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Recent developments in asymmetric catalytic addition to C=N bonds

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Abstract—Methods for enantioselective C–C bond constructions via additions to imines and related compounds are reviewed, with an emphasis on the most recent efforts involving asymmetric catalysis. Selected seminal examples are provided in order to place the recent developments in context.

Contents

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1. Introduction

Chiral α-branched amines are common substructures within biologically active materials and hence attract broad interest, particularly in the areas of synthetic methodology, bioorganic and medicinal chemistry, and natural product synthesis. Additions of carbon fragments to C=N bonds of imines and related compounds build up the carbon framework in the same operation as asymmetric induction, so this approach is one of the more attractive entries to chiral amines. As with other chiral functionalities, the stereocontrol construction of chiral amines has evolved through the use of chiral pool materials, substrate diastereoselectivity, chiral auxiliary control, and more recently asymmetric catalysis. Practical catalytic enantioselective additions to C=N bonds only began to approach general application in the last few years. In this review, we survey the most recent of these developments, as summarized in Figure 1.

This review does not cover reductions of imines or cycloadditions (e.g., aza-Diels–Alder, 1,3-dipolar, or Staudinger cycloadditions) for reasons of space. Furthermore, the many important chiral auxiliary approaches are not included here. Still, it is important to emphasize that the synthetic community has a persistent reliance on chiral auxiliaries for chiral amine synthesis for very practical reasons: First, as noted above the generality of asymmetric catalysis methods is still developing. Second, there is very sparse methodology for the use of unsubstituted imines (i.e., C=NH) in addition reactions, and in the absence of such methods, the vast majority of additions use C=NX acceptors (for example, where X is an electron-withdrawing group such as acyl,[1] sulfonyl,[2] phosphoryl,[3] etc.). As there is already the requirement to remove the auxiliary X, in principle the efficiency is not further penalized by using X as a chiral auxiliary. Third, rigorously enantiopure compounds can often be obtained by separation prior to cleavage of the chiral auxiliary, whereas asymmetric catalysis may require a difficult resolution. Thus, additions using chiral auxiliaries continue to be extensively developed to the point of truly general practicality, and have been reviewed previously.[4]

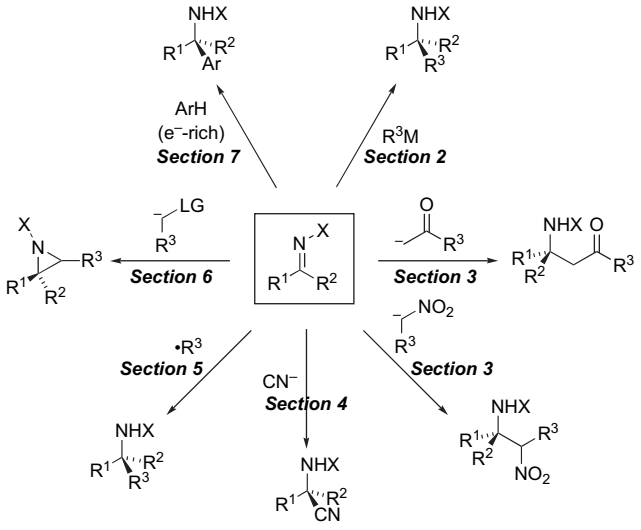
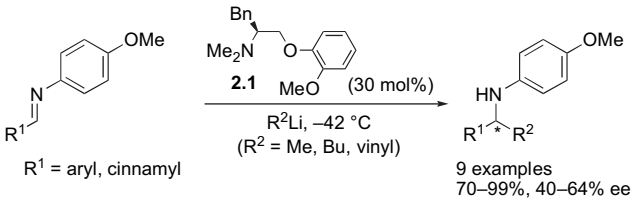


Figure 1. Summary of reviewed enantioselective additions to imino compounds.

We focus here on the recent developments in reactions involving catalytic stereocontrol, especially the literature of 2004–2006, with some earlier seminal work and benchmark methods discussed where appropriate as contextual framework for the newer methods. For more details of the earlier work, the reader is encouraged to consult prior reviews.[5] Some new examples of reagent control or racemic catalysis are noted if there is some suggested potential for asymmetric catalysis development.

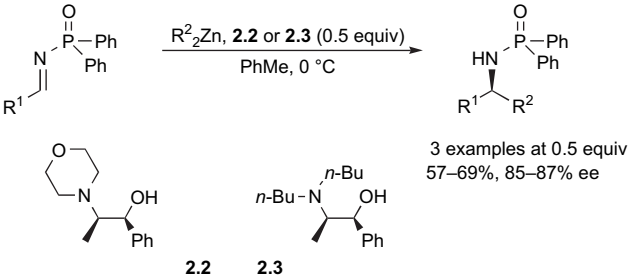
2. Addition of organometallic nucleophiles

The earliest examples of asymmetric reagent-controlled addition of organolithium compounds to imines were registered in 1990 by Tomioka, who, in the course of studies of asymmetric Michael additions to unsaturated imines, observed highly enantioselective 1,2-addition in certain cases.[6] The chiral Lewis base ligand **2.1** (Scheme 1) was found to afford moderate enantioselectivities of 40–64% at 30 mol % loading.[7]



Scheme 1.

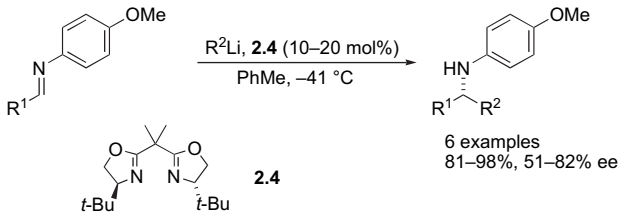
Following this lead, further work by Tomioka[8] and others during the early 1990s expanded the entry to this new avenue of research and inspired dramatic advances in catalytic asymmetric amine synthesis. For example, Soai found that dialkylzinc additions to diphenylphosphinoyl imines could be controlled with outstanding enantioselectivities using 0.5 equiv of chiral amino alcohols **2.2** and **2.3** (Scheme 2), and one example was given with 10 mol % of the chiral amino alcohol (75% ee).[9]



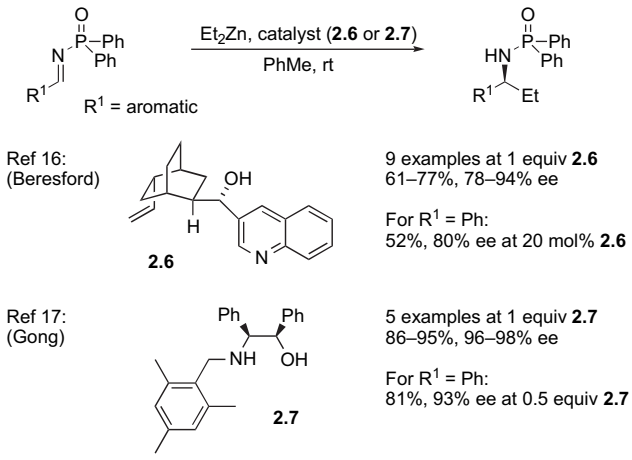
Scheme 2.

Denmark showed that outstanding yields and very good enantioselectivities could be obtained by modifying organolithium reagents with bisoxazoline ligand **2.4** (Scheme 3) or (−)-sparteine; at low temperatures the reactions were very slow in the absence of ligand.[10]

As seen in the seminal studies described above, it was discovered early on that reactivity and stereoselectivity of alkyllithium species might be controlled with Lewis basic additives. These additives exert their effects through alterations in aggregation and coordination of the reagent,



Scheme 3.



Scheme 5.

so numerous studies of the nature of complexes of organolithium species with Lewis basic additives and solvents in solution and solid state have been reported.[11] Significantly altered stereoselectivity may result from modifying speciation of the Li complexes in the reaction mixtures, as noted in recent kinetic studies by Qu and Collum (Scheme 4), who proposed alternative transition structures **2.A**–**2.D**, shown with estimated stereoselectivities for BuLi–TMEDA addition to imine **2.5**.[12] Related studies with a chiral cyclohexanediamine showed similar results,[13] whereas previous studies of simple imines showed the monomer-based pathways to be more important.[14] Though these studies improve the current awareness in structural features of organolithium species and their correlations with reactivity, application in de novo ligand design continues to present a challenge.

2.1. Organozinc reagents

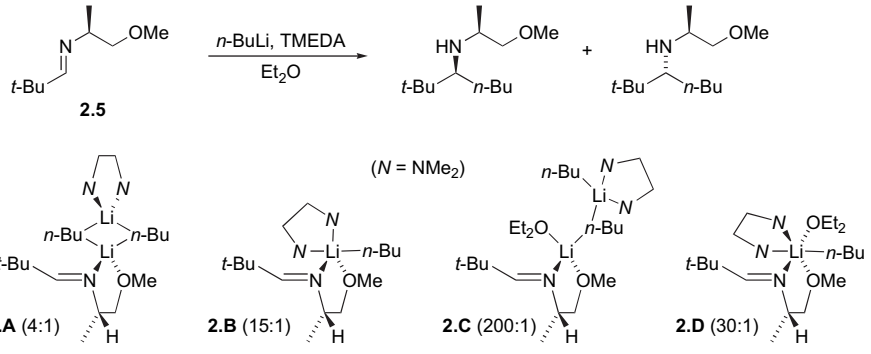
2.1.1. Lewis base activation. Soai reported early examples of the use of chiral Lewis base activation of dialkylzinc addition to imines in 1992, but since that time emphasis has shifted to the use of chiral Lewis acid catalysis of dialkylzinc additions (vide infra). However, there are a number of examples of enantioselective catalysis by amino alcohols.[15]

Cinchona alkaloids can catalyze the addition of diethylzinc to benzaldehyde diphenylphosphorylimine, leading to 80% ee at room temperature with 20 mol % loading of cinchonidine (**2.6**, Scheme 5).[16] Excellent enantioselectivity (78–94% ee) was observed for additions to eight other phosphorylimines, though stoichiometric quantities of cinchonidine were used. Imines of the type *N*-(*p*-methoxyphenyl) or *N*-Ts were inferior in these reactions.

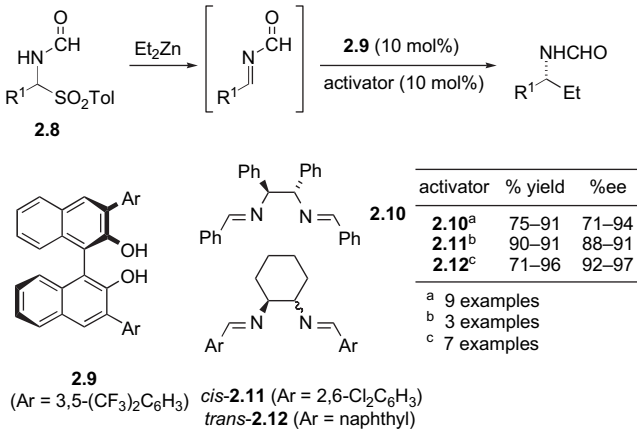
Synthetic amino alcohols offer the opportunity for broader variation and fine-tuning the selectivity. Gong et al. have reported the full details of their efforts to screen aromatic *N*-substituents on 1,2-diphenyl-2-aminoethanol for improved enantioselectivity, and found that mono-*N*-substituted catalysts such as **2.7** (Scheme 5) were superior catalysts compared to their *N*-methyl analogs or to the corresponding aldimines.[17] Additional examples using stoichiometric **2.7** were reported for dibutylzinc additions, with lower yields but equally outstanding selectivity. Computational stereocontrol models were presented.

Gong applied asymmetric activation to enhance the stereocontrol by BINOL and its derivatives in enantioselective additions of diethylzinc to in situ-generated *N*-formyl imines. The *N*-formyl imine sulfinate adduct **2.8** (Scheme 6) was treated with a ternary complex of BINOL derivative **2.9** and diimine **2.10**, leading to enhancement of selectivity to 66% ee from 15% ee with **2.9** alone. Optimizing the solvent led to a method capable of excellent enantioselectivity and yield for additions to a range of aromatic aldimines.[18] Further improvements resulted in more consistently high selectivity, as observed with imines *cis*-**2.11** and *trans*-**2.12** as activators.[19]

2.1.2. Lewis acid activation. Tomioka reported asymmetric Cu-catalyzed addition of diethylzinc to *N*-sulfonyl imines in 2000, with enantioselectivities up to 94% using phosphine **2.13** (Scheme 7).[20] Screening sulfonyl groups, Cu sources, and solvents enabled the use of catalyst loadings as low as 1 mol %, and aliphatic enolizable imines were included in application of the optimized conditions.[21] Other studies of

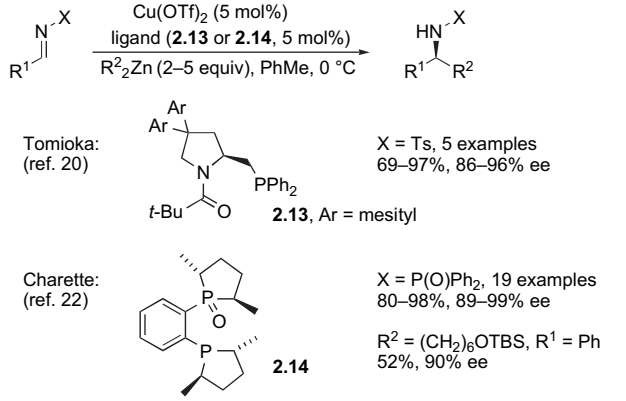


Scheme 4.



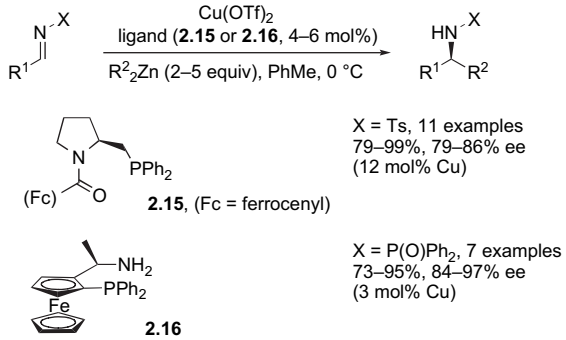
Scheme 6.

Cu-catalyzed reactions with the novel monophosphine oxide ligand **2.14** by Charette were reported shortly thereafter,[22] and are notable for the use of five different dialkylzinc reagents including one bearing remote silyloxy substituents. Bisoxazoline complexes were less efficient catalysts than those of phosphines **2.13** and **2.14**.[23]



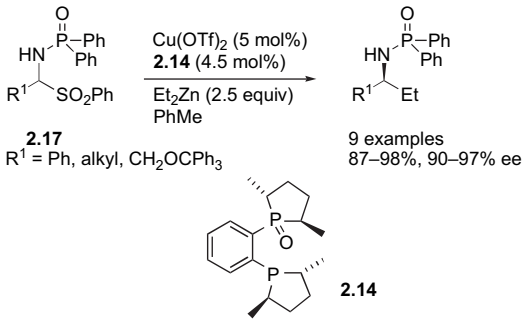
Scheme 7.

Wang et al. have reported the use of ferrocene-derived ligands for reaction conditions quite similar to those described above.[24] In ligand **2.15** (Scheme 8), the ferrocenyl group gave enhanced enantioselectivity relative to other bulky groups previously tested by Tomioka.[25] Planar-chiral ligand **2.16** gave higher selectivity, though the slightly higher catalyst loading makes a direct comparison less meaningful.[26]



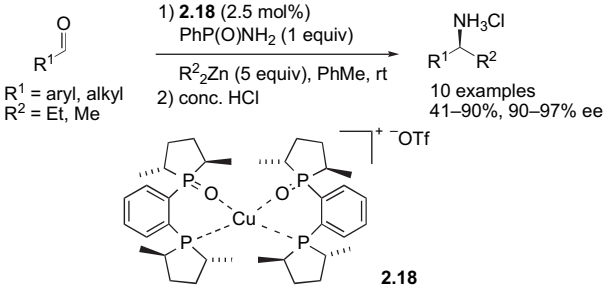
Scheme 8.

The instability of enolizable phosphorylimines was identified as a significant hindrance to further developments, and Charette et al. circumvented this difficulty with an interesting procedure to isolate the imine-sulfinate adducts **2.17** (Scheme 9), which were then converted in situ to the *N*-diphenylphosphorylimines.[27] For diethylzinc, several enolizable aldehydes gave outstanding selectivities for the ethyl adducts using **2.14**/Cu(OTf)$_2$. The sulfinate adduct trick can also be applied with glycolaldehyde derivatives, leading to a synthesis of ethylglycine in 97% ee.[28]



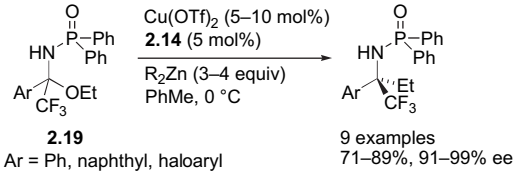
Scheme 9.

An efficient one-pot diethyl- and dimethylzinc addition method was also demonstrated by Charette; diphenylphosphinamide and aldehydes are combined with dialkylzincs in a ratio of 1:3:5, respectively, in the presence of 2.5 mol % of Cu catalyst **2.18** (Scheme 10). Yields for the process ranged from 32% to 90%, with excellent enantioselectivities across 10 examples including enolizable aliphatic aldehydes.[29] Charette's methods stand as benchmarks in scope and selectivity for organozinc additions to imines.

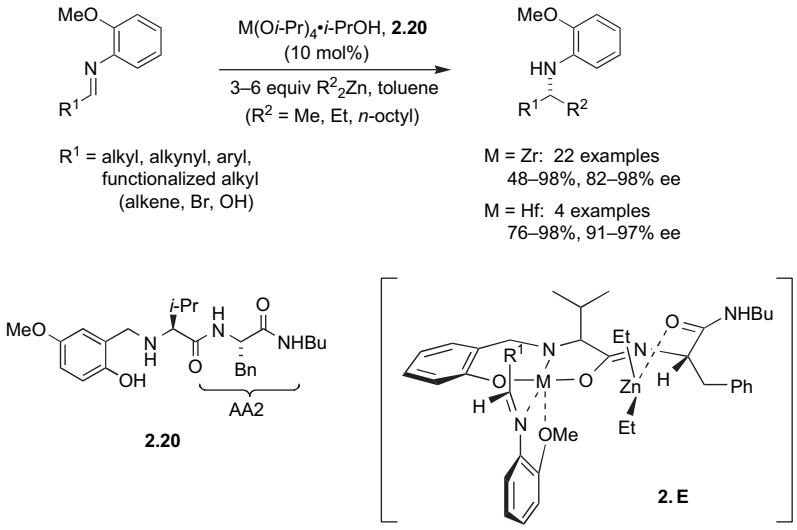


Scheme 10.

Additions to ketimines have been slower to develop, in general. Charette has designed a method for addition of diethyl- or dimethylzinc to aryl trifluoromethyl ketimines, generated in situ (Scheme 11).[30] Exploited here were novel stable hemiaminals **2.19** bearing ethoxide as the leaving group, serving the same role as the sulfinate of **2.17** (see above), and providing the acceptor for addition of dialkylzinc with excellent enantiomeric excess.



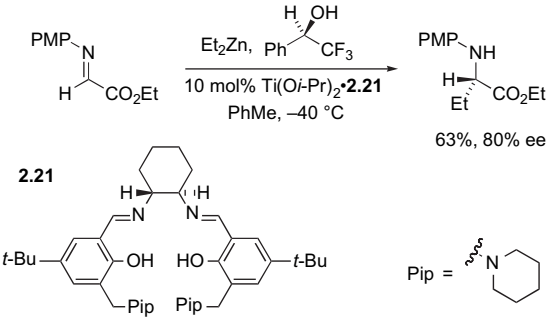
Scheme 11.



Scheme 12.

Dialkylzinc reagents were also examined by Hoveyda and Snapper, exploiting Zr–dipeptide complexes as Lewis acid activators of the imino acceptors.[31] More recently, further insights in these reactions were reported;[32] using analogous Hf complexes with enantiopure dipeptide **2.20** (Scheme 12), aryl-, alkyl-, alkenyl-, and alkynyl-substituted *N*-arylimines were all successful in enantioselective additions with improved yield and selectivity (84–98% ee). Modifications to the dipeptide revealed an active role for the AA2 position, since the inverted configuration of Phe in this position led to the enantiomeric product. A stereocontrol model **2.E** incorporating reagent delivery by the AA2 amide carbonyl was proposed.

Ethyl addition to α-aldiminoesters produced ethylglycine derivatives via a Ti-catalyzed diethylzinc addition (Scheme 13).[33] This study by Kozlowski showed some good potential of bifunctional salens; Ti(O*i*-Pr)$_2$·**2.21** bearing a piperidine substituent on the chiral ligand, along with the presence of additives in a certain pK_a range (12–14), resulted in optimized selectivities in the range of 60–80%.



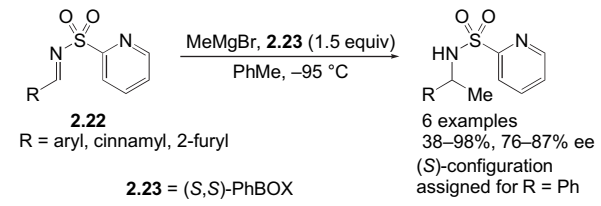
Scheme 13.

The fundamental question which remains open in most diorganozinc additions is whether the reaction can ultimately extend beyond the addition of simple alkyl groups; most such studies remain limited to ethyl addition. Few other diorganozinc reagents are commercially available. Nevertheless, this reaction class includes some of the most thoroughly optimized conditions of any asymmetric addition to C=N bonds, and some methods can be achieved with low catalyst loads well below 10 mol %. As such organozinc additions present worthwhile lessons to be considered in the design and development of new methodology in this area.

2.2. Organolithium and Grignard reagents

Although some of the earliest catalytic asymmetric additions to imino compounds involved strongly basic organolithium and Grignard reagents, these have been the subject of fewer examinations in recent years, probably due to functional group compatibility questions and complications of metalloenamine formation from enolizable imino acceptors. Still, some interesting discoveries have emerged.

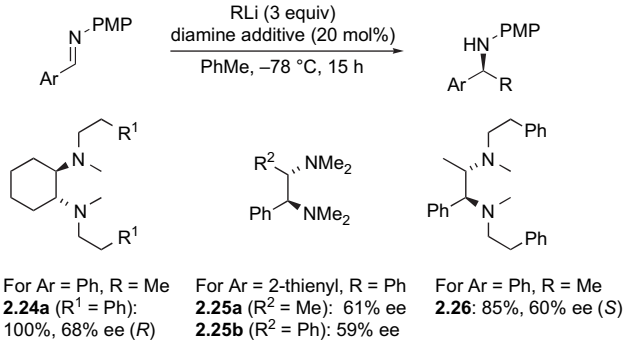
Toru et al. reported reactions of a series of *N*-(pyridylsulfonyl)imines **2.22** (Scheme 14) with Grignard reagents in the presence of stoichiometric amounts of sparteine or bisoxazoline ligands.[34] Prochirality at sulfur served a key role as a chiral relay; a chelation model involving the pyridyl nitrogen and the selective complexation of one sulfonyl oxygen was proposed with the aid of MOPAC 93/PM3 calculations. Using PhBOX ligand **2.23**, the enantioselectivity was good for MeMgX addition to a series of imines (76–87% ee), but other Grignard reagents led to moderate or low selectivity.



Scheme 14.

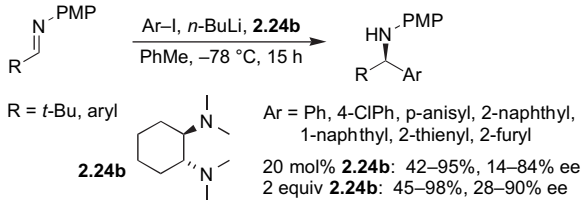
Using tertiary cyclohexanediamines such as **2.24** (Scheme 15) with variations to their *N*-substituents R^1, Alexakis found good yields for methyllithium addition across a slate of nine aromatic imines with moderate enantioselectivity

at 20 mol % loading.[35] It was noted that pseudo-C_2-symmetric ligand **2.25a**, derived conveniently from (1*S*,2*S*)-(+)-pseudoephedrine, could facilitate asymmetric additions of phenyllithium to *N*-PMP-imines (PMP=*p*-methoxyphenyl) with enantioselectivity similar to that obtained with the C_2-symmetric ligand **2.25b**.[36] The pseudosymmetric **2.26**, with a further increase of steric bulk via the *N*-phenethyl substitution, was then applied in a series of additions of methyllithium to aromatic *N*-PMP-imines (30–69% ee). With the same series of additions, C_2-symmetric **2.24** provided opposite product configuration (48–74% ee).



Scheme 15.

Alexakis also examined the use of aryllithium reagents with 1,2-diamine catalyst **2.24b** for aryl addition to aryl and pivalaldehyde-derived *N*-PMP-imines (Scheme 16).[37] With 20 mol % diamine additive, selectivities were routinely in the range of 60% ee. A study of in situ generation of aryllithiums by metal–halogen exchange from the corresponding iodides extended the generality of the reaction, although stoichiometric amounts of diamine were used in most of these examples. The use of 1-iodonaphthalene gave routinely high enantioselectivities across a series of aromatic imine acceptors.



Scheme 16.

2.3. Other organometallic methods

Transmetallation from a variety of main group or early transition metal organometallic nucleophiles is postulated as a key step in several asymmetric transition metal-catalyzed additions to imino compounds. Upon transmetallation, chiral ligands such as **2.27**–**2.33** (Table 1) in the transition metal catalyst can then effect stereocontrol. A number of interesting examples of these reactions have been reported, including Rh-catalyzed addition of arylstannanes,[38] arylboroxines,[39] and aryltitanium species,[40] as well as a Ni-catalyzed three-component coupling of alkynes, organoboranes, and imines leading to allylic amines.[41] Recent developments are compiled in Table 1.

Hayashi reported Rh-catalyzed dimethylzinc addition to *N*-tosylimines in the presence of a range of chiral ligands, finding superior results with the C_2-symmetric diene ligand **2.29**,[42] previously found to be effective for arylboroxine addition.[39] For methyl addition, the methylboronic acids were ineffective in these reaction conditions. A methylrhodium species was invoked as a reactive intermediate.

Hemilabile amidophosphine ligands based on a valinyl-prolinol dipeptide structure proved effective for Rh-catalyzed addition of arylboroxines to aromatic *N*-tosylimines.[43] Best enantioselectivities were observed with **2.30** for additions to imines derived from 2-trimethylsilylbenzaldehyde, where it was further shown that the TMS substituent could be removed or replaced with iodine.

A BINOL-derived phosphite ligand **2.31** (Table 1) proved effective for additions of boronic acids to *N*-dimethylsulfonylimines in a high yielding and highly selective transformation leading to sulfonamides, which were readily cleaved to the primary amines upon treatment with 1,3-diaminopropane with microwave irradiation.[44]

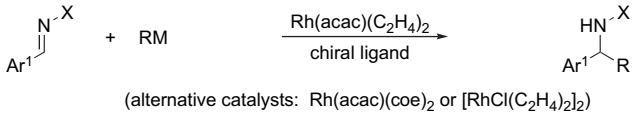
High enantioselectivities were also reported for Rh-catalyzed additions of arylboronic acids by Zhou et al.[45] Using an interesting spirocyclic phosphite ligand **2.32** (Table 1), various *ortho*-, *meta*-, and *para*-substituents were accommodated on both the arylboronic acids and the aromatic *N*-tosylimine acceptors. Reversal of configuration was accomplished with the same chiral ligand by switching the aryl groups of the reagent and substrate.

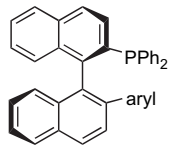
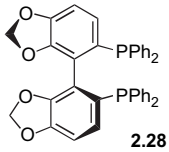
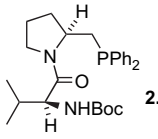
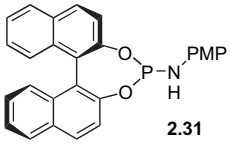
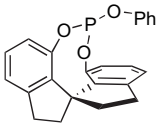
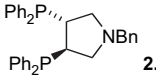
A number of asymmetric amine syntheses have emerged from Ellman's studies of chiral *N*-sulfinylimines.[4d] These are powerful chiral auxiliaries with a wide range of practical applications. Recently, Ellman reported Rh-catalyzed additions to these chiral substrates, along with a few selected examples of achiral *N*-phosphinoyl imine acceptors in which it was demonstrated that asymmetric catalysis could be achieved with DeguPHOS (**2.33**, Table 1) as the chiral ligand.[46]

2.4. Alkynylmetal reagents

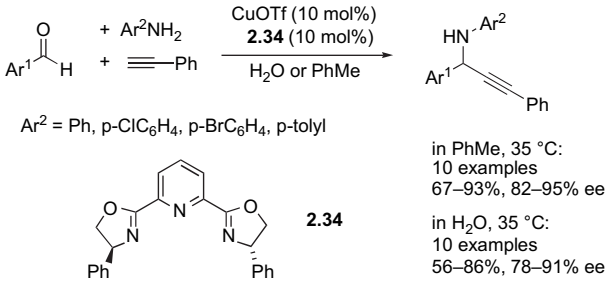
A class of addition reactions which has been quite amenable to asymmetric catalysis involves synthesis of propargylic amines through addition of metal alkynides to imino compounds. As with allylation reactions, this operation leaves suitable functionality for further manipulation. Early studies by Carreira revealed excellent potential for addition of zinc alkynides to nitrones,[47] and showed the way toward asymmetric catalysis in related additions to aldehydes.[48,49] In 2002, the first catalytic asymmetric alkyne addition to imino compounds was reported by Li, using Cu(I) and bisoxazoline ligand **2.34**, with in situ generation of the imine in water or toluene solution (Scheme 17).[50] A similar catalyst system was effective in oxidative additions to tetrahydroisoquinoline involving a C–H activation event.[51] Li has also recently reported an interesting Ag(I)-catalyzed addition method,

Table 1. Rh-catalyzed additions to imino compounds



Reference	RM, X	Chiral ligand	Results
Hayashi (Ref. 38)	Ar^2SnMe_3 (X=Ts)	 **2.27** (aryl = 4-methoxy-3,5-dimethylphenyl)	7 examples, R=aryl 69–90%, 92–96% ee
Hayashi (Ref. 40)	$Ar^2Ti(Oi\text{-}Pr)_3$ (X=triisopropyl-benzenesulfonyl)	 **2.28**	11 examples, R=aryl 86–99%, 86–96% ee
Hayashi (Ref. 39) Hayashi (Ref. 42)	$(Ar^2BO)_3$ (X=Ts) Me_2Zn (X=Ts)	 **2.29**	11 examples, R=aryl 94–99%, 96–99% ee 10 examples, R=Me 61–91%, 94–98% ee
Tomioka (Ref. 43)	$(Ar^2BO)_3$ (X=Ts)	 **2.30**	11 examples, R=aryl 83–99%, 66–94% ee
de Vries, Feringa, Minaard (Ref. 44)	$Ar^2B(OH)_2$ (X=SO_2NMe_2)	 **2.31**	11 examples, R=aryl 72–98%, 87–95% ee
Zhou (Ref. 45)	$Ar^2B(OH)_2$ (X=Ts)	 **2.32**	17 examples 56–85%, 85–96% ee
Ellman (Ref. 46)	$Ar^2B(OH)_2$ (X=$P(O)Ph_2$)	 **2.33**	4 examples 87–97%, 88–94% ee

but enantioselectivity has not yet been disclosed for this reaction.[52]

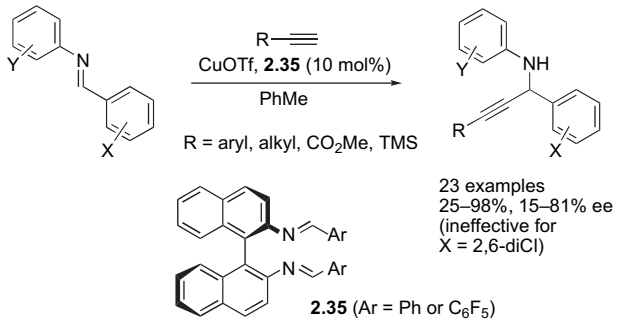


Scheme 17.

Following the seminal Li discovery, a number of modifications of the Cu-catalyzed addition of terminal alkynes have appeared. Use of ionic liquids enables opportunities for more convenient separation, recovery, and reuse of catalyst systems. The Cu(I)–pybox catalysis originally developed by Li[50] has recently been modified by Afonso; replacing toluene with several room temperature ionic liquids showed that 1-*n*-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide [bmim][NTf_2] produced yields and selectivities that were compared favorably to the original Li method. Furthermore, the recycled catalytic system exhibited only a negligible decrease in stereoselectivity over six cycles.[53]

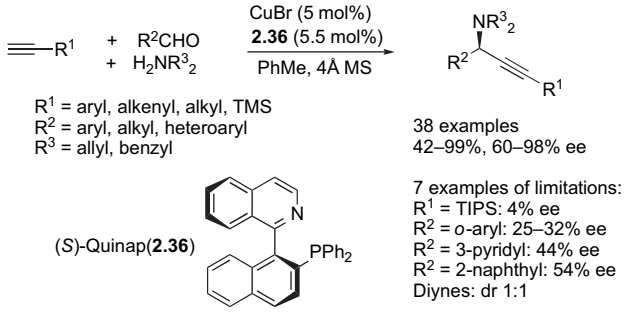
A chiral catalyst composed of CuOTf and (*R*)-binaphthyl diamine afforded variable results in the addition of lithiated phenylacetylene to *N*-phenylbenzaldehyde imine and derivatives.[54] Slightly higher enantioselectivities (up to 81% ee) and a more versatile reaction involve bis-imine ligands

2.35 (Scheme 18).[55] A recent report documents very broad study of substrate and alkyne scope. Although the enantioselectivity was still variable, the addition utilizing pentafluorophenyl-substituted bis-imine as a catalyst resulted in 98% with 81% ee for *N*-phenylbenzaldehyde imine.[56] Functionalized aryl derivatives and a range of acetylides (with aryl, alkyl, ester, and TMS groups) were accommodated, though electron-withdrawing substituents in any of the variables R, X, or Y appeared to be detrimental to yield or selectivity or both.



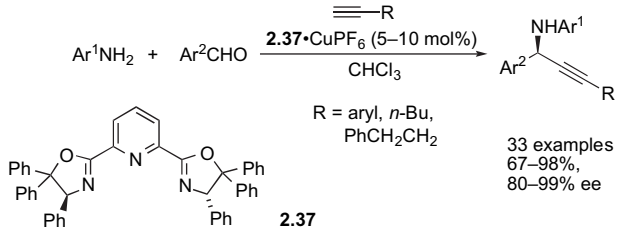
Scheme 18.

Knochel showed that a catalyst composed of CuBr and (*S*)-Quinap (**2.36**) promoted the asymmetric addition of trimethylsilylacetylene to enolizable dibenzyliminium ions with excellent yield and selectivity up to 98% ee (Scheme 19).[57] Replacement of one *N*-benzyl substituent with mesitylmethyl led to further improvement.[58] Knochel's group has also demonstrated access to chiral aminoalkyl-1,2-3-triazoles from the propargylic amine adducts via Cu-catalyzed cycloaddition with azide functionality.[59] Extensive expansion of the scope of this reaction has recently appeared, with application to a total of 45 discrete examples, including disclosure of some limitations of the reaction in a few cases.[60] Several points of additional interest emerged, including the observation of a nonlinear effect (ligand of 5% ee gives 50% ee in the product), and an example of Kagan's 'reservoir effect' based on the correlation of catalyst enantiopurity with observed reaction rates.



Scheme 19.

The modified pybox ligand **2.37** (Scheme 20) was exploited by Singh for an asymmetric three-component coupling of alkynes, benzaldehydes, and anilines with impressive scope.[61] A broad selection of aromatic functionality was tolerated, as were aryl and alkyl substituents on the terminal alkyne component. An interesting model for the activated imine complex was proposed to involve stabilization by the *gem*-diphenyl substituents through edge-to-face and π-stacking interactions with the aromatic ring of the aldehyde component (Ar^2).

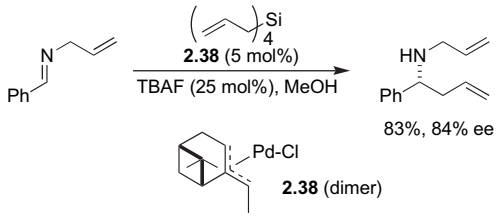


Scheme 20.

2.5. Allylmetal reagents

Addition of allyl groups to imines can achieve asymmetric amine synthesis, leaving a versatile alkene functional group for further synthetic elaboration. General reviews can be consulted for the early developments in the synthesis and chemistry of homoallylic amines.[62] Not surprisingly, extensive effort has been devoted to stereocontrol of this process.[63] Reagent control in a stoichiometric fashion has been effectively achieved, for example, using an allylzinc reagent by Hanessian,[64] chiral allylic silanes introduced by Panek[65] and Leighton,[66] Sato's chiral γ-alkoxyallyltitanium (i.e., homoenolate) reagents,[67] chiral allylstannanes by Marshall[68] and Thomas,[69] and allylboron reagents by Itsuno,[70] Ramachandran,[71] and others.[72] Activation of allyltrichlorosilane with stoichiometric amounts of chiral nucleophiles was recently developed by Kobayashi for additions to C=N acceptors.[73] In contrast to these extensive studies of the stoichiometric reactions, only a few notable successes have been achieved in asymmetric catalysis of allyl addition to C=N bonds.

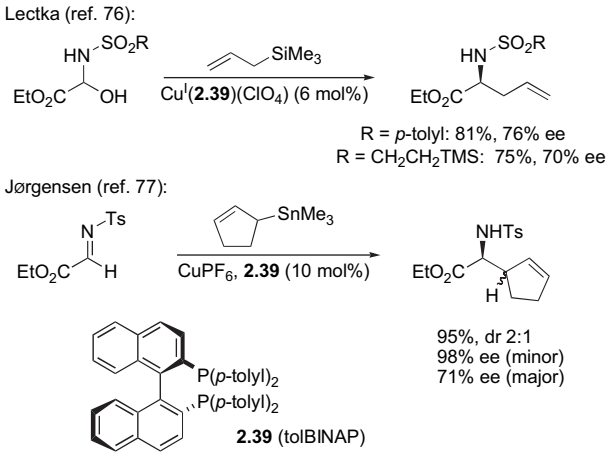
Yamamoto has reported a series of studies exploiting palladium π-allyl complexes **2.38** (Scheme 21) derived from β-(−)-pinene as effective ligands for the catalytic asymmetric allyltributylstannane addition to imines.[74] Less toxic allylsilane reagents could be substituted in the presence of TBAF (up to 94% ee for aromatic aldehyde imines).[75] With an *N*-allyl imine, this allylation reaction (83%, 84% ee) gave multifunctional amine product, which could be functionalized on two separate alkene groups. Notably, alkylimines produced lower selectivity (52% ee) compared to arylimines (up to 94% ee).



Scheme 21.

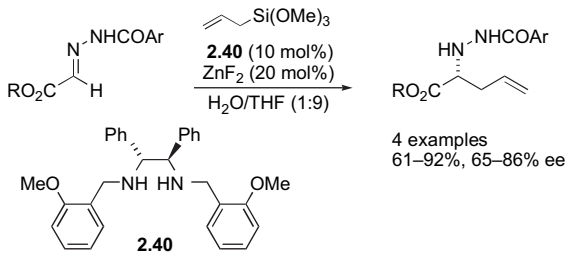
Asymmetric allylsilane and stannane additions to α-imino esters have been developed independently by Lectka[76] and Jørgensen,[77] wherein Cu(I) and tolBINAP (**2.39**) are

exploited for effective enantioselection (Scheme 22). Both exploited glyoxylate *N*-tosylimines, and Lectka has also demonstrated good stereocontrol with the use of a modified *N*-sulfonyl group bearing $CH_2CH_2SiMe_3$ to facilitate orthogonal deprotection.



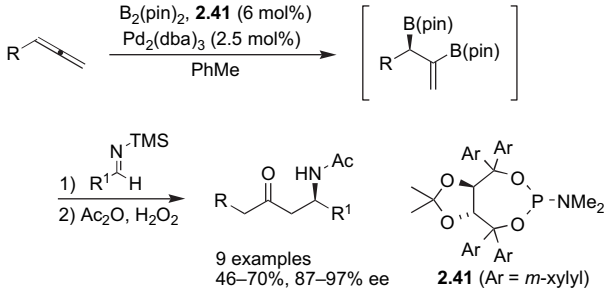
Scheme 22.

A ZnF_2 catalyst system incorporating chiral diamine **2.40** (Scheme 23) has been reported by Kobayashi, with good stereoselectivity (up to 86% ee) for addition to acylhydrazono esters in aqueous THF.[78]



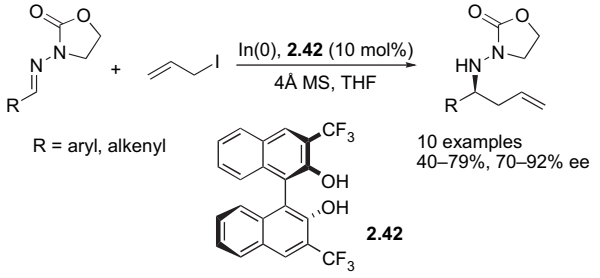
Scheme 23.

A novel indirect asymmetric catalytic process accomplished by Morken involved Pd-catalyzed asymmetric allene diboration with chiral phosphite ligand **2.41** (Scheme 24), followed by use of this in situ-generated chiral borane reagent for enantioselective addition to *N*-silyl- or *N*-H-aldimines.[79] Acetamide formation and oxidative workup afforded β-amidoketones with moderate to high conversions (30–70%) and excellent stereoselectivity (87–97% ee).



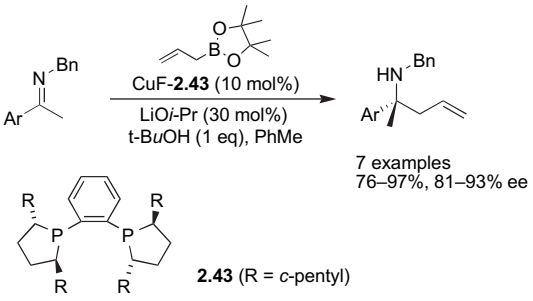
Scheme 24.

Catalytic asymmetric allylindium addition to *N*-acylhydrazones has been accomplished by Cook (Scheme 25).[80] With BINOL-derived ligand **2.42**, high selectivities and good yields were obtained in addition to non-enolizable hydrazones.



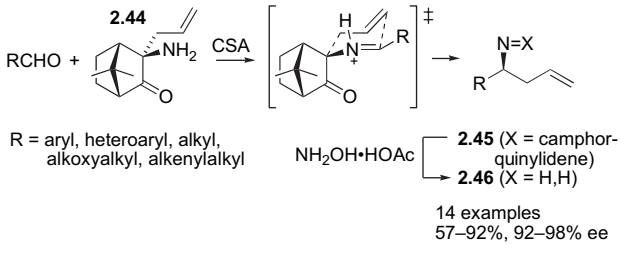
Scheme 25.

The first catalytic asymmetric allylation of ketimines was recently reported by Shibasaki. This reaction utilizes an allylcopper reagent, generated in situ from pinacol allylboronate and CuF, and modified by the chiral ligand DuPHOS (**2.43**, Scheme 26).[81] The key to the catalytic system involves activation of the B to Cu transmetallation by an alkoxide additive, facilitating catalyst turnover. Enantioselectivity was high (up to 93%) with methylarylketimines, but drastically decreased (23% ee) with a dialkylketimine.



Scheme 26.

Other catalytic allyl addition reactions seemingly offer potential for asymmetric modifications, including Tunge's recent report of Pd-catalyzed decarboxylative allyl transfer,[82] Tamaru's Pd-catalyzed additions using allylic alcohols,[83] and Kobayashi's intriguing recent development of asymmetric transfer allylation (Scheme 27).[84] The latter reaction, which occurs with excellent enantioselectivity and functional group tolerance in the absence of main group or transition metals, is worth noting in more detail here. The camphorquinone derivative **2.44** was employed by



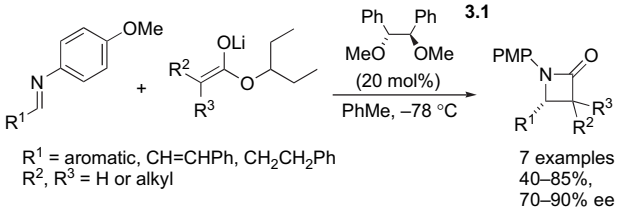
Scheme 27.

Kobayashi as an allyl carbanion equivalent, which transferred its allyl group via aza-Cope rearrangement of an intermediate iminium ion to furnish imine **2.45**. The primary amine **2.46** was easily released upon treatment with hydroxylamine. Although this stereocontrol required a stoichiometric source of asymmetry, the interesting mode of reactivity should surely attract further asymmetric catalysis studies. The fundamentally simple allyl addition reaction continues to bear fruit.

3. Mannich reactions

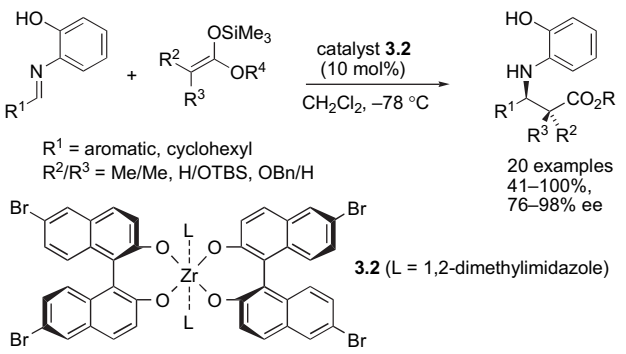
Structures incorporating β-aminocarbonyl compounds, particularly β-lactams and β-amino acids, are prevalent in many natural products of biological importance, and are fundamental building blocks for medicinal chemistry. The Mannich reaction provides a powerful and direct access to these important difunctional compounds. Extensive development of Mannich reactions has been thoroughly discussed in a number of prior reviews.[85]

In the late 1990s, a series of independent studies paved the way for the current developments of catalytic asymmetric Mannich reactions to be discussed in this review, so an overview of these seminal efforts is provided. These key seminal efforts included work with preformed enolates and imines, such as in Tomioka's discovery of activation of Li-enolate addition to imines through the intermediacy of a ternary complex involving catalytic amounts of chiral ether **3.1** (Scheme 28).[86]



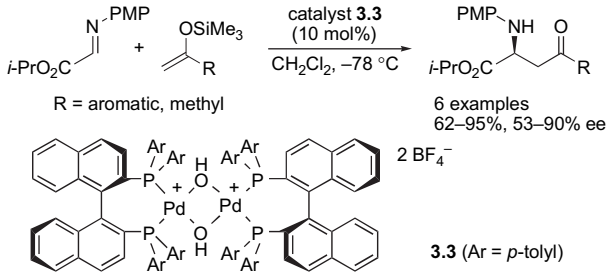
Scheme 28.

Kobayashi reported the first asymmetric Lewis acid-catalyzed Mannich-type reactions, which involved the use of Zr(IV)–BINOL species **3.2** (Scheme 29) to activate the imino acceptor for addition of Si enolates, and a silyl transfer to the nitrogen proposed to facilitate catalyst turnover.[87] The reaction was also adapted to glycolate-derived enolates, leading to *syn*- or *anti*-amino alcohols.[88]



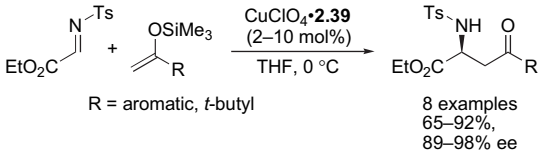
Scheme 29.

Two closely related studies of metal-catalyzed Mannich reactions of glyoxylate imines were reported shortly thereafter. Sodeoka reported catalysis by a novel binuclear Pd(II) complex **3.3** prepared with tolBINAP chiral ligands (Scheme 30),[89] and a Pd-enolate complex was proposed as a key intermediate with stabilization by intramolecular η_2-coordination to the second palladium atom.[90]



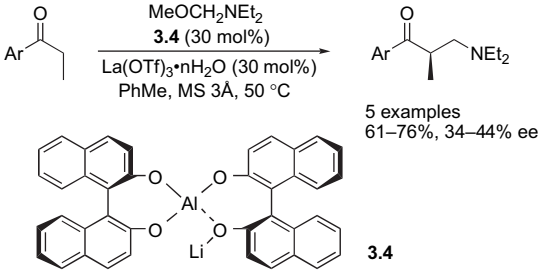
Scheme 30.

Lectka reported concurrent studies of the use of tolBINAP (**2.39**) to modify a series of late transition metal Lewis acids, finding optimal behavior with Cu(I) for catalysis of Mannich additions to ethyl glyoxylate *N*-tosylimine (Scheme 31).[91] Outstanding selectivity was obtained under these conditions.



Scheme 31.

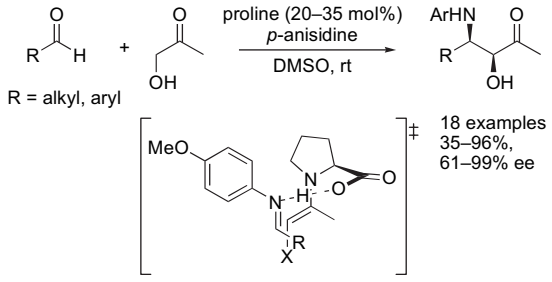
Following this series of seminal reports involving preformed enolates, the first catalytic asymmetric Mannich reaction involving unmodified ketones (i.e., enolization in situ) and aluminate **3.4** was reported by Shibasaki in 1999 (Scheme 32).[92] This anomalous example does not concern asymmetric induction at the C=N bond, but it is cited here because this so-called 'direct' Mannich reaction ushered in a wave of studies of related processes involving in situ enolization and imine formation.



Scheme 32.

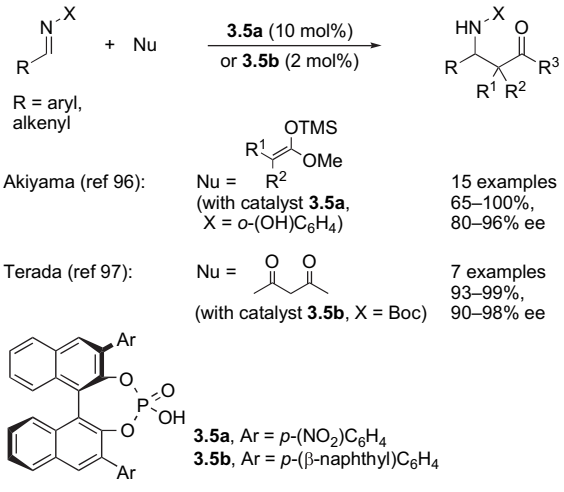
List reported the first organocatalytic direct asymmetric Mannich reactions.[93] Using proline, the reaction produced 1,2-amino alcohols with high diastereo- and enantiomeric purity from a range of aliphatic and aromatic aldehydes (Scheme 33). Acetone, hydroxyacetone, and methoxyacetone served as the nucleophilic component in this provocative

study. A series of related amino acid-catalyzed Mannich reactions followed from Barbas[94] and Cordova.[95] These developments have helped inspire the launch of numerous organocatalytic methodology studies, which continue to draw increasing attention.



Scheme 33.

A newer class of metal-free catalytic process involves the use of chiral Brønsted acids. The pioneering efforts in this area by Akiyama[96] and Terada[97] include Mannich reactions of aldimines catalyzed by BINOL-derived phosphoric acids **3.5a** and **3.5b** (Scheme 34), which were postulated to offer a bifunctional activity involving not only the protonation and H-bonding of the imine but also participation by the Lewis basic oxygen of the P═O bond. Either *O*-silyl ketene acetals or acetylacetone could be used as the nucleophilic component, with the latter involving in situ enolization. The design and application of chiral Brønsted acids is a burgeoning area of new catalyst development,[98] and further examples will appear elsewhere in this review.



Scheme 34.

With this brief overview in place, the sections to follow will focus on the most recent developments, which have appeared since the prior reviews on this topic.

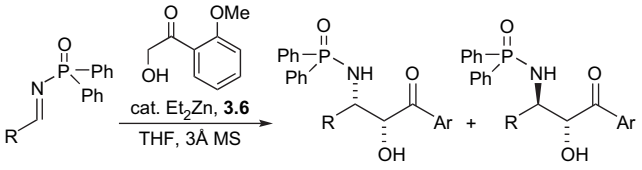
3.1. Additions of metal enolates

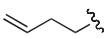
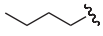
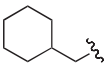
The use of metal enolates is a viable approach to highly enantioselective Mannich reactions. Though less popular for development than the methods involving silyl enol ethers or enamines, there are excellent methods for achieving this transformation. These include direct methods involving generation of the metal enolate in situ, and some new variants, which have been unveiled recently.

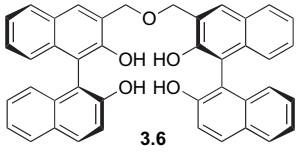
Shibasaki has extensively developed the use of metal enolates in conjunction with BINOL ligands,[99] and has recently examined the use of chiral yttrium- and zinc-BINOL species as catalysts for Mannich reaction between *N*-diphenylphosphinyl imines and α-hydroxyketones. The use of $Y[N(SiMe_3)_2]_3$ with (*S*,*S*)-BINOL formed the β-amino-α-hydroxyketone adducts in a highly *syn*-selective fashion with excellent enantioselectivity.[100] However, enolizable imines proved problematic. On the other hand, the Zn/BINOL system (with an in situ generation of *N*-diphenylphosphinoyl imines from α-amino sulfones) allowed for aliphatic *N*-phosphinoyl imines to be successfully employed (Table 2).[101] Mixtures of *syn* and *anti* adducts were obtained, and both diastereomers exhibited very high enantiomeric purity.

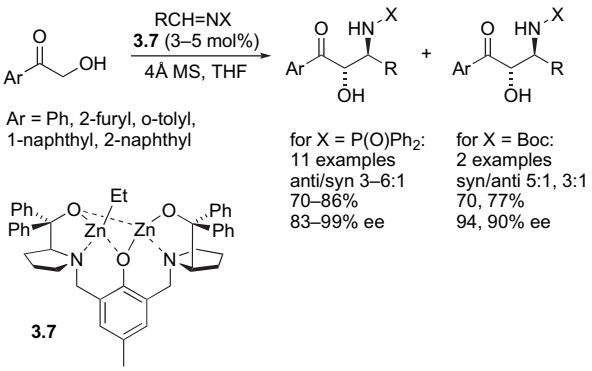
Typical Mannich reactions of α-hydroxyketone nucleophiles furnish *syn* products or diastereomeric mixtures. Trost[102] has exploited dinuclear Zn catalysts **3.7** (Scheme 35) to develop a method for control of both diastereo- and enantioselectivity based on simply switching the *N*-substituent between *N*-phosphinyl and *N*-Boc. The use of the phosphinoyl imine was essential for *anti*-selectivity; the *N*-Boc imine produced *syn* as the major product. For cyclohexanecarboxaldehyde imino acceptors, *anti*:*syn* selectivity with *N*-phosphinoyl was 5:1 (86%, 94% ee), whereas the *N*-Boc reversed the selectivity to afford a 1:5 *anti*:*syn* ratio (77%, 94% ee).

Table 2



R	Yield (%)	dr (*syn*:*anti*)	%ee *syn*/%ee *anti*
	89	76/24	96/97
	85	56/44	95/98
	79	65/35	>99/99
	89	52/48	97/94
	77	55/45	90/99
	88	35/65	96/99

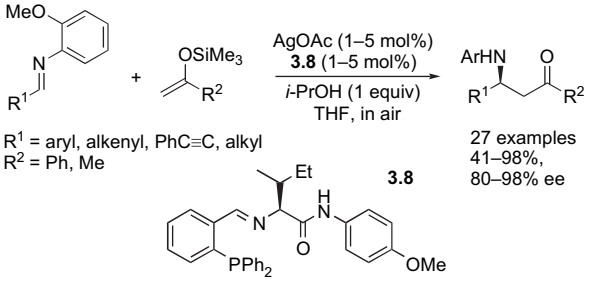




Scheme 35.

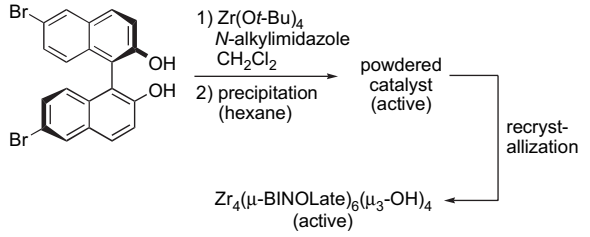
3.2. Lewis acid-catalyzed additions of enol ethers

Since Kobayashi's seminal asymmetric Mukaiyama–Mannich reactions, numerous approaches using silyl enol ethers (or silyl ketene acetals) have been explored.[103] A highlight is the widely applicable Ag-catalyzed process reported by Josephson et al.[104] A catalyst prepared from AgOAc and an isoleucine-derived phosphine ligand **3.8** (Scheme 36) afforded excellent yield and selectivity for *o*-anisidine imines bearing aryl, alkenyl, and phenylethynyl groups at the imino carbon. Though yields were somewhat lower with aliphatic imines (41–60%), selectivities remained high in these cases.



Scheme 36.

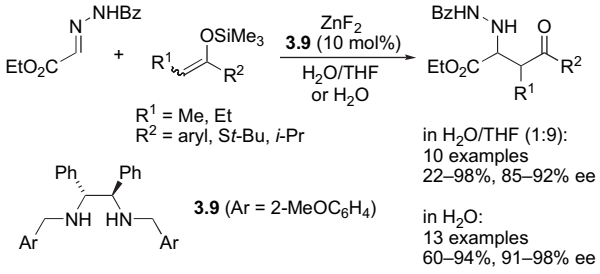
The continued investigations of chiral Lewis acids derived from Zr(IV) and BINOL derivatives have now led to the Kobayashi's very practical development of an air-stable, storable powdered form of the catalyst, prepared from a BINOL derivative and Zr-alkoxide in the presence of *N*-methyl- or *N*-benzylimidazole (Scheme 37).[105] This catalyst was active in Mannich reactions of silyl enol ethers with *N*-(2-hydroxyphenyl)imines (e.g., Scheme 29); excellent enantioselectivities (81–95%) were obtained in several examples at 10 mol % loading. The catalyst can be recovered and reused for three consecutive cycles, and can be stored



Scheme 37.

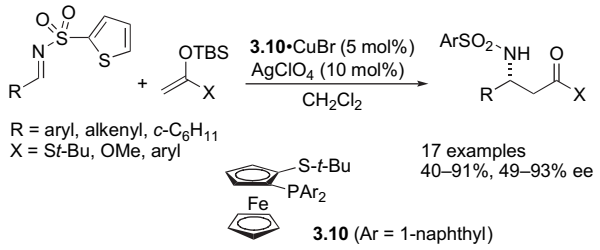
for at least six months in powdered form, each without detriment to yield or selectivity.

Mukaiyama–Mannich reactions can be carried out in aqueous media using a catalytic chiral diamine–ZnF_2 combination and hydrolysis-resistant hydrazones as imino acceptors (Scheme 38), as has been shown by Kobayashi;[106] more complete details of these studies have now been disclosed.[107] The proposed catalytic cycle, supported by a number of elegant control experiments, invokes transfer of fluoride from Me_3SiF to a ZnF(OH) intermediate to regenerate the active ZnF_2 species, which is presumed to activate both components simultaneously (dual activation).[108] The result is a highly diastereo- and enantioselective addition of a variety of silyl enol ethers, silyl ketene acetals, and silyl ketene thioacetals to glyoxylate-derived *N*-benzoylhydrazones. Stereospecificity was observed with respect to the *E*/*Z* geometry of the enol ether.



Scheme 38.

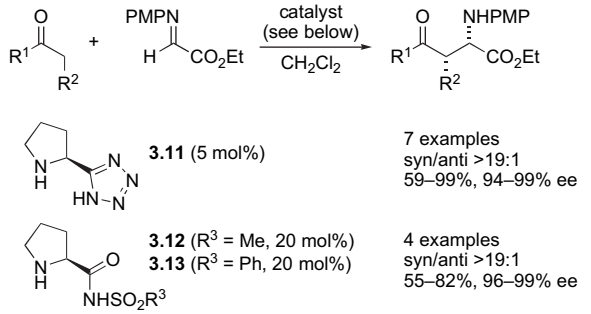
Chiral ferrocene-derived ligands were used to modify Cu(I) catalysts for addition of silyl enol ethers to *N*-(thienyl)sulfonyl aldimines by Carretero.[109] The copper(I)/Fesulphos Lewis acid **3.10** (Scheme 39) was successful with several substituted imines, including aryl, alkenyl, and one example of an alkyl group (cyclohexyl). High enantioselectivities were observed in most cases (>71% ee) though the presence of furyl groups led to diminished stereocontrol. Cleavage of the sulfonyl group was accomplished readily by Mg/MeOH.



Scheme 39.

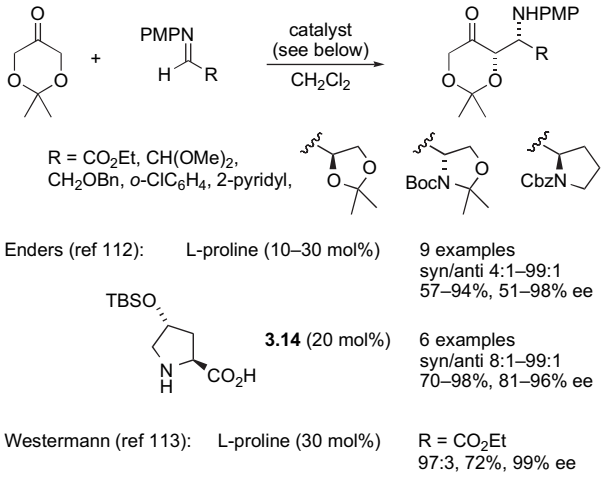
3.3. Organocatalytic Mannich reactions

Catalysts derived from L-proline have been synthesized and screened in organocatalytic Mannich reactions by Ley.[110] Catalysts **3.11**, **3.12**, and **3.13** (Scheme 40) are prepared from *N*-Cbz-proline in three or four steps, and these were applied to *syn*-selective additions of carbonyl compounds to glyoxylate *N*-(*p*-methoxyphenyl)imine with excellent enantioselectivities (94–99% ee), with the exception of fluoroacetone (14% ee).



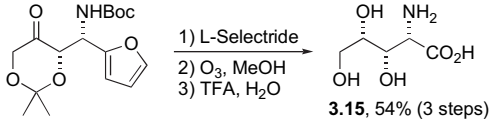
Scheme 40.

Direct organocatalytic aldol additions of hydroxycarbonyl compounds is well suited for application to de novo carbohydrate synthesis,[111] and the related Mannich additions have recently been developed for access to unusual aminosugars. Enders has found that proline and hydroxyproline **3.14** (Scheme 41) can be effective catalysts for the asymmetric Mannich addition of dihydroxyacetone acetonide to a broad range of aldimines formed in situ from difunctional aldehydes.[112] Westermann published a closely related series of reactions of dihydroxyacetone acetonide with glyoxylate *N*-(*p*-methoxyphenyl)imine catalyzed by L-proline; two related catalysts were less effective.[113]



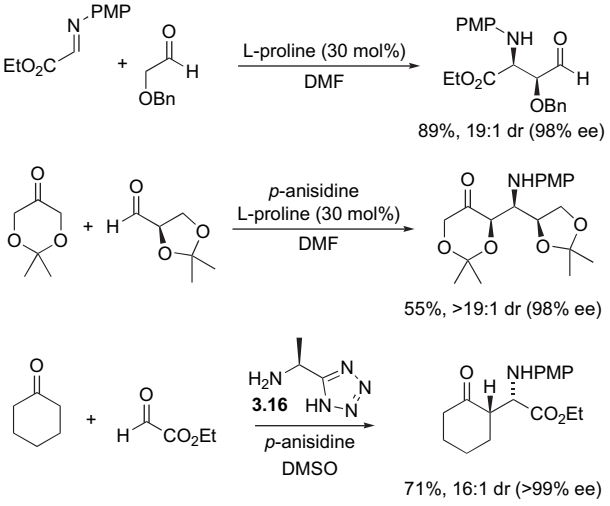
Scheme 41.

This aminosugar synthesis was effectively applied to total synthesis of polyoxamic acid (**3.15**, Scheme 42), using a furyl group as a latent carboxylate functionality. In this instance, a *N*-Boc-imine was used as the imino acceptor in the L-proline-catalyzed addition of dihydroxyacetone acetonide.[114]



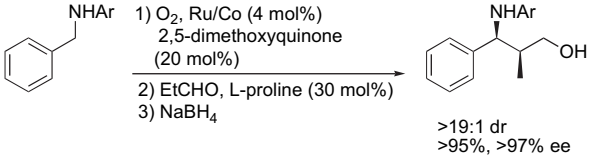
Scheme 42.

Similar approaches to carbohydrate building blocks have been reported by Córdova et al. (Scheme 43), using L-proline to catalyze cross-Mannich reactions in DMF,[115] including preparation of ketoses by proline-catalyzed reaction of dihydroxyacetone acetonide.[116] Additional amino acids and acyclic chiral amines were tested, and alanine-derived tetrazole **3.16** emerged as an efficient catalyst to provide *syn* adducts.[117]



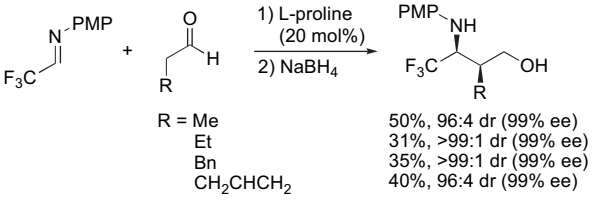
Scheme 43.

A biomimetic aerobic oxidation was reported by Backvall and Córdova to operate in tandem with the previously described proline-catalyzed Mannich reactions.[118] The Ru/Co catalyst system allowed for the aerobic oxidation of arylmethyl and (alkoxycarbonyl)methyl amines forming *N*-PMP-imines (Scheme 44). Proline-catalyzed Mannich reactions then ensued in the usual way.



Scheme 44.

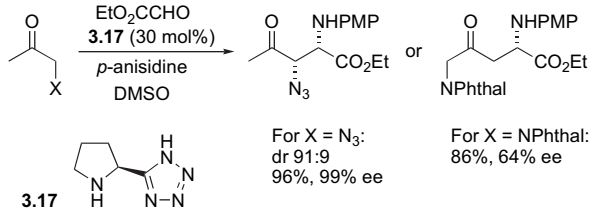
Another use of proline-catalyzed Mannich reactions is the formation of fluorinated β-amino alcohols.[119] Trifluoroacetaldehyde *N*-PMP-imine (Scheme 45) was coupled with several aldehydes in moderate yields (31–41%) and with high stereocontrol (up to >99:1 dr, and 99% ee). Interestingly, other proline derivatives failed to produce Mannich products in this fashion.



Scheme 45.

Barbas reported a regioselective synthesis of 1,2- or 1,4-diamines through a Mannich reaction pathway.[120] Protected

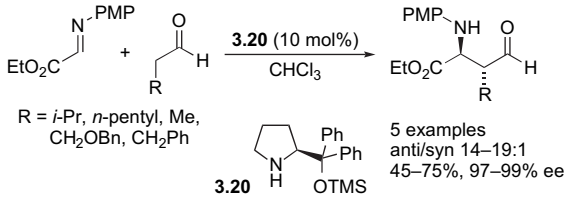
α-phthalimido ketones furnished 1,4-diamines through selective enamine formation via catalysis with L-proline-derived tetrazole **3.17** (Scheme 46). In contrast, α-azido ketones produced the complementary regioisomer.



Scheme 46.

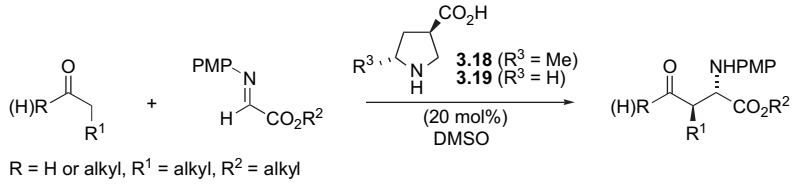
In contrast to L-proline, which provided *syn* adducts, the closely related catalyst (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (**3.18**, Scheme 47) was reported by Barbas to produce the *anti*-Mannich product selectively.[121] With the carboxylic acid in the pyrrolidine 3-position and the methyl steric directing group at the 5-position, control of the enamine C–N rotamer in the transition state was proposed to have a dihedral angle 180° from that the corresponding transition state with proline, thus reversing the stereocontrol. Use of several alkyl aldehydes with *N*-PMP-protected α-imino esters produced diastereomeric ratio of 94:6 and higher. An analogous reaction with ketones was much slower, and this was corrected by simply dispensing with the extra methyl substituent to arrive at catalyst **3.19**.[122] Only the C–N rotamer shown was hypothesized to be capable of the required hydrogen bond with the 3-carboxylate. Consistent with this scenario, ketones gave enhanced reactivity using **3.19**, while maintaining excellent *anti*-selectivity and control of absolute configuration.

Another *anti*-selective Mannich reaction was achieved by Córdova with the use of pyrrolidine catalyst **3.20** (Scheme 48), which lacks the H-bond donor functionality of proline.[123] Several substituted aldehydes were tested with *N*-PMP-protected α-imino esters producing high diastereoselectivities (14:1 to >19:1) with moderate yields and outstanding enantiocontrol.

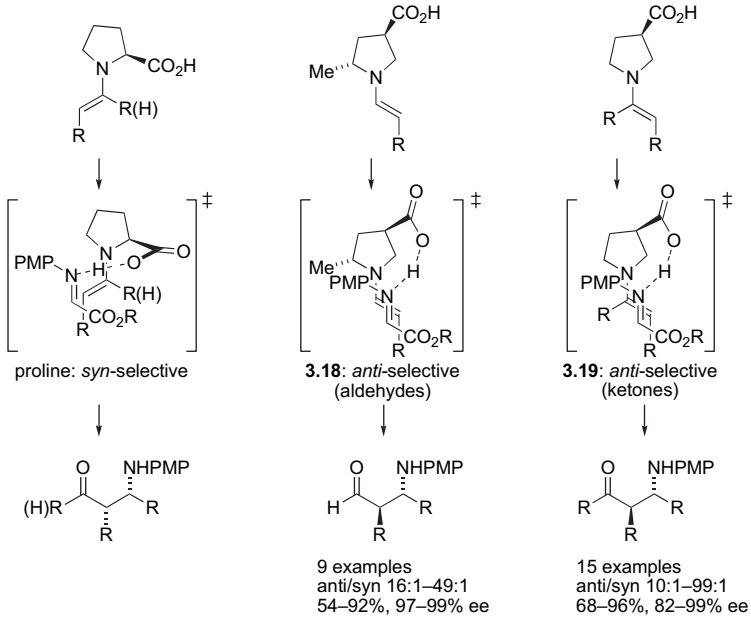


Scheme 48.

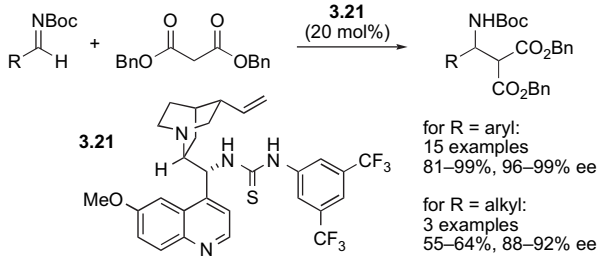
Cinchona alkaloids and their thiourea conjugates have been introduced as organocatalysts for the Mannich reaction.[124] Deng found that the quinidine-derived bifunctional H-bonding catalyst **3.21** (Scheme 49) delivered malonates to *N*-Boc protected aromatic imines with outstanding stereocontrol.[124c] Aliphatic imines gave lower yields, yet enantioselectivity remained quite high. Decarboxylation produced *N*-Boc protected β-amino acids.



Alternative transition states for syn- or anti-selective amine-catalyzed Mannich reactions:

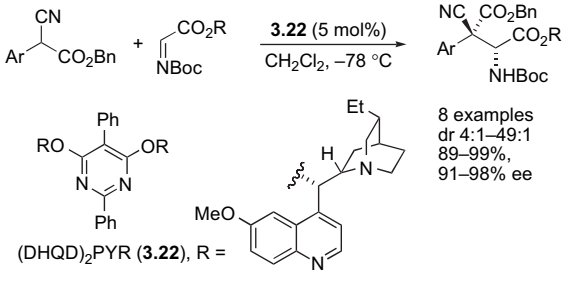


Scheme 47.



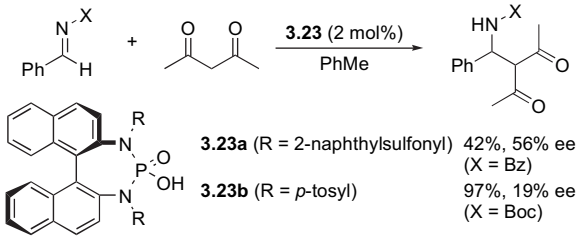
Scheme 49.

Another use of β-dicarbonyl derivatives resulted in highly enantio- and diastereoselective Mannich reactions of α-substituted α-cyanoacetates, in which Sharpless AD ligand $(DHQD)_2PYR$ (**3.22**, Scheme 50) was employed as a base catalyst.[125] Diastereomer ratios were modest (ca. 5:1), but excellent enantioselectivity was observed for a series of aromatic precursors in addition to glyoxylate *N*-(Boc)imine.



Scheme 50.

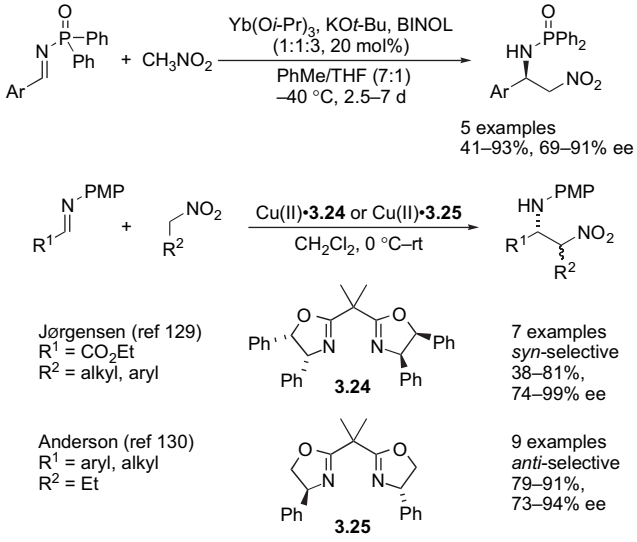
Terada has expanded the Brønsted acid catalyzed direct asymmetric Mannich reaction to a wider range of β-dicarbonyl compounds.[126] These reactions accommodated β-diketones, β-ketoesters, a β-ketoamide, and dimethyl malonate in a racemic version. Chiral phosphorodiamidic acid catalysts **3.23** (Scheme 51) derived from binaphthyl diamine led to addition of acetylacetone with modest enantioselectivity.



Scheme 51.

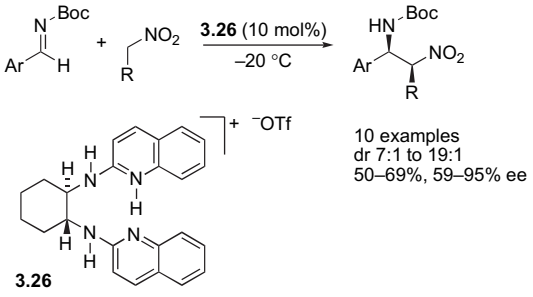
3.4. Aza-Henry reactions

Nitroalkyl anions can serve as the nucleophilic component in addition to imino compounds, and these nitro-Mannich (or aza-Henry) reactions afford adducts with orthogonal nitrogen functionality on neighboring carbons for some interesting synthetic utility.[127] Asymmetric modifications of this reaction were initiated by Shibasaki[128] and Jørgensen,[129] and their ground-breaking discoveries (Scheme 52) have enticed a surge in activity in this area. Anderson has extended the versatility of the Jørgensen method, finding conditions, which were suitable for aromatic and aliphatic aldimines with 10 mol % catalyst loading, and using only 1.5 equiv of nitropropane, as a preformed silyl nitronate.[130]



Scheme 52.

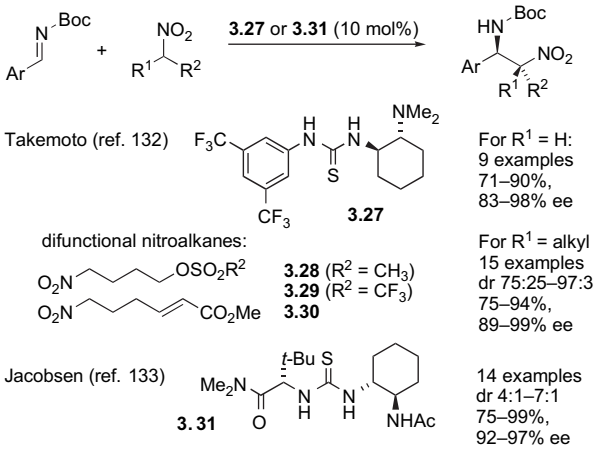
Johnston reported additions of nitromethane and nitroethane to *N*-Boc protected imines in the presence of chiral pyridinium salt **3.26** (Scheme 53) in an early example of asymmetric catalysis with chiral Brønsted acids.[131] Diastereoselective for the *syn* product, this reaction was successful for nitromethane and nitroethane in addition to aromatic aldimines in moderate yields.



Scheme 53.

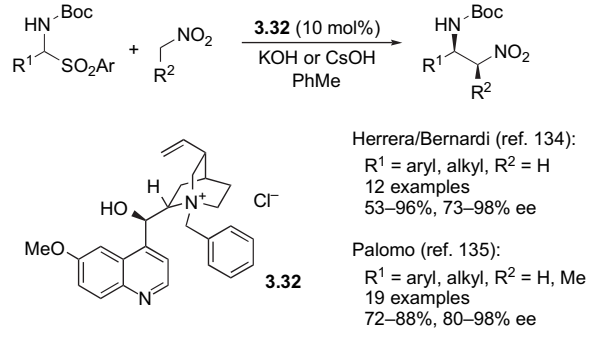
In some very impressive expansion of asymmetric aza-Henry reactions, Takemoto has introduced a bifunctional-thiourea catalyst **3.27** (Scheme 54), which incorporates both a thiourea H-bond donor and a basic nitrogen.[132] This construct was hypothesized to not only activate the acceptor for addition, but act as the base to produce the nitroalkyl nucleophile. The reactions were tested with a wide range of acceptors, with *N*-(Boc)imines showing optimal yields and selectivities, and the optimized conditions were applied in additions of nitromethane to a series of aromatic aldimines. The mild conditions enabled the reaction to tolerate additional electrophilic sites in the nitroalkane precursor, including, remarkably, mesylate, triflate, and acrylate functionality (**3.28**–**3.30**). Jacobsen and Yoon reported application of thiourea catalyst **3.31** to aza-Henry reactions of four different

nitroalkyl components and several aromatic *N*-(Boc)aldimines.[133]



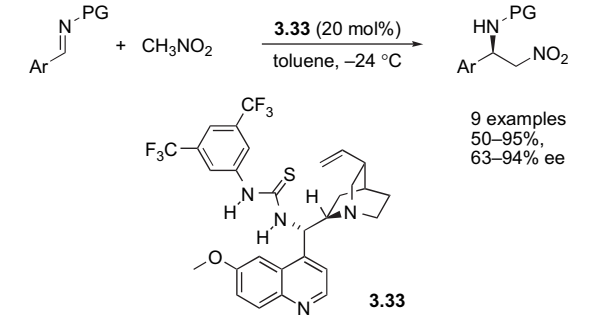
Scheme 54.

A number of reports outline the utility of phase transfer catalysis for aza-Henry reactions. A catalyst incorporating a quininium salt was examined by Herrera and Bernardi for addition to in situ-generated *N*-Boc or *N*-Cbz protected imines (Scheme 55).[134] Phase transfer of the nitronate–quininium ion pair from the KOH solid phase to toluene was critical for the asymmetric induction. Concurrently, the same approach was reported by Palomo,[135] in this case with the use of CsOH as a base; nitroethane was also found to be a suitable nucleophilic component.



Scheme 55.

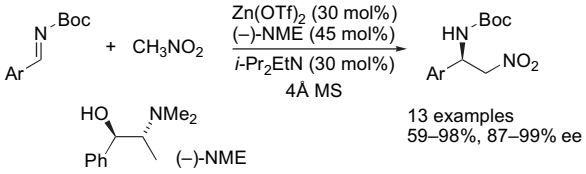
Ricci reported a survey of a range of modified cinchona alkaloids as organocatalysts for the aza-Henry reaction, culminating in an optimal structure **3.33** (Scheme 56) bearing



Scheme 56.

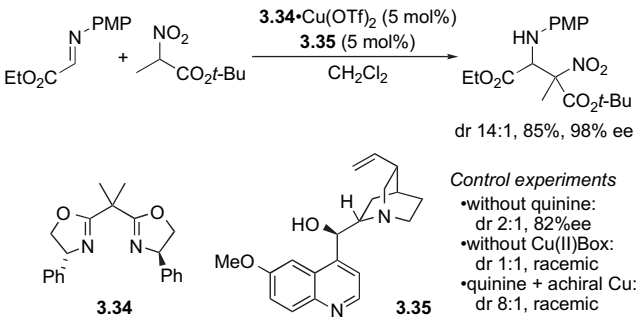
thiourea functionality, which produced a highly effective catalyst.[136]

A zinc-catalyzed aza-Henry reaction of nitromethane was reported by Palomo.[137] This system utilizes 0.5 equiv of (−)-*N*-methylephedrine (NME) and nitromethane as solvent, producing high yields and selectivities of a variety of *N*-Boc aryl aldimines (Scheme 57).



Scheme 57.

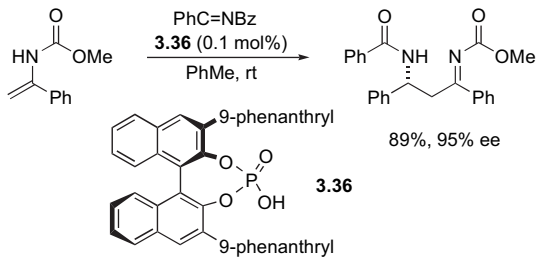
An interesting cooperative effect of quinine and chiral Lewis acid catalysts was discovered by Jørgensen. In the reaction of *tert*-butyl 2-nitropropionate with glyoxylate *N*-(PMP)-imine, the diastereoselectivity was poor despite useful enantioselection with Cu(II) and bisoxazoline ligand **3.34** (Scheme 58). Screening cinchona alkaloids as additives revealed that quinine could control the diastereoselectivity in this reaction, but only in the presence of Cu(II) cocatalysts.[138]



Scheme 58.

3.5. Other Mannich-like reactions

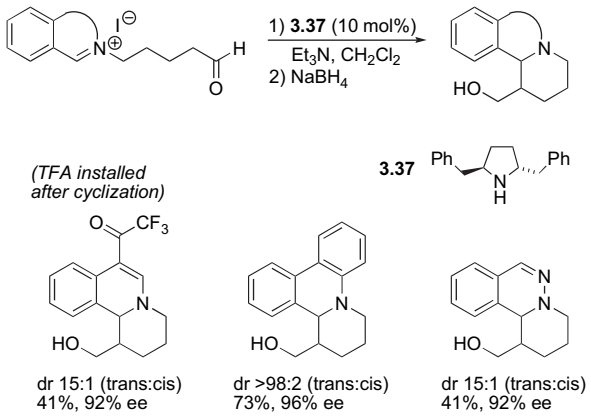
A Mannich-like aza-ene-type reaction was reported by Terada,[139] involving enamide addition to an *N*-acylimine acceptor using a chiral Brønsted acid **3.36** (Scheme 59). This chiral acid was presumed to hydrogen bond with the imine acceptor (by donating the activating proton), and to the hydrogen of the enamide nucleophile. Yield and selectivity with a methyl carbamate enamide was high using just



Scheme 59.

2 mol % of the chiral Brønsted acid, and remained high even to a mere 0.05 mol % catalyst loading (85%, 93% ee).

Jørgensen recently published an interesting variation on the amine-catalyzed asymmetric Mannich reaction in a stereoselective annulation (Scheme 60).[140] Intramolecular addition of an aldehyde functionality to various aromatic iminium ions resulted in two new stereogenic centers with stereocontrol derived from the C_2-symmetric (2*S*,5*S*)-2,5-dibenzylpyrrolidine catalyst **3.37**.

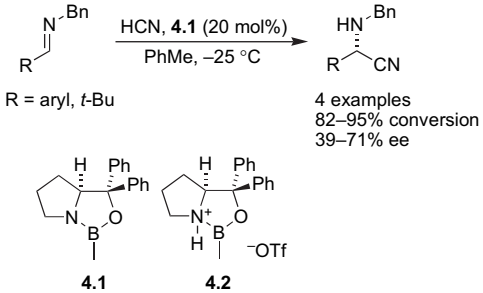


Scheme 60.

4. Strecker reactions

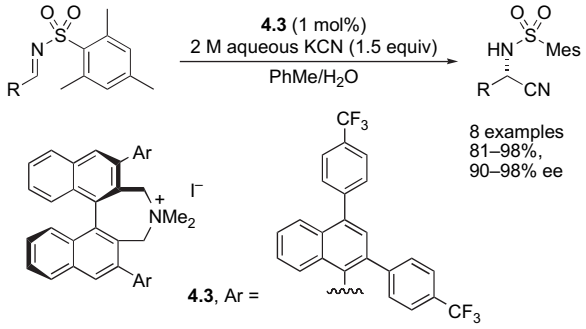
The α-amino nitrile products of cyanide addition to C=N bonds (Strecker reactions) offer a broad range of synthetic applications through hydrolysis, reduction or alkylation reactions of the nitrile functionality.[141] Intense investigation of the asymmetric Strecker-type reaction has continued over many years due to the importance of α-amino acid building blocks in medicinal chemistry.[142] These studies have led to efficient enantioselective metal Lewis acid-catalyzed processes[143] as well as a number of successful asymmetric organocatalytic approaches.[144] These asymmetric catalytic reactions have developed to the point of ready application in natural product synthesis.[145]

Recently, Berkessel utilized a chiral oxazaborolidine catalyst **4.1** (Scheme 61) for asymmetric induction, with moderate enantioselectivity.[146] Interestingly, the protonated catalyst (**4.2**) inverted the stereocontrol, although with much lower enantioselectivity.



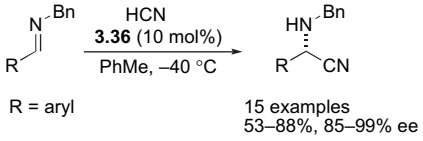
Scheme 61.

Maruoka reported phase transfer catalysis of the Strecker reaction with **4.3** (Scheme 62) using linked biaryls to further extend the effects of axial chirality in the core binaphthyl-based quaternary ammonium salt.[147]



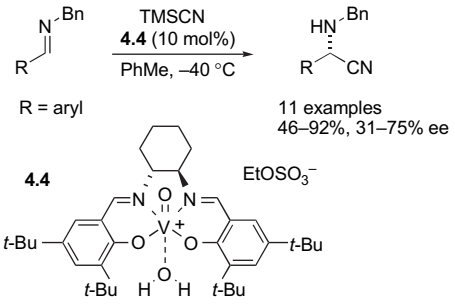
Scheme 62.

The successful application of chiral phosphate-derived Brønsted acids to catalysis of the Strecker reaction of *N*-benzylimines was reported by Rueping.[148] Using phenanthryl-substituted binaphthyl framework of **3.36** yielded the highest selectivities for addition of HCN (Scheme 63), and this catalyst was subsequently applied for additions to a range of aromatic and heteroaromatic *N*-benzylimines with excellent enantioselectivities.



Scheme 63.

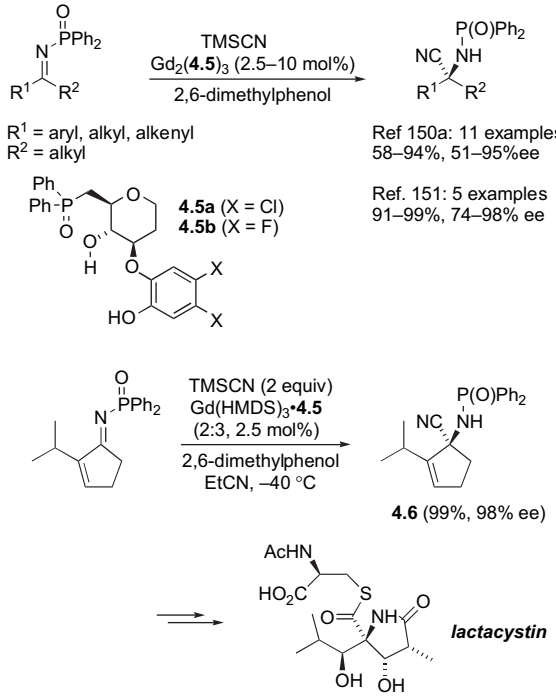
Building from earlier findings of Jacobsen,[143a,143b] vanadium- and titanium-catalyzed Strecker reactions with asymmetric induction through a salen complexes of the type **4.4** have been reported by North and Crampton (Scheme 64).[149] Beneficial presence of moisture suggested the addition was of HCN, generated in situ from TMSCN. With pivalaldehyde-derived imine (R=*t*-Bu), the reaction was efficient but with only 16% ee, and the imine from acetophenone showed some potential for application to ketimines.



Scheme 64.

Very intriguing complexes of glucose-derived ligand **4.5** (Scheme 65) with La(III) and Gd(III) have been examined by Shibasaki with the aid of crystallography and ESI-MS,

which have suggested that the catalytic activity of previous studies[150] may be dramatically altered by the different assembly modes of the complexes from the same building blocks.[151] Crystalline Gd_2L_3 gave reversed enantioselection compared to the catalyst prepared in solution in the same ratio. Although the latter could not be crystallized, based on crystallography of a related complex of La(III), the authors proposed an alternative assembly to explain the reversed enantioselection. The highly enantioselective catalytic system, active for additions to ketimines, has been exploited in a synthesis of lactacystin.[152] The nitrile functionality of ketimine Strecker adduct **4.6** was ultimately converted to the thioester of lactacystin.



Scheme 65.

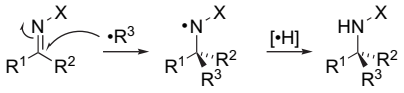
Through calculations, hexavalent Si was found to be a relevant intermediate for the TMSCN additions to imines catalyzed by chiral *N*-oxide Lewis bases.[153] The transition states proposed involve a five-membered ring, with or without prior isomerization of the Si–cyanide linkage to its isocyanide congener.

Thioureas have received significant attention as potential H-bond donors for asymmetric catalysis over the last few years.[154] Several examples of such catalysts are highlighted elsewhere in this review. Already, Jacobsen has beautifully applied the thiourea catalysis concept to the Strecker reaction in one of the finest of the asymmetric catalytic Strecker methods.[144c] Another bifunctional thiourea catalyst for the asymmetric Strecker reaction was recently explored by Tsogoeva,[155] showing beneficial effects on catalytic activity of an imidazolyl group attached to the thiourea nitrogen. New thiourea catalysts have served central roles in the development of related cyanide additions to carbonyl compounds,[156] and these catalysts may offer lessons to inspire new applications of thioureas to Strecker and related reactions.

Another new application of molecular recognition in catalysis of the Strecker reaction utilizes β-cyclodextrin to enable a Strecker reaction in water.[157] Though this is not yet an asymmetric process, it offers an intriguing new perspective to consider in future catalyst design.

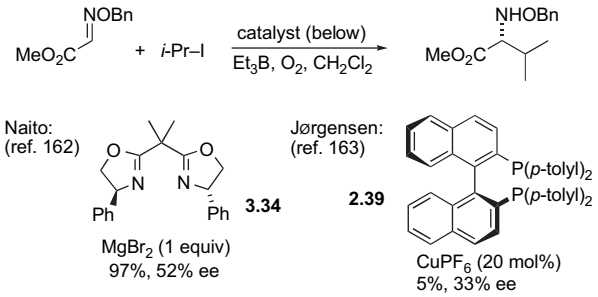
5. Radical additions

Radical reactions (Scheme 66) complement the nucleophilic reactions discussed above. Although nucleophilic additions are often limited to aromatic (or other non-enolizable) aldimines, radical additions avoid problematic aza-enolizations due to their nonpolar nature. The complementary reactivity is such that radical additions to imino compounds can be accommodated in highly functionalized structures, even those bearing protic or electrophilic functionality.[158] Despite these features, asymmetric catalysis of radical addition has seen much less development, and the vast majority of that work has been with alkenes as radical acceptors.[159] However, imino compounds are also effective radical acceptors,[160] and this offers the opportunity for new reaction development.



Scheme 66.

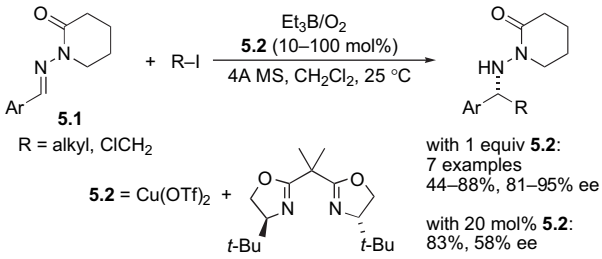
Naito reported the first asymmetric radical additions to C=N bonds using chiral auxiliary stereocontrol, mostly with simple alkyl radicals (Scheme 67).[161] These reactions, using glyoxylate imine acceptors, proved to be amenable to stereocontrol with Lewis acids bearing chiral bisoxazoline ligand **3.34**, with enantioselectivity up to 52% ee at stoichiometric loading.[162] Jørgensen published an alternative approach, using a catalytic system of Cu(I) and tolBINAP (**2.39**) for stereocontrol.[163] Unfortunately this process was of very low yield and enantioselectivity.



Scheme 67.

In 2003, we published the first (and only example to date) of catalyst turnover in an asymmetric radical addition to imino acceptors.[164] The reactions exploited Cu(I)-catalyzed addition to valerolactam-derived *N*-acylhydrazones **5.1** (Scheme 68). Aromatic aldimines were found to be suitable acceptors for several alkyl radicals, with high enantioselectivity, using the catalyst **5.2** prepared from $Cu(OTf)_2$ and *tert*-butylbisoxazoline. This enantioselectivity was diminished at lower catalyst loading, suggesting that further work to enhance catalyst turnover will be required. Recently, Tomioka has

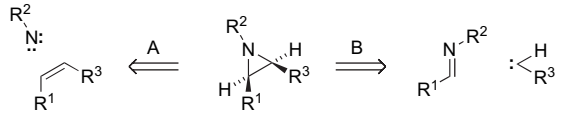
discovered related conditions, which offer improved reactivity with 10 mol % loading of Cu(I) catalysts, although the stereocontrol has not yet been discussed.[165]



Scheme 68.

6. Imine aziridination

Considerable effort has been devoted to asymmetric synthesis of aziridines due to their importance as strain-activated electrophilic precursors of chiral amines.[166] Two types of two-bond disconnections are possible (Scheme 69); transform A suggests alkene and nitrene as reactants, while transform B suggests imine and carbene precursors. For the purposes of this review, the recent developments in the context of transform B will be considered, though asymmetric variants of both approaches are available.[167]

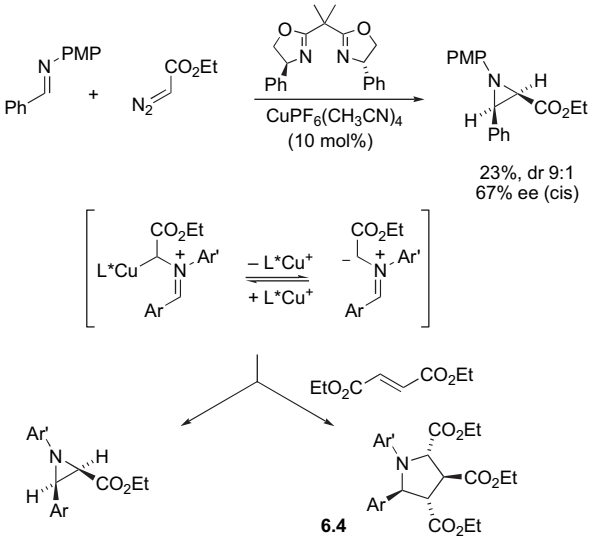


Scheme 69.

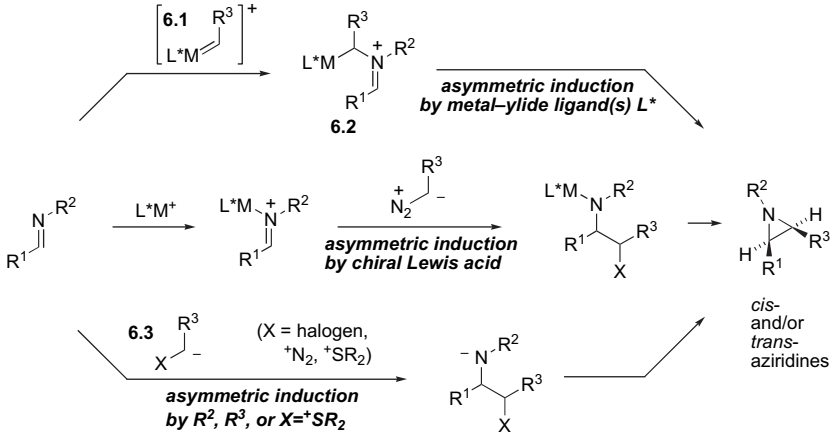
Early asymmetric C–C bond construction methods date back to the 1970s, when Johnson employed a metalated chiral sulfoximine as an alkylidene transfer agent.[168] Baret reported aziridination of imines with ethyl diazoacetate in 1972.[169] Fruitful efforts to design asymmetric imine aziridination processes can be summarized by three main mechanistic types, with a diversity of modes of asymmetric induction (Scheme 70). First, a metal carbenoid species **6.1** may react at the nitrogen of the imine, generating a metal-associated azomethine ylide **6.2**. Chiral ligands (L*) on the metal then exert stereocontrol in an enantioselective ring closure. Second, the imine may be activated as an electrophile through entry to the coordination sphere of a chiral Lewis acid. Addition of diazo compounds may then occur selectively on one face of the imine. Finally, the asymmetric induction may emerge from various substituents on either a chiral imine or a chiral nucleophile **6.3** (bromoenolate, diazo compound, or sulfur ylide). Aside from control of the absolute configuration, the diastereoselectivity may vary among these processes, favoring either *cis*-aziridine or *trans*-aziridine.

6.1. Catalysis via chiral metal carbenoids

The first asymmetric catalysis of carbenoid transfer to imines was reported by Jacobsen in 1995 using ethyl diazoacetate in the presence of 10 mol % of a Cu(I)bisoxazoline catalyst (Scheme 71), though the yields and enantioselectivities (22–67% ee) were modest.[170] The presence of dimethyl fumarate led to pyrrolidine **6.4**, allowing a mechanism to be proposed in which the C–N bond forms first; the intermediate



Scheme 71.



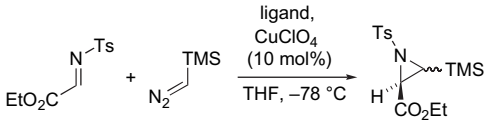
Scheme 70. Diverse sources of asymmetric induction in imine aziridination.

azomethine ylide could cyclize to the aziridine or dissociate from the metal and be trapped by the dienophile.

There has been only meager progress in asymmetric catalytic variants of this reaction. A related metal-carbenoid process involving a Ru(II)-porphyrin catalyst has been reported, and a mechanistic proposal similar to Jacobsen's has been advanced for those reactions, but they are yet to be rendered enantioselective.[171] Similarly, Bergman and Tilley found that monomeric chiral Rh(II) catalysts bearing homologated chiral phebox ligands were capable of catalyzing asymmetric cyclopropanation of alkenes with ethyl diazoacetate, but enantioselectivities for the corresponding additions to imines were poor (<11%).[172]

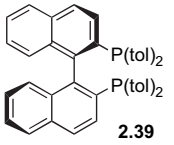
6.2. Chiral Lewis acid-catalyzed additions of diazo compounds

Jørgensen examined Cu(I)-catalyzed reactions of trimethylsilyldiazomethane with imines, leading to silyl-substituted aziridines (Scheme 72). A variety of chiral ligands, including tolBINAP (**2.39**) and bisoxazoline **3.34** were screened for asymmetric induction; enantioselectivities were promising for this process, up to 72% using a Cu(I)·**2.39** catalyst (10 mol %).[173] Either *cis* or *trans*-aziridine could be obtained with high ee by varying the conditions, though trans-selective reactions gave low enantioselectivity for the *trans*-aziridine. The failure to observe pyrrolidines characterizes these reactions as mechanistically distinct from Jacobsen's azomethine ylide mechanism, and led to the proposed mechanism involving initial C–C bond construction by nucleophilic attack of the diazo compound on a Lewis acid-activated imine. The reactivity of the silyl aziridines has been further explored.[174]

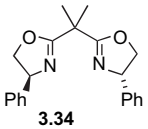


ligand	solvent	*cis*:*trans*	% ee
2.39	THF	19:1	72 (cis)
3.34	toluene	1:3	66 (cis)*
2.39	THF	2:1	63 (trans)

* The major *trans*-aziridine was racemic.



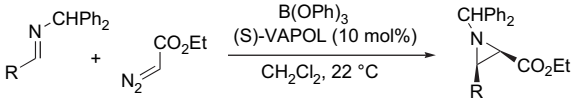
2.39



3.34

Scheme 72.

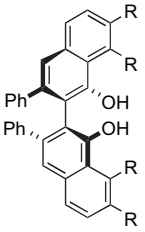
Wulff reported perhaps the most successful asymmetric catalytic aziridination method thus far, finding that chiral boron catalysts derived from vaulted biaryl ligands (*S*)-VAPOL and (*S*)-VANOL (Scheme 73) can achieve outstanding enantioselectivities in the Lewis acid-mediated aziridinations of numerous imines with ethyl diazoacetate.[175] Both aromatic and aliphatic imines can be accommodated, with very high cis-selectivity, yields in the 50–80% range and uniformly outstanding 91–99% ee. Since the seminal report in 1999, the methodology has been improved upon recognition that the $BH_3 \cdot THF$ can be replaced with borate esters to result in a much more reliable catalyst preparation. The improved method using triphenylborate shows broader applicability, including high-yielding aziridination of some imines, which were previously unreactive.[176]



cis/*trans*
38:1 → >50:1

R	% yield	% ee
Ph	77	95
p-BrC_6H_4	91	98
o-MeC_6H_4	69	94
3,4-$(OAc)_2C_6H_3$	85	96
2-furyl	55	93*
1-naphthyl	87	92
n-propyl	54	91
t-butyl	78	91
c-C_6H_{11}	74	94

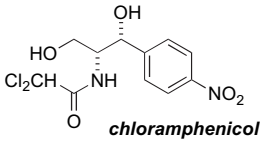
* (S)-VANOL was used.



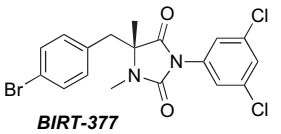
(S)-VANOL (R = H)
(S)-VAPOL (R,R = benzo-fused)

Scheme 73.

Synthetic utility has been showcased for Wulff's VAPOL-borate catalysis method in routes to access to a biologically active targets bearing chiral amine functionality. A synthesis of (−)-chloramphenicol served as a platform for further comparisons of a number of chiral ligands based on the BINOL and VAPOL motifs in the Wulff aziridination.[177] The catalysts derived from VAPOL or VANOL gave superior enantiocontrol than those from 6,6′-diphenylVAPOL, BINOL, or BANOL. Recently, the asymmetric aziridination was used in sequence with diastereoselective alkylations of the aziridine-2-carboxylate adducts with numerous electrophiles including alkyl halides, aldehydes, Bu_3SnCl, and MOMCl.[178] Together with reductive aziridine ring opening, the sequence affords efficient access to *tert*-alkylamine stereocenters as shown in the enantioselective synthesis of LFA-1 antagonist BIRT-377.



chloramphenicol

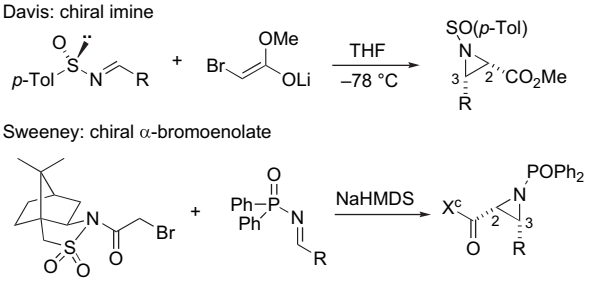


BIRT-377

A variety of other transition metals have been tested as Lewis acid catalysts for aziridination of *N*-benzylideneaniline with varying degrees of success. Iron catalysts using chiral pybox ligands, generated in situ by reaction of $FeCl_2$(pybox) with Ag(I) salts, have offered moderate asymmetric induction (up to 49% ee at 5% catalyst load).[179] Chiral cationic molybdenum complexes catalyzed aziridination, but did not afford any observable enantioselection.[180] Efficient catalysis of a three-component coupling of an aldehyde, amine, and diazoester has been demonstrated with 5 mol % $[IrCl(cod)]_2$ leading to excellent yields of aziridine, but tests of asymmetric induction have not been reported for this reaction.[181]

6.3. Asymmetric aza-Darzens and related reactions

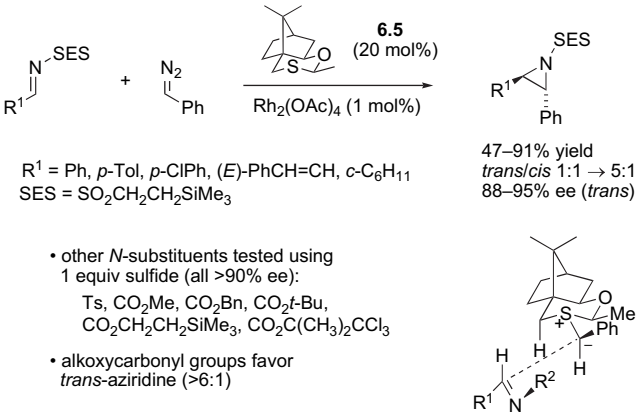
The aza-Darzens reaction involves generation of carbanion reactivity at a site bearing a leaving group, circumstances generally achieved through enolization of α-halocarbonyl compounds. Prior to the first reports of enantioselective carbenoid additions, effective asymmetric syntheses of a wide range of substituted aziridine-2-carboxylates were developed by Davis using aza-Darzens additions to chiral *N*-sulfinimines,[182] and by Sweeney using chiral camphorsultam α-bromoenolates (Scheme 74).[183] A related vinylogous aza-Darzens reaction of a chiral phosphonamide anion has been applied by Hanessian, affording access to enantiopure vinyl-substituted *N*-alkoxyaziridines.[184] Numerous applications of this very versatile aziridine synthesis include syntheses of α-amino acids, α- and β-substituted α-amino acids, thiamphenicol, β-hydroxyamino acids, sphingosines, and 2H-azirine carboxylates.[185] The extension to *tert*-alkylamines through subsequent alkylations and aziridine ring opening is noteworthy.[186] Related chemistry of α-chlorophosphonates, which give lower *syn*/*anti* selectivities in the addition, has been exploited to access α-aminophosphonates, 2H-azirine phosphonates, and piperidine phosphonates.[187] Though not catalytic in the source of asymmetry, these remain among the most practical methods for access to enantiopure aziridines.



Scheme 74.

Sulfide-mediated reactions have mechanistic similarities to aza-Darzens reactions, in that the carbanionic character of a sulfur ylide is accompanied by a sulfide leaving group at the same carbon. Should the sulfide be recycled to form another ylide, one could accomplish a catalytic process. In the mid-1990s, Aggarwal reported the first of a series of papers, which unveiled a novel catalytic aziridination reaction using a chiral sulfide as a substoichiometric source of asymmetry.[188] This reaction involves the carbenoid relay from phenyldiazomethane to $Rh_2(OAc)_4$, then to chiral sulfide **6.5** (Scheme 75); this latter step results in a sulfur ylide, which finally transfers the carbenoid to sulfonylimines with moderate trans/cis diastereoselectivity (3:1) and good yield. With **6.5** at 20 mol % loading, enantioselectivities were worthy of note, ranging from 85% to 90% ee for three imines derived from substituted benzaldehydes, although the yield was moderate (44–62%).

Subsequently, the scope and stereocontrol of this reaction was discussed in detail.[189] Interesting crossover experiments led to the conclusion that the reactions with phenyldiazomethane involved stereocontrol in an irreversible addition to the imine, while the additions of acyl-stabilized ylides were



Scheme 75.

reversible and the diastereoselectivity was controlled during ring closure of the zwitterionic adduct.[190] Deprotonated tosylhydrazones may be used to generate the diazo compounds in situ for this transformation, avoiding the need for handling potentially hazardous precursors.[191]

Dai reported related reactions in 1996,[192] and extended this to an asymmetric version shortly thereafter.[193] Here the camphor-derived chiral sulfides **6.6** were used in stoichiometric amounts, but provided very high yields and exclusively the *cis*-aziridines, with enantiomeric excesses ranging from 41% to 85%. Mechanistic evidence suggested an initial reversible addition of the sulfur ylide, followed by ring closure. In light of this, the diastereoselectivity was suggested to be subject to selection of the reactive partners; more reactive imine/ylide combinations favored *cis*-aziridines, while less reactive pairs were trans-selective.[194] Recently, calculations have supported this general scenario, in which reactions of semistabilized ylides were controlled during an irreversible addition, whereas the reversibility of additions of stabilized ylides makes the ring closure the stereocontrolling step in these cases.[195]

Further studies of the sulfur ylide-mediated aziridination have examined the use of chiral sulfides **6.7**[196] and **6.8** (Fig. 2)[197] in stoichiometric reactions, leading to very high enantioselectivities. Related chalcogenides such as selenonium[198] and telluronium[199] salts also show some promise in these reactions. In the latter case, chiral *N*-sulfinimines have been exploited in a chiral auxiliary approach with excellent diastereoselectivity.[200]

Two new modes of catalysis have recently been reported, offering potential for development of asymmetric variants. Johnston has developed Brønsted acid catalysis of aza-Darzens reactions using diazoesters.[201] The avoidance of side reactions expected to result upon protonation of the diazoester are key to the success of this reaction. Ma has reported an interesting nucleophilic catalysis procedure for addition of cyclopropene to *N*-tosylimines results in vinylaziridines using NaI as the catalyst.[202] Though not yet rendered enantioselective, these interesting approaches promise to offer some fertile ground for new metal-free catalytic reaction development.

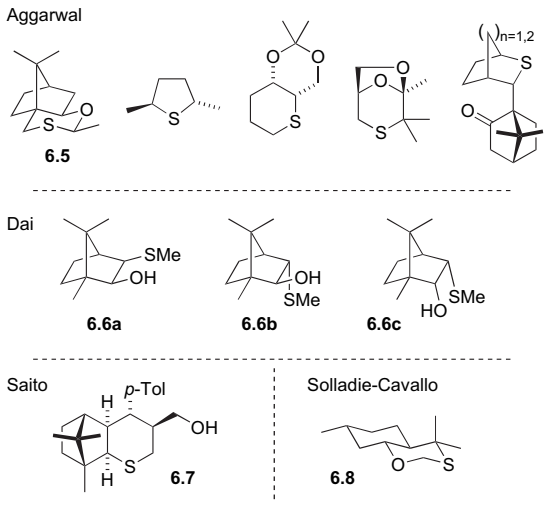
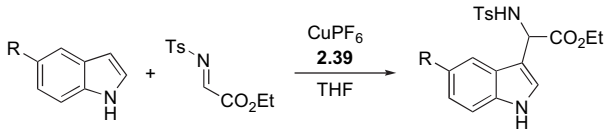


Figure 2. Sulfide catalysts for asymmetric imine aziridination.

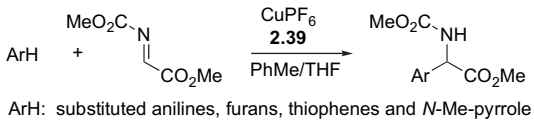
7. Friedel–Crafts additions to imines

Recently, Friedel–Crafts reactions of electron-rich aromatics have been extended to include imino compounds as electrophiles.[203] The first example of catalytic enantioselective Friedel–Crafts reactions using chiral Cu(I)-tolBINAP (**2.39**) catalysts was reported in 1999 by Johannsen, where a *N*-(tosyl)iminoester served as the electrophile for electrophilic aromatic substitution at C3 of several substituted indoles (Scheme 76).[204]



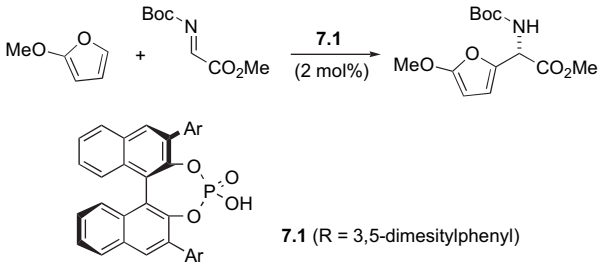
Scheme 76.

Shortly thereafter, Jørgensen reported a similar strategy employing a broad range of aromatic and heteroaromatic compounds including furans, thiophenes, and pyrroles in coupling with *N*-methoxycarbonyl imino esters (Scheme 77).[205] The *N*-Boc analogs gave inferior selectivity. With support from crystallography and calculations, a stereocontrol model was proposed with two-point binding of the imino ester independent of the methoxycarbonyl group. In the calculated structure of the Cu-complexed Boc analog, a gearing effect with the larger Boc group placed one tolyl group of the chiral ligand (tolBINAP, **2.39**) into the preferred approach trajectory, offering an explanation for the diminished enantioselection.



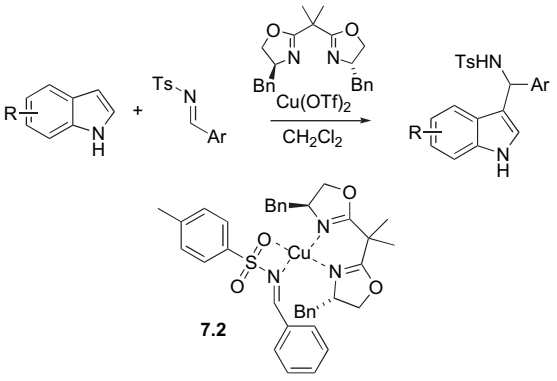
Scheme 77.

In 2004, Terada et al. recorded an example of organocatalytic asymmetric aza-Friedel–Crafts alkylation of 2-methoxyfuran using Brønsted acid **7.1** (Scheme 78) as the catalyst.[206] The reaction was extended to 13 examples, all aromatic aldimines, with excellent efficiency (80–96% yield, 86–97% ee).



Scheme 78.

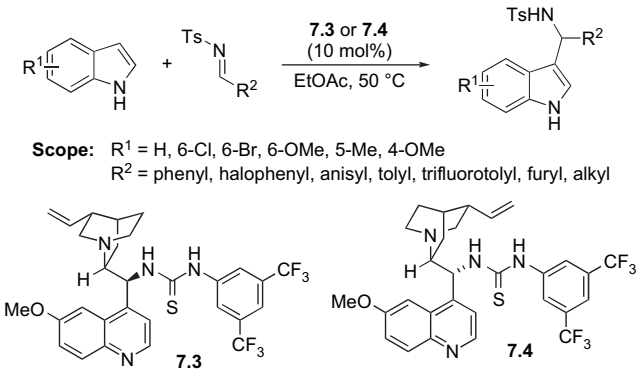
In 2006, a number of noteworthy findings have been reported with relevance to development of catalytic Friedel–Crafts reactions of imino electrophiles. A highly efficient gold/silver-catalyzed addition of arenes to imines in racemic fashion has been reported; these conditions enable the use of less activated aromatic systems but have not yet been rendered enantioselective.[207] In additions of indoles, catalysis by Cu(II) in conjunction with *N*-(2-pyridyl)sulfonyl aldimines demonstrates controlled synthesis of either unsymmetrical diaryl- or triaryl methanes.[208] Related copper(II)-catalyzed aza-Friedel–Crafts reaction of indoles to aromatic *N*-sulfonyl aldimines afforded a simple approach to 3-indolylmethanamine derivatives with high enantioselectivity across 17 examples (47–91% yield, 81–96% ee).[209] Catalysis via a four-membered Cu(II)-chelate **7.2** (Scheme 79) was proposed to account for the observation that *N*-phenylimines gave poor stereocontrol.



Scheme 79.

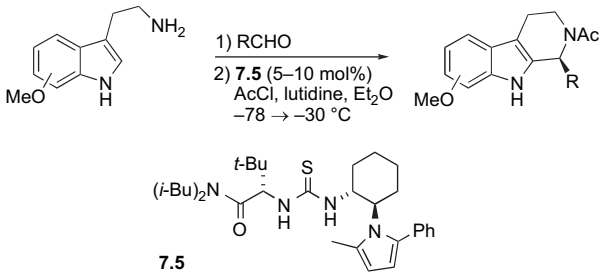
Cinchona alkaloids continue their legacy of important contributions to asymmetric catalysis with Deng's discovery of their utility in asymmetric Friedel–Crafts reactions of indoles.[210] Catalysts **7.3** and **7.4** (Scheme 80) combining quinine or quinidine with a thiourea hydrogen bonding motif has led to remarkable versatility in additions of a range of indoles—bearing substituents with either donor or acceptor properties—to *N*-sulfonyl imines. The imino electrophile also supported variations in electronic properties, and a survey of aliphatic aldimines showed good reactivity, though yields were slightly diminished.

Pictet–Spengler reactions are the intramolecular cousins of aza-Friedel–Crafts addition to imines, and first succumbed



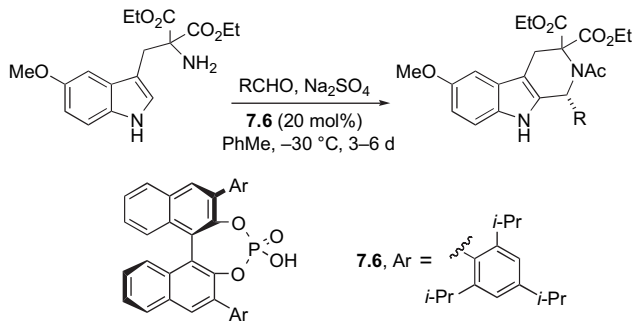
Scheme 80.

to catalytic asymmetric induction as reported in 2004 by Jacobsen and Taylor using *N*-acyliminium intermediates and a thiourea catalyst **7.5** (Scheme 81).[211] An unusual aspect of this work is the asymmetric activation of weakly Lewis basic *N*-acyliminium ions, a rare discovery with potentially broad utility.[212] The catalyst was acylated at higher temperatures needed for cyclization of aromatic aldimines, so the enantioselectivity in the sequence was limited to the use of aliphatic aldehyde precursors (65–81% yield, 95–95% ee).



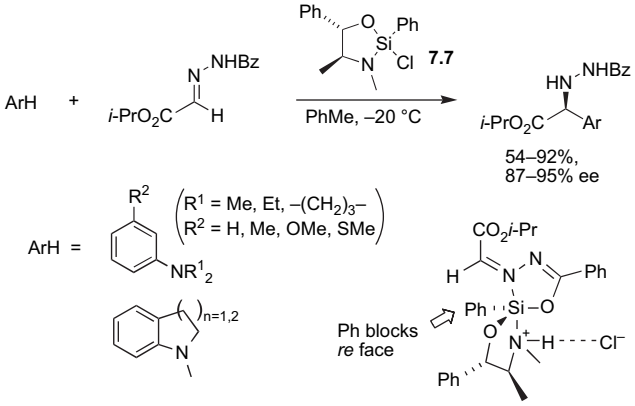
Scheme 81.

More recently, List reported the application of Brønsted acid catalysis with chiral phosphoric acid **7.6** (Scheme 82) in asymmetric Pictet–Spengler reactions of tryptamines, with scope including different substitution patterns in the tryptamine precursor as well as aliphatic and aromatic aldehydes.[213] There were 18 examples, with yields in the range of 40–98% (62–96% ee). This reaction requires a gem-diester (i.e., α-carbalkoxytryptamines), but the diester can be reduced to the monoester in group-selective fashion with high diastereoselectivity for subsequent synthetic application.



Scheme 82.

Enantioselective Friedel–Crafts alkylations with benzoylhydrazones activated by stoichiometric amounts of strained chiral silacycle **7.7** proved to be effective with a variety of anilines (Scheme 83), nitroindole, *N*-benzylpyrrole, and 2-methoxythiophene.[214] Proton transfer from the benzoylhydrazone to the enantiopure silacycle and bidentate interaction with pentavalent (Lewis acidic) silicon activates the imine for approach to the front (*si*) face.



Scheme 83.

8. Concluding remarks

From the early efforts with asymmetric addition of organolithium and enolate species, to the more recent organocatalytic and Brønsted acid-catalyzed additions to imino compounds, an ever-widening range of strategies has been applied to asymmetric catalysis in synthesis of chiral amines. The frontiers in these areas continue to be pushed back, though challenges remain in developing C–C bond construction methods which can accommodate a broad spectrum of functionality within each of the coupling components. Reactions discussed herein offer exciting prospects for future development, and it is hoped that this review will inspire creative new contributions.

Acknowledgements

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References and notes

1. Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628.
2. Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131–184.
3. Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205–1227.
4. Reviews of chiral auxiliary control in addition to C=N: (a) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157–3172; (b) Zhou, P.; Chen, B.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003–8030; (c) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253–2329; (d) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (e) Alvaro, G.; Savoia, D. *Synlett* **2002**,

651–673; (f) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438; (g) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13–18; (h) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946.
5. Reviews of reagent and catalyst control in asymmetric addition to C=N: Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392; Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999–1004.
6. Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684.
7. Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095–3098.
8. Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429–4438; Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527–2533; Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603–1606.
9. Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097–1098.
10. Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797–8798.
11. For leading references, see: Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **1998**, *120*, 5810–5811; Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. O.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201–7210; Keresztes, I.; Williard, P. G. *J. Am. Chem. Soc.* **2000**, *122*, 10228–10229; Goldfuss, B.; Steigelmann, M.; Loeschmann, T.; Schilling, G.; Rominger, F. *Chem.—Eur. J.* **2005**, *11*, 4019–4023.
12. Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2005**, *127*, 10820–10821.
13. Qu, B.; Collum, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 9355–9360.
14. Rutherford, J. L.; Hoffmann, D.; Collum, D. B. *J. Am. Chem. Soc.* **2002**, *124*, 264–271.
15. For example, see: (a) Jimeno, C.; Reddy, K. S.; Sola, L.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157–3159; (b) Hermanns, H.; Dahmen, S.; Bolm, C.; Brase, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692–3694; (c) Dahmen, S.; Brase, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941; (d) Zhang, H.-L.; Zhang, X.-M.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399–1402; (e) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322–4329.
16. Beresford, K. J. M. *Tetrahedron Lett.* **2004**, *45*, 6041–6044.
17. Zhang, H.-L.; Jiang, F.; Zhang, X.-M.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Chem.—Eur. J.* **2004**, *10*, 1481–1492.
18. Zhang, H.-L.; Liu, H.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Synlett* **2005**, 615–618.
19. Liu, H.; Zhang, H.-L.; Wang, S.-J.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2005**, *16*, 2901–2907.
20. Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055–12056.
21. Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723–9727.
22. Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692–1693; Boezio, A. A.; Pytkowitz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260–14261.
23. Li, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3819–3821.
24. Wang, M.-C.; Xu, C.-L.; Zou, Y.-X.; Liu, H.-M.; Wang, D.-K. *Tetrahedron Lett.* **2005**, *46*, 5413–5416.
25. Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Chem. Lett.* **2002**, 8–9.
26. Wang, M.-C.; Liu, L.-T.; Hua, Y.-Z.; Zhang, J.-S.; Shi, Y.-Y.; Wang, D.-K. *Tetrahedron: Asymmetry* **2005**, *16*, 2531–2534.
27. Côté, A.; Boezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405–5410.
28. Desrosiers, J.-N.; Côté, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186–6192.
29. Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864–10867.
30. Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743–2745.
31. (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984–985; (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409–10410.
32. Akullian, L.; Porter, J.; Traverse, J.; Snapper, M.; Hoveyda, A. *Adv. Synth. Catal.* **2005**, *347*, 417–425.
33. Basra, S.; Fennie, M.; Kozlowski, M. *Org. Lett.* **2006**, *8*, 2659–2662.
34. Sugimoto, H.; Nakamura, S.; Hattori, M.; Ozeki, S.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2005**, *46*, 8941–8944.
35. Kizirian, J.-C.; Cabello, N.; Pinchard, L.; Caille, J.-C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939–8946.
36. Gille, S.; Cabello, N.; Kizirian, J.; Alexakis, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1045–1047.
37. Cabello, N.; Kizirian, J.; Gille, S.; Alexakis, A.; Bernardinelli, G.; Pinchard, L.; Caille, J. *Eur. J. Org. Chem.* **2005**, 4835–4842.
38. Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976–977; Hayashi, T.; Ishigedani, M. *Tetrahedron* **2001**, *57*, 2589–2595.
39. Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584–13585.
40. Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125–6128.
41. Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3941–3944.
42. Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979–981.
43. Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128–8129.
44. Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789–2791.
45. Duan, H.; Jia, Y.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 2567–2569.
46. Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092–1093.
47. Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245–11246.
48. Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
49. Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319–4321.
50. Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638–5639.
51. Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997–4999.
52. Yao, X.; Li, C.-J. *Org. Lett.* **2005**, *7*, 4395–4398.
53. Rosa, J. N.; Santos, A. G.; Afonso, C. A. M. *J. Mol. Catal. A* **2004**, *214*, 161–165.
54. Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689–1692.

55. Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron* **2004**, *45*, 8705–8708.
56. Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064–2070.
57. Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763–5766; Gommermann, N.; Knochel, P. *Tetrahedron* **2005**, *61*, 11418–11426.
58. Gommerman, N.; Knochel, P. *Synlett* **2005**, 2799–2801.
59. Gommermann, N.; Gehrig, A.; Knochel, P. *Synlett* **2005**, 2796–2798.
60. Gommermann, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380–4392.
61. Bisai, A.; Singh, V. *Org. Lett.* **2006**, *8*, 2405–2408.
62. Reviews: (a) Kleinman, E. F.; Volkmann, R. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, NY, 1991; Vol. 2, pp 975–1006; (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (c) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595–614; (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739.
63. Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815–2829.
64. Hanessian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 8997–9000.
65. Schaus, J. V.; Jain, N.; Panek, J. S. *Tetrahedron* **2000**, *56*, 10263–10274; Lipomi, D. J.; Panek, J. S. *Org. Lett.* **2005**, *7*, 4701–4704.
66. (a) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921; (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948; (c) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596–9597; (d) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686–5687.
67. Teng, X.; Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 11916–11917.
68. Marshall, J. A.; Gill, K.; Seletsky, B. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 953–956.
69. Thomas, E. J. *Chem. Commun.* **1997**, 411–418.
70. Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1531–1534; Itsuno, S.; Watanabe, K.; Matsumoto, T.; Kuroda, S.; Yokoi, A.; El-Shehawy, A. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2011–2016; Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed.* **1997**, *36*, 109–110; Itsuno, S.; Watanabe, K.; El-Shehawy, A. A. *Adv. Synth. Catal.* **2001**, *343*, 89–94; Watanabe, K.; Kuroda, S.; Yokoi, A.; Ito, K.; Itsuno, S. *J. Organomet. Chem.* **1999**, *581*, 103–107.
71. Chen, G.-M.; Ramachandran, P. V.; Brown, H. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 825–826; Ramachandran, P. V.; Burghardt, T. E. *Chem.—Eur. J.* **2005**, *11*, 4387–4395; Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397–1406.
72. Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183; Wu, T. R.; Chong, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 9646–9647.
73. Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610–6611; Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491–6493; Kobayashi, S.; Sugiura, M.; Ogawa, C. *Adv. Synth. Catal.* **2004**, *346*, 1023–1034; Also see: Fernandez, I.; Valdivia, V.; Gori, B.; Alcudia, F.; Alvarez, E.; Khiar, N. *Org. Lett.* **2005**, *7*, 1307–1310.
74. Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242–4243; Bao, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 131–134; Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133–14139.
75. (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614–2615; (b) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735–738.
76. Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67–77.
77. Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844–4849.
78. Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927–3930.
79. Sieber, J.; Morken, J. *J. Am. Chem. Soc.* **2006**, *128*, 74–75.
80. Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767–2770.
81. Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691.
82. Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002–10003.
83. Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640.
84. Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039.
85. Reviews: Arend, M.; Westerman, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070; Denmark, S.; Nicaise, O. J.-C. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 93; Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299; Ueno, M.; Kobayashi, S. *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds.; Wiley: New York, NY, 2005; pp 139–157; Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352.
86. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061.
87. Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153–7154.
88. Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431–432.
89. Hagiwara, H.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474–2475.
90. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458.
91. Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548–4549.
92. Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *41*, 307–310.
93. List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336–9337; List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827–833.
94. Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 199–201.
95. Review: Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112.
96. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566–1568.
97. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.
98. Review of Brønsted acid catalysis: Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999–1010.

99. Shibasaki, M.; Matsunaga, S. *J. Organomet. Chem.* **2006**, *691*, 2089–2100.
100. Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339–5342.
101. Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *47*, 3985–3989.
102. Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778–2779.
103. Xue, S.; Yu, S.; Deng, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 2271–2274; Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.
104. Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 3734–3735.
105. Saruhashi, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11232–11235.
106. Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640–5641; Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7768–7769.
107. Hamada, T.; Manabe, K.; Kobayashi, S. *Chem.—Eur. J.* **2006**, *12*, 1205–1215.
108. For a review of dual activation, see: Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583.
109. González, A. S.; Arrayás, R. G.; Carretero, J. C. *Org. Lett.* **2006**, *8*, 2977–2980.
110. Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–97.
111. For examples, see: Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210–1212; Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III. *Org. Lett.* **2005**, *7*, 1383–1385; Ibrahem, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3363–3367.
112. Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079–4083.
113. Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077–4079.
114. Enders, D.; Vrettou, M. *Synthesis* **2006**, 2155–2158.
115. Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 2839–2843.
116. Ibrahem, I.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3363–3367.
117. Ibrahem, I.; Zou, W.; Engqvist, M.; Xu, Y.; Córdova, A. *Chem.—Eur. J.* **2005**, *11*, 7024–7029.
118. Ibrahem, I.; Samec, J. S. M.; Bäckvall, J. E.; Córdova, A. *Tetrahedron Lett.* **2005**, *46*, 3965–3968.
119. Fustero, S.; Jiménez, D.; Sanz-Cervera, J. F.; Sánchez-Roselló, M.; Esteban, E.; Simón-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433–3436.
120. Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839–2842.
121. Mitsumori, S.; Zhang, H.; Cheong, P. H.; Kouk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.
122. Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631.
123. Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760–1763.
124. (a) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257; (b) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003–2006; (c) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; (d) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191–1193.
125. Poulsen, T. B.; Alemparte, C.; Saaby, S.; Bella, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 2896–2899.
126. Terada, M.; Sorimachi, K.; Uraguchi, D. *Synthesis* **2006**, 133–136.
127. For a recent review see: Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151–153.
128. Yamada, K.; Harwood, S. J.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504–3506; Yamada, K.; Moll, G.; Shibasaki, M. *Synlett* **2001**, 980–982; Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276–277.
129. Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843–5844.
130. Anderson, J. C.; Blake, A. J.; Howell, G. P.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 549–555; Anderson, J. C.; Howell, G. P.; Lawrence, R. M.; Wilson, C. S. *J. Org. Chem.* **2005**, *70*, 5665–5670.
131. Nugent, B.; Yoder, R.; Johnston, J. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419.
132. Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625–627; Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2006**, *12*, 466–476.
133. Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
134. Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975–7978.
135. Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623.
136. Bernardi, L.; Fini, F.; Herrera, R.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375–380.
137. Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117–120.
138. Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362–1364.
139. Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254–2257.
140. Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058–6063.
141. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650.
142. Reviews: (a) Spino, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 1764–1766; (b) Groger, H. *Chem. Rev.* **2003**, *103*, 2795–2827; (c) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875–877; (d) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315–1392; (e) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127–5143.
143. (a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902; (b) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; (c) Krueger, C. A.; Kuntz, K. W.; Dzierba, C. D.; Wirschun, W. G.; Gleason, J. D.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285; (d) Nakamura, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1513–1516.
144. (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911; (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157–160; (c) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; (d) Jiao, Z. G.; Feng, X. M.; Liu, B.; Chen, F. X.; Zhang, G. L.; Jiang, Y. Z. *Eur. J. Org. Chem.* **2003**, 3818–3826; (e) Huang, J. K.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027–5029.
145. For example: Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T. *Synlett* **2006**, 1595–1597.
146. Berkessel, A.; Mukherjee, S.; Lex, J. *Synlett* **2006**, 41–44.

147. Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548–2549.
148. Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617–2619.
149. Blacker, J.; Clutterbuck, L. A.; Crampton, M. R.; Grosjean, C.; North, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1449–1456.
150. (a) Masumoto, S.; Usuda, H.; Suzuki, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 5634–5655; (b) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147–3151; (c) Kato, N.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3153–3155; (d) Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220–1225; (e) Suzuki, M.; Kato, N.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 2527–2530.
151. Kato, N.; Mita, T.; Kanai, M.; Therrien, B.; Kawano, M.; Yamaguchi, K.; Danjo, H.; Sei, Y.; Sato, A.; Furusho, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 6768–6769.
152. Fukuda, N.; Sasaki, K.; Sastry, T. V. R. S.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220–1225.
153. Su, Z. S.; Hu, C. W.; Qin, S.; Feng, X. M. *Tetrahedron* **2006**, *62*, 4071–4080; Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G. L.; Jiang, Y. *Eur. J. Org. Chem.* **2003**, 3818–3826.
154. Reviews of thiourea catalysis: Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419–5427; Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299–4306.
155. Tsogoeva, S.; Hateley, M.; Yalalov, D.; Meindl, K.; Weckbecker, C.; Huthmacher, K. *Bioorg. Med. Chem.* **2005**, *13*, 5680–5685.
156. Steele, R. M.; Monti, C.; Gennari, C.; Piarulli, U.; Andreoli, F.; Vanthuyne, N.; Roussel, C. *Tetrahedron: Asymmetry* **2006**, *17*, 999–1006; Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.
157. Surendra, K.; Krishnaveni, N.; Srilakshmi, M. A.; Rao, K. R. *J. Org. Chem.* **2006**, *71*, 2532–2534.
158. Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923; Friestad, G. K.; Deveau, A. M.; Marie, J.-C. *Org. Lett.* **2004**, *6*, 3249–3252; McNabb, S. B.; Ueda, M.; Naito, T. *Org. Lett.* **2004**, *6*, 1911–1914; Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190–6193; Friestad, G. K.; Qin, J.; Suh, Y.; Marié, J.-C. *J. Org. Chem.* **2006**, *71*, 7016–7027.
159. Reviews: (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296–304; (b) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163–171; (c) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: New York, NY, 2001; (d) Zimmerman, J.; Sibi, M. P. *Topics in Current Chemistry*; Gansauer, A., Ed.; Springer: Berlin, 2006; Vol. 263, pp 107–162.
160. Review: Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461–5496.
161. Miyabe, H.; Ushiro, C.; Naito, T. *Chem. Commun.* **1997**, 1789–1790; For a review of Naito's contributions, see: Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140–1157; See also: Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099–2106.
162. Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176–185.
163. Halland, N.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1290–1295.
164. Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5061–5063.
165. Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87–89.
166. Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258; McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347–1365; Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
167. Moessner, C.; Bolm, C. *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 389–402; Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919; Osborn, H. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693–1715.
168. Johnson, C. R.; Kirchhoff, R. A.; Reischer, R. J.; Katekar, G. F. *J. Am. Chem. Soc.* **1973**, *95*, 4287–4291.
169. Baret, P.; Buffet, H.; Pierre, J.-L. *Bull. Soc. Chim. Fr.* **1972**, 2493–2501.
170. Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 676–678.
171. Li, Y.; Chan, P. W. H.; Zhu, N.-Y.; Che, C.-M.; Kwong, H.-L. *Organometallics* **2004**, *23*, 54–66.
172. Krumper, J. R.; Gerisch, M.; Suh, J. M.; Bergman, R. G.; Tilley, T. D. *J. Org. Chem.* **2003**, *68*, 9705–9710.
173. Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293–2297.
174. Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335–2344.
175. Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099–5100.
176. Antilla, J. C.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4518–4521.
177. Loncaric, C.; Wulff, W. D. *Org. Lett.* **2001**, *3*, 3675–3678.
178. Patwardhan, A. P.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169–6172.
179. Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987–8990.
180. Morales, D.; Pérez, J.; Riera, L.; Riera, V.; Corzo-Suárez, R.; García-Granda, S.; Daniel Miguel, D. *Organometallics* **2002**, *21*, 1540–1545.
181. Ishii, Y.; Sakaguchi, S. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 909–920.
182. (a) Davis, F. A.; Zhou, P.; Reddy, G. V. *J. Org. Chem.* **1994**, *59*, 3243–3245; (b) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559–7567.
183. Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *Chem. Commun.* **1996**, 2631–2632; McLaren, A. B.; Sweeney, J. B. *Org. Lett.* **1999**, *1*, 1339–1341; Sweeney, J. B.; Cantrill, A. A.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3681–3693; Sweeney, J. B.; Cantrill, A. A.; Drew, M. G. B.; McLaren, A. B.; Thobhani, S. *Tetrahedron* **2006**, *62*, 3694–3703.
184. Hanessian, S.; Cantini, L.-D. *Tetrahedron Lett.* **2000**, *41*, 787–790.
185. For leading references, see Ref. 182b.
186. Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135–7143; Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345–6352.
187. Davis, F. A.; Wu, Y.; Yan, H.; McCoull, W.; Prasad, K. R. *J. Org. Chem.* **2003**, *68*, 2410–2419.
188. Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368–8369.
189. Aggarwal, V. K.; Ferrara, M.; O'Brien, C. J.; Thompson, A.; Jones, R. V. H.; Fieldhouse, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1635–1643.

190. Aggarwal, V. K.; Charmant, J. P. H.; Ciampi, C.; Hornby, J. M.; O'Brien, C. J.; Hynd, G.; Parsons, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3159–3166.
191. Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433–1436.
192. Li, A.-H.; Dai, L.-X.; Hou, X.-L.; Chen, M.-B. *J. Org. Chem.* **1996**, *61*, 4641–4648.
193. Li, A.-H.; Zhou, Y.-G.; Dai, L.-X.; Hou, X.-L.; Xia, L.-J.; Lin, L. *Angew. Chem., Int. Ed.* **1997**, *36*, 1317–1319.
194. Yang, X.-F.; Zhang, M.-J.; Hou, X.-L.; Dai, L.-X. *J. Org. Chem.* **2002**, *67*, 8097–8103.
195. Robiette, R. *J. Org. Chem.* **2006**, *71*, 2726–2734.
196. Saito, T.; Sakairi, M.; Akiba, D. *Tetrahedron Lett.* **2001**, *42*, 5451–5454.
197. Solladié-Cavallo, A.; Roje, M.; Welter, R.; Sunjic, V. *J. Org. Chem.* **2004**, *69*, 1409–1412.
198. Li, X.-L.; Wang, Y.; Huang, Z.-Z. *Aust. J. Chem.* **2005**, *58*, 749–752.
199. Liao, W.-W.; Deng, X.-M.; Tang, Y. *Chem. Commun.* **2004**, 1516–1517.
200. Zheng, J.-C.; Liao, W.-W.; Sun, X.-X.; Sun, X.-L.; Tang, Y.; Dai, L.-X.; Deng, J.-G. *Org. Lett.* **2005**, *7*, 5789–5792.
201. Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612–1613.
202. Ma, S.; Zhang, J.; Lu, L.; Jin, X.; Cai, Y.; Hou, H. *Chem. Commun.* **2005**, 909–911.
203. Reviews of asymmetric Friedel–Crafts reactions: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550–556; Jørgensen, K. A. *Synthesis* **2003**, 1117–1125.
204. Johannsen, M. *Chem. Commun.* **1999**, 2233–2234.
205. Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114–4116; Saaby, S.; Bayon, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352–4361.
206. Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805.
207. Luo, Y. M.; Li, C. J. *Chem. Commun.* **2004**, 1930–1931.
208. Esquivias, J.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629–633.
209. Jia, Y. X.; Xie, J. H.; Duan, H. F.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1621–1624.
210. Wang, Y. Q.; Song, J.; Hong, R.; Li, H. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.
211. Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558–10559.
212. Jacobsen notes only one prior precedent for activation of *N*-acyliminium ion with a chiral catalyst. (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; (b) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 6801–6802; (c) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784–10785.
213. Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086–1087.
214. Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858–2859.

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