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The state of the art in asymmetric induction: the aldol reaction as a case study

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ABSTRACT

This review highlights the achievements in asymmetric induction in the context of the aldol reaction during the years 2003–2007. While chiral auxiliary-mediated methods are the best understood and developed, catalytic methods based on chiral metal–ligand complexes and more recently organocatalysts promise to improve the efficacy and economics of asymmetric induction. This review provides a brief summary of work prior to 2003 on chiral auxiliaries, metal catalysts and organocatalysts, and then delineates the state of the art in each process. It appears that no one method of achieving asymmetric induction in the aldol reaction is universally superior.

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1. Introduction

Carbon–carbon bond formation is fundamental to organic chemistry. This review focuses on asymmetric carbon–carbon bond formation, and on the construction of the skeletal framework of organic molecules. The aldol reaction is one of the best-known and most widely used methods for generating carbon–carbon bonds with stereocontrol, and we have chosen to focus on this reaction as a means of evaluating the state of the art in asymmetric induction in general. We do not undervalue the importance of functionalization reactions; indeed the 2001 Nobel Prize in Chemistry was awarded to innovators in asymmetric functionalization of organic molecules for their work on catalyzed asymmetric oxidation and reduction reactions.[1–3] Moreover, several excellent recent reviews have dealt with various aspects of asymmetric functionalization reactions.[4–8]

Much work has been devoted to developing efficient methods to induce asymmetry in achiral molecules, and tremendous progress

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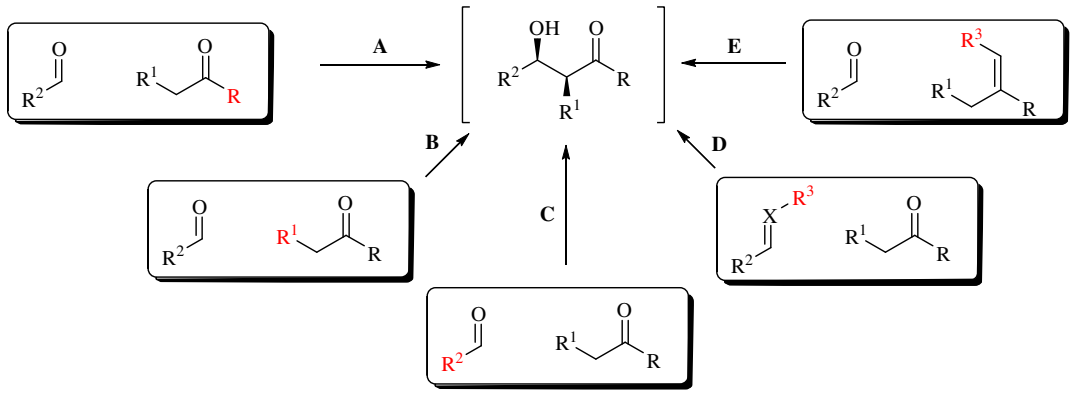
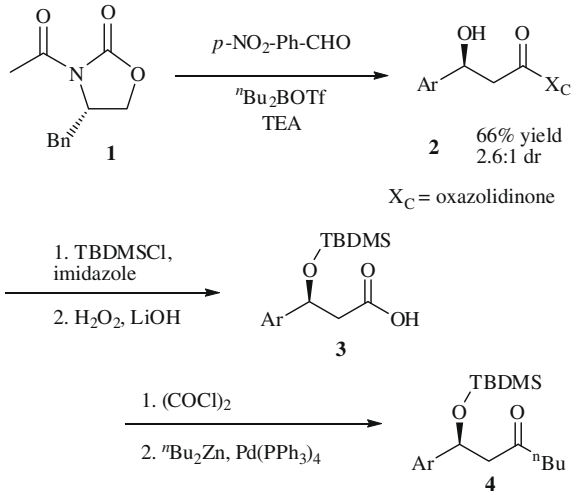


Figure 1. Possible covalent attachment of auxiliaries to aldol substrates. The chiral component is shown in red.

has been made in the area of asymmetric induction. The intent of the review is to highlight and analyze the achievements in asymmetric induction in the aldol reaction in the period 2003–2007 inclusive. Our discussion is limited to processes in which the chiral inducer is distinct (at least conceptually) from the structure of interest—thus many exquisite reactions which leverage stereochemical features intrinsic to the substrate or target structure have been excluded. The reader interested in the earlier history of asymmetric synthesis using chiral auxiliaries or metal/ligand catalyst systems is referred to two books published in the mid-90s.[9,10] The review begins by introducing methods of asymmetric induction and describes the general state of the art early in the 21st century. Then, the recent literature will be described, focusing on key objectives that have been met and on difficulties that have been overcome. We note here that an overview of chiral auxiliaries appeared while the present review was in preparation.[11] At the end of each section, there will be a summary in which shortcomings and gaps will be pointed out. We will suggest possible goals for future development where it seems appropriate to do so.

This review will focus on advances made in the areas of chiral auxiliaries, chiral metal catalysts and small-molecule organocatalysts. We will not discuss biotransformations. Those interested in enzyme-catalyzed[12] and antibody-catalyzed aldol reactions[13] are encouraged to consult the recently published book on modern aldol reactions[14] for an excellent overview and leading references.



Scheme 1. Example of a post-aldol transformation of an imide to a ketone; towards the synthesis of a marine natural product.

There appears to be a general consensus that chiral auxiliaries are old fashioned and intrinsically less efficient than chiral catalysts. In this review, we hope to offer a balanced critical analysis of the capabilities and limitations of auxiliaries, metal catalysts and organocatalysts. In the end, our goal is that readers will recognize the power of modern asymmetric synthesis, and also be able to see where there is room for improvement in catalytic and stoichiometric approaches alike.

2. Chiral auxiliaries

Chiral auxiliary-mediated processes are the best-studied and best-understood methods of obtaining stereocontrol in the aldol reaction. In principle, a stoichiometric auxiliary could be employed in several different manners (Fig. 1). However, the consensus is that the chiral-directing group should be incorporated into the (enolate) nucleophile (Fig. 1, Eqs. A, B and E). An example of a chiral auxiliary in the electrophilic component has been reported recently (Scheme 22, below),[15] though this is uncommon.

The imide-type chiral auxiliaries (Fig. 1, Eq. A) are limited to acid derivatives as substrates. Of course, after cleavage from the chiral auxiliary, the product can be manipulated to afford a variety of derivatives, and this is frequently seen. For example, acyl oxazolidinone **1** ultimately provided chiral ketone **4** (Scheme 1)[16] via asymmetric aldol reaction and subsequent Negishi coupling.

SAMP ((*S*)-1-amino-2-methyoxymethylpyrrolidine)-and RAMP ((*R*)-1-amino-2-methyoxymethylpyrrolidine)-based hydrazones offer stoichiometric stereocontrol in reactions of ketones. Many ketones easily form derivatives with (*S*)- or (*R*)-proline-derived hydrazines. The resulting hydrazones are then used as enolate equivalents in aldol reactions.[17] Eq. E in Figure 1 is a schematic representation of SAMP and RAMP methodology. The similarity between SAMP and RAMP technology and recent enamine-based organocatalysis (see Section 4) is obvious.

Many chiral auxiliaries that perform well in diastereoselective propionate aldol reactions give unsatisfactory results when the nucleophilic component is derived from an acetate.[18] One way of compensating for the absence of substituents at the α-carbon of the enolate (which often provide much of the stereocontrol) is to use chiral auxiliaries featuring conformational rigidity and/or very highly crowded environments. Braun's (*R*)-1,1,2-triphenylethylene glycol **5**,[19] Yamamoto's 2,6-bis(2-isopropylphenyl)-3,5-dimethylphenol **7**[20] and the sterically hindered 4,4-diphenyl-5-isopropylthiazolidine-2-thione **8** (Fig. 2)[21] are particularly effective auxiliaries for acetate aldol reactions. The SAMP and related hydrazines **6** have also been successful chiral inducers in aldol reactions of methyl ketones.[17]

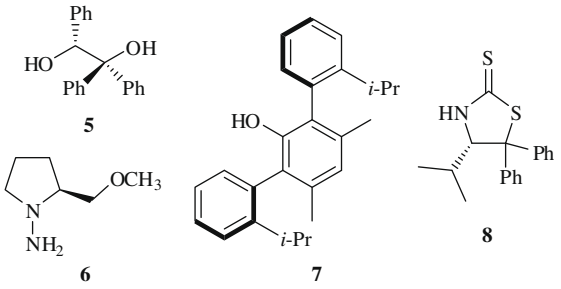


Figure 2. Chiral auxiliaries suitable for acetate aldol additions.

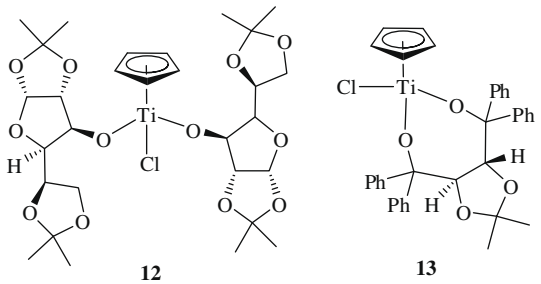


Figure 3. Chiral titanium complexes.

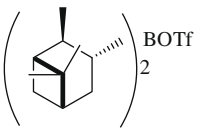


Figure 4. (−)-Ipc$_2$BOTf.

To circumvent the intrinsic difficulties associated with the acetate aldol addition, several alternatives have been developed. These include aldol reactions of bromoacetate **9a**,[22–24] chloroacetate **10a**[25] and thioacetate **11**[26–28] enolates, in which the α-halo substituent is reductively removed after the aldol addition to give adducts **9c**–**11c** (Scheme 2).

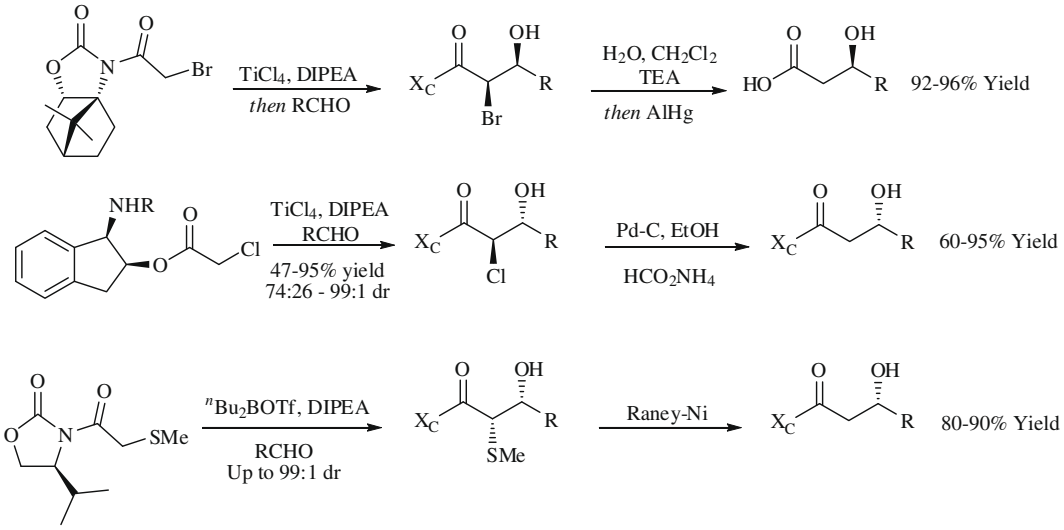
As an alternative to covalently affixing the chiral auxiliary to the substrate, one could also transiently incorporate a chiral auxiliary via chiral metal complexes. In the late 1980s and early 1990s, Duthaler investigated titanium-carbohydrate and titanium-TADDOLate complexes[29–36] (for summaries on TADDOLs, their complexes and reactivities, readers are encouraged to consult two reviews[37,38]). The chiral titanium enolates are easily obtained by quenching a lithium enolate with stoichiometric amounts of either **12** or **13** (Fig. 3). Notably, these complexes permitted highly enantioselective propionate and acetate aldol additions; however, the need for a pre-formed enolate detracts from their overall utility. Similar Mukaiyama aldol reactions promoted by substoichiometric amounts of chiral titanium complexes are discussed below in Section 3.1, and these examples may be more efficient versions of this approach.

In a related process, the Paterson group studied chiral boron reagents in asymmetric aldol additions in the 1980s and early 1990s.[39–43] Both (−)-Ipc$_2$BOTf (**14**, Fig. 4) and (+)-Ipc$_2$BOTf (di[isopinocampheyl]boron triflate) could generate *syn*-aldol adducts in moderate to good enantiomeric excess with ethyl ketones.[39,40] Unfortunately, analogous reactions with methyl ketones met with less success.[41,42] In general, reactions of unsymmetrical ketones occurred with high regioselectivity. Interestingly, the same chiral boron reagent gave opposite enantiofacial selectivity when applied to ethyl and methyl ketones.[41,42]

Carbohydrate-based chiral auxiliaries were reviewed about 10 years ago.[44] Reactions of lithium enolates of *N*-acyl oxazolidinones on a carbohydrate scaffold with various aldehydes were largely poor yielding and/or only moderately diastereoselectivite.[45,46] More recently, a D-mannitol-derived oxazolidinone was demonstrated to give both non-Evans *syn*- and Evans *syn*-adducts selectively via titanium enolates,[47] akin to Crimmins work.[48] While carbohydrates have demonstrated only limited utility in the aldol addition, recent reviews highlight the many other useful applications of carbohydrates in organic synthesis.[49,50]

2.1. Oxazolidinones, oxazolidinethiones and thiazolidinethiones

In 2000, Arya and Qin published an excellent review covering recent advances in asymmetric enolate methodology.[51] The boron-mediated aldol reaction of N-acylated oxazolidinones with aldehydes to give *syn*-aldol products constitutes one of the best-known aldol processes.[52] The stereochemical outcomes of these reactions have traditionally been rationalized using Zimmerman–Traxler chair-like transition states.[53] However, despite the success of the Zimmermann–Traxler model, it is by no means clear that the aldol transition state is generally chair-like. In certain cases



Scheme 2. Alternative approaches to the acetate aldol.

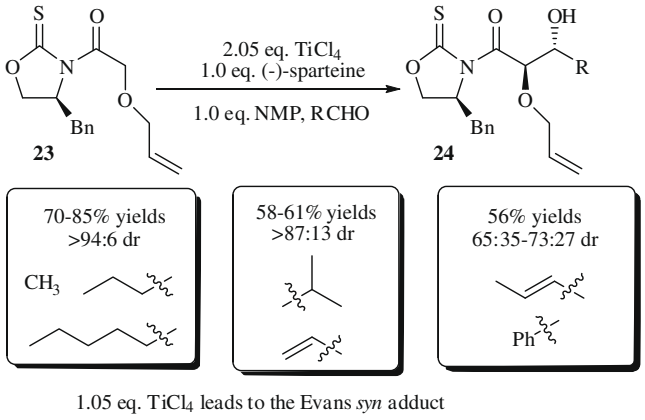
boat-like or open transition state models have given better rationalizations, suggesting that a complete understanding of these processes remains elusive.[54–57]

The use of oxazolidinethiones and thiazolidinethiones in asymmetric synthesis was reviewed in 2002.[58] Scheme 3 highlights the general behaviour of oxazolidinones, oxazolidinethiones and thiazolidinethiones **15** as understood through 2002. Evans first reported the use of a chiral oxazolidinone to generate *syn*-aldol adducts **16** via boron enolates in 1981 (Scheme 3, Eq. A).[26] These conditions have become the gold standard of boron-mediated chiral auxiliary processes. As Evans' process generates only one of the four possible diastereomers, much effort has been invested in developing selective conditions to generate the remaining diastereomers.

In 1991, Heathcock reported success in generating non-Evans *syn*-(Scheme 3, Eq. B, **17**) and *anti*-adducts (Scheme 3, Eq. C, **18**).[59] A pair of papers recently appeared that improved the scope and increased the yields of the Heathcock-type processes. Crimmins reported the facile synthesis of both Evans and non-Evans *syn*-aldol adducts **19** and **20** via titanium-mediated chemistry (Scheme 3, Eqs. D and E, respectively).[48,60] Yan et al. had reported similar results for camphor-based oxazolidinone and oxazolidinethione several years earlier.[61]

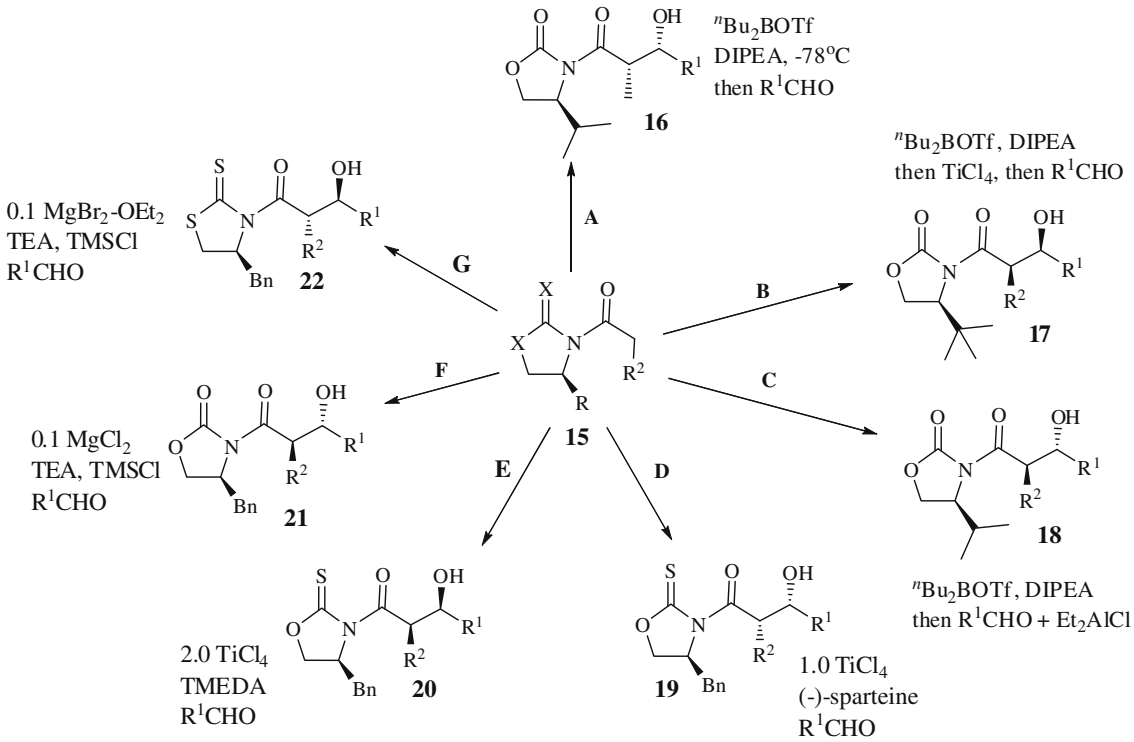
In 2002, Evans revealed methods giving easy access to both *anti*-adducts (**21** and **22**) via magnesium-catalyzed aldol additions (Scheme 3, Eqs. F and G).[62,63] Control reactions demonstrated that the chlorotrimethylsilane was required to release the metal aldolate, and these reactions did not and could not proceed via a silyl enol ether. Unfortunately, these reactions gave low conversion to **21** and **22** in cases where R^2 was β-branched. Later, Wei and Pare reported that stoichiometric amounts of MgI_2 promoted *anti*-selective aldol additions between unmodified ketones and aldehydes.[64] These methods allow selective access to multiple isomers from a single chiral-inducing agent simply by changing the reagents and/or reaction conditions. Furthermore, Evans' reports[62,63] are the first to use substoichiometric amounts of a metal salt in chiral auxiliary-mediated aldol additions, a significant advance in this technology. These advances provided the basis for further developments described in the rest of this section.

The Crimmins group has published methods of generating the *anti*-aldol product **24** using *N*-glycolyloxazolidinethione **23** (Scheme 4).[65] The best results were obtained with aliphatic aldehydes, although moderate selectivities and yields were found with olefinic and aromatic aldehydes. In addition to titanium and a base, 1 equiv of *N*-methyl pyrrolidinone (NMP) was required. To generate the *anti*-adduct efficiently, reactions of aliphatic aldehydes required >2.0 equiv of $TiCl_4$, while those of unsaturated aldehydes required >3.0 equiv of $TiCl_4$ per mole of aldehyde. Without this excess of Lewis acid, the Evans *syn*-adducts were formed. Crimmins interpreted this result in terms of chelation of 2 equiv of $TiCl_4$ at the transition state.



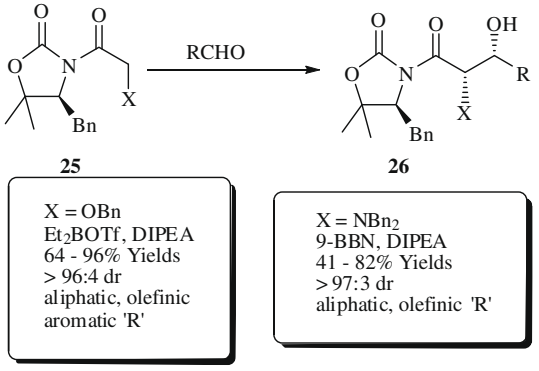
Scheme 4. *anti*-Selective glycolate aldol reaction using an oxazolidinethione auxiliary.

Davies et al. recently reported that benzyl-protected α-hydroxy and α-amino oxazolidinone imides **25** were transformed into



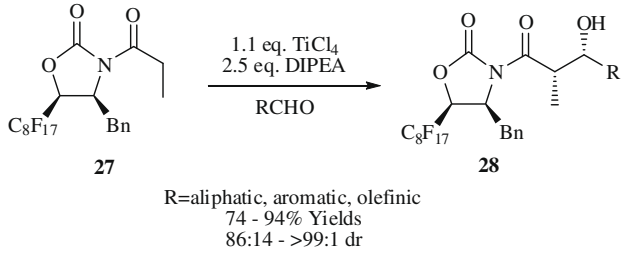
Scheme 3. Diastereomers accessible using oxazolidinone, oxazolidinethione and thiazolidinethione chiral auxiliaries (1981–2002).

syn-α,β-dihydroxyaldehydes via aldol adducts **26** (Scheme 5).[66] Some difficulties arose in removing the aldol adducts from the chiral auxiliary, a long-standing problem with many chiral auxiliary approaches. A variety of reductive conditions gave no reaction or led to endocyclic cleavage. Solvolysis with LiOMe also gave endocyclic cleavage, but ultimately triethylsilane (TES) protection for the hydroxyl group in **26** permitted a two-step reduction/solvolysis sequence to detach the adducts from the auxiliary. Unfortunately, the α-amino-β-hydroxy analogues could not be selectively cleaved in this manner.



Scheme 5. Evans-*syn*-selective aldol addition employing a 4,4′-disubstituted oxazolidinone chiral auxiliary.

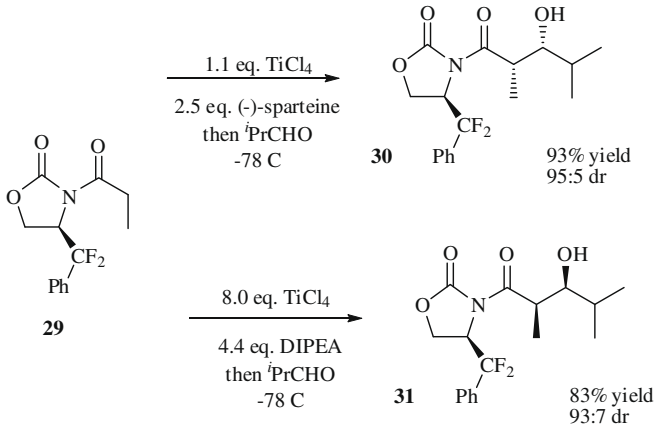
Polymer supports are widely used in high-throughput organic synthesis. Akin to the development of solid-phase chiral auxiliary methodologies, a *fluorous*-supported chiral oxazolidinone (**27**) has been reported (Scheme 6).[67] The fluorous-supported version was soluble in common reaction media, and performed as well as the traditional Evans oxazolidinone in terms of both yield and stereoselectivity.[26] The fluorous support allowed selective isolation of the *syn*-adduct **28** via fluorous solid-phase extraction (FSPE).[68] Fluorous supports allow solution-phase chemistry the benefit of simple isolation procedures typically associated with solid-phase reactions.[69]



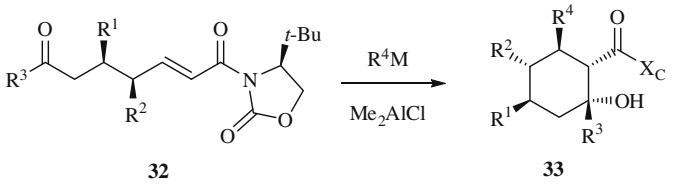
Scheme 6. Fluorous-modified oxazolidinone to generate Evans *syn*-adducts.

A second fluorinated (but not fluorous[69]) chiral auxiliary **29** was recently synthesized.[70] The chiral auxiliary was demonstrated to give good yields and selectivities in generating both Evans *syn*-**30** and non-Evans *syn*-adducts **31** (Scheme 7). While the yields reported for the single acceptor aldehyde examined were higher than those reported by Crimmins,[48] the large excesses of $TiCl_4$ and diisopropylethylamine (DIPEA) required for good diastereoselectivity in generating the non-Evans *syn*-adduct **31** are a small drawback to this method.

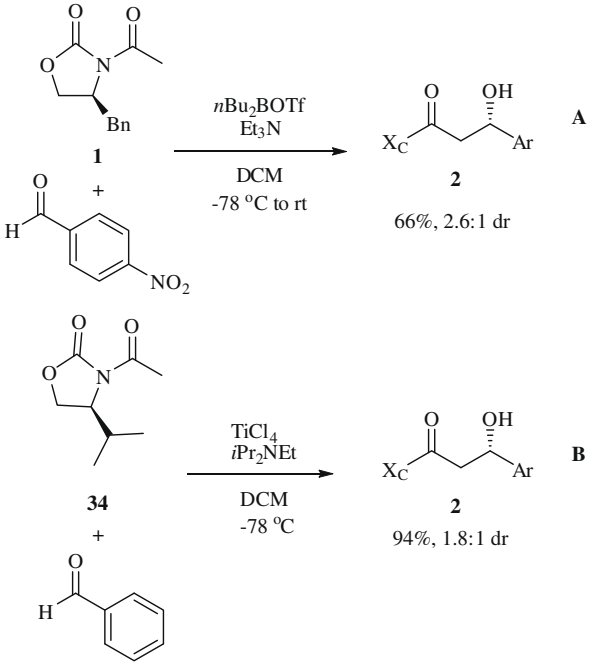
Reaction cascades (also called 'domino reactions') offer attractive synthetic possibilities. An interesting example in which an oxazolidinone controlled the stereochemistry of sequential Michael addition and aldol cyclization of **32** to synthesize substituted cyclohexanes **33** is shown in Scheme 8.[71] Yields were moderate to good, and only one diastereomer could be detected by NMR in all cases. It is noteworthy that the oxazolidinone group also facilitated



Scheme 7. Selective synthesis of both Evans *syn*- and non-Evans *syn*-adducts using titanium-mediated aldol additions on a fluorinated oxazolidinone.



Scheme 8. Tandem Michael addition–aldol reaction to generate substituted cyclohexanes.



Scheme 9. Typical 'direct' acetate aldol reactions employing oxazolidinone auxiliaries.

the stereoselective preparation of the starting material **32**, using sequential aldol reaction and Cope rearrangement. Cleavage of the oxazolidinone from the adducts was achieved using $LiSCH_2Ph$ (Damon reagent).[72]

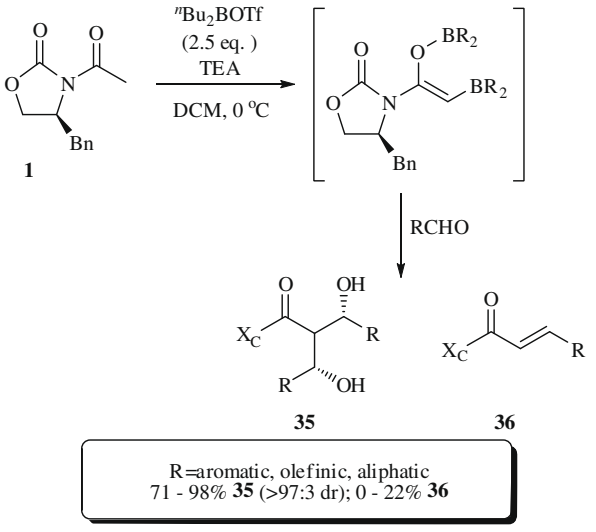
As previously mentioned, oxazolidinones and related heterocycles generally have performed poorly as chiral auxiliaries in acetate aldol additions.[18,27] However, chemists continue to seek ways of improving this situation.[16,73,74] The results shown in Scheme 9 are typical of 'direct' acetate aldol approaches. In reaction A, a boryl

enolate led to formation of a 2.6:1 mixture of diastereomeric adducts **2**, although both stereoisomeric products **2** could be obtained in pure form after chromatography.[16] Reaction B afforded similar results via a Ti(IV) enolate of **34**.[73] As suggested by the examples in Scheme 2, the most successful routes employ temporary substituents on the enolizable centre to assist in transferring the chirality of the auxiliary.

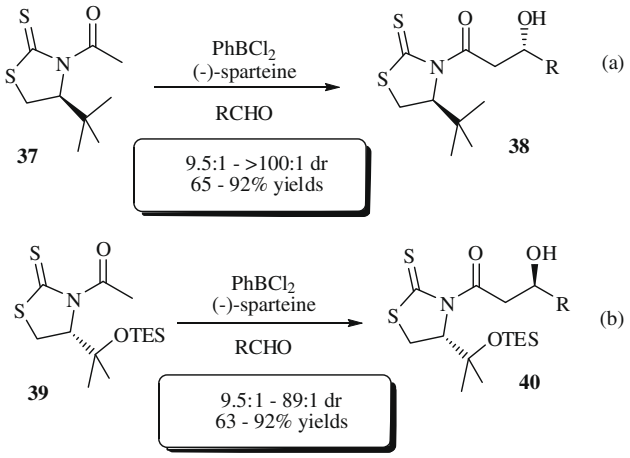
It is generally assumed that boryl enolates exist solely in the *O*-boryl form.[14] In contrast, Abiko et al. observed that when acetate esters or imides are treated with 1 equiv of a dialkylboron triflate and an amine base at −23 °C, a mixture of *O*-boryl enolate, *O*-,*C*-diboryl enolate and unreacted carbonyl precursor results. In the presence of excess boryl triflate, the doubly borylated enolates may be formed quantitatively.[74–78] The double di(*n*butyl)boryl enolate of *N*-acetyloxazolidinone **1** underwent double aldol addition with a variety of aldehydes, giving diols **35** (Scheme 10) as essentially single diastereomers.[74] In some cases, the dehydration products **36** were formed as minor side products. Double boryl enolates could likewise be prepared using the bulkier 9-BBNOTf or $^{c}Hex_2$-BOTf, but their reactions with aldehydes were typically too slow to be useful.

The high selectivity of these formal acetate aldol reactions is probably related to the presence of the bulky *C*-boryl group on the enolate in the first aldol addition, while the second aldol reaction benefits from the presence of the hydroxyalkyl group added in the first step. These results together with those in Scheme 2 reinforce the important role of an α-substituent in effectively transferring stereochemical information. However, in 2004, Sammakia et al. reported a new sterically encumbered chiral auxiliary that was able to efficiently induce asymmetry in the acetate aldol addition (Scheme 11).[79,80] With thiazolidinethiones **37** and **39**, both isomers of the acetate aldol adduct (**38** and **40**) are easily accessible. The authors later examined both **37** and **39** in aldol reactions with chiral aldehyde acceptors, and found that the diastereoselection was decreased to as little as 4.5:1 with an α-alkyl stereocentre.[81] The presence of α-oxyalkyl and β-stereocentres in the aldehyde acceptor had less influence on the diastereoselection, and led to adducts **38** and **40** in between 12:1 and 26:1 ratios.

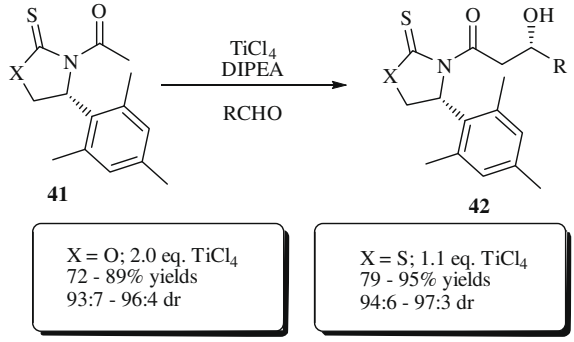
Crimmins recently published a paper in which conceptually similar thiazolidinethione and oxazolidinethione auxiliaries **41** were successful in the acetate aldol addition.[82] Both auxiliary classes generated the acetate aldol adducts **42** in good yields and excellent selectivity (Scheme 12). Sammakia's and Crimmins' work



Scheme 10. Double aldol addition via a diboryl enolate with an oxazolidinone auxiliary.



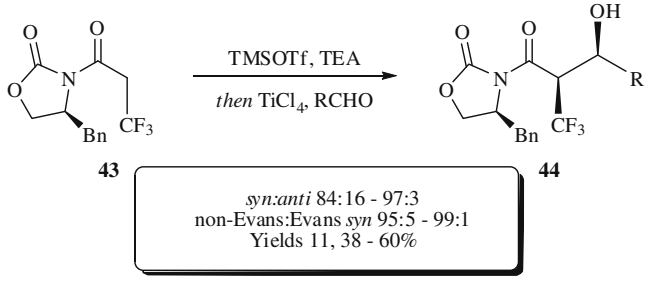
Scheme 11. Diastereoselective aldol addition using thiazolidinethiones.



Scheme 12. Oxazolidinethione and thiazolidinethione auxiliaries useful in acetate aldol additions.

may point the way towards a general solution to the challenge of the stereoselective acetate aldol reaction.

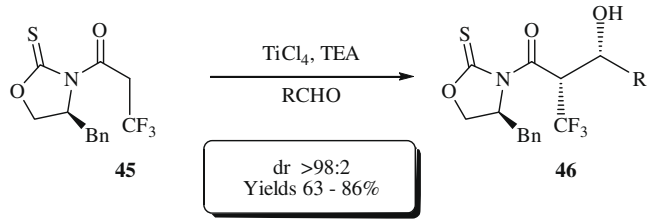
Ishihara et al. demonstrated the use of oxazolidinone **43** to yield non-Evans *syn*-adduct **44** (Scheme 13) via an in situ-generated silyl enol ether.[83] They obtained the best results using 0.3 equiv of $TiCl_4$ to promote the aldol addition, but the yields and diastereoselectivities were significantly decreased when either $BF_3{\cdot}OEt_2$ or Et_2AlCl was used. Ishihara's results may be compared to Crimmins' observation that the use of 2.0 equiv of $TiCl_4$ in conjunction with the analogous oxazolidinethione or 1.0 equiv of $TiCl_4$ with the thiazolidinethione gave the non-Evans *syn*-adduct as the major isomer.[48] However, Crimmins reported the synthesis of Evans *syn*-adducts from *N*-acyl oxazolidinones; the generation of non-Evans *syn*-adducts was never mentioned. But to distinguish the two processes, Ishihara utilized a silyl enol ether generated in situ,[83] whereas Crimmins' procedure was direct.[48] It is unclear from Ishihara's



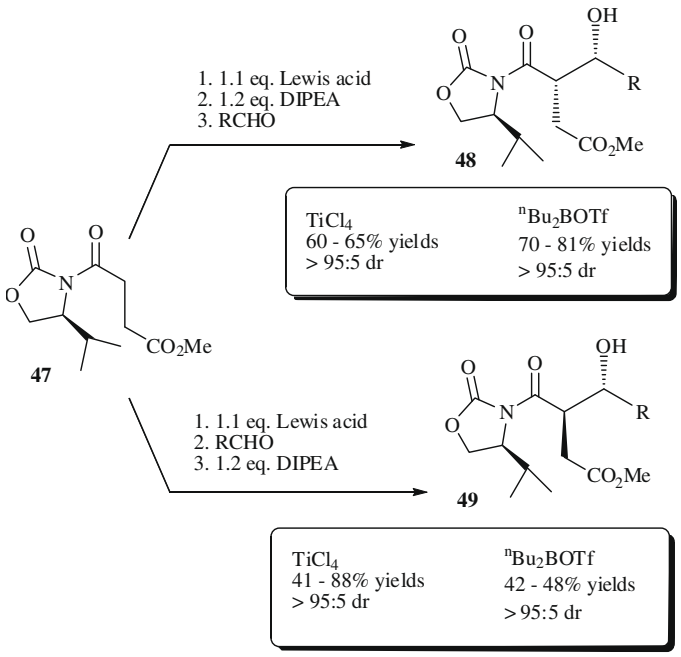
Scheme 13. Non-Evans *syn*-adducts via an in situ-generated silyl enol ether.

work whether it is the oxazolidinone carbonyl or the pre-formed silyl enol ether that is responsible for the formation of the non-Evans *syn*-aldol adduct as the major isomer.

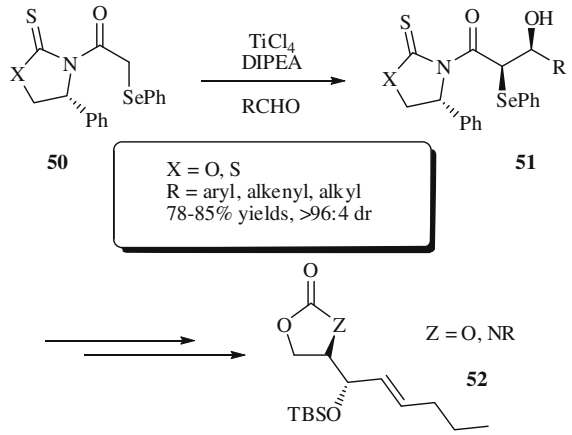
Consistent with Crimmins' earlier report, Figadère et al. reported that oxazolidinethione **45** generated the Evans *syn*-adduct **46** when treated with 1.0 equiv of $TiCl_4$ (Scheme 14).[84]



Scheme 14. Generation of Evans *syn*-aldol adducts from an α-trifluoromethyl acyl thiazolidinethione.



Scheme 15. Selective generation of either *syn*- or *anti*-aldol adducts by changing the order of addition of reagents.



Scheme 16. Functionalized *N*-phenylselenylacyl auxiliaries generated by diastereoselective *syn*-aldol addition can be further transformed into either oxazolidinones or carbonates.

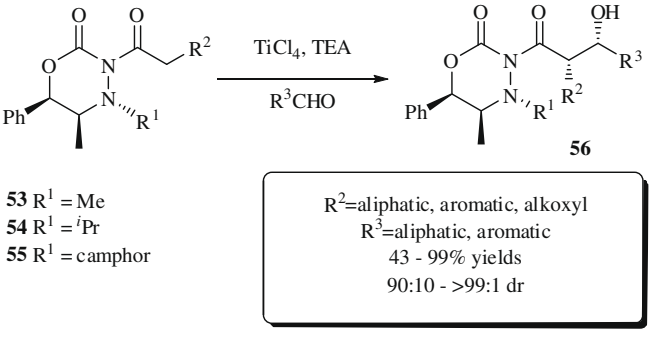
Hajra et al. recently demonstrated that changing the order of addition of the reagents changes the aldol diastereomer generated.[85] Treating *N*-acyloxazolidinone **47** sequentially with a Lewis acid and an amine base followed by an aldehyde yields *syn*-adducts **48**, while treating **47** with a Lewis acid, an aldehyde followed by an amine base generates *anti*-adducts **49** (Scheme 15). Other N-acylated oxazolidinones gave similar results.

N-Phenylselenylacyl oxazolidinethione and thiazolidinethione **50** were recently demonstrated to give Evans *syn*-adducts **51** in good yields and selectivities (Scheme 16). Post-aldol modification of the adducts generated either cyclic carbonates or oxazolidinones **52**.

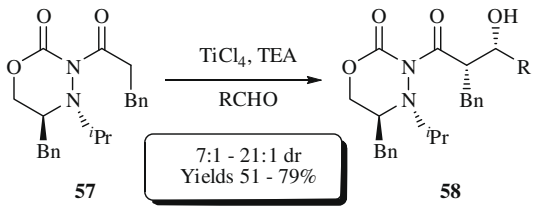
2.2. Oxadiazinones

Over the last three or four years, Hitchcock's group has been developing oxadiazinone chiral auxiliaries. The first of these (**53**) utilized an *N*-methyl group as a stereodirector.[86] Normally, the configuration of trivalent nitrogen is unstable; however, in these systems the two fixed stereogenic centres at C5 and C6 bias the *N*-methyl configuration (Scheme 17). These auxiliaries thus function through a chiral-relay system. Hitchcock's laboratory has studied aldol reactions of propionate- and glycolate-derived Ti(IV) enolates linked to oxadiazinone auxiliaries bearing *N*-methyl (**53**), *N*-isopropyl (**54**) or *N*-camphoryl (**56**) groups.[86–91] Although there was some variability in the yields, these reactions consistently delivered very good levels of diastereoselectivity.

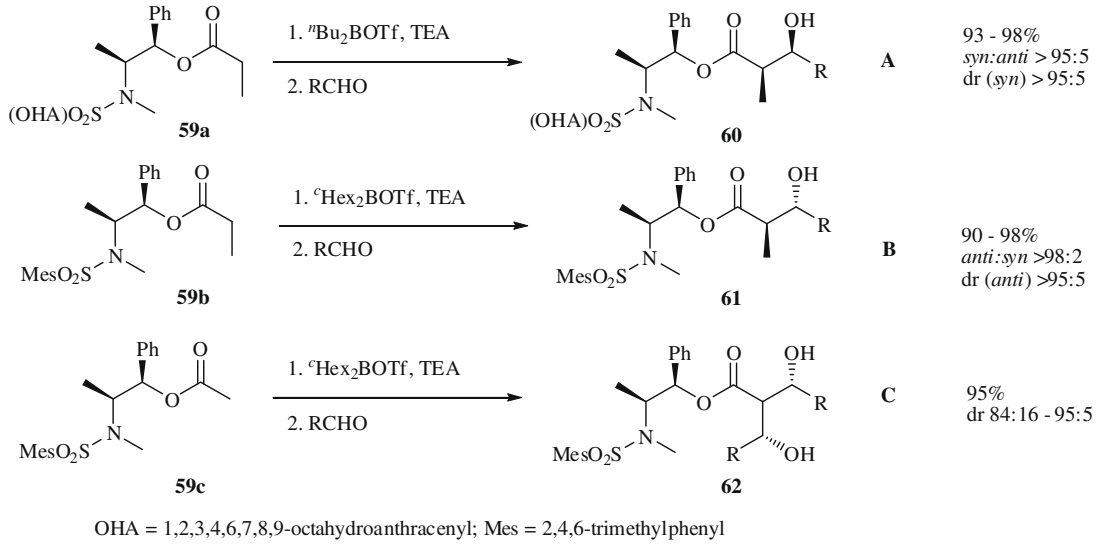
In general, reactions of **54** were more diastereoselective than those of **53**, which was attributed to the greater bulk of *N*-^{i}Pr versus *N*-Me (Scheme 17). It was thus predicted that **55** containing the still larger *N*-camphoryl-directing group should deliver still greater stereoselectivity. Surprisingly, this was not the case. The authors also found that they were unable to cleave the aldol adducts from this chiral auxiliary. In contrast, adducts could easily be removed from **53** or **54**, making auxiliary **54** the most synthetically useful. The authors have also recently examined the α-halo aldol addition.[91] Again, the *syn*-isomer predominated, but in lower yields and selectivities than were found with α-alkyl or α-alkoxyl. To date, only *syn*-aldol adducts **56** have been obtained using this class



Scheme 17. *syn*-Selective aldol reactions using various oxadiazinones.



Scheme 18. *syn*-Selective aldol additions.



Scheme 19. Summary of the scope of ephedrine-based chiral auxiliaries. Selectivity for the *syn*-adduct (Eq. B) or the *anti*-adduct (Eq. A) is controlled by the steric bulk of the boryl substituents. The double aldol adduct is available through an acetate-type process (Eq. C).

of chiral auxiliary. It remains to be seen how oxadiazinones fare in the acetate aldol reaction, or if *anti*-adducts can be selectively synthesized.

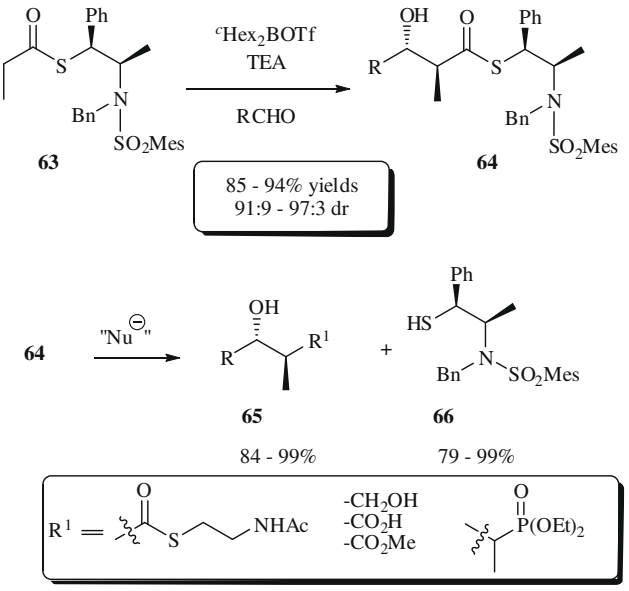
In an effort to examine the influence of the C6 phenyl substituent in **53**–**55** on the ability of an oxadiazinone to effectively induce asymmetry, Hitchcock et al. also studied chiral auxiliary **57** (Scheme 18).[92] As in the aldol reactions of oxadiazinones **53**–**55**, the *syn*-adduct **58** predominated, albeit with lower diastereoselectivity than was previously observed. Thus, it appears that the C6 phenyl group in **53**–**55** is required in order to generate consistently high diastereoselectivities.

2.3. Other chiral auxiliaries

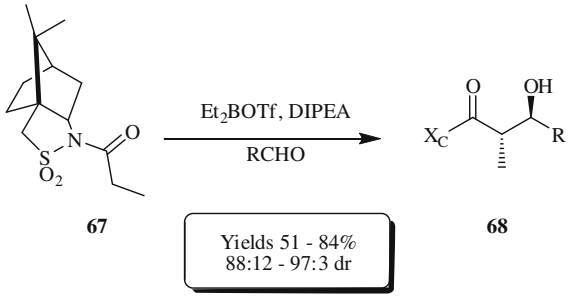
The ephedrine-based auxiliaries **59** (Scheme 19) devised by Abiko and Masamune[78] are remarkably versatile, affording the *syn*-aldol adducts **60**, *anti*-adducts **61** or double addition products **62** in consistently high yields and selectivities.[75,77,93,94] The double aldol addition (Scheme 19, reaction C)[75] is similar to that shown in Scheme 10 using an oxazolidinone auxiliary. The structurally intriguing double boron enolate intermediate in this reaction has been spectroscopically characterized.[76,77] These acyclic ephedrine auxiliaries create conformational rigidity in their enolate intermediates through chelation, leading to levels of diastereoselectivity comparable to those found with the cyclic auxiliaries.[95] Remarkably, these methods do not appear to be influenced by the structure of the aldehyde acceptor, and show high reactivity and selectivity in generating both *anti*- and *syn*-adducts.

Hulme et al. modified Abiko and Masamune's chiral auxiliary as shown in **63** (Scheme 20) to facilitate nucleophilic displacements of the aldol adduct **64** from the auxiliary.[96] The aldol adduct could readily be transformed into alcohols, carboxylic acids and esters, phosphonate esters, and thio esters of general structure **65**, and the chiral auxiliary **66** was recovered in all cases in high yields.

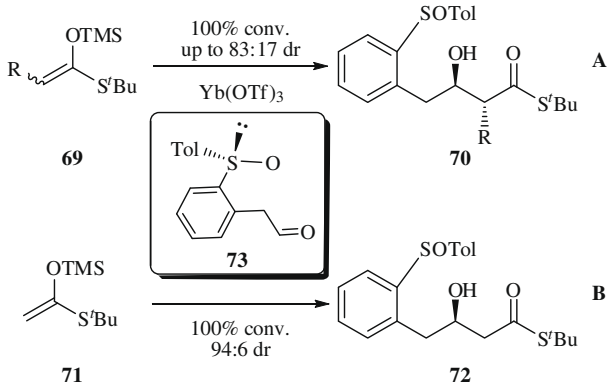
Oppolzer explored the use of chiral sultams as chiral auxiliaries in the early 1990s. In his original paper, Oppolzer reported methods for selectively generating both *syn*-diastereomers of the aldol adducts from camphor-derived sultam **67** via boron and lithium or tin enolates.[97] Oppolzer later developed conditions for acetate aldol additions[98] and for the synthesis of *anti*-adducts via Ti(IV) enolates.[99] Oppolzer briefly explored the use of boron enolates for the generation of *anti*-adducts, but found titanium(IV) to give more satisfactory results.[97,99] However, in 2006, Perlmutter et al. developed conditions for successful, boron-mediated *anti*-aldol additions (Scheme 21).[100] Unfortunately, Perlmutter's method



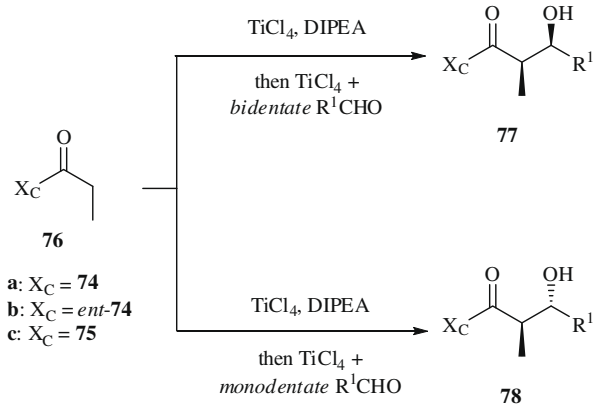
Scheme 20. Generation of *anti*-adducts using ephedrine-based thioesters as chiral auxiliaries.



Scheme 21. Generation of *anti*-adducts utilizing Oppolzer's sultam.



Scheme 22. *anti*-Selective and acetate-type aldol additions using ketene thioacetals.



Scheme 23. Influence of aldehyde on diastereoselectivity of titanium-mediated aldol additions.

required 15 equiv of aldehyde and 3 equiv of diethylboron triflate to produce good isolated yields of adduct **68**.

As discussed in the introduction, it is uncommon for the chiral auxiliary to be incorporated into the aldol *acceptor*. A recent paper reported the use of a chiral tolyl sulfinyl group covalently bound to the aldol acceptor, which could be reductively removed following the aldol addition. The reaction between *O*,*S*-thioacetal **69** and chiral sulfoxide **73** was reported to produce *anti*-aldol adducts **70** stereoselectively, regardless of the geometry of the thioacetal (Scheme 22, Eq. A).[15] Reaction between **73** and ketene *O*,*S*-thioacetal **71** was also successful, forming adduct **72** in high diastereomeric excess (Scheme 22, Eq. B). Interestingly, neither silyl enol ethers nor silyl ketene acetals were reactive under these conditions. The sulfinyl chiral-directing group could be reductively cleaved from the phenyl ring following the aldol addition.

Ghosh et al. have been examining both boron-mediated and titanium-mediated aldol additions utilizing chiral aminoindanol (and related) auxiliaries since 1992. Early work examined the use of oxazolidinones from *cis*-1-amino-2-hydroxyindane[101] and (1*S*,2*R*)-2-aminocyclopentan-1-ol.[102] More recent work examined ester-derived *N*-tosylaminoindanols **74** and **75** (Fig. 5).[103–105] The authors found that for reaction to occur, first the titanium enolate of *O*-propionyl-**70** needed to be formed, and the aldehyde needed to be precomplexed with additional $TiCl_4$.[105] Interestingly, the diastereochemical outcome was shown to be greatly influenced by the structure of the acceptor aldehyde (Scheme 23). *O*-Propionyl derivatives **76** of auxiliaries **74**, *ent*-**74** and **75** were demonstrated to give **77** or *ent*-**77** when bidentate (α-, β- or γ-hydroxyl) aldehydes were acceptors.[103–105] All other aldehydes examined gave *anti*-**78** in high diastereomeric excess. The decreased conformational flexibility of auxiliary **75**[103] as compared to that of **74** did not appear to give any advantage to the system, and required more steps to synthesize, leaving **74**[104,105] as the practical choice. While yields were moderate to excellent, the substrate-dependent diastereoselectivity and relatively large amounts of titanium required (>3 equiv) somewhat detract from the general utility of the system. However, in the case of non-chelating aldehydes, the *anti*-selectivity is excellent, providing an alternate approach to that scaffold. A review discussing aminoindanol derivatives as chiral auxiliaries (and ligands) was recently published.[106]

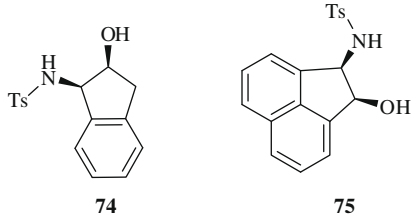


Figure 5. Ghosh's chiral aminoindanol auxiliaries.

2.4. Summary of advances in chiral auxiliaries

Chiral auxiliary methods for asymmetric aldol additions to aldehydes are diverse, in terms of both diastereomers accessible and substrate range. Recent work by several groups has demonstrated ease of synthesis of all diastereomers, as well as success in the acetate aldol addition, leaving these long-standing problems largely solved.

Additions to ketones with chiral auxiliary-based methods are less well known. There are only a few examples using Evans's oxazolidinones, and these are generally less diastereoselective than analogous additions to aldehydes;[107–112] there are even fewer examples using oxazolidinethiones.[113–115] To the best of our knowledge, there have only been two examples utilizing Braun's auxiliary **5** (Fig. 2).[116,117] Peters et al. examined several chiral auxiliaries (including ephedrine-based **59c** and similar compounds, Braun's auxiliary and Oppolzer's sultam) in the acetate aldol addition to a pyridinyl ketone, and found an Evans' oxazolidinone to be superior.[118] However, there appears to be no systematic survey of the generality of the reaction of chiral auxiliary-linked aldol additions to ketones.

We have noted a few examples of aldol additions of chiral auxiliary-linked glycolate enolates, from the groups of Crimmins,[65] Davies[66] and Hitchcock.[89] With thiazolidinethione **23** (Scheme 4), superstoichiometric amounts of $TiCl_4$ were required for good conversions and selectivity to *syn*-isomers in these glycolate reactions. Likewise, some reactions of oxadiazinones **54** (Scheme 17) required an excess of $TiCl_4$, while others did not. In contrast, oxazolidinone **25** (Scheme 5) provided high levels of selectivity and good conversion using essentially stoichiometric amounts of all components. Oxazolidinone **25** appeared to be the most economic and general in terms of amounts of reagents required, scope, yield and selectivity; however, cleavage following aldolization proved difficult and required several steps to yield the α,β-dihydroxyaldehyde derivative. In contrast, oxadiazinone adducts **56** could be directly hydrolyzed to the corresponding glycolic acid derivatives. Only thiazolidinethione **23** was demonstrated in *anti*-selective glycolate aldol additions (Scheme 4).

Chiral auxiliary methods do have a few well-known drawbacks, including additional steps for installing and cleaving the auxiliary, as well as the large amounts of metals required in addition to the chiral source. Evans' recent results using catalytic amounts of magnesium salts may suggest a general solution to this problem,

despite the need for stoichiometric amounts of silyl chloride (arguably equivalent in terms of efficiency to a Mukaiyama aldol addition, albeit mechanistically different).[62,63] The flexibility inherent in chiral auxiliary methods counters the problem of affixing the auxiliary to the substrate to some extent.

3. Chiral metal catalysts

The use of chiral metal catalysts in the aldol reaction has become a major area of study. The intrinsic efficiency of catalytic methods is the major driving force behind research in this area. The need for more cost-effective and 'greener' synthetic methods especially for industrial applications has been widely recognized. Catalytic methods for the aldol reaction potentially offer very mild reaction conditions, with the attendant tolerance for a range of functional groups that this implies. Further, the ability to 'tune' a catalytic metal centre by judicious ligand design is an attractive feature. Several summaries of catalytic enantioselective aldol reactions published through the year 2000 have appeared.[119–127] An excellent review of asymmetric catalysis in the aldol reaction was published in 2002.[128]

Early applications of chiral metal catalysts in the aldol reaction were largely limited to Mukaiyama aldol reactions of pre-formed silyl enol ether nucleophiles. Many of the first-generation catalysts had very narrow applicability,[51] nor were predictive models generally available. Like chiral auxiliaries, metal catalysts have also had difficulties delivering high selectivity in the acetate aldol addition, particularly in direct (as opposed to Mukaiyama-type) aldol reactions.[128]

Despite success in developing catalysts for the Mukaiyama aldol addition, only recently has the direct catalytic aldol reaction received serious attention. Several reviews have been published on this topic,[128–130] and an extensive review on catalytic enantioselective aldol reactions appeared while the present review was in preparation.[131] Our survey of recent developments in catalyzed asymmetric aldol processes will be organized by ligand and metal.

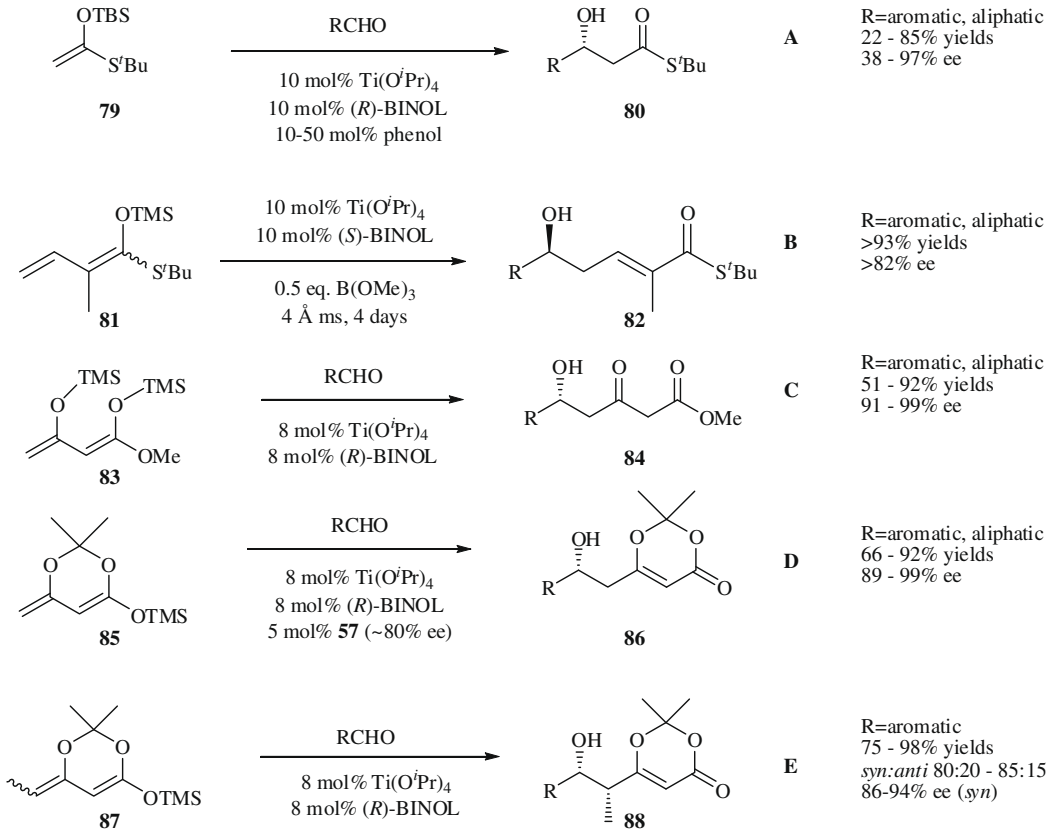
3.1. BINOL/BINAP and related ligands

BINOL, BINAP and their derivatives are used extensively as chiral ligands in synthesis.[132,133] The first of these was developed by Carreira in the early 1990s,[134] and these still form one of the largest groups of chiral ligands used in metal-catalyzed aldol reactions over the last five years.

Keck first reported the success of Ti(IV)-BINOL-catalyzed Mukaiyama aldol additions in 1995.[135] Recently, there have been several more reports expanding the scope of this process. Zimmer et al. have described the Ti-(*R*)-BINOL-catalyzed reactions of *O*-silyl, *S*-alkyl ketene acetal **79** with a wide variety of aldehyde electrophiles (Scheme 24, Eq. A).[136] In most cases, the addition of 10–50 mol % of phenol was required. These reactions afforded highly variable yields and enantioselectivities, and in a few cases no reaction was observed at all.

Heumann and Keck have recently studied the Ti(IV)-BINOL catalytic system in the asymmetric vinylogous Mukaiyama aldol reaction with dienol silyl ketene *O*,*S*-thioacetals **81** to give adducts **82** (Scheme 24, Eq. B).[137] The authors found that 0.5 equiv of $B(OMe)_3$ was required for efficient catalysis. Yields and selectivities were very high, though prolonged reaction times were required. Both aromatic and aliphatic aldehydes could be successfully employed; however, the use of unsaturated aldehydes led to decreased conversion and lower selectivity.

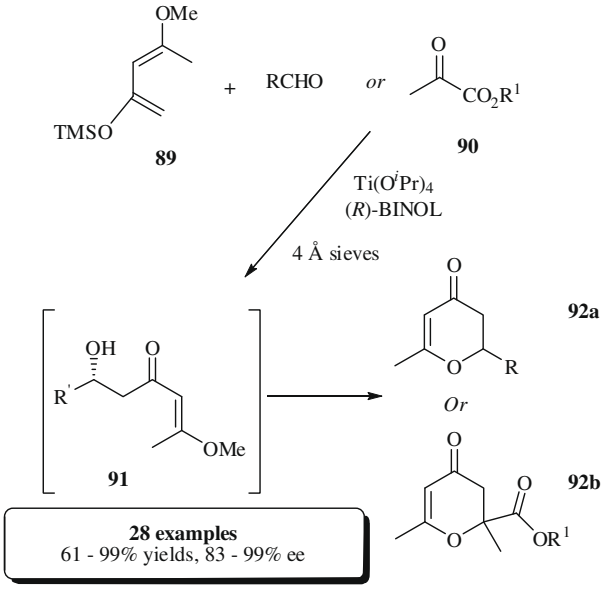
Aldol reactions of dienol ethers catalyzed by Ti-(*R*)-BINOL were studied by Scettri et al. The nucleophiles in these studies were the masked acetoacetates **83**[138–140] and **85**[141–144] (Scheme 24, Eqs. C and D). In some cases, the products **84** were isolated as mixtures



Scheme 24. The use of Ti-BINOL to catalyze Mukaiyama aldol and vinylogous aldol reactions.

of the δ-hydroxy and δ-(trimethylsilyloxy) carbonyl compounds. The authors found that using an in situ desilylation procedure based on Carreira's work[145] rather than post-aldol desilylation led to greater enantiomeric purity of the adducts, indicating that the adducts were sensitive to racemization.[140] It was noted that enantiomerically pure (*R*)-BINOL ligand afforded the product as a single enantiomer, and BINOL of only 69% ee gave the aldol product in 94% ee.[138,139] To explain this nonlinear relationship between the enantiomeric purity of the ligand and the enantioselectivity of the reaction, the authors proposed that the active catalyst was a 'homochiral oligomer' containing only the major ligand enantiomer, while the minor enantiomer of the ligand was largely incorporated into a less-active 'heterochiral oligomer'.

The Ti(IV)-BINOL catalyst promoted the formation of *syn*-aldol adducts **88** via an uncommon vinylogous Mukaiyama process (Scheme 24, Eq. E),[142] These Ti-BINOL-catalyzed vinylogous aldol reactions of **87** were successful with both aromatic and conjugated aldehyde acceptors, but simple aliphatic aldehydes gave unsatisfactory results.



Scheme 25. Mukaiyama acetate aldol reaction of dienol ether **58** with aldehydes or β-keto esters.

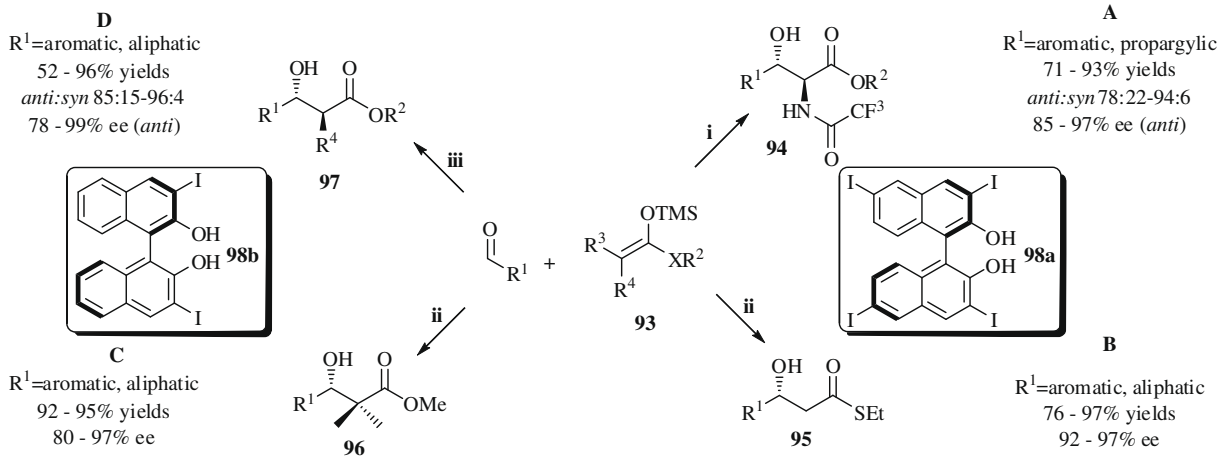
An interesting application of this catalytic system is the synthesis of hetero-Diels–Alder (HDA)-like adducts via a Mukaiyama aldol process (Scheme 25).[146] When diene **89** reacted with aromatic or aliphatic aldehydes or β-keto esters, the cyclic adducts **92** were formed. The yields and enantioselectivities of these reactions ranged from fair to excellent. These processes could conceivably occur by either a cycloaddition pathway or an aldol/Michael addition sequence via **91**. By careful isolation procedures, the intermediate **91** was identified, indicating that the reactions actually were aldol/Michael tandem processes and not hetero-Diels–Alder reactions.

Zirconium(IV)-BINOL catalysts have been evaluated by Kobayashi et al. The complex between **98a** and $Zr(O^tBu)_4$ was found to be an efficient catalyst for the acetate aldol addition of *Z*-glycinate ketene acetal **93** and aromatic or propargylic aldehydes to give *anti*-adducts **94** (Scheme 26, Eq. A).[147] In analogous processes (Scheme 26, Eqs. B, C and D), the Zr(IV)-**98a** catalyst promoted the coupling of ketene acetals **93** with aromatic or aliphatic aldehydes RCHO to give adducts **95**, **96** and **97** in good yields and in excellent diastereo- and enantioselectivities.[148,149] It was found that the addition of protic additives and small amounts of water was critical for catalyst turnover and formation, respectively, in the reactions catalyzed by Zr(IV)-**98**. While the catalyst could be prepared and stored for at least 3 months with minimal degradation in activity and selectivity, it was found that when prepared in situ, the enantioselectivity improved slightly.[148]

Catalyst Zr(IV)-**98a** has some advantage over Ti(IV)-BINOL catalysts in acetate aldol additions of ketene silyl acetals **93** and **79**, respectively; in general, the Zr-catalyzed processes (Scheme 26, Eq. B)[148,149] had both higher enantioselectivities and higher yields, and appeared to be less influenced by substrate structure than were the analogous Ti-catalyzed reactions (Scheme 24, Eq. A).[136]

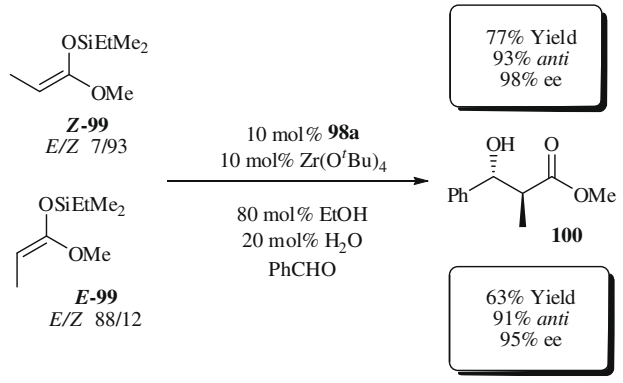
The *anti*-selectivity observed in the Zr(IV)-catalyzed reactions of *E*-**93** to give adducts **97** was remarkable.[149] As was the case for chiral auxiliaries, generation of *anti*-adducts has been a long-standing problem in catalytic Mukaiyama aldol processes. Most catalysts for this reaction promote the *syn*-aldol pathway, regardless of the configuration of the enol silane. In contrast, the Zr(IV) catalyst favoured the *anti*-product regardless of the starting geometry (Scheme 27); both *E*- and *Z*-**99** led to *anti*-**100**.

There are only a few recent examples of catalyzed stereoselective aldol reactions involving ketone acceptors, with pyruvates being the major exception.[150] This scarcity reflects the attenuated reactivity of ketones and the intrinsic reversibility of their aldol

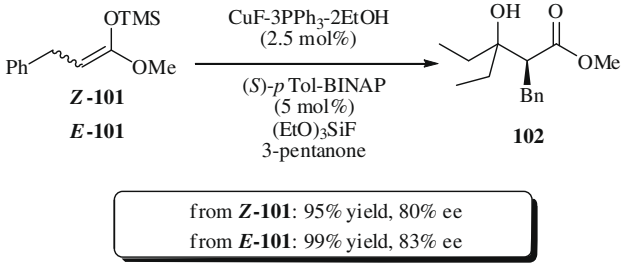


Scheme 26. Zr(IV) catalysts for Mukaiyama aldol reactions: applications of BINOL ligands. Reagents and conditions: (i) 12 mol % **98a**, 10 mol % $Zr(O^tBu)_4$, 300 mol % ROH; (ii) 12 mol % **98b**, 10 mol % $Zr(O^tBu)_4$, 80 mol % ROH, 20 mol % H_2O; (iii) 24 mol % **98b**, 20 mol % $Zr(O^tBu)_4$, 160 mol % ROH, 20 mol % H_2O (aliphatic R^1), conditions (ii) for aromatic R^1.

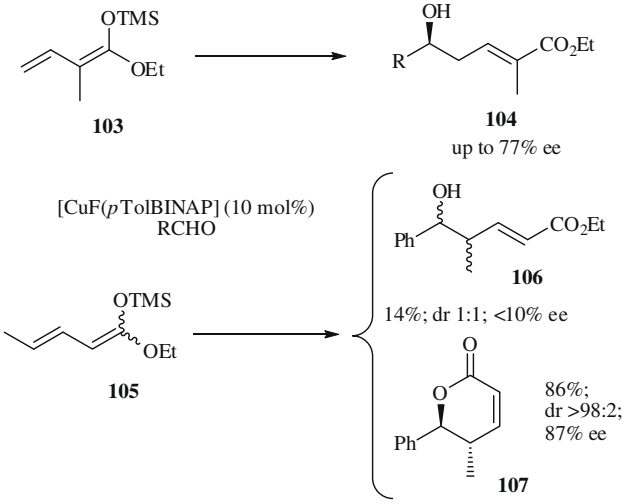
additions. Stereocontrol is also a challenge because of the steric similarity of the two entities flanking the ketone carbonyl. Shibasaki developed the CuF/*p*-Tol-BINAP catalyst system based on the earlier work of Carreira[145,151] to overcome this problem.[152] Excellent yields and moderate enantioselectivities were observed in the reactions of trimethylsilyl ketene acetals **101** with 3-pentanone; the same enantiomer **102** was obtained from both the *E*- and *Z*-ketene acetals (Scheme 28). While this paper only demonstrated enantioselectivity for a single set of substrates, the authors reported an extensive study of the achiral version of the Cu(I) catalyst which suggests that this catalytic system has great potential.[152]



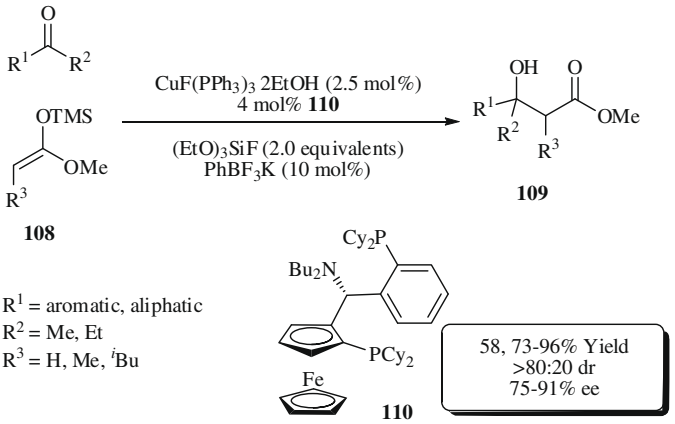
Scheme 27. Zr(IV)-**98a**-catalyzed *anti*-selective aldol reactions.



Scheme 28. Enantioselective catalyzed aldol reactions of silyl enol ethers *E*-**101** and *Z*-**101** with 3-pentanone.



Scheme 29. Enantioselective Cu(I)-promoted vinylogous aldol additions.

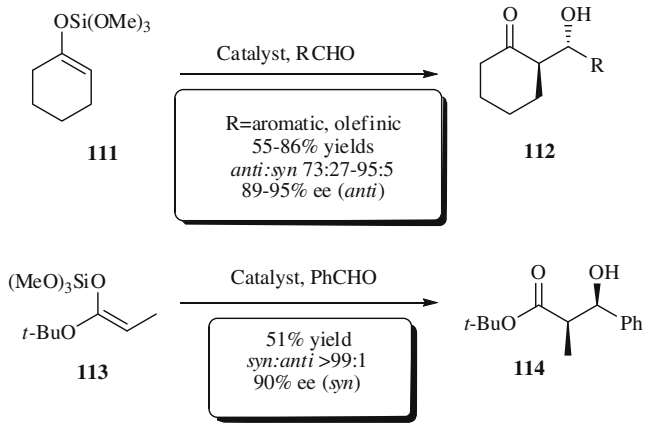


Scheme 30. Efficient Cu-bisphosphine catalyst for the Mukaiyama aldol addition to ketones.

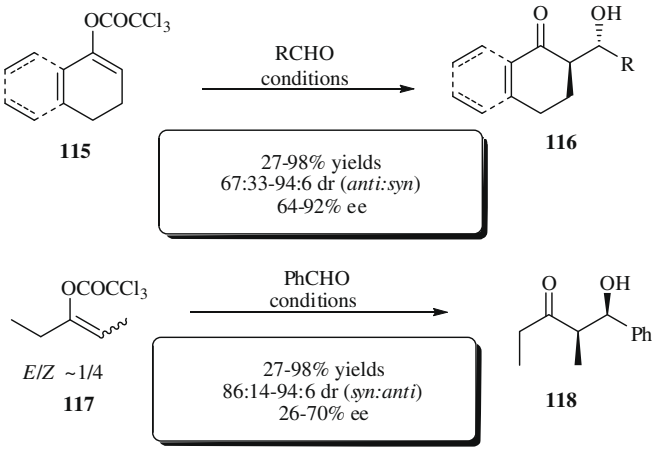
Campagne et al. also became interested in the Carreira catalytic system for vinylogous aldol additions.[153,154] They found that the α-substituted ketene acetal **103** reacted with aldehydes to give hydroxyesters **104** in moderate ee (Scheme 29).[153] However, in later studies using the γ-substituted ketene acetal **105**, hydroxyester **106** was obtained in a 14:86 ratio with the lactone product **107**. Curiously, the hydroxyester **106** appeared to have been formed non-stereoselectively (Scheme 29).[154] In contrast, lactones **107** were obtained in high diastereo- and enantiomeric excess from reactions of **105** with either aromatic or aliphatic aldehydes.

Based on their mechanistic studies, Campagne et al. concluded that the hydroxyester **106** was formed from a non-selective vinylogous aldol reaction. On the other hand, the lactone **107** did not actually arise from an aldol process at all. Instead, they suggested that an initial unselective α-aldol was followed by a retro-aldol to give a Cu(I)-allyl species. This apparently attacked the aldehyde to give the enantiomerically enriched lactone. The unselective Cu(I)-promoted vinylogous aldol reaction leading to **106** is an interesting contrast to the highly successful Ti(IV)-BINOL-catalyzed reactions of thioester **81** to give adducts **82** previously described (Scheme 24, Eq. B).[137]

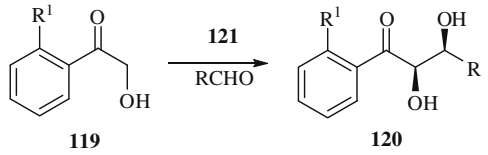
Recently, Shibasaki et al. developed a ferrocenyl ligand **110** (Taniaphos; Scheme 30) for use with Cu(I) in asymmetric Mukaiyama aldol additions.[155] The general structure of this catalyst system is similar to those of the Cu-BINAP complexes previously developed by Carreira,[145,151] Shibasaki (Scheme 28)[152] and



Scheme 31. Ag(I)-catalyzed Mukaiyama aldol reactions; (*E*)-enolates lead to *anti*-adducts, and (*Z*)-enolates yield *syn*-adducts. Catalytic system: 6% (*R*)-BINAP, 10% AgOTf 5–10% KF, 5–10% 18-crown-6.

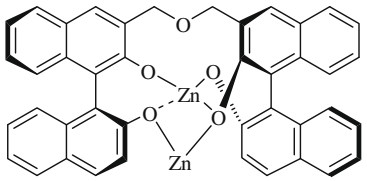


Scheme 32. Trichloroacetate enol ethers as donors in a Mukaiyama-type aldol addition catalyzed by Ag(I). Reagents and conditions: 8% (*R*)-BINAP, 17% AgOTf, 6% $Bu_2Sn(OMe)_2$, 5 equiv MeOH THF, 3 Å ms, −20 °C, 24–96 h.



119a, 120a: R^1 = H;
10 mol% **121**; 20 mol% Ph_3PO
79 - 89% yields
67:33 - 88:12 dr
77-86% ee

119b, 120b: R^1 = OMe; 1 mol% **121**
81 - 95% yields
72:28 - 97:3 dr
87-89% ee



121

Scheme 33. *syn*-Selective glycolate aldol reactions promoted by zinc catalyst **121**.

Campagne (Scheme 29).[153,154] Shibasaki's early work had demonstrated the use of ketones as acceptors, albeit with only one example using BINAP as the ligand (Scheme 28).[152] Various other bisphosphine ligands afforded only mediocre results.[156] However, Cu(I) complexes with bisphosphine **110** promoted highly successful Mukaiyama aldol additions of ketene silyl acetals **108** with a variety of ketones (Scheme 30).[155]

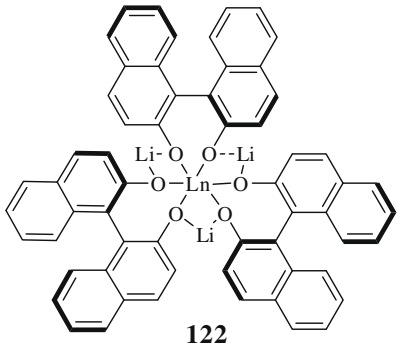
Yamamoto et al. described asymmetric Mukaiyama aldol reactions of trimethoxysilyl enol ethers with various aldehydes catalyzed by (*S*)-*p*-Tol-BINAP/Ag(I) complexes.[157] Good levels of both diastereoselectivity and enantioselectivity were attained (Scheme 31). Cyclic enol ethers **111** gave predominantly *anti*-adducts **112**, while the acyclic (*Z*)-enol ether **113** afforded the *syn*-adducts **114**.

Similar results were recently reported for aldol reactions of alkenyl trichloroacetate donors **115** and **117**;[158] yields and selectivities of adducts **116** and **118** were moderate to excellent (Scheme 32). However, in this catalytic system, 6 mol % of $Bu_2Sn(OMe)_2$ was required in addition to silver triflate and (*R*)-BINAP ligand in contrast to the conditions reported for silyl enol ethers and ketene acetals in Scheme 31. The authors postulate that the alkenyl trichloroacetate initially reacts with the tin species to generate the corresponding tin enolate, which then undergoes the asymmetric aldol addition to either aromatic or aliphatic aldehydes catalyzed by Ag(I).

Direct asymmetric aldol processes, a major goal in the field of chiral metal catalysis for long, are now quite feasible.[128] The (*S*,*S*)-Zn–Zn-linked BINOL catalyst **121** promotes direct aldol reactions of α-hydroxyacetophenone with aldehydes, providing excellent yields and high levels of diastereo- and enantioselectivity (Scheme 33).[159] When hydroxyacetophenone (**119a**, R^1 = H) was the ketone donor, good yields and moderate stereoselectivities of *syn*-diol products **120a** were obtained without the need to protect the hydroxyl group in the donor (Scheme 33).[160–162] However, a high proportion of catalyst was required (10 mol %), and the results were consistently better with α-branched aldol acceptors. When 2-methoxy-2′-hydroxyacetophenone (**119b**, R^1 = OMe) was the donor, the yield, diastereoselectivity and enantioselectivity increased, and only 1 mol % of catalyst was needed.[160,161]

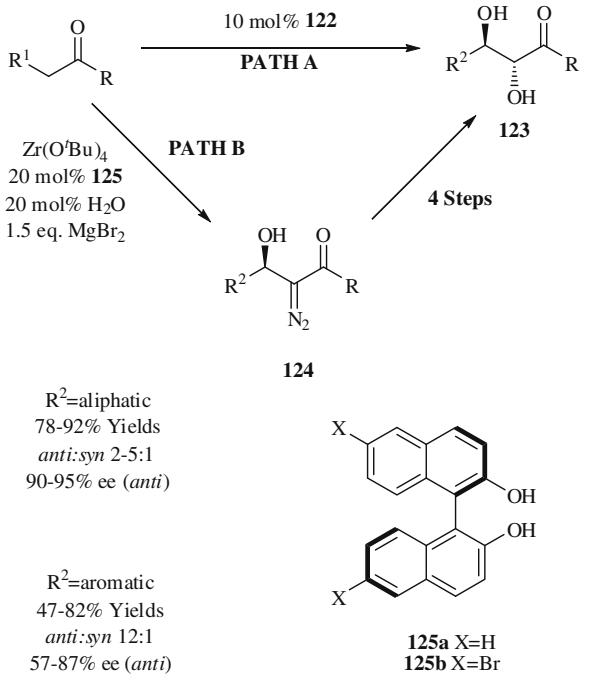
The improved yield and selectivity obtained from the additional chelating group in **119b** are noteworthy. The authors pointed out that this structural requirement does not really restrict the application of their method, as the electron-rich aryl group permits easy modification by Baeyer–Villiger or Beckmann chemistry, leading to products formally derived from esters or amides, but not directly accessible by a catalytic aldol (or Claisen) reaction. However, aromatic substituents on acceptor aldehydes were found to influence both diastereo- and enantioselectivity,[163] and as a result this catalyst is only useful for aliphatic aldehydes.

While the Zn(II) catalyst promotes the formation of *syn*-glycolate adducts,[162] the $LnLi_3$ tris[(*R*)-binaphthoxide] catalyst **122** (LLB, Fig. 6)[161] and Zr(IV)-complexes of BINOL **125**[164] catalyze the production of the *anti*-glycolate adduct **123** (Scheme 34). LLB **122** accesses the *anti*-adducts directly, and is particularly successful with aliphatic aldehydes as acceptors (Scheme 34, path A); in contrast, Zr(IV)-**125** catalyst accesses *anti*-adducts **123** only indirectly via manipulation of an α-diazo group as in **124** (Scheme 34, path B).[164] Chemical yields and/or enantioselectivities obtained in these reactions were highly variable and were typically only moderate for the majority of aldehydes, even with a high loading of 20 mol % catalyst. These two catalytic systems are complementary in the sense that LLB is most successful with aliphatic aldehydes, while the zirconium catalyst is best with aromatic, heteroaromatic and unsaturated aldehydes. It should also be pointed out that the LLB catalyst **122** yields the *anti*-adducts **123**[128] predominantly, whereas Zn-BINOL **121** yielded the *syn*-adducts **120**[160–162] from similar substrates (Scheme 33).



122

Figure 6. Structure of LLB (122).



Scheme 34. Direct and indirect generation of *anti*-diols **123** via LLB-catalyzed and Zr-BINOL-catalyzed aldol additions, respectively.

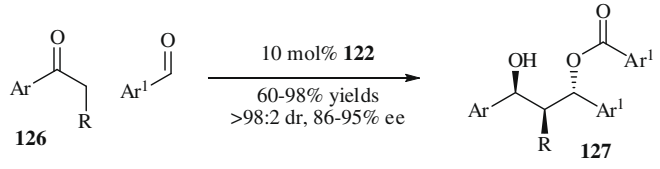
The aldol-Tischenko reaction is a useful method for generating 1,3-diols.[165] In a direct aldol-Tischenko reaction of ketones **126** with aromatic aldehydes catalyzed by **122**, *syn*-adducts **127** were obtained with very high levels of diastereoselectivity and good to excellent enantioselectivity (Scheme 35).[166,167]

Another interesting example of an aldol-Tischenko reaction was demonstrated in which the metal enolate was formed via a retro-aldol process (Scheme 36).[168] Aldol adduct **128** underwent a retro-aldol process in the presence of $Zr(O^tBu)_4$ and ligand **130** to give aldol-Tischenko adduct **129** in moderate yields and enantioselectivities, and in high *anti*-diastereoselectivities.

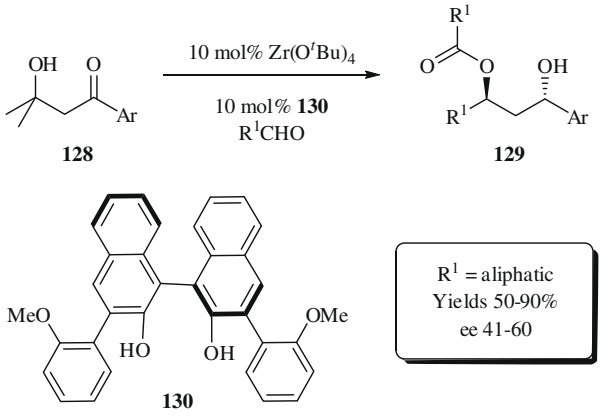
Kanai and Shibasaki et al. developed a Cu(II)-(*R*)-difluorphos (**133**) catalytic system effective in a homoaldol-like multicomponent coupling process.[169] This system could efficiently generate unsaturated lactones **132** by assembling allenyl esters **131**, ketones and dialkylzincs (Scheme 37). The Lewis basic additives (HMPA, DMSO or $Ph_2S{=}O$) were crucial to the generation of lactone **132** by promoting retro-aldolization of the undesired α-aldol product, thus favouring the γ-adduct.

Development of catalytic systems for activating esters or methylene ketones as nucleophiles in direct aldol-type reactions is more challenging. Mahrwald found that Ti(IV) alkoxide complexes with (*R*)-mandelic acid and *racemic* BINOL (**134** and **135**, Fig. 7) catalyzed crossed-aldol reactions of 3-pentanone with various aldehydes to yield predominantly *syn*-adducts. The levels of diastereo- and enantioselectivity were generally good, albeit somewhat lower than those for Mukaiyama aldol additions with Ti-BINOL (Scheme 24). The initial work that was reported used stoichiometric amounts of Ti(IV),[170] but in a subsequent paper Mahrwald reported that as low as 0.2 mol % of catalyst in a neat mixture of aldehyde and ketone was effective.[171] Interestingly, both Ti(IV) and mandelic acid were required for *reaction*; neither $Ti(OR)_4$ nor mandelic acid alone was able to catalyze the direct aldol addition. While the origin of this reactivity is unclear, these results may point towards a general alternative to the Mukaiyama aldol addition catalyzed by Ti(IV)-BINOL reported earlier (Scheme 24).

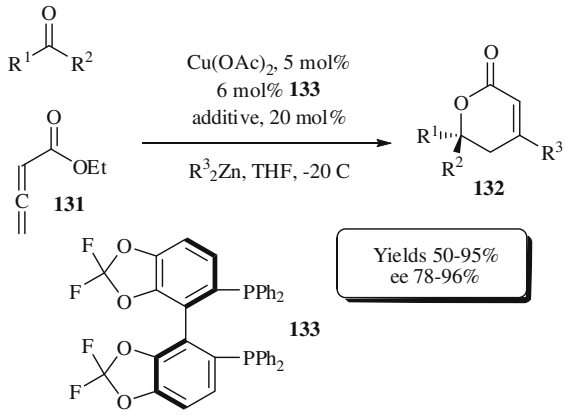
Mahrwald's catalysts displayed some curious features. On heating, mixtures of $Ti(O^iPr)_4$ and *R*-mandelic acid formed crystalline Ti_2(*R*-mandelate)$(O^iPr)_7$, which catalyzed highly *syn*-selective aldol reactions but afforded no enantioselectivity. When this complex was treated with *rac*-BINOL, a new complex was formed that the



Scheme 35. Direct aldol-Tischenko reaction catalyzed by LLB **122** to yield *syn*-adducts **127**.



Scheme 36. Catalyzed retro-aldol, aldol-Tischenko addition.



Scheme 37. Three-component assembly to generate lactones catalyzed by Cu(II)-(*R*)-difluorphos.

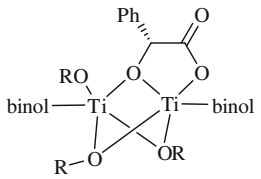


Figure 7. Proposed structures of Mahrwald's Ti(IV) aldol catalysts.

authors identified as (*rac*-binol)$_2$-Ti$_2$(O^iPr)$_3$-mandelate (**134**).[171] They did not report the characterization of this material, but found that it catalyzed aldol reactions with high *syn*-selectivity and *good enantioselectivity*. What is puzzling is their observation that while BINOL was essential for enantioselectivity, the same result was obtained using catalysts based on racemic or pure enantiomer of BINOL! Further, in his initial publication,[170] Mahrwald remarked that catalysts prepared from (*S*)-mandelic acid rather than from (*R*)-mandelic acid apparently were much less enantioselective, but offered no explanation for this curious observation. A later publication[172] reported that Ti$_4$(μ-BINOLato)$_6$(μ$_3$-OH)$_4$ clusters always contained only one BINOL enantiomer whether the catalyst was formed from pure *R*- or *S*-BINOL or from the racemate. Very recently, Mahrwald et al. reported a tetranuclear BINOL-titanium complex that was able to catalyze the direct aldol addition with high regio- and diastereoselectivity; however, extended reaction times were required, and enantioselectivities were not reported.[173]

3.2. Bis(oxazolidine) (BOX) ligands

It has been known for at least 10 years that the combination of Cu(OTf)$_2$ and a chiral BOX ligand is an efficient catalyst for aldol reactions, affording high chemical yields and excellent levels of diastereoselectivity and enantioselectivity.[174–176] The use of BOX ligands in asymmetric catalysis in general was reviewed in 2006.[177] Historically, the use of metal-BOX catalysts has been restricted to Mukaiyama-type processes; however, recent developments related to the aldol reaction have focused on supported BOX catalysts, expanding the range of substrate types that can be employed, as well as direct aldol additions.

Heterogeneous catalysts are easily separated from reaction products, and this has made them preferable to most homogeneous catalysts in process chemistry. A comprehensive review of supported and recoverable chiral catalysts has appeared, as well as a review of supported BOX catalysts in particular.[178,179] In a recent example, Cu(OTf)$_2$/**136** (Fig. 8) was shown to catalyze the Mukaiyama aldol reaction of **71** with methyl pyruvate **90** (Scheme 38, Eq. A). The reaction was slower than the homogenous version, but still gave a 90% yield of adducts **138** and **139** in 1 h with 92% ee.

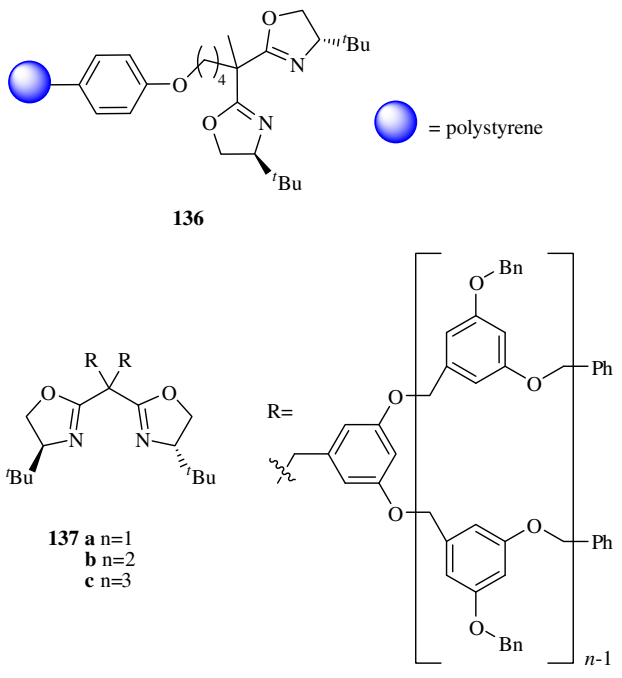
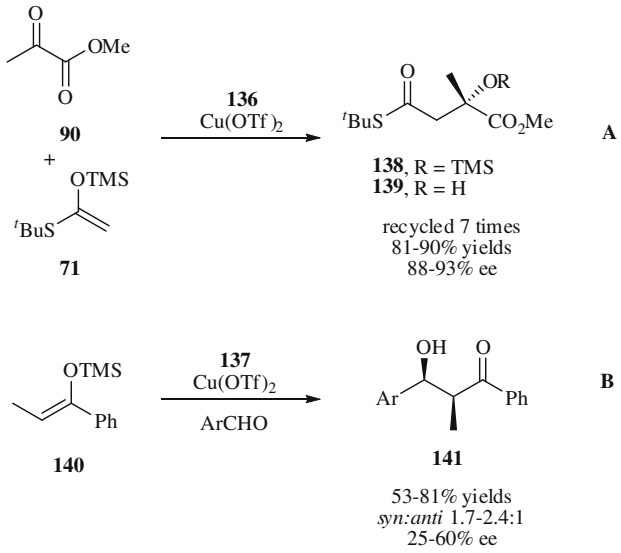


Figure 8. Polymer- and dendrimer-supported BOX ligands.

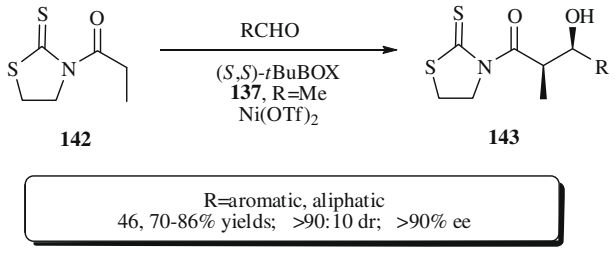


Scheme 38. Recent applications of heterogeneous supported-BOX catalysts **136** and **137** in asymmetric aldol reactions.

The polymer-bound catalyst was re-used up to seven times.[180] This increased the reaction times from 60 to 240 min, but the stereoselectivity of the reactions remained fairly consistent from cycle to cycle. The authors found that the yields declined, and more of the alcohol **139** was formed in subsequent cycles. These observations were explained by the accumulation of moisture in the polymer. Addition of fresh molecular sieves removed this water, leading to 96% yields of **138** and **139** in the final cycles.

Dendrimer-supported BOX ligands **137** (Fig. 8) have also been prepared.[181] The Cu(II)/**137** complexes promoted Mukaiyama aldol reactions in aqueous/organic solvent mixtures (Scheme 38, Eq. B) in which they are reasonably soluble. At the end of the reaction, the catalyst was cleanly precipitated by adding cold methanol, and was collected by filtration. Thus, the reactions occurred in a homogeneous medium, but the advantages of an insoluble support were maintained. The authors suggested that the dendrimer structure may offer better control of the deposition of the catalytic species, bridging the gap between soluble and insoluble polymeric supports. The performance of **137**/Cu(II) was comparable to that of unsupported BOX/Cu(II) in similar aqueous solvents, although the enantioselectivities were modest.[181] The dendrimeric catalyst was re-usable, but the yields, diastereo- and enantioselectivities of the reactions greatly decreased with each subsequent run.

The first examples of catalytic, enantioselective direct aldol reactions of simple carboxylic acid derivatives have been reported by Evans et al.,[182] using propionyl thiazolidinethione nucleophiles. Attempts to adapt their successful MgCl$_2$-catalyzed *anti*-selective aldol reactions of chiral oxazolidinone auxiliaries[62] to a catalytic protocol were unsuccessful.[182] However, they found that *syn*-aldol adducts **143** were generated with high stereoselectivity in the presence of 2,6-lutidine and TMSOTf, using [Ni((*S*,*S*)-^{t}BuBOX)](OTf)$_2$ as catalyst, when the nucleophile contained a thiazolidinethione group (e.g., **142**, Scheme 39). One limitation of this system is the requirement for a chelating group in the nucleophilic component in order to obtain sufficient levels of diastereo- and enantioselectivity. If one has to transiently incorporate a covalently bound chelating functionality into the substrate to achieve efficient asymmetric catalysis as in Scheme 39, arguably a thiazolidinethione chiral auxiliary would be an equally logical choice. This is not the only catalytic system that requires an additional chelating source, Zn-based catalyst **121** discussed earlier (Scheme 33) did as well.



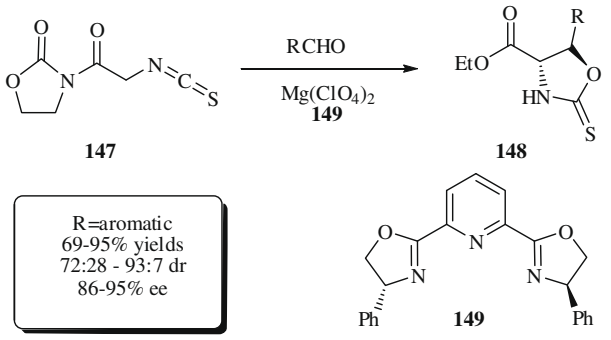
Scheme 39. Synthesis of *syn*-adducts from *N*-propionyl thiazolidinethione catalyzed by chiral Ni-BOX.

A particularly interesting and very useful application of a bis(oxazoline) (**146**) was published by Shair in 2005 (Scheme 40).[183] Here, the aldol donor is activated by decarboxylation of β-ketoacid **144** in the presence of the aldehyde acceptor. This system tolerates many functional groups, including protic groups that are incompatible with base-mediated aldol conditions. The reactions provide good yields and diastereoselectivities, along with excellent enantioselectivities of *syn*-adducts **145**. Shair's method is less successful with α-branched aldehydes, requiring excess aldehyde to obtain good conversion, nor does it accept α,β-unsaturated or electron-rich aryl aldehydes. This method will likely be very useful, as it can afford remarkable levels of regioselectivity, chemoselectivity and stereoselectivity in many cases, and alleviates the need for pre-formed enolates.

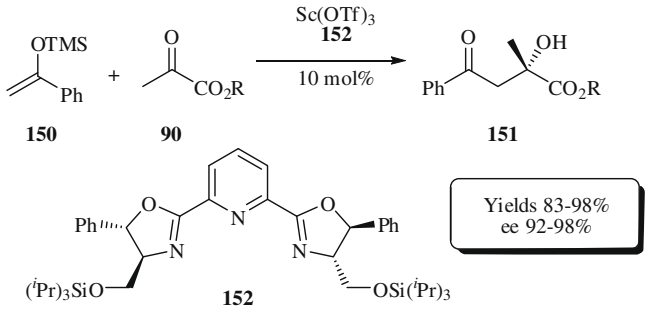
A PyBOX ligand was recently applied to the asymmetric synthesis of β-hydroxy-α-amino acids (Scheme 41).[184] The catalyst was derived from ligand **149** and $Mg(ClO_4)_2$. Several aromatic aldehydes were reacted with *N*-(isothiocyanatoacyl) oxazolidinone **147** to yield oxazolidinethione adducts **148**, which could be hydrolyzed to form the corresponding β-hydroxy-α-amino acids. The reactions proceeded in good to excellent yields. The stereoselectivity of these processes was generally good, but showed wide variability as a function of the aldehyde used.

The lanthanide-PyBOX **152** catalytic system was recently demonstrated in a Mukaiyama-type aldol reaction between **150** and ketoester acceptors **90** to give adducts **151** (Scheme 42).[185]

Mlynarski et al. have reported that both iron(II) chloride[186] and zinc triflate[187] with PyBOX ligands **153** or **154** were able to catalyze Mukaiyama aldol reactions in aqueous media (Scheme 43). Silyl enol ether *Z*-**140** and aromatic aldehydes were successfully coupled to give *syn*-adducts **141**. Fe(II)/**153** was superior to Fe(II)/**154**,[186] while the Zn(II)/**154** catalyst gave better results than



Scheme 41. Synthesis of oxazolidinethiones promoted by Mg(II)-PyBOX **149**.

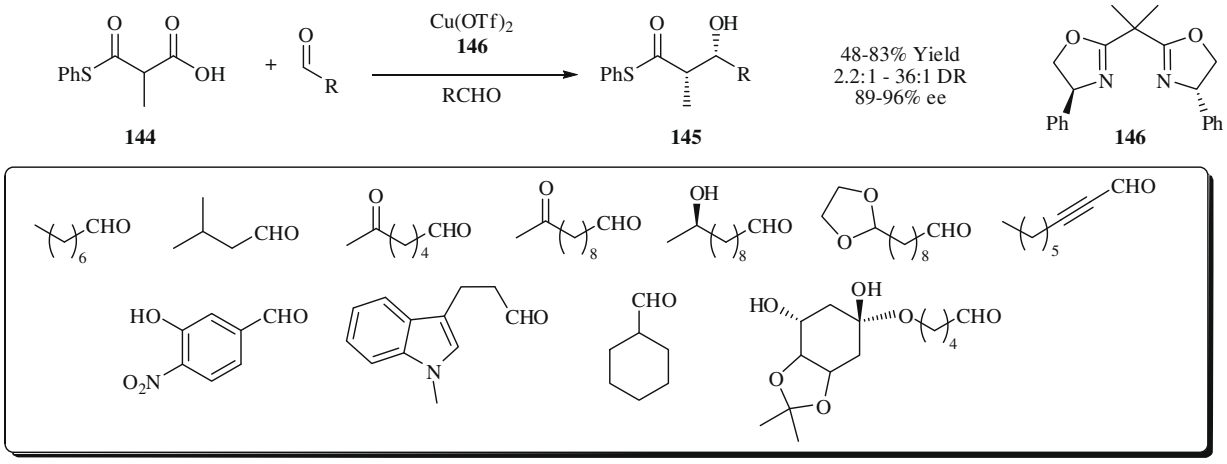


Scheme 42. PyBOX–Sc complex catalyzes enantioselective additions to pyruvate esters.

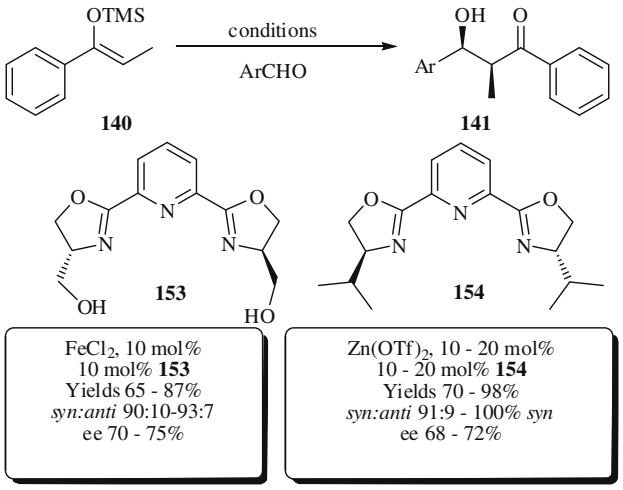
did the Zn(II)/**153** complex.[187] Unfortunately, aldol additions to olefinic and aliphatic aldehydes were lower yielding and less selective, and thus these catalysts are only practical for aromatic aldehydes. This is in contrast to the zinc catalysts reported earlier which were only successful for aliphatic aldehydes (Scheme 33).[162] This is the first example of a chiral iron complex active in aqueous media in Mukaiyama-type aldol additions.[186]

Mlynarski et al. recently published on a modified ligand **155**, also successful in aqueous solutions (Scheme 44).[188] Zinc triflate slightly outperformed iron chloride in both yields and selectivity. While both metals were less successful with aliphatic aldehydes, unsaturated aldehydes could be successfully utilized, in contrast to the earlier catalytic systems with ligands **153** and **154**.[186,187]

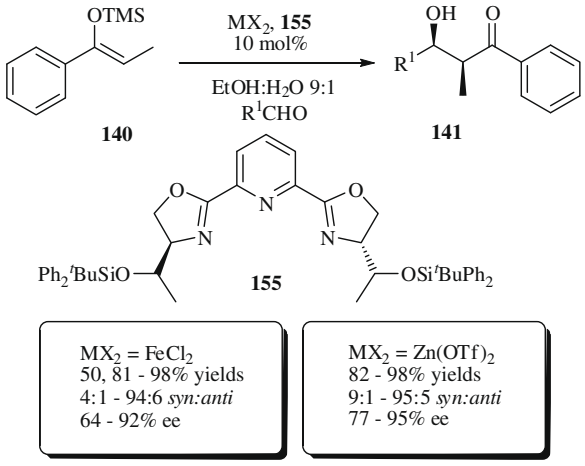
Loh et al. evaluated the PyBOX ligand **154** in Mukaiyama aldol additions catalyzed by In(III) triflate (Scheme 45).[189] Unlike the



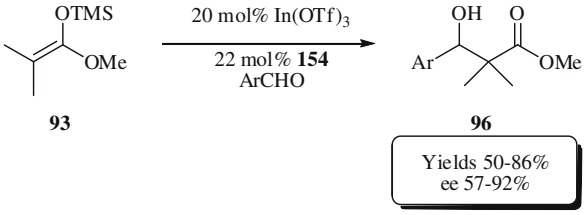
Scheme 40. In situ activation of an aldol donor by decarboxylation promoted by Cu(II)-BOX catalyst.



Scheme 43. *syn*-Selective Mukaiyama aldol additions promoted by M-PyBOX catalysts.



Scheme 44. Iron(II)- and zinc(II)-PyBOX complexes in asymmetric Mukaiyama aldol additions.



Scheme 45. Mukaiyama aldol additions to aromatic aldehydes catalyzed by In(III)/**154**.

aqueous chemistry in Scheme 43,[186] these additions required dry conditions. Loh et al. found that the aldol additions between silyl enol ethers **93** and aromatic aldehydes gave adducts **96** in moderate yield and enantioselectivity (Scheme 45). Just as Mlynarski et al. found,[186] Loh et al. obtained less satisfactory results with aliphatic aldehydes.[189] They also found that adding *iso*-propylalcohol or 2,6-di-*tert*-butyl-4-methylpyridine decreased the enantioselectivity of these catalysts, while addition of TMSCl resulted in complete loss of enantioselectivity.[189] The Zr(IV)-**98b** catalytic system previously discussed (Scheme 26, Eq. C) has some advantages over this In(III)-**154** system; not only did the zirconium system tolerate water (in fact, it required water for catalytic turnover), but it also generated adducts **96** in higher, less variable yields and enantioselectivities, and demonstrated a broader substrate tolerance.[148,149]

3.3. Salen ligands

For readers interested in a general overview of the catalytic properties of salen–metal complexes, an excellent review was recently published.[190]

The salen complexes **156**[191–193] and **157**[194] (Fig. 9) are efficient catalysts for vinylogous aldol reactions of the heterocyclic dienol ethers **158** and **161**, respectively. Katsuki et al. showed that Cr(II) salen **156** was effective at only 2.5 mol % to give adducts **159** or **160** from either aliphatic or aromatic aldehydes (Scheme 46, Eq. A).[191–193] The authors noted that addition of water or secondary alcohols improved the yields of these reactions, and suggested that hydroxylic substances promoted release of the aldol product from the catalyst, and thus suppressed the competing retro-aldol process. The presence of water or alcohol had only modest and inconsistent effects on the levels of diastereo- or enantioselectivity in these reactions. Evans earlier found that 5–10 mol % of aluminium salen hexafluoroantimonate complex **157** promoted reactions of aromatic aldehydes to give **162** (Scheme 46, Eq. B).[194]

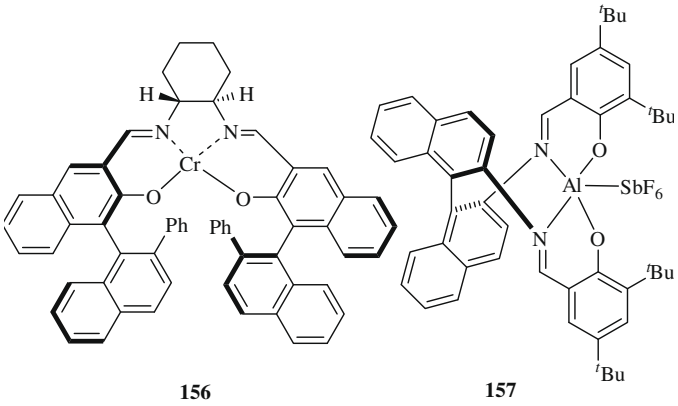
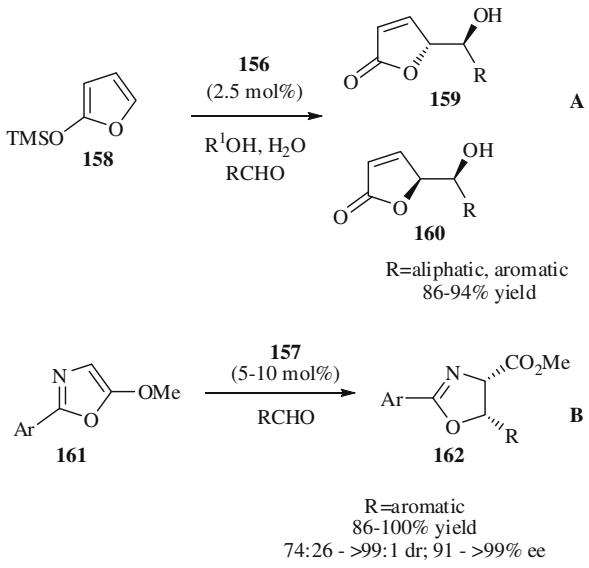


Figure 9. Cr(II)– and Al(III)–salen complexes **156** and **157** employed as catalysts for asymmetric vinylogous aldol reactions.



Scheme 46. Metal–salen catalyzed additions of heterocyclic dienol ethers to aliphatic and aromatic aldehydes.

A catalyst derived from $Cu(OTf)_2$ and chiral sulfonimine **166** was successfully used in Mukaiyama-type aldol addition between dienol **163** and α-keto ester **164** (Scheme 47).[195–198] It was determined that 1.2 equiv of 2,2,2-trifluoroethanol was crucial to generate high yields, but had no influence on the enantioselectivity.

3.4. Semi-crown ligands

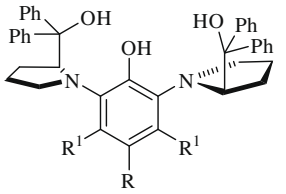
The semi-crown ligands developed by Trost et al. **167a** and **b** (Fig. 10), complex with Et_2Zn to function as double-activation catalysts.[199–205] These catalysts were successfully applied in direct acetate aldol reactions between various aldehydes and ketones.

While early work utilizing acetone as the donor and ligands **167** with Et_2Zn had moderate success in terms of yield and enantioselectivity, the formation of significant amounts of the dehydration product limited the utility of this reaction.[200] Later work utilizing ynones **168** and enones **171** as donors proved much more successful (Scheme 48).[204,205] This catalytic system is remarkable for several reasons. No dehydration byproducts were detected in these cases. No Michael addition products formed, despite the high propensity of ynones to react in that manner. Finally, there was no need for a large excess of one of the components, and both acceptor and donor were present in nearly stoichiometric amounts. However, these reactions were only successful with aliphatic aldehydes.

The Zn catalyst derived from **167a** and Et_2Zn also works very well in the reaction of α-hydroxy acetophenone with aliphatic aldehydes to yield *syn*-aldol adducts *ent*-**120** in good yield and enantioselectivity, but the reaction only provides modest levels of diastereoselectivity (Scheme 49).[206] Zn-**167** gives results similar to those of Zn-BINOL **121** (Scheme 33)[159–162] without the need for an additional chelating group in the donor substrate, as was required by the BINOL catalyst.

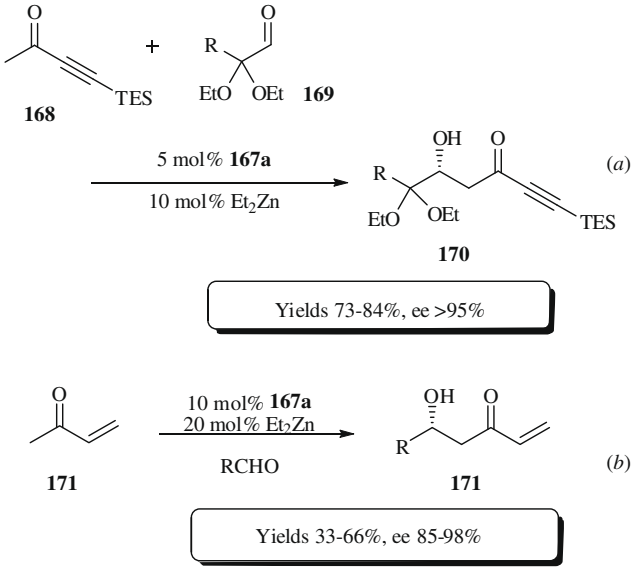
Mukaiyama aldol reactions between enol silanes **172** and aromatic aldehydes catalyzed by the Ga(III) complex with chiral semi-crown ligand **167b** provided *syn*-adducts **173** (Scheme 50).[207,208] Reactions with aromatic aldehydes were quite satisfactory, but unfortunately the aldol reactions of **172** with *n*-hexanal gave products having only low enantiomeric excess (30%). Likewise, acetate aldol reactions promoted by this catalyst proceeded in low yields and enantioselectivities. Even so, its success with aromatic substrates combined with the fact that the solvent used was a water–ethanol mixture makes this system very useful.

Kobayashi et al. found that Pr(III) triflate complexes of ligand **175** promoted reactions between enol silane **140** and a variety of aromatic aldehydes in aqueous ethanol, affording the *syn*-adducts

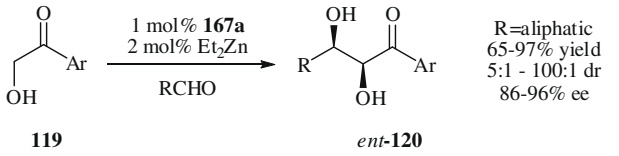


167 **a** R=Me, R^1=H
b R=H, R^1=Me
c R=^{t}Bu, R^1=H

Figure 10. Semi-crown ligand **167**.

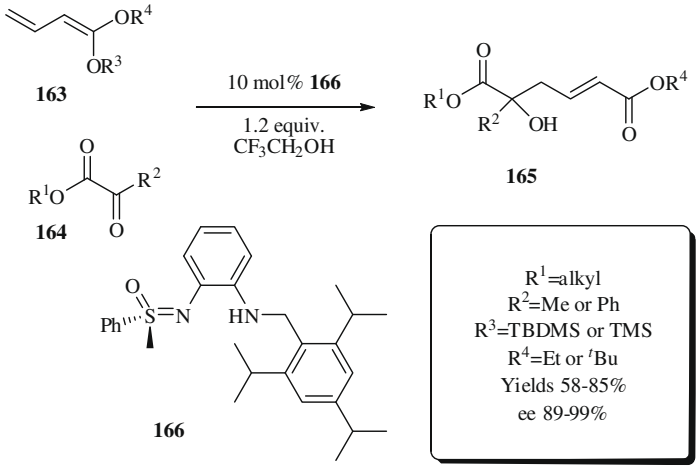


Scheme 48. Ynones and enones as aldol donors.

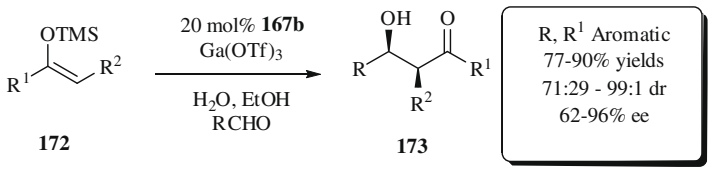


Scheme 49. Zn-semi-crown **167a**-promoted synthesis of *syn*-diols.

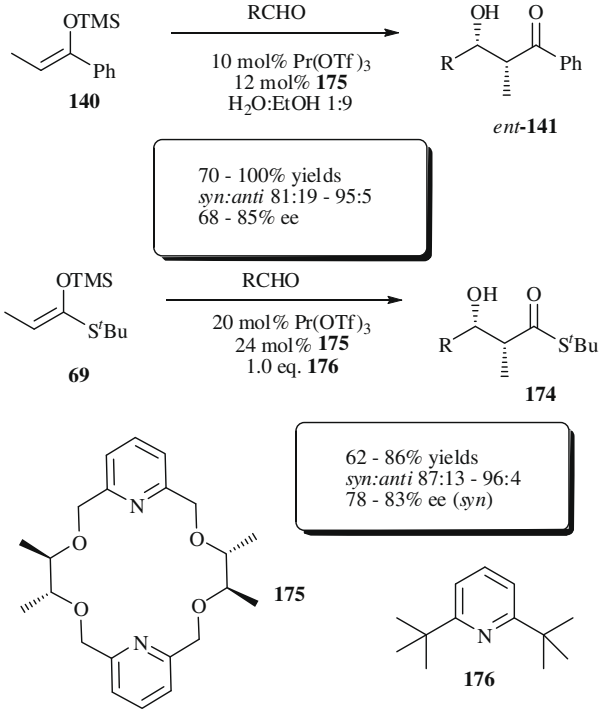
ent-**141** (Scheme 51).[209] Reactions of enol thioester **69** rather than those of the enol ether **140** required twice as much catalyst as well



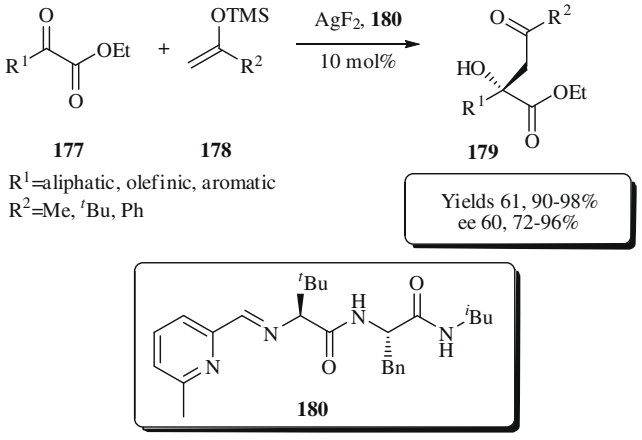
Scheme 47. Vinylogous Mukaiyama aldol addition promoted by Cu-**166**.



Scheme 50. Ga-semi-crown ligand **167b**-promoted Mukaiyama aldol reaction to give *syn*-adducts.

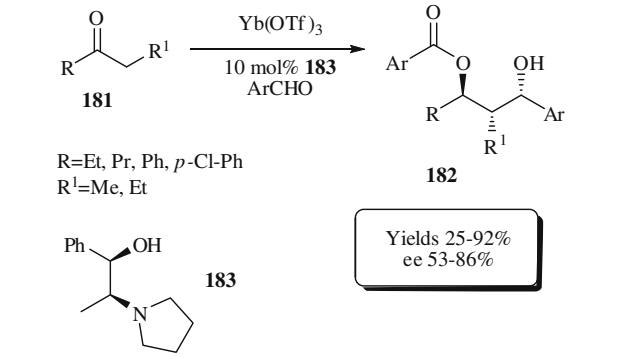


Scheme 51. Chiral aza-crown ether Pr(III) catalysts for Mukaiyama aldol reactions.

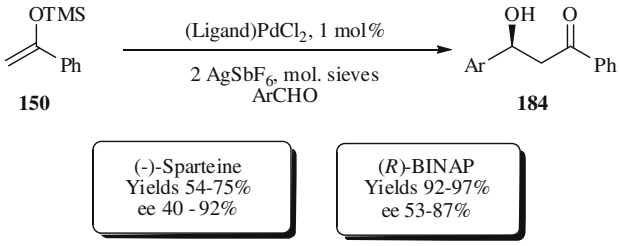


Scheme 52. Ag(II)-peptide-catalyzed Mukaiyama aldol additions to pyruvate derivatives.

as a stoichiometric amount of base **176** in order to proceed smoothly.[209] The size of the metal cation greatly influenced the levels of both diastereo- and enantioselectivity obtained from these reactions.[209,210] Although the Pr(III)-catalyzed reactions proceeded well in 9:1 EtOH/H_2O, larger proportions of water reduced the yields and selectivities observed.



Scheme 53. Yb-catalyzed aldol-Tischenko reaction.



Scheme 54. Pd(II)-mediated Mukaiyama aldol reactions.

3.5. Other catalytic systems

The catalyst derived from peptide ligand **180** and AgF_2 was found to successfully promote Mukaiyama aldol additions between α-keto esters **177** and silyl enol ethers **178** to give adducts **179** (Scheme 52).[211] The authors reported that when the aldol reactions performed on scales larger than 50 mg, 1 equiv of methanol was required to achieve complete conversion; it was thought that trace moisture present in small-scale reactions promoted the conversion, although the mechanistic details have yet to be elucidated.

A chiral Yb(III) complex obtained from $Yb(OTf)_3$ and amino alcohol **183** proved useful in catalyzed aldol-Tischenko reactions.[212,213] Ketones **181** and aromatic aldehydes were coupled to give 1,3-*anti*-diols **182** (Scheme 53). These reactions were sensitive to the electronic nature of the aldehyde acceptor; however, in most

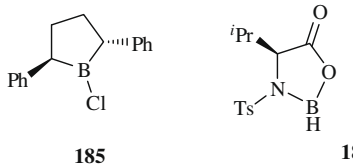


Figure 11. Early examples of chiral boron Lewis acids used in stoichiometric amounts to promote asymmetric aldol reactions.

examples, the yields and selectivities were moderate to good. All the reported examples utilized either symmetric aliphatic ketones or acetophenones. The Yb(III)/**183** catalytic system gives the same stereochemical outcome in aldol-Tischenko reactions as did LLB **122** (cf. **127**, Scheme 35).[166,167]

Sparteine-Pd(II) and BINAP-Pd(II) catalysts were evaluated in the Mukaiyama aldol reaction.[214,215] Enol ether **150** successfully coupled with aromatic aldehydes to give adducts **184** (Scheme 54). Unfortunately, reactions with aliphatic aldehydes were much lower yielding. NMR data supported the idea that the aldol reactions proceeded via a palladium enolate.

Boron Lewis acids have been known in the Mukaiyama aldol addition for over 20 years. The first examples required the Lewis acid in stoichiometric amounts, for example, chloroborane **185**[216] and valine-based **186**[217–221] (Fig. 11). Lewis acid **186** was shown to be successful for a variety of mono- and di-α-substituted silyl ketene acetals, but was less successful in acetate-type Mukaiyama aldol additions.[217–221] Lewis acid **186** promoted aldol additions of **172** to generate *syn*-adducts **173** in a reaction analogous to that shown in Scheme 50.

The 1990s saw a number of chiral boron Lewis acids synthesized and examined as catalysts for Mukaiyama aldol additions.

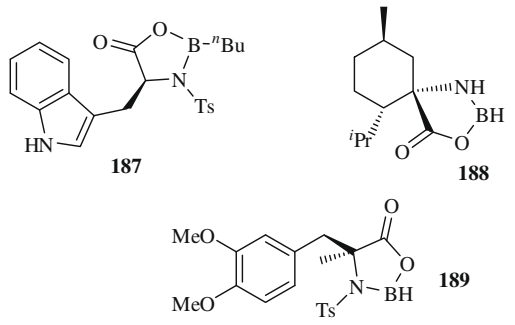
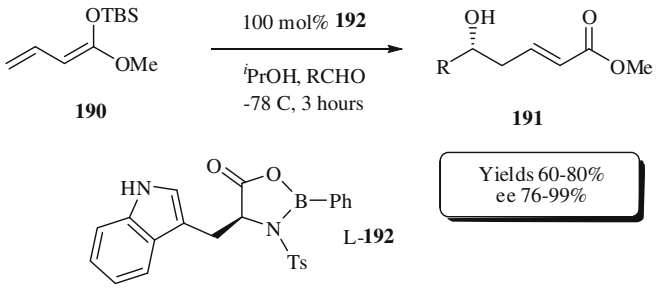


Figure 12. Other chiral boron Lewis acids.



Scheme 55. Oxazaborolidine-mediated vinylogous Mukaiyama aldol additions.

Representative examples of these are shown in Figure 12. Lewis acid **187** was first examined by Corey[222] and later by Yamamoto[223] in additions of silyl enol ethers, and it could be used in as little as 10 mol %. Compounds **188** and **189** were developed by Masamune et al. around the same time, and found similar success.[224,225] As is typical, reactions involving acetate-derived substrates are somewhat less enantioselective than those involving propionyl substrates; however, by modifying the substituent on the nitrogen[224,225] or boron,[223] enantioselectivity can be improved. A number of similar Lewis acids have been synthesized and evaluated; an overview was given in the recently published book on aldol additions.[226]

More recently, Kalesse et al. reported a tryptophan-derived oxazaborolidine efficient in mediating vinylogous Mukaiyama aldol additions between silyl ketene acetal **190** and a variety of aldehydes (Scheme 55).[227] While as little as 20 mol % **192** could generate good enantioselectivity, the authors found stoichiometric amounts of **192** were required for good chemical conversion to adducts **191**. In addition to the substrates described below, the authors also studied the influence of α-chiral aldehydes as acceptors with both L- and D-**192**. In most cases, catalyst **192** was able to overcome the stereochemical influence of the aldehydes.

3.6. Summary of advances in chiral metal catalysts

An early review of aqueous Mukaiyama aldol additions was published in 2001,[228] and another[229] appeared while the present review was being edited. Several examples of catalytic Mukaiyama aldol additions of propiophenone silyl enol ethers to aldehydes are summarized in Table 1. All these processes were successful in aqueous media, but consistent results were only obtained with aromatic aldehyde acceptors. Reactions with aliphatic aldehydes under these conditions gave variable yields and/or levels of stereoselectivity.

Several of the reports discussed above describe catalysts for the addition of silyl enol ethers to pyruvates. A summary of these can be found in Table 2. Many of the catalysts function effectively with loadings of 10 mol %, and afford similar yields and levels of enantioselectivity.

To date, most metal-catalyzed aldol reactions have been of the Mukaiyama type. As we have seen, this situation is changing as catalysts capable of promoting *direct* asymmetric aldol reactions are developed.[128] Shibasaki has suggested that a catalyst for a direct aldol reaction should present the combination of Lewis acidity and Brønsted basicity. His LLB complex based on this principle (Fig. 6) was the first to catalyze a direct asymmetric aldol between an aldehyde and an unmodified ketone. Shibasaki has emphasized on heterobimetallic catalysts as the best way to achieve the required balance of acid–base properties.[230] However, in 1998 he also reported that a monometallic Ba(II)-BINOLato complex moderately promoted enantioselective acetate aldol additions at only 5 mol % loading.[231]

Table 1
Catalyzed asymmetric Mukaiayama aldol additions of propiophenone to various aldehydes in aqueous media

Metal (mol %)	$Cu(OTf)_2$ (n.g.)[a]	$FeCl_2$ (10)	$Zn(OTf)_2$ (10–20)	$Ga(OTf)_3$ (20)	$Pr(OTf)_3$ (10)
Ligand (mol %)	Supported BOX **137** (n.g.)[a]	PyBOX **153** and **155** (10)	PyBOX **154** and **155** (10–20)	Semi-crown **167b** (20)	Semi-crown **175** (12)
Substrates tolerated	PhCHO	Aromatic RCHO[b]	Aromatic RCHO[c]	Aromatic RCHO[d]	Aromatic RCHO[b]
Yields	53–81%	65–98%	70–98%	77–90%	70–100%
Diastereoselectivity	1.7:1–2.4:1 *syn:anti*	4:1–94:6 *syn:anti*	9:1–>99:1 *syn:anti*	71:29–99:1 *syn:anti*	81:19–95:5 *syn:anti*
Enantioselectivity	25–60%	64–92%	68–95%	62–96%	68–85%
Reference	Scheme 38[181]	Schemes 43 and 44[186,188]	Schemes 43 and 44[187,188]	Scheme 50[207,208]	Scheme 51[209,210]

[a] n.g. = not given in paper.
[b] When aliphatic aldehydes were used, the conversion greatly decreased.
[c] In some cases, aliphatic aldehydes could be utilized with success, but were highly substrate- and condition-dependent.
[d] Adducts from aliphatic aldehydes were formed in good yields, but the enantioselectivities were low.

Table 2
Summary of catalysts for asymmetric Mukaiyama additions to pyruvate esters and derivatives

Metal (mol %)	$Ti(O^iPr)_4$ (20)	$Cu(OTf)_2$ (7)	$Sc(OTf)_3$ (10)	$Cu(OTf)_2$ (10)	AgF_2 (10)
Ligand (mol %)	(*R*)-BINOL (22)	Supported BOX **136**	PyBOX **152** (10)	Salen **166** (10)	Peptide **180** (10)
Notes	4 Å sieves	Recycled 7 times; 4 Å sieves	3–4 day rxn time	Vinylogous; 1.2 equiv CF_3CH_2OH	1–2 day rxn time
Yields	61–99%	81–90%	83–98%	58–85%	61, 90–98%
Enantioselectivity	83–99%	88–93%	92–98%	89–99%	60, 72–96%
Reference	Scheme 25[146]	Scheme 38[180]	Scheme 42[185]	Scheme 47[195–198]	Scheme 52[211]

Other results suggest that it is not essential to employ mixed-metal catalysts, although polynuclear complexes seem to have predominated. We have noted Mahrwald's homobimetallic Ti(IV) catalysts (**134** and **135**, Fig. 7).[171] Mahrwald has further demonstrated that complexes containing four Ti(IV) ions are likewise effective in stereoselective direct aldol additions.[172,173] Similarly, bimetallic zinc complexes **121** (Scheme 33) and those derived from Et_2Zn and **167** (Fig. 10, Schemes 48 and 49) have been utilized to promote direct aldol additions. Clearly, the structural prerequisites for metal-based direct aldol catalysts have not yet been fully delineated.

The stereoselectivity of metal catalysts can often be 'tuned' by changes in the ligand structure, the metal centre and/or use of additives in the reaction medium, giving them a distinct advantage over chiral auxiliaries. The selectivity obtainable using a chiral auxiliary is generally restricted to modulation only by additives, or by substantial changes in the reagents used. However, metal catalysts appear to be more susceptible to influence by structural variations in the substrates. It is not clear from these methodology papers how much substrate functionality the catalysts can tolerate. It appears that considerable screening may be required to determine the optimal catalyst for a given synthetic transformation.

4. Chiral organocatalysts

Organocatalysis is one of the most exciting advances in the field in recent years. Aldol additions of unmodified ketones or aldehydes promoted by small organic molecules arose from attempts to mimic the action of aldolase enzymes, but it was the work of Macmillan that brought organocatalysts to the fore. An interesting historical look at organocatalysis was recently published.[232] There are already several excellent reviews discussing organocatalysis in the aldol reaction, as well as organocatalysis in general.[233–241] Alleman et al. recently discussed stereoselectivity models for proline- and imidazolidinone-catalyzed aldol reactions.[233] As well, many papers have presented models and discussed theoretical aspects of organocatalysis[242–245] based on the earlier Hajos-Parrish[246] and/or Agami models.[247]

A general limitation of organocatalysis in crossed-aldol reactions of ketones with aldehydes is the requirement for a large excess of the ketone as aldehydes can also act as donors; acetaldehyde can trimerize (4% yield, 84% ee).[248] The use of enolizable aldehydes has also long been problematic,[249] but the proline-catalyzed aldolization has unexpectedly opened new routes towards this challenging goal. The cross-aldol reaction of aldehydes is a formidable challenge on account of the propensity of aldehydes to polymerize and because non-equivalent aldehydes must partition selectively into two discrete components, a nucleophilic donor and an electrophilic acceptor. One way that this has been achieved is the slow (syringe pump) addition of the donor aldehyde to a mixture of proline **193** (10 mol %) and acceptor,[250] although recently an alternative to this has been reported (vide infra).

4.1. Proline

Proline **193** (Fig. 13), its derivatives and close structural analogues were among the first organocatalysts utilized in the aldol reaction. Several computational studies of the mechanism of proline-catalyzed aldol reactions have appeared.[242,243,251,252] The early studies utilizing proline as a catalyst reported several issues, including variable yields and diastereoselectivities and dehydration of the adducts as a competing reaction.[253,254] Also, α-unbranched (and thus readily enolizable) aldehydes generally afforded low yields due to competing self-aldolization and the formation of unwanted condensation products.[253–256] However, through the perseverance of many research groups, organocatalysis is beginning to evolve into a reliable method for inducing asymmetry in the aldol reaction (Fig. 13).

One interesting and synthetically useful extension of the acetate aldol reaction involved a three-component, one-pot synthesis of β-amino alcohols.[257] Acetone, an aldehyde and an azodicarboxylate **194** undergo consecutive aldol and aldol-like additions to form adducts **195** (Scheme 56). While the overall yields and enantioselectivities were excellent, the diastereoselectivities to *anti*-adducts were generally only moderate, and the configuration of the major diastereomer was inconsistent.

L-Proline-catalyzed aldol reactions between simple cyclic ketones **196** and **199** and aldehyde acceptors have been reported to yield predominantly *anti*-adducts (Scheme 57).[253] The diastereoselectivity of such reactions was moderate, but *anti*-adducts **197** and **200** were formed in fair to good enantiomeric excesses.

One very interesting application of proline organocatalysis was the first report of asymmetric *enolexo* aldolizations.[245] Cyclization of dicarbonyl compounds **202** to form cyclic β-hydroxy aldehydes **203** generally proceeded in high yields, enantioselectivities and diastereoselectivities (Scheme 58). The sole exception was 4-methylheptanedial (**202**, R^{1-6} = H, R^4 = Me), which afforded a mixture of all four possible diastereomers.

A second example of proline-catalyzed *enolexo* cyclization of ketoaldehydes **204** was recently reported.[258] Substituted pyrrolidine **205** was formed in good yield and selectivity (Scheme 59).

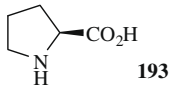


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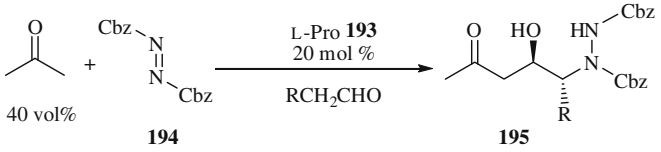
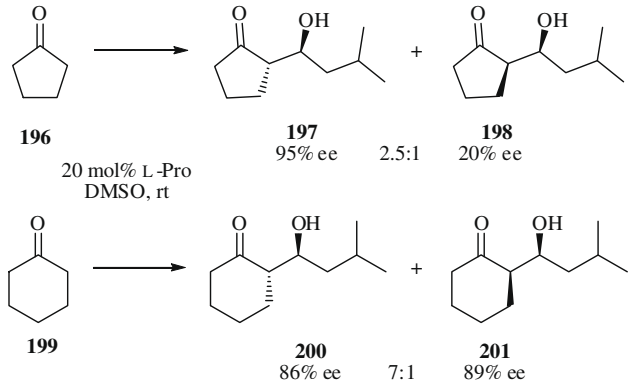
Figure 13. L-Proline, a conceptual basis for organocatalysts in the aldol reaction.



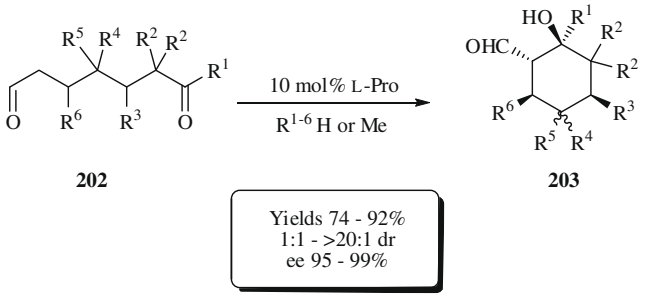
R = aliphatic
Yields 76-85%
anti:*syn* 29:71 - 85:15
ee (*anti*/*syn*) >99%/(13-91%)

Scheme 56. Synthesis of β-amino alcohols via consecutive aldol type additions catalyzed by L-proline.

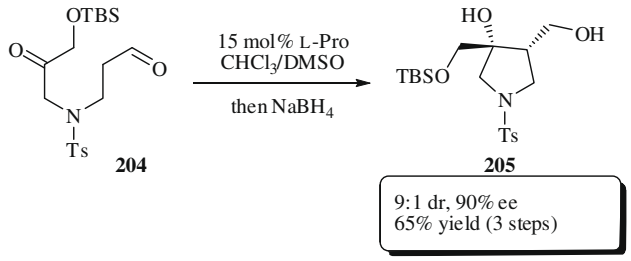


Scheme 57. Simple *anti*-selective aldol reactions of cyclic ketones and *i*-butyraldehyde catalyzed by L-Pro.

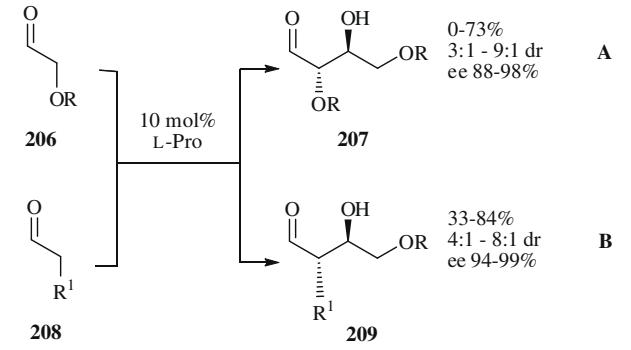
In a 2004 paper, both self-aldolization (Scheme 60, Eq. A) and a crossed-aldol reaction between aliphatic aldehyde donors **208** and an α-oxyaldehyde **206** were examined (Scheme 60, Eq. B).[259] Excellent enantioselectivities were obtained in these reactions, albeit



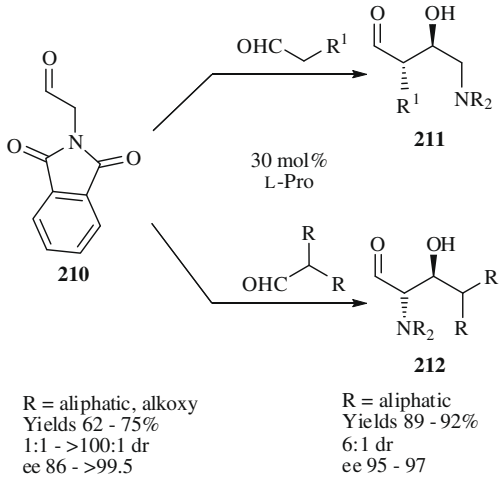
Scheme 58. *Enolexo* cyclization reactions catalyzed by L-proline.



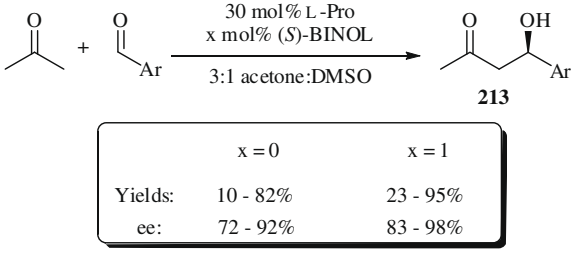
Scheme 59. Proline-catalyzed *enolexo* cyclization leading to a substituted pyrrolidine.



Scheme 60. Aldol synthesis of 1,2,3-triols and 2,3-diols catalyzed by L-proline.

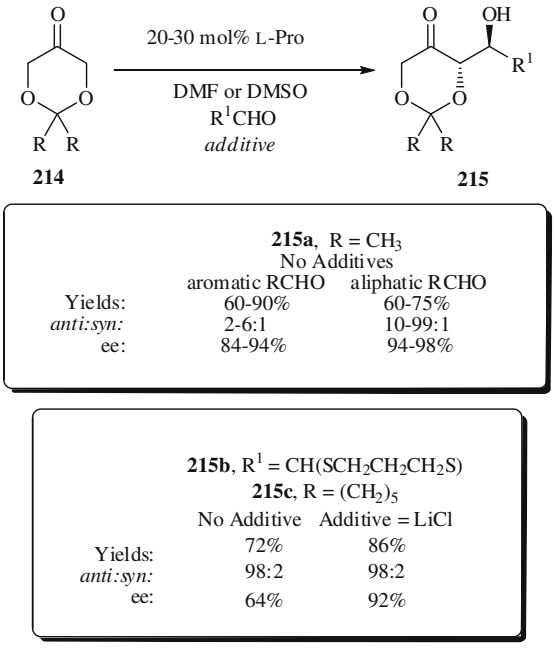


Scheme 61. Synthesis of β-hydroxy-α-amino aldehydes and β-hydroxy-γ-amino aldehydes.



Scheme 62. Effects of BINOL on the enantioselectivity of organocatalyzed aldol reactions of acetone.

with moderate yields and diastereoselectivities of both **207** and **209**. In Scheme 60, Eq. B, the α-oxyaldehyde acted as the electrophile, unless the aldehyde nucleophile was α-disubstituted. A recent review discusses organocatalysis in the synthesis of carbohydrates.[260]



Scheme 63. Aldol additions of dihydroxyacetone derivatives catalyzed by L-proline.

Examples of direct aldol reactions with glycine enolate donors are very limited. In a process similar to that described above,[259] L-Proline has been used to catalyze the synthesis of β-hydroxy-α-amino aldehydes **212** and β-hydroxy-γ-amino aldehydes **211** from glycyl aldehyde **210** (Scheme 61).[261] The difference in regioselectivity reflects the reactivity differences of the two aldehydes; α-disubstituted aldehyde enolates are less reactive donors and thus these aldehydes only act as acceptors. In contrast, when α-monosubstituted aldehydes were used under the same conditions the opposite regioselectivity was seen. This is analogous to the results obtained in L-proline organocatalyzed aldol reactions of α-oxyaldehydes **206** shown in Scheme 60 above.[259]

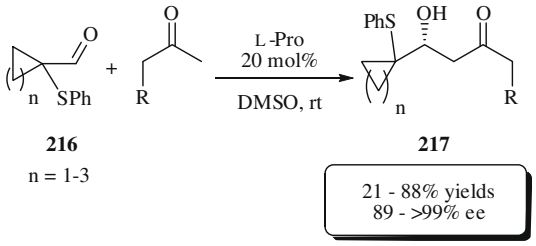
Zhou and Shan reported in 2006 that adding only 1% of (*S*)-BINOL to proline-catalyzed aldol additions between acetone and aromatic aldehydes increased the enantiomeric purity of the aldol adducts **213** (Scheme 62).[262,263]

Hydroxyacetone is an effective donor in proline-catalyzed aldol additions, but dihydroxyacetone was found to be unreactive unless the hydroxyl groups were blocked.[264] Once protected as ketal **214**, *anti*-adducts **215** were formed in good yields and selectivities (Scheme 63). The reaction was sensitive to the nature of the diol-protecting group,[264,265] but was successful for both aliphatic and aromatic aldehyde acceptors.[264] One group found that addition of either pyridinium *p*-toluene sulfonate (PPTS) or LiCl increased both yields and enantioselectivities, with LiCl being most effective.[265]

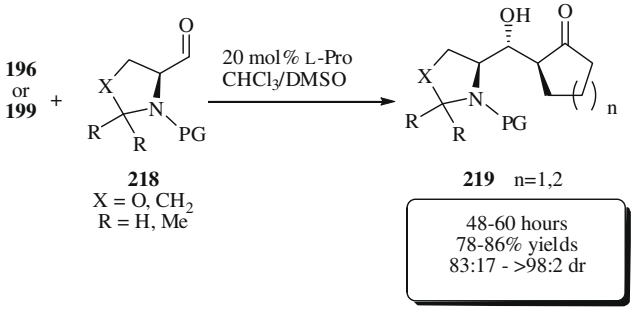
L-Proline was also found to catalyze the addition of methyl ketones to α-thio-substituted cycloalkyl aldehydes **216** (Scheme 64).[266] While yields were somewhat variable, the adducts **217** were generally formed with excellent enantioselectivity.

α-Amino aldehydes **218** (PG = protecting group) were also recently found to be good acceptors in proline-catalyzed additions with cyclic ketones **196** and **199**.[267] Both yields and selectivities of **219** were generally high (Scheme 65).

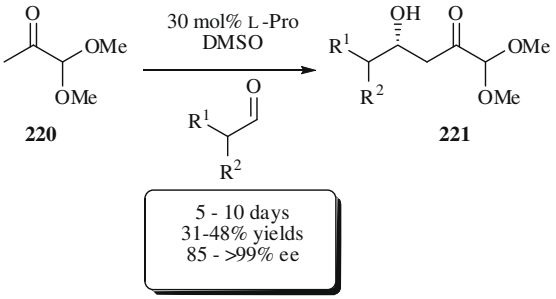
In developing methods for the synthesis of ulosonic acids, Enders and Gasperi found that proline was an effective catalyst for the addition of keto dimethylacetal **220** to aldehydes to generate adducts **221**.[268] While the reaction times were quite long, a variety of α-disubstituted aldehydes (both chiral and achiral) could be utilized as acceptors (Scheme 66).



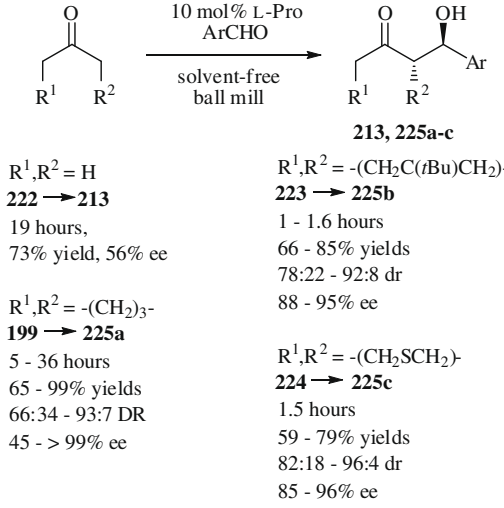
Scheme 64. Proline-catalyzed aldol additions to α-thioalkyl aldehydes.



Scheme 65. Proline-catalyzed synthesis of amino alcohols.



Scheme 66. Proline-catalyzed aldol additions to synthesize highly oxygenated adducts.



Scheme 67. Proline-catalyzed aldol additions in a ball mill apparatus.

Bolm et al. recently developed efficient, solvent-free, proline-catalyzed aldol additions between acetone, cyclohexanone (**199**), **223** or **224** and aromatic aldehydes.[269] They compared reactions of neat mixtures that were simply stirred to reactions of the same mixtures subjected to a ball-milling process (Scheme 67). In general, the stirred reactions were much slower than those performed in the ball mill apparatus, but this may simply reflect the fact that ball milling raised the temperatures of the reactions significantly. The yields of **213** or **225a–c** were comparable from either stirred or milled reactions, and the levels of stereoselectivity obtained were likewise similar, except when milling was conducted at high speeds. This again is consistent with a thermal effect.

4.2. Proline derivatives

Many proline derivatives have also been studied. One of the first to be evaluated was 5,5-dimethylthiazolidinium-4-carboxylate (DMTC **226**, Fig. 14). Barbas et al. found that while effective, DMTC did not offer advantages over L-proline itself as a catalyst,[234] but many other proline analogues and derivatives have been shown to be effective organocatalysts. Recently, Hayashi et al. utilized cat-

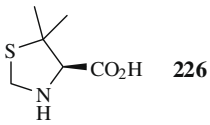
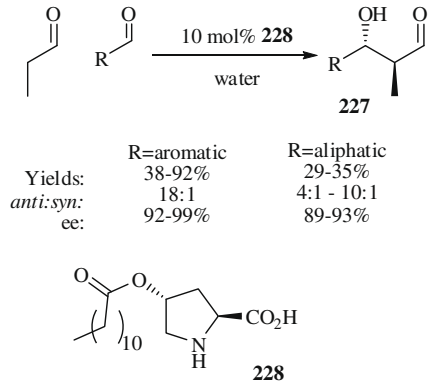


Figure 14. 5,5-Dimethyl thiazolidinium-4-carboxylate, DMTC.

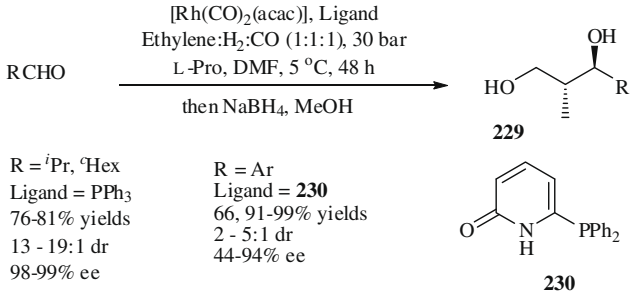
alyst **228** to promote a crossed-aldol reaction between two aldehydes to give adducts **227** (Scheme 68).[270] This study is notable for successfully addressing the challenges of the crossed-aldol reaction between two aldehydes. It was also among the first to successfully apply water as a solvent. Despite numerous papers published recently on the aldol reaction in aqueous media, achieving consistently high stereoselectivity remains a challenge in such reactions.[237,271–281] However, in the reactions of Scheme 68, efficient mixing leading to emulsion formation was believed to be crucial to the success of the reaction.[270]

Hayashi also reported in a follow-up paper that by reducing the amount of water from 18 equiv to 3 or 5 equiv, L-proline itself could catalyze the reactions presented in Scheme 68 in good yields and selectivities.[282] Hayashi was not the first to attempt a crossed-aldol reaction between aldehydes; MacMillan and Northrup first reported this reaction in 2002 using L-proline as the catalyst.[250] Under MacMillan's optimized conditions, the aldehyde donor was added via syringe pump over periods of up to 20 h. While inconvenient, this allowed the use of only a twofold excess of one of the aldehyde components. In contrast, Hayashi et al. required a fivefold excess of the donor aldehyde.[270] These results underscore the difficulty in developing an efficient crossed-aldol reaction.

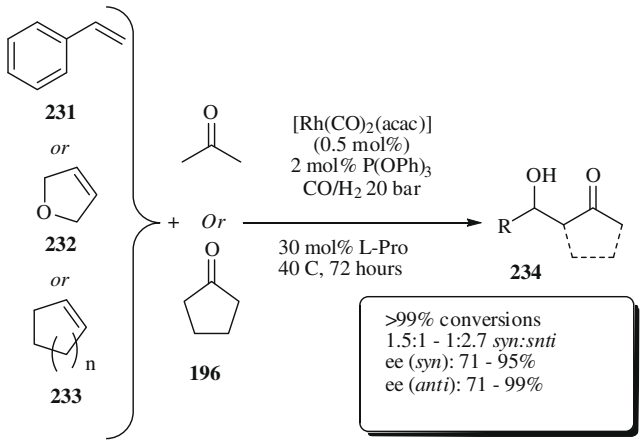
To address the problem of self-condensation of aldehydes, two groups recently and independently published a domino hydroformylation–aldol addition that avoids the need for syringe pump addition or a large excess of aldehyde acceptor.[283,284] Abillard and Breit described an efficient cross-aldol reaction between propanal generated in situ via hydroformylation and a variety of aldehydes to give diols **229** (Scheme 69).[283] Both the rhodium and proline catalysts could be used in very small amounts (0.5 mol % and 6 mol %, respectively). The ligand played a significant role in the efficiency of this domino process, with PPh_3 being best when



Scheme 68. Crossed-aldol addition catalyzed by L-4-hydroxyproline derivative **228**.



Scheme 69. Abillard and Breit's domino hydroformylation-crossed-aldol addition between aldehydes.



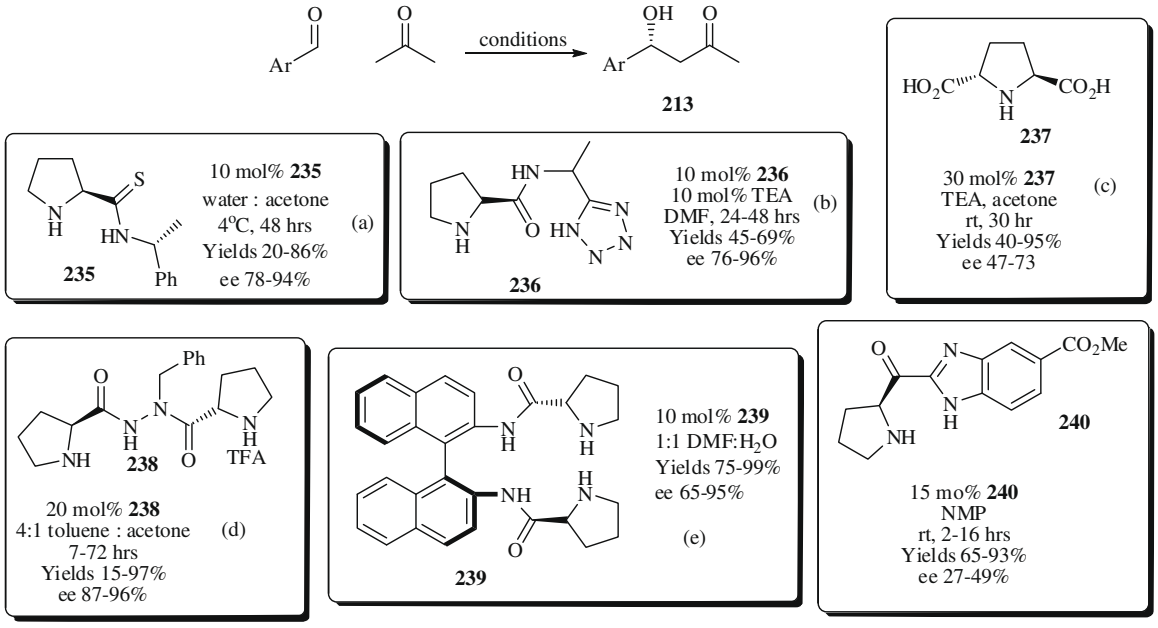
Scheme 70. Chercheja and Eilbracht's domino hydroformylation–aldol addition.

aliphatic aldehydes were used as acceptors, while **230** gave the best results with aromatic aldehyde acceptors. This reflects the balance between the rate of formation of propanal and the rate of the subsequent organocatalyzed aldol reaction.

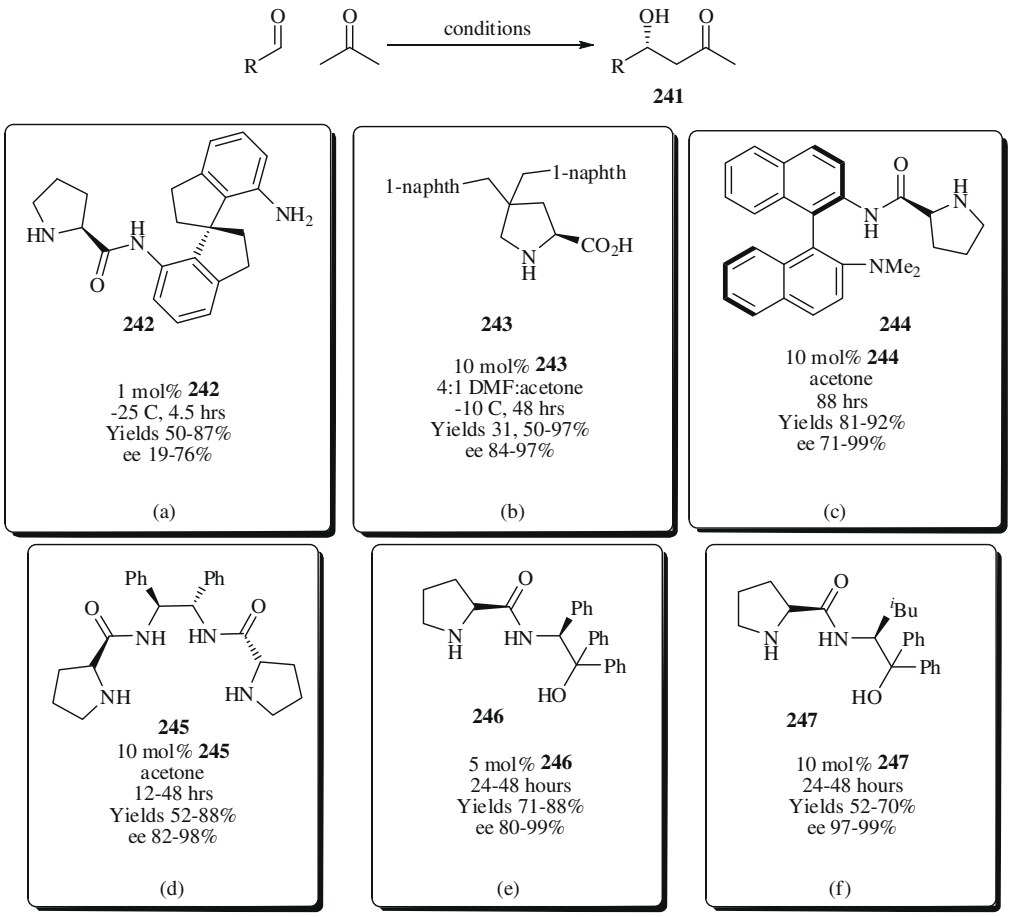
Chercheja and Eilbracht developed a similar process for the reaction between ketone donors and a variety of aldehydes from their respective alkenes (**231**–**233**) to give β-hydroxyketones **234** (Scheme 70).[284] The key to success in both processes was to develop conditions that would generate the aldehyde at a rate comparable to that of the aldol addition, preventing significant accumulation of that component. While these processes do not yet deliver synthetically useful levels of diastereoselectivity, the in situ formation of propanal suggests a general solution to the crossed-aldol problem.

Scheme 71 summarizes effective proline-derived organocatalysts for direct aldol additions between acetone and aromatic aldehydes only, while Scheme 72 presents those able to promote direct aldol reactions between acetone and either aromatic or aliphatic aldehydes. There are two general concepts behind the catalysts depicted in Schemes 71 and 72: the first is that replacing the carboxylic acid functionality present in proline will modulate the acidity and/or solubility of the catalyst (catalysts **235**,[285] **236**,[286] **238**,[287] **239**[288], **240**[289]); the second is that using C_2 symmetry (catalysts **237**[290] and **239**[288]) will reduce the number of stereoisomeric transition states available, thus potentially increasing enantioselectivity.[290] As it is well known that electron-poor aldehydes are more reactive acceptors, the lower ends of the yield and enantioselectivity ranges reported arose from reactions of electron-rich aldehyde acceptors. BINAM-prolinamide **239** proved to be the most general of the catalysts depicted, even in the aldol addition to electron-rich aldehydes.[288] Notably, both catalysts **235**[285] and **239**[288] were successful in promoting aldol reactions in aqueous media.

Catalysts **242**–**247** were found to be useful in the direct aldol addition between acetone and both aliphatic and aromatic aldehydes (Scheme 72). Interestingly, aldol additions catalyzed by spiro diamine **242** were generally higher yielding when aromatic aldehydes were utilized, but gave better levels of enantioselectivity with aliphatic aldehydes (Scheme 72).[291] Organocatalyst **242** was particularly effective, as reactions proceeded rapidly using only 1 mol % of the catalyst.[291] Dinaphthylproline **243**,[292] BINAM-prolinamide **244**,[293] and C_2 symmetric bis(prolinamide) **245**[294] gave generally moderate to good yields and enantioselectivities. When catalyst **245** was examined in an aqueous environment, good yields and enantioselectivies were observed only when $Zn(OTf)_2$ was used as a co-catalyst.[295] Prolinamides **246** and **247** were found to be excellent catalysts for direct aldol reactions in acetone (Scheme 72).[296] Interestingly, phenyl-substituted **246** generally



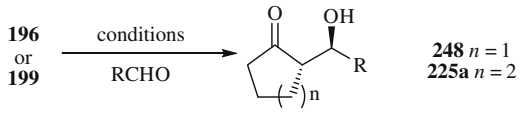
Scheme 71. Proline derivatives catalyzing aldol additions of methyl ketones with aromatic aldehydes.



Scheme 72. Proline derivatives effective as catalysts in the aldol addition of acetone with both aromatic and aliphatic aldehydes.

afforded higher yields, while *i*-butyl-substituted **247** showed remarkably high enantioselectivities.[296] Recently, the authors found that performing the reaction in a 4:1 acetone:brine medium afforded increased yields of the aldol product, decreasing reaction times and allowing the catalyst to be used in as little as 0.5 mol %.[297] These organocatalysts have also been shown to be effective in reactions of other ketones.

Organocatalyzed aldol reactions in which cyclopentanone or cyclohexanone served as donors are shown in Scheme 73. Several catalysts have been evaluated in these reactions; the structures



Scheme 73. Organocatalyzed *anti*-selective aldol additions of cyclic ketones.

can be found in Schemes 71 and 72 and in Figure 15. As is evidenced by the data in Table 3, there appears to be no solution to the problem of a crossed-aldol reaction between cyclopentanone **196** and aldehydes; generally, the diastereoselectivities are very low and often the enantioselectivity is higher for the minor diastereomer. The high levels of diastereo- and enantioselectivity obtained with catalysts **250**[298] and **251**[299] are especially notable; with **251**[299] the authors found that the loading of the catalyst could be reduced to 1 mol % with only minimal decrease in diastereoselectivity, though this was only determined for a single set of substrates. The reactions with both aromatic and aliphatic aldehyde acceptors were performed in water, making the high selectivity especially remarkable. Catalyst **252**, while only reported for use with aromatic aldehydes, could also successfully be utilized in water when cyclohexanone **199** was the donor ketone.[300] Catalyst **253** was employed in water; only 2 mol % was required, and the ratio of donor ketone to acceptor aldehyde was 1:1![301] Dipeptide catalyst **255** was also employed in aqueous solutions; in these reactions 20 mol % of the base *N*-methylmorpholine or DABCO

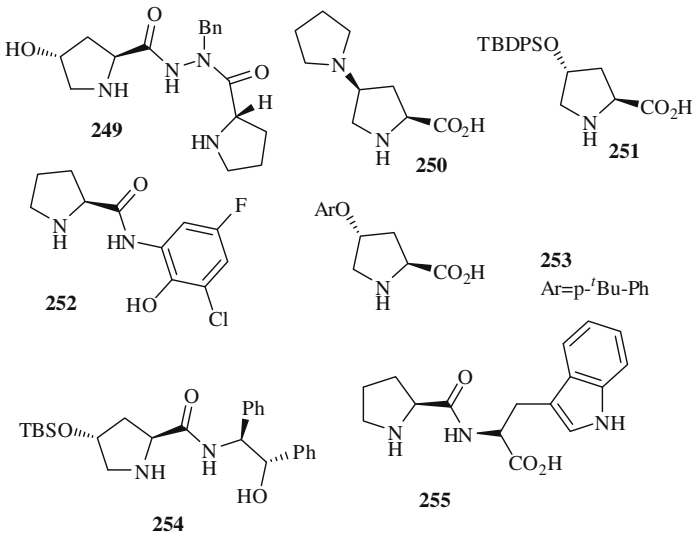


Figure 15. Other substituted proline organocatalysts.

Table 3
Summary of organocatalyzed aldol additions between cyclopentanone and various aldehydes

Catalyst (mol %)	Yield (%) 248	*Anti:syn*	% ee (isomer)	Aldehyde type	Ref.
235 (10)	87	25:75	21 (*syn*)	Aromatic	285
236·TFA (10)	96	11:89	29 (*syn*) 79 (*anti*)	Aromatic	286
238 (20)	95	25:75	74 (*syn*)	Aromatic	287
243 (10)	71	46:54	94 (*anti*)	Aromatic	292
245 (10)	62	60:40	82 (*anti*)	Aromatic	294
255 (20)	80–85	41:59–35:65	79–88 (*anti*); 40–72 (*syn*)	Aromatic	302
252 (10)	96	33:67	79 (*anti*)	Aromatic	300

Table 4
Summary of organocatalyzed aldol additions between cyclohexanone and various aldehydes

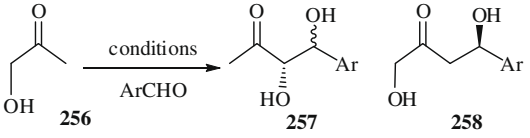
Catalyst (mol %)	Yield (%) **225a**	*Anti:syn*	% ee (isomer)	Aldehyde type	Ref.
235 (5)	25–96	88:12–>95:5	83–98 (*anti*)	Aromatic	305,306
237 (30)	55	2:3	88 (*syn*) 87 (*anti*)	Aromatic	290
238 (20)	98	92:8	92 (*anti*)	Aromatic	287
239 (10)	98–99	4.3:1–10:1	90–93	Aromatic	288
243 (10)	90	9:1	94 (*anti*)	Aromatic	292
244 (10)	35–88	>98:2	68–87 (*anti*)	Aromatic, aliphatic	293
245 (10)	78	3:97	93 (*syn*)	Aromatic	294
246, **247** (0.5)	69–85	87:13–99:1	85–99 (*anti*)	Aromatic	297
249·TFA (20)	39–99	89:11–99:1	92–99 (*anti*)	Aromatic	307
250 (20)	28–99	94:6–99:1	97–99 (*anti*)	Aromatic	298
251 (10)	21–86	4.7:1–25:1	95–99 (*anti*)	Aromatic, aliphatic	299
252 (10)	65–91	88:12–97:3	90–97 (*anti*)	Aromatic	300
254 (5)	38–95	>97:3	>96	Aromatic, aliphatic	308
255 (20)	67–94	53:47–>99:1	80–97 (*anti*)	Aromatic	302
253 (2)	62–100	84:16–>99:1	96–99 (*anti*)	Aromatic	301

and 5 mol % of a surfactant such as SDS or PEG400 were also required for efficient catalysis.[302]

Catalysts **237**,[290] **239**[303,304] and **245**[294] were also evaluated in the direct aldol addition between hydroxyacetone (**256**) and aromatic aldehydes to give adducts **257** and **258** (Scheme 74); the results are summarized in Table 5. Dicarboxylic acid catalyst **237** provided excellent regioselectivity, but poor diastereoselectivity in favour of *anti*-**257**;[290] bisprolinamide **245** showed poor regioselectivity, but excellent diastereoselectivity in favour of *syn*-**257**.[292] While bisproline-BINAM **239** showed the best overall results,[303,304] there is still plenty of room for improvement in this class of organocatalyzed reactions.

Catalyst **254**, in addition to the success found in additions of cyclohexanone to both aliphatic and aromatic aldehydes (Table 3)[308], was also found to successfully desymmetrize 4-alkylcyclohexan-2-ones **259** in the aldol addition to aromatic aldehydes (Scheme 75).[309] The authors found that without the 4-silyloxy group in **254**, lower enantioselectivity resulted. Only one product diastereomer could be detected. It is also interesting that **254** and **294**[310] (see below, Scheme 85) catalyze the formation of different diastereomers, despite the fact that both are derived from L-proline.

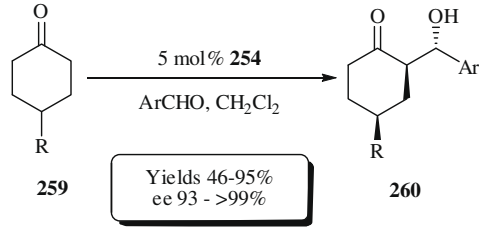
Protected prolinol **264** was found to be very useful in tandem Michael-aldol additions leading to chiral thiochromenes **263** (Scheme 76)[311] When 2-thiobenzaldehydes **262** and α,β-unsaturated aldehydes **261** were treated with catalyst **264** and an acid, thiochromenes **263** were formed in high yields and enantioselectivities (Scheme 76).[311] Related reactions of aldehydes **261** and α-thioacetophenone **265** catalyzed by **264** gave quite different products depending on whether an acid or a base was added (Scheme 77).[312] In the presence of $NaHCO_3$, tetrahydrothiophene **266** was formed, whereas **267** was formed in the presence of $PhCO_2H$.



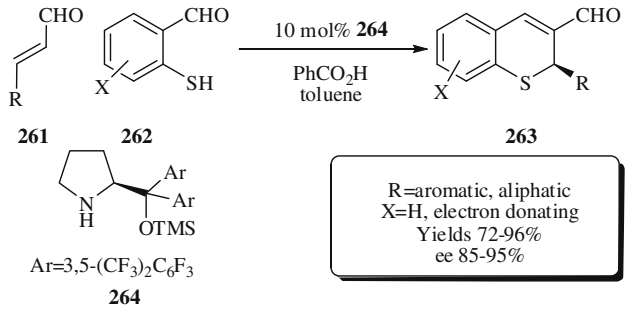
Scheme 74. Regioselectivity in organocatalyzed aldol additions of hydroxyacetone.

Table 5
Summary of organocatalyzed aldol reactions between hydroxyacetone and aromatic aldehydes (Scheme 74)

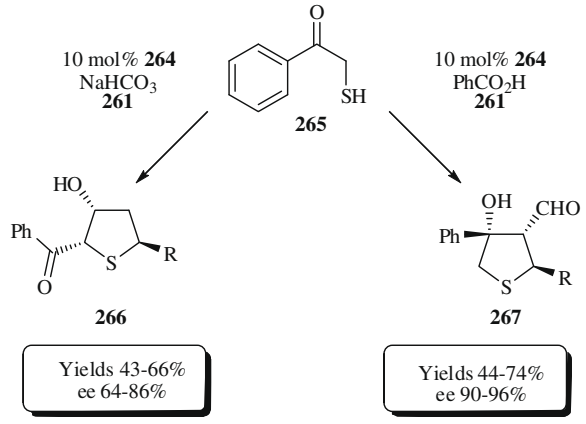
Catalyst (mol %)	**237** (30)	**239** (10)	**245** (10)
Yields (%)	53-77	77–79	90
257:**258**	100% 257	9:2–50:1	1:1.3
anti:*syn* **257**	1:1–1.5:1	2:1–7:1	100% *syn*
ee (*anti*-**257**)	28–90	73–97	—
ee (*syn*-**257**)		24–99	66
ee (*iso* **258**)	—	—	97



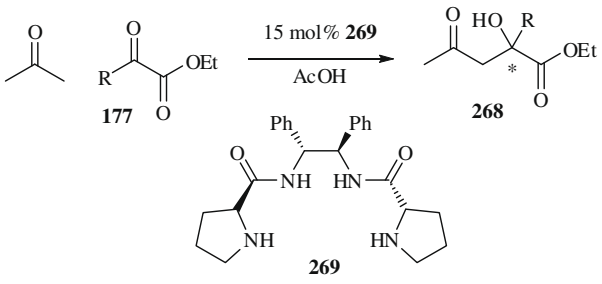
Scheme 75. Desymmetrization and aldol addition of 4-alkyl cyclohexanones.



Scheme 76. Organocatalytic synthesis of thiochromenes.



Scheme 77. Selective organocatalyzed aldol syntheses of tetrahydrothiophenes.



Scheme 78. Aldol additions promoted by C_2-symmetric organocatalyst **269**.

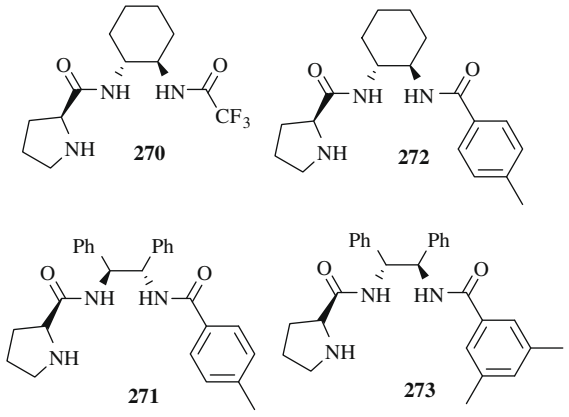
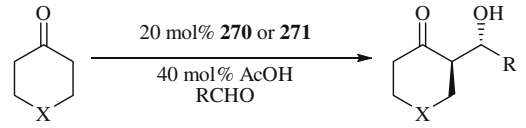


Figure 16. Unsymmetrical bifunctional prolinamides.



X	Yields	dr	ee
S; **223** → **225c**	37-99%	89:11 - 99:1	>97%
NBoc; **274** → **276a**	32-91%	91:9 - 99:1	86-98%
O; **275** → **276b**	55-96%	95:5 - >99:1	>98%

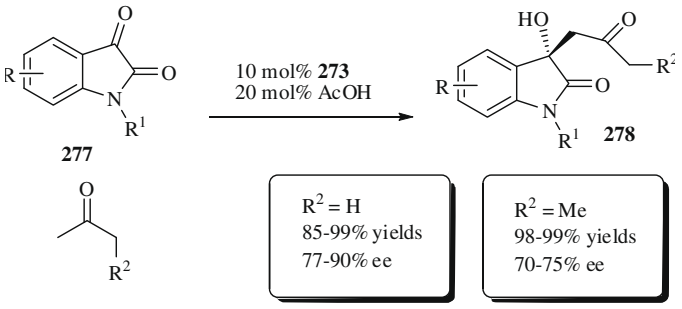
Scheme 79. Bifunctional organocatalysts in *anti*-selective aldol additions to cyclic ketones.

Symmetrical bifunctional prolinamide **269** (a diastereomer of **245** in Scheme 72) has been shown to catalyze the addition of acetone to α-ketoesters **177**.[313] Reaction times were fairly short (up to 16 h), and a variety of ketoesters could be used (Scheme 78). The absolute configurations of the products **268** were not determined in this study.

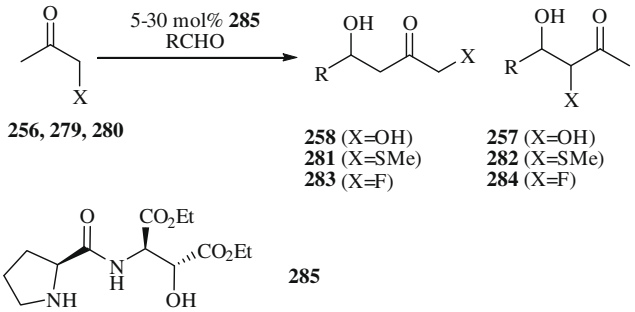
Unsymmetrical bifunctional prolinamides **270**–**273** (Fig. 16) derived from C_2-symmetric diamines have been reported by several groups to catalyze the addition of various ketones to both aldehydes and α-ketoamides.[314–316] These catalysts were designed to permit easy 'tuning' of both steric and electronic properties by modification of the second amide group. Both **270** and **271** catalyzed direct aldol addition reactions between ketones **223**, **274** or **275** with aromatic aldehydes in the presence of acetic acid (Scheme 79).[314] Excellent levels of both diastereo- and enantioselectivity were obtained. It should be noted that with oxanone and thiooxanone donors (X = O, S), 10 M equiv of water was required for a successful aldol addition.

Prolinamide **272** was found to catalyze the addition of cyclohexanone **199** to aromatic aldehydes to generate adducts **225a** in good yields and selectivies (Scheme 73).[316] Prolinamide **273** catalyzed the addition of ketones to isatins **277** to give adducts **278** (Scheme 80). When 2-butanone was used as the donor, a highly regioselective aldol reaction leading to **278** was observed.

Gong et al. have examined catalyst **285** generated by combining L-proline and a chiral aminoalcohol.[317,318] Catalyst **285** was found to be active and selective in the reaction between hydroxyacetone **256**,[318] fluoroacetone **280**[318] or thiomethoxyacetone **279** (Scheme 81) to give adducts **258**, **281** and **282**.[317] The aldol reactions favoured enolization at the unsubstituted side of the unsymmetrical ketone donors. However, the authors found that when fluoroacetone was the donor, the presence of water led to **284** selectively, and in the absence of water, **282** was formed in good diastereo- and enantioselectivity. Catalyst **285** promotes the formation of **258** as the major regioisomer in aldol additions of hydroxyacetone with various aldehydes. Thus, **285** nicely complements proline organocatalysts **237** and **239** which afford the regioisomeric adducts **257** as the major products (Scheme 74, Table 5).

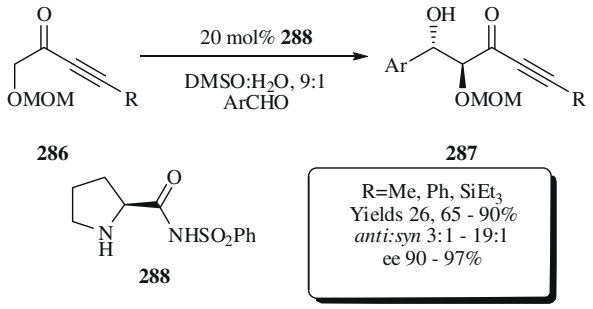


Scheme 80. Prolinamide-catalyzed addition to isatins.

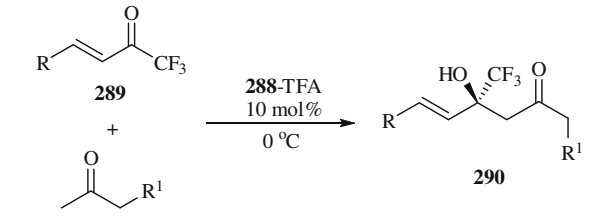


X	Yields	ee
OH	44-95% (**258**); <5 - 12% (**257**)	91-99%
SMe	24-81% (**281**)	92 - >99%
F	55-65% (**282**)	80-91%

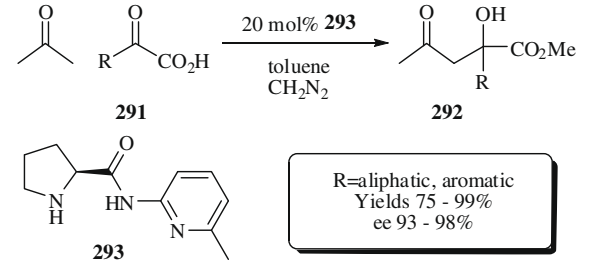
Scheme 81. Regioselective organocatalyzed aldol reactions between α-monosubstituted acetone and aldehydes.



Scheme 82. Aldol coupling of ynones with aromatic aldehydes catalyzed by L-proline sulfonamide.



Scheme 83. Prolinamide-catalyzed aldol additions to trifluoroketones.



Scheme 84. Bifunctional organocatalysis of aldol additions to α-ketoacids.

Ynone donors are fairly uncommon nucleophiles in aldol reactions due to their propensity to undergo Michael additions.

Nevertheless, aldol additions of ynones **286** to aromatic aldehydes catalyzed by L-proline sulfonimide **288** quite effectively led to adducts **287** (Scheme 82).[319] The mild conditions of this organocatalyzed reaction avoided potential side reactions, although a large proportion of catalyst was required.

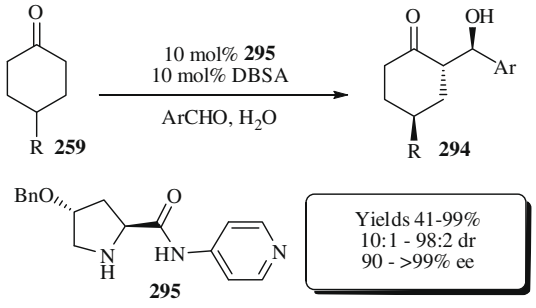
Compound **288**, in conjunction with trifluoroacetic acid, was also shown to be a useful catalyst for the addition of methyl ketones to a large variety of unsaturated trifluoromethylketones **289** (Scheme 83).[320]

The idea that bifunctional organocatalysts can exploit additional interactions with the reaction substrates has been widely developed. In a survey of nine similar organocatalysts in aldol reactions between acetone and α-ketoacid acceptors **291**, **293** emerged as the most successful (Scheme 84).[321] Diazomethane was added to these reactions to facilitate isolation of the products as the methyl esters. Cyclopentanone was also used as a model of cyclic ketone donors, but these aldol reactions suffered from lower yields and poor levels of diastereoselectivity. In a second paper, the authors demonstrated that other methyl ketones could act as donors with the same catalytic system.[322]

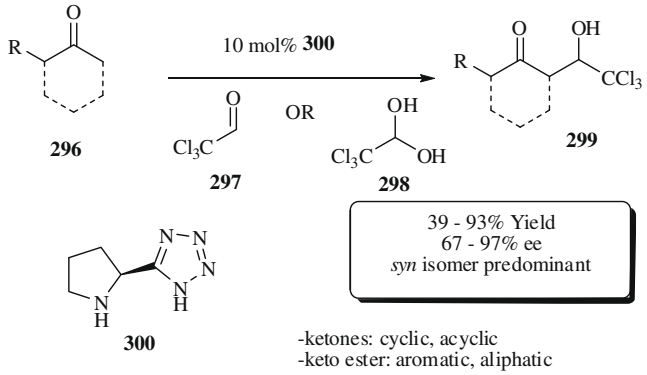
A catalyst similar to **293** was synthesized recently.[310] Catalyst **295** could successfully couple ketones with aromatic aldehydes in modest yields and in excellent selectivity (Scheme 85). The reaction could be performed in water, and a catalytic amount of the surfactant Brønsted acid *p*-dodecyl benzenesulfonic acid (DBSA) was required for good yield and selectivity. As noted previously, catalysts **254** (Scheme 75) and **295** generate different diastereomers, **260** and **294**, respectively, offering complimentary selectivity.

Tetrazoles such as **300** are quite acidic, and were found to be highly effective organocatalysts for aldol reactions.[323,324] In particular, catalyst **300** functioned well with smaller excesses of ketone donor than did other diamines[325,326] in acetonitrile solutions. A series of aldol reactions between ketones and either chloral **297** or chloral hydrate **298** were used to explore the role of water in catalysis by **300** (Scheme 86), and it was found that 1 equiv of water was necessary for catalysis. Tetrazole **300** promoted the formation of *syn*-adduct **299** when donor ketone **296** was cyclic, in contrast to the *anti*-preference of proline. The tetrazole-catalyzed reactions were also much faster than those promoted by proline. These reactions are not yet general synthetic tools, but the results published to date illustrate some interesting mechanistic points.

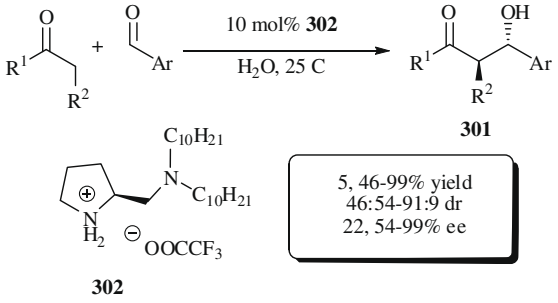
In a study of organocatalysis in water (Scheme 87), Takabe, Barbas et al. determined that neither an acidic functional group in the catalyst nor an acid additive was required for efficient catalysis, but that it was essential for the organocatalyst to contain a hydrophobic alkyl chain.[327] On the other hand, the presence of acid was essential for enantioselectivity. Reactions performed without an acid additive afforded high yields and good diastereoselectivity, but the aldol products were nearly racemic. Direct aldol additions catalyzed by diamine **302** between aromatic aldehydes and ketones (cyclohexanone **199**, acetone, 2-butanone and *iso*-pentanone) generally had fair to excellent yields and selectivities.



Scheme 85. Prolinamide-catalyzed aqueous direct aldol addition.



Scheme 86. Chloral or chloral hydrate as acceptors for ketone donors, as catalyzed by tetrazole.



Scheme 87. *anti*-Selective organocatalyzed aldol additions in water.

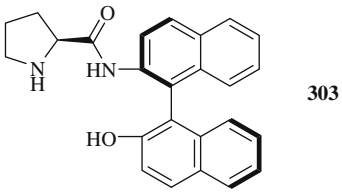
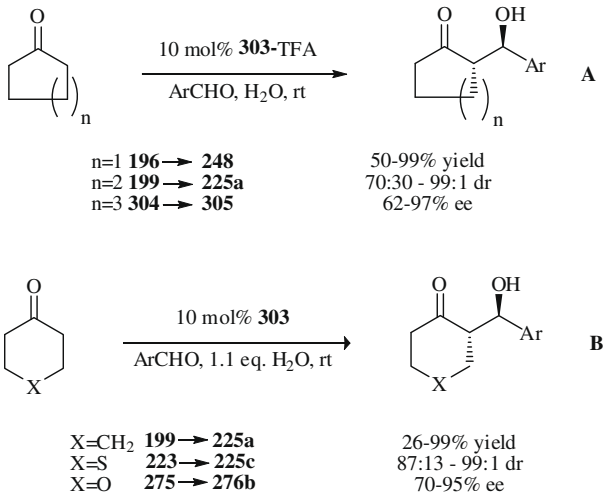


Figure 17. (*S*)-NOBIN-L-proline.



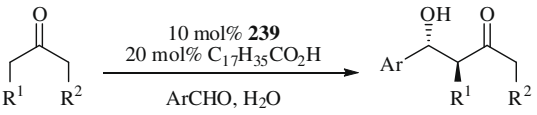
Scheme 88. NOBIN-prolinamide-catalyzed aldol additions.

Two groups have recently published the use of (*S*)-NOBIN-L-proline (**303**; Fig. 17) as a new catalyst for the aldol reaction between ketones and aromatic aldehydes.[328–330] As the TFA salt, **303** could be employed in neat water (Scheme 88, Eq. A);[330] in the absence of acid, **303** was utilized in dioxane containing 1 equiv of water (Scheme 88, Eq. B).[328,329] The reactions were generally faster in the presence of acid.[330] In the presence of TFA, the reaction between cyclopentanone **196** and *p*-nitrobenzaldehyde gave the corresponding *anti*-adduct **248** as a 70:20 *anti:syn* mixture in 90% yield. The major diastereomer was obtained in 83% ee.[330] Interestingly, in the *absence* of acid, the reaction between cyclopentanone and *p*-nitrobenzaldehyde gave the corresponding *syn*-adduct in 98% yield, 65:35 *syn:anti* and 92% ee.[328] The source of this difference in selectivity is unclear.

Two groups have examined the structurally similar (*S*)-BINAM-(L-proline)$_2$ (**239**, see Scheme 71).[8,288,303,331–333] In aqueous stearic acid mixtures, the aldol reaction between several methyl ketones or cyclohexanone with aromatic aldehyde acceptors proceeded in generally reasonable yields and in good selectivity (Scheme 89).[288,333] In the absence of an acidic additive, the reaction was slower and less selective. Nájera et al. have studied **239** as a catalyst for the reaction between α-functionalized acetone derivatives and aromatic aldehydes (Scheme 90 and Table 6).[303,331,332] The products of the aldol reactions of α-chloroacetone **308** racemized readily, hindering purification; as a solution, the α-chloro-β-hydroxy adducts **310** were transformed into the corresponding α,β-epoxyketones prior to purification.[331] Both under solvent-free conditions and in DMF/H_2O solutions, the authors found that hydroxyacetone required protection to achieve good enantioselectivity.[303,332] In all cases, α-(thiomethyl)acetone **279** as the donor led to the preferential formation of adduct **281** (Scheme 90, Table 6).[303,332] Interestingly, the authors found that when benzyloxyacetone **256c** was the donor, either the *syn*- or *anti*-**257c** adducts could be formed selectively; under solvent-free conditions, the *anti*-isomer predominated,[332] while in DMF, the *syn*-isomer predominated.[303]

Benzimidazole-pyrrolidine **314** (BIP, Fig. .18) has recently been synthesized as a catalyst for the aldol addition.[334,335] While this organocatalyst has not been extensively studied as of yet, it has been shown to be effective for the reactions between cyclohexanone, cyclopentanone, or 2-pentanone and *p*-nitrobenzaldehyde. In addition, the authors demonstrated its use in conjunction with Lewis acids Cu(OAc)$_2$ and Zn(OTf)$_2$ with reasonable success.

In efforts towards developing 'green' chemistry, several methods of supporting and recycling L-proline organocatalysts have been examined in the last five years. These include ionic liquid solvents,[336–342] polyammonium salts,[343] dendrimers[344] and polystyrene.[345–348] Several reviews of these studies have been published.[349–351]



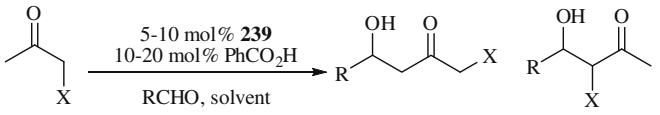
37-100% yields
1:1; 90:10-99:1 dr
65-93% ee

R^1,R^2: -$(CH_2)_3$- (**225a**)

37 - 100% yields
1:1 - 99:1 dr
87-93% ee

R^1=H;
R^2=H (**213**),
CH_3 (**306**),
$^nC_5H_{11}$ (**307**)

Scheme 89. BINAM-prolinamide-catalyzed aldol additions.



256 (X=OR)
279 (X=SMe)
308 (X=Cl)
311 (X=Me)

258 (X=OR)
281 (X=SMe)
309 (X=Cl)
312 (X=Me)

257 (X=OR)
283 (X=SMe)
310 (X=Cl)
312 (X=Me)

Scheme 90. BINAM-prolinamide-catalyzed regioselective aldol reactions.

Early studies of the L-proline-catalyzed direct acetate aldol addition in the ionic liquid solvent [bmim][PF_6] showed results consistent with those observed in conventional organic solvents.[340] While the aldol adduct could be removed easily from the L-proline-containing ionic liquid by extraction, the yields and selectivities of subsequent runs dropped off, albeit only slightly. It was also recently reported that covalently binding L-proline to the ionic liquid offered little advantage in terms of recyclability.[337] It is not evident that ionic liquid media offer significant advantages over conventional solvents or over solvent-free reaction systems in the aldol reaction.

Imidazolium ions have been covalently bound to silica gels (**315** and **316**, Schemes 91 and 92).[338,339] These modified silica gels have been studied as solid-supported ionic liquid media for reactions. L-Proline could be adsorbed on the ionic liquid-like surface of the modified silica. Solvent-free direct aldol additions of methyl ketones with either aromatic or aliphatic aldehyde acceptors could be promoted by this supported organocatalyst system. The yields and levels of enantioselectivity obtained in these reactions were comparable to those obtained in conventional L-proline-catalyzed reactions, and remained consistent over four uses (Scheme 91).[338,339] Proline remained adsorbed on the ionic liquid-silica, permitting the aldol adducts **241** to be separated from the catalyst simply by washing with ether. A prolyl tripeptide **317** was also studied in a similar supported ionic liquid medium. Tripeptide **317** was quite catalytically active, as it could be used in as little as 5 mol % in conjunction with modified silica gel **316**. On the other hand, the yields dropped off markedly upon recycling (Scheme 92). The enantioselectivities of successive reactions remained consistent, however.[342]

Similarly, an onium ion-tagged L-proline organocatalyst (**319**) has proved useful in the crossed-aldol additions of several ketones with aromatic aldehydes in the ionic liquid solvent [bmim][Tf_2N] (Scheme 93).[341] The catalyst could be recovered and reused with only minimal degradation in enantioselectivity; unfortunately, the conversions dropped off dramatically with the recycled catalyst. This reduced catalytic activity may reflect the difficulty in drying the ionic material after its recovery.

L-Proline has also been supported on poly(diallyldimethylammonium) salts (**320**, Scheme 94).[343] A sequence of direct acetate aldol additions of acetone with aromatic aldehydes afforded consistent yields of adducts **213**, and the levels of enantioselectivity were reproducible over six cycles. However, the results obtained when cyclopentanone or cyclohexanone was employed as aldol donors were disappointing. Only a moderate degree of diastereoselectivity and highly variable levels of enantioselectivity were obtained, even in the first cycle of the catalyst.

Unidirectional dendrimers have also been utilized as supports for proline-based organocatalysts.[344] Dendritic L-proline sulfonimide **321**-catalyzed aldol reactions of cyclohexanone **199** (Scheme 95) gave yields and stereoselectivities comparable to those obtained in reactions promoted by simple L-proline sulfonimide organocatalysts (cf. **288**, Scheme 82). However, the dendritic catalyst could be precipitated and recovered from the reaction solutions. The same sample of catalyst was recycled five times

Table 6
Results of the aldol reactions shown in Scheme 90

Starting material	Product ratios	Yields (major product)	dr	ee
256 (Solventless)	63:37–>99:1 (**258**:**257**)	76–99% (**258**)	83:17–>99:1 (*anti*:*syn*)	16, 60–97% (*anti*)
256 (DMF/H_2O)	5:1–>50:1 (**258**:**257**)	90–98% (**258**)	3:1–12:1[a]	68–85%
279 (Solventless)	16:84 (**281**:**283**)	83% (**283**)	1:1	86%
279 (Water)	1:8 (**281**:**283**)	89% (**283**)	1:1	93%
308 (DMF/H_2O)	3:1–>99:1 (**309**:**310**)	27–93% (**308**)	2:1–>99:1 (*anti*:*syn*)	49–98%
311	63:37–>99:1 (**312**:**312**)	76–99% (**312**)	83:17–>99:1 (*anti*:*syn*)	16, 60–97% (*anti*)

[a] When X = OH, OMe, *anti* > *syn*; when X = OBn, *syn* > *anti*.

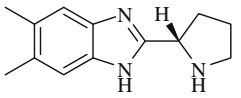
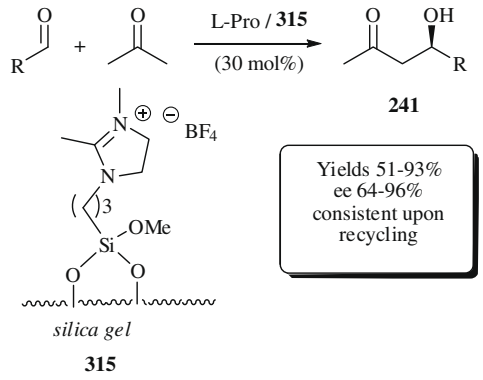
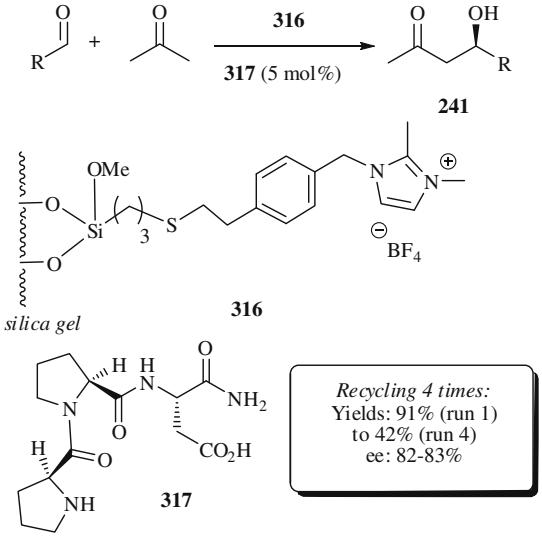


Figure 18. Benzimidazole-pyrrolidine (BIP) organocatalyst.



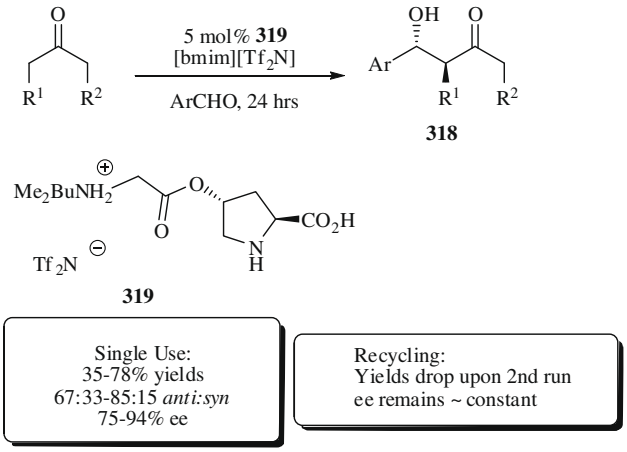
Scheme 91. Enantioselective aldol additions of methyl ketones catalyzed by L-proline on a solid-supported 'ionic liquid phase'.



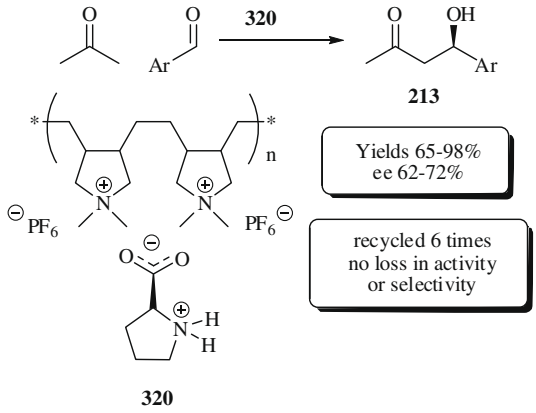
Scheme 92. Enantioselective aldol additions of methyl ketones catalyzed by an L-prolyl tripeptide on a solid-supported 'ionic liquid phase'.

without any apparent loss of efficiency. Also notable here is the use of water as the solvent.

Several polystyrene-supported 3-hydroxy(amino)-L-proline organocatalysts **322**–**324** could also be easily recovered after completion of an aldol reaction by filtration; the yields observed in these reactions were not only consistent with those obtained using



Scheme 93. Alkylammonium ion-tagged proline organocatalyst.

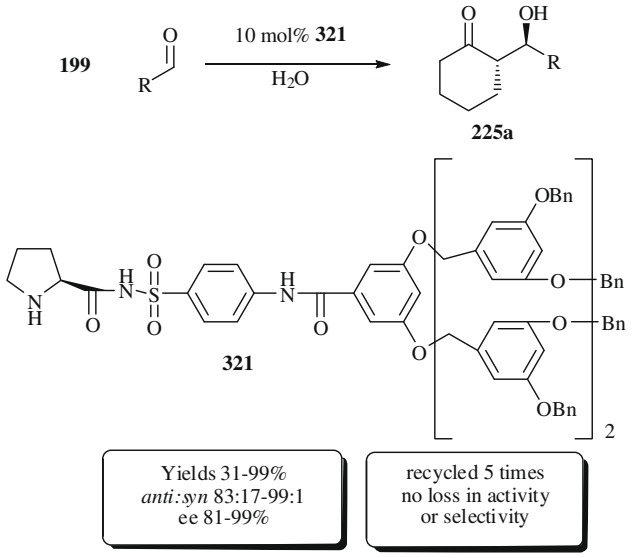


Scheme 94. Polyammonium salt-supported L-proline as a catalyst for enantioselective aldol additions of methyl ketones.

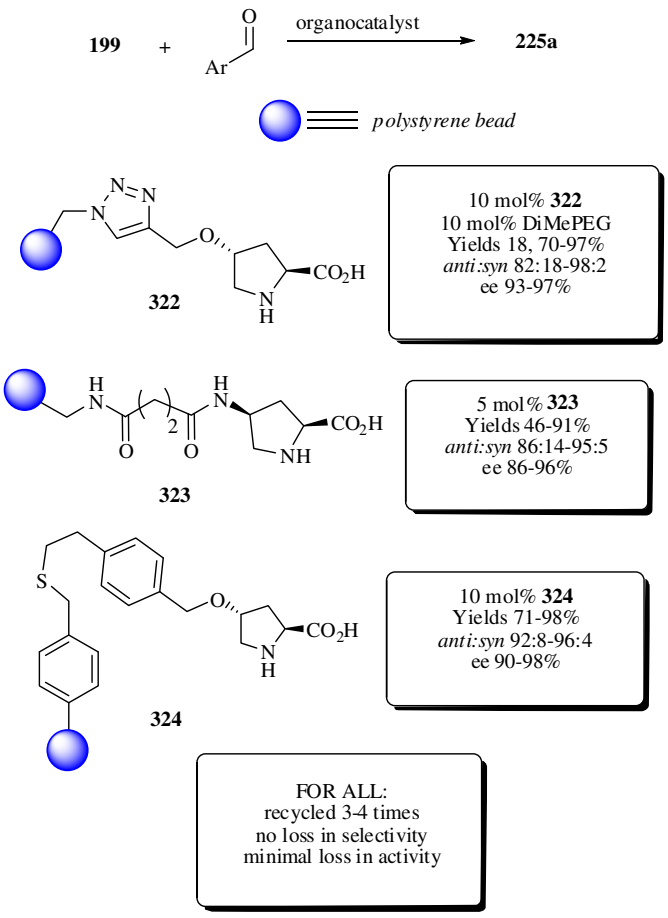
similar unsupported catalysts,[270,299,327] but were reproducible over three uses of the same catalyst (Scheme 96).[345–348]

4.3. Other amino acids and derivatives

Many other amino acids and small peptides have also been examined, and a recent review discusses the roles of amino acids as organocatalysts.[352] L-Alanine, the simplest chiral amino acid, induced excellent levels of diastereoselectivity and enantioselectivity in aldol reactions between ketone donors **199**, **214**, **325** or **326** and aromatic aldehyde acceptors (Scheme 97).[353] Cyclic ketones consistently afforded good selectivities, while the single acyclic substrate (**326**) gave only modest results. Alanine peptides have also been evaluated as organocatalysts, but selectivity and yield decreased as the length of the peptide increased.[354] In a third study



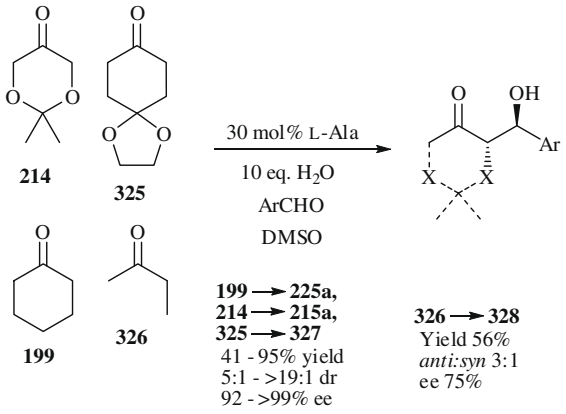
Scheme 95. Dendrimer-supported L-proline organocatalyst.



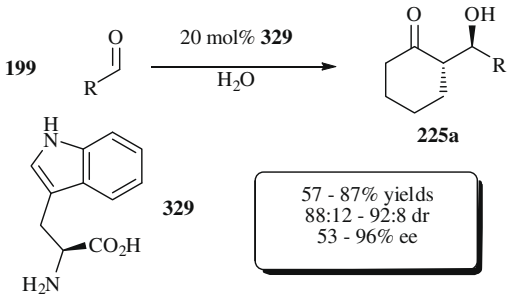
Scheme 96. Polystyrene-supported L-proline organocatalysts.

of various dipeptides, valine–phenylalanine appeared to be the most promising organocatalyst. Under aqueous conditions it promoted aldol reactions with several ketone donors; while enantioselectivity was often quite high, diastereoselectivity was generally poor.[355]

Other groups have recently published studies of simple amino acids as organocatalysts in aqueous solutions.[356–358] Amedjkouh



Scheme 97. *anti*-Selective aldol reactions catalyzed by L-alanine.

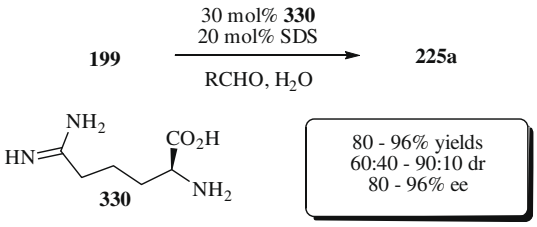


Scheme 98. Tryptophan-catalyzed aldol additions.

found that in water L-tryptophan (**329**) gave the best conversion and selectivity in the model reaction of cyclohexanone with aromatic aldehydes. The process proved to be fairly general using only a twofold excess of cyclohexanone (Scheme 98).[356] Fair to excellent levels of diastereoselectivity were obtained, while enantioselectivity ranged from poor to excellent.

Deng and Cai surveyed conditions for optimizing the same model reaction using L-alanine as the catalyst.[357] They found that 20 mol % of a surfactant (SDS) was required for efficient catalysis. When they further studied the process with other amino acid organocatalysts, L-arginine **330** proved to be the most generally useful catalyst, even for aldehydes containing electron-donating groups; however, a ninefold excess of ketone was necessary to drive the reactions to completion (Scheme 99). Both Amedjkouh and Deng and Cai evaluated L-phenylalanine as the catalyst, but observed very different results when the reactions were conducted in the presence of a surfactant. From the results shown in Table 7, it appears that the proportion of surfactant used is very important to the activity of the organocatalyst. These data highlight the importance of stoichiometry in these aqueous organocatalytic processes.

Lu et al. have also surveyed a range of amino acids as potential organocatalysts for aldol reactions.[358] In contrast to the results



Scheme 99. Arginine as organocatalyst.

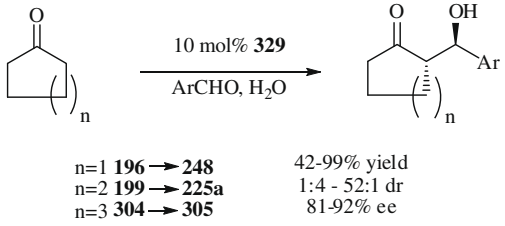
Table 7
Importance of stoichiometry in phenylalanine-catalyzed aldol additions under aqueous conditions

Catalyst (mol %)	L-Phe (20)	L-Phe (20)	L-Phe (30)
Additive (mol %)	None	SDS (100)	SDS (20)
Yield	52	0	78
anti:*syn*	19:1	—	62:38
ee (*anti*, %)	76	—	—
Reference	356	356	357

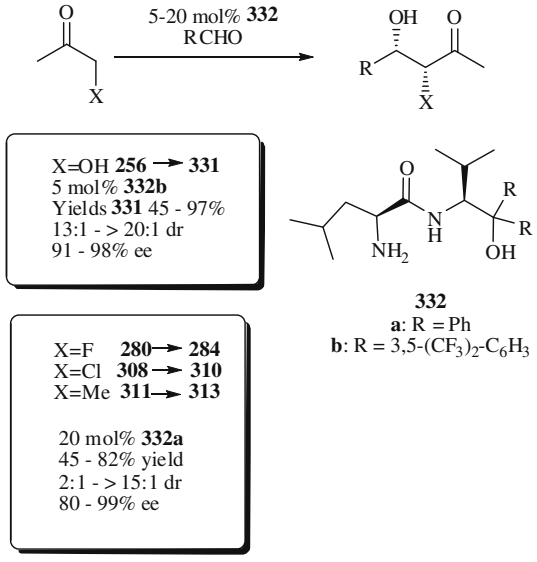
shown in Scheme 97,[353] they obtained racemic products using L-alanine, whereas L-tryptophan **329** gave the best results (Scheme 100). Consistently high yields and selectivities were obtained when cyclopentanone **196** was the donor, but cyclohexanone **199** and cycloheptanone **304** underwent aldol reactions with only poor levels of diastereoselectivity.[358]

In the aldol addition of α-functionalized acetone derivatives to aldehydes, isoleucinamide **332** was highly selective for the formation of branched isomers by reaction at the more-substituted site of the nucleophile (Scheme 101).[359] *ayn*-Adducts were formed in good yield and selectivity. This process is a nice complement to reactions promoted by the similar prolinamide catalyst **285** that selectively promotes reaction at the less-substituted site under similar conditions (Scheme 81).[317,318]

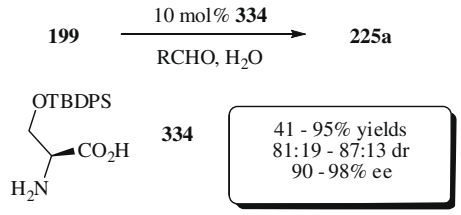
Silyl-protected serine derivative **334** proved to be an effective, but simple organocatalyst as studied by Teo.[360] Cyclohexanone **199** could be used as a donor with aromatic aldehydes to give adducts **225a** in moderate yield and good selectivities, however, analogous reactions with cyclopentanone or acetone suffered from lower conversions and selectivity (Scheme 102).



Scheme 100. *anti*-Selective aldol reactions catalyzed by L-tryptophan.



Scheme 101. *syn*-1,2-Diols and halohydrins via organocatalyzed aldol reactions of hydroxyacetone or haloacetones.



Scheme 102. O-Protected L-serine as organocatalyst.

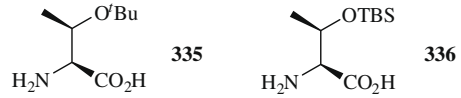
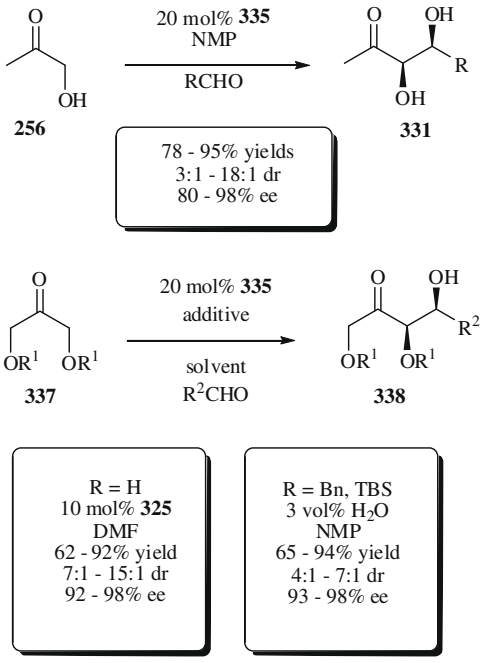


Figure 19. Protected threonine derivatives that can function as organocatalysts in aldol reactions.

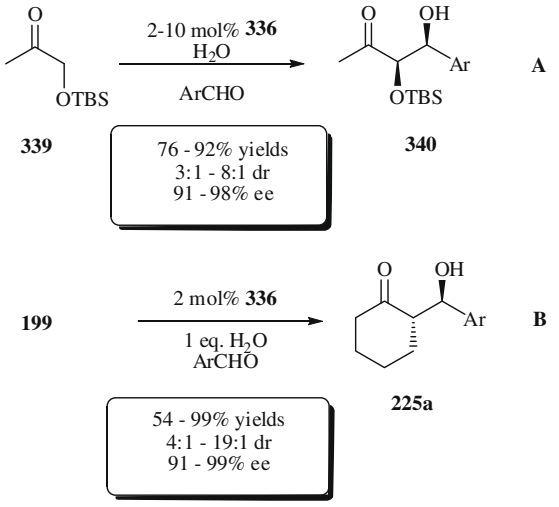


Scheme 103. *O-tert*-Butyl L-threonine organocatalyzed crossed-aldol reactions of hydroxyacetone and dihydroxyacetone with aldehydes.

The groups of Barbas and Lu have recently examined *O*-protected L-threonines **335** and **336** as organocatalysts.[361–364] Barbas et al. had also found that unprotected L-threonine can function as a catalyst, but yields were generally higher with O*t*Bu-L-Thr **335**[363,364] (Fig. 19).

Barbas et al. studied the aldol reactions between hydroxyacetone, dihydroxyacetone and protected dihydroxyacetone; the results are summarized in Scheme 103.[362–364] While reactions with aryl aldehydes were generally quite successful, this catalytic system remains less able to promote reactions with aliphatic aldehydes, as is common in organocatalyzed reactions. While the yields are generally higher for the reaction between dihydroxyacetone and aldehydes catalyzed by **335** than for those catalyzed by L-alanine (Scheme 97),[353] L-alanine selectively promotes the formation of the *anti*-isomer, whereas **335** gives the *syn*- isomer predominantly.

Lu et al. utilized **336** as a catalyst; silylated hydroxyacetone was found to add to aromatic aldehydes in good yield and selectivity under aqueous conditions (Scheme 104, Eq. A).[361] In addition,



Scheme 104. *O*-TBS L-threonine organocatalysis.

cyclohexanone could be used as donor to give *anti*-adducts **225a** (Scheme 104, Eq. B).

4.4. Other organocatalysts

A recent review focuses on the design of bifunctional acid–base catalysis for the asymmetric direct aldol addition,[236] and another focuses on protonated chiral catalysts.[365] Amine-acid salts have been studied extensively, and it has been found that the acidic part of an amine-acid catalyst plays a large role in determining catalytic efficiency, and can influence the enantioselectivity.[236] An overview of chiral Lewis base-mediated reactions was published in 2000,[366] and an excellent mechanistic analysis of these processes appeared in 2008.[367] This catalyst type functions through simultaneous activation of the nucleophiles and the electrophile around a hypervalent cationic silicon centre. Mechanistic details can be found elsewhere.[368,369]

Denmark developed the first effective method for enantioselective crossed-aldol reactions of aldehydes using phosphoramide catalysts **341**[370–376] and **342**[368,369,377–387] (Fig. 20). An essential part of this method was the stereocontrolled formation of trichlorosilyl enol ethers from the corresponding trialkylsilyl enol ethers. The utility of Denmark's method has been greatly enhanced by the advent of methods to generate these enol ethers in situ.[377,379,380] Under optimized conditions, trichlorosilyl enolates of aldehydes undergo high-yielding additions to aldehydes in the presence of **342** (Scheme 105).[383,385] Generally, *syn*-adducts are the predominant species obtained in aldol reactions of *Z*-enolates promoted by Denmark's phosphoramides, while *E*-enolates give *anti*-adducts[384] (although some exceptions have been observed[376]).

Denmark et al. have applied these phosphoramide catalysts in a variety of Mukaiyama aldol reactions (Scheme 105).[379–382,386,387] Reactions of aliphatic aldehyde acceptors were inconsistent. Generally, higher catalyst loadings and longer reaction times were needed to produce acceptable yields in comparison to similar reactions employing aromatic aldehydes. Vinylogous Mukaiyama aldol reactions of dienol ethers **351** having methyl groups in both the α- and γ-positions (i.e., $R^3 = R^5 = Me$) were unsuccessful with aliphatic aldehyde acceptors, posing a limitation on the applicability of this system.

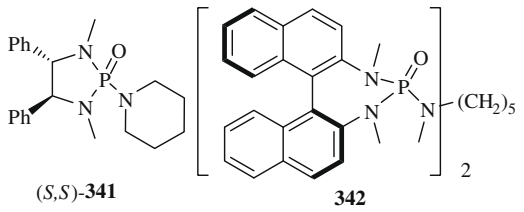


Figure 20. Denmark's first and second generation chiral phosphoramide Lewis basic catalysts.

It has also been discovered that nornicotine **359** (Fig. 21) can catalyze aldol reactions.[388] These reactions have been shown to proceed faster than corresponding proline-catalyzed processes in an aqueous buffered system. Furthermore, no dehydration products were observed in the nornicotine-catalyzed reactions. Studies are still underway to develop **359** as an efficient catalyst. Recently, theoretical and mechanistic studies of this catalyst system have been published.[389–391]

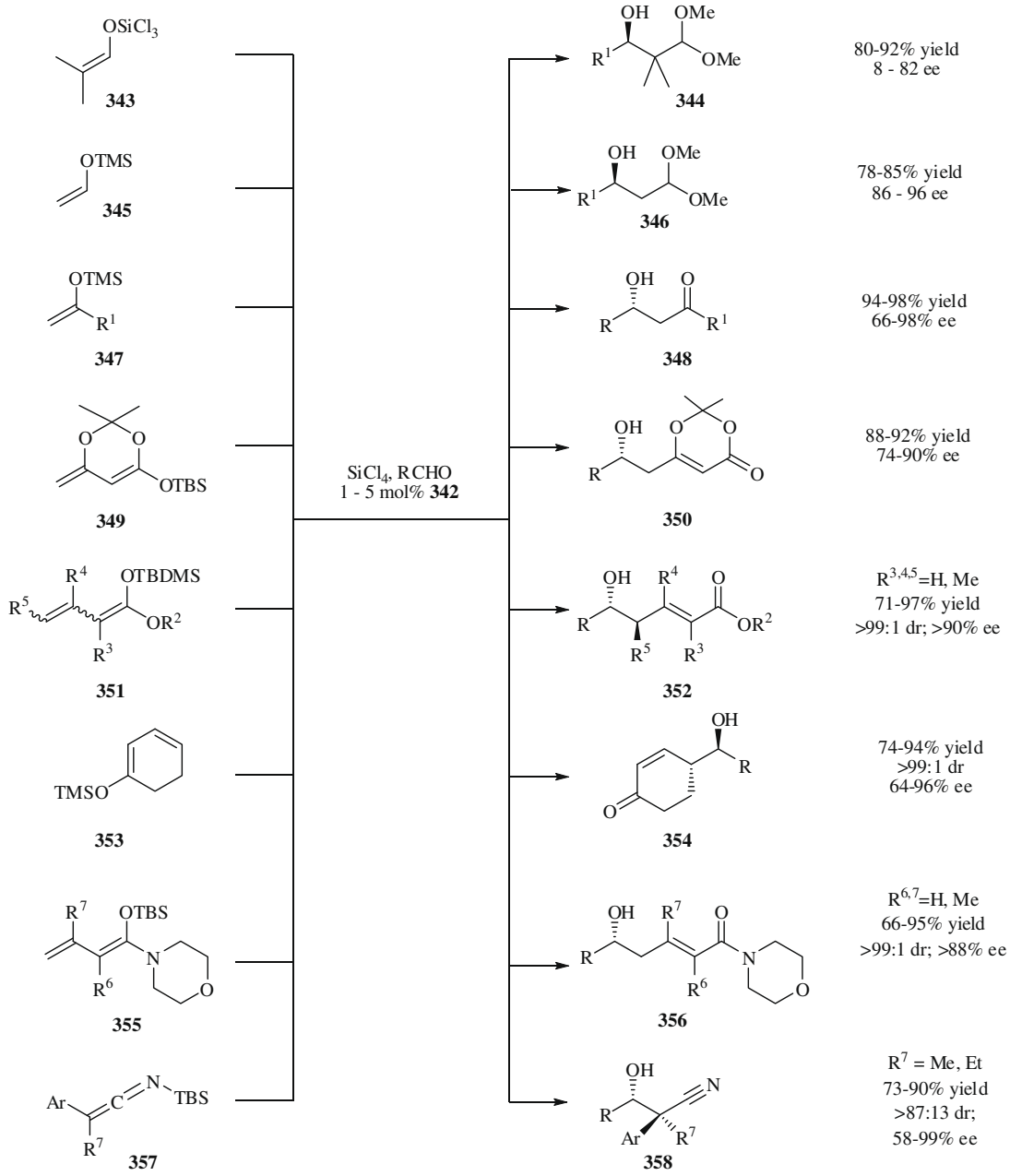
A simple diamine **361** was recently shown to catalyze the aldol addition of ketones to aldehydes (Scheme 106).[392] The yields of adducts **360** were generally good, as was the regioselectivity ratio (rr) favouring the isomer depicted in Scheme 106. The levels of diastereo- and enantioselectivity were likewise excellent. It is notable that the major adduct obtained in these reactions is the *syn*-diastereomer. Interestingly, when unsymmetrical methyl ketones were studied, 2-butanone and benzyloxyacetone gave preferentially the branched isomer (Scheme 106), but 2-pentanone and 4-methyl-2-pentanone gave the linear isomer (Scheme 106), despite the small differences in structure. It is also notable that good selectivities (>20:1 rr, 4:1 dr and 96% ee) were achieved when 3-hexanone was utilized as a donor, despite the steric similarities of both groups flanking the carbonyl.

Several cinchona alkaloid-derived organocatalysts (**362**–**365**, Fig. 22) have recently been examined as promoters in asymmetric aldol reactions. Both $(DHQ)_2PHAL$ **362** and $(DHQD)_2PHAL$ **363**, best known for their use as ligands in Sharpless asymmetric dihydroxylation reactions, can function on their own as organocatalysts for the enantioselective additions of oxindoles to trifluoromethyl ketones (Scheme 107).[393] Several α-substituted oxindoles **366** underwent efficient addition to trifluoromethylketones to give adducts **367**. Both organocatalysts were equally active and gave similar degrees of selectivity; however, either product isomer could be accessed depending on which alkaloid was chosen as the organocatalyst.

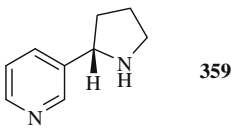
Cinchona alkaloid **364** also catalyzed the addition of cyclic ketones to aromatic aldehydes (Scheme 108).[394] Aldehydes containing electron-withdrawing groups were the most successful; those with electron-neutral groups, those with electron-donating groups and heteroaryl aldehydes could also be used, though adducts were formed in lower yields and somewhat lower selectivities. In fact, reaction with furfural actually gave the opposite *syn*-diastereomer as the major product.

An interesting application of cinchona alkaloids as organocatalysts was published in 2006 by Wang et al.[395] In tandem Michael-intramolecular aldol additions, a variety of thiochromanes **358** could be synthesized from 2-mercaptobenzaldehyes **262** and α,β-unsaturated acyl oxazolidinones **357** using only 1 mol % of thiourea **354** as catalyst (Scheme 109). It should be noted that these tandem reactions promoted by catalyst **354** stopped at the thiochromane (**358**) stage; as previously noted, the prolinol derivative **264** promoted elimination of **358** to generate thiochromenes, albeit in good yield and enantioselectivity (Scheme 76).[311] The alkaloid-derived catalyst **354** was designed to activate both partners simultaneously, aligning them for intermolecular addition. These results, and those of others,[321,359,396–398] clearly show the success of rational catalyst design, and the blossoming of enzyme mimicry by small molecules.

A TADDOL derivative (**372**; Scheme 110) was recently found to be an effective organocatalyst in Mukaiyama aldol additions of silyl



Scheme 105. Phosphoramide-promoted Mukaiyama aldol reactions of enolsilanes with aldehydes.



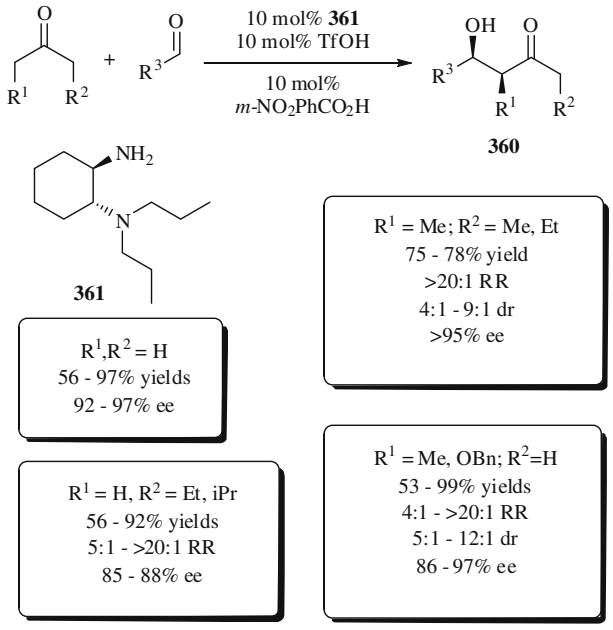
359

Figure 21. Nornicotine.

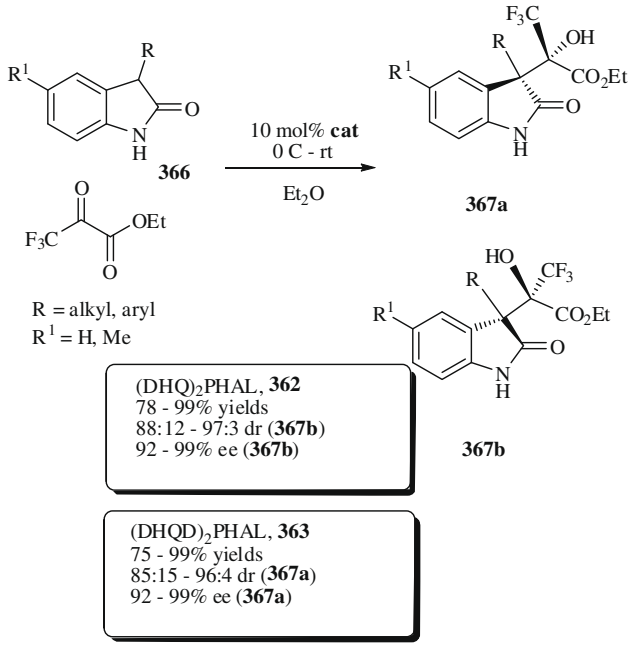
ketene aminals **370**.[399] Aminals **370** (the silyl enol ether derivatives of amides) underwent aldol additions with either aromatic or aliphatic aldehydes when treated with TADDOL **372** to give *syn*-adducts **371** in good yields and high selectivities (Scheme 110, Eq. A). The authors could transform the chiral amide products to aldehydes using Schwartz's reagent [$Cp_2Zr(H)Cl$] with little or no epimerization at the α-centre. Additionally, other researchers found that **372** could also promote vinylogous Mukaiyama aldol additions to give adducts **84**, albeit less successfully (Scheme 110, Eq. B).[400]

BINAPO **374** was also recently found to be a good catalyst for the Mukaiyama aldol addition.[401,402] Several trichlorosilyl enol ethers (e.g., **373**) were demonstrated to be good donors for the addition to a range of aromatic aldehydes (Scheme 111). As was the case with reactions promoted by transition metal-based chiral catalysts, the geometry of the product was dependent on the geometry of the enol ether; (*E*)-enol ethers gave *anti*-adducts and (*Z*)-enol ethers gave *syn*-adducts. A particularly notable feature of catalyst **374** was its success in promoting aldol additions to electron-rich aldehyde acceptors, which we previously noted were generally problematic cases.

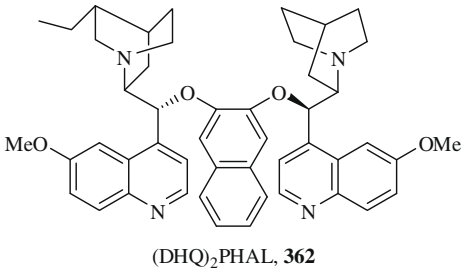
Chiral phosphoric acid **377** ((*R*)-TRIP) was recently shown to catalyze a cascade reaction between diones and amines to give substituted cyclohexyl amines.[403] Through a proposed combina-

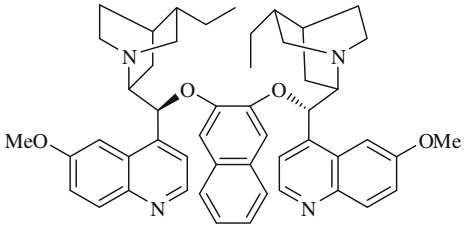


Scheme 106. Diaminocyclohexane organocatalysis of crossed-aldol reactions.



Scheme 107. Cinchona alkaloid-catalyzed additions to trifluoropyruvate esters.


(DHQ)2PHAL, **362**


(DHQD)2PHAL,
363

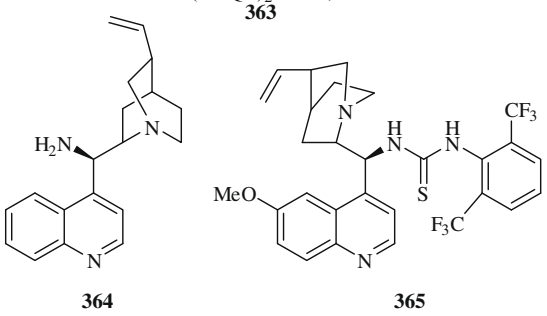
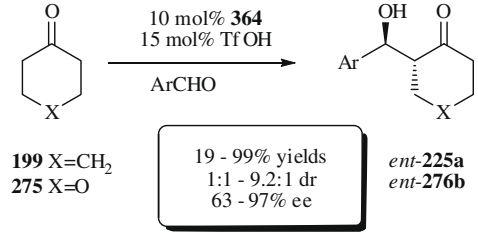
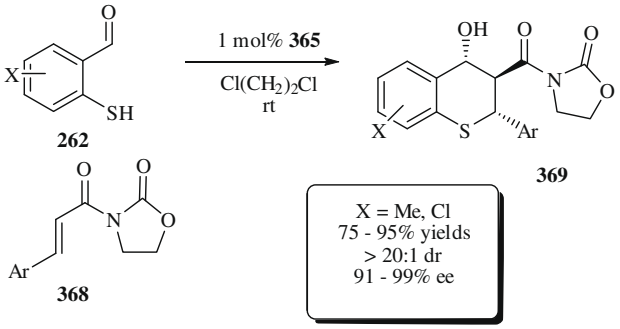

364 **365**

Figure 22. Cinchona alkaloid-based organocatalysts.



Scheme 108. Cinchona alkaloid organocatalysis of crossed-aldol reactions.

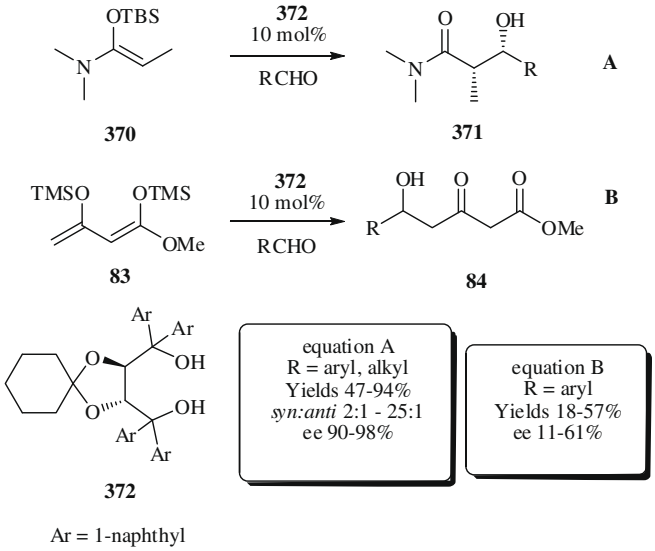


Scheme 109. Organocatalysis of tandem Michael-aldol reactions to form thiochromanes.

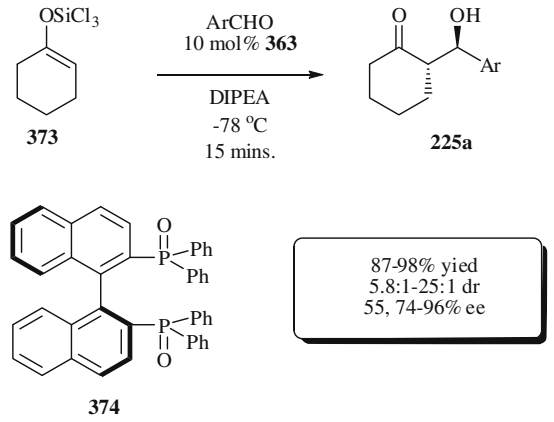
tion of enamine, iminium and Brønsted acid catalysis, diones **375** and protected primary amines efficiently condense to give a variety of substituted cyclohexylamines **376** via an in situ reduction by the Hantzsch ester **378** (Scheme 112). While the reaction was highly successful for a variety of diketones **375**, when X = S the process suffered from low yields.

The use of an axially chiral amino acid organocatalyst **379** (Fig. 23) was recently published.[404] Catalyst **379** could be effectively utilized at a loading of only 0.5 mol % in direct acetate aldol additions with both aromatic and aliphatic aldehydes (cf. Scheme 71). The yields of these reactions were somewhat variable, but the levels of enantioselectivity obtained were excellent.

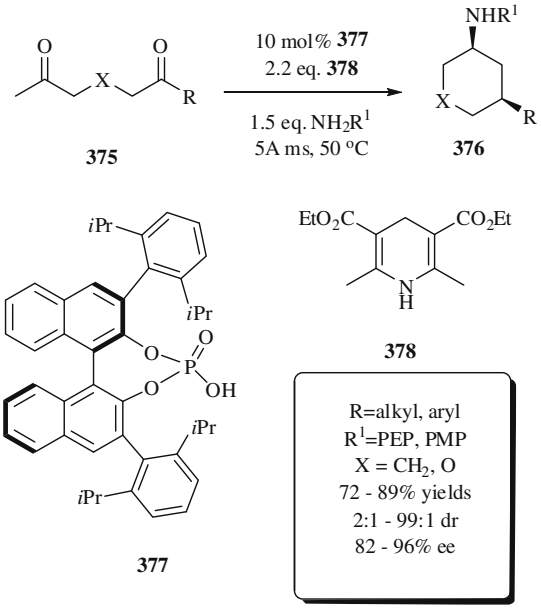
A similar axially chiral sulfonamide organocatalyst was recently shown to promote the crossed-aldol addition between aldehydes.[405] With only 5 mol % of **381**, aldol additions proceeded in



Scheme 110. *syn*-Selective Mukaiyama aldol additions promoted by a TADDOL organocatalyst.



Scheme 111. BINAPO-catalyzed *anti*-aldol addition.



Scheme 112. Aldol-reductive amination–reduction cascade promoted by a chiral phosphoric acid derivative.

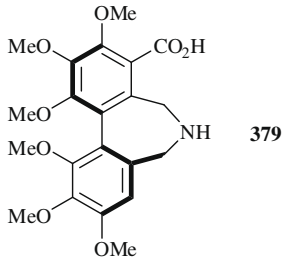
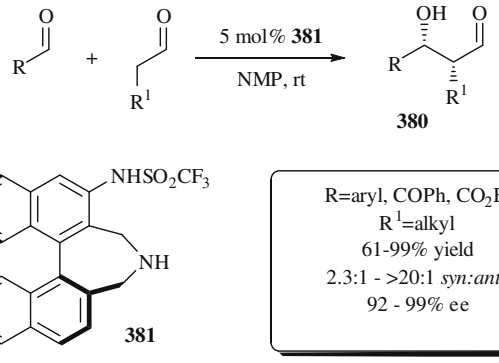


Figure 23. Axially chiral amino acid organocatalyst.



Scheme 113. Binaphthyl trifluoromethylsulfonamide organocatalysis.

good yields and excellent selectivities to give *syn*-adduct **380** (Scheme 113). Interestingly, when dioxane, toluene or methylene chloride was used as solvent, the *anti*-adduct predominated, albeit in lower selectivity. Use of *N*-methylpyrrolidinone as the solvent led to high selectivity for the *syn*-adducts.

Maruoka et al. have demonstrated that a chiral quaternary ammonium salt[406] (**382**, Fig. 24) is an efficient phase-transfer catalyst for aldol additions between glycine imine derivative **383** and aldehydes to generate *anti*-β-hydroxy-α-amino acid derivatives **384** (Scheme 114).[407,408] These reactions rely on the enhanced acidity of the glycyl imine to permit efficient enolate formation under the phase-transfer conditions employed. As discussed above, proline could also catalyze a similar reaction to generate *anti*-β-hydroxy-α-amino aldehydes (Scheme 61);[261] however, in that exam-

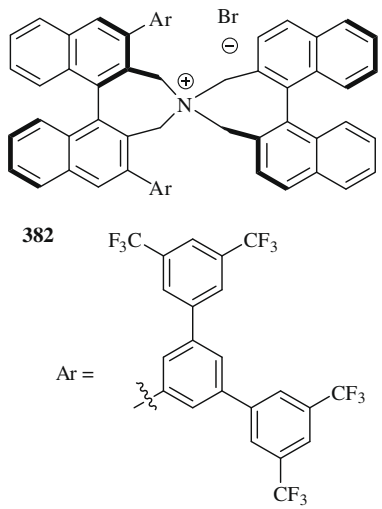
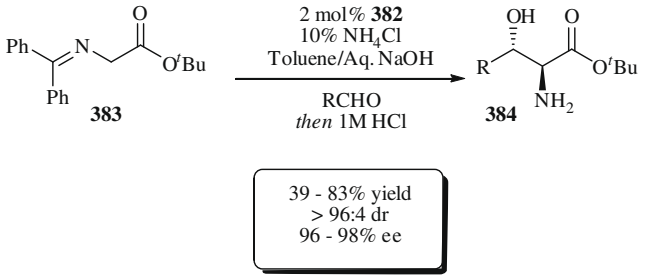


Figure 24. Chiral quaternary ammonium salt for use in phase-transfer catalysis.



Scheme 114. Synthesis of *anti*-β-hydroxy-α-amino esters using chiral phase-transfer catalysis.

ple, proline was required in 30 mol %, making Maruoka's catalyst much more efficient at 2 mol %. The quaternary salt was also consistently more diastereoselective than was L-proline in these reactions. These phase-transfer-catalyzed reactions are mechanistically quite different from the majority of organocatalyzed aldol reactions, but are mentioned here for completeness.

4.5. Summary of advances in organocatalysis

Organocatalytic methods are developing at an explosive pace. The number of papers on the subject published in the last two years alone is remarkable; many of the results discussed here were published in 2006 and 2007. In 2000 and 2001 when organocatalyzed aldol additions were just beginning, the 'state of the art' of this pioneering work was characterized by variable yields and selectivities, large excesses of one component and high catalyst loadings.[254,256,409,410] It is remarkable that only a few short years later, the perseverance of many research groups has transformed organocatalysis into a method that has far greater substrate breadth and scope, is more selective and is more efficient than would have been imagined possible.

There have been many reports in the last few years on the organocatalytic synthesis of 1,2-diols employing an aldol approach. A summary of these can be found in Table 8. In general, reactions of α-hydroxy- or α-alkoxy-substituted carbonyl donors with aromatic aldehydes have worked well. However, organocatalyzed aldol reactions with aliphatic aldehydes remain problematic. Only L-proline and dipeptide catalyst **332** have been reported to be successful in this regard. It is also notable that there are several catalysts that can generate 1,2-*anti*-diols selectively (proline, **237**, **239**, alanine and **288**), and several that can generate 1,2-*syn*-diols selectively (**332**, **335** and **336**). Of these, not only is **332** a useful catalyst towards both aliphatic and aromatic aldehydes at only 5 mol % loading, but it also consistently affords good levels of diastereoselectivity and enantioselectivity, although the yields of these reactions are somewhat variable. Organocatalyst **332** appears to be more efficient than zinc catalyst **121** (which also generates 1,2-*syn*-diols, Scheme 33), as the zinc catalyst is required in higher loadings, and requires an additional chelating group for good selectivity. As well, **121** was only useful for aliphatic aldehyde acceptors. The success of **332** is a great achievement for organocatalysts, and shows promise for future development.

Similarly, organocatalyst **288** (Scheme 82) is as efficient as LLB **122** (Scheme 34) in generating *anti*-diols; diastereoselectivities, enantioselectivities and yields are comparable between the two catalytic methods. However, LLB is much more successful when aliphatic aldehydes are utilized as acceptors, providing a useful method for generating that adduct type.

As we have noted, aldol additions to pyruvate derivatives are synthetically useful processes. However, the examples discussed in that section were based on Mukaiyama aldol additions (Table 1). In contrast, prolinamides **269**[313] and **293**[321] were able to catalyze similar additions *directly* without the need for pre-formed silyl enol ethers for a variety of methyl ketones (Schemes 78 and 84, respectively). Despite the somewhat increased loading of the prolinamide as compared to the metal catalysts (15–20 mol % vs 7–10 mol %), the direct reaction provides a great advantage, and this should prove to be a very useful method.

Individual organocatalysts have not been reported to consistently give either *syn*- or *anti*-aldol products, and the level of diastereoselectivity obtained has often been only moderate. As it currently stands, the formation of *syn*- or *anti*-adducts in organocatalyzed aldol reactions seems to be dependent on the donor substrate itself. Further development of organocatalysts is needed to provide fully catalyst-controlled stereoselectivity in these reactions. Further, reaction conditions evidently have a large impact on the selectivity of organocatalytic reactions. More work is needed to develop a solid understanding of the impact of surfactants, emulsion formation and acidity on the outcome of these processes. The intrinsic attractiveness of organocatalytic reactions makes it obvious that these methods will be continued to be developed in the years to come, and we expect that these studies will lead to exciting new synthetic possibilities.

5. Summary and conclusions

A vast amount of work has been done in the last five years to further develop and understand asymmetric control in the aldol addition, particularly by catalytic methods. Catalysis is intrinsically elegant and economical, but it appears that, at least for the time being, it is limited to simpler substrates in most cases. The scope of asymmetric catalysis is constantly increasing, however. Furthermore, as pointed out in a recent paper, the level of enantioselectivity afforded by chiral auxiliaries is generally directly dependent on the enantiomeric purity of the auxiliary, whereas chiral catalysts often provide asymmetric amplification.[411]

Table 8
Organocatalytic approaches to 1,2-diols

Catalyst (mol %)	Donor	Accept.[a]	Yields (%)	dr[b]	ee (%)	Ref.
L-Pro (10) **193**	Oxy-aldehyde (protected)	Oxy-aldehyde (protected)	0–73	3:1–9:1 *A:S*	88–98	Scheme 60[259]
Pro-deriv. **237** (30)	Hydroxy-acetone	Aro. RCHO	53–77	1:1–5:1 *A:S*	28–90	Table 5
Pro-deriv. **239** (10)	Hydroxy-acetone	Aro. RCHO	77–79	9:2–50:1 *A:S*	73–97	Table 5
Peptide **332** (5)	Hydroxy-acetone	Aro. and Aliph. RCHO	45–97	13:1–20:1 *S:A*	91–98	Scheme 101[359]
L-Thr **335** (20)	Hydroxy-acetone	Aro. RCHO	78–95	3:1–18:1 *S:A*	80–98	Scheme 103[364]
L-Thr **336** (2–10) H_2O	Hydroxy-acetone (protected)	Aro. RCHO	76–92	3:1–8:1 *S:A*	91–98	Scheme 104[361]
L-Thr **335** (20)	Dihydroxy-acetone	Aro. RCHO	62–92	7:1–15:1 *S:A*	92–98	Scheme 103[363]
L-Ala (30) + 10 equiv H_2O	Dihydroxy-acetone (protected)	Aro. RCHO	75–77	5:1–6:1 *A:S*	97–99	Scheme 97[353]
L-Thr **335** (20) + H_2O	Dihydroxy-acetone (protected)	Aro. RCHO	65–94	4:1–7:1 *S:A*	93–98	Scheme 103[362]
L-Pro (20–30) **193**	Dihydroxy-acetone (protected)	Aro. and aliph. RCHO	60–90	2:1–99:1 *A:S*	84–98	Scheme 63[264,265]
Pro-deriv. **288** (20)	Hydroxy-ynone	Aro. RCHO	26, 65–90	3:1–19:1 *A:S*	90–97	Scheme 82[319]

[a] Accept. = acceptor. Aro. = aromatic aldehyde, aliph. = aliphatic aldehyde.
[B] dr—*A* = *anti*; *S* = *syn*.

Some interesting differences can be observed between the structures of chiral metal catalysts and chiral auxiliaries or organocatalysts that have proven successful in the aldol reaction. Both chiral auxiliaries and organocatalysts typically have quite simple structures, yet they efficiently induce asymmetry; in contrast, metal-based catalysts often employ structurally complex and expensive ligands to achieve similar levels of selectivity. As well, current organocatalysts and most chiral auxiliaries are derivatives of materials from the chiral pool,[91,96,412–422] while ligands for metal catalysts are frequently acquired through asymmetric synthesis.[404,423–439]

Chiral auxiliaries have been successful in aldol reactions of both simple and complex substrates, as is evidenced by the diversity in Table 4. Chiral auxiliary methods have been devised to access three of four possible diastereomers from a single starting structure simply by modifying the reaction conditions (e.g., Scheme 3). This kind of flexibility has not yet been obtained from catalytic aldol methods. A set of four aldol catalysts, each capable of predictably promoting an enantio- and diastereoselective aldol reaction between various reaction partners (similar to the versatility of the dihydroxylation reactions promoted by the AD-mix catalyst/reagent mixtures), would be highly desirable.

A general solution to the crossed-aldol reaction between two aldehydes remains elusive. This is not surprising, given the issues inherent in the problem. In this review, three examples were given. L-Proline was demonstrated to be a successful catalyst in the niche reaction between an aliphatic aldehyde and an α-hydroxy aldehyde (Schemes 60 and 61). Proline derivative **228** could be used as a catalyst, provided one component was present in a fivefold excess (Scheme 68).[270]

As this review has demonstrated, there is not a 'one-size-fits-all' method for performing regio-, diastereo- and enantioselective aldol reactions. While chiral auxiliary methods may still offer the most broadly applicable approach to the stereoselective aldol reaction, this dominance is rapidly being eroded by the success of organocatalytic methods. Chiral catalysts will certainly begin to outnumber chiral auxiliaries in target-oriented syntheses in the very near future. We can anticipate that as the ability for rational catalyst design grows it may soon be possible to use chiral catalysis for the majority of asymmetric C–C bond forming reactions.

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