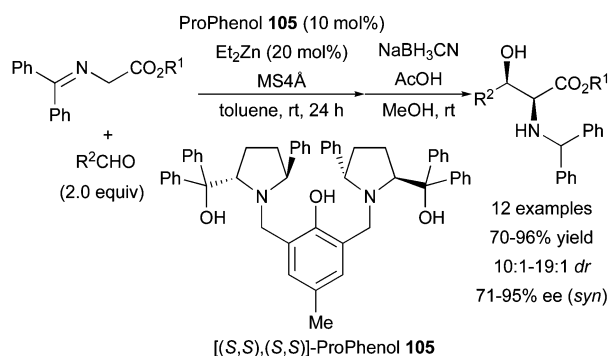
Scheme 112 LLB-Catalyzed aldol reactions of glycinate Schiff bases.



Scheme 113 Silver-catalyzed direct aldol reactions of α -sulfanyl lactones with aldehydes.

aldol reactions of α -sulfanyl lactones with aldehydes (Scheme 113).²³⁷ They hypothesized that the α -sulfanyl esters would be more susceptible to deprotonation than aldehydes in the presence of a soft Lewis acid, which would selectively coordinate to the α -sulfanyl moiety. Furthermore, the retro-aldol reaction would be suppressed since the catalyst may not activate the sulfide-containing product due to steric hindrance. The authors found that $\text{AgPF}_6/\text{BIPHEP } 104/\text{DBU}$ was the best soft Lewis acid/amine binary catalytic system, and a wide variety of aliphatic aldehydes were converted to the corresponding β -hydroxy α -sulfanyl lactones in high yields, high diastereoselectivities, and outstanding enantioselectivities. The catalyst system was examined for the enantioselective synthesis of an intermediate of serine palmitoyl transferase (SPT) inhibitors, such as viridofungin A and NA 808. Control experiments revealed that 2-methoxy- γ -butyrolactone, as an oxygen analog of the substrate, did not form a new species with the silver complex, and no desired aldol adduct was obtained under the reaction conditions. On the other hand, a new species was formed between the α -sulfanyl lactone and silver complex, which was detected by NMR analysis.

In 2014, Trost and co-workers reported a dinuclear zinc complex as a catalyst for the enantioselective aldol reactions of glycinate Schiff bases (Scheme 114).²³⁸ The ProPhenol ligand **105**, bearing *trans* 2,5-disubstituted pyrrolidines, was designed with the expectation that the C5 substituents would exert a constraining effect by interacting with the central phenoxy ring. The zinc-ProPhenol **105** catalyst system was found to be



Scheme 114 Zinc-catalyzed aldol reactions of glycinate Schiff bases.

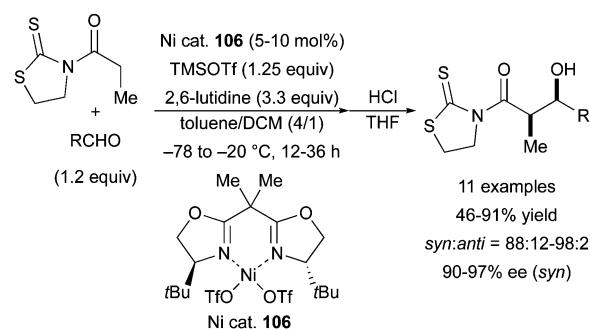
efficient for the asymmetric aldol reactions with various aldehydes to afford the corresponding *syn* β -hydroxy- α -amino esters in high yields with excellent diastereoselectivities and high enantioselectivities.

3.4. Reaction of activated amides

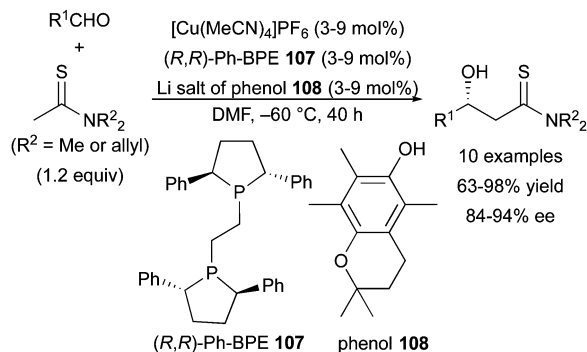
As described in Section 3.3, the direct aldol reaction of esters and amides is a challenging task in the absence of an electron-withdrawing group at the α -position. In this section, an alternative strategy to utilize aldol donors in the carboxylic acid oxidation state is introduced: the aldol reactions of reactive ester equivalents.

In 2003, Evans and co-workers reported nickel(II)-catalyzed enantioselective aldol reactions of *N*-propionylthiazolidinethione (Scheme 115).²³⁹ The preformed nickel(II) catalyst **106**, prepared by the complexation of NiCl_2 and a chiral bisoxazoline ligand and the subsequent treatment with AgOTf , exhibited greater activity in the presence of an excess amount of the base than the *in situ*-prepared catalyst. Both aromatic and aliphatic aldehydes were applicable under the optimized conditions and the corresponding *syn*-adducts were obtained in excellent enantioselectivities. In these reactions, stoichiometric amounts of the silylating reagent (TMSOTf) were required since the silylation of aldolate would facilitate decomplexation of the aldol product from the catalyst. Although the role of the TMSOTf could be to generate *in situ* the silicon enolate, this hypothesis was denied from results of their control studies.

In 2009, Kumagai, Shibasaki, and co-workers reported a soft Lewis acid/hard Brønsted base cooperative catalyst system for the enantioselective aldol reactions of thioacetamides with aliphatic aldehydes (Scheme 116).²⁴⁰ Thioamides were selected as C2 aldol donors since the soft Lewis basic character of the thioamide functionality could be chemoselectively activated by the soft Lewis acid/hard Brønsted base catalysts to generate thioamide enolates. The use of a Lewis basic solvent, *e.g.*, DMF, was found to be important and was assumed to prevent product inhibition. Moreover, a strong Brønsted base, namely the lithium salt of 2,2,5,7,8-pentamethylchromanol **108**, was used to maintain the catalytic activity at a lower reaction temperature. Under the optimized conditions, various aliphatic aldehydes were transformed into the corresponding β -hydroxy thioamides in high yields and enantioselectivities. The high chemoselective



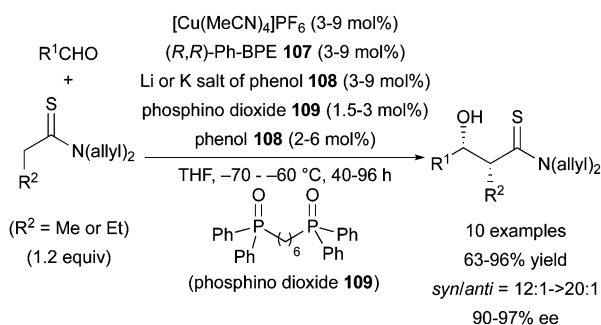
Scheme 115 Nickel(II)-catalyzed aldol reactions of *N*-propionylthiazolidinethione.



Scheme 116 Copper(I)-catalyzed aldol reactions of thioacetamides.

nature of the catalyst system for nucleophilic activation of the thioamide functionality was confirmed by the competitive experiments using thioacetamide and acetophenone. The authors demonstrated that only thioacetamide reacted, even though acetophenone was more prone to form an enolate since it possessed a more acid α -C-H bond. Finally, the conversion of the thioamide functionality to the aldehyde was achieved by utilizing Schwartz's reagent. One limitation of the current system was that aromatic aldehydes were not viable substrates due to the retro-aldol reaction and dehydration of the aldol product. However, in 2010, the same group tuned the reaction conditions to expand the substrate scope to include aromatic aldehydes.²⁴¹ Here, a THF/DMF mixed solvent system attenuated the Brønsted basicity of $\text{Li}(\text{OC}_6\text{H}_4\text{-}i\text{-Pr-OMe})$ and prevented the dehydration of the aldol product at -70°C . Under the modified conditions, aromatic aldehydes were tolerant, and the desired aldol adducts were obtained in good to high yields and enantioselectivities (74–94% yields, 67–91% ees). These catalyst systems were applied for drug synthesis, such as for (*R*)-fluoxetine and duloxetine.²⁴²

In 2011, Kumagai and Shibasaki reported a ternary soft Lewis acid/hard Brønsted base/hard Lewis base cooperative catalyst for the direct enantioselective aldol reactions of thiopropionamides and thiobutyroamides (Scheme 117).²⁴³ The optimal conditions (Scheme 116) for the aldol reaction of thioacetamides resulted in the formation of a racemic aldol product when thiopropionamide was used as the substrate. On the other hand, the authors found that the reaction performed in THF showed excellent enantioselectivity, but resulted in a low chemical yield. The poor

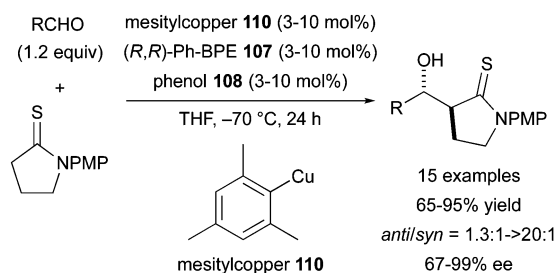


Scheme 117 Copper(I)-catalyzed aldol reactions of thiopropionamides and thiobutyroamides.

observed enantioselectivity in DMF was attributed to rapid retro-aldol reactions occurring in DMF. However a Lewis basic species, such as DMF, was essential for the catalytic turnover. Therefore, appropriate hard Lewis basic additives were explored and they found that 1,6-bis(diphenylphosphino)hexane dioxide **109** was able to facilitate the catalyst turnover. Moreover, the use of phenol **108**, as a proton source, was beneficial for achieving a higher catalytic efficiency and for suppression of the retro-aldol pathway. Various aliphatic aldehydes were utilized for this new reaction conditions and the *cis*-aldol adducts were obtained in good to high yields with excellent diastereo- and enantioselectivities. Control experiments revealed that the strict control of the amount of the hard Lewis basic additive was essential to achieve high stereoselectivity.

Although the above-mentioned copper complex/LiOAr catalyst systems were effective, the catalyst preparation method was complicated and freshly prepared lithium aryloxide solution was required. Therefore, the same group developed a second-generation catalyst, comprising mesitylcopper(I) **110** and Ph-BPE **107**, to simplify the reaction for the enantioselective aldol reactions of thioacetamide with aliphatic aldehydes.²⁴⁴ In contrast to the previous system using a lithium cation, the reaction proceeded without any Lewis basic species and the reaction results were similar with DMF or THF as the solvent. In the new catalyst system, the following catalytic cycle was assumed: (1) mesitylcopper and a thioamide substrate would generate the thioamide enolate intermediate, (2) subsequent addition to the aldehyde would generate a copper aldolate species, and (3) the copper aldolate would function as a soft Lewis acid/hard Brønsted base cooperative catalyst to generate the next enolate intermediate from a thioamide substrate to close the catalytic cycle. This second-generation catalytic system enabled both branched and linear aliphatic aldehydes to undergo asymmetric aldol reactions without self-condensation, and a similar catalytic performance with the previous system was observed. This new copper catalyst system was also applied for the synthesis of drug molecules, such as, atorvastatin,²⁴⁵ and for the total synthesis of a natural product, thuggacin B.²⁴⁶ Moreover, an iterative enantioselective aldol reaction was performed using this methodology to create an all-*syn* polyketide array with four consecutive stereogenic centers.²⁴⁷ This strategy led to an enantioselective total synthesis of (–)-membrenone A and B.

In 2012, Kumagai, Shibasaki, and co-workers reported a mesitylcopper(I) **110**/(*R,R*)-Ph-BPE **107** catalyst system for the enantioselective aldol reactions of thiolactams (Scheme 118).²⁴⁸

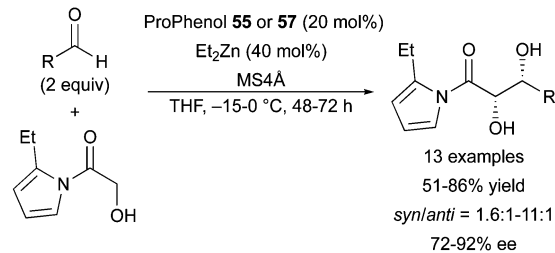


Scheme 118 Copper(I)-catalyzed aldol reactions of thiolactams.

In the presence of phenol **108**, which was used to accelerate the proton-transfer process, the reaction proceeded smoothly to provide the *anti*-adducts in high enantioselectivities. The effect of the protecting group for the thiolactam was examined, and the authors settled on the *p*-methoxyphenyl (PMP) group, since an increase in the enantioselectivity was observed and this was amenable to oxidative removal. The reaction of PMP-protected five-membered thiolactam with a wide range of aliphatic aldehydes was shown to proceed smoothly and the corresponding *anti*-aldol adducts were obtained in good to excellent yields, diastereoselectivities, and enantioselectivities. The asymmetric aldol reaction with aromatic aldehydes showed lower stereoselectivities even though the retro-aldol pathway was not prominent. Moreover, the reaction with six-membered thiolactam produced the aldol products with only a slight preference for *anti*-diastereoselectivity.

Later, the same group reported more detailed studies about the effect of additives and the retro-aldol process in the mesitylcopper(i) catalyst system.²⁴⁹ They observed that in this system, the reaction of α -branched aldehydes and thiopropionamides produced various stereochemical outcomes that were highly sensitive to the reaction conditions, such as catalyst loading and reaction time, and that the retro-aldol process was a serious issue that decreased the stereochemical outcome. Both experimental and computational investigations revealed that the tendency of the retro-aldol reaction was closely related to the steric properties of the product. To prevent such an undesired retro-aldol process, the effects of the additive were examined. The authors found that when a dummy product **111**, which shares the partial structure of the aldol adduct process, was used as an additive, the retro-aldol reaction was suppressed due to the additive competitively binding to the catalyst to kinetically retard re-entry of the product into the retro-aldol cycle. Consequently, the aldol products from branched aldehydes were obtained in high enantioselectivities under the newly optimized conditions (Scheme 119).

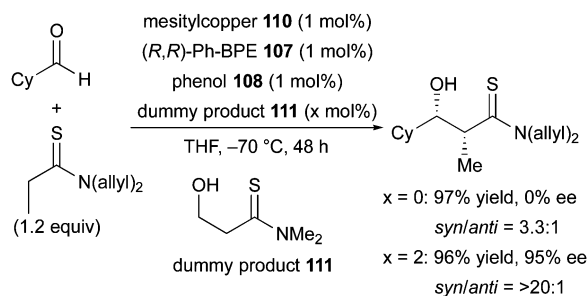
In 2013, Trost and co-workers reported a zinc(II)-ProPhenol complex as a catalyst for the enantioselective aldol reactions of α -hydroxyacetate with activated ester equivalents (Scheme 120).^{250,251} Several activated ester structures were examined, and the authors found that the reaction with *N*-(α -hydroxyacetyl)-2-ethylpyrrole gave the best results, while additional optimization studies led to the conditions that enabled a wide variety of



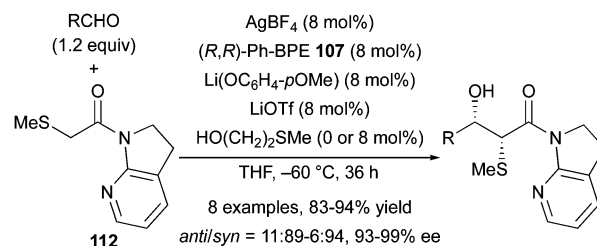
Scheme 120 Dinuclear zinc(II)-catalyzed α -hydroxyacetate aldol reactions with activated ester equivalents.

aliphatic aldehydes to undergo the asymmetric aldol reaction to generate the corresponding *cis*-diols in moderate to high yields, diastereoselectivities, and enantioselectivities. Aromatic aldehydes and cinnamyl aldehydes could also be used as substrates to provide the aldol adducts with high enantioselectivities; however, low diastereoselectivities were observed (< 2 : 1).

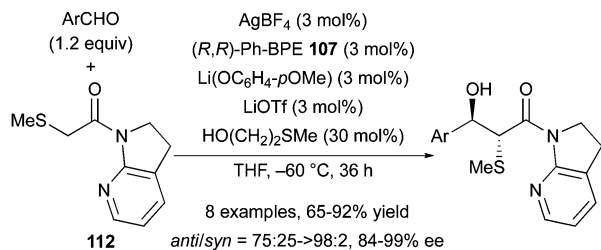
In 2014, Kumagai, Shibasaki, and co-workers reported the use of the α -sulfanyl 7-azaindolinyllamide **112** as an aldol donor in enantioselective aldol reactions.²⁵² The authors believed that since the designed ester equivalent **112** preferred the *E* amide rotamer, it would undergo facile bidentate coordination with the soft Lewis acid to form the seven-membered chelated structure. The authors hypothesized that chelation would induce tilting of the indolino group to diminish amide conjugation to facilitate the formation of the amide-derived enolate under mild basic conditions. With these considerations in mind, the authors found that the enantioselective aldol reactions of amide **112** and enolizable aliphatic aldehydes could be achieved using a soft Lewis acid/hard Brønsted base cooperative catalysis, such as $\text{AgBF}_4/\text{LiOAr}$. Under optimized conditions, several aliphatic aldehydes were converted to the corresponding *syn*-adducts in high yields and selectivities (Scheme 121). In some instances, the addition of a dummy product, *i.e.*, 2-methylthioethanol, was beneficial for improving the stereoselectivity of the aldol reaction since the additive could suppress the undesired retro-aldol reaction. For asymmetric aldol reactions with aromatic aldehydes, the reactions proceeded faster than with aliphatic aldehydes. However, retro-aldol reactions easily occurred, and the use of 2-methylthioethanol was essential to suppress these retro-aldol reactions. With the modified conditions, the desired *anti*-products could be obtained in good to high yields and selectivities (Scheme 122). The authors also demonstrated that



Scheme 119 Representative example of the additive effect for the mesitylcopper-catalyzed aldol reaction.



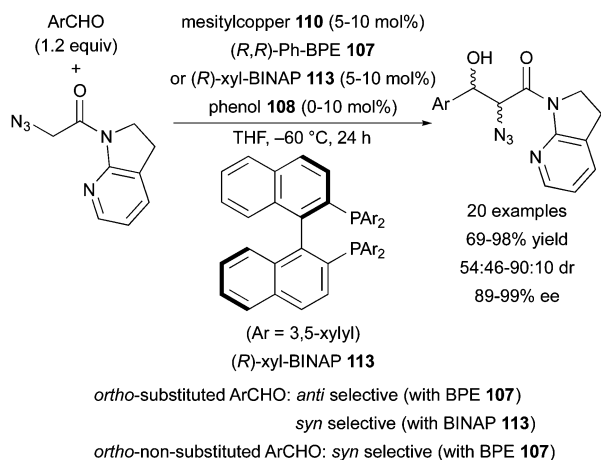
Scheme 121 Silver/lithium-catalyzed aldol reactions of α -sulfanyl 7-azaindolinyllamide with aliphatic aldehydes.



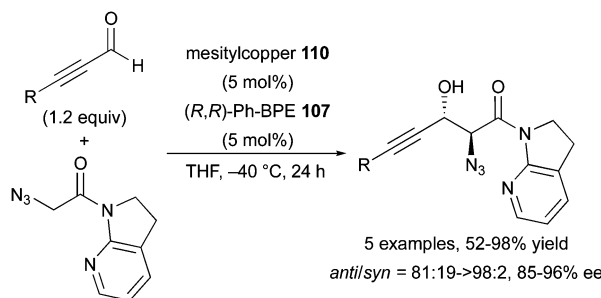
Scheme 122 Silver/lithium-catalyzed aldol reactions of α -sulfanyl 7-azaindolylamide with aromatic aldehydes.

7-azaindolylamides could be easily reduced selectively to aldehydes or alcohols by choosing the appropriate reductants.

In 2015, Kumagai, Shibasaki, and co-workers reported mesitylcopper **110**-based catalyst systems for enantioselective aldol reactions of α -azido 7-azaindolylacetamide with aromatic aldehydes (Scheme 123) or ynals (Scheme 124).²⁵³ When the asymmetric aldol reaction was investigated with *ortho*-substituted aryl aldehydes, they found that the diastereoselectivity could be switched by changing the chiral diphosphine ligand. Specifically, the catalyst prepared from (R,R)-Ph-BPE **107** showed *anti*-selectivities, while the catalyst prepared from (R)-xyl-BINAP **113** showed *syn*-selectivities. On the other hand, in the reaction with *ortho*-non-substituted aryl aldehydes, the



Scheme 123 Copper(i)-catalyzed aldol reactions of α -azido amides with aromatic aldehydes.

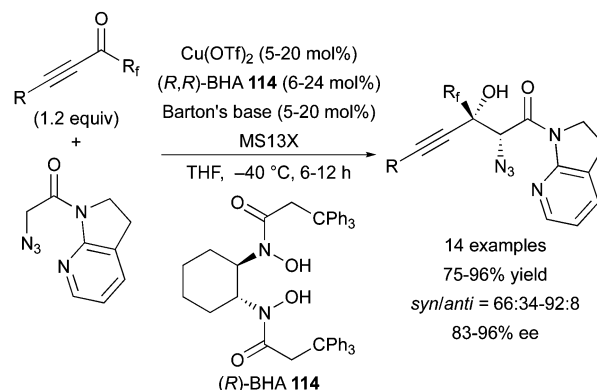


Scheme 124 Copper(i)-catalyzed aldol reactions of α -azido amides with ynals.

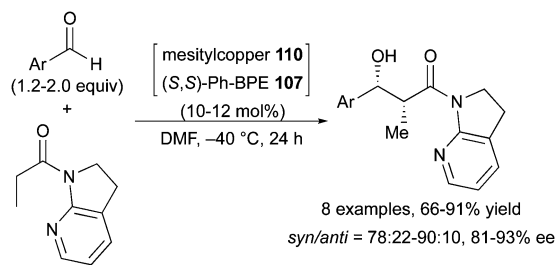
opposite selectivities, *i.e.*, *syn*-selectivities, were observed when (R,R)-Ph-BPE **107** was used. The authors also investigated the asymmetric reactions with ynals using (R,R)-Ph-BPE **113** as a ligand and observed that *anti*-aldol products could be obtained. In all cases, high to excellent enantioselectivities were observed.

In 2017, the same group expanded the scope of the enantioselective aldol reactions of α -azido 7-azaindolylacetamide to α -fluorinated ynones (Scheme 125).²⁵⁴ When the copper(i) catalyst system was applied for the aldol reaction with an alkynyl trifluoromethyl ketone, diastereoselectivity was found to be almost non-existent. Optimization studies revealed that the combination of Cu(OTf)₂, bishydroxamic acid (BHA **114**), and Barton's base led to an active catalyst that enabled the asymmetric aldol reactions to occur with a wide variety of alkynyl trifluoromethyl ketones to afford the corresponding *syn*-adducts in high to excellent yields, diastereoselectivities, and enantioselectivities. Since a methyl ester variant of BHA **114** led to poor diastereoselectivity, it was assumed that the high stereoselectivity in the current system arose from non-bonding interactions involving fluorine atoms and the acidic protons in the ligand. Moreover, the reactions with CHF₂, CF₂Cl, and CF₂Br ketones also proceeded under the optimized conditions to give *syn*-adducts in high yields and enantioselectivities. The decrease in diastereoselectivity found in the reaction with a CHF₂ ketone was in agreement with the transition states controlled by non-bonding interactions. Detailed mechanistic studies suggested a bifunctional role of the copper(ii)/BHA **114** complex: (1) activation of the amide as a Lewis acid, and (2) deprotonation of the α -proton by a Brønsted base. In the latter role, copper-hydroxamate was believed to be responsible for the enolization of the amide rather than the Barton's base.

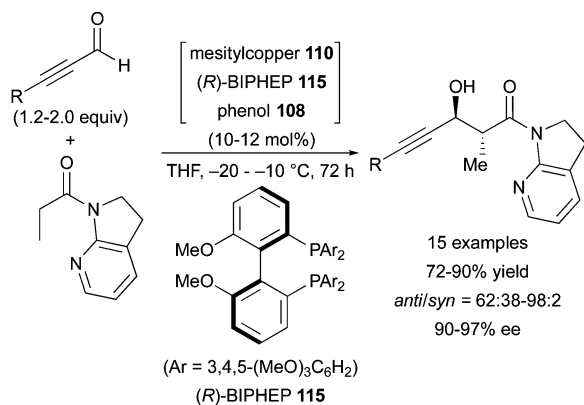
In 2017, Kumagai, Shibasaki, and co-workers reported a copper(i) complex as a catalyst for the enantioselective aldol reactions of α -alkyl 7-azaindoline amide with aromatic aldehydes (Scheme 126) or ynals (Scheme 127).²⁵⁵ They found that the enolization of 7-azaindoline amides was possible even without an electron-withdrawing group at the α -position, as it could readily isomerize to the *Z* conformation in the presence of a soft Lewis acid to form an activated chelate with a carbonyl group. The reactions with aromatic aldehydes proceeded smoothly in



Scheme 125 Copper(ii)-catalyzed aldol reactions of α -azido amides with α -fluorinated ynones.



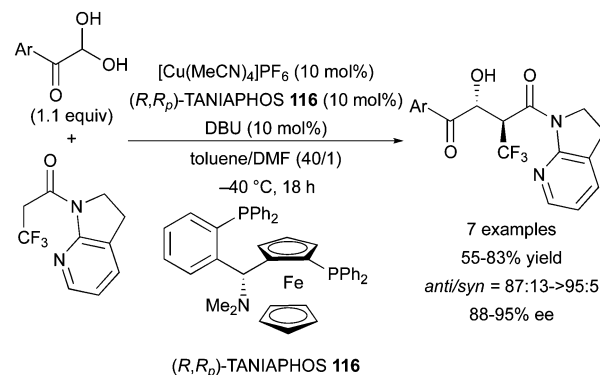
Scheme 126 Copper(I)-catalyzed aldol reactions of α -alkyl amides with aromatic aldehydes.



Scheme 127 Copper(I)-catalyzed aldol reactions of α -alkyl amides with ynals.

the presence of mesitylcopper **110**/Ph-BPE **107** to afford *syn*-adducts in high to excellent selectivities. On the other hand, reactions with ynals were catalyzed by mesitylcopper **110**/trimethoxy-Biphep **115** in the presence of a proton source to afford *anti*-adducts in high to excellent selectivities. The difference in diastereoselectivities was explained by the nature of the substrates. Namely, the sterics around the carbonyl group or weak secondary interactions between the triple bond and copper(I) were believed to cause significant difference in the prochiral face selection of aldehydes.

In 2017, Kumagai, Shibasaki, and co-workers reported copper(I) complex-catalyzed enantioselective aldol reactions of α -CF₃ 7-azaindoline amide with arylglyoxal hydrates (Scheme 128).²⁵⁶ One of the problems associated with the aldol reaction of α -CF₃ carbonyl compounds is the instability of α -CF₃ enolates due to β -fluoride elimination triggered by strong metal-fluorine interactions. Their designed amide was hypothesized to provide a solution to this issue by employing a chelating unit that prevents direct metal contact with the fluorine atoms of the CF₃ group. The use of the copper(I)-TANIAPHOS **116** complex as a catalyst and DBU as a base allowed the asymmetric aldol reactions to proceed with several arylglyoxal hydrates, and the corresponding *anti*-adducts were obtained in good yields and excellent selectivities. The authors examined the pK_a values of 7-azaindolineacetamide and structurally related amides in DMSO were calculated computationally and their reactivity were compared. Although 7-azaindolineacetamide



Scheme 128 Copper(I)-catalyzed aldol reactions of α -CF₃ amides with arylglyoxal hydrates.

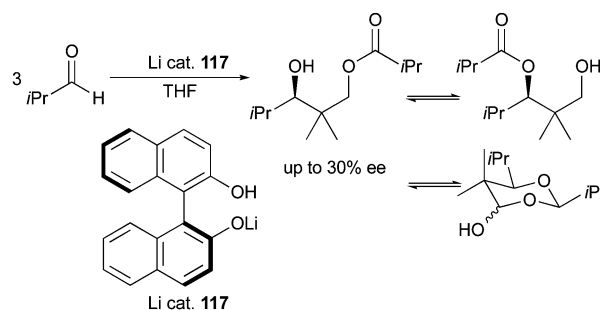
possessed a relatively high pK_a value (30.4), other more acidic amides failed to yield the aldol adducts, which indicated the importance of the bidentate coordination of amides to the copper catalyst.

3.5. Aldol-Tishchenko reactions

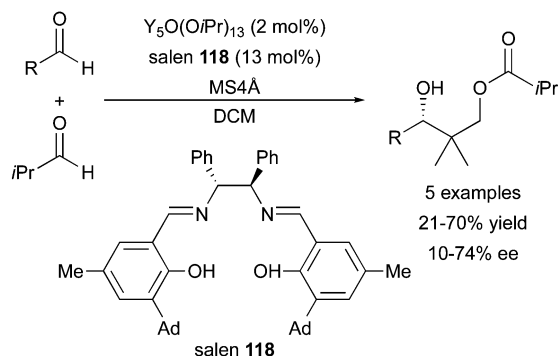
Discovered in 1906, the Tishchenko reaction involves the disproportionation of an aldehyde in the presence of an alkoxide to generate the corresponding ester.²⁵⁷ A tandem process involving an aldol reaction and a Tishchenko reaction, the so-called aldol-Tishchenko reaction, is a powerful method to access *anti*-1,3-diol monoesters with three adjacent stereogenic centers from aldehydes and ketones. Although early research in to aldol-Tishchenko reactions appeared at the end of nineteenth century, its enantioselective variants were not achieved for a long time.^{258,259}

The enantioselective version of the catalytic aldol-Tishchenko reaction was pioneered by Mäeorg and co-workers, and in 1998 and 1999, they reported a chiral oxylithium **117** as a catalyst for the self-condensation of 2-methylpropanal (Scheme 129).^{260,261} In this initial report, a low enantioselectivity was obtained and the authors hypothesized that the poor observed enantioselectivity was due to the poor stereocontrol ability of the chiral catalyst and the various equilibrium reactions that gave the 1,3-migrated adduct and aldoxanes.

In 2001, Morken and co-workers reported the first catalytic asymmetric aldol-Tishchenko reactions between two different



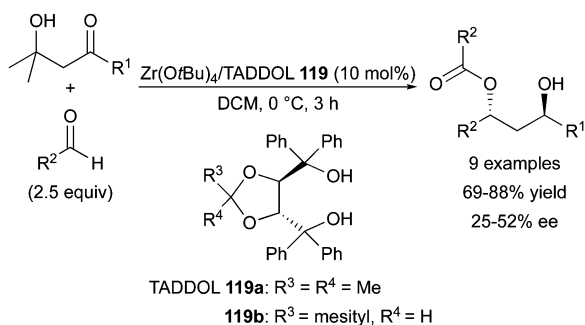
Scheme 129 Self-condensation of 2-methylpropanal with a chiral lithium catalyst.



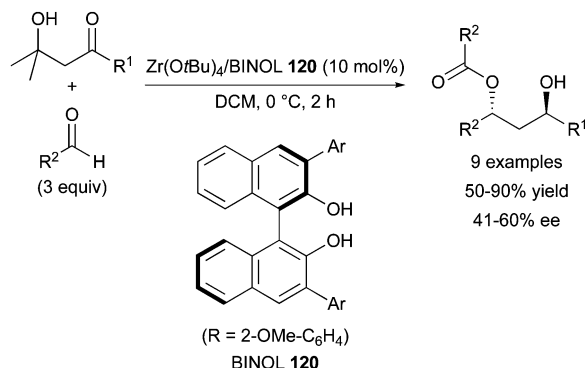
Scheme 130 Yttrium-catalyzed aldol–Tishchenko reaction with aromatic aldehydes and 2-methylpropanal.

aldehydes (Scheme 130).²⁶² The yttrium complex with a salen-type ligand **118** was found to be the optimal catalyst for the condensation between several types of aromatic aldehydes and 2-methylpropanal, and the corresponding 1,3-glycol monoesters were obtained in good enantioselectivities. When the racemic aldol adduct, derived from benzaldehyde and 2-methylpropanal, was subjected to the reaction conditions in the presence of isobutyraldehyde, the aldol–Tishchenko adduct was obtained in a good enantioselectivity, which indicated that the Tishchenko reduction was slower than the retro-aldol reaction.

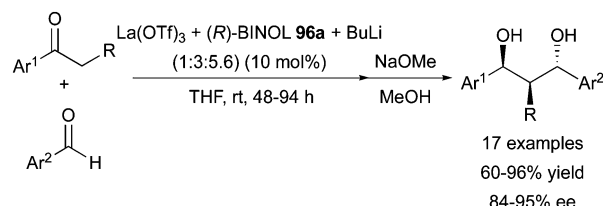
In 2003, Schneider and co-workers reported the first example of enantioselective aldol–Tishchenko reactions of ketone aldol adducts (Scheme 131).²⁶³ Ketone aldol adducts are typically used as precursors of metal enolates formed *in situ* through a retro-aldol process in the presence of zirconium- or aluminum-based catalysts.^{264,265} A chiral zirconium complex prepared from $\text{Zr}(\text{OtBu})_4$ and the tartaric acid-derived chiral ligand, TADDOL **119**, was found to catalyze the enantioselective version of the reaction with several aliphatic aldehydes to afford the 1,3-*anti*-diol monoesters in good yields, complete *anti*-diastereocontrol, and moderate enantioselectivities. In 2006, the same group improved their zirconium catalyst systems by using 3,3'-substituted binaphthol (BINOL **120**) as a chiral ligand. The new system was applied for the enantioselective aldol–Tishchenko reactions of aromatic ketone aldol adducts to provide the corresponding 1,3-*anti*-diol monoesters in high yields, complete *anti*-diastereocontrol, and moderate enantioselectivities (Scheme 132).²⁶⁶



Scheme 131 Zirconium-catalyzed aldol–Tishchenko reactions of aliphatic ketone aldol adducts.



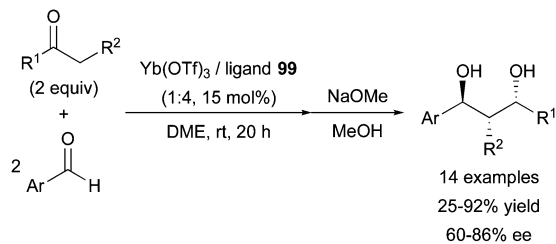
Scheme 132 Zirconium-catalyzed aldol–Tishchenko reactions of aromatic ketone aldol adducts.



Scheme 133 Lanthanum-catalyzed direct aldol–Tishchenko reactions of propionate equivalents.

In 2004, Shibasaki and co-workers reported lanthanum-catalyzed direct enantioselective aldol–Tishchenko reactions of propionate equivalents (Scheme 133).²⁶⁷ The direct aldol reaction of ethyl ketones is challenging since these substrates have a strong tendency toward retro-aldol reactions. It was assumed that an irreversible Tishchenko reaction could overcome the retro-aldol reaction problem. The authors found that a catalytic system formed by the mixture of $\text{La}(\text{OTf})_3$, BINOL **96a** and BuLi with a ratio of 1:3:5.6 allowed a wide variety of aromatic ketones with an electron-withdrawing group and aromatic aldehydes to undergo enantioselective aldol–Tishchenko reactions, whereupon a subsequent hydrolysis provided the corresponding diols in high yields and enantioselectivities. When a racemic aldol adduct was used as a starting material, the product was obtained in a good enantioselectivity, which indicated a rapid retro-aldol cleavage of the metal aldolate and the essential role of the Tishchenko reaction for control of the stereoselectivity. They also discovered that LiOTf promoted a dynamic structural change in LLB **53** to generate a binuclear $[\text{La}_2\text{--Li}_4(\text{binaphthoxide})_5]$ complex, whose structure was determined by X-ray crystallography.²⁶⁸ The results from ESI-MS, CSI-MS, ^{13}C NMR spectroscopy, and experiments of the concentration effects suggested that the active species was an oligomeric species consisting of LLB **53**, the binuclear complex, $\text{Li}_2(\text{binol})$, and LiOTf .

In the same year, Mlynarski and co-workers reported a ytterbium-catalyzed enantioselective aldol–Tishchenko reaction of aldehydes and aliphatic ketones.²⁶⁹ After catalyst screening, the $\text{Yb}(\text{OTf})_3$ –(*S,S*)-hydrobenzoin complex was found to be the most promising catalyst for the condensation reaction,

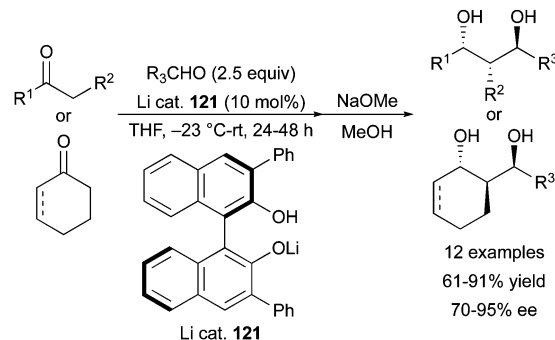


Scheme 134 Ytterbium-catalyzed aldol–Tishchenko reaction of aldehydes and aliphatic ketones.

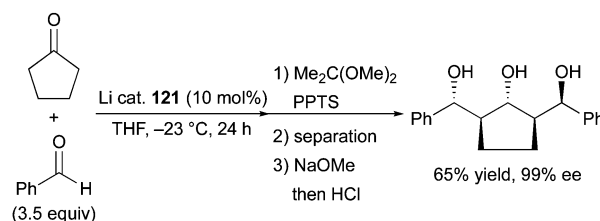
and moderate enantioselectivity was observed in the presence of a tertiary amine. Later, the same group improved their catalyst systems by utilizing a chiral ytterbium catalyst derived from $\text{Yb}(\text{OTf})_3$ and ephedrine-type aminoalcohol **99** (Scheme 134).^{270,271} They found that the improved catalyst provided mixtures of regioisomeric 1,3-diol monoesters in similar enantiopurities, suggesting that an intramolecular acyl migration occurred after formation of the aldol–Tishchenko product. Subsequent hydrolysis gave the corresponding diols in moderate to high yields and moderate to good enantioselectivities for various aromatic aldehydes and ketones. When the *syn*-racemic hydroxyketone (aldol adduct) was subjected to the current catalyst system, the corresponding 1,2-*anti*-1,3-*anti*-Tishchenko product was obtained with 70% ee. This result strongly indicated that the Tishchenko reduction step is slower than the retro-aldol reaction, and is the stereo-determining step.

In 2008, the same group investigated ytterbium complexes with chiral bis(ester) and bis(amide) ligands for the aldol–Tishchenko reactions of aromatic aldehydes with ketones.²⁷² The ligands were readily prepared in their enantiomerically pure form by reacting (*S,S*)-hydrobenzoin or (*S,S*)-diphenylethylenediamine with various chiral amino acids. Although extensive optimization of the chiral ligand structure was performed, the desired product was obtained in a moderate enantioselectivity (up to 64% ee). In 2011, the same group examined amino acid-derived esters as chiral ligands for the ytterbium-catalyzed aldol–Tishchenko reaction of aromatic aldehydes with aliphatic ketones.²⁷³ The chiral ligands were readily prepared (in two steps) from inexpensive chiral sources, with the sterically hindered mesityl-derived ester chosen as the most promising ligand, which provided the aldol–Tishchenko product in a moderate enantioselectivity (up to 50% ee).

In 2011 and 2012, Nakajima and co-workers reported a dilithium 3,3'-diphenylbinaphtholate **121** catalyst for enantioselective direct aldol–Tishchenko reactions (Scheme 135).^{273,274} After the asymmetric aldol–Tishchenko process, hydrolysis of the aldol–Tishchenko adducts afforded the desired chiral 1,3-diols. The lithium catalyst systems worked for various substrates, including acyclic, cyclic, and unsaturated ketones, as aldol donors to provide the 1,3-diols with high enantioselectivities. They found that the reactions of acyclic ketones led to 1,2-*syn*-1,3-*anti*-diol derivatives, whereas the reactions of cyclic ketones provided 1,2-*anti*-1,3-*anti*-diol derivatives. For the aldol–Tishchenko reaction of cyclopentanone, a highly enolizable aldol donor was observed, with the product derived



Scheme 135 Lithium-catalyzed aldol–Tishchenko reactions of aldehydes and ketones.



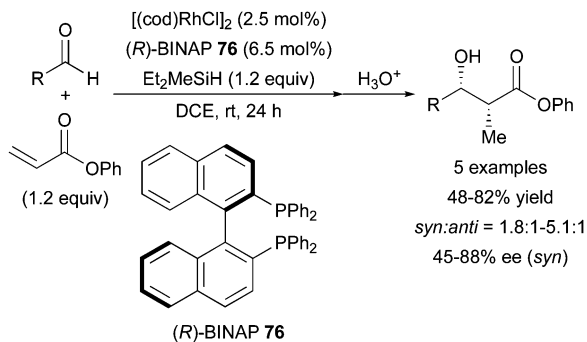
Scheme 136 Lithium-catalyzed successive aldol–aldol–Tishchenko reaction.

from a sequential double aldol and Tishchenko reaction. By increasing the equivalents of benzaldehyde, and the subsequent conversion to acetonides, to separate the diastereomers, followed by hydrolysis, a triol derivative, with five consecutive chiral centers, was afforded in a good yield and with excellent enantioselectivity (Scheme 136).

3.6. Reductive aldol reactions

The reductive aldol reaction is a sequential process that involves a conjugate reduction of an α,β -unsaturated carbonyl group with a hydride, followed by the subsequent aldol reaction of the reaction intermediate toward another carbonyl group as an aldol acceptor. The advantage of this method is that the pre-synthesis of enolate species is not necessary, and instead the reactive intermediate can be generated *in situ* without the use of strong bases. Therefore, the generation of enolate species from less acidic carbonyl compounds, such as esters, can be easily achieved from the corresponding unsaturated compounds, and regioselective enolates of nonsymmetric ketones may also be possible using this approach. The challenges with the reductive aldol reactions are achieving stereocontrol and suppressing competing reactions, such as the reductions of carbonyl groups and/or olefins.

In 2000, Morken and co-workers reported the first example of enantioselective reductive aldol reactions (Scheme 137).²⁷⁵ A chiral rhodium complex, prepared from a $\text{Rh}(\text{I})$ source and (*R*)-BINAP **76**, was utilized for asymmetric reductive aldol reactions with aldehydes and acrylates in the presence of Et_2MeSiH as a reductant. The reaction with phenyl acrylate led to better diastereoselectivities and various aldehydes were converted to the corresponding β -hydroxy esters in moderate *syn*-selectivities

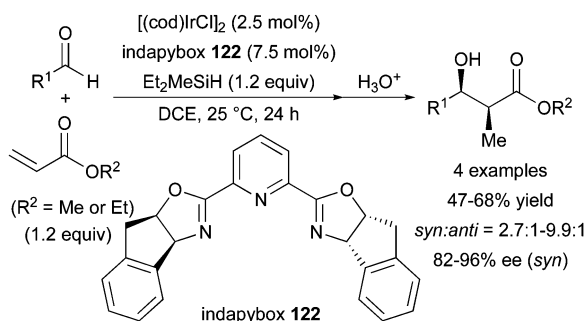


Scheme 137 Rhodium-catalyzed reductive aldol reactions with acrylate.

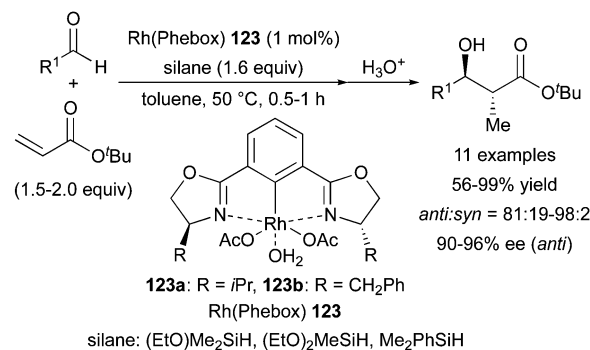
and high enantioselectivities. Preliminary mechanistic experiments, such as deuterium-labeled experiments, indicated that the silane hydrogen was transferred to the acrylate β-carbon, and it was confirmed that silyl ketene acetal intermediates were not involved in the catalytic cycle. In 2004, the same group conducted further mechanistic studies, including a stereochemical analysis of the reaction products and the detection of transition metal species by NMR analysis, and proposed that the reductive aldol reaction proceeds by the addition of a rhodium(i) hydride, generated *in situ* from a dimeric rhodium species, to the acrylate to generate a rhodium(i) enolate intermediate, followed by the stereochemistry-controlling aldol addition reaction.²⁷⁶ On the basis of this hypothesis, the reaction conditions were tuned and the substrate scope was successfully expanded to include various unsaturated aldehydes as aldol acceptors and crotonate derivatives as enolate precursors. In 2005, the same group examined the effect of silanes for the rhodium–BINAP catalyst system.²⁷⁷ They found that Me₂PrSiH was highly selective for the formation of silylated propionate adducts *versus* acylated aldol adducts.

In 2001, Morken and co-workers reported an iridium–indapybox **122** complex as a catalyst for enantioselective reductive aldol reactions with aldehydes and acrylates (Scheme 138).²⁷⁸ The catalytic system showed excellent enantioselectivities for asymmetric reactions with benzaldehyde and α-alkoxy aldehydes, but they found that an aliphatic aldehyde and cinnamaldehyde hardly reacted.

In 2005, Nishiyama and co-workers reported a rhodium(iii) complex, prepared from a C₂-symmetric N–C–N chiral ligand,



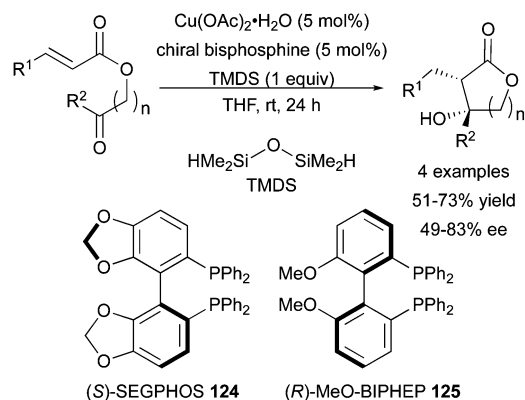
Scheme 138 Iridium-catalyzed reductive aldol reactions with acrylate.

Scheme 139 Rhodium(Phebox)-catalyzed reductive aldol reactions of *tert*-butyl acrylate.

Phebox, as a catalyst for the enantioselective reductive aldol reactions of aldehydes and *tert*-butyl acrylate (Scheme 139).²⁷⁹ Unlike the Morken rhodium–BINAP catalyst, high *anti*-selectivities were observed in the rhodium–Phebox catalyst system. Further, both aromatic and aliphatic aldehydes could be converted to the corresponding β-hydroxy esters in high yields, with high *anti*-selectivities and excellent enantioselectivities in the presence of 1 mol% rhodium catalyst. It was confirmed that the silylketene acetal species, obtained from Me₂PhSiH, were inactive for the aldol reaction. On the other hand, the silylketene acetal species obtained from (EtO)₂MeSiH could react with benzaldehyde to provide racemic aldol products with high *syn*-selectivities. These results suggested that the aldol reaction occurred on the rhodium metal. The same group then examined the effect of substitutions on the phenyl ring of the Phebox ligand.²⁸⁰ They found that the effect was not significant; for instance, 4-nitro-substituted catalysts showed a slight increase in the *anti*-selectivity and enantioselectivity of the reductive aldol reaction. Wu and co-workers computationally investigated the detailed mechanism for the reductive aldol reaction, and their studies suggested that the most favorable pathway involved five steps: (1) oxidative addition of hydrosilane to rhodium, (2) hydride migration to the C–C double bond of the acrylate, (3) tautomerization from the rhodium-bound C-enolate to the rhodium-bound O-enolate, (4) aldol reaction with benzaldehyde, and (5) reductive elimination to regenerate the catalyst and release the product.²⁸¹ They determined that the hydride migration step was the rate-determining step, with an activation barrier of 23.3 kcal mol^{−1}.

In 2005, Lam and co-workers reported copper(ii)–bisphosphine complex-catalyzed asymmetric intramolecular reductive aldol cyclizations (Scheme 140).²⁸² In the presence of 1,1,3,3-tetramethylhydrosiloxane (TMDS) as a reductant, chiral bisphosphine ligands, such as BINAP **76**, SEGPHOS **124**, and MeO-BIPHEP **125**, were screened for several substrates and the corresponding five- and six-membered β-hydroxylactones were obtained in moderate to good enantioselectivities.

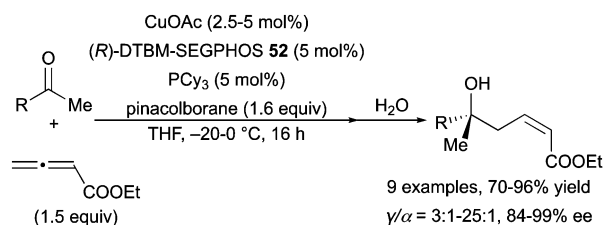
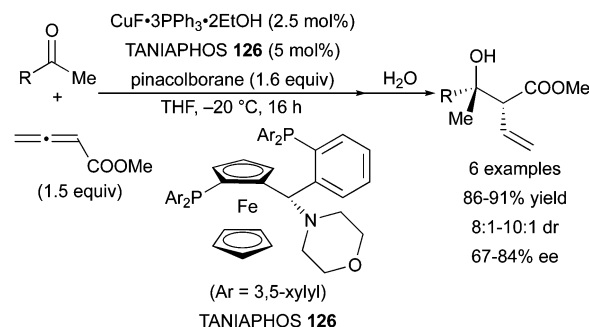
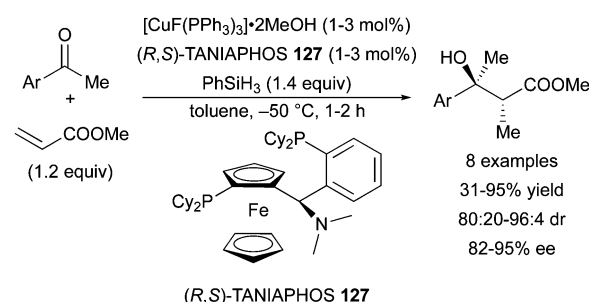
In 2006, Kanai, Shibasaki, and co-workers reported the first example of intermolecular enantioselective reductive aldol reactions to ketones.²⁸³ Initially, they examined the combination of CuF₃·3PPh₃·2EtOH, which was found to be effective



Scheme 140 Copper-catalyzed intramolecular reductive aldol cyclization.

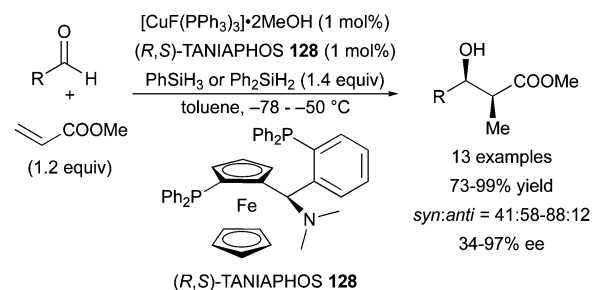
for the aldol reaction of ketene trimethylsilyl acetals to simple ketones,²⁸⁴ and several chiral diphosphine ligands to generate chiral copper complexes, and then examined them as catalysts for enantioselective reductive aldol reactions. In the presence of trialkoxysilane as a reductant, the reductive aldol reactions with acetophenone and methyl acrylate proceeded and only low diastereoselectivities and enantioselectivities were observed (up to 30% ee). On the other hand, reactions between symmetric ketones and crotonates provided the desired products in high yields and good enantioselectivities (up to 82% ee). Additionally, reactions with acetophenone derivatives and an allenic ester were examined in the presence of pinacolborane as a reductant, and γ -*cis* adducts were obtained in excellent enantioselectivities, but with poor yields and regioselectivities. Based on these results, further investigations were conducted and an improved asymmetric reductive aldol reaction of allenic esters and ketones was developed with a chiral copper(I) complex as the catalyst.²⁸⁵ The authors found that the combination of CuOAc/(*R*)-DTBM-SEGPHOS **52**/PCy₃ (1:2:3) significantly improved the γ/α regioselectivity and the yield without any loss of enantioselectivity (Scheme 141). Furthermore, both aromatic and aliphatic ketones could be converted to the corresponding γ -*cis* adducts in high yields, with high regioselectivities and excellent enantioselectivities. The γ/α regioselectivity could be switched when Taniaphos-type ligands were used, with various α -products of the reductive aldol reactions with aromatic ketones obtained in high yields, diastereoselectivities, and enantioselectivities (Scheme 142).

Riant and co-workers reported chiral copper(I) complex-catalyzed enantioselective reductive aldol reactions of ketones with

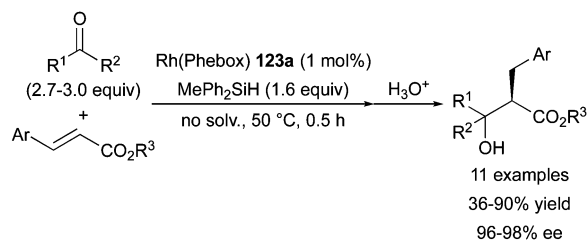
Scheme 141 Copper-catalyzed γ -*cis*-selective reductive aldol reactions of allenic esters to ketones.Scheme 142 Copper-catalyzed α -selective reductive aldol reactions of allenic esters to ketones.

Scheme 143 Copper-catalyzed reductive aldol reactions of aromatic ketones with methyl acrylate.

methyl acrylate using PhSiH₃ as a reductant (Scheme 143).²⁸⁶ They chose PhSiH₃ as a reductant due to its ability to not form stable silyl enol ethers upon transmetalation with the copper enolate intermediates, and a chiral copper(I) catalyst, prepared from CuF·3PPh₃·2MeOH and TANIAPHOS **127**, was shown to be an effective catalyst for the reductive aldol reactions using aromatic ketones, and the desired *erythro* isomers of β -hydroxy esters were obtained in high yields, diastereoselectivities, and enantioselectivities. A similar catalyst system was applied for the enantioselective reductive aldol reactions of aldehydes with methyl acrylate (Scheme 144).²⁸⁷ It was found that by using TANIAPHOS **128** as a chiral ligand, and either PhSiH₃ or PhSiH₂ as a reductant, various aldehydes, including aliphatic, aromatic and heteroaromatic aldehydes, could be employed in the asymmetric reductive aldol reaction to furnish the desired *syn*-products with good to high enantioselectivities, albeit with low diastereoselectivities in some cases.



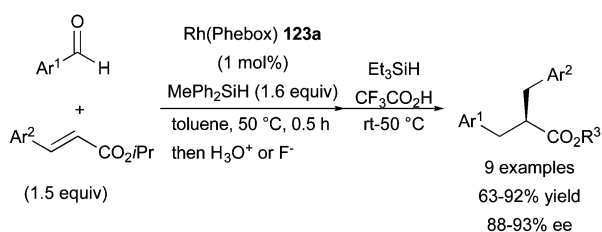
Scheme 144 Copper-catalyzed reductive aldol reactions of aldehydes with methyl acrylate.



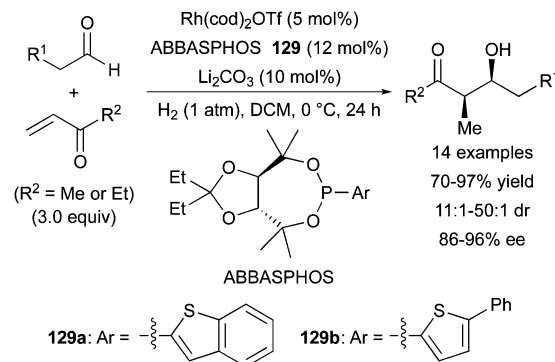
Scheme 145 Rhodium-catalyzed reductive aldol reactions of cinnamates and ketones.

In 2007, Nishiyama and co-workers reported a rhodium(Phebox) **123a** complex as a catalyst for enantioselective reductive aldol reactions of cinnamates and ketones using MePh_2SiH as a reductant (Scheme 145).²⁸⁸ They found that when using acetone as both a substrate and solvent, the asymmetric reductive aldol reaction with several cinnamates proceeded smoothly to provide the corresponding esters bearing β-tertiary alcohols in high yields and excellent enantioselectivities. When a cyclic ketone and various linear ketones were examined as aldol acceptors, the desired products were obtained in excellent enantioselectivities. Although the reductive process with methyl ethyl ketone led to a low diastereoselectivity, the reaction with acetophenone provided the desired product in a high diastereoselectivity (96:4). The rhodium(Phebox) catalyst system was applied for enantioselective reductive aldol reactions with substituted cinnamates and aromatic aldehydes, and after dehydroxylation of the reductive aldol products, various α-chiral dihydrocinnamates were obtained in high yields and enantioselectivities (Scheme 146).²⁸⁹

In 2008, Krische and co-workers reported the first example of enantioselective reductive aldol reactions of vinyl ketones mediated by hydrogen gas (Scheme 147).²⁹⁰ Based on their previous studies, an achiral rhodium(I) complex prepared from monodentate and π-acidic ligands was found to be suitable for the reductive aldol reactions of vinyl ketones.²⁹¹ To achieve the enantioselective variant, TADDOL-like phosphonites were designed as a chiral ligand. The authors identified three key structural elements of the ligand: (1) the *P*-aryl moiety, (2) the ketal substructure, and (3) the groups appended to the tertiary carbinol center, which were independently optimized. After optimization, they found that ABBASPHOS **129a** and **129b** were the most promising ligands and the chiral rhodium catalysts derived from these ligands were shown to be efficient for the asymmetric aldol reaction with various aldehydes, including



Scheme 146 Asymmetric synthesis of dihydrocinnamates with aryl aldehydes and cinnamates.

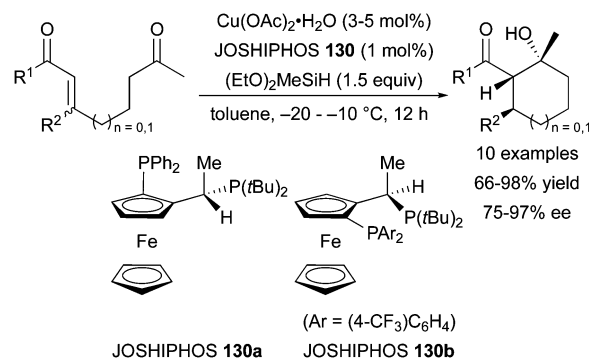


Scheme 147 Rhodium-catalyzed hydrogenative aldol reactions of vinyl ketones.

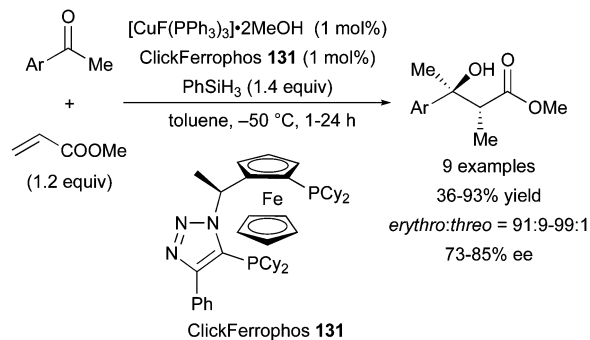
β- or γ-heteroatom-substituted aldehydes and α-(hetero)aryl aldehydes, providing the desired chiral alcohols in high to excellent yields, diastereoselectivities, and enantioselectivities.

In 2008, Lipshutz and co-workers reported a chiral CuH catalyst for the enantioselective intramolecular reductive aldol reactions of β,β-disubstituted enones (Scheme 148).²⁹² Using JOSIPHOS **130** as a chiral ligand and $(\text{EtO})_2\text{MeSiH}$ as the reductant, both *E*- and *Z*-methyl enone pairs gave the desired cyclization products in high yields and enantioselectivities. In addition, they found that a heterogeneous copper source, Cu/C, in the presence of NaOPh (10–20 mol%) and with $(\text{EtO})_2\text{MeSiH}$ could also be used to enable enantioselective intramolecular reductive aldol reactions. They also demonstrated that the asymmetric reductive aldol reaction could be performed under micellar conditions, using nanomicelle-forming PTS²⁹³ (a nonionic, vitamin E-based surfactant; 2% by weight) and excess PhSiH_3 .

In 2009, Fukuzawa and co-workers reported a chiral copper complex as a catalyst for the enantioselective reductive aldol reactions of acetophenone derivatives with methyl acrylate (Scheme 149).²⁹⁴ They developed a family of triazole-group-substituted chiral ferrocenyl diphosphine ligands, ClickFerrophos, and examined them as chiral ligands in copper-catalyzed enantioselective reductive aldol reactions. They found ClickFerrophos **131**, bearing dicyclohexylphosphine moieties, was the optimal chiral ligand and consequently they performed reductive aldol reactions with various aromatic aldehydes to afford the corresponding



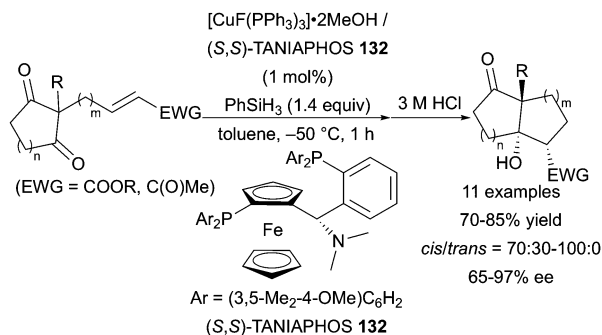
Scheme 148 Copper-catalyzed intramolecular reductive aldol reactions of β,β-disubstituted enones.



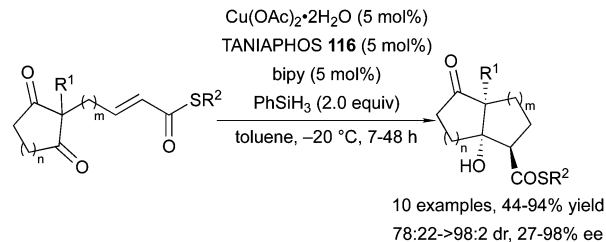
Scheme 149 Copper-ClickFerrophos-catalyzed reductive aldol reactions of aromatic ketones with methyl acrylate.

erythro adducts in excellent diastereoselectivities and good to high enantioselectivities. Compared with Taniaphos,²⁸⁶ ClickFerrophos provided the desired products with higher diastereoselectivities, although the enantioselectivity was not as high as that achieved with Taniaphos as a ligand.

Riant and co-workers reported copper(I)-catalyzed enantioselective desymmetrizing reductive aldol cyclizations, using PhSiH₃ as a reductant, to synthesize chiral bicyclic compounds (Scheme 150).^{295,296} They examined several chiral diphosphines and found that the catalyst prepared from (*S,S*)-TANIAPHOS 132 showed excellent *cis*-selectivity. Using the optimal chiral catalyst, various unsaturated esters and ketones were converted to the corresponding *cis*-bicyclic compounds in high yields, diastereoselectivities, and enantioselectivities. The conversion of the obtained bicyclic products, bearing an allyl group (R = allyl), to tricyclic adducts was also demonstrated. In 2012, Chiu and co-workers reported that unsaturated thioesters could be utilized in enantioselective desymmetrizing reductive aldol cyclizations.²⁹⁷ A chiral copper catalyst, prepared from Cu(OAc)₂·H₂O and TANIAPHOS 116, was found to be the optimal catalyst, and consequently the asymmetric aldol reaction, in the presence of PhSiH₃, yielded the desired bicyclic compounds, bearing a thioester group, in excellent diastereoselectivities and enantioselectivities (up to >98:2 dr, up to 96% ee). The same group made further improvements and found that by using bipyridine (bipy) as an additive, the rate of the reaction could be enhanced without diminishing the



Scheme 150 Copper-catalyzed desymmetrizing reductive aldol cyclizations of unsaturated ketones and esters.



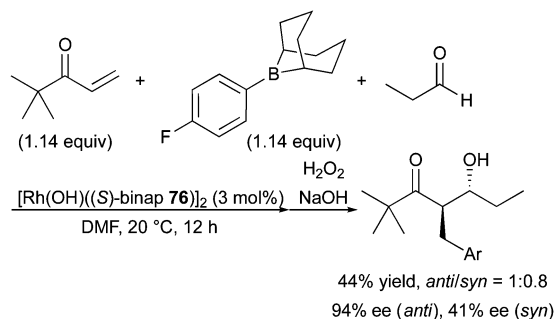
Scheme 151 Copper-catalyzed desymmetrizing reductive aldol cyclizations of unsaturated thioesters.

diastereo- and enantioselectivities of the asymmetric process (Scheme 151).²⁹⁸ The authors hypothesized that bipy may play a role in the post-reduction and post-cyclization events. Hence, they analyzed the crystal structure of the monomeric TANIAPHOS 116–CuBr complex by X-ray crystallography. The results indicated that the dimethylamino group of the ligand did not coordinate to copper and effectively blocked the β -face of the copper complex, leaving the α -face open for coordination and the approach.

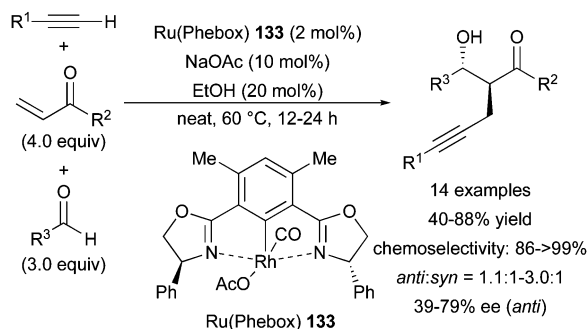
3.7. Tandem conjugate addition/aldol reactions

Similar to reductive aldol reactions described in the previous section, the 1,4-addition of carbon-based nucleophiles to unsaturated carbonyl compounds can generate enolate intermediates that can be intercepted by aldol acceptors. The tandem conjugate addition/aldol reaction is an attractive process that can rapidly construct two new C–C bonds. This strategy has been employed in metal-catalyzed enantioselective 1,4-additions/aldol reactions,^{299–303} and has also been well studied.^{304–306} In addition, it was found that not only carbon nucleophiles, but also other types of nucleophiles, such as borane³⁰⁷ and thiol,³⁰⁸ are viable substrates. It should be noted that for the tandem Michael/aldol reaction of β -substituted α,β -unsaturated compounds, a chiral center is generated prior to the aldol event and since it is difficult to judge whether the aldol reaction occurs in a diastereoselective manner or in an enantioselective manner, these examples are not covered in this review.

In 2002, Hayashi and co-workers reported rhodium-catalyzed tandem 1,4-addition of aryl boron reagents to vinyl ketones/enantioselective aldol reactions (Scheme 152).³⁰⁹ They found that a chiral rhodium complex prepared from BINAP 76 could be used as a catalyst to perform the asymmetric arylative aldol reaction with 9-aryl-9-borabicyclo-[3.3.1]nonanes (Ar-9BBN),



Scheme 152 Rhodium-catalyzed tandem 1,4-addition-aldol reaction.



Scheme 153 Ruthenium-catalyzed three-component coupling reactions of alkynes, enones, and aldehydes.

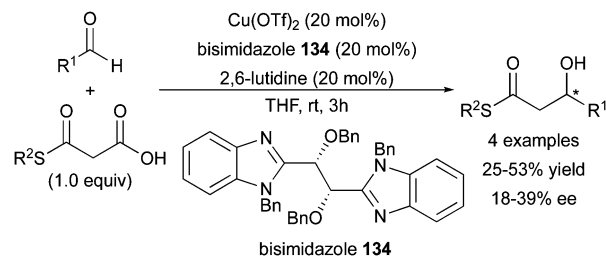
vinyl ketones, and aldehydes to provide the corresponding *anti*-products with excellent enantioselectivities. However, the yields and the diastereoselectivities of the tandem process were low.

In 2016, Nishiyama and co-workers reported a ruthenium-catalyzed tandem conjugate addition of terminal alkynes to α,β -unsaturated carbonyl compounds/enantioselective aldol reactions (Scheme 153).³¹⁰ They found that the ruthenium(Phebox) catalyst **133** could be utilized under the neat condition and various aromatic alkynes and aromatic aldehydes could act as substrates to deliver the corresponding β -hydroxyketone derivatives, possessing α -propargyl groups, in low diastereoselectivities and moderate to good enantioselectivities. The authors observed retro-aldol reactions, which were catalyzed by the sodium acetate additive, when the reactions were performed over a long period. In addition, they found that γ -alkynyl ketones, which were produced *in situ* by the conjugate addition of alkynes to enones or through the retro-aldol reaction of the products, could not undergo the aldol reaction. These results implied that the ruthenium enolate species, generated through the conjugate addition of alkynes to enones, served as a key intermediate for the enantioselective aldol reaction.

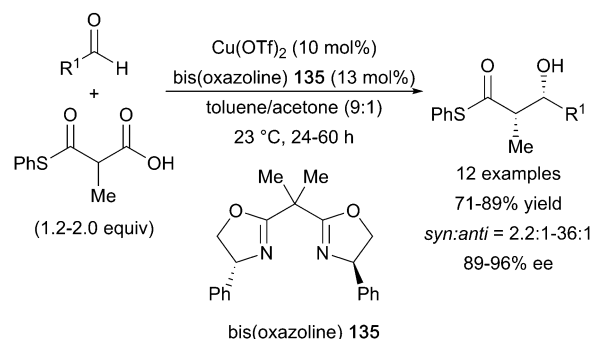
3.8. Decarboxylative aldol reactions

Nature can synthesize polyketides and fatty acids through a decarboxylative aldol process, in which the decarboxylation of β -carbonyl carboxylic acids generates enolates species that can undergo aldol reactions.³¹¹ Inspired by the enzymatic activation of malonic acid half thioesters to generate enolates for cross-Claisen reactions, Shair and co-workers reported a copper(II)-catalyzed thioester aldol reaction in 2003.³¹²

In 2004, Cozzi and co-workers reported the first example of enantioselective decarboxylative aldol reactions between malonic acid hemithioesters and aldehydes using a chiral copper catalyst (Scheme 154).³¹³ They found that the combination of $\text{Cu}(\text{OAc})_2$ and chiral bisimidazole **134** led to a chiral complex that enabled this catalytic process to proceed with low enantioselectivities. In 2005, Shair demonstrated that the use of the bis(oxazoline)-type ligand **135** as a chiral ligand enabled the asymmetric decarboxylative aldol reaction to proceed between malonic acid half thioesters and aldehydes to furnish the desired products in high yields and enantioselectivities (Scheme 155).³¹⁴



Scheme 154 Copper(II)-catalyzed decarboxylative aldol reactions between malonic acid hemithioesters and aldehydes (1).

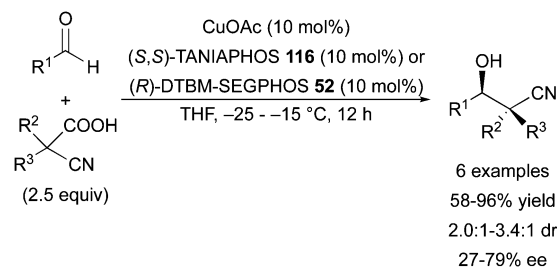


Scheme 155 Copper(II)-catalyzed decarboxylative aldol reactions between malonic acid hemithioesters and aldehydes (2).

Since the reaction conditions were quite mild, various functional groups, which would normally be incompatible with ester enolates, such as hydroxyl groups, phenols, enolizable aldehydes, enolizable methyl ketones, and carboxylic acid, were shown to be tolerated.

In 2007, the same group further investigated the reaction mechanism of this transformation and concluded that unlike enzymatic reactions, decarboxylation occurred after the addition to aldehydes.³¹⁵ They also rationalized that the compatibility with protic functional groups was due to the low concentration of the strongly basic intermediates that were generated late in the catalytic cycle.

In 2012, Kanai, Shibasaki, and co-workers reported a copper(I) complex-catalyzed enantioselective decarboxylative aldol-type reaction with α,α -disubstituted cyanoacetic acid (Scheme 156).³¹⁶ They found that copper(I) acetate-TANIAPHOS **116** or DTBM-SEGPHOS **52** generated an active chiral catalyst that provided the corresponding α,β -trisubstituted- β -hydroxy nitriles, with the all-carbon

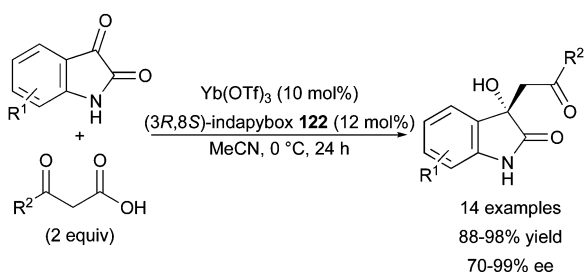


Scheme 156 Copper(I)-catalyzed decarboxylative aldol-type reaction with cyanoacetic acid.

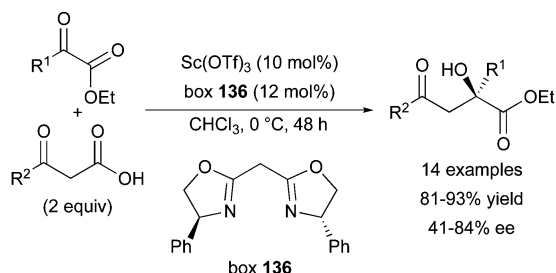
quaternary center, in moderate diastereo- and enantioselectivities. The authors also demonstrated that the asymmetric decarboxylative Mannich reaction with the same catalyst system led to an undecarboxylated addition product as the major product, which suggested that the soft-soft interaction between the chiral copper(I) catalyst and the cyano group of the nucleophile precursors played a key role in facilitating the decarboxylative process.

In 2013, Wang reported a chiral ytterbium complex as a catalyst for the enantioselective decarboxylative addition reactions of β -ketoacids to isatins (Scheme 157).³¹⁷ They demonstrated that $\text{Yb}(\text{OTf})_3$ -indapybox **122** was the best catalyst for this reaction, and various β -ketoacids, including aliphatic substrates, could be utilized to afford chiral 3-hydroxy oxindoles in high yields and good to excellent enantioselectivities. In 2014, the same group developed a chiral Lewis acid-catalyzed decarboxylative addition of β -ketoacids to α -keto esters (Scheme 158).³¹⁸ In this case, the chiral catalyst, derived from the $\text{Sc}(\text{OTf})_3$ -bisoxazoline (box) ligand **136**, provided the desired product in good yields, but with moderate to good enantioselectivities.

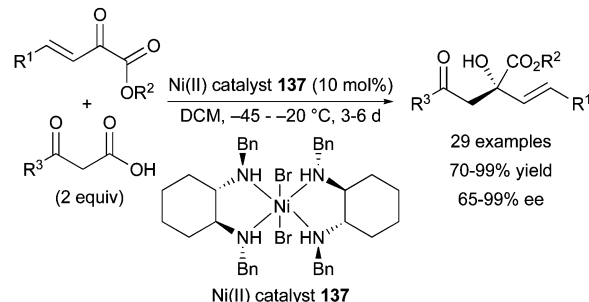
In 2015, Ma and co-workers reported the nickel(II) complex **137** as a catalyst for enantioselective decarboxylative aldol reactions with β -ketoacids and β,γ -unsaturated α -ketoesters (Scheme 159).³¹⁹ They showed that various types of aromatic β,γ -unsaturated α -ketoesters and aromatic β -ketoacids reacted smoothly to afford the desired products in excellent yields and enantioselectivities. The mechanistic studies, based on ^{13}C NMR spectroscopic experiments, revealed that one of the diamine ligands could undergo exchange from the nickel complex to the β -ketoacid and then the liberated diamine ligand could



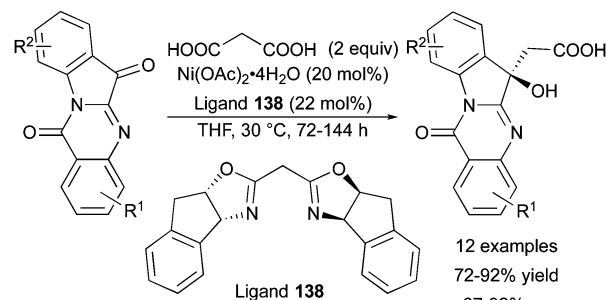
Scheme 157 Ytterbium-catalyzed decarboxylative addition of β -ketoacids to isatins.



Scheme 158 Scandium-catalyzed decarboxylative addition of β -ketoacids to α -keto esters.



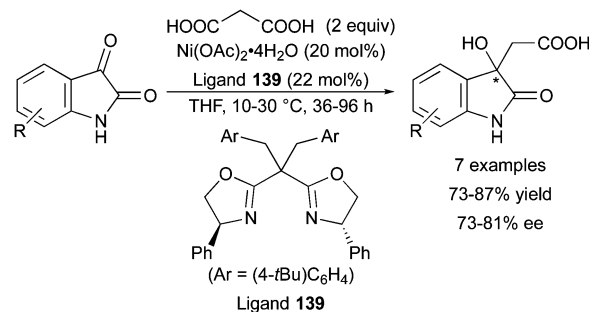
Scheme 159 Nickel(II)-catalyzed decarboxylative aldol reactions with β -ketoacids and α -ketoesters.



Scheme 160 Nickel-catalyzed decarboxylative addition of malonic acid and tryptanthrin.

deprotonate the metal-bound substrate to generate the enolate intermediate. Control experiments also suggested that the aldol reaction occurred prior to the decarboxylation step.

In 2015, Jiang and co-workers reported a nickel(II)-catalyzed enantioselective synthesis of β -hydroxy acids from malonic acid and isatin derivatives.³²⁰ They showed that chiral bisoxazoline ligand-nickel(II) complexes were suitable for these decarboxylative enantioselective additions of malonic acid. With the optimized ligand structure, both tryptanthrin (Scheme 160) and isatin derivatives (Scheme 161) were converted to the corresponding β -hydroxy acids in high yields and enantioselectivities. High resolution mass spectroscopy (HRMS) analysis of the reaction between isatin and malonic acid revealed that the nucleophilic addition of malonic acid to isatin occurred first and then decarboxylation of the intermediate afforded the product.



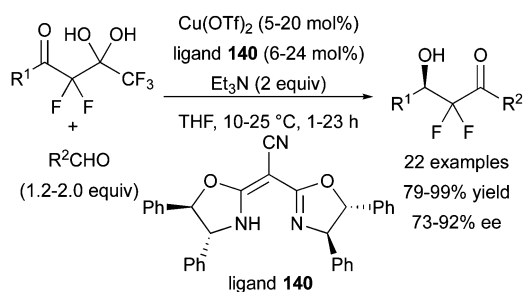
Scheme 161 Nickel-catalyzed decarboxylative addition of malonic acid and isatin.

3.9. Detrifuoroacetylative aldol reactions

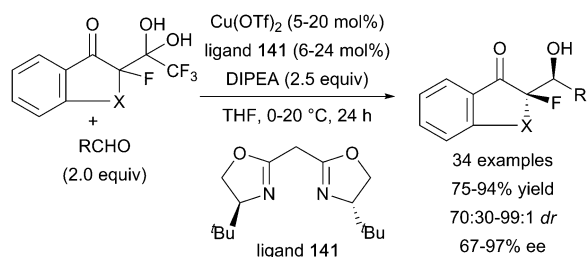
Fluorine-containing chiral compounds are of great interest in medicinal chemistry as the high electronegativity of the fluorine atom changes the chemical properties of molecules. As such, it was considered that enantioselective aldol reactions of α -fluorinated enolates would be a powerful tool to construct α -fluoro- β -hydroxy ketones. Consequently, in 2011, Colby and co-workers developed a trifluoroacetate-releasing strategy to generate *in situ* reactive α -fluorinated enolates from the *gem*-diols of trifluoromethyl ketones under mild conditions, with these fluorine-containing enolates then used in aldol reactions.³²¹

In 2013, Wolf and co-workers reported a chiral copper(II) complex as a catalyst for the enantioselective aldol reaction of α,α -difluoroenolates to aldehydes (Scheme 162).³²² They utilized trifluoromethyl α,α -difluorinated β -keto *gem*-diol derivatives as a starting material to generate *in situ* the α,α -difluoroenolates, and found that with a chiral copper complex, prepared from Cu(OTf)₂ and the chiral bisoxazoline ligand **140**, as a catalyst, asymmetric aldol reactions of various aromatic aldehydes proceeded smoothly to afford the corresponding α,α -difluoro- β -hydroxy ketones in high yields and good enantioselectivities. They also demonstrated that aliphatic aldehydes could be utilized when the catalyst loading was increased.

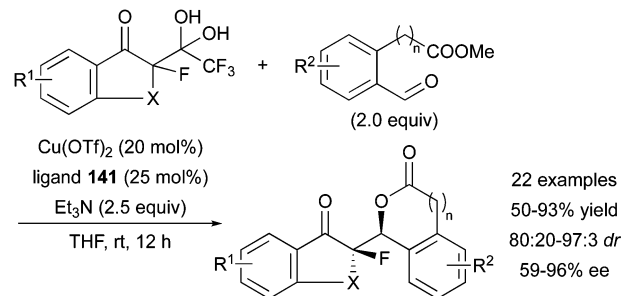
In 2015, Han and co-workers reported a copper(II) complex-catalyzed enantioselective aldol reaction of 2-fluoro-1,3-diketones/hydrates derived from cyclic ketones (Scheme 163).³²³ They found that detrifuoroacetylative aldol reactions could be efficiently catalyzed by a copper(II) complex, prepared from Cu(OTf)₂ and the chiral bisoxazoline ligand **141**, to afford the corresponding α -fluoro- β -hydroxy ketones containing C-F quaternary stereogenic centers. A wide variety of aromatic aldehydes and vinyl-type aldehydes were tolerant and could afford the aldol products



Scheme 162 Copper(II)-catalyzed aldol reaction of α,α -difluoroenolates.



Scheme 163 Copper(II)-catalyzed aldol reaction of 2-fluoro-1,3-diketones/hydrates derived from cyclic ketones.



Scheme 164 Copper(II)-catalyzed detrifuoroacetylative aldol-cyclization cascade reactions.

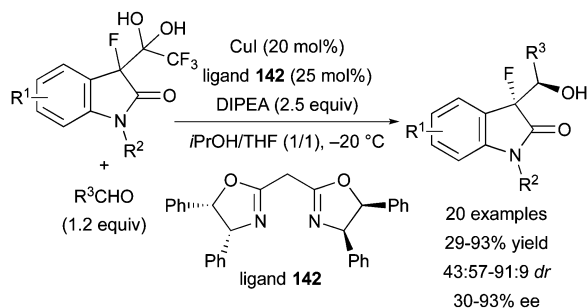
in high to excellent yields and selectivities. However, they found that enantioselective aldol reactions with aliphatic aldehydes, with the exception of 2-phenylacetaldehyde, resulted in relatively low yields and enantioselectivities. In the cases of substrates containing electron-withdrawing substituents, the background reaction occurs, which slightly diminishes the observed enantioselectivities. In 2016, Soloshonok, Han, and co-workers expanded the scope of these reactions to include aliphatic aldehydes.³²⁴ The major problems associated with these substrates were its low reactivity and the protonation of the enolate intermediate to generate 2-fluoro-3,4-dihydronaphthalen-1-one. While the reaction at low temperature was very sluggish, the aldol reaction of aliphatic aldehydes at room temperature afforded the desired products in low to high yields and high selectivities (18 examples, 23–91% yield, 87:13–98:2 dr, 87–98% ee).

In 2016, Han and co-workers reported a Cu(OTf)₂/**141** complex as a catalyst for the enantioselective detrifuoroacetylative aldol-cyclization cascade reactions of 2-fluoro-1,3-diketones/hydrates derived from cyclic ketones (Scheme 164).³²⁵ Under similar conditions used for their previously developed enantioselective detrifuoroacetylative aldol reactions, 2-formyl benzoates were converted to the corresponding fluorinated quaternary stereogenic α,α -dialkyl/cyclo-alkyl- β -ketoesters through a sequence of an aldol reaction followed by an intramolecular cyclization to provide the aldol adducts in moderate to high yields and selectivities. They also demonstrated that while a six-membered lactone could be synthesized by this method, a seven-membered lactone could not be accessed.

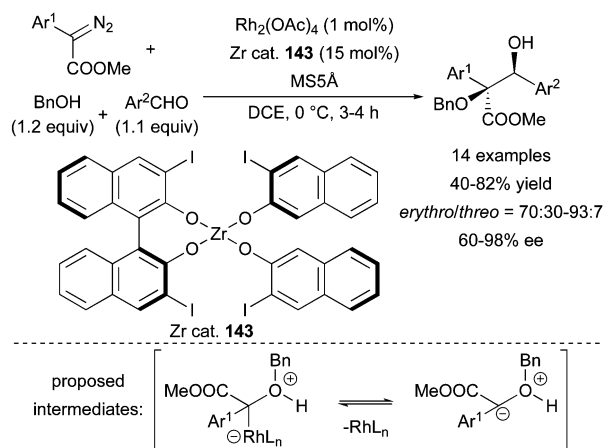
In 2017, Soloshonok, Han, and co-workers reported a copper(I) complex as a catalyst for the enantioselective detrifuoroacetylative aldol reactions of 3-(1,1-dihydroxy-2,2,2-trifluoroethyl)-substituted derivatives of 3-fluoro-2-oxindoles (Scheme 165).³²⁶ In the presence of the CuI/bisoxazoline ligand **142** complex and a base, the asymmetric aldol reactions proceeded smoothly to afford α -fluoro- β -hydroxy-indolin-2-ones in low to high yields and selectivities. They also showed that an unprotected N-H on the indolinone was also tolerant under their optimized conditions.

3.10. Miscellaneous

In 2008, Hu and co-workers reported a chiral rhodium(II)/chiral zirconium(IV) complex as a catalyst for enantioselective three-component reactions combining aryl diazoacetates, benzyl alcohols,



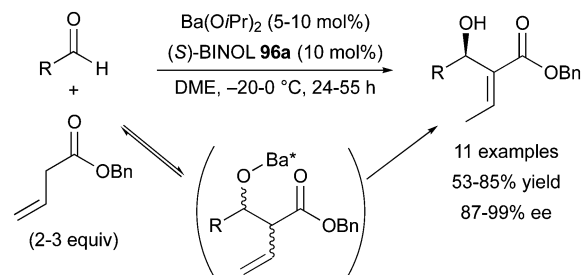
Scheme 165 Copper(I)-catalyzed detrifluoroacetylative aldol reactions of 3-fluoro-indolinone derivatives.



Scheme 166 Rhodium(II)/zirconium(IV)-catalyzed three-component reactions of aryl diazoacetates, benzyl alcohol, and aromatic aldehydes.

and aromatic aldehydes (Scheme 166).³²⁷ They envisioned that alcoholic oxonium ylide intermediates, which form *in situ* from rhodium carbenoid insertion in the oxygen atom of alcohols,³²⁸ can undergo enantioselective aldol-type reactions with aldehydes activated with an appropriate chiral Lewis acid catalyst to generate chiral α,β -dihydroxy acid derivatives. They found that the chiral zirconium complex **143** was a suitable catalyst for the asymmetric aldol reaction to afford *erythro* adducts in moderate to high yields and selectivities from various combinations of aryl diazoacetates and aromatic aldehydes.

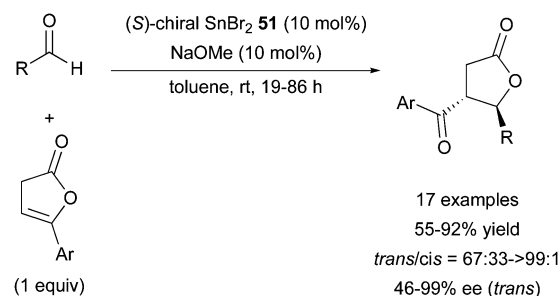
In 2009, Matsunaga, Shibasaki, and co-workers reported dynamic kinetic asymmetric transformations (DYKAT) for the catalytic asymmetric synthesis of α -alkylidene- β -hydroxy esters involving barium(II)-catalyzed direct aldol/retro-aldol reactions (Scheme 167).³²⁹ The authors used β,γ -unsaturated esters as aldol donors and hypothesized that if a chiral catalyst could promote rapid retro-aldol reactions of the α -aldol adducts, isomerization of the α -aldol adducts to the more thermodynamically stable α -alkylidene- β -hydroxy esters would allow the DYKAT to occur. In the presence of a $\text{Ba}(\text{O}^i\text{Pr})_2$ /BINOL **96a** complex as a catalyst, the desired (*E*)- α -alkylidene- β -hydroxy esters were obtained from various kinds of aldehydes in high yields and excellent enantioselectivities. Moreover, it was found that an allenyl ester could also be used as a substrate.



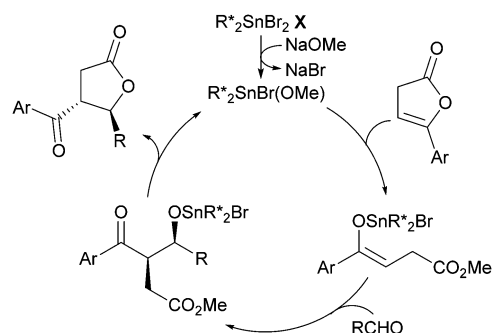
Scheme 167 Dynamic kinetic asymmetric transformations involving a barium(II)-catalyzed aldol reaction.

They performed several control experiments and these results suggested that the isomerization step from the α -aldol adducts to α -alkylidene- β -hydroxy esters was highly enantioselective.

In 2011, Yanagisawa and co-workers reported a chiral tin complex as a catalyst for the tandem enantioselective aldol reaction/cyclization of β,γ -didehydro- γ -lactones with aldehydes (Scheme 168).³³⁰ They employed an alkenyl lactone as an enolate precursor and found that in the presence of the chiral SnBr_2 complex **51** and NaOMe, the desired *trans*- β,γ -disubstituted γ -butyrolactones were selectively obtained in moderate to high yields and moderate to excellent enantioselectivities. Tertiary aldehydes were particularly good substrates to furnish the aldol products in excellent diastereo- and enantioselectivities. The authors proposed the reaction mechanism shown in Scheme 169. Initially, the key chiral tin bromide methoxide was formed from the chiral SnBr_2 **51** and NaOMe. Next, the chiral tin bromide methoxide was added to the lactone substrate to yield a chiral



Scheme 168 Tin-catalyzed tandem aldol reaction/cyclization of β,γ -didehydro- γ -lactones with aldehydes.



Scheme 169 Plausible reaction mechanism.

tin enolate, which then underwent an aldol reaction with the aldehyde to afford the tin alkoxide of β -hydroxy ketone. Finally, the tin alkoxide underwent intramolecular cyclization to the ester moiety to afford the product and regenerate the chiral tin bromide methoxide catalyst.

4. Catalytic enantioselective direct-type aldol reactions using organocatalysts

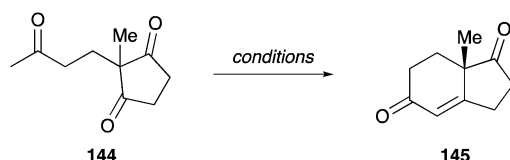
While the application of chiral metal complexes as catalysts for asymmetric aldol reactions has been well studied, the use of purely chiral organic molecules as catalysts has gained equal attention over the last two decades. Historically, the use of an organocatalyst, proline, for the direct aldol reaction was reported as early as the 1970s (Scheme 170).^{331,332}

However, the transformational power of chiral organic molecules as asymmetric catalysts was not fully appreciated until the seminal report by List and Barbas, who disclosed that proline could be utilized to induce the intermolecular asymmetric aldol reaction.³³³ Since then, numerous improved organocatalysts have been developed and their potency has been demonstrated for a variety of asymmetric processes, including the direct aldol reaction.

4.1. Amine-based organocatalysts

4.1.1. Proline-derived organocatalysts. A common mode of activation of carbonyl compounds for electrophilic substitution at the α -position is through enamine catalysis, and the most widely observed structural motifs for organocatalysts that are capable of promoting the asymmetric direct aldol reactions are chiral amines. The earliest example of a catalytic asymmetric aldol reaction was reported by Wiechert, in which a substoichiometric amount of (*S*)-proline promoted the intramolecular aldol reaction of triketone **144** to provide the enantioenriched bicyclic diketone **145** (Scheme 170).³³² This transformation was subsequently improved by Hajos to provide a catalytic system capable of delivering **145** with high enantiopurity.³³¹ The transformative nature of these seminal reports was unrecognized until List and Barbas disclosed their efforts to develop a chiral amine-catalyzed intermolecular asymmetric aldol reaction (Scheme 171).³³³

During their studies, various amino acids were examined, and they found that both the pyrrolidine ring and the carboxylic



Eder-Sauer-Wiechert:

(*S*)-proline (47 mol%), HClO_4 (1 N), MeCN, 80 °C, 20 h (87%, 84% ee)

Hajos-Parrish:

(*S*)-proline (3 mol%), DMF, 23 °C, 20 h; then *p*-TsOH, benzene (quant., 93% ee)

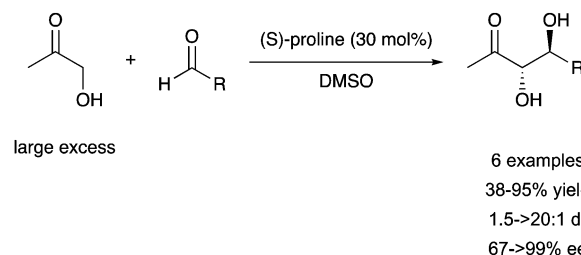
Scheme 170 Hajos–Parrish–Eder–Sauer–Wiechert reaction.



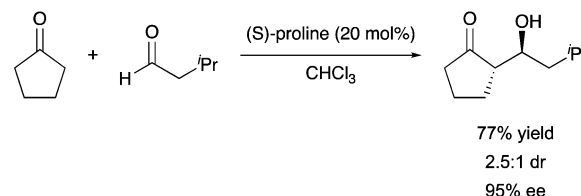
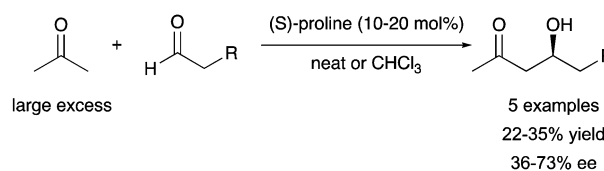
Scheme 171 Proline-catalyzed asymmetric aldol reactions.

acid were essential for effective catalysis. They proposed that the pyrrolidine enables the formation of the key enamine intermediate, while the carboxylic acid acts as a co-catalyst to facilitate the various steps of the mechanism. With respect to the substrate scope, the direct aldol reaction between acetone and aromatic aldehydes provided aldol adducts with moderate to excellent yields (54–94%) and good enantioselectivities (60–77% ee). Moreover, the proline-catalyzed reaction between acetone and isobutyraldehyde resulted in the formation of the aldol adduct in a 97% yield and 96% ee. This catalytic system was subsequently extended by List for the asymmetric aldol reaction between hydroxyacetone and aldehydes to prepare *anti*-1,2-diols (Scheme 172).³³⁴

The direct aldol reaction of α -unsubstituted aldehydes and ketones is a challenging process since the catalyst has a difficulty in differentiating the α -protons of the acceptor aldehyde and donor ketone, and this leads to self-aldol products. List found that by changing the solvent from DMSO to either one under neat conditions or chloroform led to the cross-aldol adducts with modest yields and good enantioselectivities (Scheme 173).³³⁵



Scheme 172 Proline-catalyzed asymmetric aldol reactions of hydroxyacetone and aldehydes.



Scheme 173 Proline-catalyzed asymmetric aldol reactions between ketones and α -unsubstituted aldehydes.

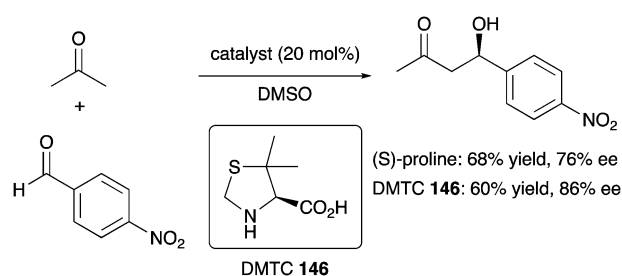
The only examples of high yields and enantioselectivities were when cyclic ketones were examined as aldol donors.

Independently, Barbas reported similar asymmetric direct aldol reactions between ketones or hydroxyacetone and aldehydes using secondary amino acids as organocatalysts.³³⁶ Extensive catalyst screening studies revealed that both (*S*)-proline and (*R*)-5,5-dimethylthiazolidine-4-carboxylic acid (DMTC) **146** were the most effective chiral catalysts, with the best catalyst depending on the nature of the substrates. For instance, DMTC **146** often provided superior enantioselectivities when aromatic aldehydes were used as the aldol acceptors, while the chemical yields of the aldol reaction were generally better with proline as the organocatalyst (Scheme 174).

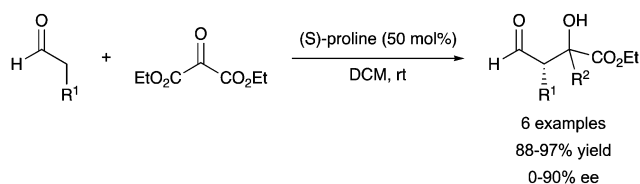
Along with these initial reports, the direct aldol reaction between ketones and aldehydes catalyzed by proline has been intensively investigated, with slight modifications to improve the asymmetric reaction, including by the use of alternative solvents (ionic liquids,^{337–343} polyethylene glycol^{344,345}), high pressure,^{346,347} and additives (acids,^{348–353} alcohols^{354,355}).

Although the typical direct aldol reaction between ketones and aldehydes occurs with the ketone acting as an aldol donor and the aldehyde acting as an acceptor, role reversal of these substrates has also been reported (Scheme 175).³⁵⁶ To achieve this, highly activated ketones bearing electron-withdrawing moieties were utilized as substrates, and with substoichiometric amounts of proline, various optically active β -hydroxycarboxylic acid derivatives were obtained. In most cases, high yields and enantioselectivities were obtained when various aldehydes were reacted with diethyl ketomalonate, with the exception of phenyl-ethanal ($R^1 = \text{Ph}$) as an aldol donor.

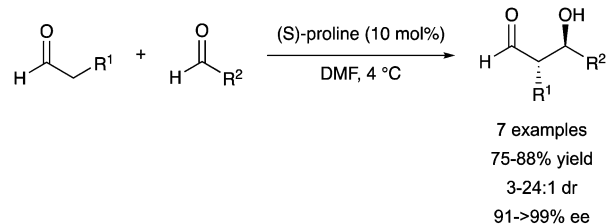
In addition to the direct asymmetric aldol reaction between ketones and aldehydes, other combinations of carbonyl moieties have been demonstrated for the asymmetric aldol reactions with proline as a chiral catalyst. It was shown that proline could be



Scheme 174 Direct asymmetric aldol reaction catalyzed by (*S*)-proline and (*R*)-DMTC.



Scheme 175 Direct catalytic asymmetric aldol reactions of aldehydes and activated ketones.



Scheme 176 Direct asymmetric cross-aldol reactions between two non-equivalent aldehydes.

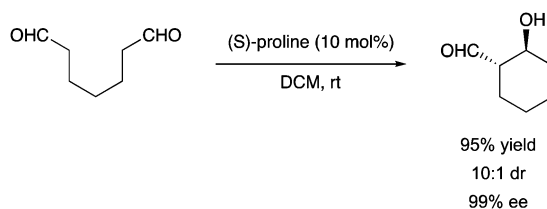
utilized as an organocatalyst for the challenging asymmetric cross-aldol reaction between two non-equivalent aldehydes (Scheme 176).³⁵⁷ With the slow addition of the aldol donor *via* a syringe pump, various cross-aldol adducts were obtained in excellent yields with good to excellent diastereoselectivities and excellent enantioselectivities. In addition, the aldol adducts of α -functionalized aldehydes, derived from homo- and cross-aldol reactions, has been employed to prepare important biomolecules, such as sugars^{358–364} and amino acids.³⁶⁵

Intramolecular direct asymmetric aldol reactions have also been reported using proline as an organocatalyst. While the Hajos–Parrish–Eder–Sauer–Wiechert reaction proceeds in a 6-*enolendo* fashion, it was found that pentane-1,5-dialdehydes underwent asymmetric aldolization in a 6-*enolexo* manner with excellent enantioselectivities and good diastereoselectivities (Scheme 177).³⁶⁶

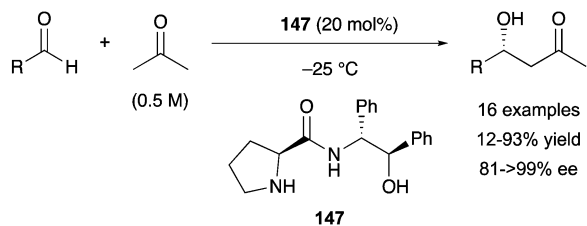
While only a few examples of asymmetric intramolecular direct aldol reactions have been investigated using proline as an organocatalyst, all of these cases provided the *enolendo* adducts.^{367–369}

4.1.2. Modified proline derivatives as organocatalysts.

While the synthetic utility of proline as an organocatalyst for the asymmetric aldol reaction has been demonstrated, improvements in the catalyst design are needed to overcome some of the deficiencies in proline-catalyzed transformations, such as the need for high catalyst loadings and the limited solubility in organic solvents. The most easily modifiable component of proline is the carboxylic acid moiety, and numerous groups have exploited this fact to design novel classes of organocatalysts. The earliest catalyst modifications made use of simple peptide coupling chemistry to create new chiral organocatalysts. In 2003, Wu and co-workers synthesized numerous (*S*)-pyrrolidine-2-carboxamides and evaluated their utility as small molecule catalysts for the direct asymmetric aldol reactions of acetones and aldehydes (Scheme 178).^{370,371}



Scheme 177 Direct catalytic asymmetric aldolizations of dicarbonyl compounds.



Scheme 178 Highly enantioselective direct aldol reactions of acetone and aldehydes.

To understand the critical role the acidic proton of proline plays in the catalysis, Wu studied L-prolinamides derived from the coupling of L-proline and α,β -hydroxyamines, and found prolinamide **147** was the best catalyst. Following this work, numerous groups have investigated the asymmetric aldol reactions between ketones (aldol donor) and aldehydes (aldol acceptor)

using prolinamides, synthesized from the peptide coupling of proline and amines, as catalysts with varying degrees of success (Chart 1).^{372–401}

Prolinamides have also been examined as efficient organo-catalysts for the direct enantioselective aldol condensation reactions of acetone with activated ketones as electrophiles. In 2015, Tomasini and co-workers found that dipeptides could work as an organocatalyst for the aldol reaction of isatin derivatives with acetone (Scheme 179).⁴⁰²

After screening several simple dipeptides, they found that the prolinamide **148**, derived from proline and β^3 -homophenylglycine, afforded aldol adducts with excellent yields and good enantioselectivities. Subsequently, other prolinamides derivatives^{397,403–405} were examined using isatins as aldol acceptors, and slight improvements were found in some cases.

Similarly, a few examples of direct asymmetric aldol reactions were reported with α -keto esters as electrophiles using

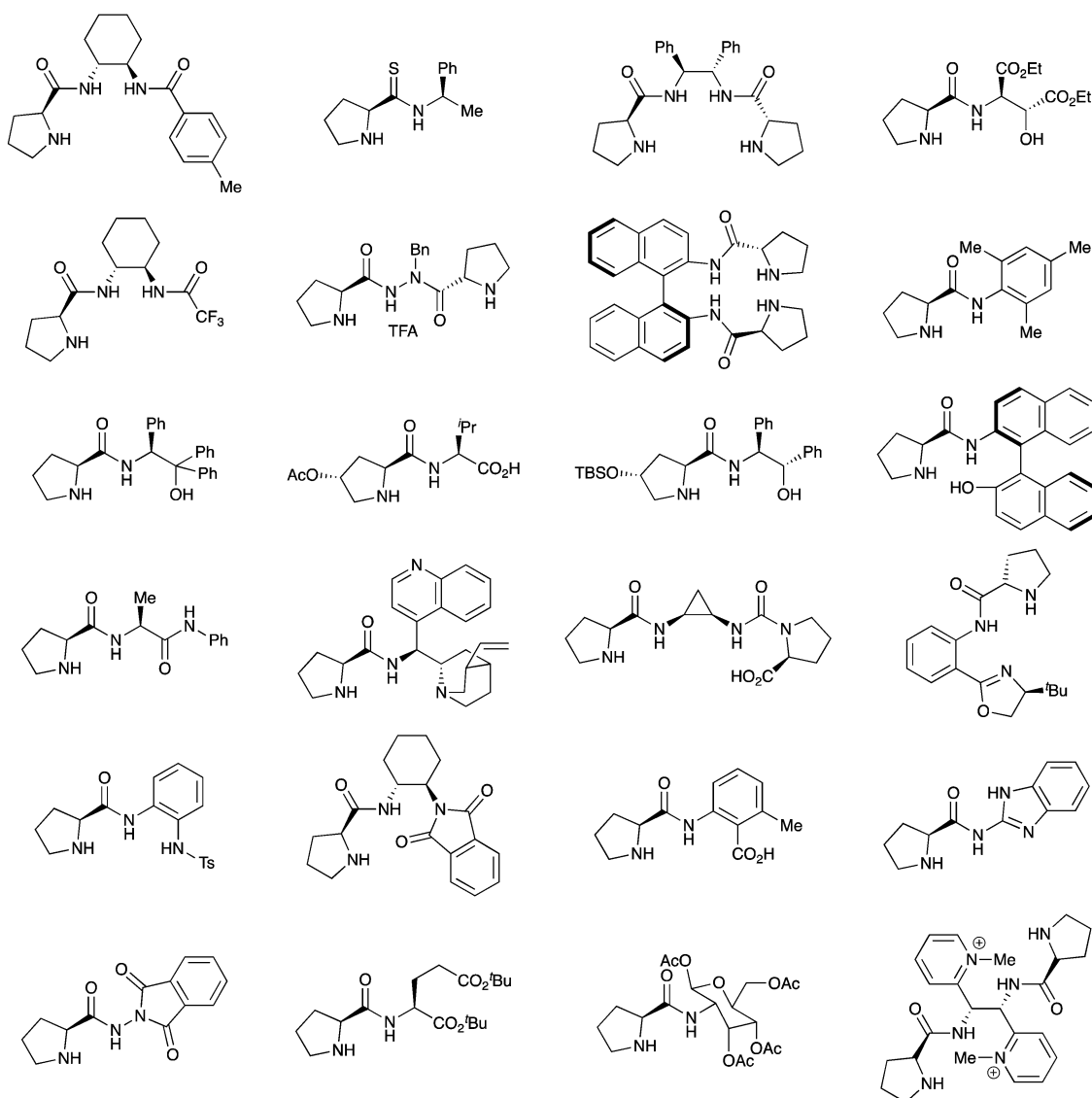
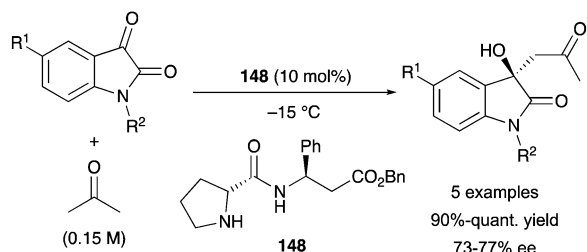
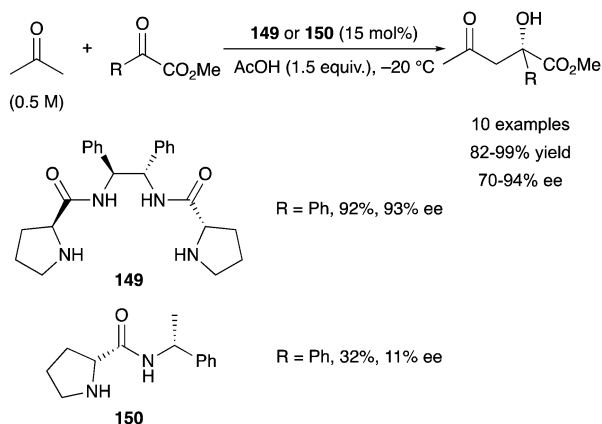


Chart 1 Representative examples of L-prolinamides as catalysts for the enantioselective aldol reactions of ketones and aldehydes.



Scheme 179 Diastereoselective asymmetric aldol reactions of acetone and isatin derivatives.



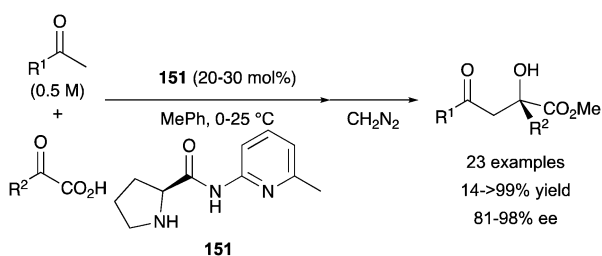
Scheme 180 Direct asymmetric aldol reactions of α -keto esters and acetone.

chiral prolinamides as a catalyst. For example, Feng and co-workers reported that a *C*-symmetrical bisprolinamide **149** enabled the direct aldol reaction of acetone with α -keto esters using acetic acid as a co-catalyst (Scheme 180).⁴⁰⁶

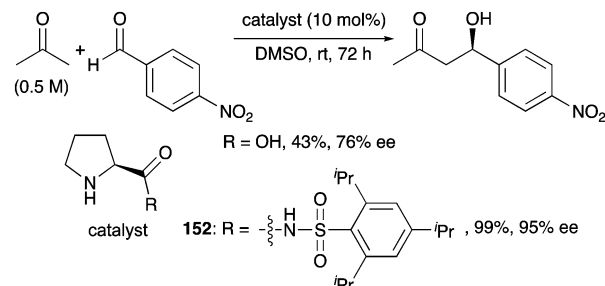
Interestingly, they found that the two distant amino groups were critical for the success of the asymmetric process, and proposed that one of the prolinamide units reacted with acetone to form the enamine intermediate, while the other prolinamide was protonated and acted as a hydrogen-bonding catalyst to activate the α -keto ester.

A similar type of strategy was also employed by Gong and co-workers to facilitate the asymmetric aldol reaction of ketones with α -keto acids (Scheme 181).^{407,408}

By taking advantage of the acidity of α -keto acids, Gong modified L-proline to install an aminopyridine moiety, which is known to undergo self-assembly with carboxylic acids. They found



Scheme 181 Direct asymmetric aldol reactions of α -keto acids and ketones.



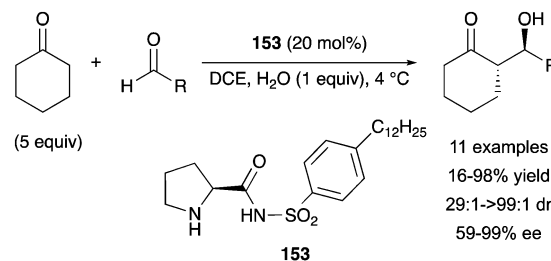
Scheme 182 Proline-derived *N*-sulfonylcarboxamide-catalyzed asymmetric aldol reaction between acetone and 4-nitrobenzaldehyde.

that the prolinamide **151** catalyzed the direct aldol reaction of a wide range of α -keto acids and ketones in excellent yields and enantioselectivities, and that the aldol adducts could undergo a sequential diastereoselective reduction and acid-catalyzed cyclization to afford 2-hydroxy- γ -butyrolactones.

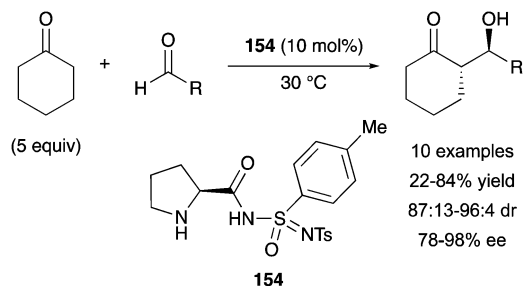
While the modification of proline by amide coupling reactions with chiral amines enables the construction of a wide range of chiral organocatalysts for the aldol reaction, the loss of the acidic carboxylic acids can be problematic since keeping the acidity of the organocatalyst is important to maintain the bifunctional nature of the proline-derived organocatalyst. With this in mind, Berkessel and co-workers reported the use of *N*-arylsulfonylproline amides as catalysts for the asymmetric aldol reaction of acetone and 4-nitrobenzaldehyde (Scheme 182).⁴⁰⁹

They found that the modification of proline by introducing a simple acylsulfonamide group greatly enhanced both the yields and enantioselectivities of the direct aldol reaction, and they speculated that the stronger hydrogen bonding enabled by the acidic N-H proton, in conjunction with the greater shielding of one of the enantiotopic faces of the aldehyde by the aryl ring, was responsible for the improved catalytic activity when compared to proline alone. Similar reports by other groups also detailed the utilization of proline-derived *N*-sulfonylcarboxamides as organocatalysts for enantioselective aldol reactions.⁴¹⁰⁻⁴¹⁵ One modified prolyl sulfonamide catalyst that is noteworthy was that disclosed by Carter and co-worker, in which a long alkyl chain was incorporated into the catalyst design to improve the solubility profile of the organocatalyst in nonpolar solvents (Scheme 183).⁴¹³

A wide range of substrates was found to be amenable for the asymmetric aldol reaction and excellent yields, enantioselectivities, and diastereoselectivities were enjoyed when using the



Scheme 183 Efficient asymmetric aldol reactions catalyzed by a sulfonamide-based organocatalyst.



Scheme 184 Prolyl sulfonimidamide-catalyzed asymmetric aldol reactions.

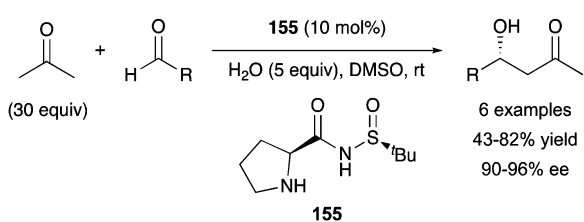
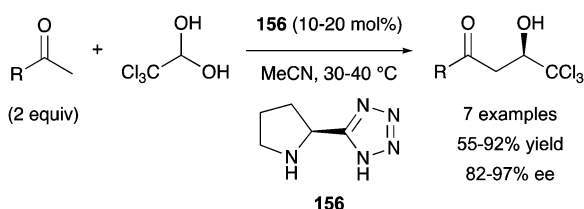
greasy organocatalyst **153**. Although the catalyst loadings were relatively high, they noted that the amount of the ketone (aldol donor) needed could be reduced to 5 equiv., which is typically relatively difficult to achieve in direct aldol reactions.

Related to *N*-sulfonylcarboxamides, the aza-analogs were investigated by Bolm and co-worker for the direct enantioselective aldol reaction of aldehydes and ketones (Scheme 184).⁴¹⁶

They anticipated that the *S*-centered chirality could impact the enantiomeric purity of the aldol products, but such an effect was not observed. Similarly, Ellman and co-workers studied the proline-derived organocatalyst **155**, incorporating an *N*-sulfinyl amide moiety that could serve as a hydrogen bond donor, a chiral-directing group, and a solubilizing element (Scheme 185).⁴¹⁷

Similar to the rationale given for the modification of proline to the corresponding acylsulfonamide, the conversion of the carboxylic acid functionality to a tetrazolic acid moiety was examined in 2004 by Yamamoto and co-workers, who demonstrated the effectiveness of a proline-derived tetrazole catalyst for the enantioselective aldol reactions of ketones to chloral (Scheme 186).⁴¹⁸

During their studies, they found an interesting positive effect of water, in which the yield and enantioselectivity increased in the presence of water. The authors speculated that the water may

Scheme 185 *N*-Sulfinyl prolinamide-catalyzed enantioselective aldol reactions.

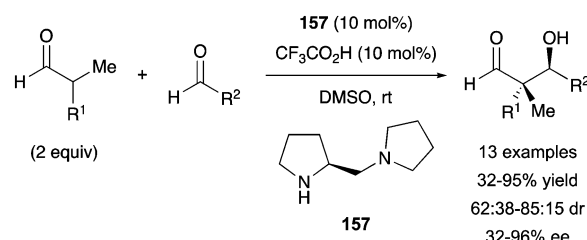
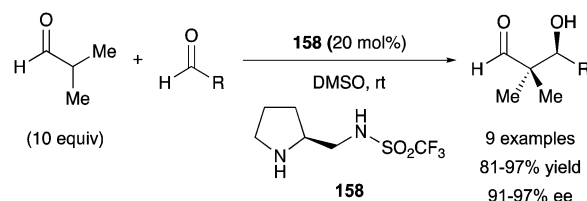
Scheme 186 Asymmetric direct aldol reactions of ketones with chloral monohydrate catalyzed by a proline-derived tetrazole catalyst.

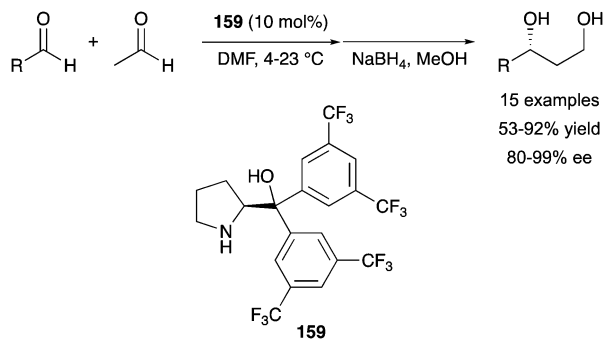
shift the aldehyde–iminium ion equilibrium and/or the generation of the hydrate form of chloral might prevent the iminium ion formation derived from chloral and the tetrazole catalyst. Although this initial report focused only on chloral as the aldol acceptor, other groups demonstrated the generality of the chiral tetrazole catalyst for a wide range of asymmetric aldol reaction.^{419–424}

Although most derivatives of proline that have been utilized in asymmetric aldol reactions have maintained their carbonyl moiety, in principle, the key structural component of these organocatalysts is the pyrrolidine ring, since the formation of the enamine intermediate is important in the catalytic cycle. As such, Tanaka, Barbas, and co-workers utilized a fluorescence detection system to determine an excellent catalytic system for the Michael addition reaction of acetone to a fluorescent maleimide derivative, and applied the findings of the fluorescence-based assay to direct asymmetric aldol reactions using α,α -dialkyl aldehyde donors to generate enantiomerically enriched quaternary carbon centers (Scheme 187).⁴²⁵

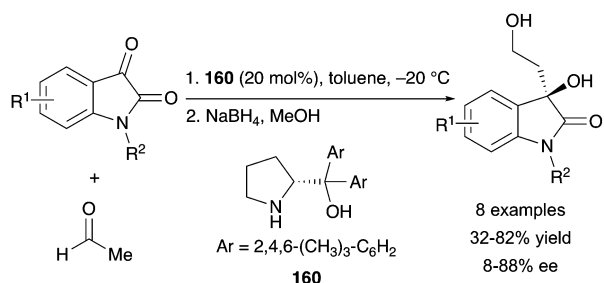
They found that the chiral diamine **157**, with $\text{CF}_3\text{CO}_2\text{H}$ as a co-catalyst, could catalyze the direct aldol reactions to generate β -hydroxyaldehydes. They speculated that the secondary amine of **157** was responsible for the formation of the enamine intermediate and that the protonated form of the tertiary amine interacted with the aldol acceptor *via* hydrogen-bonding interactions. The combination of **157** and an acid co-catalyst has also been employed in other asymmetric aldol reactions.^{426–428}

Structurally related pyrrolidine sulfonamides were also shown to promote the direct asymmetric aldol reactions between α,α -dialkyl aldehydes and aromatic aldehydes (Scheme 188).⁴²⁹ In this case, the relatively strong acidity of the sulfonamide functional group allowed this reaction to proceed in the absence of an acid co-catalyst.

Scheme 187 Direct enantioselective aldol reactions of α,α -dialkyl aldehydes and aromatic aldehydes.Scheme 188 Pyrrolidine sulfonamide-catalyzed enantioselective aldol reactions of α,α -dialkyl aldehydes and aromatic aldehydes.



Scheme 189 Asymmetric direct cross-aldol reactions of acetaldehyde and aromatic aldehydes catalyzed by a diarylprolinol.



Scheme 190 Pyrrolidinylsilanol-catalyzed cross-aldol reaction of acetaldehyde and isatin derivatives.

Amino alcohols derived from proline have also been examined as organocatalysts for asymmetric direct aldol reactions. In 2008, Hayashi and co-workers investigated the direct aldol reaction using acetaldehyde as an aldol donor, and found that the diarylprolinol **159** could efficiently catalyze the cross-aldol reaction (Scheme 189).⁴³⁰

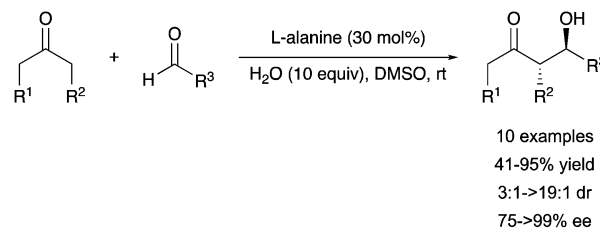
Interestingly, they noted that the acidity of the alcohol was important for the catalyst performance, and the role of the hydroxyl group was believed to activate the aldol acceptor through hydrogen bonding. In addition, this diarylprolinol was found to be a general catalyst that could enable asymmetric cross-aldol reactions with other combinations of aldol acceptors and donors to proceed.⁴³¹⁻⁴³⁵

Related to the structurally similar diarylprolinols, Franz and co-workers examined enantiopure pyrrolidinylsilanols as a chiral catalyst for the direct aldol reaction between acetaldehyde and isatin derivatives (Scheme 190).⁴³⁶

Due to the increased acidity of silanols, they hypothesized that this class of chiral hybrid compounds could act as an organocatalyst for the asymmetric aldol reaction. The potential drawback of utilizing silanols, however, is their propensity to undergo condensation to form siloxanes, but Franz found that this process could be suppressed by introducing bulky substituents on the silicon atom.

4.2. Other amine-based organocatalysts

While there are numerous examples of proline and its derivatives as organocatalysts for enantioselective direct aldol reactions, other classes of chiral amines capable of generating the key enamine intermediate can be used as catalysts also.



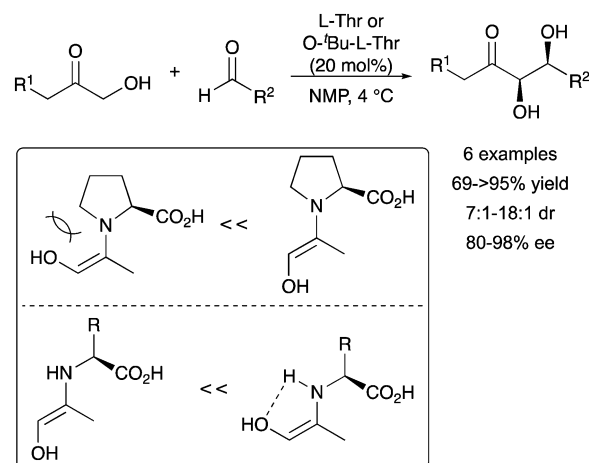
Scheme 191 Alanine-catalyzed enantioselective direct aldol reactions.

4.2.1. Primary amino acids. Although initial reports suggested that linear amino acids were poor catalysts for the asymmetric aldol reaction, in 2005, Córdova and co-workers found that quite a few acyclic amino acids could function as effective catalysts for the direct asymmetric intermolecular aldol reaction (Scheme 191).^{437,438}

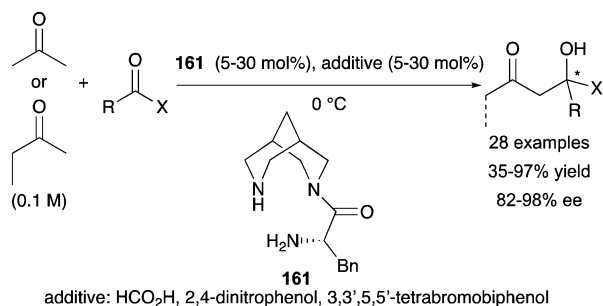
A key additive for these aldol reactions was the inclusion of water, which improved the catalyst turnover, suppressed catalyst inhibition, and increased the Brønsted acidity of amino acids. Interestingly, increasing the amount of water (> 15 vol%) led to decreases in the observed enantioselectivity, which gave support for the notion of hydrogen bonding as an essential feature in the catalytic intermediates. Córdova's group also demonstrated that dipeptides derived from simple acyclic amino acids could also function in a similar fashion to provide aldol adducts in good yields, moderate to good diastereoselectivities, and excellent enantioselectivities.^{439,440}

Primary amino acid derivatives have also been studied for the direct catalytic asymmetric synthesis of enantiopure 1,2-diols (Scheme 192).

Barbas demonstrated that L-threonine and its *tert*-butyl ester derivative acted as efficient catalysts for the *syn*-selective aldol reaction of α -hydroxyketones and aromatic aldehydes, which is in stark contrast to the proline-catalyzed process.⁴⁴¹ The difference in diastereoselectivities observed between the two amino acids was rationalized by the different steric environment of the enamine intermediates, which gave rise to different enamine geometries.



Scheme 192 Threonine-based amino ester as a catalyst for the synthesis of *syn*-1,2-diols.



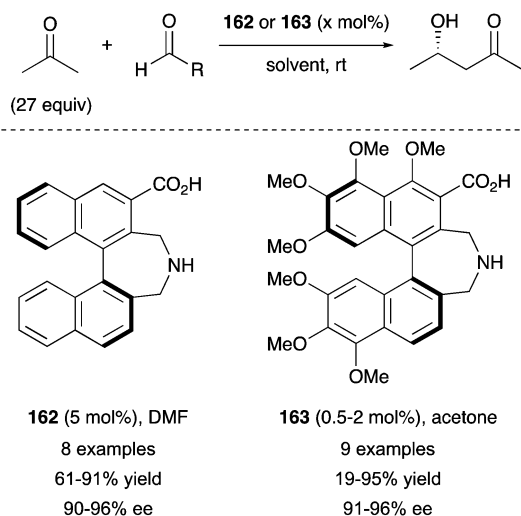
Scheme 193 Bispidine-derived organocatalyst-catalyzed asymmetric aldol reactions of functionalized ketones.

Similarly, peptides derived from acyclic amino acids were also found to be effective *syn*-selective catalysts for the direct aldol reaction with α -heteroatom (OR,F,Cl)-substituted ketones.^{442–447}

The use of acyclic amino acid derivatives as catalysts can be expended to more challenging asymmetric aldol reactions. In 2008, Feng, Hu, and co-workers employed amino acids functionalized with a bicyclic bispidine framework as catalysts for the direct aldol reactions of functionalized α -ketones (Scheme 193).⁴⁴⁸

They found that excellent yields and enantioselectivities were observed for the aldol adducts of acetone or 2-butanone with various activated ketones, such as α -keto esters, α,α -dialkoxy ketones, and α -keto phosphonates.

4.2.2. Unnatural amino acid-based organocatalysts. While Nature provides an abundance of enantiopure amino acid building blocks, a catalyst design that relies solely on the structural modification of naturally occurring amino acids can severely limit the design space to make efficient organocatalysts. In addition, due to the high catalysts loading and propensity of proline to degrade, more robust artificial amino acids are needed. With this in mind, Maruoka and co-workers developed axially chiral secondary amino acids **162** and evaluated them as organocatalysts for the direct asymmetric aldol reaction (Scheme 194).^{449–451}



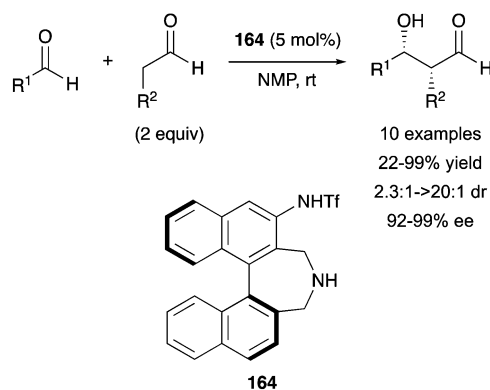
Scheme 194 Axially chiral amino acid as a catalyst for asymmetric aldol reactions.

Unlike the proline-catalyzed aldol reaction, it was found that the binaphthyl-based amino acid **162** enabled the asymmetric aldol reaction to occur with high yields and enantioselectivities with relatively low catalyst loadings. Monitoring the reaction profile of **162** and proline revealed that the initial reaction with proline was rapid, but the yield diminished over time, whereas in the binaphthyl-based amino acid-catalyzed process, the yield gradually increased over time.⁴⁴⁹ These observations indicated that proline degraded under the reaction conditions, in practice *via* decarboxylation of an iminium salt intermediate, while the designed amino acid was chemically stable. On the other hand, Maruoka and co-workers desired to improve their biphenyl-based axially chiral amino acid further. One strategy they employed to achieve this was to increase the nucleophilicity of the benzylic amine moiety in **163**, namely by introducing electron-donating substituents on the aromatic ring.⁴⁵⁰ The other approach was to modulate the acidity of the organocatalyst, and this was achieved by replacing the carboxylic acid moiety with triflamide. They found that the axially chiral amino sulfonamide **164** was an excellent catalyst for *syn*-selective cross-aldol reactions (Scheme 195).^{452,453}

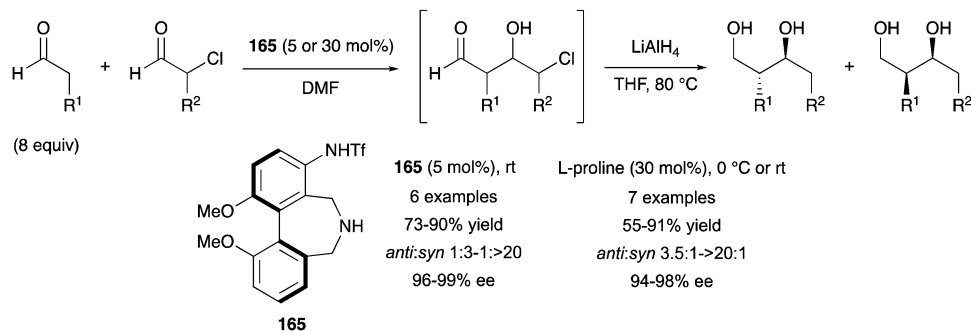
In addition, the designed chiral amino sulfonamide **164** was found to be an excellent catalyst for the *syn*-selective asymmetric aldol reaction of aliphatic aldehydes with α -ketoesters⁴⁵⁴ and α,β -unsaturated aldehydes.⁴⁵⁵

The direct cross-aldol reaction between simple aliphatic aldehydes is a challenging endeavor since aldehydes can function both as a nucleophile and as an electrophile, and this can potentially lead to two cross-aldol and two homo-aldol adducts. To overcome this problem, Maruoka and co-workers utilized a chloro substituent on the α -position of the acceptor aldehyde to differentiate the two aldehydes and then examined their functioning with the asymmetric intermolecular cross-aldol reaction (Scheme 196).⁴⁵⁶

They found that axially chiral sulfonamide **165** provided the *syn*-aldol adducts as the major product in high yields and enantioselectivity. Conversely, the use of L-proline as an organocatalyst led to the opposite diastereomer. In both cases, the key to accessing the cross-aldol product in a selective manner relied on the use of α -chloroaldehydes, in which the halogen



Scheme 195 Axially chiral amino sulfonamide-catalyzed *syn*-selective aldol reactions.



Scheme 196 Organocatalytic cross-aldol reaction between aliphatic and α -chloroaldehydes.

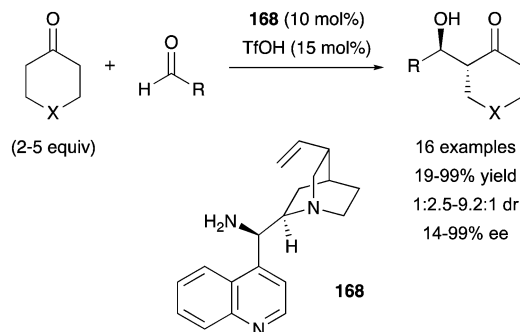
prevented the formation of the enamine intermediate and also electronically activated the aldehydes.

4.2.3. Non-amino acid-based organocatalysts. Direct enantioselective aldol reactions are not exclusively catalyzed by amino acid derivatives as chiral amines that can generate enamine intermediates also all the potential to act as organocatalysts for this asymmetric process. For instance, MacMillan and co-workers found that chiral imidazolidinones, prepared from phenylalanine, could act as an efficient catalyst for the direct cross-aldol reaction of non-equivalent aldehydes (Scheme 197).⁴⁵⁷

They found that by using excess amounts of the aldol acceptor and the slow addition of the aldol donor enabled the cross-aldol reaction to proceed, and, after methanolysis of the aldol hemi-acetal products, provided bench-stable β -hydroxy dimethoxyacetals.

Luo, Cheng, and co-workers reported the use of a chiral *trans*-*N,N*-dialkylated diaminocyclohexanes as an efficient organocatalyst for enantioselective aldol reactions (Scheme 198).⁴⁵⁸

Similar to other diamines with an achiral acid co-catalyst, the role of the primary amine is to form the enamine, whereas the protonated tertiary nitrogen is expected to activate the aldol



Scheme 199 Cinchonidine-derived primary amine-catalyzed enantioselective direct aldol reaction.

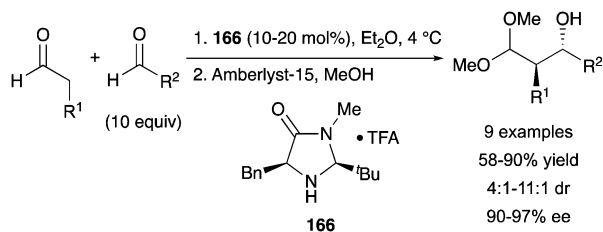
donor *via* hydrogen bonding. Along with this report, other groups have also demonstrated the use of chiral diamine catalysts modified from the 1,2-diaminocyclohexane framework in various asymmetric aldol reactions.⁴⁵⁹⁻⁴⁶⁷

A chiral primary-tertiary diamine **168** derived from cinchonidine was reported by Liu and co-workers as an organocatalyst for the enantioselective aldol reactions of aldehydes with cyclic ketones (Scheme 199).⁴⁶⁸

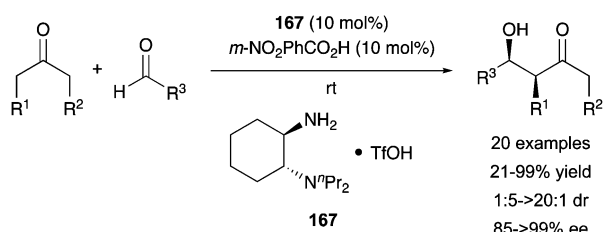
These organocatalysts, which are readily accessible from natural sources, provided the aldol adducts in good yields and enantioselectivities, albeit with modest diastereoselectivities. Further, these cinchonidine-based organocatalysts have also been investigated for other types of asymmetric aldol reactions.⁴⁶⁹⁻⁴⁷⁵

4.3. Non-enamine-based organocatalyst

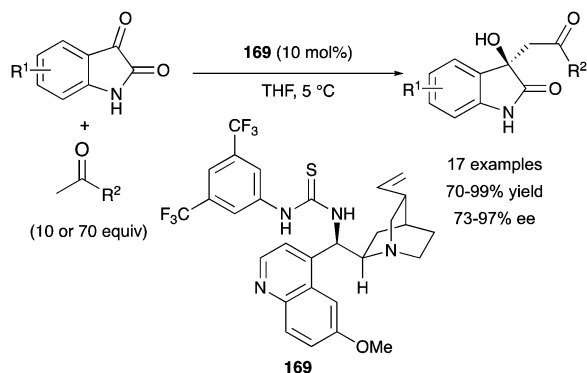
The vast majority of chiral organocatalysts utilized in asymmetric direct aldol reactions are primary and secondary amines that can generate the key enamine intermediate to obtain the desired aldol adducts. However, in the original aldol reaction, the key intermediates were enols and enolates, but these intermediates are difficult to access due to the acidity of the α -hydrogen of ketones being relatively low. Despite this challenge, Zhao and co-workers hypothesized that with sufficiently activated aldol acceptors, organocatalytic direct aldol reactions, *via* an enolate mechanism, should be possible, and they found that a bifunctional organocatalyst derived from quinidine functionalized with a thiourea moiety was an excellent catalyst for the asymmetric direct cross-aldol reaction of isatin and ketones (Scheme 200).⁴⁷⁶



Scheme 197 Chiral imidazolidinone-based synthesis of enantiopure β -hydroxy dimethoxyacetals.



Scheme 198 Asymmetric direct aldol reactions using a simple chiral diamine catalyst.



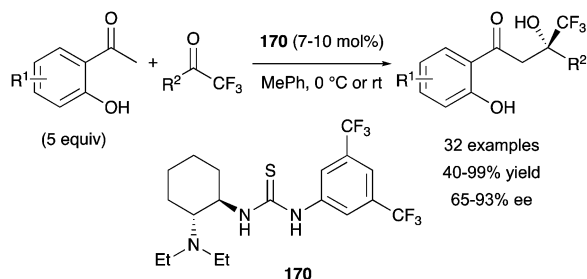
Scheme 200 Direct aldol reactions between isatins and ketones catalyzed by a bifunctional quinidine thiourea organocatalyst.

The authors proposed that the role of the tertiary amine of their bifunctional catalyst was to deprotonate the ketone to generate the enolate, and that the thiourea activated the isatin carbonyl groups for the enolate attack and directed the approach of isatin. The use of the bifunctional quinidine catalyst **169** was also employed by Zhao for the asymmetric cross-aldol reactions between ketones with activated aldol acceptors, such as β,γ -unsaturated α -ketoesters and phenylglyoxal hydrates.⁴⁷⁷

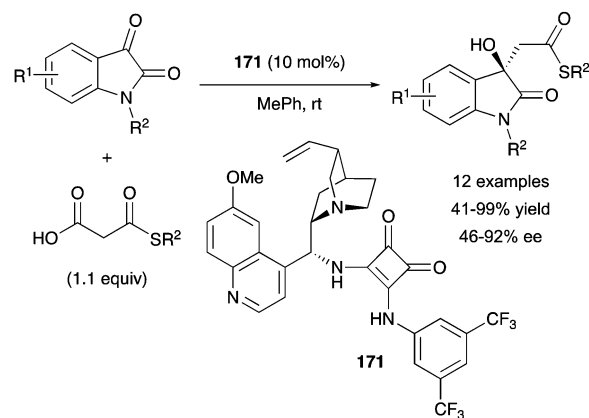
Bifunctional thiourea-tertiary amine catalysts can also be constructed from other chiral tertiary amine sources. Da and co-workers reported the use of a chiral thiourea organocatalyst, derived from 1,2-cyclohexanediamine, which enabled the enantioselective cross-aldol reaction between *o*-hydroxyacetophenones and trifluoromethyl ketones to proceed (Scheme 201).⁴⁷⁸

They found that the presence of the *ortho*-hydroxy moiety on the acetophenone was critical since intramolecular hydrogen bonding led to an increased acidity of the α -hydrogen and aided the formation of the enolate intermediate. In addition, the trifluoromethyl moiety of the aldol acceptor was important to improve the reactivity and selectivity of the aldol reaction.

For direct asymmetric aldol reaction with an organocatalyst that activates the aldol donors *via* enols and enolates intermediates, the use of activated carbonyl compounds has been reported. For instance, malonic acid half thioesters (MAHTs) were used in the biosynthesis of polyketides and fatty acids, and its applications for organocatalyzed decarboxylative aldol reactions have also been reported. In 2011, Nakamura, Shibata, and co-workers reported the use of the chiral squaramide **171**



Scheme 201 Enantioselective intermolecular aldol reactions of *o*-hydroxyacetophenones and trifluoromethyl ketones.



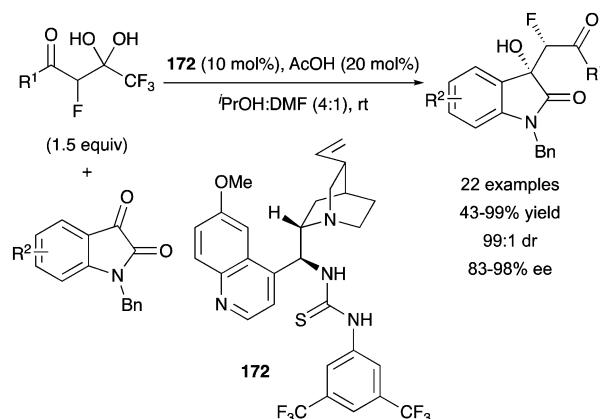
Scheme 202 Decarboxylative asymmetric aldol addition of malonic acid half thioesters.

as an efficient catalyst for the decarboxylative aldol reactions of MAHTs with isatin derivatives (Scheme 202).⁴⁷⁹

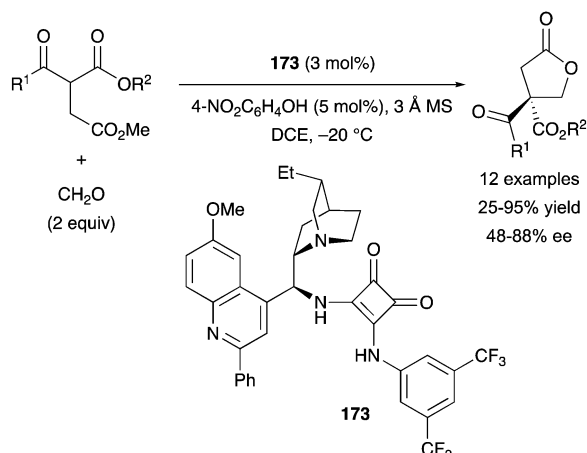
Although the decarboxylative process proceeded well to furnish the desired aldol adducts in good yields and enantioselectivities, the MAHTs were limited to arylthio esters. In addition, the authors demonstrated the synthetic utility of their protocol by synthesizing optically active (–)-flustraminol B using the asymmetric decarboxylative aldol reaction as a key step. Other groups have also investigated the decarboxylative aldol reactions of MAHTs, and have shown that aldehydes can act as the aldol acceptor.^{480,481} Moreover, other β -ketoacids were utilized as the aldol donor in the presence of activated aldehydes,^{482–484} α -ketophosphonates,⁴⁸⁵ and isatin derivatives.^{486,487}

Analogous to the decarboxylative aldol reaction, Fang, Wu, and co-workers employed α -fluorinated β -keto *gem*-diols as masked α -fluorinated enolates for asymmetric aldol reactions with *N*-benzylated isatin derivatives (Scheme 203).⁴⁸⁸

The synthesis of β -keto *gem*-diols could be easily achieved through a copper-catalyzed process with Selectfluor and trifluoro-1,3-diones, with these reagents shown to act as masked aldol donors *via* the release of trifluoroacetate, and underwent the asymmetric aldol reaction to generate enantiopure fluorinated 3-hydroxy oxindoles in excellent yields and diastereoselectivity.



Scheme 203 Enantioselective synthesis of 3-hydroxy oxindoles.

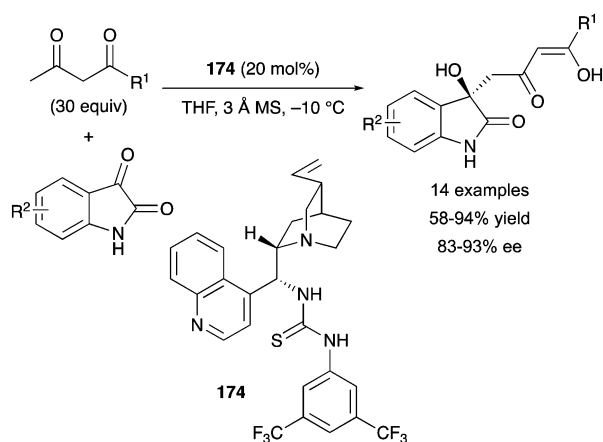
Scheme 204 Enantioselective synthesis of γ -butyrolactones.

Some other examples of 1,3-dicarbonyl compounds in direct aldol reactions have been reported. For instance, Lattanzi and co-workers examined a one-pot, sequential enantioselective aldol/lactonization process between acylated succinic esters with aqueous formaldehyde (Scheme 204).⁴⁸⁹

To achieve this enantioselective process, various bifunctional chiral amines bearing hydrogen-bonding functionalities were investigated, and they found that the *epi*-hydroquinine-derived squaramide **173** provided the β,β -disubstituted γ -butyrolactones in good yields and enantioselectivities. An important additive for this tandem process was 4-nitrophenol, which improved the conversion of the reaction at lower reaction temperatures.

In 2012, Wu, Jiang, and co-workers found that acetylacetone and related derivatives could undergo the asymmetric aldol reaction at the C-1 position (Scheme 205).⁴⁹⁰

While the high acidity of the methylene position of 1,3-dicarbonyl compounds resulted in the formation of the enolate at the C-3 position, the double deprotonation of acetylacetone and related compounds enabled nucleophilic addition at the more reactive C-1 position. They found that the use of the thiourea catalyst **174** provided the expected products in high yields



Scheme 205 Regioselectivity reversed asymmetric aldol reactions of 1,3-dicarbonyl compounds.

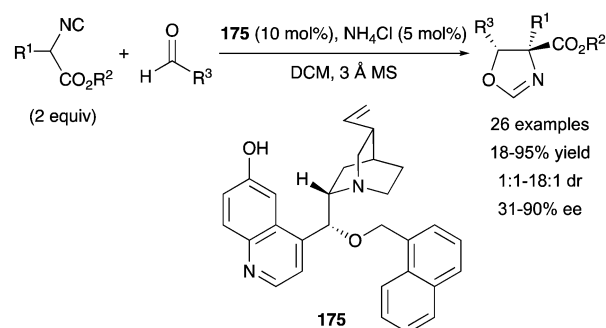
and enantioselectivity, and that the resulting oxindoles could then undergo an iron-catalyzed hemiketalization/dehydration cascade process to generate spirobutyrolactones.

The presence of other types of electron-withdrawing moieties on the α -position of carbonyl compounds has been reported as beneficial for them to serve as effective aldol donors in organo-catalyzed asymmetric aldol reactions. For instance, isocyanoacetates are known to undergo formal [3+2] cycloaddition reactions, *via* aldol reaction/condensation, with carbonyl compounds to produce oxazoline derivatives. In 2009, Gong and co-workers reported that cinchona alkaloid **175** was an efficient catalyst for the formal asymmetric [3+2] cycloaddition of α -aryl isocyanoesters with aldehydes (Scheme 206).⁴⁹¹

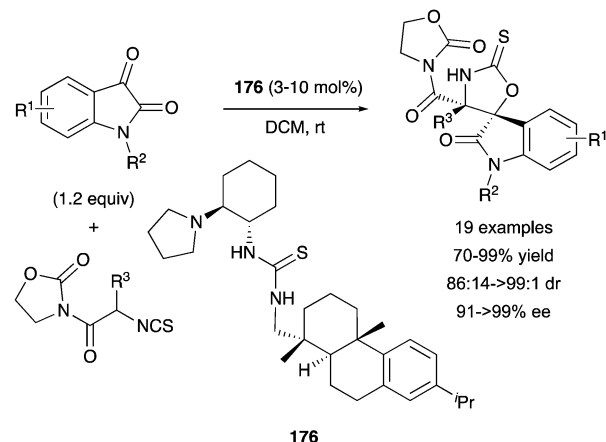
The related synthesis of optically active oxazolines was reported using bifunctional cinchona alkaloids bearing thiourea moieties as chiral organocatalysts with other aldol acceptors, such as aldehydes,⁴⁹² α -keto esters,^{493,494} and isatins.⁴⁹⁵

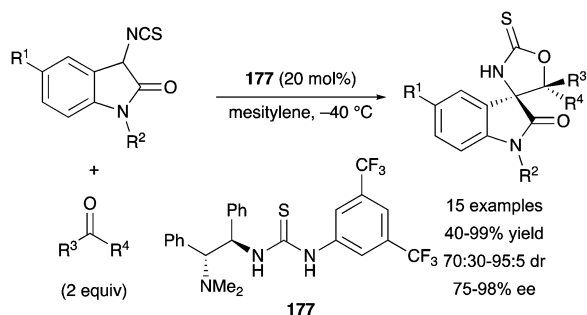
Due to the prevalence of spirooxindole frameworks in pharmaceuticals and natural products, Wang and co-workers investigated and reported the intramolecular aldol-cyclization reactions of α -isothiocyanato imides to electron-deficient isatins to generate spiro[thiocarbamate-3,3'-oxindoles] (Scheme 207).⁴⁹⁶

They found that a rosin-derived thiourea organocatalyst **176** gave access to a diverse set of spirocyclic thiocarbamates in excellent yields, and with excellent diastereo- and enantioselectivities.



Scheme 206 Asymmetric synthesis of chiral oxazoline derivatives.

Scheme 207 Synthesis of optically active spirooxazolines *via* the aldol cyclization-reaction.

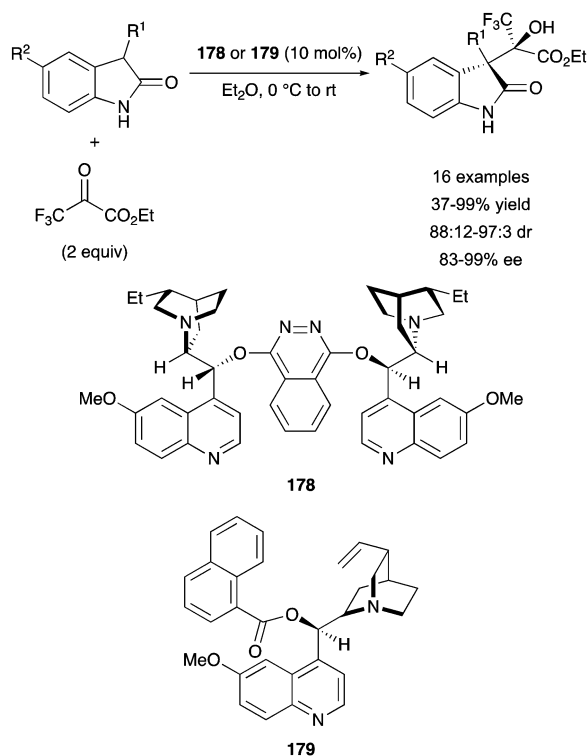


Scheme 208 Direct asymmetric intermolecular aldol reactions of 3-isothiocyanato oxindoles to simple ketones.

Moreover, these thiocarbamates were converted to various optically active spirooxazolines in the presence of methyl iodide under basic conditions. It was found that several of these spirooxindoles could reduce LPS-induced fever.

In a similar fashion, Yuan and co-workers reported a bifunctional catalyst **177**, derived from 1,2-diphenylethylenediamine, as an efficient catalyst for the direct asymmetric aldol reactions of 3-isothiocyanato oxindoles to ketones to generate enantioenriched spirocyclic oxindoles (Scheme 208).⁴⁹⁷

Due to the prevalence of chiral 2-oxindole derivatives in biologically active natural products and pharmaceuticals, asymmetric direct aldol reactions using oxindoles as aldol donors have been reported. In 2007, Shibata, Toru, and co-workers demonstrated that cinchonidine was an excellent organocatalyst



Scheme 209 Direct aldol reactions of oxindoles using cinchona alkaloid catalysts.

that facilitated the direct aldol reaction of oxindoles with ethyl trifluoropyruvates (Scheme 209).⁴⁹⁸

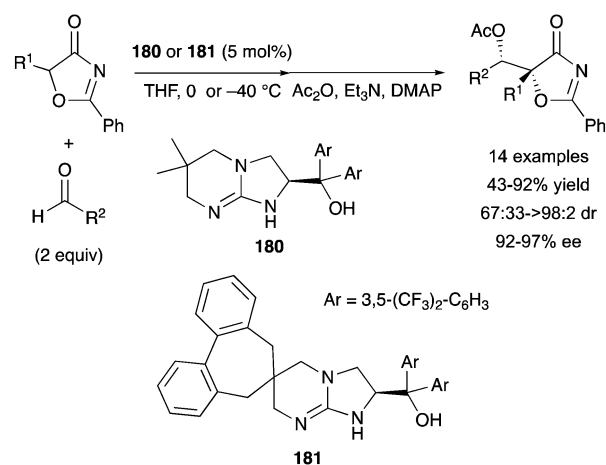
When several cinchona alkaloids were examined, (DHQ)₂PHAL **178** and quinine naphthoate **179** were found to be excellent catalysts that enabled the enantioselective aldol reaction to occur in high yields and enantioselectivities. In addition, the use of pseudoenantiomeric (DHQD)₂PHAL provided the opposite enantiomer of the aldol product in equally impressive yields and enantioselectivities. The ability of cinchona alkaloid-derived organocatalysts to catalyze the direct asymmetric aldol reactions of oxindoles has been reported with ethyl glyoxylate⁴⁹⁹ and formaldehyde^{500–502} as aldol acceptors.

Another class of carbonyl compounds that can serve as aldol donors in asymmetric aldol reactions is azalactones. In 2010, Misaki, Sugimura, and a co-worker demonstrated that the chiral guanidines **180** and **181** could catalyze the direct asymmetric aldol reactions between 5H-oxazol-4-ones and aliphatic aldehydes (Scheme 210).⁵⁰³

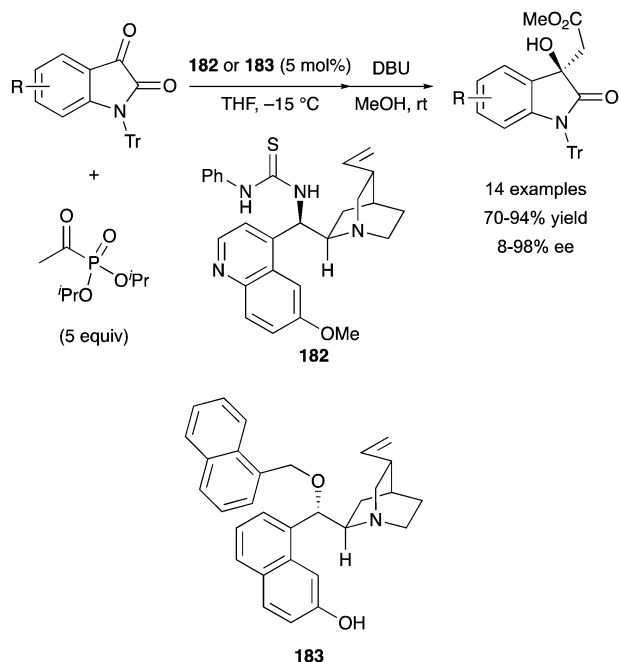
The authors found that the chiral guanidine **181** provided improved *syn/anti*-selectivity, whereas the less sterically bulky catalyst **180** was found to improve the reactivity. While simple linear aldehydes led to modest diastereoselectivities, the aldol adducts of α -branched aldehydes were obtained in excellent *syn/anti*-selectivities and enantioselectivities. It was also shown that the asymmetric aldol reaction of azalactones and aliphatic aldehydes could also be catalyzed by chiral cinchona alkaloid catalysts.⁵⁰⁴

While most of the activated aldol donors possess an electron-withdrawing moiety on the α -position of the carbonyl group, the direct attachment of an electron-withdrawing group to the carbonyl can also activate aldol donors and these substrates can then be used in asymmetric aldol reactions. Zhao and co-workers demonstrated that acetylphosphonates could act as the surrogates of acetates or acetamides in organocatalyzed enantioselective aldol reactions (Scheme 211).⁵⁰⁵

In addition to isatins, Zhao and co-workers showed that phenylglyoxals and α -keto esters could undergo the asymmetric process using cinchona-alkaloid-derived organocatalysts. Other groups also demonstrated that similar classes of activated



Scheme 210 Direct asymmetric aldol reactions of azalactones and aldehydes.

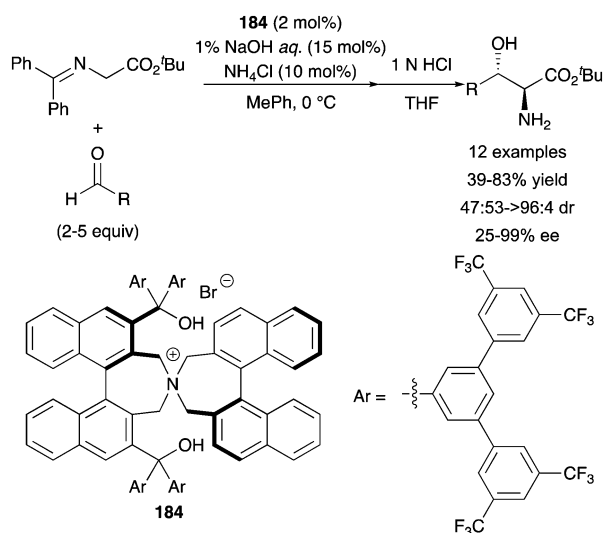


Scheme 211 Highly enantioselective aldol reactions of acetylphosphonates and activated carbonyl compounds.

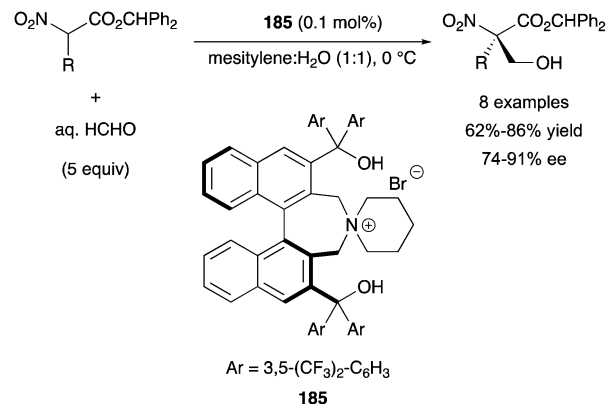
aldol donors, such as α -ketoesters,^{506,507} and α -ketoamides,⁵⁰⁸ could be utilized in asymmetric aldol reactions.

Although most organocatalysts that enable efficient asymmetric aldol reactions are derived from chiral amine bases, other modes of activations can be used to promote these asymmetric processes. For instance, Maruoka and co-workers reported the preparation and application of a chiral phase-transfer catalyst that facilitated a highly efficient direct asymmetric aldol reaction of glycine Schiff bases with aldehydes (Scheme 212).^{509,510}

One of the major challenges of performing aldol reactions under strong basic conditions is the possibility of the retro-aldol reaction



Scheme 212 Chiral quaternary ammonium salt-catalyzed asymmetric aldol reaction of glycine Schiff bases.



Scheme 213 Direct asymmetric aldol reactions of α -substituted nitroacetates with aqueous formaldehyde.

occurring. However, Maruoka and co-workers found that reducing the amount of the aqueous base and carefully adjusting the pH of the reaction system using ammonium chloride as an additive could minimize this process. By using the *N*-spiro C_2 -symmetric chiral phase-transfer catalyst **184** as a phase-transfer catalyst, excellent yields, diastereoselectivities, and enantioselectivities were obtained for the asymmetric aldol reactions of glycinate Schiff bases and aldehydes. It was also shown that similar ammonium salts, derived from the alkylation of chiral cinchona alkaloids, could also act as efficient phase-transfer catalysts for direct aldol reactions involving glycine Schiff bases.^{511,512}

In addition to glycine Schiff bases, other activated aldol donors can be used as substrates for the asymmetric aldol reaction under phase-transfer conditions. For instance, Maruoka and co-workers reported the direct asymmetric aldol reaction of α -substituted nitroacetates with formaldehyde to obtain a wide range of α -alkyl serines (Scheme 213).⁵¹³

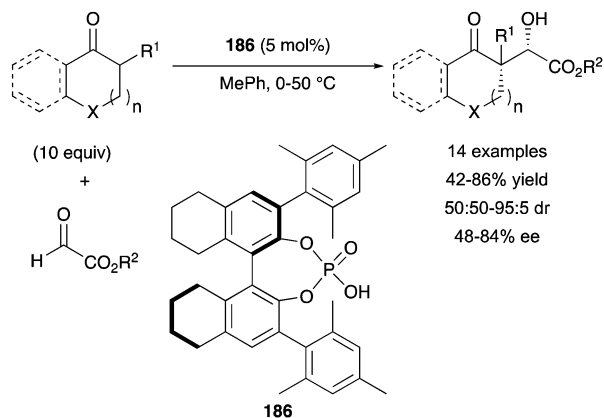
A noteworthy aspect of this report was that this enantioselective direct aldol reaction could be achieved under base-free neutral phase-transfer conditions.

While the organocatalyzed aldol reactions are dominated by chiral amines as catalysts, some limited examples of using chiral phosphoric acid have been reported. For instance, in 2010, Blanchet and co-workers found that chiral phosphoric acid **186** was an excellent catalyst for the direct asymmetric aldol reaction between ketones and α -ketoesters (Scheme 214).⁵¹⁴

Although the substrate scope of the aldol acceptor was limited to activated substrates, the noteworthy aspect of this work was the ability of this catalyst system to enable the use of α,β -unsaturated ketones as an aldol donor.⁵¹⁵ These substrates are typically considered to be challenging due to the possibility of chiral amines undergoing aza-Michael reactions with these unsaturated systems.

5. Catalytic enantioselective aldol reactions in aqueous media

Synthetic organic chemistry remains reliant upon organic solvents as the reaction media despite the use of water being



Scheme 214 Brønsted acid-catalyzed asymmetric aldol reaction.

more advantageous from the viewpoint of green sustainability due to its abundance, safety, and environmental benignity. This is because most organic substances are immiscible with water, and reactive reagents and catalysts can potentially be decomposed or deactivated under aqueous conditions. Inspired by biological reactions that take place in aqueous environments, chemists have made tremendous efforts to devise tools that could allow catalytic reactions to occur even in aqueous solutions. In particular, there have been significant advances made in catalytic organic transformations using water as a solvent in aldol reactions. In Nature, aldolases that are responsible for *in vivo* stereoselective aldol reactions are found in many biosynthetic pathways of carbohydrates and occur through an enamine mechanism and a metal-centered mechanism. We herein overview the enantioselective aldol reactions using solvent amounts of water.

One of the key advantages of conducting catalytic reactions using water as a solvent is that undesired side reactions arising from weak interactions can be inhibited, and also that transition states can be more strictly controlled owing to the hydrogen bond network, specific solvation, and hydrophobic interactions that can exist in aqueous media. In addition, the hydrolysis of catalyst-bound products can also facilitate regeneration of the catalyst to promote catalyst turnover. However, a major difficulty associated with performing asymmetric catalysis in aqueous environments lies in the fact that noncovalent interactions between substrates and chiral catalysts are vulnerable under competitive polar conditions. With this in mind, it is clear that covalent catalysis is well suited to overcoming this problem and could effectively enable efficient asymmetric catalysis to occur in water. Indeed, in the embryonic stage of enamine catalysis, amino acids were used in the aldol reaction in water.⁵¹⁶ Progressive developments in the field of asymmetric aldol reactions, both in organic solvents and in aqueous media (Fig. 1, see Introduction), represent the epitome of the evolution of catalytic asymmetric C-C bond formation. The story of asymmetric aldol reactions in aqueous media dates from 1995 in the field of catalytic antibodies (abzymes),⁵¹⁷ followed by the emergence of water-compatible chiral metal complexes in 1999.⁵¹⁸⁻⁵²⁰ Although asymmetric aldol reactions have been achieved without using preformed

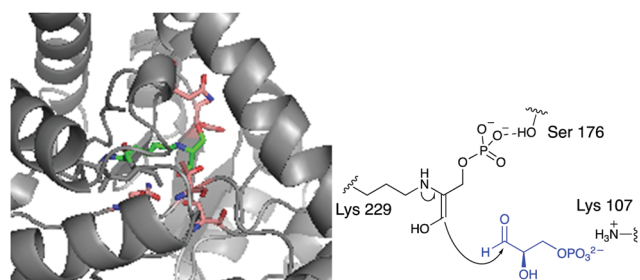
enolates, even in aqueous environments, catalyst development still remains in the realm of trial and error, presumably owing to low stability of the enolate form in aqueous environments.

5.1. Biocatalysis

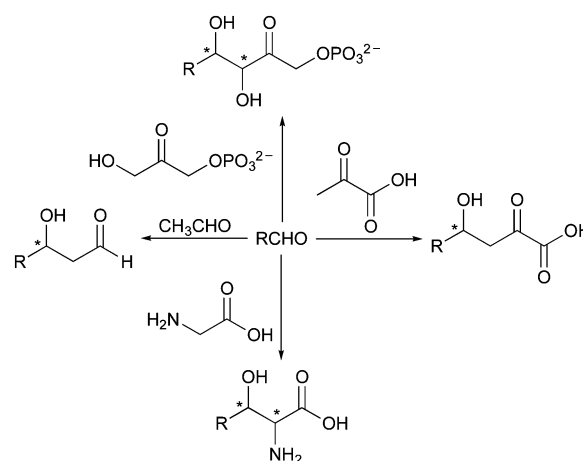
5.1.1. Type I and II aldolases. In 1936, Meyerhof, Lohmann, and Schuster discovered from the extracts of rabbit muscles that certain enzymes, termed aldolases, could catalyze aldol reactions. Since then, numerous enzymes that promote the aldol reactions have been discovered, and these can be divided into two classes based on their mechanisms: type I and type II.^{521,522}

Type I aldolases, principally found in eukaryotes, form a covalent Schiff's base intermediate with a lysine residue in their active site, and the resulting enamine then takes part in enantioface-selective attack on the aldol acceptor to form a lysine-bound imine, followed by hydrolysis to generate the new C-C bond (Scheme 215).⁵²³ On the basis of the donor substrates (dihydroxyacetone phosphate (DHAP), pyruvic acid, glycine, and acetaldehyde), there are four classifications of aldolases (Scheme 216).

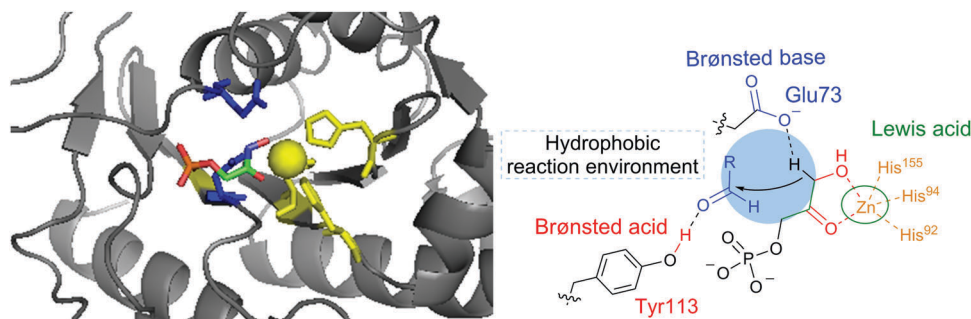
In contrast, type II aldolases, primarily found in bacteria and fungi, are zinc-dependent enzymes for direct-type enantioselective aldol reactions in organisms (Scheme 217).⁵²⁴ In the active site



Scheme 215 (left) Structure of the active site of transaldolase B with the reduced Schiff's base intermediate (PDB ID 1UCW). (right) Accepted mechanism involving the active site of type I aldolases. Figures were prepared using PyMOL.



Scheme 216 Classification of aldolases-catalyzed reactions. Dihydroxyacetone phosphate (DHAP), pyruvate, glycine, and acetaldehyde-dependent aldolases.



Scheme 217 (left) Structure of the active site of fuculose-1-phosphate aldolase (PDB ID 4FUA; yellow sphere represents Zn^{2+}). (right) Accepted mechanism involving the active site of type II FBP aldolases. Figures were prepared using PyMOL.

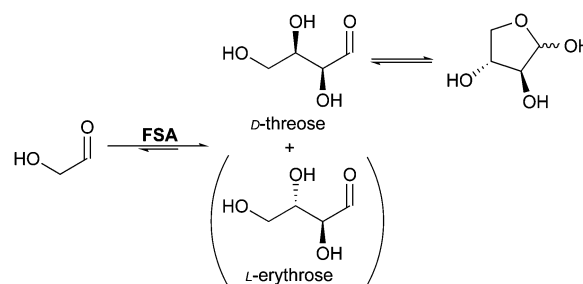
of the representative fructose-1,6-bisphosphate (FBP) aldolase, the Zn^{2+} cofactor is surrounded by three histidine residues and a glutamate residue (Glu73), which is also involved in the coordination in the absence of DHAP. During the rate-determining step of the reaction, Glu73 behaves as a Brønsted base to deprotonate the α -position. The phosphate group in DHAP is fixed inside the cavity through several hydrogen-bonding interactions with donors, such as serine, threonine, and asparagine. The incoming aldehyde is activated by a tyrosine residue (Tyr113), which acts as a Brønsted acid.

5.1.2. Engineered aldolases. The aldolase-based approach is beneficial for the synthesis of water-soluble polyfunctionalized carbohydrates since conventional routes are not suitable.^{525,526} Several mutagenesis techniques have been used to alter the properties of natural aldolases, such as the stability, activity, substrate applicability, and stereoselectivity, to produce tailor-made aldolases. The directed evolution of aldolases based on error-prone PCR⁵²⁷ and DNA shuffling⁵²⁸ has led to an enhanced catalytic efficiency and altered the substrate specificity.⁵²⁹ The bottleneck in the directed evolution is the development of reliable high-throughput assays, which are typically tedious and time-consuming processes. An early example by Hilvert and co-worker showed that a single active-site mutation was able to convert an alanine racemase into an aldolase.⁵³⁰ The FBP aldolase was shown to acquire increased thermostability and solvent tolerance through DNA shuffling.⁵³¹ Since this area has already been reviewed,^{532–534} the focus of this review is on recent studies mainly on D-fructose-6-phosphate aldolases (FSAs) from *Escherichia coli* to exemplify the importance of the engineered enzymes in asymmetric aldol reactions.

The wild-type FSA is a versatile class I aldolase of unknown physiological function, and has some advantage over DHAP-dependent aldolases since unphosphorylated donor substrates can be used.⁵³⁵ FSAs can accept unphosphorylated dihydroxyacetone analogs, such as hydroxyacetone, hydroxybutanone, and glycolaldehyde. The latter offers the possibility of performing stereoselective homo- and cross-aldol additions of glycolaldehyde with an unmatched breadth of nucleophile selectivity, producing small sugars and functionally diverse analogs. It is also known to show a remarkably high thermostability ($t_{1/2}$ of 16 h at 75 °C), and tolerance to wide pH ranges (pH 6–12) and organic cosolvents such as DMF.⁵³⁵ It was recently found that the minimalist engineering of

wild-type FSA enables a significant expansion of the substrates scope. Schürmann and Sprenger targeted the residue A129, and found a remarkable rate enhancement.⁵³⁵ In the active site, involving K85–enamine nucleophile intermediates, the residues D6 and T26 formed hydrogen bonds with the hemiaminal intermediates comprising hydroxyacetone and the hemiaminal hydroxy group oriented toward the deeper part of cavity, but in relative proximity (<5 Å) to the hydrophobic L107, A129, and A165 residues. A combination of mutations in L107, A129, and A165 furnished a toolbox that can expand the scope in the cross-aldol additions of glycolaldehyde.⁵³⁶ An improved catalytic efficiency toward dihydroxyacetone (DHA) was observed when the mutant FSA A129S was used.⁵³⁷ A structure-guided redesign was devised to broaden the aldol acceptors to include α -substituted and conformationally constrained aldehydes, leading to A129S/R134X/A165G/S166G and L107Y/A129G/R134X/A165G/S166G variants, where X was R, V, P, or S, for DHA, hydroxyacetone, and glycolaldehyde.⁵³⁸ In the active site of wild-type FSA, the residue R134 was suggested to be involved in the binding of the phosphate group of the acceptor. The engineered variants (L107A/L163A,⁵³⁹ D6H⁵⁴⁰) were shown to extensively broaden the nucleophile scope to accept a wide variety of aliphatic aldehydes or ketones to 3-hydroxypropanal, D-glycer-aldehyde-3-phosphate. When mutated at L107 and A129, which are amino acids that reside inside the active-site cavity, the FSA variants exhibited a higher donor activity and selectivity. The A165G mutation was believed to provide increased available space to enhance the reactivity of inactive aldehydes.

Another feature of FSA is the synthetic possibilities toward an access to carbohydrate compounds. The homo-aldol addition of glycolaldehyde furnished D-threose (Scheme 218).⁵⁴¹



Scheme 218 Homo-aldol addition of glycolaldehyde to furnish D-threose.

Mutated variants A129G, A129T, or A129V were found to be superior to the wild-type.^{536,542}

In 2015, Clapés and co-workers reported that engineered FSA could be used to prepare various aldose carbohydrates and their derivatives.⁵⁴² They demonstrated that 2 equivalents of glycolaldehyde to an equivalent of formaldehyde provided a double addition product: *L*-xylose (Scheme 219 above). Glycolaldehyde was added portionwise to minimize the formation of *D*-threose. When the residues A129 and A65 were mutated, the catalytic activity and selectivity were shown to be improved.

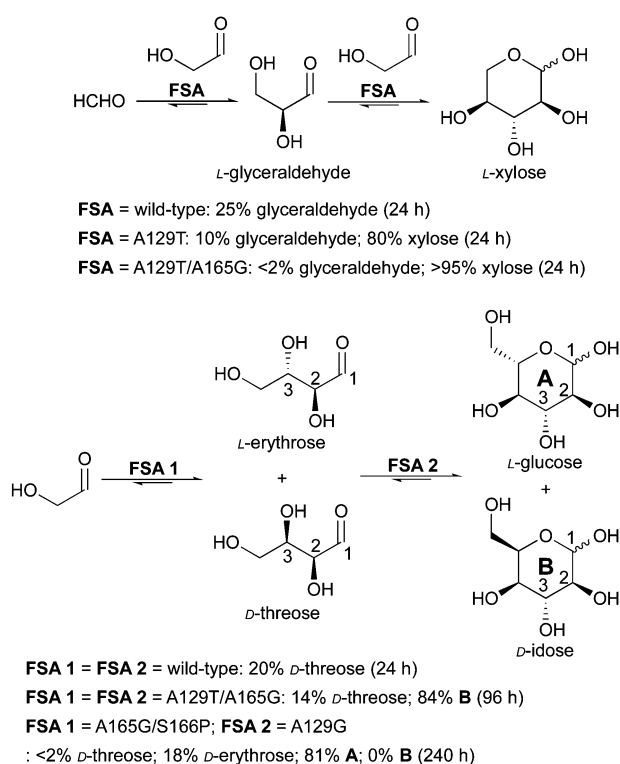
The consecutive aldol reaction of three glycolaldehyde molecules is ideal to deliver *L*-glucose. However, this is a challenging task because it is difficult to control the stereochemistry of the tandem aldol reaction. However, the homo-aldol addition of glycolaldehyde can furnish *D*-threose and *L*-erythrose, and the subsequent aldol addition to these intermediates can deliver *L*-glucose and *D*-idose, respectively (Scheme 219 below). The retro-aldolization of *D*-threose, due to the low concentration of its acyclic form, made the subsequent addition slower than the first step in the presence of wild-type FSA, resulting in the formation of 20% *D*-threose. It was found that engineering FSA A165G resulted in modifying the stereochemical outcome of the first self-aldol reaction of glycolaldehyde to generate a mixture of *D*-threose and *L*-erythrose. As a result of screening, the first step catalyzed by FSA A165G/S166P was seen to furnish *L*-erythrose predominantly, while a further addition of FSA A129G catalyzed the addition of glycolaldehyde to *L*-erythrose to furnish *L*-glucose. A high yield of *L*-glucose was obtained due

to the higher thermodynamic stability of *L*-glucose, relative to *D*-idose, as well as due to the inability of FSA A129G to cleave *L*-erythrose.

In 2017, Hilvert and co-workers examined individual steps in the multistep aldolase RA95-based aldol reaction pathway to determine how mutations influenced the enzymatic kinetics.⁵⁴³ Isotope experiments indicated that either C–C bond formation or product release should be the rate limiting step.

5.1.3. Catalytic antibodies. In 1986, Lerner and Schultz developed the first “abzymes” as alternatives to enzymes.^{544,545} Abzymes are based upon the Haldane–Pauling “key and lock” hypothesis of transition state stabilization, with the concept commonly coined as “reactive immunization.” Abzymes are formed by immunizing an animal with transition state analogs of a given reaction. Synthetic chemists designed abzymes to complement the substrate scope of aldolases.⁵¹⁷ Antibody 38C2 (Ab 38C2) or 33F12 elicited by a reaction immunization with a 1,3-diketone hapten was found to catalyze a wide variety of cross-, self-, and retro-aldol reactions, including intramolecular transformation, with rate accelerations approaching those of natural aldolases.^{546–549} Typical values of the Michaelis–Menten constants range from 1 mM to 1 M for the aldol donors, reflecting the ability of abzymes to accept a wide range of ketones.^{547,550,551} Ab 38C2 was applied for the enantioselective synthesis of natural compounds, such as brevicomins (>99% ee),⁵⁵² 1-deoxy-*L*-xylulose (97% ee),⁵⁵³ and epothilones.⁵⁵⁴ Ab 33F12 Fab' with a diketone was cocrystallized and revealed that only a few residues are essential for amine catalysis in a hydrophobic environment.⁵⁵⁵ Kinetic experiments on the pH-reaction rate profiles and enolization catalysis suggested that the C–C bond formation was both the rate and enantio-determining steps.⁵⁵⁶ The enamine formed between acetone and LysH93 in 33F12 and 38C2 is known to react with benzaldehyde to produce the (*S*)-aldol product exclusively, whereas 84G3 and 93F3 yields the (*R*)-aldol product. This fact also indicates that enantioselectivity is dictated by the C–C bond forming step.

In 2014, Acevedo and co-worker attempted to rationalize the difference in catalysis in water⁵⁵⁷ between catalytic antibodies and (*S*)-prolinamide.⁵⁵⁸ QM/MM Monte Carlo calculations and free-energy perturbation (MC/FEP) theory revealed that a site-specific electrostatic stabilization of TyrL36 phenoxide by the adjacent TrpH103, SerH100, and AsnL34 enabled the active site to facilitate the *Si*-face attack to benzaldehyde. However, the *Si*-face conformation of benzaldehyde was unfavorable for the organocatalyst. Solution-phase calculations found an increased free energy in the activation difference, $\Delta\Delta G^\ddagger$, for organocatalyst-based enamines in water than in acetone, resulting in the enhanced enantioselectivity predicted from 87% ee to 94% ee (experimentally, 93% ee). This could be explained as a more compact *Si*-face transition structure would reduce the accessibility of water molecules to the catalytic site with a “closed state” steric barrier compared with an “open state” for the *Re*-face. The transition state away from the water molecules allow the reactants to benefit from the hydrophobic portion while stabilizing the carbonyl *via* specific hydrogen bonding with the interfacial waters. Similarly, a strong hydrogen bond



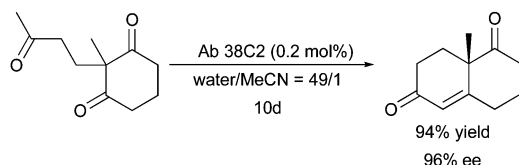
Scheme 219 (left) Engineered FSA-catalyzed double addition of glycolaldehyde with formaldehyde. (right) Stereoselective synthesis of *L*-glucose.

network and hydrophilic residues were predicted to help anchor the proton donor in an appropriate position to participate in a proton-transfer event and adopt the *Si*-face orientation. As a result, hydrophobic residues surrounding LysH93 enamine were able to construct a microenvironment. The pK_a value of the active site (LysH93) of Ab 38C2 was estimated to be 6.0,⁵⁴⁷ whereas that of the ϵ -amino group of free lysine was 10.5⁵⁵¹ in solution. The large shift of pK_a was attributed to the extremely hydrophobic microenvironment encompassing the active site,^{559,560} underlying the high efficiency of Ab 38C2 for direct aldol reactions. Since typical amines would be protonated in water and would be ineffective for the reaction, quantitative evaluation of the hydrophobicity, and in particular hydrogen bonding, is of great importance (*vide infra* 5.1.4). Native antibody heavy chain variable domain (V_H) gene shuffling was then adopted to reconstruct the aldolase antibodies while retaining the catalytic residues and mechanism of the parental antibodies.⁵⁶¹

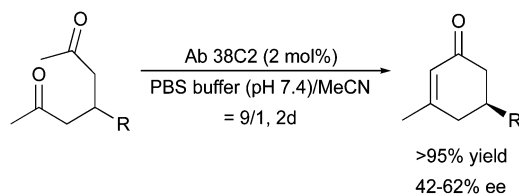
Abzymes have been also applied for enantioselective aldol reactions in aqueous environments. In 1997, an enantioselective Robinson annulation catalyzed by an abzyme was reported in order to access optically active Wieland–Miescher ketones with high enantiopurity (Scheme 220).⁵⁶²

Enantioselective cyclohydration represents an analogous transformation catalyzed by L-proline ($\sim 30\%$ yield, 0–47% ee enantioselectivity),⁵⁶³ and Lerner, Barbas, and co-worker demonstrated that Ab 38C2 was capable of performing the enantioselective cyclohydration of 4-substituted 2,6-heptanediones to the 5-substituted 3-methyl-2-cyclohexen-1-ones in aqueous media to afford the products with excellent yields, but only with moderate selectivities (Scheme 221).⁵⁶⁴

5.1.4. Immobilized aldolases. Since reusable enzymes are desirable for their commercialization, enzyme immobilization with enhanced reproducibility and durability has been investigated in recent years. The simple immobilization of an aldolase antibody into mesoporous silica was reported to show increased catalytic activity in nonaqueous media.⁵⁶⁵ Consecutive microwave irradiation was also reported to assist in aldolase immobilization in mesocellular siliceous foam (MCFs) in a stable and efficient manner.⁵⁶⁶



Scheme 220 Antibody-catalyzed enantioselective Robinson annulation.



Scheme 221 Antibody-catalyzed enantioselective aldol cyclodehydration.

5.1.5. Other biocatalysts. In 2008, Yu and co-workers reported that lipase from porcine pancreas (PPL) or pepsin could catalyze enantioselective cross-aldol reactions of 4-nitrobenzaldehyde with acetone to yield the aldol product in up to 22% yield with 44% ee enantioselectivity.⁵⁶⁷ In addition, protease from *Bacillus licheniformis* was identified as a catalyst for several C–C bond forming processes, including the aldol reaction between 4-nitrobenzaldehyde and acetone, with a low enantioselectivity (up to 13% ee).⁵⁶⁸ The promiscuous behavior of the protease used in the cross-linked enzyme aggregates immobilized form (Alcalase-CLEA[®]) was successfully demonstrated. In 2016, an enzyme isolated from *Daucus carota* root was shown to be able to act as a catalyst for the reaction of 4-nitrobenzaldehyde with acetone to afford the desired aldol product in a 95% yield with a 98% ee.⁵⁶⁹ It was also reported that a crude extract from earthworms could act as a biocatalyst for enantioselective aldol reactions with high stereoselectivity (dr of up to >99/1, ee of up to 98%).⁵⁷⁰

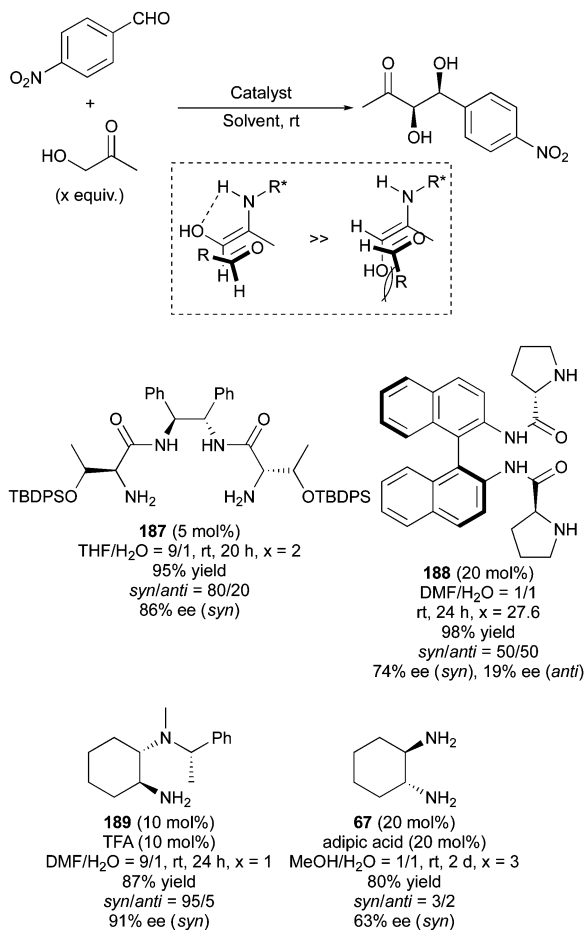
5.2. Nonmetal catalysis

5.2.1. Enamine catalysis

5.2.1.1. Direct aldol reactions between ketones and aldehydes.

Tremendous efforts have been dedicated to developing small organic molecules that can imitate aldolase-like mechanisms to achieve efficient enantioselective aldol reactions. Some reactions, including with enantioselective variants, have been performed and the beneficial role of water in a small amount has been reported^{418,571–573} and is well documented.^{574,575} Although organocatalysts that activate substrates through covalent interactions are robust in water, reactions using a large amount of water or buffer media are, by and large, sluggish and unselective.^{571,576} However, some strategies to overcome the challenges associated with performing organocatalyzed direct enantioselective aldol reactions in aqueous media have been reported and are summarized below.

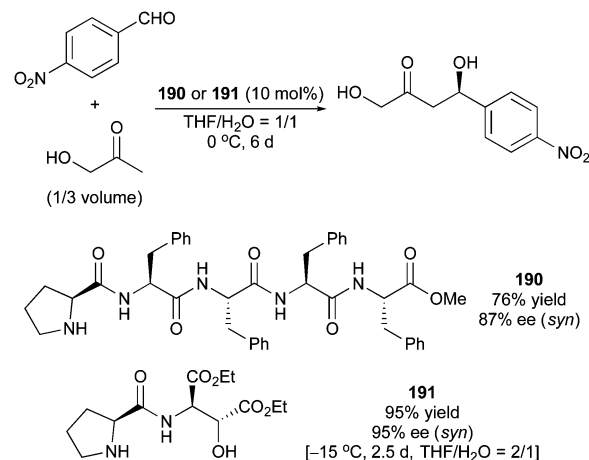
One strategy employed to successfully conduct enantioselective aldol reactions in aqueous media is by creating a hydrophobic cavity that shields the reaction intermediates from water or by utilizing a larger excess of an organic cosolvent and/or substrate to overwhelm the effects of water. Some illustrative examples of these strategies for the asymmetric direct aldol reactions of hydroxyacetone and 4-nitrobenzaldehyde are shown in Scheme 222. For example, β -aminosulfonamide **187**⁵⁷⁷ and (*S*)-(–)-1,1'-binaphthyl-2,2'-diamine **188**⁵⁷⁸ are representatives of catalysts bearing a hydrophobic structure. The *Z*-enamine formed with hydroxyacetone is recognized to be stabilized by hydrogen bonding between the hydroxyl group of hydroxyacetone and the enamine amide, as well as possessing a smaller steric repulsion than the corresponding *E*-enamine.⁵⁷⁹ Direct aldol reactions of hydroxy- or dihydroxyacetone are important tools for the enantioselective synthesis of deoxyketoses and ketoses.⁵⁸⁰ Mlynarski and co-workers used a siloxyserrine moiety to form hydrophobic pockets for an efficient reaction (**187**); whereas Nájera and co-workers utilized **188** and also reported that a small amount (1/>50) of the regioisomer was formed competitively with an enantioselectivity of 85% ee.



Scheme 222 Chiral bisamine-catalyzed enantioselective aldol reaction using hydroxyacetone.

Chiral diamines coupled with acid additives were also found to be effective catalysts for the asymmetric aldol reaction. The chiral enamine intermediate is more important to determine the stereoselective outcome than the face-selective activation of the aldehyde.⁵⁸¹ For example, chiral 1,2-diaminocyclohexane **67** was used as a catalyst, together with adipic acid, in aqueous methanol.⁴⁶³ Singh and co-workers reported a chiral cyclohexyl-diamine-based catalyst **189** containing an aromatic ring.⁵⁸² Here, the presence of a strong Brønsted acid, such as TFA or adipic acid, was essential for both the reactivity and selectivity.

In 2004, Gong and co-workers utilized a L-proline-based pentapeptide **190** as a catalyst for the formation of a chiral 1,4-diol and found that this aldol reaction occurred when water was used as a solvent, which is usually disfavored with either aldolases or L-proline (Scheme 223 above).⁵⁸³ They demonstrated that the peptide size played an important role in stereocontrol of the aldol reaction. Later, the same group found that the proline-amide structure and water were crucial for the regiocontrol, albeit with a lower selectivity.⁵⁸⁴ Reactions catalyzed by prolineamides derived from chiral amino alcohols were found to be more active and more regio- and enantioselective (Scheme 223 below; see also Scheme 226). Instead of hydroxyacetone, fluoroacetone could be reacted only when water was added. According to

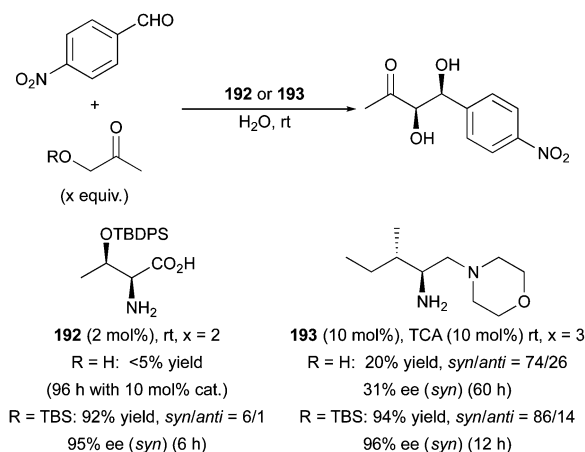


Scheme 223 Pentapeptide-catalyzed enantioselective aldol reaction of hydroxyacetone.

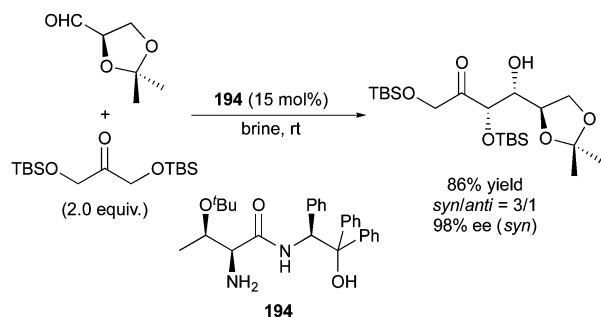
theoretical studies, hydrogen bonds between water molecules and the amide oxygen of the prolinamide **191** or the OH group of hydroxyacetone determine the regioselectivity.

Increasing the hydrophobicity of the substrate is one of the most common methods to minimize the amount of organic cosolvents used in mixed solvent systems with water. The L-threonine-based organocatalyst **192**, bearing a hydrophobic siloxy group,⁵⁸⁵ and L-isoleucine-derived morphinyl amine **193**, with trichloroacetic acid (TCA),⁵⁸⁶ were found to be effective catalysts for the enantioselective direct aldol reaction of hydroxyacetone with 4-nitrobenzaldehyde in water (Scheme 224). The reaction of unprotected hydroxyacetone resulted in a significant decrease in the yield and selectivity, whereas the use of TBS-protected hydroxyacetone provided the desired product in a high yield with high enantioselectivity.

The enantioselective transformation of DHA by non-natural catalysts is still in its infancy. Barbas and co-workers reported that TBS-protected DHA could serve as an aldol donor for enantioselective *syn*-aldol reactions with various aldehydes in brine (Scheme 225).⁵⁸⁷ The O^t-Bu-L-threonine-based catalyst **194**



Scheme 224 Enantioselective aldol reaction of protected/unprotected hydroxyacetone in water.



Scheme 225 Enantioselective aldol reaction of protected dihydroxyacetone (DHA) in water.

was found to be an active catalyst and enabled the synthesis of aldol adducts in high enantioselectivities. The asymmetric aldol reaction of the acetonide of *D*-glyceraldehyde is also noteworthy, and this catalyst system furnished the protected *D*-sorbitol derivative with an excellent enantioselectivity.

In order to establish organocatalytic asymmetric aldol reactions in 100% water, one common strategy that has been employed is to replicate the hydrophobic environment found in aldolases. In Scheme 226, some representative examples of organocatalysts used in the enantioselective aldol reactions of cyclohexanone with 4-nitrobenzaldehyde in solvent amounts of water are shown. In 2006, Hayashi and co-workers focused on incorporating a surfactant or water-immiscible functionality into the structure of a proline-based organocatalyst, and then evaluated the modified catalyst for enantioselective aldol reactions in water.⁵⁸⁸ They found that *trans*-*L*-siloxypyrrolidine **195** conspicuously formed an emulsion with lipophilic substrates, and the desired aldol adducts could be obtained in good yields with good enantioselectivities. In the same year, Barbas and co-workers coincidentally developed the diamine **196**, bearing a long alkyl chain, and found that when this organocatalyst was coupled with an acid additive, the asymmetric aldol process could be performed using water as the sole solvent.⁵⁸⁹ Unfortunately, neither catalyst was efficient when unactivated aldehydes or water-soluble substrates were used. Proline analogs, mostly through derivatization of the carboxyl or with the hydroxyl group of 4-hydroxyproline, have been made and evaluated for asymmetric aldol reactions.

Singh⁵⁵⁸ and Gong,⁵⁹⁰ reported prolineamide-based chiral catalysts (**197** and **198**) that were capable of performing asymmetric aldol reactions in water with low catalyst loadings. The excellent efficiency of these catalysts was ascribed to their capability to activate aldehydes through hydrogen bonding and by the hydrophobic “salting-out” effect. They also pointed out that an acid, formed *via* auto-oxidation from the aldehyde, alters the reaction kinetics and selectivity in a significant manner.⁵⁹¹ When the dipeptide-like *D*-Pro-*D*-Val-*S*-amine **199**, which possessed a hydrogen bonding site, was used as a catalyst, the aldol reaction proceeded even at a low catalyst loading.⁵⁹² As was the case with Hayashi's seminal catalyst **195**, hydrophobic substituents were installed on the hydroxyl group of 4-hydroxyproline by two groups: the pyrene-derived structure **200** by Gruttadauria,⁵⁹³

and the isosteviol-proline conjugated catalyst **201** by Tao.⁵⁹⁴ Both catalysts showed high efficiency for direct enantioselective aldol reactions in water.

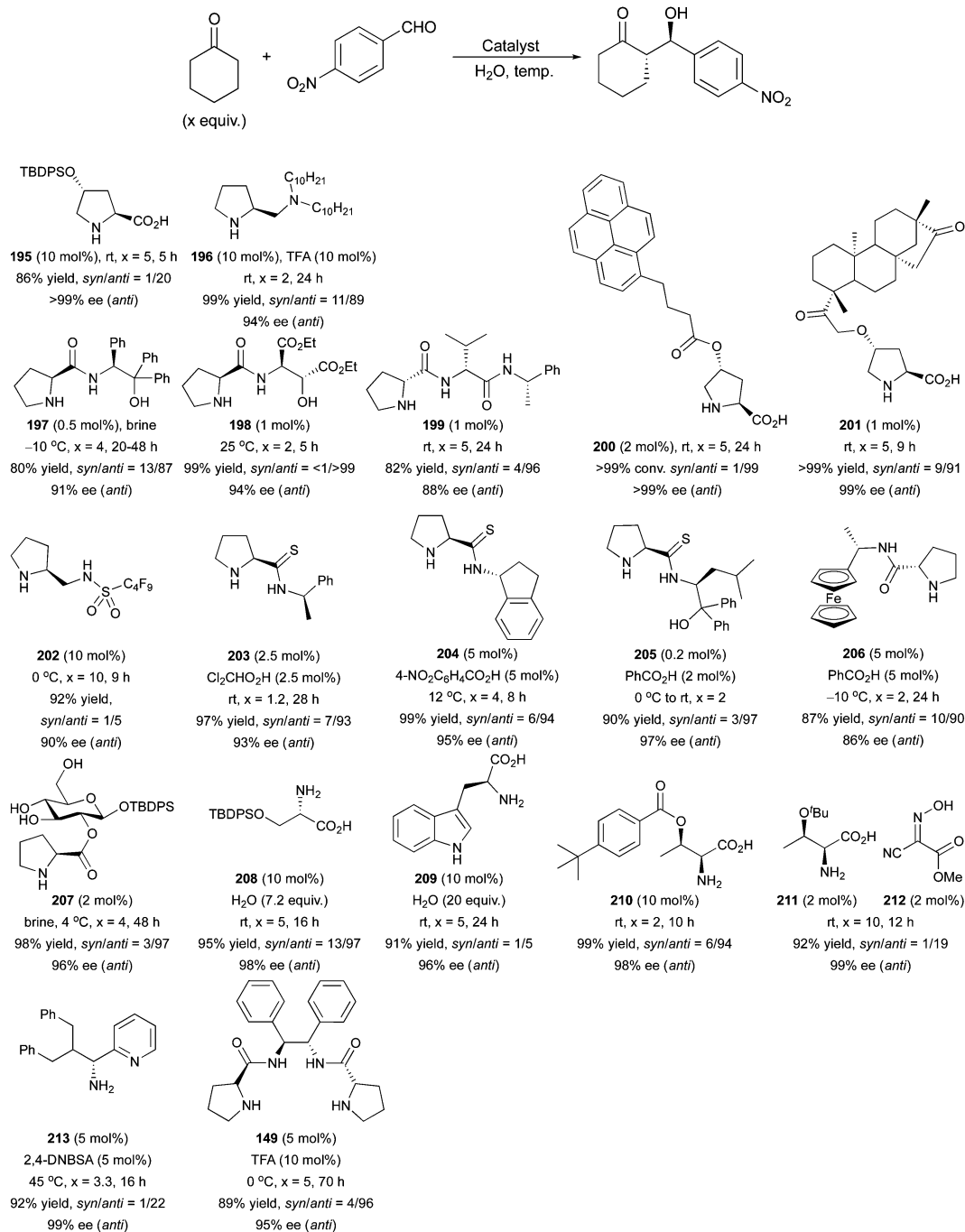
With respect to diamine frameworks as reported by Barbas and co-workers, Wang and co-workers reported the use of a fluorosulfonyl pyrrolidine sulfonamide **202**^{595,596} as a catalyst for the direct asymmetric aldol reaction in water. The authors demonstrated that catalyst recovery by fluorosulfonyl extraction was possible and it could be reused for up to seven cycles. Gryko,⁵⁹⁷ Nájera⁵⁹⁸ and Singh's⁵⁹⁹ groups reported prolinethioamide-based organocatalysts (**203–205**), coupled with acid additives, as effective chiral catalysts for this reaction. Gryko and co-workers verified that the hydrophobic aggregation that occurs in water is critical and showed that it affected the rate and stereochemistry of the reaction. Ferrocenyl substituents were also evaluated as a lipophilic moiety to increase the hydrophobicity of the chiral catalyst, and Patti and co-worker found that the ferrocenyl-proline amide **206** could act as an effective catalyst for enantioselective aldol reactions in water.⁶⁰⁰

In addition to amide-based structures, Nisco, Caputo, and co-workers reported that the *O*-TBDPS *D*-glucosamine-equipped *L*-proline **207** could be successfully applied for enantioselective aldol reactions in water.⁶⁰¹

Although other amino acids, such as siloxy-*L*-seline **208**⁶⁰² or *L*-tryptophan **209**,⁶⁰³ could catalyze enantioselective aldol reactions, it was found that a further increase in the amount of water resulted in a decreased reactivity and selectivity. In contrast, the protected threonine derivatives did not face such problems, and several examples have been reported using these amino acid derivatives as organocatalysts for asymmetric aldol reactions. Fu and co-workers revealed that the *O*-acylated threonine **210** was an efficient catalyst that could be easily recovered and reused without an erosion of the enantioselectivity after six runs.⁶⁰⁴ Córdova and co-workers combined the *O*-*tert*-butyl threonine **211** with the hydrogen-bond-donating hydroxy oxime **212** to generate a bifunctional organocatalyst for the aldol reaction.⁶⁰⁵ Interestingly, the aldol reaction was significantly accelerated in water when compared with in toluene. Chiral 2-picolylamine **213**, in conjunction with 2,4-dinitrobenzenesulfonic acid (2,4-DNBSA), was found to be an efficient organocatalyst in water.⁶⁰⁶ Chiral *C*₂-symmetrical bisprolineamide **149** is also known to work as an effective chiral catalyst for asymmetric aldol reactions.⁶⁰⁷

Most catalysts face a common problem of decreased activity when water-miscible ketones, without any directing groups, are utilized as substrates in water. However, several groups have demonstrated that it is possible to overcome this problem (Scheme 227). For example, Singh⁵⁵⁸ and Gong⁵⁹⁰ reported that the chiral prolinamides **214** and **215** were able to utilize acetone as an aldol donor for enantioselective direct aldol reactions. Further, while the aldol reaction could be performed with low catalyst loadings, they found that the selectivities using acetone as a substrate were worse than those found using cyclohexanone.

Four-membered constrained amino acids, such as azetidine-2-carboxamides, have also been reported for the enantioselective direct aldol reactions of acetone with 17 examples of substituted benzaldehydes in brine.⁶⁰⁸ The remaining examples

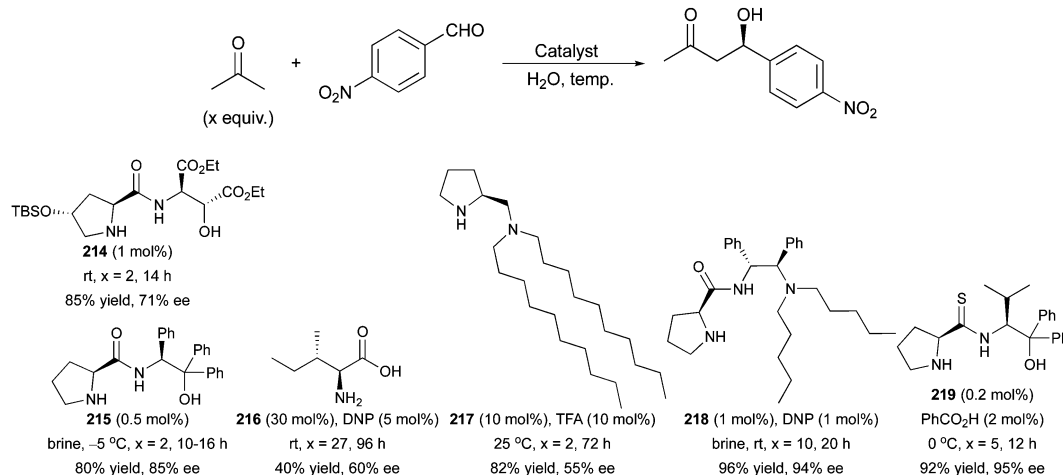


Scheme 226 Some examples of enantioselective catalysis for direct aldol reactions between cyclohexanone and 4-nitrobenzaldehyde in water.

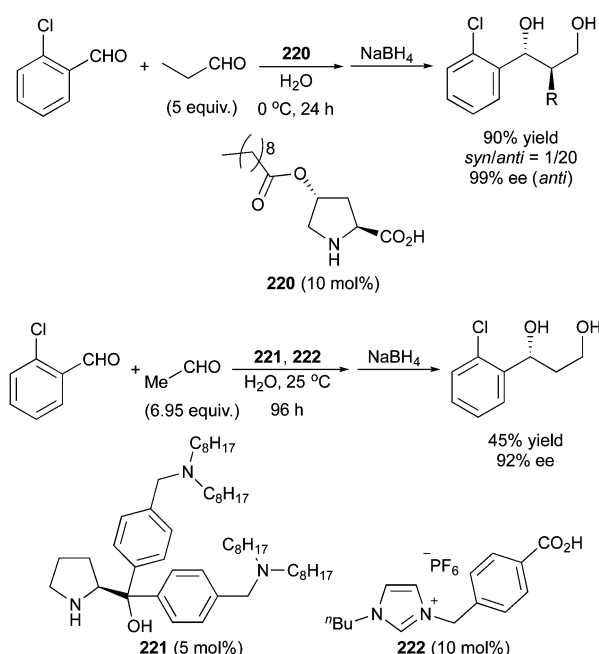
rely on the amine/acid cooperative catalysis. In 2010, the catalytic activity of L-isoleucine **216**, in the presence of 2,4-dinitrophenol (DNP), was found by Ji and co-workers.⁶⁰⁹ Even considering the report on L-proline **217** tethering a longer alkyl chain by Barbas in 2006,⁵⁸⁹ there remains room for improvement in the stereocontrol. The most active examples are the prolinamide-based catalyst **218**, developed by Da,⁶¹⁰ and the prolinethioamide **219**, used by Li.⁶¹¹

5.2.1.2. Direct cross-aldol reactions of two aldehydes. In 2006, Hayashi and co-workers were the first to achieve the enantioselective

cross-aldol reactions of two different aldehydes in water by equipping L-proline with long alkyl chain moieties (**220**; Scheme 228 above).⁶¹² The installation of a decanoate side chain resulted in a catalyst that enabled the aldol reaction to proceed to provide the desired adducts, after reduction, in high yields with high enantioselectivities *anti*-selectivities. Some enantioselective cross-aldol reactions of acetaldehyde were also achieved in brine with a diarylprolinol-based catalyst **221**, bearing dioctylamine, along with an ionic-liquid-supported benzoic acid **222** as a co-catalyst (Scheme 228 below).⁶¹³

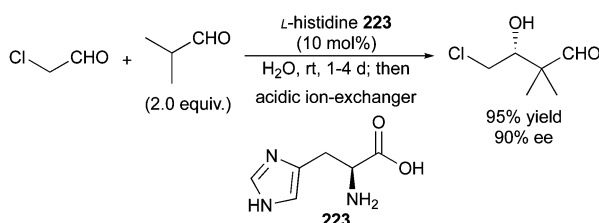


Scheme 227 Enantioselective catalysis for direct aldol reactions between acetone and 4-nitrobenzaldehyde in water.



Scheme 228 Enantioselective catalysis for cross-aldol reactions between aliphatic aldehydes and aromatic aldehydes in water.

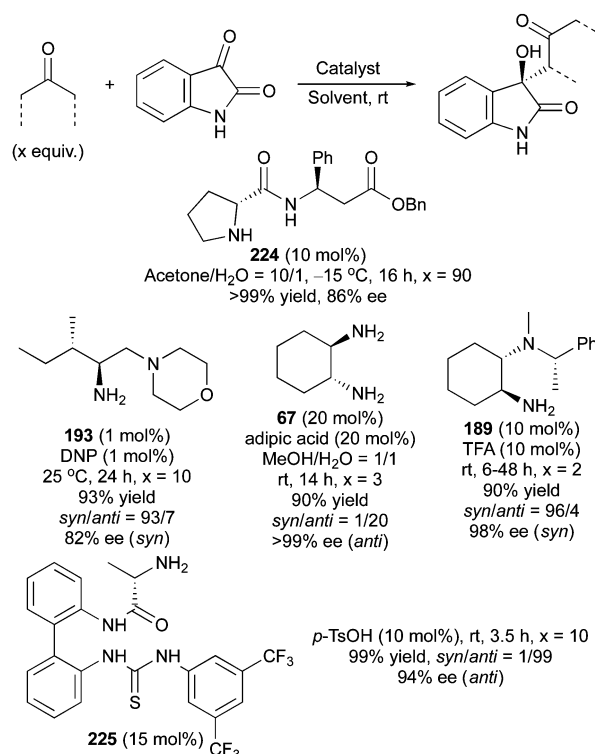
In 2009, Maharwald and co-workers developed enantioselective cross-aldol reactions of two aliphatic aldehydes in water that were catalyzed by L-histidine **223** (Scheme 229).⁶¹⁴ The formed acetals



Scheme 229 Asymmetric catalysis for the cross-aldol reactions between aliphatic aldehydes in water.

were cleaved by treatment with an acidic ion-exchange resin (DOWEX[®]-50WX2).

5.2.1.3. Direct cross-aldol reactions of two ketones. There have been a limited number of reports on the enantioselective cross-aldol reactions of ketones in water (Scheme 230). In 2009, Tomasini and co-workers disclosed that small quantities of water could enhance the enantioselectivities in prolinamide **224**-catalyzed aldol reactions of acetone to isatins.⁶¹⁵ The addition of large quantities of water was found to be detrimental. Computational studies revealed that the incorporation of a water molecule in the transition state led to two lowest energy transition states,



Scheme 230 Asymmetric catalysis for ketone-isatin aldolizations in water.

where the water molecule passively participates. The chiral primary–tertiary amine **193** assisted by DNP was shown to catalyze the *syn*-selective cyclohexanone-isatin aldolization in water.⁶¹⁶ In addition, it was shown that the reaction of acetone could also deliver the desired product with good enantioselectivity (70% ee). In contrast, 1,2-diaminocyclohexane-derived catalysts (**67** and **189**) showed a preference for the *anti*-adduct in the presence of a Brønsted acid.^{617,618} However, acetone was found to be a poor substrate for these *anti*-selective aldol catalysts. The biaryl-based diamine/thiourea bifunctional catalyst **225**, coupled with *p*-toluenesulfonic acid (*p*-TsOH), was also found to be an effective catalyst for enantioselective aldolization in water and provided aldol adducts in an *anti*-selective manner.⁶¹⁹

Landais and co-workers reported the enantioselective synthesis of isotetronic acid derived from the aldol reaction of oxobutyric acid and isobutyraldehyde using the chiral diamine **226** as a catalyst (Scheme 231).⁶²⁰ In 2012, Li and co-workers developed an amphiphilic organocatalyst **227**, bearing an imidazole motif, as an effective catalyst for the synthesis of functionalized isotetronic acids.⁶²¹ When non-substituted or short-chain alkyl-substituted chiral amphiphiles were used as catalysts, low conversions, as well as moderate enantioselectivities, were observed. The authors noted that the reaction under neat, dry chloroform, and ethanol conditions resulted in decreased enantioselectivities. Fluorescence microscopic imaging indicated that the organocatalyst was mainly distributed on the surface of emulsion droplets.

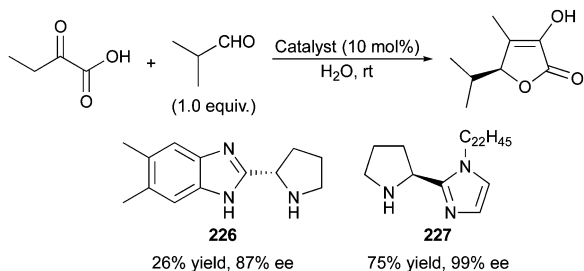
5.2.2. Solid enamine catalysis. Water-compatible solid organocatalysts have recently commanded considerable attention, due to offering a number of practical advantages, including ease of handling and recycling. Being inexpensive and readily available, L-proline may not be worth considering to be immobilized. In addition, incipient attempts to support peptides on polyethyleneglycol grafted on cross-linked polystyrene (PEG-PS) resin were not successful due to the decreased enantioselectivities when used in water.⁶²² Polymer chains, however, seem to be suitable to procure aldolase-mimic microenvironments surrounded by hydrophobicity, leading to a number of fruitful achievements. Although the use of solid chiral organocatalysts have been reviewed elsewhere,⁶²³ selected contributions will be described here (Scheme 232). Pericàs' group reported a series of polymer-supported organocatalysts, and successfully applied them for enantioselective reactions in water. 4-Hydroxyproline derivatives anchored to a polystyrene resin, through Huisgen

cycloaddition reactions, (**228**) showed high catalytic performance for direct enantioselective aldol reactions in water.⁶²⁴ The addition of a catalytic amount of water-soluble DiMePEG (MW ~ 2000) was shown to be effective to improve the reactivity of the catalyst since it facilitated the diffusion of the substrates into the hydrophobic resin. Huisgen cycloadditions were also used to fabricate a multifunctional C₃-symmetrical dendritic prolinamide with a hydrophobic aromatic core and hydrophilic triazolinium arms.⁶²⁵ Noto and co-workers examined proline or prolinamide linked with mercaptomethyl polymer-bound (**229**, **230**) as catalysts for enantioselective direct aldol reactions in water.^{626–628} Meijer, Palmans, and co-workers introduced a folded, catalytically active L-proline-functionalized chiral BTA polymer **231**, where oligo(ethylene glycol) (OEG) units played an important role in ensuring the water-compatibility of the catalyst.⁶²⁹ Their reversible folding–unfolding behaviors were studied, and their catalytic activity was only expressed in their folded conformation, which is only accessible when water is used as a solvent.

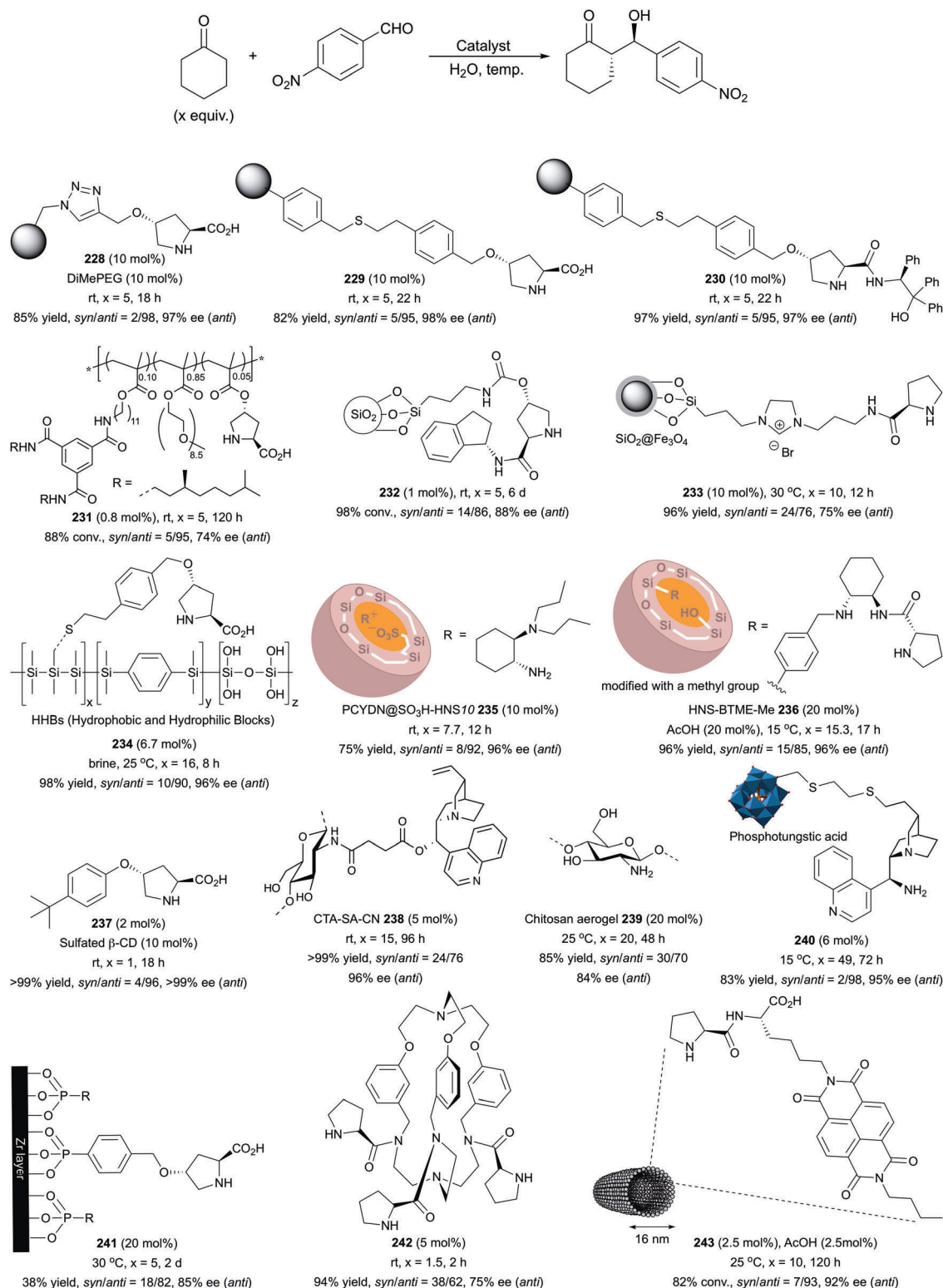
Several silica-supported organocatalysts have also been reported. In 2012, Pleixats and co-workers surveyed a few methods to prepare recyclable monosilylated proliamide catalysts for direct enantioselective aldol reactions performed in water.⁶³⁰ The organosilica catalyst **232** was obtained by sol-gel co-condensation between a monosilylated 4-hydroxyproline and tetraethyl orthosilicate (TEOS) with a ratio of 1 : 5 using tetrabutylammonium fluoride (TBAF). The solid catalyst showed a better selectivity than the homogeneous analog, and could be recovered and reused up to five runs without a significant loss in the yields and enantioselectivities. Similarly, Tan, Yin, and co-workers reported that ionic liquid-modified magnetic nanoparticles (NPs) could serve as a support for L-proline (**233**).⁶³¹ The authors believed that the ionic liquid moiety facilitated the accessibility of hydrophobic substrates to the active sites in water and stabilized the enamine intermediate during the reaction. Under identical reaction conditions, L-proline alone as the catalyst did not afford any of the aldol product in water. The catalyst was shown to be magnetically recoverable and could be used five times without significant loss of activity. He and co-workers examined L-proline-grafted mesoporous silica **234**, with alternating hydrophobic and hydrophilic blocks (HHBs), as a catalyst for enantioselective aldol reactions in water.⁶³²

Yang and co-workers developed chirally functionalized hollow nanospheres containing chiral *N,N*-dipropyl cyclohexanedi-amine (PCYDN) through the SO₃H functionalization (**235**)⁶³³ or L-prolinamide through covalent attachment (**236**).⁶³⁴ These hollow-nanosphere catalysts were found to be more active than those based on mesoporous materials with bulk particle sizes. The authors believed that these properties may have arisen from the unique morphology of the hollow nanospheres, which gave reactants facile access to the active sites.

The incorporation of a chiral organocatalyst into a hydrophobic cavity was achieved by the immobilization of *tert*-butylphenoxyproline (**237**) on to sulfated β-cyclodextrin (β-CD), and this solid catalyst was shown to catalyze the enantioselective aldol reaction to provide the desired aldol adducts with high stereoselectivities in water.⁶³⁵ In 2017, Deng and co-worker



Scheme 231 Enantioselective synthesis of isotetronic acid in water.



Scheme 232 Selected examples of solid enamine catalysis in water.

reported an interesting category of optically active microspheres through the suspension copolymerization of chiral and achiral substituted acetylenic monomers.⁶³⁶ The helical polymer chains with ferrocenyl amino acid derivative pendants, with TsOH as

a co-catalyst, enabled the spheres to possess catalytic activity for enantioselective aldol reactions (up to 93% ee) in brine.

In 2015, Cui and co-workers reported a chitosan-supported succinic anhydride-cinchonine (CTS-SA-CN **238**) as a catalyst

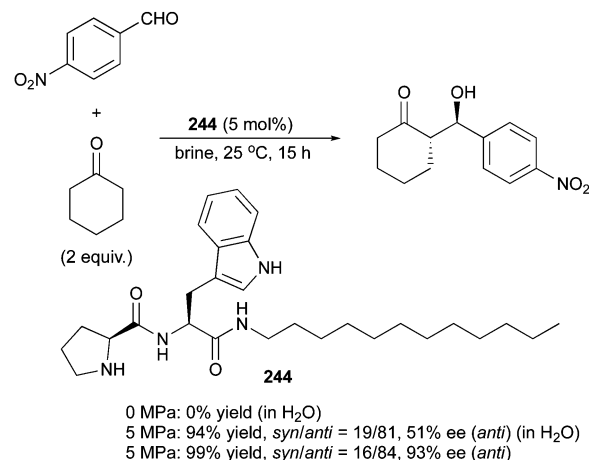
for direct enantioselective aldol reactions in water.⁶³⁷ The catalyst could be recycled up to five times by filtration after completion of the reaction. Interestingly, aerogel microspheres of chitosan **239** were also identified as an active catalyst for enantioselective aldol reactions in water, and a recyclability of up to 4 runs of was demonstrated.^{638,639}

In 2016, Ma and co-workers adopted phosphotungstic acid as a solid support for a cinchonidine-derived organocatalyst.⁶⁴⁰ The solid catalyst **240** showed good reusability without any significant loss of catalytic performance in five consecutive enantioselective aldol reactions in water. The L-proline-functionalized zirconium phosphate **241** was also used for enantioselective aldol reactions.⁶⁴¹ A benzoyloxy spacer between the zirconium layer and the active site (L-proline), as well as the protruding P-Me or P-Ph groups on the zirconium layer, was proposed to play an important role in increasing both the hydrophobicity of the solid surface and the conformational freedom of the reactive intermediate. The covalent anchoring of amino acids on a graphene sheet was also reported using a modified Hummer and Offeman method to covalently immobilize the chiral amino acids to graphene.⁶⁴²

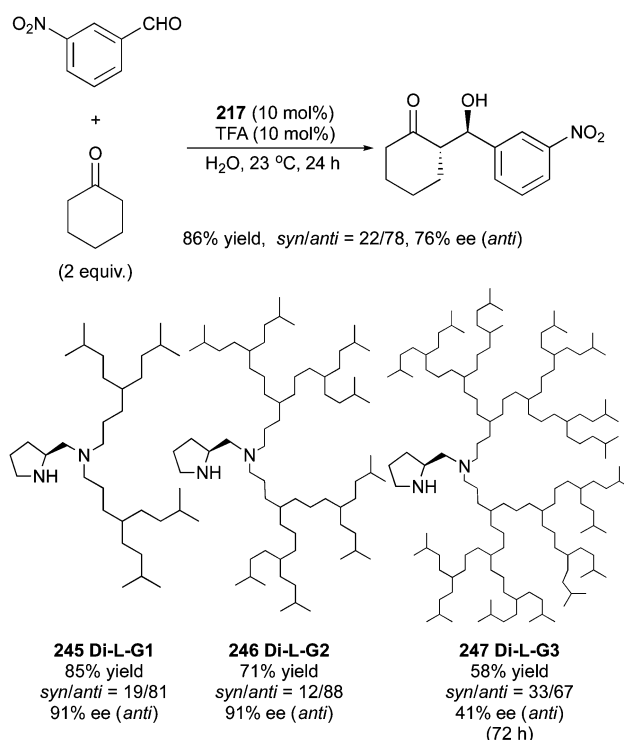
A number of applications of organocatalysts with supramolecular structures have been reported in catalytic enantioselective aldol reactions. Laterally nonsymmetric oxa-aza cryptands derivatized with L-proline (**242**) were disclosed to catalyze enantioselective aldol reactions in water with enantioselectivity of up to 75% ee.⁶⁴³ Parquette and co-workers designed a zwitterionic L-proline-L-lysine dipeptide **243**, functionalized with a 1,4,5,8-naphthalenetetracarboxylic acid diimide (NDI) chromophore, on the side chain and this dipeptide was shown to form nanotubes through the progressive helical winding of a β -sheet bilayer assembly.⁶⁴⁴ The self-assembled structure provided hydrophobic microenvironments capable of catalyzing enantioselective aldol reactions in water. Transmission electron microscopy (TEM) micrographs revealed the presence of a mixture of nanofibers, helically twisted nanoribbons, and nanotubes. The decreased intensity and red-shift of the NDI bands observed in the UV-vis absorption spectra were associated with π - π interactions in the self-assembly molecule. The catalyst could be recovered by ultra-centrifugation to sediment the nanotubes from the aqueous layer.

Dipeptide **244**-based supramolecular chiral vesicles formed in supercritical CO₂ were found to be capable of promoting enantioselective aldol reactions in water (Scheme 233).⁶⁴⁵ Compressed CO₂ soluble in water allowed the Pro-Trp **244** capped with a long alkyl chain to form vesicles. Being practically insoluble in water, the catalyst **244** only showed catalytic activity when in supercritical CO₂. Recycling of the catalyst was realized over several cycles with constant catalytic activity and enantioselectivity by recovering the aqueous phase accompanied by the simultaneous release of CO₂.

Chow and co-worker also prepared three series of chiral amphiphilic G1–G3 dendritic organocatalysts (**245–247**) containing an optically active polar L-proline-derived core and one, two, or three nonpolar hydrocarbon dendrons (Scheme 234).⁶⁴⁶ The application of these dendritic organocatalysts to enantioselective

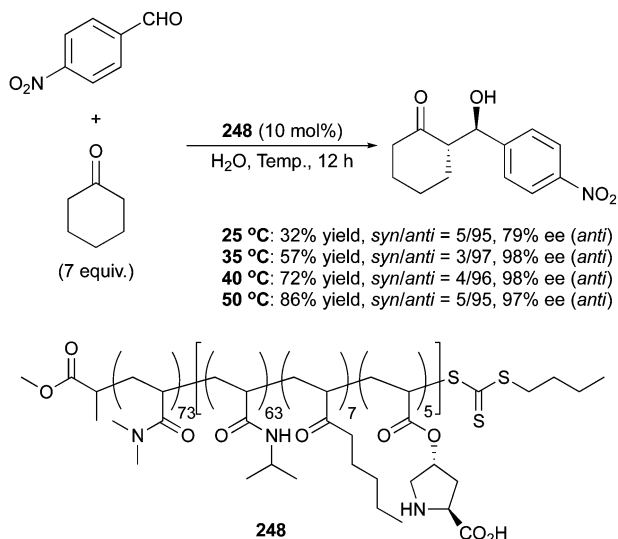


Scheme 233 Self-assembled vesicles regulated by compressed CO₂ as a catalyst for direct enantioselective aldol reactions in water.



Scheme 234 Chiral amphiphilic dendritic nonmetal catalysts for direct enantioselective aldol reactions in aqueous media.

aldol and nitro-Michael additions in water revealed that increasing the size and number of the dendrons led to higher product enantioselectivity. For example, a higher enantioselectivity was achieved for the reaction of 3-nitrobenzaldehyde in water than for the nondendritic catalyst reported by Barbas (catalyst **217**).⁵⁸⁹ The reactivity trend was: nondendritic $\sim$ **Di-L-G1** > **Di-L-G2** > **Di-L-G3**, and the best stereoselection was observed in the case of G1 and G2. The authors concluded that steric inhibition was still the dominating factor in determining the rate of the reaction, while the emulsion stabilization effect was of secondary importance.

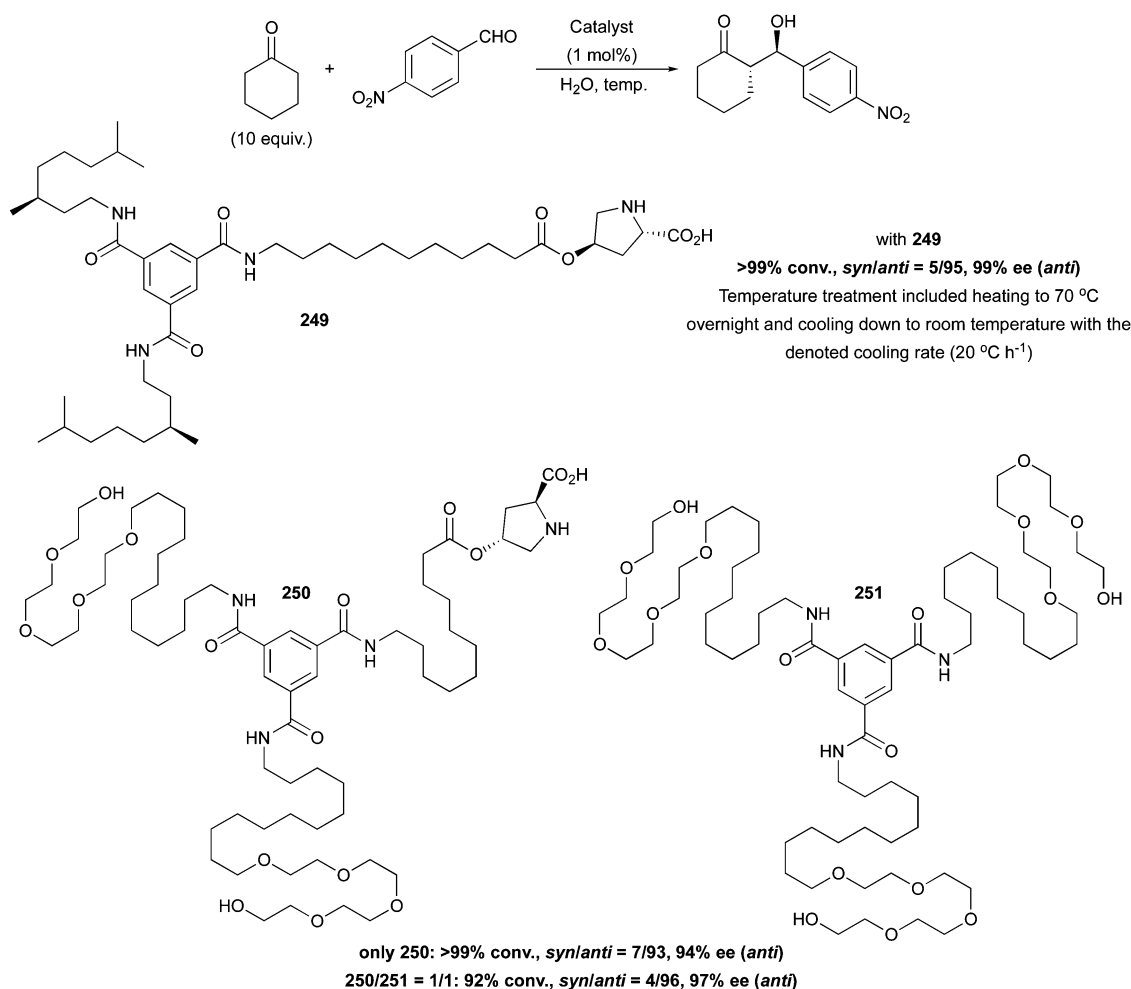


Scheme 235 Thermoresponsive catalyst for direct enantioselective aldol reactions in aqueous media.

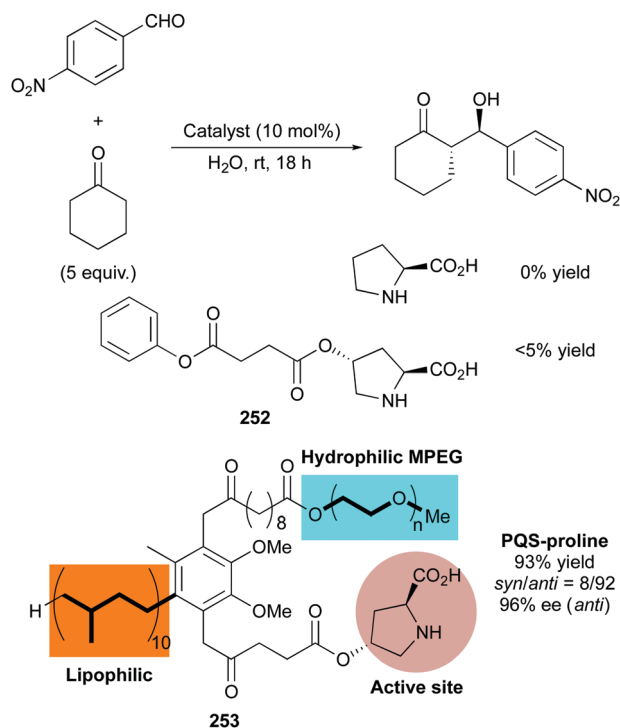
O'Reilly, Monteiro, and co-workers designed a catalytic thermoresponsive nanoreactor **248** for enantioselective aldol

reactions in water (Scheme 235).⁶⁴⁷ At temperatures above the lower critical solution temperature (LCST) of the polymer, ranging from 25 °C to 40 °C, the thermoresponsive block copolymer containing the poly(*N*-isopropylacrylamide) (NIPAM) block was expected to be hydrophobic enough to form micelles with a diameter of approximately 15–20 nm. When the temperature was set below LCST, the micelle dissociated into fully water-soluble polymer chains and the pure aldol product was precipitated from the nanoreactors. The product could be isolated and collected through centrifugation, and the nanoreactors could be reused by heating the polymer above the LCST.

Benzene-1,3,5-tricarboxamide (BTA) has received much attention for its ability to form a rod-like architecture through intermolecular π - π stacking and a triple array of hydrogen-bonding interactions.⁶⁴⁸ The alluring features of chiral BTA motifs have been intensely studied by Meijer's group. Among them, folded L-proline-functionalized chiral BTA polymers, bearing oligo(ethylene glycol) (OEG) units, were examined for enantioselective aldol reactions in water (catalyst **231** in Scheme 232).⁶²⁹ The catalytic activity of the nonpolymerized L-proline-functionalized BTA nanofiber assembly was also evaluated in an enantioselective aldol reaction in water (Scheme 236).^{649,650} The reaction took



Scheme 236 Chiral nanofibers for catalytic asymmetric aldol reactions in water.

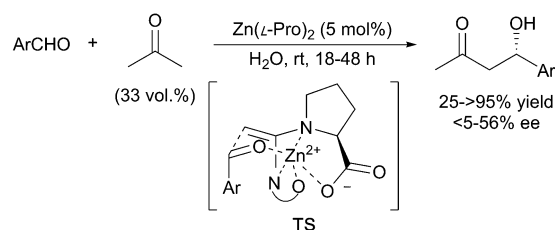


Scheme 237 Coenzyme Q_{10} -derived surfactant catalyst for direct enantioselective aldol reactions in aqueous media.

place with high stereoselectivity in the presence of the fiber, whereas only a racemic product was produced in the presence of the unassembled BTAs.

Lipshutz and co-workers devised a new surfactant **253** derived from coenzyme Q_{10} with a covalently bound *L*-proline (Scheme 237).⁶⁵¹ The designed molecule was soluble in water through spontaneous nanomicelle formation, and was shown to catalyze the enantioselective aldol reaction in water in good yields with high enantioselectivities. It is also noteworthy that, upon the completion of the reaction, typical extractive workup was not required, and in-flask recycling of the catalyst could be easily performed, since the amphiphilic catalyst remained in the aqueous phase in the flask.

5.2.4. Amine/metal cooperative catalysis. Based on the mechanism of class II FBP aldolases, chiral zinc complexes have frequently been adopted as catalysts to activate substrates and to control the selectivity. In 2003, Darbre and co-worker reported that a $Zn(L-Pro)_2$ complex, prepared by a simple mixing between *L*-proline and $Zn(OAc)_2$, could act as a catalyst for the direct-type aldol reactions in water using solvent amounts of acetone and activated aromatic aldehydes (Scheme 238).^{652,653} They found that with their catalyst system, the desired aldol products could be obtained with low to moderate enantioselectivities in aqueous media. They postulated that the mechanism involved an organocatalytic enamine formation that was then stabilized through a zinc-assisted complexation process.^{155,577,654,655} The use of Lewis acids, as an additive for *L*-proline catalysis, revealed that the group 12 elements ($ZnCl_2$, $CdCl_2$, and $HgCl_2$) afforded the highest stereoselectivities and

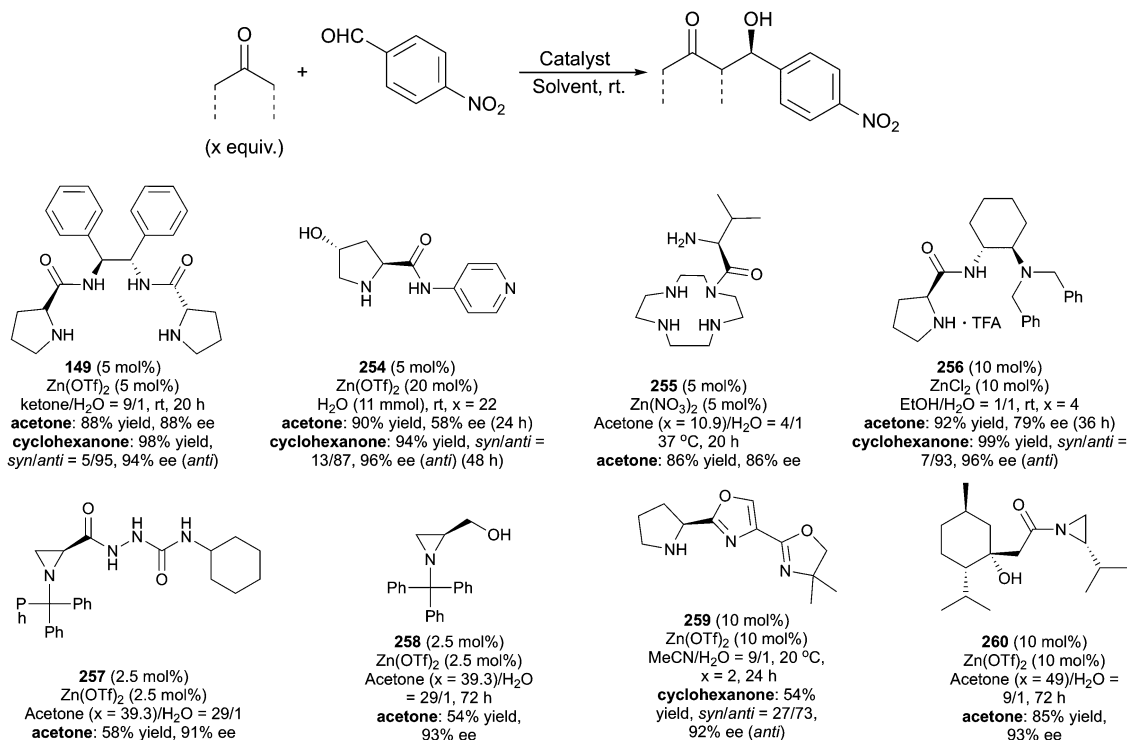


Scheme 238 Zinc bis(*L*-proline) complex as a catalyst for direct enantioselective aldol reactions in aqueous media.

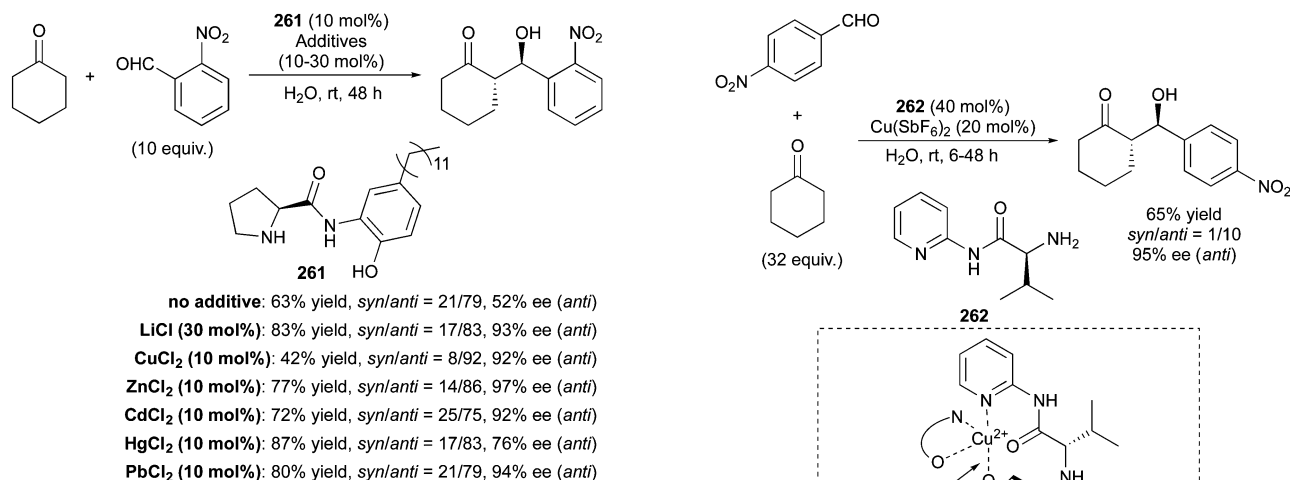
conversions when a 2 : 1 ratio of *L*-proline/metal salt was used.⁶⁵⁶ The zinc complex was also used in the self-aldolization of glycoaldehyde to furnish tetroses in aqueous media, albeit with a slow reaction rate and low enantioselectivity (10% ee).⁶⁵⁷

Selected examples of effective enamine/zinc catalysis are shown in Scheme 239. Zinc bis(prolinamide) complexes formed from C_2 -symmetrical bis(prolinamide) **149** catalyzed the aldol reactions of acetone and cyclohexanone with 4-nitrobenzaldehyde with high enantioselectivity.⁶⁵⁸ Although a large excess of the ketone was required, both water-soluble and insoluble substrates could react in a highly stereoselective manner. The system was also demonstrated to promote the enantioselective reaction of formaldehyde with cyclic ketones in aqueous ethanol. A family of amino acid-based bis(amide) ligands was extensively studied for direct aldol reactions in aqueous media.⁵⁷⁷ When a series of chiral prolinamides was used, in conjugation with $Zn(OTf)_2$ as a chiral catalyst, the desired aldol adducts could be obtained in excellent yields with good enantioselectivities. Han, Pan, and co-workers revealed that the zinc-prolinamide complex **254**, containing a pyridyl group, could smoothly promote enantioselective direct aldol reactions.⁶⁵⁹ Aoki and co-workers designed, synthesized, and applied chiral amino acids-tethered zinc(II)-cyclen (12-membered tetraamine **255**) complexes for enantioselective direct aldol reactions of acetone.⁶⁶⁰ Potentiometric pH titrations revealed that the Lewis acidity of Zn^{2+} in the zinc(II)-cyclen complex was stronger than that in the analogous 15-membered cyclic pentaamines. When mixed with acetylacetone (acac), the zinc(II)-cyclen complex induced the formation of a monoanionic acac adduct, whereas proline formed a Schiff base with a small equilibrium constant, and the formation of Zn^{2+} -enolate was more favorable than enamine formation both thermodynamically and kinetically. Fu and co-workers discovered that a bifunctional zinc(II)-cyclohexyldiaminoproline **256** could be efficiently used for enantioselective aldol reactions.⁶⁶¹ The aziridine-based ligands **257** and **258** were also examined as chiral ligands with Zn^{2+} Lewis acids for the enantioselective aldol reactions of acetone.^{662,663} Investigations to discover heterocyclic scaffolds capable of supporting bifunctional Lewis acid/Lewis base catalysis led to a successful application of the oxazole-oxazoline ligand **259** for direct cross-aldol reactions in aqueous media.⁶⁶⁴⁻⁶⁶⁶ The aziridine amide **260** linked with the chiral skeletons of naturally occurring menthone was also reported to have good activity as a chiral catalyst for direct aldol reactions.⁶⁶⁷

Tao and co-workers evaluated the combination of various water-compatible Lewis acids with an amphiphilic prolinamide



Scheme 239 Amine/zinc cooperative catalysis for direct enantioselective aldol reactions in aqueous media.



Scheme 240 Metal salt screening in prolinamide-catalyzed direct enantioselective aldol reactions in water.

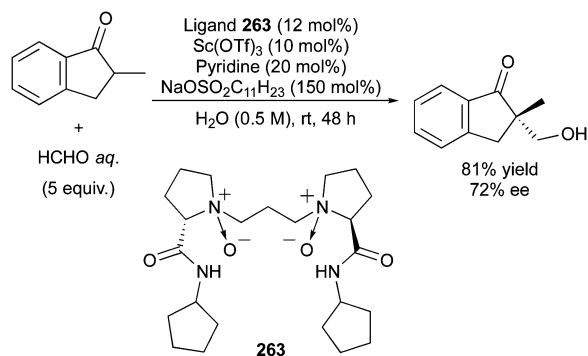
261 for direct enantioselective aldol reactions in water (Scheme 240).⁶⁶⁸ Not only the group 12 elements, but also the use of LiCl, SnCl₂, and PbCl₂ led to high levels of stereoselection. Several other metals, such as copper,^{669,670} cadmium,⁶⁵⁶ and tin,⁶⁷¹ have also exhibited catalytic activity for direct aldol reactions.

Another example of enamine catalysis coupled with Lewis acidic activation of an aldehyde is shown in Scheme 241.⁶⁷² The bifunctional catalyst **262**, coupled with a copper(II) salt, displayed high activity for the aldol reactions of electron-rich and electron-poor aldehydes, albeit with high catalyst loadings.

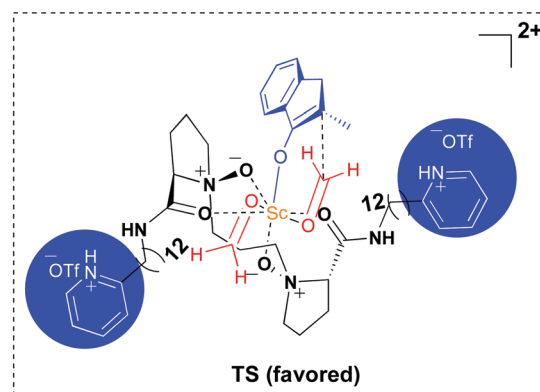
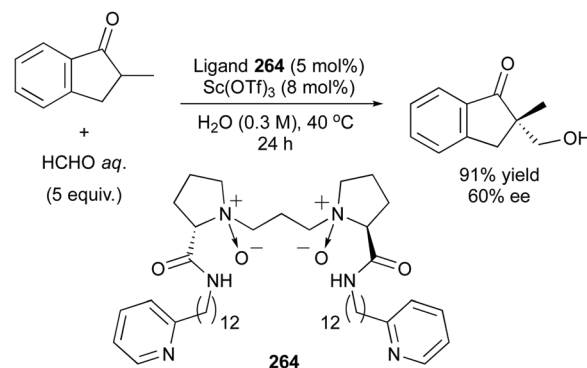
Scheme 241 Copper-catalyzed direct enantioselective aldol reactions in water.

5.3. Metal catalysis for direct enantioselective aldol reactions in water

In contrast to the growth of enamine-based organocatalysts for direct enantioselective aldol reactions, metal-based catalysis that does not rely on enamine formation has hardly been explored. That is because the deprotonated enolates of ketone are recognized as short-lived, unstable, and reversible, and the stabilization of enolates by noncovalent interaction with metals is much more fragile than the covalent enamine intermediates,



Scheme 242 Chiral scandium-catalyzed enantioselective direct aldol reaction using formaldehyde in 100% water.



Scheme 243 Design of a highly systemized catalytic system for the enantioselective direct aldol reaction using formaldehyde in 100% water.

especially under competitive polar aqueous media. Nevertheless, there are some limited examples of chiral metal catalysts used for direct asymmetric aldol reactions in aqueous media.

Kobayashi and co-workers reported the first example of an asymmetric direct aldol reaction in aqueous media (Scheme 242).⁶⁷³ They found that a chiral scandium complex, derived from $\text{Sc}(\text{OTf})_3$ and N,N' -dioxide **263** could act as an efficient catalyst for the direct enantioselective aldol reaction between 2-methylindanone and aqueous formaldehyde. The key for this asymmetric process was the use of $\text{NaOSO}_2\text{C}_{11}\text{H}_{23}$ as a surfactant, and pyridine as a base. They demonstrated that the hydroxymethylation proceeded to deliver the desired products in high yields and good enantioselectivities. Lewis acid-catalyzed enantioselective reactions in water, using hydrophilic substrates, are recognized as highly challenging even when a large excess of surfactant is added.^{674,675}

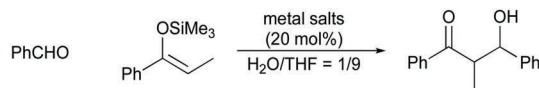
In 2015, Kobayashi and co-workers reported a new scandium-based system, bearing an N,N' -dioxide moiety **264** as a scaffold of a Lewis acid and pyridine, which was found to offer an efficient microenvironment in water for enantioselective direct aldol reactions (Scheme 243).⁶⁷⁶ They found that a significant rate acceleration, as well as enhanced enantioselectivity, was observed through the integration of the functional components of the chiral complex, with approximately 16 times higher activity than that of an independently functioning system involving a non-surfactant ligand (12 mol%), $\text{Sc}(\text{OTf})_3$ (10 mol%), pyridine (20 mol%), and SDS (20 mol%).

5.4. Enantioselective Mukaiyama aldol reactions in water

The power of Lewis acids in the aldol reactions of silyl enol ethers with aldehydes has dominated the history of asymmetric C–C bond formation reactions.⁶⁷⁷ In 1991, it was reported that the Lewis acidic nature of lanthanide trifluoromethanesulfonates (triflates) ($\text{Ln}(\text{OTf})_3$) was maintained in water, leading to rate acceleration for the Mukaiyama aldol reaction in aqueous media (water/organic solvents).^{678–682} For example, $\text{Yb}(\text{OTf})_3$ was revealed to have superior performance in Mukaiyama aldol reactions of both hydrophobic and hydrophilic aldehydes with silicon enolate in water–THF⁶⁸³ or in a water–ethanol–toluene cosolvent system.⁶⁸⁴ The rare earth triflates ($\text{Sc}(\text{OTf})_3$,⁶⁸⁵ $\text{Y}(\text{OTf})_3$, $\text{Ln}(\text{OTf})_3$) are now recognized as representative water-compatible

Lewis acids and are applicable to various practical organic transformations. A comprehensive study on the Lewis acidity of group 1–15 metal chlorides, perchlorates, and triflates was carried out in a water–THF cosolvent system (Scheme 244).⁶⁸⁶ In addition to rare earth metal cations, Fe^{II} , Cu^{II} , Zn^{II} , Cd^{II} , and Pb^{II} were disclosed as efficient and promising Lewis acids in an aqueous environment. To comprehend how the metal cations were correlated with their catalytic activities, hydrolysis constants (K_{h})^{687,688} and exchange rate constants for the substitution of inner-sphere water ligands (water-exchange-rate constants (WERCs))⁶⁸⁹ were propounded together with conventional absolute hardness⁶⁹⁰ (the HOMO–LUMO gap). The active elements were predicted to have $\text{p}K_{\text{h}}$ values in the range from about 4.3 (for Sc^{III}) to 10.08 (for Cd^{II}) and WERC values greater than $3.2 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. Cations with a large $\text{p}K_{\text{h}}$ value do not generally undergo efficient hydrolysis. In the case of $\text{p}K_{\text{h}}$ values being less than 4.3, cations are readily hydrolyzed to produce protons in a sufficient number to cause a rapid decomposition of silicon enolates. When the $\text{p}K_{\text{h}}$ values are higher than 10, the Lewis acidities of the cations are too low to catalyze the aldol reaction.

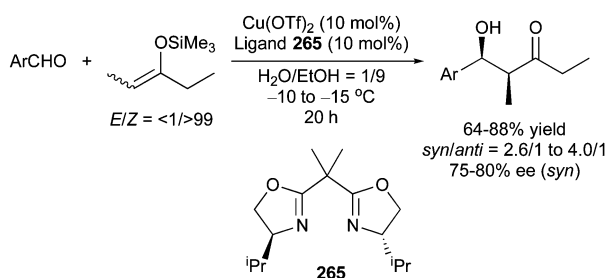
Among the water-compatible Lewis acids, copper(II) aqua structures formed with chiral bis(oxazoline) templates are found in many reports even though they are normally prepared under anhydrous conditions.^{691,692} The latent stability of the copper(II)-bis(oxazoline) **265** complex in an aqueous environment was exploited in the first example of an enantioselective Mukaiyama aldol reaction in aqueous media.^{519,693} The copper(II)-**265**



Li ⁺¹		Be		M ⁺ⁿ		B ⁺³		C		N	
13.64	—	—	—	pK _h ^a	—	—	—	—	—	—	—
4.7x10 ⁷	—	—	—	WERC ^b	—	—	—	—	—	—	—
Na ⁺¹		Mg ⁺²				Al ⁺³		Si ⁺⁴		P ⁺⁵	
14.18	11.44	—	—	—	—	4.97	—	—	—	—	—
1.9x10 ⁸	5.3x10 ⁵	—	—	—	—	1.6x10 ⁰	—	—	—	—	—
K ⁺¹		Ca ⁺²		Sc ⁺³		Ti ⁺⁴		V ⁺³		Cr ⁺³	
14.46	12.85	4.3	≤ 2.3	2.26	4.0	10.59	9.5	9.65	9.86	7.53	8.96
1.5x10 ⁸	5x10 ⁷	4.8x10 ⁷	—	1x10 ³	5.8x10 ⁻⁷	3.1x10 ⁷	3.2x10 ⁶	2x10 ⁵	2.7x10 ⁴	2x10 ⁸	5x10 ⁸
Rb		Sr		Y ⁺³		Zr ⁺⁴		Nb ⁺⁵		Mo ⁺⁵	
—	—	—	—	7.7	0.22	(0.6)	—	—	—	—	—
—	—	—	—	1.3x10 ⁷	—	—	—	—	—	—	—
Cs		Ba ⁺²		Ln ⁺³		Hf ⁺⁴		Ta ⁺⁵		W ⁺⁶	
—	—	13.47	7.6-8.5	—	—	0.25	—	(-1)	—	—	—
—	—	>6x10 ⁷	10 ⁶ -10 ⁸	—	—	—	—	—	—	—	—
La ⁺³		Ce ⁺³		Pr ⁺³		Nd ⁺³		Pm		Sm ⁺³	
8.5	8.3	8.1	8.0	—	—	—	—	—	—	7.9	7.8
2.1x10 ⁸	2.7x10 ⁸	3.1x10 ⁸	3.9x10 ⁸	—	—	—	—	—	—	5.9x10 ⁸	6.5x10 ⁸
Gd ⁺³		Tb ⁺³		Dy ⁺³		Ho ⁺³		Er ⁺³		Tm ⁺³	
8.0	7.9	8.0	8.0	8.0	8.0	8.0	8.0	7.9	7.7	7.7	7.6
6.3x10 ⁷	7.8x10 ⁷	6.3x10 ⁷	6.3x10 ⁷	6.1x10 ⁷	6.1x10 ⁷	6.1x10 ⁷	6.1x10 ⁷	6.4x10 ⁶	8x10 ⁷	8x10 ⁷	6x10 ⁷

^a pK_h = -log K_h.^b Exchange rate constants for substitution of inner-sphere water ligands.

Scheme 244 Hydrolysis constants and WERCs for estimating the Lewis acidity. Superior catalytic performance was observed using metal salts highlighted by a red square.



Scheme 245 First example of an enantioselective Mukaiyama aldol reaction in aqueous media.

complex showed a high catalytic activity for Mukaiyama aldol reactions of (*Z*)-enolate derived from 3-pentanone with aldehydes in aqueous ethanol (H₂O/EtOH = 1/9) to afford the desired aldol adducts with moderate to good yields and enantioselectivities (Scheme 245). The (*Z*)-isomer provided higher yields and diastereo- and enantioselectivities than the (*E*)-isomer. It was noted that much lower yields and selectivities were observed under anhydrous conditions with this catalytic system.

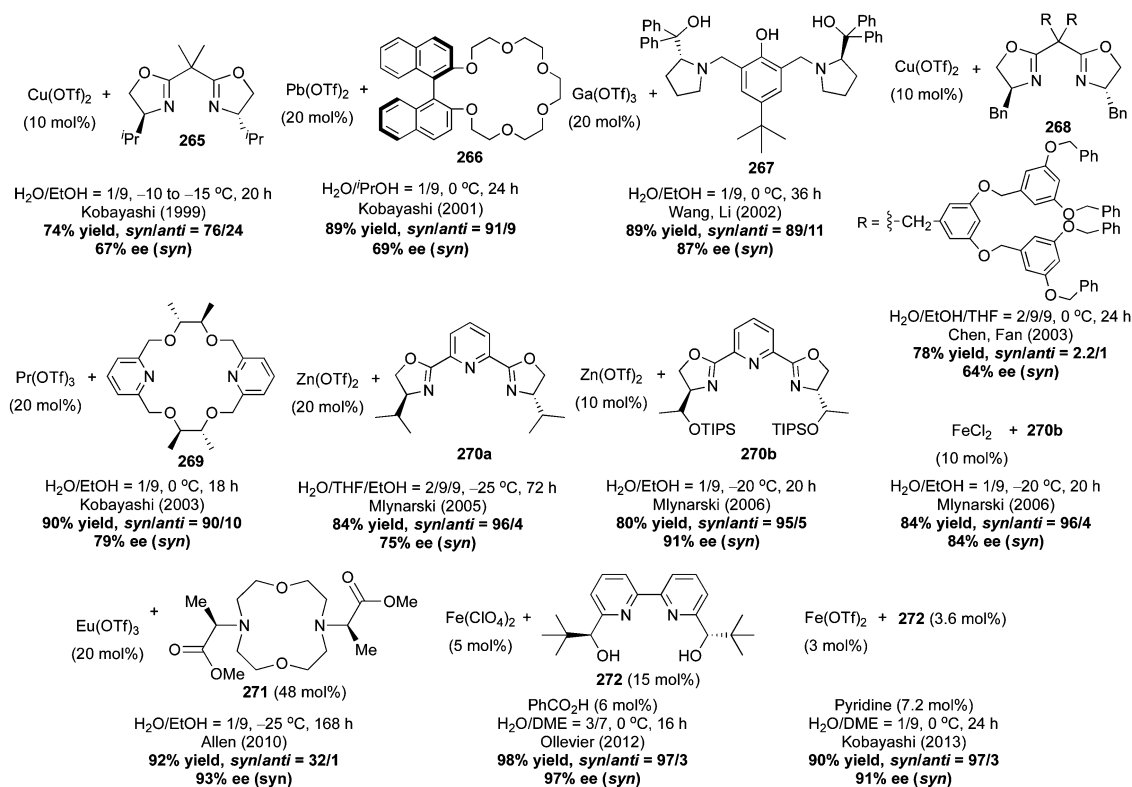
The catalytic system was then applied to the first example of a Lewis acid-catalyzed enantioselective aldol reaction using water as a single solvent under the concept of a Lewis acid-surfactant combined catalyst (LASC).⁵²⁰ The concept of LASC relied on a Lewis acid catalyst consolidated with a surfactant's emulsifying ability. The chiral bis(oxazoline) complex, derived from Cu(DS)₂ (DS = OSO₃C₁₂H₂₅) with **265**, catalyzed the asymmetric aldol reaction to afford the desired aldol products with moderate enantioselectivities. The addition of lauric acid as an additive was found to improve the reaction yield.

Some successful catalyst systems for enantioselective Mukaiyama aldol reactions between hydrophobic substrates

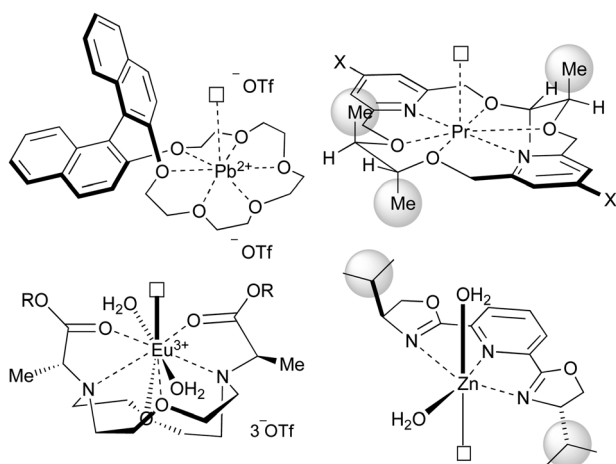
in aqueous media are shown in Scheme 246. With the exception of the example with copper(II)-**265**, multi-coordination served as a solution to overcome the instability of chiral metal complexes in the aqueous environment. The common characteristic of the early successful examples was a quasi-planar coordination geometry with a vacant site at the apical position (Scheme 247).

In 2001, Kobayashi and co-workers found, through detailed investigations into the combination of chiral crown ethers and metal triflates, on the basis of ionic radii^{694,695} and the hole sizes,^{696,697} that the chiral lead(II)-**266** complex was an effective catalyst for enantioselective Mukaiyama aldol reactions of benzaldehyde in aqueous media.⁶⁹⁸⁻⁷⁰⁰ Complex **266** was characterized by one longer bond between lead and the oxygen connected to the naphthalene rings, which could be ascribed to the dihedral angle between the two naphthalene rings. It was assumed that the water molecule at the apical position was replaced by an aldehyde, facilitating catalyst turnover. The Pb(OTf)₂-crown ether **266** complex is distinct in that thio ketene silyl acetals could be utilized as a substrate. Kinetic studies performed for the enantioselective reaction and for the Pb(OTf)₂-catalyzed achiral reaction revealed that almost comparable reaction rates and the same levels of diastereoselectivity were observed.

In 2002, Wang, Li, and co-workers reported a chiral complex, derived from Ga(OTf)₃ with the chiral Trost-type semicrown bisphenol **267** as a chiral catalyst for the Mukaiyama aldol reaction in water.⁷⁰¹ When the asymmetric Mukaiyama aldol reaction was performed with thio ketene silyl acetals, satisfactory levels of diastereo- and enantioselectivities were obtained when the aldol acceptors were aromatic aldehydes. On the other hand, poor enantioselectivities were observed when aliphatic aldehydes were utilized. They also found that the ligand played a



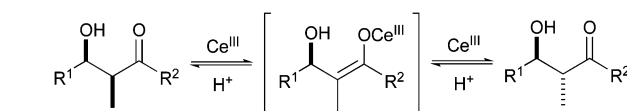
Scheme 246 Line up of chiral catalysts for enantioselective aldol reactions between a hydrophobic donor and acceptor in aqueous cosolvents.



Scheme 247 Coordination geometry of some successful examples.

key role in accelerating the reaction and suppressing the hydrolysis of the silicon enolates, while UV-vis titration and ESI-MS analysis confirmed this gallium complex to be a 1:1 complex.⁷⁰² In 2003, the C_2 -symmetric bis(oxazolines) **268** disubstituted with two Fréchet-type polyether dendrimers was reported as a ligand for the enantioselective copper(II)-catalyzed aldol reaction in aqueous media.⁷⁰³

In 2003, Kobayashi and co-workers developed a chiral complex comprising $\text{Ln}(\text{OTf})_3$ and the chiral bis-pyridino-18-crown-6 **269**.^{704–706} Unlike first-row transition metals, the precise control of lanthanides is challenging due to the larger ionic radii,



Scheme 248 Plausible epimerization induced by lanthanides.

greater coordination numbers, and larger WERCs of these transition metals. Lanthanide coordination takes place predominantly *via* ionic interactions, leading to a strong preference for negatively charged donor groups. Lanthanides are even known to promote epimerization between *syn*- and *anti*-adducts *via* keto-enolization (Scheme 248).⁷⁰⁷ In spite of such difficulties, good enantioselection was attained. In the structure, the praseodymium cation was located nearly in the plane of the crown ring, while the methyl groups of **269** were all in the axial positions. A vacant site at the apical position of the praseodymium cation was suggested to be crucial for the catalytic activity since it could serve as a binding site for an aldehyde molecule. They found that the enantioselective reaction was slightly slower compared with the achiral pathway. The highly selective stereocontrol was attributed to the size-fitting between the crown ethers and the metal cations, with larger cations such as lanthanum, cerium, praseodymium, and neodymium, yielding the aldol adducts with high diastereo- and enantioselectivities, while smaller cations, such as dysprosium, holmium, ytterbium, yttrium, and Sc, resulted in lower selectivities. The introduction of an electron-donating (MeO) group at the 4-position of the pyridine rings afforded high selectivities for the larger cations and lower

selectivities for the smaller cations. In the case of an electron-withdrawing (Br) group, although similar tendencies were observed, the effect of the ionic radii was found to be more significant.

In 2005, Mlynarski and co-workers reported chiral catalysts, derived from the complexation between $\text{Zn}(\text{OTf})_2$ and the ^iPr -pybox ligand **270a**^{708,709} or FeCl_2 and the hydroxymethyl-pybox ligand were effective catalysts for Mukaiyama aldol reactions in aqueous media.⁷¹⁰ Although both aliphatic and aromatic aldehydes were viable substrates to provide the aldol adducts with moderate selectivities, aldehydes bearing heteroatoms and aqueous aldehydes were apt to be unsuccessful in the zinc system. On the other hand, the chiral zinc catalyst was found to be effective for the aldol reactions of aromatic aldehydes. To overcome the instability, capriciousness, and sensitivity of chiral iron(II) and zinc(II) complexes, the lipophilic pybox ligand **270b** bearing a sterically bulky silyl group was developed in 2007.^{711,712} Although the selectivity was improved comparatively in the reactions of some substrates, the reactions involving aliphatic aldehydes still suffered from a significant drop in reactivity and selectivity.

In 2010, Allen and co-workers found that europium(III) or neodymium(III) complexes, formed with **271** could act as catalysts for enantioselective Mukaiyama aldol reactions in aqueous media. Unfortunately, these complexes possessed low catalytic activities and the activities were highly dependent on the substrates.^{713,714} The europium-**271** complex adopts a similar geometry as the above examples. Preliminary experiments by Allen and co-workers revealed the change in the coordination number of water molecules on Eu^{3+} upon the addition of substrates and products (a decrease of up to 0.34).⁷¹⁵ They also revealed an unequivocal interrelationship between the coordination environment of lanthanide triflates and the steady-state reaction rate of the Mukaiyama aldol reaction through luminescence-decay measurements, in combination with high-performance liquid chromatography analysis.^{716–718} The reactivity was shown to increase with the increased number of metal-bound water molecules. An analogous tendency was reported in 1994 by Kobayashi and co-workers.⁷¹⁹ The amount of water was found to govern the stereochemical outcome, as well as the consequent catalytic turnover in water/THF solution. While the ytterbium-catalyzed reaction of benzaldehyde with cyclohexanone-derived silicon enolates proceeded with *anti*-preference in the absence of water, the stereochemistry of the product underwent a change toward *syn* conformations as the amount of water increased. However, the selectivity did not change further (up to *syn/anti* = 73/27) when more than 15 equivalents of water were added. Presumably, when the equivalents of water were gradually increased, the coordination of water molecules induced the generation of the naked active cation with its high water-exchange rate constant to activate aldehydes effectively and catalyze the reaction *via* an acyclic transition state. That is, the structural fluctuation of the coordinated water molecules around the lanthanide ions determined the favorable transition states (TS) in terms of the entropy, promoting hydration of the silicon enolate and proton transfer

to the aldehyde, as well activating both substrates. Thus, the elaborate exploitation of the unique properties of water in irreversible Mukaiyama aldol reactions is expected to facilitate the catalytic turnover with a simultaneous desilylation for direct access to aldol adducts, while in conventional acid- or base-catalyzed aldol reactions, the reaction yields of the aldol adducts are destined to depend upon their thermodynamic stabilities due to the reversibility of the reactions.

In spite of the significant efforts made in developing chiral Lewis acid catalysts for asymmetric Mukaiyama aldol reactions, most catalytic systems require 10–20 mol% of the Lewis acids, in conjunction with 12–48 mol% of chiral ligands, and possess limited scope for use with some substrates, such as aliphatic aldehydes, for which remarkable drops in enantioselectivities are commonly observed. In 2012, Ollevier reported a chiral iron(II) complex, comprising $\text{Fe}(\text{ClO}_4)_2$ and the chiral 2,2'-bipyridine **272**^{720,721} as an efficient catalyst for enantioselective aldol reactions in aqueous media.⁷²² Although the catalyst loading could be reduced to 5 mol% in the presence of benzoic acid as an additive, an excessive use of the chiral ligand was required for high conversion and a high level of stereoselection for the Mukaiyama aldol reaction. Crystallographic investigations revealed that the central iron(II) ion was held in an almost square-planar fashion, while the axial position of the pentagonal bipyramidal iron(II) complex was occupied by an additional water molecule. ESI-MS measurements corroborated the formation of a 1:1 complex in the reaction solution.⁷²³ Concurrently, Kobayashi and co-workers achieved a similar catalyst system comprised of 3 mol% of iron(II) salt with 3.6 mol% of **272** in aqueous media.^{724,725} They conducted a comprehensive study on the catalytic activity of metal-**272** complexes and found that lanthanides, Al^{III} , Yb^{III} , Lu^{III} , and Hg^{II} afforded higher selectivities in the presence of 1.2 equivalents of **272**. However, when an excess of **272** was used, Fe^{II} , Cu^{II} , Sn^{II} , and Bi^{III} could generate a better chiral Lewis acid complex than the one derived from 1.2 equivalents of **272**. With further optimization, they discovered that the use of pyridine or benzoic acid as an additive enabled iron(II)-**272** and bismuth(III)-**272** complexes to cover a wide range of substrates for asymmetric Mukaiyama aldol reactions. The superiority of this methodology over conventional methods was demonstrated in terms of a high catalytic activity, the simplicity of the experimental procedures, and it covering a wide substrate range, including aqueous aldehydes, for which the stereochemistry had previously been regarded to be difficult to govern. Furthermore, the facile synthesis of the chiral ligand underscored its versatility. The enantioselective variant, without an organic solvent, was also achieved by using iron(II)-based LASC.⁷²⁶ In 2015, Morokuma and co-workers utilized density functional theory (DFT), combined with the artificial force-induced reaction (AFIR) method, to establish the mechanism of the aqueous Mukaiyama aldol reactions catalyzed by a chiral iron(II) complex, derived from $\text{Fe}(\text{OTf})_2$ and the chiral ligand **272**.⁷²⁷ This is an effective method to search many important reaction pathways, such as the study of europium-catalyzed Mukaiyama aldol reactions in water,^{728,729} in which more than 160 TS structures have been

found for the selectivity-determining carbon–carbon formation step, with about 10 of them found to contribute to the enantioselectivity of the reaction. On the basis of the calculations, several thermodynamically stable six- or seven-coordinate complexes were identified in solution, where the high-spin quintet state is the ground state. Among them, the active intermediates for the selectivity-determining outer-sphere carbon–carbon bond formation were proposed. The multicomponent artificial force-induced reaction (MC-AFIR) method found key transition states for the carbon–carbon bond formation, and explained the enantioselectivity and diastereoselectivity. The overall mechanism consisted of the coordination of the aldehyde, carbon–carbon bond formation, the rate-determining proton transfer from water to the aldehyde, and the dissociation of the trimethyl silyl group. The calculated catalytic cycle was consistent with the experiments. This study provided important mechanistic insights into the transition-metal-catalyzed Mukaiyama aldol reaction in aqueous media.

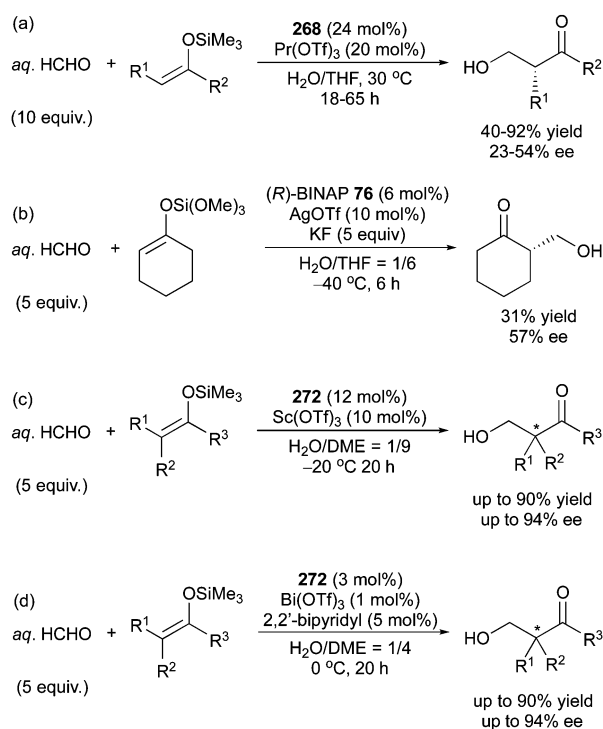
The highly coordinative nature of these successful ligands appears to be key to understanding the catalytic behavior of metal cations in an aqueous environment. The model also agrees with the reaction of aqueous formaldehyde. Some successful examples are shown in Scheme 249. The chiral praseodymium-**268** complex was shown to enable the catalytic asymmetric hydroxymethylation reaction, albeit with low selectivity.⁷³⁰ This was the first report on the catalytic asymmetric hydroxymethylation of silicon enolates. Yamamoto and co-workers reported a bifunctional system consisting of a (*R*)-BINAP **76**–AgOTf complex, with a fluoride source as a Lewis base catalyst, for the

enantioselective hydroxymethylation of trimethoxysilyl enol ethers derived from cyclohexanone (31% yield, 57% ee enantioselectivity) or α -tetralone (18% yield, 57% ee enantioselectivity) in aqueous tetrahydrofuran, albeit in low yields.⁷³¹ In 2004, Kobayashi and co-workers devised an excellent catalytic system based on a chiral scandium complex. Chiral 2,2'-bipyridine **272** was chosen as a ligand candidate, due to it possessing multiple coordinating N and O atoms. The reaction proceeded smoothly to afford hydroxymethylated products with higher yields and enantioselectivities when compared with previous systems.⁷³² Kinetic studies by Kobayashi showed the first-order dependence of the silicon enolate, while the catalyst had an overall rate law of $\text{rate} = [\text{silicon enolate}][\text{catalyst}]$.⁷³³ The observation of a first-order dependence on both the silicon enolate and the catalyst negated the possibility of a scandium enolate as an intermediate and the involvement of discrete molecules of the catalyst. Moreover, saturation kinetics was not observed, which also ruled out direct bond formation between the chiral scandium-**272** catalyst and the silicon enolate.

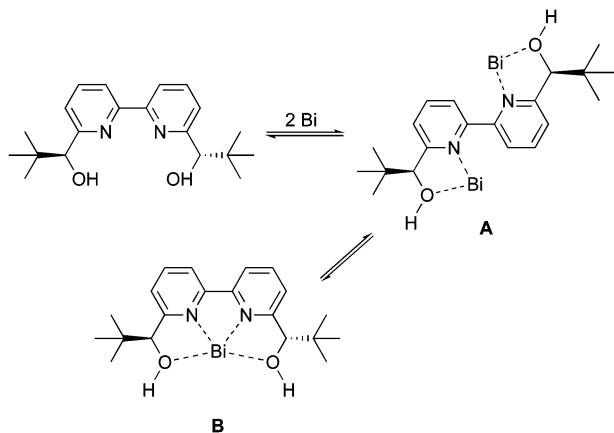
Extensive effort was also dedicated to enantioselective hydroxymethylation in aqueous media, leading to the discovery of a new catalytic system composed of Bi(OTf)₃ and **272**.^{734,735} Given the ease of hydrolysis in the presence of water,⁷³⁶ as well as the great discrepancy in the ionic diameters between bismuth (2.34 Å for 8-coordination) and scandium (1.74 Å for 8-coordination), this unexpected result offered an interesting insight into asymmetric catalysis in an aqueous environment. Indeed, only a trace amount of hydroxymethylated adduct was obtained using Bi(OTf)₃ in the absence of **272**, owing to rapid decomposition of the silicon enolate promoted by the TfOH generated readily from Bi(OTf)₃ in water. The ligand acceleration effect by **272** suggested that the stabilization of Bi(OTf)₃ was due to the coordination of **272** in water. A chiral bismuth catalyst comprising 1 mol% of Bi(OTf)₃, 3 mol% of **272**, and 5 mol% of 2,2'-bipyridyl was shown to afford the desired product in high yields with high enantioselectivities. Fundamental elucidation of the catalyst structure through NMR spectroscopy indicated that two equivalents of Bi(OTf)₃ and one equivalent of **272** formed complex **A**, and that complex **B**, consisting of one equivalent of Bi(OTf)₃ and one equivalent of **272**, was generated when an excess amount of **272** was added (Scheme 250).

Catalytic asymmetric hydroxymethylation reactions without the use of any organic solvent were successfully carried out with 10 mol% of Sc(DS)₃ and 12 mol% of **272** in the presence of Triton X-705 **273** or with 10 mol% of Sc(OSO₂C₁₂H₂₅)₃ and 12 mol% of chiral *N,N'*-dioxide ligand **27** in the presence of C₁₂H₂₅SO₃Na to afford the desired aldol adducts in high yields and with high enantioselectivities (Scheme 251).⁷³⁷ A wide range of silicon enolates, including thioketene silyl acetals, reacted smoothly, and high enantioselectivities were attained. The centrifugation of the reaction mixture (3000 rpm, 20 min) led to a successful separation of the colloidal dispersion into three phases: upper, middle, and bottom phases, corresponding to the water, surfactant, and organic layers, respectively.

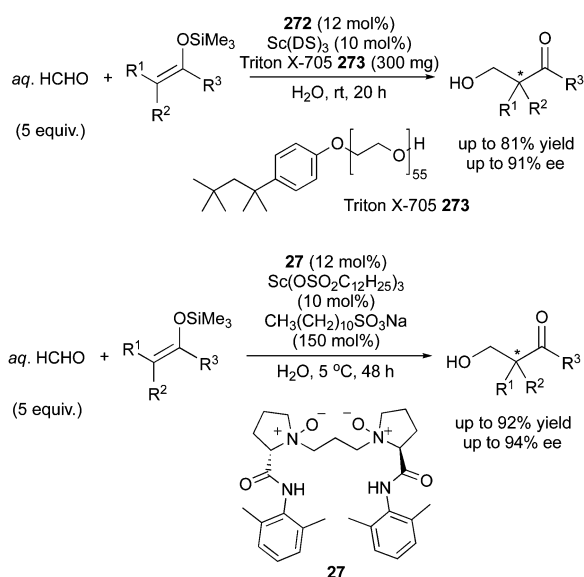
Chiral disulfonated binaphthyl dialkyl ethers **274** with Ga(OTf)₃ and Cu(OTf)₂ catalyzed the enantioselective Mukaiyama aldol



Scheme 249 Some successful examples of enantioselective aldol reactions using aqueous formaldehyde.

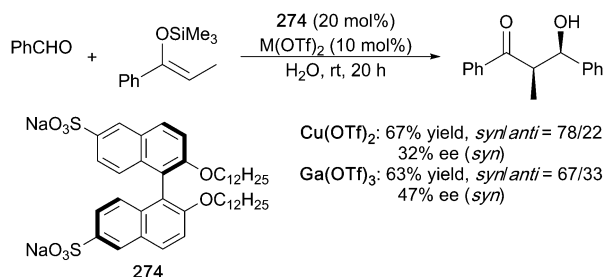


Scheme 250 Equilibrium between bismuth-272 complexes.

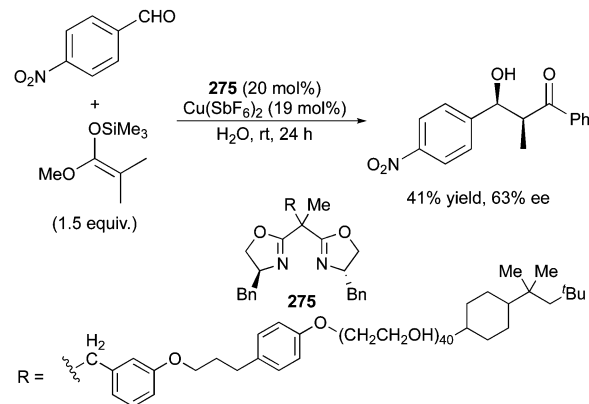


Scheme 251 Enantioselective Mukaiyama aldol reactions using form-aldehyde in water.

reactions more efficiently than $\text{Sc}(\text{OTf})_3$ in water with moderate selectivities (Scheme 252).⁷³⁸ The chiral amphiphile, which has been mainly used in enantiomer separation by capillary electrochromatography,^{739,740} formed micelles in water, and the changes in the torsion between two naphthyl rings could result in chiral induction.



Scheme 252 Chiral surfactant for enantioselective Mukaiyama aldol reactions.

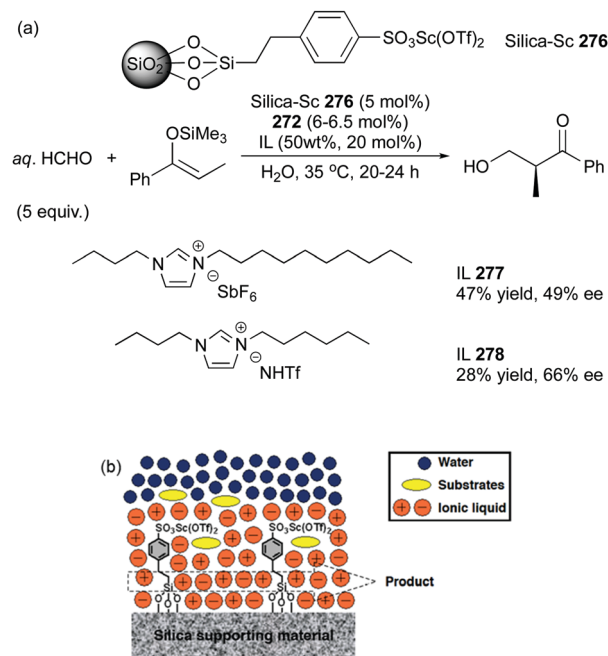


Scheme 253 Triton®-supported chiral copper(III) complex for enantioselective Mukaiyama aldol reactions.

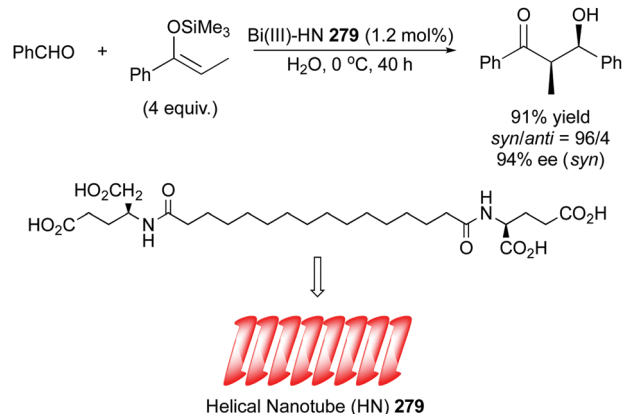
PEG- or Triton®-supported chiral bis(oxazoline) 275 has been employed, in combination with copper(II) salts, as a catalyst for Mukaiyama aldol reactions of ketene silyl acetal, derived from methyl isobutyrate, with aldehydes in water (Scheme 253).⁷⁴¹

Kobayashi and co-workers developed a solid scandium catalyst coated with an ionic liquid [DBIm]SbF₆ 277, and Silica-Sc 276.⁷⁴² In racemic Mukaiyama aldol reactions, the reaction rate was found to be much faster in water than in organic solvents or under neat conditions. They determined that ionic liquids played a crucial role in the construction of an efficient hydrophobic environment in water. In the presence of 272, the Silica-Sc(276)-IL(278) system enabled enantioselective addition to occur with moderate yields and enantioselectivities (Scheme 254). The high solubility of these ligands in water allowed a very convenient catalyst-recycling procedure.

A helical single-walled nanotube was fabricated by gelation through the self-assembly of a bolaamphiphile terminated with



Scheme 254 Catalytic asymmetric hydroxymethylation using Silica-Sc-IL.



Scheme 255 Metal-coordinated helical nanotube (M-HN) catalysts.

L-glutamic acid in water. Dispersion of the nanotube into aqueous solutions, containing various metal ions, could produce metal-coordinated single-walled helical nanotubes (M-HN **279**) with *M*-chirality, in which the coordination sites could serve as catalytic sites for enantioselective reactions, such as Diels–Alder reactions⁷⁴³ and Mukaiyama aldol reactions, even at low catalyst loadings (Scheme 255).⁷⁴⁴ The morphology of the helical nanotube could be retained by regulating the amount of metal ions.

6. Summary and future direction

In this article, recent developments in catalytic asymmetric aldol reactions have been summarized. Enantioselective aldol reactions are important methods to synthesize β-hydroxy carbonyl compounds in an optically pure form, and as such, numerous successful chiral catalysts have been designed and applied for asymmetric aldol reactions. From a historical perspective, the first milestone in the development of catalytic enantioselective aldol reactions was the development of catalytic enantioselective Mukaiyama aldol reactions using preformed enolates. This methodology demonstrated for the first time that chiral reagents could perform catalytically for enantioselective aldol reactions. It should be noted that the development of this methodology significantly influenced not only enantioselective aldol reactions, but also other enantioselective carbon–carbon bond forming processes and opened the floodgate to new research in asymmetric synthesis. The next milestone was the development of catalytic direct-type enantioselective aldol reactions using carbonyl pronucleophiles. These reactions represent the most atom-economical enantioselective reactions, and here the chiral catalyst plays a key role in controlling both the enolization and enantioselective aldol reaction of carbonyl pronucleophiles. Initially developed using chiral metal catalysts, the emergence of robust organocatalysts led to a more sustainable aldol reaction. To improve the greenness of asymmetric aldol reactions, research into minimizing the use of organic solvents has led to synthetic protocols that can employ water as a solvent. Thus, the end goal toward the ideal enantioselective aldol reaction is nearly in reach. There are still challenges that need

to be overcome but these are anticipated to be solved in the near future. For example, compared to other practical catalytic enantioselective reactions, such as catalytic enantioselective hydrogenation reactions, the catalyst amount required for the state-of-the-art aldol reaction is still high. Therefore, more efficient chiral catalysts are needed for the ideal enantioselective aldol reactions. Alternatively, flow chemistry may address this issue.^{742,745} Furthermore, while many types of carbonyl pronucleophiles can be successfully employed, weakly acidic carbonyl pronucleophiles, such as non-activated esters and amides, are challenging and new synthetic methodologies that can employ them are desirable.

Conflicts of interest

There are no conflicts to declare.

References

- B. M. Trost and I. Fleming, *Comprehensive Organic Synthesis: Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*, Elsevier Science Limited, 1991.
- P. Knochel and G. A. Molander, *Comprehensive Organic Synthesis*, Elsevier Science, 2014.
- A. T. Nielsen and W. J. Houlihan, *Organic Reactions*, John Wiley & Sons, Inc., 2004.
- T. Mukaiyama, *Organic Reactions*, John Wiley & Sons, Inc., 2004.
- L. M. Geary and P. G. Hultin, *Tetrahedron: Asymmetry*, 2009, **20**, 131.
- C. J. Cowden and I. Paterson, *Organic Reactions*, John Wiley & Sons, Inc., 2004.
- R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095.
- D. A. Evans, J. Bartroli and T. L. Shih, *J. Am. Chem. Soc.*, 1981, **103**, 2127.
- A. M. P. Koskinen, *Chem. Rec.*, 2014, **14**, 52.
- E. M. Carreira, A. Fettes and C. Marti, *Organic Reactions*, John Wiley & Sons, Inc., 2004.
- T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, 1011.
- J.-i. Matsuo and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 9109.
- S. B. J. Kan, K. K. H. Ng and I. Paterson, *Angew. Chem., Int. Ed.*, 2013, **52**, 9097.
- T. Mukaiyama, S. Kobayashi, H. Uchiro and I. Shiina, *Chem. Lett.*, 1990, 129.
- S. Kobayashi, Y. Fujishita and T. Mukaiyama, *Chem. Lett.*, 1990, 1455.
- S. Kobayashi, M. Furuya, A. Ohtsubo and T. Mukaiyama, *Tetrahedron: Asymmetry*, 1991, **2**, 635.
- S. Kobayashi, H. Uchiro, Y. Fujishita, I. Shiina and T. Mukaiyama, *J. Am. Chem. Soc.*, 1991, **113**, 4247.
- T. Mukaiyama, M. Furuya, A. Ohtsubo and S. Kobayashi, *Chem. Lett.*, 1991, 989.

- 19 S. Kobayashi, H. Uchiro, I. Shiina and T. Mukaiyama, *Tetrahedron*, 1993, **49**, 1761.
- 20 S. Kobayashi and T. Kawasuji, *Synlett*, 1993, 911.
- 21 S. Kobayashi, T. Kawasuji and N. Mori, *Chem. Lett.*, 1994, 217.
- 22 I. Shiina, *Chem. Rec.*, 2014, **14**, 144.
- 23 T. Mukaiyama, A. Inubushi, S. Suda, R. Hara and S. Kobayashi, *Chem. Lett.*, 1990, 1015.
- 24 K. Mikami and S. Matsukawa, *J. Am. Chem. Soc.*, 1993, **115**, 7039.
- 25 K. Mikami, S. Matsukawa, M. Nagashima, H. Funabashi and H. Morishima, *Tetrahedron Lett.*, 1997, **38**, 579.
- 26 K. Mikami, T. Yajima, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimarui and M. Maruta, *Tetrahedron*, 1996, **52**, 85.
- 27 E. M. Carreira, R. A. Singer and W. Lee, *J. Am. Chem. Soc.*, 1994, **116**, 8837.
- 28 R. A. Singer and E. M. Carreira, *Tetrahedron Lett.*, 1997, **38**, 927.
- 29 E. M. Carreira, W. Lee and R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649.
- 30 G. E. Keck and D. Krishnamurthy, *J. Am. Chem. Soc.*, 1995, **117**, 2363.
- 31 R. Zimmer, A. Peritz, R. Czerwonka, L. Schefzig and H.-U. Reißig, *Eur. J. Org. Chem.*, 2002, 3419.
- 32 A. Soriente, M. De Rosa, M. Stanzione, R. Villano and A. Scettri, *Tetrahedron: Asymmetry*, 2001, **12**, 959.
- 33 Nissan Chemical Industries, Ltd. Process for producing optically active oxoheptenoic acid ester, *PCT Intl. Appl.*, WO2003042180.
- 34 H. Ishitani, Y. Yamashita, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 5403.
- 35 Y. Yamashita, H. Ishitani, H. Shimizu and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 3292.
- 36 S. Kobayashi, S. Saito, M. Ueno and Y. Yamashita, *Chem. Commun.*, 2003, 2016.
- 37 K. Seki, M. Ueno and S. Kobayashi, *Org. Biomol. Chem.*, 2007, **5**, 1347.
- 38 J. Kobayashi, M. Nakamura, Y. Mori, Y. Yamashita and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 9192.
- 39 T. Isoda, R. Akiyama, H. Oyamada and S. Kobayashi, *Adv. Synth. Catal.*, 2006, **348**, 1813.
- 40 K. Furuta, T. Maruyama and H. Yamamoto, *J. Am. Chem. Soc.*, 1991, **113**, 1041.
- 41 K. Furuta, T. Maruyama and H. Yamamoto, *Synlett*, 1991, 439.
- 42 K. Ishihara, T. Maruyama, M. Mouri, Q. Z. Gao, K. Furuta and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 3483.
- 43 E. R. Parmee, O. Tempkin, S. Masamune and A. Abiko, *J. Am. Chem. Soc.*, 1991, **113**, 9365.
- 44 E. R. Parmee, Y. Hong, O. Tempkin and S. Masamune, *Tetrahedron Lett.*, 1992, **33**, 1729.
- 45 S. Kiyooka, Y. Kaneko and K. Kume, *Tetrahedron Lett.*, 1992, **33**, 4927.
- 46 E. J. Corey, C. L. Cywin and T. D. Roper, *Tetrahedron Lett.*, 1992, **33**, 6907.
- 47 K. Ishihara, S. Kondo and H. Yamamoto, *Synlett*, 1999, 1283.
- 48 K. Ishihara, S. Kondo and H. Yamamoto, *J. Org. Chem.*, 2000, **65**, 9125.
- 49 G. Li, H.-X. Wei, B. S. Phelps, D. W. Purkiss and S. H. Kim, *Org. Lett.*, 2001, **3**, 823.
- 50 S. Adachi and T. Harada, *Org. Lett.*, 2008, **10**, 4999.
- 51 B. K. Senapati, L. Gao, S. I. Lee, G. S. Hwang and H. Ryu do, *Org. Lett.*, 2010, **12**, 5088.
- 52 M. Sodeoka, K. Ohrai and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 2648.
- 53 M. Sodeoka, R. Tokunoh, F. Miyazaki, E. Hagiwara and M. Shibasaki, *Synlett*, 1997, 463.
- 54 M. Sodeoka and Y. Hamashima, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 941.
- 55 O. Fujimura, *J. Am. Chem. Soc.*, 1998, **120**, 10032.
- 56 S.-i. Kiyooka, S. Hosokawa and S. Tsukasa, *Tetrahedron Lett.*, 2006, **47**, 3959.
- 57 S.-i. Kiyooka, Y. Takeshita, Y. Tanaka, T. Higaki and Y. Wada, *Tetrahedron Lett.*, 2006, **47**, 4453.
- 58 S. Kiyooka, S. Matsumoto, T. Shibata and K. Shinozaki, *Tetrahedron*, 2010, **66**, 1806.
- 59 M. Ohkouchi, M. Yamaguchi and T. Yamagishi, *Enantiomer*, 2000, **5**, 71.
- 60 M. Ohkouchi, D. Masui, M. Yamaguchi and T. Yamagishi, *J. Mol. Catal. A: Chem.*, 2001, **170**, 1.
- 61 L. C. Akullian, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2006, **128**, 6532.
- 62 D. A. Evans, J. A. Murry and M. C. Kozlowski, *J. Am. Chem. Soc.*, 1996, **118**, 5814.
- 63 D. A. Evans, M. C. Kozlowski, J. A. Murry, C. S. Burgey, K. R. Campos, B. T. Connell and R. J. Staples, *J. Am. Chem. Soc.*, 1999, **121**, 669.
- 64 D. A. Evans, C. S. Burgey, M. C. Kozlowski and S. W. Tregay, *J. Am. Chem. Soc.*, 1999, **121**, 686.
- 65 S. Orlandi, A. Mandoli, D. Pini and P. Salvadori, *Angew. Chem., Int. Ed.*, 2001, **40**, 2519.
- 66 S. Doherty, J. G. Knight, J. R. Ellison, P. Goodrich, L. Hall, C. Hardacre, M. J. Muldoon, S. Park, A. Ribeiro, C. A. N. de Castro, M. J. Lourenco and P. Davey, *Green Chem.*, 2014, **16**, 1470.
- 67 D. A. Evans, D. W. C. MacMillan and K. R. Campos, *J. Am. Chem. Soc.*, 1997, **119**, 10859.
- 68 D. A. Evans, C. E. Masse and J. Wu, *Org. Lett.*, 2002, **4**, 3375.
- 69 D. A. Evans, J. Wu, C. E. Masse and D. W. C. MacMillan, *Org. Lett.*, 2002, **4**, 3379.
- 70 A. Landa, A. Minkila, G. Blay and K. A. Jorgensen, *Chemistry*, 2006, **12**, 3472.
- 71 F. Fu, Y.-C. Teo and T.-P. Loh, *Tetrahedron Lett.*, 2006, **47**, 4267.
- 72 G. Desimoni, G. Faita, F. Piccinini and M. Toscanini, *Eur. J. Org. Chem.*, 2006, 5228.
- 73 M. Langner and C. Bolm, *Angew. Chem., Int. Ed.*, 2004, **43**, 5984.
- 74 M. Langner, P. Remy and C. Bolm, *Chemistry*, 2005, **11**, 6254.

- 75 K. Oisaki, D. B. Zhao, Y. Suto, M. Kanai and M. Shibasaki, *Tetrahedron Lett.*, 2005, **46**, 4325.
- 76 K. Oisaki, D. Zhao, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 7164.
- 77 J. Zhao, K. Zheng, Y. Yang, J. Shi, L. Lin, X. Liu and X. Feng, *Synlett*, 2011, 903.
- 78 R. Gotoh and M. Yamanaka, *Molecules*, 2012, **17**, 9010.
- 79 G. Gil-Ramirez, S. Hoekman, M. O. Kitching, D. A. Leigh, I. J. Vitorica-Yrezabal and G. Zhang, *J. Am. Chem. Soc.*, 2016, **138**, 13159.
- 80 A. Ando, T. Miura, T. Tatematsu and T. Shioiri, *Tetrahedron Lett.*, 1993, **34**, 1507.
- 81 C. T. Chen, S. D. Chao, K. C. Yen, C. H. Chen, I. C. Chou and S. W. Hon, *J. Am. Chem. Soc.*, 1997, **119**, 11341.
- 82 M. Horikawa, J. Busch-Petersen and E. J. Corey, *Tetrahedron Lett.*, 1999, **40**, 3843.
- 83 T. Ooi, K. Doda and K. Maruoka, *Org. Lett.*, 2001, **3**, 1273.
- 84 W. Zhuang, T. B. Poulsen and K. A. Jorgensen, *Org. Biomol. Chem.*, 2005, **3**, 3284.
- 85 J. D. McGilvra, A. K. Unni, K. Modi and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2006, **45**, 6130.
- 86 V. B. Gondi, K. Hagihara and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2009, **48**, 776.
- 87 P. García-García, F. Lay, P. García-García, C. Rabalakos and B. List, *Angew. Chem., Int. Ed.*, 2009, **48**, 4363.
- 88 C. H. Cheon and H. Yamamoto, *Org. Lett.*, 2010, **12**, 2476.
- 89 M. Sai and H. Yamamoto, *J. Am. Chem. Soc.*, 2015, **137**, 7091.
- 90 P.-S. Wang, K.-N. Li, X.-L. Zhou, X. Wu, Z.-Y. Han, R. Guo and L.-Z. Gong, *Chem. – Eur. J.*, 2013, **19**, 6234.
- 91 S. E. Denmark, T. Wynn and G. L. Beutner, *J. Am. Chem. Soc.*, 2002, **124**, 13405.
- 92 S. E. Denmark and J. R. Heemstra, *Org. Lett.*, 2003, **5**, 2303.
- 93 S. E. Denmark and T. Bui, *J. Org. Chem.*, 2005, **70**, 10190.
- 94 S. E. Denmark, B. M. Eklov, P. J. Yao and M. D. Eastgate, *J. Am. Chem. Soc.*, 2009, **131**, 11770.
- 95 S. E. Denmark, S. B. D. Winter, X. Su and K.-T. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 7404.
- 96 S. E. Denmark and S. B. D. Winter, *Synlett*, 1997, 1087.
- 97 S. E. Denmark, K.-T. Wong and R. A. Stavenger, *J. Am. Chem. Soc.*, 1997, **119**, 2333.
- 98 S. E. Denmark, R. A. Stavenger and K.-T. Wong, *J. Org. Chem.*, 1998, **63**, 918.
- 99 S. E. Denmark, X. Su and Y. Nishigaichi, *J. Am. Chem. Soc.*, 1998, **120**, 12990.
- 100 S. E. Denmark and R. A. Stavenger, *J. Org. Chem.*, 1998, **63**, 9524.
- 101 S. E. Denmark, R. A. Stavenger and K.-T. Wong, *Tetrahedron*, 1998, **54**, 10389.
- 102 S. E. Denmark, R. A. Stavenger, K.-T. Wong and X. Su, *J. Am. Chem. Soc.*, 1999, **121**, 4982.
- 103 S. E. Denmark and R. A. Stavenger, *J. Am. Chem. Soc.*, 2000, **122**, 8837.
- 104 S. E. Denmark and R. A. Stavenger, *Acc. Chem. Res.*, 2000, **33**, 432.
- 105 S. E. Denmark and S. M. Pham, *Helv. Chim. Acta*, 2000, **83**, 1846.
- 106 S. E. Denmark and S. Fujimori, *Org. Lett.*, 2002, **4**, 3477.
- 107 S. E. Denmark and S. M. Pham, *J. Org. Chem.*, 2003, **68**, 5045.
- 108 S. E. Denmark, S. M. Pham, R. A. Stavenger, X. Su, K.-T. Wong and Y. Nishigaichi, *J. Org. Chem.*, 2006, **71**, 3904.
- 109 S. E. Denmark and S. K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 4759.
- 110 S. E. Denmark and T. Bui, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5439.
- 111 S. E. Denmark and T. Bui, *J. Org. Chem.*, 2005, **70**, 10393.
- 112 S. E. Denmark and S. K. Ghosh, *Tetrahedron*, 2007, **63**, 8636.
- 113 M. Nakajima, T. Yokota, M. Saito and S. Hashimoto, *Tetrahedron Lett.*, 2004, **45**, 61.
- 114 S. Kotani, S. Hashimoto and M. Nakajima, *Synlett*, 2006, 1116.
- 115 S. Kotani, S. Hashimoto and M. Nakajima, *Tetrahedron*, 2007, **63**, 3122.
- 116 A. Yanagisawa, Y. Nakatsuka, K. Asakawa, H. Kageyama and H. Yamamoto, *Synlett*, 2001, 0069.
- 117 M. Wadamoto, N. Ozasa, A. Yanagisawa and H. Yamamoto, *J. Org. Chem.*, 2003, **68**, 5593.
- 118 M. Nakajima, Y. Orito, T. Ishizuka and S. Hashimoto, *Org. Lett.*, 2004, **6**, 3763.
- 119 Y. Orito, S. Hashimoto, T. Ishizuka and M. Nakajima, *Tetrahedron*, 2006, **62**, 390.
- 120 T. Ichibakase, T. Kaneko, Y. Orito, S. Kotani and M. Nakajima, *Tetrahedron*, 2012, **68**, 4210.
- 121 A. Yanagisawa, Y. Matsumoto, H. Nakashima, K. Asakawa and H. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 9319.
- 122 A. Yanagisawa, Y. Matsumoto, K. Asakawa and H. Yamamoto, *J. Am. Chem. Soc.*, 1999, **121**, 892.
- 123 A. Yanagisawa, Y. Matsumoto, K. Asakawa and H. Yamamoto, *Tetrahedron*, 2002, **58**, 8331.
- 124 A. Yanagisawa, T. Ichikawa and T. Arai, *J. Organomet. Chem.*, 2007, **692**, 550.
- 125 A. Yanagisawa, T. Satou, A. Izumiseki, Y. Tanaka, M. Miyagi, T. Arai and K. Yoshida, *Chem. – Eur. J.*, 2009, **15**, 11450.
- 126 A. Yanagisawa, R. Miyake and K. Yoshida, *Eur. J. Org. Chem.*, 2014, 4248.
- 127 L. Lin, K. Yamamoto, H. Mitsunuma, Y. Kanzaki, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.*, 2015, **137**, 15418.
- 128 W.-D. Fessner, A. Schneider, H. Held, G. Sinerius, C. Walter, M. Hixon and J. V. Schloss, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2219.
- 129 H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418.
- 130 Y. M. A. Yamada, N. Yoshikawa, H. Sasai and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1871.
- 131 N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1999, **121**, 4168.
- 132 D. Sawada, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2000, **122**, 10521.

- 133 Y. M. A. Yamada and M. Shibasaki, *Tetrahedron Lett.*, 1998, **39**, 5561.
- 134 B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12003.
- 135 B. M. Trost, H. Ito and E. R. Silcoff, *J. Am. Chem. Soc.*, 2001, **123**, 3367.
- 136 B. M. Trost and V. S. C. Yeh, *Org. Lett.*, 2002, **4**, 3513.
- 137 B. M. Trost, E. R. Silcoff and H. Ito, *Org. Lett.*, 2001, **3**, 2497.
- 138 N. Yoshikawa and M. Shibasaki, *Tetrahedron*, 2001, **57**, 2569.
- 139 N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Ohshima, T. Suzuki and M. Shibasaki, *J. Am. Chem. Soc.*, 2001, **123**, 2466.
- 140 N. Kumagai, S. Matsunaga, N. Yoshikawa, T. Ohshima and M. Shibasaki, *Org. Lett.*, 2001, **3**, 1539.
- 141 N. Yoshikawa, T. Suzuki and M. Shibasaki, *J. Org. Chem.*, 2002, **67**, 2556.
- 142 N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2169.
- 143 T. Suzuki, N. Yamagiwa, Y. Matsuo, S. Sakamoto, K. Yamaguchi, M. Shibasaki and R. Noyori, *Tetrahedron Lett.*, 2001, **42**, 4669.
- 144 R. Mahrwald and B. Ziemer, *Tetrahedron Lett.*, 2002, **43**, 4459.
- 145 M. A. Calter and R. K. Orr, *Tetrahedron Lett.*, 2003, **44**, 5699.
- 146 H. Inoue, M. Kikuchi, J.-i. Ito and H. Nishiyama, *Tetrahedron*, 2008, **64**, 493.
- 147 H. Li, C. S. Da, Y. H. Xiao, X. Li and Y. N. Su, *J. Org. Chem.*, 2008, **73**, 7398.
- 148 X. Li, L. Zhang, Y. H. Xiao, Q. P. Guo, C. S. Da, H. Li, X. J. Liu, X. R. Ma and Y. J. Ma, *Russ. J. Gen. Chem.*, 2016, **86**, 1922.
- 149 E. Wojaczynska, J. Skarzewski, L. Sidorowicz, R. Wieczorek and J. Wojczynski, *New J. Chem.*, 2016, **40**, 9795.
- 150 E. Gomez-Bengoa, J. M. Garcia, S. Jimenez, I. Lapuerta, A. Mielgo, J. M. Odriozola, I. Otazo, J. Razkin, I. Urruzuno, S. Vera, M. Oiarbide and C. Palomo, *Chem. Sci.*, 2013, **4**, 3198.
- 151 A. Karmakar, T. Maji, S. Wittmann and O. Reiser, *Chem. – Eur. J.*, 2011, **17**, 11024.
- 152 C. Andreu, F. Sanz and G. Asensio, *Eur. J. Org. Chem.*, 2012, 4185.
- 153 C. Andreu, M. del Olmo and G. Asensio, *Tetrahedron*, 2012, **68**, 7966.
- 154 C. Andreu, T. Varea and G. Asensio, *Tetrahedron*, 2011, **67**, 8705.
- 155 C. Andreu and G. Asensio, *Tetrahedron*, 2011, **67**, 7050.
- 156 A. Quintard and J. Rodriguez, *Chem. Commun.*, 2015, **51**, 9523.
- 157 Y. Lu, M. Wang, X. H. Zhao, X. H. Liu, L. L. Lin and X. M. Feng, *Synlett*, 2015, 1545.
- 158 B. M. Choudary, L. Chakrapani, T. Ramani, K. V. Kumar and M. L. Kantam, *Tetrahedron*, 2006, **62**, 9571.
- 159 M. L. Kantam, T. Ramani, L. Chakrapani and K. V. Kumar, *Tetrahedron Lett.*, 2008, **49**, 1498.
- 160 Z. H. Xu, P. Daka, I. Budik, H. Wang, F. Q. Bai and H. X. Zhang, *Eur. J. Org. Chem.*, 2009, 4581.
- 161 Z. G. Xu, P. Daka and H. Wang, *Chem. Commun.*, 2009, 6825.
- 162 H. W. Zhao, H. L. Li, Y. Y. Yue, X. Qin, Z. H. Sheng, J. Cui, S. Su, X. Q. Song, H. Yan and R. G. Zhong, *Synlett*, 2012, 1990.
- 163 K. Tanaka, A. Asakura, T. Muraoka, P. Kalicki and Z. Urbanczyk-Lipkowska, *New J. Chem.*, 2013, **37**, 2851.
- 164 Q. Y. Zhang, X. L. Cui, L. Zhang, S. Z. Luo, H. Wang and Y. J. Wu, *Angew. Chem., Int. Ed.*, 2015, **54**, 5210.
- 165 B. M. Trost, S. Shin and J. A. Sclafani, *J. Am. Chem. Soc.*, 2005, **127**, 8602.
- 166 M. Mizuno, H. Inoue, T. Naito, L. Zhou and H. Nishiyama, *Chem. – Eur. J.*, 2009, **15**, 8985.
- 167 H. Maheswaran, P. J. A. Joseph, K. L. Prasanth, S. Priyadarshini, P. Satyanarayana, P. R. Likhar and M. L. Kantam, *Tetrahedron: Asymmetry*, 2010, **21**, 2158.
- 168 K. Maki, R. Motoki, K. Fujii, M. Kanai, T. Kobayashi, S. Tamura and M. Shibasaki, *J. Am. Chem. Soc.*, 2005, **127**, 17111.
- 169 K. Fujii, K. Maki, M. Kanai and M. Shibasaki, *Org. Lett.*, 2003, **5**, 733.
- 170 B. M. Trost, A. Fettes and B. T. Shireman, *J. Am. Chem. Soc.*, 2004, **126**, 2660.
- 171 B. M. Trost, M. U. Frederiksen, J. P. N. Papillon, P. E. Harrington, S. Shin and B. T. Shireman, *J. Am. Chem. Soc.*, 2005, **127**, 3666.
- 172 S. L. Shi, M. Kanai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 3932.
- 173 D. Sinha, A. Biswas and V. K. Singh, *Org. Lett.*, 2015, **17**, 3302.
- 174 A. V. Gulevich, A. G. Zhdanko, R. V. A. Orru and V. G. Nenajdenko, *Chem. Rev.*, 2010, **110**, 5235.
- 175 H. Mihara, Y. Xu, N. E. Shepherd, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 8384.
- 176 S. X. Wang, M. X. Wang, D. X. Wang and J. P. Zhu, *Org. Lett.*, 2007, **9**, 3615.
- 177 S. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Eur. J. Org. Chem.*, 2007, 4076.
- 178 Y. Ito, M. Sawamura and T. Hayashi, *J. Am. Chem. Soc.*, 1986, **108**, 6405.
- 179 M. Sawamura, Y. Ito and T. Hayashi, *Tetrahedron Lett.*, 1990, **31**, 2723.
- 180 Y. Ito, M. Sawamura and T. Hayashi, *Tetrahedron Lett.*, 1987, **28**, 6215.
- 181 T. Hayashi, M. Sawamura and Y. Ito, *Tetrahedron*, 1992, **48**, 1999.
- 182 Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 235.
- 183 Y. Ito, M. Sawamura, H. Hamashima, T. Emura and T. Hayashi, *Tetrahedron Lett.*, 1989, **30**, 4681.
- 184 V. A. Soloshonok and T. Hayashi, *Tetrahedron Lett.*, 1994, **35**, 2713.
- 185 V. A. Soloshonok and T. Hayashi, *Tetrahedron: Asymmetry*, 1994, **5**, 1091.

- 186 V. A. Soloshonok, A. D. Kacharov and T. Hayashi, *Tetrahedron*, 1996, **52**, 245.
- 187 Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki and T. Hayashi, *Tetrahedron*, 1988, **44**, 5253.
- 188 Y. Ito, M. Sawamura, M. Kobayashi and T. Hayashi, *Tetrahedron Lett.*, 1988, **29**, 6321.
- 189 M. Sawamura, Y. Ito and T. Hayashi, *Tetrahedron Lett.*, 1989, **30**, 2247.
- 190 M. Sawamura, Y. Nakayama, T. Kato and Y. Ito, *J. Org. Chem.*, 1995, **60**, 1727.
- 191 S. D. Pastor and A. Togni, *J. Am. Chem. Soc.*, 1989, **111**, 2333.
- 192 A. Togni and S. D. Pastor, *J. Org. Chem.*, 1990, **55**, 1649.
- 193 S. D. Pastor and A. Togni, *Tetrahedron Lett.*, 1990, **31**, 839.
- 194 A. Togni and R. Häusel, *Synlett*, 1990, 633.
- 195 S. D. Pastor and A. Togni, *Helv. Chim. Acta*, 1991, **74**, 905.
- 196 S. D. Pastor, R. Kesselring and A. Togni, *J. Organomet. Chem.*, 1992, **429**, 415.
- 197 M. Sawamura, H. Hamashima and Y. Ito, *J. Org. Chem.*, 1990, **55**, 5935.
- 198 T. Hayashi, Y. Uozumi, A. Yamazaki, M. Sawamura, H. Hamashima and Y. Ito, *Tetrahedron Lett.*, 1991, **32**, 2799.
- 199 F. Gorla, A. Togni, L. M. Venzani, A. Albinati and F. Lianza, *Organometallics*, 1994, **13**, 1607.
- 200 J. M. Longmire, X. M. Zhang and M. Y. Shang, *Organometallics*, 1998, **17**, 4374.
- 201 Y. Motoyama, H. Kawakami, K. Shimozone, K. Aoki and H. Nishiyama, *Organometallics*, 2002, **21**, 3408.
- 202 M. S. Yoon, R. Ramesh, J. Kim, D. Ryu and K. H. Ahn, *J. Organomet. Chem.*, 2006, **691**, 5927.
- 203 S. Gosiewska, S. Martinez Herreras, M. Lutz, A. L. Spek, R. W. A. Havenith, G. P. M. van Klink, G. van Koten and R. J. M. K. Gebbink, *Organometallics*, 2008, **27**, 2549.
- 204 H. Y. Kim and K. Oh, *Org. Lett.*, 2011, **13**, 1306.
- 205 F. Sladojevich, A. Trabocchi, A. Guarna and D. J. Dixon, *J. Am. Chem. Soc.*, 2011, **133**, 1710.
- 206 A. Franchino, P. Jakubec and D. J. Dixon, *Org. Biomol. Chem.*, 2016, **14**, 93.
- 207 R. de la Campa, I. Ortin and D. J. Dixon, *Angew. Chem., Int. Ed.*, 2015, **54**, 4895.
- 208 D. A. Evans and A. E. Weber, *J. Am. Chem. Soc.*, 1987, **109**, 7151.
- 209 M. C. Willis, G. A. Cutting, V. J. D. Piccio, M. J. Durbin and M. P. John, *Angew. Chem., Int. Ed.*, 2005, **44**, 1543.
- 210 T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 17082.
- 211 X. H. Chen, Y. Zhu, Z. Qiao, M. S. Xie, L. L. Lin, X. H. Liu and X. M. Feng, *Chem. – Eur. J.*, 2010, **16**, 10124.
- 212 S. Kato, M. Kanai and S. Matsunaga, *Chem. – Asian J.*, 2013, **8**, 1768.
- 213 S. Kato, T. Yoshino, M. Shibasaki, M. Kanai and S. Matsunaga, *Angew. Chem., Int. Ed.*, 2012, **51**, 7007.
- 214 X. H. Zhao, M. S. Xie, X. H. Liu, Y. L. Zhang, X. Xiao, L. L. Lin and X. M. Feng, *Adv. Synth. Catal.*, 2013, **355**, 3253.
- 215 N. Gathergood, K. Juhl, T. B. Poulsen, K. Thordrup and K. A. Jorgensen, *Org. Biomol. Chem.*, 2004, **2**, 1077.
- 216 I. Fukuchi, Y. Hamashima and M. Sodeoka, *Adv. Synth. Catal.*, 2007, **349**, 509.
- 217 N. Umebayashi, Y. Hamashima, D. Hashizume and M. Sodeoka, *Angew. Chem., Int. Ed.*, 2008, **47**, 4196.
- 218 S. Mouri, Z. H. Chen, S. Matsunaga and M. Shibasaki, *Chem. Commun.*, 2009, 5138.
- 219 S. Matsunaga and M. Shibasaki, *Synthesis*, 2013, 421.
- 220 M. P. Doyle, M. A. McKerver and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley, New York, 1998.
- 221 W. Yao and J. Wang, *Org. Lett.*, 2003, **5**, 1527.
- 222 H. Ishitani, M. Ueno and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, **122**, 8180.
- 223 W. Wang, K. Shen, X. Hu, J. Wang, X. Liu and X. Feng, *Synlett*, 2009, 1655.
- 224 B. M. Trost, S. Malhotra and B. A. Fried, *J. Am. Chem. Soc.*, 2009, **131**, 1674.
- 225 B. M. Trost, S. Malhotra, P. Koschker and P. Ellerbrock, *J. Am. Chem. Soc.*, 2012, **134**, 2075.
- 226 B. M. Trost, S. Malhotra and P. Ellerbrock, *Org. Lett.*, 2013, **15**, 440.
- 227 F. Benfatti, S. Yilmaz and P. G. Cozzi, *Adv. Synth. Catal.*, 2009, **351**, 1763.
- 228 F. Wang, X. H. Liu, Y. L. Zhang, L. L. Lin and X. M. Feng, *Chem. Commun.*, 2009, 7297.
- 229 M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911.
- 230 L. Ren, X. L. Lian and L. Z. Gong, *Chem. – Eur. J.*, 2013, **19**, 3315.
- 231 K. Shen, X. H. Liu, L. L. Lin and X. M. Feng, *Chem. Sci.*, 2012, **3**, 327.
- 232 K. Shen, X. H. Liu, K. Zheng, W. Li, X. L. Hu, L. L. Lin and X. M. Feng, *Chem. – Eur. J.*, 2010, **16**, 3736.
- 233 K. Shen, X. H. Liu, W. T. Wang, G. Wang, W. D. Cao, W. Li, X. L. Hu, L. L. Lin and X. M. Feng, *Chem. Sci.*, 2010, **1**, 590.
- 234 R. Kuwano, H. Miyazaki and Y. Ito, *Chem. Commun.*, 1998, 71.
- 235 R. Kuwano, H. Miyazaki and Y. Ito, *J. Organomet. Chem.*, 2000, **603**, 18.
- 236 N. Yoshikawa and M. Shibasaki, *Tetrahedron*, 2002, **58**, 8289.
- 237 S. Takechi, S. Yasuda, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 4218.
- 238 B. M. Trost and F. Miede, *J. Am. Chem. Soc.*, 2014, **136**, 3016.
- 239 D. A. Evans, C. W. Downey and J. L. Hubbs, *J. Am. Chem. Soc.*, 2003, **125**, 8706.
- 240 M. Iwata, R. Yazaki, Y. Suzuki, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 18244.
- 241 M. Iwata, R. Yazaki, N. Kumagai and M. Shibasaki, *Tetrahedron: Asymmetry*, 2010, **21**, 1688.
- 242 Y. Suzuki, M. Iwata, R. Yazaki, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2012, **77**, 4496.
- 243 M. Iwata, R. Yazaki, I. H. Chen, D. Sureshkumar, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2011, **133**, 5554.
- 244 Y. Kawato, M. Iwata, R. Yazaki, N. Kumagai and M. Shibasaki, *Tetrahedron*, 2011, **67**, 6539.

- 245 Y. Kawato, S. Chaudhary, N. Kumagai and M. Shibasaki, *Chem. – Eur. J.*, 2013, **19**, 3802.
- 246 A. Matsuzawa, C. R. Opie, N. Kumagai and M. Shibasaki, *Chem. – Eur. J.*, 2014, **20**, 68.
- 247 K. Alagiri, S. Q. Lin, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2014, **16**, 5301.
- 248 D. Sureshkumar, Y. Kawato, M. Iwata, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2012, **14**, 3108.
- 249 Y. M. Bao, N. Kumagai and M. Shibasaki, *Chem. Sci.*, 2015, **6**, 6124.
- 250 B. M. Trost, D. J. Michaelis and M. I. Truica, *Org. Lett.*, 2013, **15**, 4516.
- 251 B. M. Trost, W. M. Seganish, C. K. Chung and D. Amans, *Chem. – Eur. J.*, 2012, **18**, 2948.
- 252 K. Weidner, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2014, **53**, 6150.
- 253 K. Weidner, Z. D. Sun, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2015, **54**, 6236.
- 254 H. Noda, F. Amemiya, K. Weidner, N. Kumagai and M. Shibasaki, *Chem. Sci.*, 2017, **8**, 3260.
- 255 Z. Liu, T. Takeuchi, R. Pluta, F. A. Arteaga, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2017, **19**, 710.
- 256 A. Matsuzawa, H. Noda, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2017, **82**, 8304.
- 257 W. Tishchenko, *J. Russ. Phys.-Chem. Soc.*, 1906, **38**, 355.
- 258 J. Mlynarski, *Eur. J. Org. Chem.*, 2006, 4779.
- 259 M. Brauchbar and L. Kohn, *Monatsh. Chem.*, 1898, **19**, 16.
- 260 O. Loog and U. Maeorg, *Tetrahedron: Asymmetry*, 1999, **10**, 2411.
- 261 O. Loog and U. Maeorg, *Proc. Est. Acad. Sci. Chem.*, 1998, **47**, 193.
- 262 C. M. Mascarenhas, S. P. Miller, P. S. White and J. P. Morken, *Angew. Chem., Int. Ed.*, 2001, **40**, 601.
- 263 C. Schneider and M. Hansch, *Synlett*, 2003, 837.
- 264 C. Schneider and M. Hansch, *Chem. Commun.*, 2001, 1218.
- 265 I. Simpura and V. Nevalainen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3422.
- 266 C. Schneider, M. Hansch and P. Sreekumar, *Tetrahedron: Asymmetry*, 2006, **17**, 2738.
- 267 V. Gnanadesikan, Y. Horiuchi, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.*, 2004, **126**, 7782.
- 268 Y. Horiuchi, V. Gnanadesikan, T. Ohshima, H. Masu, K. Katagiri, Y. Sei, K. Yamaguchi and M. Shibasaki, *Chem. – Eur. J.*, 2005, **11**, 5195.
- 269 J. Mlynarski and M. Mitura, *Tetrahedron Lett.*, 2004, **45**, 7549.
- 270 J. Mlynarski, B. Rakiel, M. Stodulski, A. Suszczynska and J. Frelek, *Chem. – Eur. J.*, 2006, **12**, 8158.
- 271 J. Mlynarski, J. Jankowska and B. Rakiel, *Chem. Commun.*, 2005, 4854.
- 272 M. Stodulski, J. Jazwiński and J. Mlynarski, *Eur. J. Org. Chem.*, 2008, 5553.
- 273 M. Stodulski, A. Maminska and J. Mlynarski, *Tetrahedron: Asymmetry*, 2011, **22**, 464.
- 274 T. Ichibakase and M. Nakajima, *Synthesis*, 2012, 3145.
- 275 S. J. Taylor, M. O. Duffey and J. P. Morken, *J. Am. Chem. Soc.*, 2000, **122**, 4528.
- 276 A. E. Russell, N. O. Fuller, S. J. Taylor, P. Aurriset and J. P. Morken, *Org. Lett.*, 2004, **6**, 2309.
- 277 N. O. Fuller and J. P. Morken, *Synlett*, 2005, 1459.
- 278 C. X. Zhao, M. O. Duffey, S. J. Taylor and J. P. Morken, *Org. Lett.*, 2001, **3**, 1829.
- 279 H. Nishiyama, T. Shiomi, Y. Tsuchiya and I. Matsuda, *J. Am. Chem. Soc.*, 2005, **127**, 6972.
- 280 T. Shiomi, J. I. Ito, Y. Yamamoto and H. Nishiyama, *Eur. J. Org. Chem.*, 2006, 5594.
- 281 Y. F. Yang, T. Shi, X. H. Zhang, Z. X. Tang, Z. Y. Wen, J. M. Quan and Y. D. Wu, *Org. Biomol. Chem.*, 2011, **9**, 5845.
- 282 H. W. Lam and P. M. Joensuu, *Org. Lett.*, 2005, **7**, 4225.
- 283 D. B. Zhao, K. Oisaki, M. Kanai and M. Shibasaki, *Tetrahedron Lett.*, 2006, **47**, 1403.
- 284 K. Oisaki, Y. Suto, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 5644.
- 285 D. Zhao, K. Oisaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 14440.
- 286 J. Deschamp, O. Chuzel, J. Hannedouche and O. Riant, *Angew. Chem., Int. Ed.*, 2006, **45**, 1292.
- 287 O. Chuzel, J. Deschamp, C. Chausteur and O. Riant, *Org. Lett.*, 2006, **8**, 5943.
- 288 T. Shiomi and H. Nishiyama, *Org. Lett.*, 2007, **9**, 1651.
- 289 T. Hashimoto, T. Shiomi, J. I. Ito and H. Nishiyama, *Tetrahedron*, 2007, **63**, 12883.
- 290 C. Bee, S. B. Han, A. Hassan, H. Iida and M. J. Krische, *J. Am. Chem. Soc.*, 2008, **130**, 2746.
- 291 S. B. Han, A. Hassan and M. J. Krische, *Synthesis*, 2008, 2669.
- 292 B. H. Lipshutz, B. Amorelli and J. B. Unger, *J. Am. Chem. Soc.*, 2008, **130**, 14378.
- 293 B. H. Lipshutz, D. W. Chung and B. Rich, *Org. Lett.*, 2008, **10**, 3793.
- 294 M. Kato, H. Oki, K. Ogata and S. Fukuzawa, *Synlett*, 2009, 1299.
- 295 J. Deschamp, T. Hermant and O. Riant, *Tetrahedron*, 2012, **68**, 3457.
- 296 J. Deschamp and O. Riant, *Org. Lett.*, 2009, **11**, 1217.
- 297 J. Ou, W. T. Wong and P. Chiu, *Tetrahedron*, 2012, **68**, 3450.
- 298 J. Ou, W.-T. Wong and P. Chiu, *Org. Biomol. Chem.*, 2012, **10**, 5971.
- 299 R. Naasz, L. A. Arnold, M. Pineschi, E. Keller and B. L. Feringa, *J. Am. Chem. Soc.*, 1999, **121**, 1104.
- 300 K.-i. Yamada, T. Arai, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1998, **63**, 3666.
- 301 E. Keller, J. Maurer, R. Naasz, T. Schader, A. Meetsma and B. L. Feringa, *Tetrahedron: Asymmetry*, 1998, **9**, 2409.
- 302 B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620.
- 303 T. Arai, H. Sasai, K.-i. Aoe, K. Okamura, T. Date and M. Shibasaki, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 104.
- 304 Z. Galestokova and R. Sebesta, *Eur. J. Org. Chem.*, 2012, 6688.

- 305 S. W. Youn, *Eur. J. Org. Chem.*, 2009, 2597.
- 306 H. C. Guo and J. A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354.
- 307 A. R. Burns, J. S. Gonzalez and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, **51**, 10827.
- 308 P. Zhou, Y. Cai, L. Lin, X. Lian, Y. Xia, X. Liu and X. Feng, *Adv. Synth. Catal.*, 2015, **357**, 695.
- 309 K. Yoshida, M. Ogasawara and T. Hayashi, *J. Am. Chem. Soc.*, 2002, **124**, 10984.
- 310 S. Ubukata, J. Ito, R. Oguri and H. Nishiyama, *J. Org. Chem.*, 2016, **81**, 3347.
- 311 A. M. Hill, *Nat. Prod. Rep.*, 2006, **23**, 256.
- 312 G. Lalic, A. D. Aloise and M. D. Shair, *J. Am. Chem. Soc.*, 2003, **125**, 2852.
- 313 S. Orlandi, M. Benaglia and F. Cozzi, *Tetrahedron Lett.*, 2004, **45**, 1747.
- 314 D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise and M. D. Shair, *J. Am. Chem. Soc.*, 2005, **127**, 7284.
- 315 K. C. Fortner and M. D. Shair, *J. Am. Chem. Soc.*, 2007, **129**, 1032.
- 316 L. Yin, M. Kanai and M. Shibasaki, *Tetrahedron*, 2012, **68**, 3497.
- 317 Z. Duan, J. Han, P. Qian, Z. Zhang, Y. Wang and Y. Pan, *Org. Biomol. Chem.*, 2013, **11**, 6456.
- 318 Z. Duan, J. Han, P. Qian, Z. Zhang, Y. Wang and Y. Pan, *Beilstein J. Org. Chem.*, 2014, **10**, 969.
- 319 A. J. Wei, J. Nie, Y. Zheng and J. A. Ma, *J. Org. Chem.*, 2015, **80**, 3766.
- 320 H. Gao, Z. L. Luo, P. J. Ge, J. Q. He, F. Zhou, P. P. Zheng and J. Jiang, *Org. Lett.*, 2015, **17**, 5962.
- 321 C. Han, E. H. Kim and D. A. Colby, *J. Am. Chem. Soc.*, 2011, **133**, 5802.
- 322 P. Zhang and C. Wolf, *Angew. Chem., Int. Ed.*, 2013, **52**, 7869.
- 323 C. Xie, L. M. Wu, J. L. Han, V. A. Soloshonok and Y. Pan, *Angew. Chem., Int. Ed.*, 2015, **54**, 6019.
- 324 L. Zhang, C. Xie, Y. Dai, H. Mei, J. Han, V. A. Soloshonok and Y. Pan, *J. Fluorine Chem.*, 2016, **184**, 28.
- 325 W. X. Sha, L. J. Zhang, W. Z. Zhang, H. B. Mei, V. A. Soloshonok, J. L. Han and Y. Pan, *Org. Biomol. Chem.*, 2016, **14**, 7295.
- 326 L. J. Zhang, W. Z. Zhang, H. B. Mei, J. L. Han, V. A. Soloshonok and Y. Pan, *Org. Biomol. Chem.*, 2017, **15**, 311.
- 327 X. Zhang, H. Huang, X. Guo, X. Guan, L. Yang and W. Hu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6647.
- 328 C.-D. Lu, H. Liu, Z.-Y. Chen, W.-H. Hu and A.-Q. Mi, *Org. Lett.*, 2005, **7**, 83.
- 329 A. Yamaguchi, S. Matsunaga and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 10842.
- 330 A. Yanagisawa, N. Kushiara and K. Yoshida, *Org. Lett.*, 2011, **13**, 1576.
- 331 Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.
- 332 U. Eder, G. Sauer and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 496.
- 333 B. List, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 2395.
- 334 W. Notz and B. List, *J. Am. Chem. Soc.*, 2000, **122**, 7386.
- 335 B. List, P. Pojarliev and C. Castello, *Org. Lett.*, 2001, **3**, 573.
- 336 K. Sakthivel, W. Notz, T. Bui and C. F. Barbas, *J. Am. Chem. Soc.*, 2001, **123**, 5260.
- 337 R. Martínez, L. Berbegal, G. Guillena and D. J. Ramón, *Green Chem.*, 2016, **18**, 1724.
- 338 L. González, J. Escorihuela, B. Altava, M. I. Burguete and S. V. Luis, *Eur. J. Org. Chem.*, 2014, 5356.
- 339 Y. Qian, X. Zheng, X. Wang, S. Xiao and Y. Wang, *Chem. Lett.*, 2009, **38**, 576.
- 340 J. Shah, H. Blumenthal, Z. Yacob and J. Liebscher, *Adv. Synth. Catal.*, 2008, **350**, 1267.
- 341 S. Hu, T. Jiang, Z. Zhang, A. Zhu, B. Han, J. Song, Y. Xie and W. Li, *Tetrahedron Lett.*, 2007, **48**, 5613.
- 342 W. Miao and T. H. Chan, *Adv. Synth. Catal.*, 2006, **348**, 1711.
- 343 P. Kotrusz, I. Kmentová, B. Gotov, Š. Toma and E. Solcániová, *Chem. Commun.*, 2002, 2510.
- 344 M. Benaglia, M. Cinquini, F. Cozzi, A. Puglisi and G. Celentano, *Adv. Synth. Catal.*, 2002, **344**, 533.
- 345 M. Benaglia, G. Celentano and F. Cozzi, *Adv. Synth. Catal.*, 2001, **343**, 171.
- 346 Y. Hayashi, W. Tsuboi, M. Shoji and N. Suzuki, *Tetrahedron Lett.*, 2004, **45**, 4353.
- 347 Y. Sekiguchi, A. Sasaoka, A. Shimomoto, S. Fujioka and H. Kotsuki, *Synlett*, 2003, 1655.
- 348 A. Obregón-Zúñiga, M. Milán and E. Juaristi, *Org. Lett.*, 2017, **19**, 1108.
- 349 D. B. Ramachary and K. S. Shruthi, *J. Org. Chem.*, 2016, **81**, 2405.
- 350 E. Cho, H. Lee and T. H. Kim, *Bull. Korean Chem. Soc.*, 2015, **36**, 410.
- 351 N. El-Hamdouni, X. Companyó, R. Rios and A. Moyano, *Chem. – Eur. J.*, 2010, **16**, 1142.
- 352 A. S. Demir and S. Eymur, *Tetrahedron: Asymmetry*, 2010, **21**, 405.
- 353 M. Majewski, I. Niewczas and N. Palyam, *Synlett*, 2006, 2387.
- 354 Y. Zhou and Z. Shan, *Tetrahedron: Asymmetry*, 2006, **17**, 1671.
- 355 Y. Zhou and Z. Shan, *J. Org. Chem.*, 2006, **71**, 9510.
- 356 A. Bøgevig, N. Kumaragurubaran and K. Anker Jørgensen, *Chem. Commun.*, 2002, 620.
- 357 A. B. Northrup and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 6798.
- 358 A. B. Northrup and D. W. C. MacMillan, *Science*, 2004, **305**, 1752.
- 359 N. S. Chowdari, D. B. Ramachary, A. Córdova and C. F. Barbas, *Tetrahedron Lett.*, 2002, **43**, 9591.
- 360 M. Bergeron-Brlek, T. Teoh and R. Britton, *Org. Lett.*, 2013, **15**, 3554.
- 361 J. T. Suri, S. Mitsumori, K. Albertshofer, F. Tanaka and C. F. Barbas, *J. Org. Chem.*, 2006, **71**, 3822.
- 362 I. Ibrahim, W. Zou, Y. Xu and A. Córdova, *Adv. Synth. Catal.*, 2006, **348**, 211.
- 363 C. Grondal and D. Enders, *Tetrahedron*, 2006, **62**, 329.

- 364 D. Enders, J. Paleček and C. Grondal, *Chem. Commun.*, 2006, 655.
- 365 R. Thayumanavan, F. Tanaka and C. F. Barbas, *Org. Lett.*, 2004, **6**, 3541.
- 366 C. Pidathala, L. Hoang, N. Vignola and B. List, *Angew. Chem., Int. Ed.*, 2003, **42**, 2785.
- 367 I. Kumar, S. R. Bhide and C. V. Rode, *Tetrahedron: Asymmetry*, 2007, **18**, 1210.
- 368 D. Enders, O. Niemeier and L. Straver, *Synlett*, 2006, 3399.
- 369 N. Itagaki, M. Kimura, T. Sugahara and Y. Iwabuchi, *Org. Lett.*, 2005, **7**, 4185.
- 370 Z. Tang, F. Jiang, X. Cui, L. Z. Gong, A. Q. Mi, Y. Z. Jiang and Y. D. Wu, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5755.
- 371 Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang and Y.-D. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 5262.
- 372 D. Gryko, B. Kowalczyk and Ł. Zawadzki, *Synlett*, 2006, 1059.
- 373 C. Cheng, J. Sun, C. Wang, Y. Zhang, S. Wei, F. Jiang and Y. Wu, *Chem. Commun.*, 2006, 215.
- 374 J.-R. Chen, X.-Y. Li, X.-N. Xing and W.-J. Xiao, *J. Org. Chem.*, 2006, **71**, 8198.
- 375 Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2005, **127**, 9285.
- 376 S. Samanta, J. Liu, R. Dodda and C.-G. Zhao, *Org. Lett.*, 2005, **7**, 5321.
- 377 D. Gryko and R. Lipiński, *Adv. Synth. Catal.*, 2005, **347**, 1948.
- 378 J.-R. Chen, H.-H. Lu, X.-Y. Li, L. Cheng, J. Wan and W.-J. Xiao, *Org. Lett.*, 2005, **7**, 4543.
- 379 L. He, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Tetrahedron*, 2006, **62**, 346.
- 380 D. Gryko and R. Lipiński, *Eur. J. Org. Chem.*, 2006, 3864.
- 381 M. Raj, Vishnumaya, S. K. Ginotra and V. K. Singh, *Org. Lett.*, 2006, **8**, 4097.
- 382 R. Dodda and C.-G. Zhao, *Synlett*, 2007, 1605.
- 383 A. Russo, G. Botta and A. Lattanzi, *Synlett*, 2007, 0795.
- 384 A. Russo, G. Botta and A. Lattanzi, *Tetrahedron*, 2007, **63**, 11886.
- 385 J. Jiang, L. He, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *Chem. Commun.*, 2007, 736.
- 386 L. He, J. Jiang, Z. Tang, X. Cui, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Tetrahedron: Asymmetry*, 2007, **18**, 265.
- 387 V. D'Elia, H. Zwicknagl and O. Reiser, *J. Org. Chem.*, 2008, **73**, 3262.
- 388 J.-R. Chen, X.-L. An, X.-Y. Zhu, X.-F. Wang and W.-J. Xiao, *J. Org. Chem.*, 2008, **73**, 6006.
- 389 F. Chen, S. Huang, H. Zhang, F. Liu and Y. Peng, *Tetrahedron*, 2008, **64**, 9585.
- 390 X.-Y. Xu, Y.-Z. Wang, L.-F. Cun and L.-Z. Gong, *Tetrahedron: Asymmetry*, 2007, **18**, 237.
- 391 V. G. Lisnyak, A. S. Kucherenko, E. F. Valeev and S. G. Zlotin, *J. Org. Chem.*, 2015, **80**, 9570.
- 392 X. Han, Y. Wang, X. Gai and X. Zeng, *Synlett*, 2015, 2858.
- 393 A. Bisticha, I. Triandafillidi and C. G. Kokotos, *Tetrahedron: Asymmetry*, 2015, **26**, 102.
- 394 T. P. Kumar, N. C. Vavle, V. Patro and K. Haribabu, *Tetrahedron: Asymmetry*, 2014, **25**, 457.
- 395 G. Tang, Ü. Gün and H.-J. Altenbach, *Tetrahedron*, 2012, **68**, 10230.
- 396 A. J. Pearson and S. Panda, *Tetrahedron*, 2011, **67**, 3969.
- 397 A. J. Pearson and S. Panda, *Org. Lett.*, 2011, **13**, 5548.
- 398 H. Zhang, S. Zhang, L. Liu, G. Luo, W. Duan and W. Wang, *J. Org. Chem.*, 2010, **75**, 368.
- 399 Y. Yang, Y.-H. He, Z. Guan and W.-D. Huang, *Adv. Synth. Catal.*, 2010, **352**, 2579.
- 400 S. Saha and J. N. Moorthy, *Tetrahedron Lett.*, 2010, **51**, 912.
- 401 S. Doherty, J. G. Knight, A. McRae, R. W. Harrington and W. Clegg, *Eur. J. Org. Chem.*, 2008, 1759.
- 402 G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman and C. Tomasini, *J. Org. Chem.*, 2005, **70**, 7418.
- 403 T. P. Kumar, N. Manjula and K. Katragunta, *Tetrahedron: Asymmetry*, 2015, **26**, 1281.
- 404 Y. Lu, Y. Ma, S. Yang, M. Ma, H. Chu and C. Song, *Tetrahedron: Asymmetry*, 2013, **24**, 1082.
- 405 J.-R. Chen, X.-P. Liu, X.-Y. Zhu, L. Li, Y.-F. Qiao, J.-M. Zhang and W.-J. Xiao, *Tetrahedron*, 2007, **63**, 10437.
- 406 F. Wang, Y. Xiong, X. Liu and X. Feng, *Adv. Synth. Catal.*, 2007, **349**, 2665.
- 407 X.-Y. Xu, Z. Tang, Y.-Z. Wang, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *J. Org. Chem.*, 2007, **72**, 9905.
- 408 Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Org. Lett.*, 2006, **8**, 1263.
- 409 A. Berkessel, B. Koch and J. Lex, *Adv. Synth. Catal.*, 2004, **346**, 1141.
- 410 F. Secci, E. Cadoni, C. Fattuoni, A. Frongia, G. Bruno and F. Nicolò, *Tetrahedron*, 2012, **68**, 4773.
- 411 R. Rani and R. K. Peddinti, *Tetrahedron: Asymmetry*, 2010, **21**, 775.
- 412 E. Tsandi, C. G. Kokotos, S. Kousidou, V. Ragoussis and G. Kokotos, *Tetrahedron*, 2009, **65**, 1444.
- 413 H. Yang and R. G. Carter, *Org. Lett.*, 2008, **10**, 4649.
- 414 X.-J. Wang, Y. Zhao and J.-T. Liu, *Org. Lett.*, 2007, **9**, 1343.
- 415 E. Bellis, K. Vasilatou and G. Kokotos, *Synthesis*, 2005, 2407.
- 416 C. Worch and C. Bolm, *Synlett*, 2009, 2425.
- 417 M. T. Robak, M. A. Herbage and J. A. Ellman, *Tetrahedron*, 2011, **67**, 4412.
- 418 H. Torii, M. Nakadai, K. Ishihara, S. Saito and H. Yamamoto, *Angew. Chem., Int. Ed.*, 2004, **43**, 1983.
- 419 K. Funabiki, Y. Itoh, Y. Kubota and M. Matsui, *J. Org. Chem.*, 2011, **76**, 3545.
- 420 F. Xue, S. Zhang, L. Liu, W. Duan and W. Wang, *Chem. – Asian J.*, 2009, **4**, 1664.
- 421 A. Odedra and P. H. Seeberger, *Angew. Chem., Int. Ed.*, 2009, **48**, 2699.
- 422 S.-T. Tong, P. W. R. Harris, D. Barker and M. A. Brimble, *Eur. J. Org. Chem.*, 2008, 164.
- 423 A. Hartikka and P. I. Arvidsson, *Eur. J. Org. Chem.*, 2005, 4287.
- 424 A. Hartikka and P. I. Arvidsson, *Tetrahedron: Asymmetry*, 2004, **15**, 1831.

- 425 N. Mase, F. Tanaka and C. F. Barbas, *Angew. Chem., Int. Ed.*, 2004, **43**, 2420.
- 426 S. Luo, J. Li, H. Xu, L. Zhang and J.-P. Cheng, *Org. Lett.*, 2007, **9**, 3675.
- 427 Y. Hayashi, H. Sekizawa, J. Yamaguchi and H. Gotoh, *J. Org. Chem.*, 2007, **72**, 6493.
- 428 P. Dambruoso, A. Massi and A. Dondoni, *Org. Lett.*, 2005, **7**, 4657.
- 429 W. Wang, H. Li and J. Wang, *Tetrahedron Lett.*, 2005, **46**, 5077.
- 430 Y. Hayashi, T. Itoh, S. Aratake and H. Ishikawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 2082.
- 431 Y. Hayashi and M. Kojima, *ChemCatChem*, 2013, **5**, 2883.
- 432 Y. Hayashi, Y. Yasui, M. Kojima, T. Kawamura and H. Ishikawa, *Chem. Commun.*, 2012, **48**, 4570.
- 433 Y. Hayashi, Y. Yasui, T. Kawamura, M. Kojima and H. Ishikawa, *Synlett*, 2011, 485.
- 434 T. Urushima, Y. Yasui, H. Ishikawa and Y. Hayashi, *Org. Lett.*, 2010, **12**, 2966.
- 435 A. Lattanzi, *Chem. Commun.*, 2009, 1452.
- 436 T. Min, J. C. Fettinger and A. K. Franz, *ACS Catal.*, 2012, **2**, 1661.
- 437 A. Córdova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist and W.-W. Liao, *Chem. Commun.*, 2005, 3586.
- 438 A. Bassan, W. Zou, E. Reyes, F. Himo and A. Córdova, *Angew. Chem., Int. Ed.*, 2005, **44**, 7028.
- 439 A. Córdova, W. Zou, P. Dziedzic, I. Ibrahim, E. Reyes and Y. Xu, *Chem. – Eur. J.*, 2006, **12**, 5383.
- 440 W. Zou, I. Ibrahim, P. Dziedzic, H. Sundén and A. Córdova, *Chem. Commun.*, 2005, 4946.
- 441 S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2007, **129**, 288.
- 442 D. Sarkar, K. Harman, S. Ghosh and A. D. Headley, *Tetrahedron: Asymmetry*, 2011, **22**, 1051.
- 443 X. Wu, Z. Ma, Z. Ye, S. Qian and G. Zhao, *Adv. Synth. Catal.*, 2009, **351**, 158.
- 444 C.-S. Da, L.-P. Che, Q.-P. Guo, F.-C. Wu, M. Xiao and Y.-N. Jia, *J. Org. Chem.*, 2009, **74**, 2541.
- 445 M.-K. Zhu, X.-Y. Xu and L.-Z. Gong, *Adv. Synth. Catal.*, 2008, **350**, 1390.
- 446 S. S. V. Ramasastry, K. Albertshofer, N. Utsumi and C. F. Barbas, *Org. Lett.*, 2008, **10**, 1621.
- 447 X.-Y. Xu, Y.-Z. Wang and L.-Z. Gong, *Org. Lett.*, 2007, **9**, 4247.
- 448 J. Liu, Z. Yang, Z. Wang, F. Wang, X. Chen, X. Liu, X. Feng, Z. Su and C. Hu, *J. Am. Chem. Soc.*, 2008, **130**, 5654.
- 449 T. Kano, O. Tokuda, J. Takai and K. Maruoka, *Chem. – Asian J.*, 2006, **1**, 210.
- 450 T. Kano, O. Tokuda and K. Maruoka, *Tetrahedron Lett.*, 2006, **47**, 7423.
- 451 T. Kano, J. Takai, O. Tokuda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 3055.
- 452 T. Kano, Y. Yamaguchi and K. Maruoka, *Chem. – Eur. J.*, 2009, **15**, 6678.
- 453 T. Kano, Y. Yamaguchi, Y. Tanaka and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 1738.
- 454 T. Kano, A. Noishiki, R. Sakamoto and K. Maruoka, *Chem. Commun.*, 2011, **47**, 10626.
- 455 T. Kano, H. Maruyama, R. Sakamoto and K. Maruoka, *Chem. Commun.*, 2015, **51**, 10062.
- 456 T. Kano, H. Sugimoto and K. Maruoka, *J. Am. Chem. Soc.*, 2011, **133**, 18130.
- 457 I. K. Mangion, A. B. Northrup and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2004, **43**, 6722.
- 458 S. Luo, H. Xu, J. Li, L. Zhang and J.-P. Cheng, *J. Am. Chem. Soc.*, 2007, **129**, 3074.
- 459 Q. Zhang, X. Cui, L. Zhang, S. Luo, H. Wang and Y. Wu, *Angew. Chem., Int. Ed.*, 2015, **54**, 5210.
- 460 L. Li, S. Gou and F. Liu, *Tetrahedron: Asymmetry*, 2014, **25**, 193.
- 461 B. Xu, L. Li and S. Gou, *Tetrahedron: Asymmetry*, 2013, **24**, 1556.
- 462 L. Li, S. Gou and F. Liu, *Tetrahedron Lett.*, 2013, **54**, 6358.
- 463 Y. Liu, J. Wang, Q. Sun and R. Li, *Tetrahedron Lett.*, 2011, **52**, 3584.
- 464 J. Gao, S. Bai, Q. Gao, Y. Liu and Q. Yang, *Chem. Commun.*, 2011, **47**, 6716.
- 465 S. Luo, P. Zhou, J. Li and J.-P. Cheng, *Chem. – Eur. J.*, 2010, **16**, 4457.
- 466 S. Luo, Y. Qiao, L. Zhang, J. Li, X. Li and J.-P. Cheng, *J. Org. Chem.*, 2009, **74**, 9521.
- 467 S. Luo, H. Xu, L. Chen and J.-P. Cheng, *Org. Lett.*, 2008, **10**, 1775.
- 468 B.-L. Zheng, Q.-Z. Liu, C.-S. Guo, X.-L. Wang and L. He, *Org. Biomol. Chem.*, 2007, **5**, 2913.
- 469 H. Zong, H. Huang, G. Bian and L. Song, *J. Org. Chem.*, 2014, **79**, 11768.
- 470 P. Barrulas, M. Benaglia and A. J. Burke, *Tetrahedron: Asymmetry*, 2014, **25**, 923.
- 471 Q. Guo and J. C.-G. Zhao, *Tetrahedron Lett.*, 2012, **53**, 1768.
- 472 P. Czarnecki, A. Plutecka, J. Gawroński and K. Kacprzak, *Green Chem.*, 2011, **13**, 1280.
- 473 P. Li, J. Zhao, F. Li, A. S. C. Chan and F. Y. Kwong, *Org. Lett.*, 2010, **12**, 5616.
- 474 J. Paradowska, M. Rogozińska and J. Mlynarski, *Tetrahedron Lett.*, 2009, **50**, 1639.
- 475 J. Zhou, V. Wakchaure, P. Kraft and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 7656.
- 476 Q. Guo, M. Bhanushali and C.-G. Zhao, *Angew. Chem., Int. Ed.*, 2010, **49**, 9460.
- 477 S. Konda, Q.-S. Guo, M. Abe, H. Huang, H. Arman and J. C. G. Zhao, *J. Org. Chem.*, 2015, **80**, 806.
- 478 P. Wang, H.-F. Li, J.-Z. Zhao, Z.-H. Du and C.-S. Da, *Org. Lett.*, 2017, **19**, 2634.
- 479 N. Hara, S. Nakamura, Y. Funahashi and N. Shibata, *Adv. Synth. Catal.*, 2011, **353**, 2976.
- 480 J. Saadi and H. Wennemers, *Nat. Chem.*, 2016, **8**, 276.
- 481 H. Y. Bae, J. H. Sim, J.-W. Lee, B. List and C. E. Song, *Angew. Chem., Int. Ed.*, 2013, **52**, 12143.
- 482 T. March, A. Murata, Y. Kobayashi and Y. Takemoto, *Synlett*, 2017, 1295.

- 483 Z.-Y. Yang, J.-L. Zeng, N. Ren, W. Meng, J. Nie and J.-A. Ma, *Org. Lett.*, 2016, **18**, 6364.
- 484 Y. Zheng, H.-Y. Xiong, J. Nie, M.-Q. Hua and J.-A. Ma, *Chem. Commun.*, 2012, **48**, 4308.
- 485 G. B. Vamisetti, R. Chowdhury and S. K. Ghosh, *Org. Biomol. Chem.*, 2017, **15**, 3869.
- 486 C. W. Suh, C. W. Chang, K. W. Choi, Y. J. Lim and D. Y. Kim, *Tetrahedron Lett.*, 2013, **54**, 3651.
- 487 F. Zhong, W. Yao, X. Dou and Y. Lu, *Org. Lett.*, 2012, **14**, 4018.
- 488 I. Saidalimu, X. Fang, X.-P. He, J. Liang, X. Yang and F. Wu, *Angew. Chem., Int. Ed.*, 2013, **52**, 5566.
- 489 S. Meninno, T. Fuoco, C. Tedesco and A. Lattanzi, *Org. Lett.*, 2014, **16**, 4746.
- 490 H. Liu, H. Wu, Z. Luo, J. Shen, G. Kang, B. Liu, Z. Wan and J. Jiang, *Chem. – Eur. J.*, 2012, **18**, 11899.
- 491 M.-X. Xue, C. Guo and L.-Z. Gong, *Synlett*, 2009, 2191.
- 492 S. Sakamoto, N. Kazumi, Y. Kobayashi, C. Tsukano and Y. Takemoto, *Org. Lett.*, 2014, **16**, 4758.
- 493 F. Wang, J. Chen and Y. Huang, *Synlett*, 2017, 1300.
- 494 N. Lin, Y.-Q. Deng, Z.-W. Zhang, Q. Wang and G. Lu, *Tetrahedron: Asymmetry*, 2014, **25**, 650.
- 495 M.-X. Zhao, H. Zhou, W.-H. Tang, W.-S. Qu and M. Shi, *Adv. Synth. Catal.*, 2013, **355**, 1277.
- 496 X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328.
- 497 W.-B. Chen, Z.-J. Wu, J. Hu, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2011, **13**, 2472.
- 498 S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2007, **46**, 8666.
- 499 F. Pesciaoli, P. Righi, A. Mazzanti, C. Gianelli, M. Mancinelli, G. Bartoli and G. Bencivenni, *Adv. Synth. Catal.*, 2011, **353**, 2953.
- 500 X. Gao, J. Han and L. Wang, *Org. Chem. Front.*, 2016, **3**, 656.
- 501 S. De, M. K. Das, A. Roy and A. Bisai, *J. Org. Chem.*, 2016, **81**, 12258.
- 502 X.-L. Liu, Y.-H. Liao, Z.-J. Wu, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *J. Org. Chem.*, 2010, **75**, 4872.
- 503 T. Misaki, G. Takimoto and T. Sugimura, *J. Am. Chem. Soc.*, 2010, **132**, 6286.
- 504 Y. Zheng and L. Deng, *Chem. Sci.*, 2015, **6**, 6510.
- 505 J. Guang, Q. Guo and J. C.-G. Zhao, *Org. Lett.*, 2012, **14**, 3174.
- 506 M. A. Molenda, S. Baś and J. Mlynarski, *Eur. J. Org. Chem.*, 2016, 4394.
- 507 W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu and C. Li, *Chem. – Eur. J.*, 2014, **20**, 8545.
- 508 H. Echave, R. López and C. Palomo, *Angew. Chem., Int. Ed.*, 2016, **55**, 3364.
- 509 T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685.
- 510 T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 4542.
- 511 B. Ma, J. L. Parkinson and S. L. Castle, *Tetrahedron Lett.*, 2007, **48**, 2083.
- 512 S. Mettath, G. S. C. Srikanth, B. S. Dangerfield and S. L. Castle, *J. Org. Chem.*, 2004, **69**, 6489.
- 513 S. Shirakawa, K. Ota, S. J. Terao and K. Maruoka, *Org. Biomol. Chem.*, 2012, **10**, 5753.
- 514 G. Pousse, F. L. Cavelier, L. Humphreys, J. Rouden and J. Blanchet, *Org. Lett.*, 2010, **12**, 3582.
- 515 J. Das, F. Le Cavelier, J. Rouden and J. Blanchet, *Eur. J. Org. Chem.*, 2011, 6628.
- 516 H. D. Dakin, *J. Biol. Chem.*, 1909, **7**, 49.
- 517 J. Wagner, R. A. Lerner and C. F. Barbas, *Science*, 1995, **270**, 1797.
- 518 S. Kobayashi, S. Nagayama and T. Busujima, *Chem. Lett.*, 1999, 71.
- 519 S. Kobayashi, S. Nagayama and T. Busujima, *Tetrahedron*, 1999, **55**, 8739.
- 520 S. Kobayashi, Y. Mori, S. Nagayama and K. Manabe, *Green Chem.*, 1999, **1**, 175.
- 521 O. Meyerhof, K. Lohmann and P. Schuster, *Biochem. Z.*, 1936, **286**, 319.
- 522 O. Meyerhof, K. Lohmann and P. Schuster, *Biochem. Z.*, 1936, **286**, 301.
- 523 J. Jia, Y. Lindqvist, G. Schneider, U. Schörken and G. A. Sprenger, *Protein Sci.*, 1997, **6**, 119.
- 524 M. K. Dreyer and G. E. Schulz, *J. Mol. Biol.*, 1996, **259**, 458.
- 525 E. Busto, *ChemCatChem*, 2016, **8**, 2589.
- 526 G. M. Whitesides and C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 617.
- 527 R. C. Cadwell and G. F. Joyce, *Genome Res.*, 1992, **2**, 28.
- 528 W. P. Stemmer, *Proc. Natl. Acad. Sci. U. S. A.*, 1994, **91**, 10747.
- 529 S. Fong, T. D. Machajewski, C. C. Mak and C.-H. Wong, *Cell Chem. Biol.*, 2000, **7**, 873.
- 530 F. P. Seebeck and D. Hilvert, *J. Am. Chem. Soc.*, 2003, **125**, 10158.
- 531 J. Hao and A. Berry, *Protein Eng., Des. Sel.*, 2004, **17**, 689.
- 532 M. M. Heravi, V. Zadsirjan, M. Dehghani and N. Hosseintash, *Tetrahedron: Asymmetry*, 2017, **28**, 587.
- 533 C. L. Windle, M. Müller, A. Nelson and A. Berry, *Curr. Opin. Chem. Biol.*, 2014, **19**, 25.
- 534 A. Bolt, A. Berry and A. Nelson, *Arch. Biochem. Biophys.*, 2008, **474**, 318.
- 535 M. Schürmann and G. A. Sprenger, *J. Biol. Chem.*, 2001, **276**, 11055.
- 536 A. Szekrenyi, A. Soler, X. Garrabou, C. Guérard-Hélaine, T. Parella, J. Joglar, M. Lemaire, J. Bujons and P. Clapés, *Chem. – Eur. J.*, 2014, **20**, 12572.
- 537 J. A. Castillo, C. Guérard-Hélaine, M. Gutiérrez, X. Garrabou, M. Sancelme, M. Schürmann, T. Inoue, V. Hélaine, F. Charmantray, T. Gefflaut, L. Hecquet, J. Joglar, P. Clapés, G. A. Sprenger and M. Lemaire, *Adv. Synth. Catal.*, 2010, **352**, 1039.
- 538 A. Soler, M. L. Gutiérrez, J. Bujons, T. Parella, C. Minguillon, J. Joglar and P. Clapés, *Adv. Synth. Catal.*, 2015, **357**, 1787.
- 539 D. Güclü, A. Szekrenyi, X. Garrabou, M. Kickstein, S. Junker, P. Clapés and W.-D. Fessner, *ACS Catal.*, 2016, **6**, 1848.

- 540 R. Roldán, I. Sanchez-Moreno, T. Scheidt, V. Hélaine, M. Lemaire, T. Parella, P. Clapés, W.-D. Fessner and C. Guérard-Hélaine, *Chem. – Eur. J.*, 2017, **23**, 5005.
- 541 X. Garrabou, J. A. Castillo, C. Guérard-Hélaine, T. Parella, J. Joglar, M. Lemaire and P. Clapés, *Angew. Chem., Int. Ed.*, 2009, **48**, 5521.
- 542 A. Szekrenyi, X. Garrabou, T. Parella, J. Joglar, J. Bujons and P. Clapés, *Nat. Chem.*, 2015, **7**, 724.
- 543 C. Zeymer, R. Zschoche and D. Hilvert, *J. Am. Chem. Soc.*, 2017, **139**, 12541.
- 544 A. Tramontano, K. D. Janda and R. A. Lerner, *Science*, 1986, **234**, 1566.
- 545 S. J. Pollack, J. W. Jacobs and P. G. Schultz, *Science*, 1986, **234**, 1570.
- 546 J. Wagner, R. A. Lerner and C. F. Barbas, *Science*, 1995, **270**, 1797.
- 547 C. F. Barbas, A. Heine, G. Zhong, T. Hoffmann, S. Gramatikova, R. Björnstedt, B. List, J. Anderson, E. A. Stura, I. A. Wilson and R. A. Lerner, *Science*, 1997, **278**, 2085.
- 548 J.-L. Reymond and Y. Chen, *J. Org. Chem.*, 1995, **60**, 6970.
- 549 J.-L. Reymond and Y. Chen, *Tetrahedron Lett.*, 1995, **36**, 2575.
- 550 G. Zhong, R. A. Lerner and C. F. Barbas, *Angew. Chem., Int. Ed.*, 1999, **38**, 3738.
- 551 T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 1998, **120**, 2768.
- 552 B. List, D. Shabat, C. F. Barbas and R. A. Lerner, *Chem. – Eur. J.*, 1998, **4**, 881.
- 553 D. Shabat, B. List, R. A. Lerner and C. F. Barbas, *Tetrahedron Lett.*, 1999, **40**, 1437.
- 554 S. C. Sinha, C. F. Barbas and R. A. Lerner, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 14603.
- 555 X. Zhu, F. Tanaka, R. A. Lerner, C. F. Barbas III and I. A. Wilson, *J. Am. Chem. Soc.*, 2009, **131**, 18206.
- 556 J.-L. Reymond, *J. Mol. Catal. B: Enzym.*, 1998, **5**, 331.
- 557 K. Armacost and O. Acevedo, *J. Am. Chem. Soc.*, 2014, **136**, 147.
- 558 V. Maya, M. Raj and V. K. Singh, *Org. Lett.*, 2007, **9**, 2593.
- 559 A. Karlstrom, G. Zhong, C. Rader, N. A. Larsen, A. Heine, R. Fuller, B. List, F. Tanaka, I. A. Wilson, C. F. Barbas and R. A. Lerner, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 3878.
- 560 E. L. Mehler, M. Fuxreiter, I. Simon and E. B. Garcia-Moreno, *Proteins: Struct., Funct., Bioinf.*, 2002, **48**, 283.
- 561 F. Tanaka, R. A. Lerner and C. F. Barbas, *J. Am. Chem. Soc.*, 2000, **122**, 4835.
- 562 G. Zhong, T. Hoffmann, R. A. Lerner, S. Danishefsky and C. F. Barbas, *J. Am. Chem. Soc.*, 1997, **119**, 8131.
- 563 C. Agami, N. Platzer and H. Sevestre, *Bull. Soc. Chim. Fr.*, 1987, 358.
- 564 B. List, R. A. Lerner and C. F. Barbas, *Org. Lett.*, 1999, **1**, 59.
- 565 S. Seelan, A. K. Sinha, K. Kato and Y. Yokogawa, *Adv. Mater.*, 2006, **18**, 3001.
- 566 A. Wang, M. Wang, Q. Wang, F. Chen, F. Zhang, H. Li, Z. Zeng and T. Xie, *Bioresour. Technol.*, 2011, **102**, 469.
- 567 C. Li, X.-W. Feng, N. Wang, Y.-J. Zhou and X.-Q. Yu, *Green Chem.*, 2008, **10**, 616.
- 568 M. López-Iglesias, E. Busto, V. Gotor and V. Gotor-Fernández, *Adv. Synth. Catal.*, 2011, **353**, 2345.
- 569 C. Acharya, M. Mandal, T. Dutta, A. K. Ghosh and P. Jaisankar, *Tetrahedron Lett.*, 2016, **57**, 4382.
- 570 G.-Y. Zhang, Y.-L. Chen, H.-H. Li, Z. Guan and Y.-H. He, *SLAS Discovery*, 2017, **22**, 1162.
- 571 E. Montroni, S. P. Sanap, M. Lombardo, A. Quintavalla, C. Trombini and D. D. Dhavale, *Adv. Synth. Catal.*, 2011, **353**, 3234.
- 572 M. Amedjkouh, *Tetrahedron: Asymmetry*, 2005, **16**, 1411.
- 573 A. I. Nyberg, A. Usano and P. M. Pihko, *Synlett*, 2004, 1891.
- 574 J. Mlynarski and S. Bas, *Chem. Soc. Rev.*, 2014, **43**, 577.
- 575 B. M. Trost and C. S. Brindle, *Chem. Soc. Rev.*, 2010, **39**, 1600.
- 576 K. Sakthivel, W. Notz, T. Bui and C. F. Barbas, *J. Am. Chem. Soc.*, 2001, **123**, 5260.
- 577 Example on β -aminosulfonamide for asymmetric aldol reaction in water: J. Paradowska, M. Pasternak, B. Gut, B. Gryzlo and J. Mlynarski, *J. Org. Chem.*, 2012, **77**, 173.
- 578 G. Guillena, M. d. C. Hita and C. Nájera, *Tetrahedron: Asymmetry*, 2006, **17**, 1027.
- 579 S. S. V. Ramasastry, H. Zhang, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2007, **129**, 288.
- 580 O. Popik, M. Pasternak-Suder, K. Leśniak, M. Jawiczuk, M. Górecki, J. Frelek and J. Mlynarski, *J. Org. Chem.*, 2014, **79**, 5728.
- 581 R. L. Sutar and N. N. Joshi, *Synth. Commun.*, 2014, **44**, 352.
- 582 M. Raj, G. S. Parashari and V. K. Singh, *Adv. Synth. Catal.*, 2009, **351**, 1284.
- 583 Z. Tang, Z.-H. Yang, L.-F. Cun, L.-Z. Gong, A.-Q. Mi and Y.-Z. Jiang, *Org. Lett.*, 2004, **6**, 2285.
- 584 X.-H. Chen, S.-W. Luo, Z. Tang, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang and L.-Z. Gong, *Chem. – Eur. J.*, 2007, **13**, 689.
- 585 X. Wu, Z. Jiang, H.-M. Shen and Y. Lu, *Adv. Synth. Catal.*, 2007, **349**, 812.
- 586 A. Kumar, S. Singh, V. Kumar and S. Singh Chimni, *Org. Biomol. Chem.*, 2011, **9**, 2731.
- 587 S. S. V. Ramasastry, K. Albertshofer, N. Utsumi and C. F. Barbas, *Org. Lett.*, 2008, **10**, 1621.
- 588 Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 958.
- 589 N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas, *J. Am. Chem. Soc.*, 2006, **128**, 734.
- 590 J.-F. Zhao, L. He, J. Jiang, Z. Tang, L.-F. Cun and L.-Z. Gong, *Tetrahedron Lett.*, 2008, **49**, 3372.
- 591 M. Heidlindemann, A. Berkessel and H. Gröger, *ChemCatChem*, 2017, **9**, 1383.
- 592 X.-M. Hu, D.-X. Zhang, S.-Y. Zhang and P.-A. Wang, *RSC Adv.*, 2015, **5**, 39557.
- 593 F. Giacalone, M. Gruttadauria, P. L. Meo, S. Riela and R. Noto, *Adv. Synth. Catal.*, 2008, **350**, 2747.
- 594 Y.-J. An, Y.-X. Zhang, Y. Wu, Z.-M. Liu, C. Pi and J.-C. Tao, *Tetrahedron: Asymmetry*, 2010, **21**, 688.

- 595 T. Miura, M. Ina, K. Imai, K. Nakashima, Y. Yasaku, N. Koyata, Y. Murakami, N. Imai, N. Tada and A. Itoh, *Tetrahedron: Asymmetry*, 2011, **22**, 1028.
- 596 L. Zu, H. Xie, H. Li, J. Wang and W. Wang, *Org. Lett.*, 2008, **10**, 1211.
- 597 D. Gryko and W. J. Saletta, *Org. Biomol. Chem.*, 2007, **5**, 2148.
- 598 D. Almaşi, D. A. Alonso, A.-N. Balaguer and C. Nájera, *Adv. Synth. Catal.*, 2009, **351**, 1123.
- 599 M. R. Vishnumaya and V. K. Singh, *J. Org. Chem.*, 2009, **74**, 4289.
- 600 A. Patti and S. Pedotti, *Eur. J. Org. Chem.*, 2014, 624.
- 601 S. Pedatella, M. De Nisco, D. Mastroianni, D. Naviglio, A. Nucci and R. Caputo, *Adv. Synth. Catal.*, 2011, **353**, 1443.
- 602 Y.-C. Teo, *Tetrahedron: Asymmetry*, 2007, **18**, 1155.
- 603 Z. Jiang, H. Yang, X. Han, J. Luo, M. W. Wong and Y. Lu, *Org. Biomol. Chem.*, 2010, **8**, 1368.
- 604 C. Wu, X. Fu and S. Li, *Eur. J. Org. Chem.*, 2011, 1291.
- 605 M. Mridha, G. Ma, C. Palo-Nieto, S. Afewerki and A. Cordova, *Synthesis*, 2017, 383.
- 606 T. C. Nugent, M. N. Umar and A. Bibi, *Org. Biomol. Chem.*, 2010, **8**, 4085.
- 607 J. Paradowska, M. Pasternak, B. Gut, B. Gryzłó and J. Mlynarski, *J. Org. Chem.*, 2012, **77**, 173.
- 608 X. Song, A.-X. Liu, S.-S. Liu, W.-C. Gao, M.-C. Wang and J. Chang, *Tetrahedron*, 2014, **70**, 1464.
- 609 D. Deng, P. Liu, B. Ji, W. Fu and L. Li, *Catal. Lett.*, 2010, **137**, 163.
- 610 Y.-N. Jia, F.-C. Wu, X. Ma, G.-J. Zhu and C.-S. Da, *Tetrahedron Lett.*, 2009, **50**, 3059.
- 611 B. Wang, X.-w. Liu, L.-y. Liu, W.-x. Chang and J. Li, *Eur. J. Org. Chem.*, 2010, 5951.
- 612 Y. Hayashi, S. Aratake, T. Okano, J. Takahashi, T. Sumiya and M. Shoji, *Angew. Chem., Int. Ed.*, 2006, **45**, 5527.
- 613 Y. Qiao, Q. Chen, S. Lin, B. Ni and A. D. Headley, *J. Org. Chem.*, 2013, **78**, 2693.
- 614 M. Markert, U. Scheffler and R. Mahrwald, *J. Am. Chem. Soc.*, 2009, **131**, 16642.
- 615 G. Angelici, R. J. Corrêa, S. J. Garden and C. Tomasini, *Tetrahedron Lett.*, 2009, **50**, 814.
- 616 A. Kumar and S. S. Chimni, *Tetrahedron*, 2013, **69**, 5197.
- 617 Y. Liu, P. Gao, J. Wang, Q. Sun, Z. Ge and R. Li, *Synlett*, 2012, 1031.
- 618 M. Raj, N. Veerasamy and V. K. Singh, *Tetrahedron Lett.*, 2010, **51**, 2157.
- 619 H. Zhao, W. Meng, Z. Yang, T. Tian, Z. Sheng, H. Li, X. Song, Y. Zhang, S. Yang and B. Li, *Chin. J. Chem.*, 2014, **32**, 417.
- 620 J.-M. Vincent, C. Margottin, M. Berlande, D. Cavagnat, T. Buffeteau and Y. Landais, *Chem. Commun.*, 2007, 4782.
- 621 B. Zhang, Z. Jiang, X. Zhou, S. Lu, J. Li, Y. Liu and C. Li, *Angew. Chem., Int. Ed.*, 2012, **51**, 13159.
- 622 K. Akagawa, S. Sakamoto and K. Kudo, *Tetrahedron Lett.*, 2005, **46**, 8185.
- 623 M. Bartók, *Catal. Rev.*, 2015, **57**, 192.
- 624 D. Font, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2006, **8**, 4653.
- 625 S. Paladhi, J. Das, P. K. Mishra and J. Dash, *Adv. Synth. Catal.*, 2013, **355**, 274.
- 626 M. Gruttadauria, F. Giacalone, A. M. Marculescu and R. Noto, *Adv. Synth. Catal.*, 2008, **350**, 1397.
- 627 M. Gruttadauria, F. Giacalone, A. Mossuto Marculescu, P. Lo Meo, S. Riela and R. Noto, *Eur. J. Org. Chem.*, 2007, 4688.
- 628 F. Giacalone, M. Gruttadauria, A. M. Marculescu and R. Noto, *Tetrahedron Lett.*, 2007, **48**, 255.
- 629 E. Huerta, P. J. M. Stals, E. W. Meijer and A. R. A. Palmans, *Angew. Chem., Int. Ed.*, 2013, **52**, 2906.
- 630 A. Monge-Marcet, X. Cattoën, D. A. Alonso, C. Nájera, M. W. C. Man and R. Pleixats, *Green Chem.*, 2012, **14**, 1601.
- 631 Y. Kong, R. Tan, L. Zhao and D. Yin, *Green Chem.*, 2013, **15**, 2422.
- 632 Z. An, Y. Guo, L. Zhao, Z. Li and J. He, *ACS Catal.*, 2014, **4**, 2566.
- 633 J. Gao, J. Liu, S. Bai, P. Wang, H. Zhong, Q. Yang and C. Li, *J. Mater. Chem.*, 2009, **19**, 8580.
- 634 J. Gao, J. Liu, J. Tang, D. Jiang, B. Li and Q. Yang, *Chem. – Eur. J.*, 2010, **16**, 7852.
- 635 J. Huang, X. Zhang and D. W. Armstrong, *Angew. Chem., Int. Ed.*, 2007, **46**, 9073.
- 636 J. Deng and J. Deng, *Polymer*, 2017, **125**, 200.
- 637 W. Zhao, C. Qu, L. Yang and Y. Cui, *Chin. J. Catal.*, 2015, **36**, 367.
- 638 C. Gioia, A. Ricci, L. Bernardi, K. Bourahla, N. Tanchoux, M. Robitzer and F. Quignard, *Eur. J. Org. Chem.*, 2013, 588.
- 639 A. Ricci, L. Bernardi, C. Gioia, S. Vierucci, M. Robitzer and F. Quignard, *Chem. Commun.*, 2010, **46**, 6288.
- 640 L. Lan, G. Xie, T. Wu, D. Feng and X. Ma, *RSC Adv.*, 2016, **6**, 55894.
- 641 M. Angeloni, O. Piermatti, F. Pizzo and L. Vaccaro, *Eur. J. Org. Chem.*, 2014, 1716.
- 642 M. Sadiq, R. Aman, K. Saeed, M. S. Ahmad and M. A. Zia, *Mod. Res. Catal.*, 2015, **4**, 43.
- 643 D. De, A. Bhattacharyya and P. K. Bharadwaj, *Inorg. Chem.*, 2017, **56**, 11443.
- 644 K. S. Lee and J. R. Parquette, *Chem. Commun.*, 2015, **51**, 15653.
- 645 L. Qin, L. Zhang, Q. Jin, J. Zhang, B. Han and M. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 7761.
- 646 C.-M. Lo and H.-F. Chow, *J. Org. Chem.*, 2009, **74**, 5181.
- 647 H. A. Zayas, A. Lu, D. Valade, F. Amir, Z. Jia, R. K. O'Reilly and M. J. Monteiro, *ACS Macro Lett.*, 2013, **2**, 327.
- 648 S. Cantekin, T. F. A. de Greef and A. R. A. Palmans, *Chem. Soc. Rev.*, 2012, **41**, 6125.
- 649 L. N. Neumann, M. B. Baker, C. M. A. Leenders, I. K. Voets, R. P. M. Lafleur, A. R. A. Palmans and E. W. Meijer, *Org. Biomol. Chem.*, 2015, **13**, 7711.
- 650 E. Huerta, B. van Genabeek, B. A. G. Lamers, M. M. E. Koenigs, E. W. Meijer and A. R. A. Palmans, *Chem. – Eur. J.*, 2015, **21**, 3682.
- 651 B. H. Lipshutz and S. Ghorai, *Org. Lett.*, 2012, **14**, 422.

- 652 T. Darbre and M. Machuqueiro, *Chem. Commun.*, 2003, 1090.
- 653 The metal complexes formed with amino acid esters were used for direct-type aldol reaction in 1985 for the first time, albeit in an almost racemic manner: M. Nakagawa, H. Nakao and K. Watanabe, *Chem. Lett.*, 1985, 391.
- 654 J. Kofoed, T. Darbre and J.-L. Reymond, *Chem. Commun.*, 2006, 1482.
- 655 R. Fernandez-Lopez, J. Kofoed, M. Machuqueiro and T. Darbre, *Eur. J. Org. Chem.*, 2005, 5268.
- 656 M. Penhoat, D. Barbry and C. Rolando, *Tetrahedron Lett.*, 2011, 52, 159.
- 657 J. Kofoed, M. Machuqueiro, J.-L. Reymond and T. Darbre, *Chem. Commun.*, 2004, 1540.
- 658 J. Paradowska, M. Stodulski and J. Mlynarski, *Adv. Synth. Catal.*, 2007, 349, 1041.
- 659 Z. Lu, H. Mei, G. Zhang, J. Han and Y. Pan, *Sci. China: Chem.*, 2010, 53, 2291.
- 660 S. Itoh, M. Kitamura, Y. Yamada and S. Aoki, *Chem. – Eur. J.*, 2009, 15, 10570.
- 661 G. Chen, X. Fu, C. Li, C. Wu and Q. Miao, *J. Organomet. Chem.*, 2012, 702, 19.
- 662 A. M. Pieczonka, S. Jarzyński, Z. Wujkowska, S. Leśniak and M. Rachwalski, *Tetrahedron Lett.*, 2015, 56, 6506.
- 663 A. M. Pieczonka, S. Leśniak and M. Rachwalski, *Tetrahedron Lett.*, 2014, 55, 2373.
- 664 D. Wiedenhoeft, A. R. Benoit, Y. Wu, J. D. Porter, E. Meyle, T. H. W. Yeung, R. Huff, S. V. Lindeman and C. Dockendorff, *Tetrahedron*, 2016, 72, 3905.
- 665 D. Wiedenhoeft, A. R. Benoit, J. D. Porter, Y. Wu, R. S. Viridi, A. Shanaa and C. Dockendorff, *Synthesis*, 2016, 2413.
- 666 E. Shah and H. P. Soni, *RSC Adv.*, 2013, 3, 17453.
- 667 Z. Wujkowska, A. Strojewska, A. M. Pieczonka, S. Leśniak and M. Rachwalski, *Chirality*, 2017, 29, 213.
- 668 T. Zhang, Y. Zhang, Z. Li, Z. Song, H. Liu and J. Tao, *Chin. J. Chem.*, 2013, 31, 247.
- 669 S. Alkan, F. Ç. Telli, Y. Salman and S. T. Astley, *Carbohydr. Res.*, 2015, 407, 97.
- 670 G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha and Z. Wang, *Chem. – Eur. J.*, 2011, 17, 1114.
- 671 Y. Zhou, G. Yang, C. Lu, J. Nie, Z. Chen and J. Ren, *Catal. Commun.*, 2016, 75, 23.
- 672 P. Daka, Z. Xu, A. Alexa and H. Wang, *Chem. Commun.*, 2011, 47, 224.
- 673 S. Kobayashi, M. Kokubo, K. Kawasumi and T. Nagano, *Chem. – Asian J.*, 2010, 5, 490.
- 674 S. Kobayashi and C. Ogawa, *Asymmetric Synthesis: The Essentials*, Wiley, 2007.
- 675 S. Meninno and A. Lattanzi, *Chem. Rec.*, 2016, 16, 2016.
- 676 T. Kitanosono and S. Kobayashi, *Chem. – Asian J.*, 2015, 10, 133.
- 677 T. Kitanosono and S. Kobayashi, *Adv. Synth. Catal.*, 2013, 355, 3095.
- 678 S. Kobayashi and C. Ogawa, *Chem. – Eur. J.*, 2006, 12, 5954.
- 679 S. Kobayashi, *Lanthanides: Chemistry and Use in Organic Synthesis*, Springer, Berlin, Heidelberg, 2003.
- 680 S. Kobayashi, M. Sugiura, H. Kitagawa and W. W. L. Lam, *Chem. Rev.*, 2002, 102, 2227.
- 681 S. Kobayashi, *Eur. J. Org. Chem.*, 1999, 15.
- 682 S. Kobayashi, *Synlett*, 1994, 689.
- 683 S. Kobayashi, *Chem. Lett.*, 1991, 2187.
- 684 S. Kobayashi, I. Hachiya and Y. Yamanoi, *Bull. Chem. Soc. Jpn.*, 1994, 67, 2342.
- 685 S. Kobayashi, I. Hachiya, M. Araki and H. Ishitani, *Tetrahedron Lett.*, 1993, 34, 3755.
- 686 S. Kobayashi, S. Nagayama and T. Busujima, *J. Am. Chem. Soc.*, 1998, 120, 8287.
- 687 K. B. Yatsimirskii, *Instability Constants of Complex Compounds*, Springer US, 2012.
- 688 C. F. Baes and R. E. Mesmer, *The Hydrolysis of Cations*, R.E. Krieger, 1986.
- 689 A. E. Martell, *Coordination Chemistry*, Van Nostrand Reinhold Company, 1971.
- 690 R. G. Pearson, *J. Am. Chem. Soc.*, 1985, 107, 6801.
- 691 D. A. Evans, S. J. Miller, T. Lectka and P. von Matt, *J. Am. Chem. Soc.*, 1999, 121, 7559.
- 692 D. A. Evans, E. J. Olhava, J. S. Johnson and J. M. Janey, *Angew. Chem., Int. Ed.*, 1998, 37, 3372.
- 693 S. Kobayashi, S. Nagayama and T. Busujima, *Chem. Lett.*, 1999, 71.
- 694 R. Shannon, *Acta Crystallogr., Sect. A: Cryst. Phys., Diffraction, Theor. Gen. Crystallogr.*, 1976, 32, 751.
- 695 R. D. Shannon and C. T. Prewitt, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1969, 25, 925.
- 696 E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore and D. J. Cram, *J. Am. Chem. Soc.*, 1977, 99, 2564.
- 697 E. P. Kyba, G. W. Gokel, F. De Jong, K. Koga, L. R. Sousa, M. G. Siegel, L. Kaplan, G. D. Y. Sogah and D. J. Cram, *J. Org. Chem.*, 1977, 42, 4173.
- 698 Ionic diameter of Pb^{2+} (CN = 8) is 258 pm (see ref. 695) and the hole size of 18-crown-6 was reported to be 260–320 pm.
- 699 S. Kobayashi, T. Hamada, S. Nagayama and K. Manabe, *J. Braz. Chem. Soc.*, 2001, 12, 627.
- 700 S. Nagayama and S. Kobayashi, *J. Am. Chem. Soc.*, 2000, 122, 11531.
- 701 H.-J. Li, H.-Y. Tian, Y.-J. Chen, D. Wang and C.-J. Li, *Chem. Commun.*, 2002, 2994.
- 702 H.-J. Li, H.-Y. Tian, Y.-C. Wu, Y.-J. Chen, L. Liu, D. Wang and C.-J. Li, *Adv. Synth. Catal.*, 2005, 347, 1247.
- 703 B.-Y. Yang, X.-M. Chen, G.-J. Deng, Y.-L. Zhang and Q.-H. Fan, *Tetrahedron Lett.*, 2003, 44, 3535.
- 704 J. Morrison, *Asymmetric Synthesis*, Elsevier Science, 2012.
- 705 T. Hamada, K. Manabe, S. Ishikawa, S. Nagayama, M. Shiro and S. Kobayashi, *J. Am. Chem. Soc.*, 2003, 125, 2989.
- 706 S. Kobayashi, T. Hamada, S. Nagayama and K. Manabe, *Org. Lett.*, 2001, 3, 165.
- 707 O. Muñoz-Muñoz, M. Quintanar-Audelo and E. Juaristi, *J. Org. Chem.*, 2003, 68, 1622.
- 708 J. Jankowska and J. Mlynarski, *J. Org. Chem.*, 2006, 71, 1317.
- 709 J. Mlynarski and J. Jankowska, *Adv. Synth. Catal.*, 2005, 347, 521.

- 710 J. Jankowska, J. Paradowska and J. Mlynarski, *Tetrahedron Lett.*, 2006, **47**, 5281.
- 711 J. Mlynarski and J. Paradowska, *Chem. Soc. Rev.*, 2008, **37**, 1502.
- 712 J. Jankowska, J. Paradowska, B. Rakiel and J. Mlynarski, *J. Org. Chem.*, 2007, **72**, 2228.
- 713 Y. Mei, D. J. Averill and M. J. Allen, *J. Org. Chem.*, 2012, **77**, 5624.
- 714 Y. Mei, P. Dissanayake and M. J. Allen, *J. Am. Chem. Soc.*, 2010, **132**, 12871.
- 715 P. Dissanayake and M. J. Allen, *J. Am. Chem. Soc.*, 2009, **131**, 6342.
- 716 M. J. Allen, *Synlett*, 2016, 1310.
- 717 D. J. Averill and M. J. Allen, *Catal. Sci. Technol.*, 2014, **4**, 4129.
- 718 D. J. Averill, P. Dissanayake and M. J. Allen, *Molecules*, 2012, **17**, 2073.
- 719 S. Kobayashi and I. Hachiya, *J. Org. Chem.*, 1994, **59**, 3590.
- 720 C. Bolm, M. Ewald, M. Felder and G. Schlingloff, *Chem. Ber.*, 1992, **125**, 1169.
- 721 C. Bolm, M. Zehnder and D. Bur, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 205.
- 722 T. Ollevier and B. Plancq, *Chem. Commun.*, 2012, **48**, 2289.
- 723 B. Plancq and T. Ollevier, *Chem. Commun.*, 2012, **48**, 3806.
- 724 T. Kitanosono and S. Kobayashi, *Chem. Rec.*, 2014, **14**, 130.
- 725 T. Kitanosono, T. Ollevier and S. Kobayashi, *Chem. – Asian J.*, 2013, **8**, 3051.
- 726 M. Lafantaisie, A. Mirabaud, B. Plancq and T. Ollevier, *ChemCatChem*, 2014, **6**, 2244.
- 727 W. M. C. Sameera, M. Hatanaka, T. Kitanosono, S. Kobayashi and K. Morokuma, *J. Am. Chem. Soc.*, 2015, **137**, 11085.
- 728 M. Hatanaka and K. Morokuma, *J. Am. Chem. Soc.*, 2013, **135**, 13972.
- 729 M. Hatanaka, S. Maeda and K. Morokuma, *J. Chem. Theory Comput.*, 2013, **9**, 2882.
- 730 K. Manabe, S. Ishikawa, T. Hamada and S. Kobayashi, *Tetrahedron*, 2003, **59**, 10439.
- 731 N. Ozasa, M. Wadamoto, K. Ishihara and H. Yamamoto, *Synlett*, 2003, 2219.
- 732 S. Ishikawa, T. Hamada, K. Manabe and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 12236.
- 733 C. Mukherjee, T. Kitanosono and S. Kobayashi, *Chem. – Asian J.*, 2011, **6**, 2308.
- 734 S. Kobayashi, M. Ueno and T. Kitanosono, *Top. Curr. Chem.*, 2012, **311**, 1.
- 735 S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada and K. Manabe, *Org. Lett.*, 2005, **7**, 4729.
- 736 S. Répichet, A. Zwick, L. Vendier, C. Le Roux and J. Dubac, *Tetrahedron Lett.*, 2002, **43**, 993.
- 737 M. Kokubo, C. Ogawa and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2008, **47**, 6909.
- 738 H. J. Li, H. Y. Tian, Y. J. Chen, D. Wang and C. J. Li, *J. Chem. Res.*, 2003, 153.
- 739 K. Otsuka and S. Terabe, *J. Chromatogr. A*, 2000, **875**, 163.
- 740 P. Camilleri, *Electrophoresis*, 1997, **18**, 2322.
- 741 M. Benaglia, M. Cinquini, F. Cozzi and G. Celentano, *Org. Biomol. Chem.*, 2004, **2**, 3401.
- 742 Y. Gu, C. Ogawa, J. Kobayashi, Y. Mori and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 7217.
- 743 Q. Jin, L. Zhang, H. Cao, T. Wang, X. Zhu, J. Jiang and M. Liu, *Langmuir*, 2011, **27**, 13847.
- 744 J. Jiang, Y. Meng, L. Zhang and M. Liu, *J. Am. Chem. Soc.*, 2016, **138**, 15629.
- 745 S. Kobayashi, *Chem. – Asian J.*, 2016, **11**, 425.