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Stereoselective Formation of Amines by Nucleophilic Addition to Azomethine Derivatives

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Abstract This chapter describes state-of-the-art methods to prepare α-chiral amines by the addition of nonstabilized nucleophiles to imine derivatives. The first part of the chapter illustrates the most effective diastereoselective addition reaction (substrate controlled and chiral auxiliary based methods) whereas the second part focuses on catalytic asymmetric methods.

Keywords Azomethine · Chiral amines · Chiral auxiliaries · Chiral catalysts · Chiral ligands · Nucleophilic addition

Contents

Abbreviations

DuPHOS	[2,5-Dimethylphospholano]benzene
EWG	Electron-withdrawing group
PG	Protecting group

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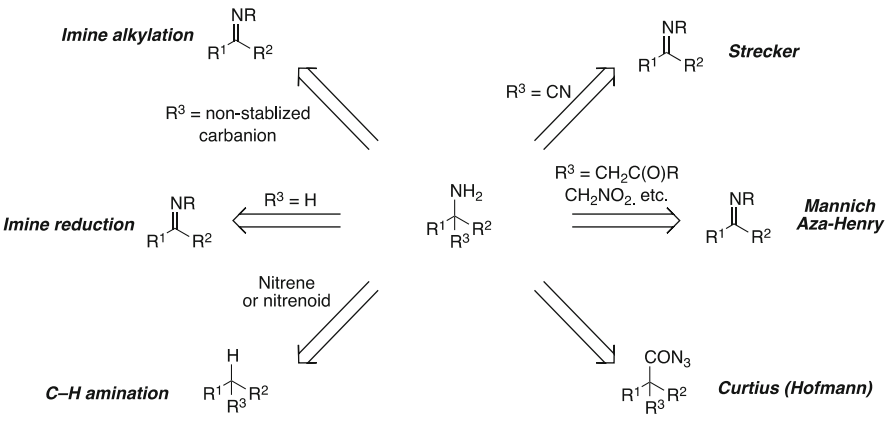
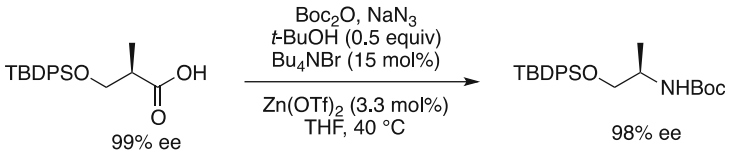


Fig. 1 Most common approaches to α-chiral amines

1 Introduction

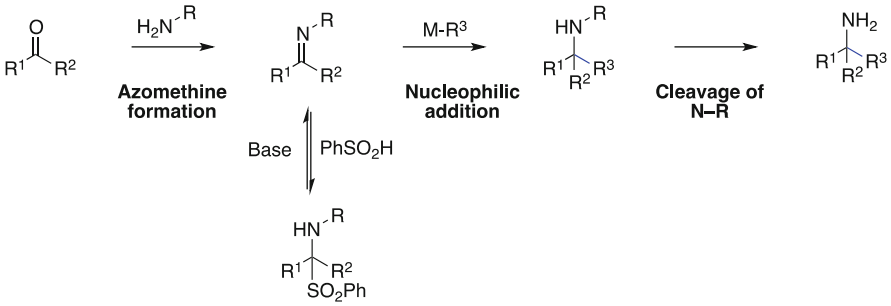
The ubiquity of α-chiral amines in bioactive molecules and natural products has been a constant source of inspiration for the development of new and more effective methods for their formation. Various approaches to α-chiral amines are shown in Fig. 1. Common approaches to generate α-chiral amines include imine reduction [1] and Strecker [2] and Mannich type (aza-Henry) reactions [3, 4].

It is also possible to generate α-chiral amines starting from α-chiral carboxylic acids by a Curtius rearrangement. The process occurs with retention of configuration (1) [5]:



(1)

This chapter will cover the recent advances in the area of stereoselective azomethine alkylation only [6]. The sections are divided according to the type of electrophiles and nucleophiles used in the reactions and whether the processes required stoichiometric or catalytic amounts of a chiral inductor.



Scheme 1 Preparation of α-chiral amines from carbonyl derivatives

2 1,2-Addition of Unstabilized Carbanions to Chiral Azomethine Derivatives

Recent advances in the synthesis of various azomethine derivatives from aldehydes have greatly contributed to increasing the scope of accessible substrates for addition reactions.

These compounds are typically prepared by condensation of protected amines with aldehydes or ketones, leading respectively to aldimines and ketoimines with elimination of water (Scheme 1). In cases where imines are not very stable (some alkyl-substituted imines with enolizable protons), it is possible to isolate them in the form of their sulfinic acid adducts. These adducts break down to imines in the presence of base (or excess nucleophile). Following the addition of the nucleophile, the amino protective group is removed to provide access to a free amine.

The overall efficiency of these processes is often regarded as a combination of these three reactions. Ideally, the imine used or its equivalent must be accessible in high yield from an aldehyde or a ketone, possessing the appropriate electrophilicity for a nucleophilic addition under mild conditions, and the *N*-protective group should be easily removed afterwards.

2.1 Electrophilicity of Azomethine Derivatives

The electrophilicity of azomethines is highly dependent upon the nature of the *N*-substituent of the substrate. Each type of *N*-substituted imine has its own reactivity profile and is not usually interchangeable for a given methodology. These azomethines can be subdivided into six main classes depending of the type of *N*-substituent, each of which have significantly different electrophilicities, Lewis basicities, and modes of activation: (1) *N*-alkyl groups, (2) *N*-aryl groups, (3) *N*-heteroatoms, (4) *N*-electron-withdrawing groups, (5) iminium salts, and (6) *N*-ylides (Fig. 2).

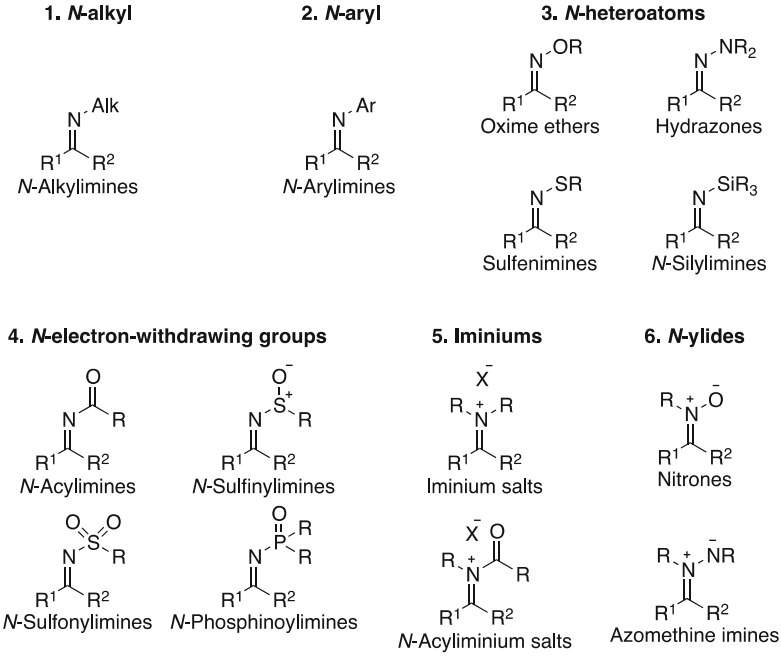


Fig. 2 Classes of azomethine derivatives in nucleophilic addition reactions

Compared to carbonyl derivatives, simple *N*-alkyl or *N*-aryl imines are usually more basic and less electrophilic, which means that they are sometimes more readily activated with a Lewis acid or a transition metal. In order to increase the electrophilicity of the C=N bond, various strategies have been employed, including the use of an electron-withdrawing substituent as a substituent directly linked to the imine carbon atom such as in glyoxal derivatives. Since the presence of an α-electron-withdrawing substituent is not always desired in the final product, a more general approach consists of using *N*-EWG imines as electrophiles, where the EWG, acting as a protective and an activating group, can be cleaved after the addition to liberate a free amine. In order to quantify the effect of such *N*-substitution on the imine electrophilicity, various data can be used (Fig. 3) [7, 8]. *N*-Acylimines and *N*-tosylimines are the most electrophilic of the *N*-EWG imines, while *N*-alkyl and *N*-aryl substituted imines are significantly less reactive than aldehydes. Thus, strong nucleophiles such as Grignard reagents are often needed for the addition to occur to simple *N*-alkylimines. On the other hand, the use of *N*-EWG imines as electrophiles is particularly common in catalytic asymmetric addition reactions using various transition metals such as rhodium, copper, iridium, or palladium. It should be noted that, due to the purely electronic nature of these calculations, the values depicted here are independent of the different steric effects at the approach of the nucleophile and of the mode of activation employed for the addition.

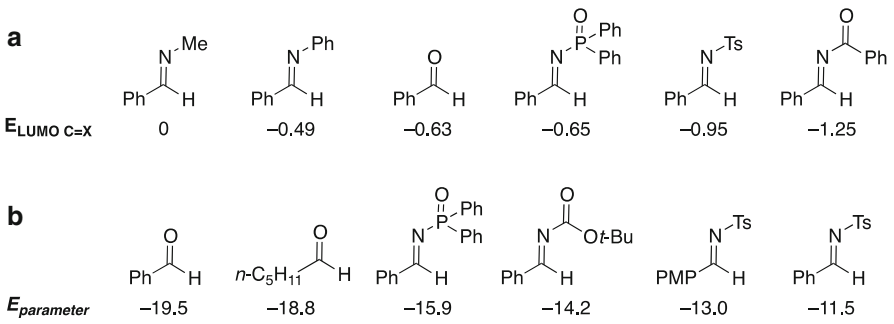


Fig. 3 Relative electrophilicity of C=X functionalities. (**a**) LUMO energies in eV (geometry optimized at B3LYP/6-31G(d)) [7]. (**b**) Mayr's *E* parameters [8]

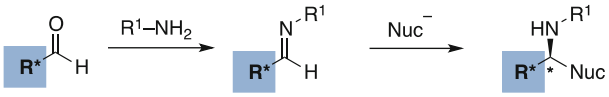
2.2 Diastereoselective Addition to Chiral Imines

Two classes of diastereoselective nucleophilic addition reactions to imines will be discussed separately. The first involves nucleophilic addition reactions to chiral imines in which the chirality resides on the C-terminus (Fig. 4, type 1). One of the most reliable ways to achieve the preparation of enantiomerically enriched α-chiral amines is the use covalently-bound chiral auxiliaries, which can be located on the imine *N*-substituent (Fig. 4, type 2). These methodologies are typically designed to allow cleavage of the N–R* bond to liberate a free amine.

2.2.1 Chiral Imines and Derivatives Obtained from Chiral Carbonyl Derivatives

When the imine electrophile is derived from a chiral aldehyde, several competing predictive models are available, where the sense of induction greatly depends on the nature of the chiral group and the nucleophile employed. In analogy to the extensively studied addition of nucleophiles to carbonyl substrates, the predictive Cram, Felkin–Ahn, and Cornforth models are also applicable to imine chemistry. Thus in principle a non-chelating chiral group at the α-position of the acyclic imine will afford the Felkin–Ahn product issued from minimization of torsional strain at the transition state and subsequent attack on the most accessible face of the imine (Fig. 5a). Conversely, the presence of a chelating functionality at this position leads to the product issued from the addition on the least hindered face of the chelate intermediate according to Cram's cyclic model, under the appropriate reaction conditions favoring the formation of such chelate (Fig. 5b). It is noteworthy that Cram's cyclic model is usually effective only with *N*-alkyl or *N*-arylimine derivatives where the most Lewis basic site of the substrate is the nitrogen atom. As in carbonyl addition chemistry, it is sometimes possible to access either diastereomer when appropriate reaction conditions are used.

Type 1. ***Imines derived from chiral carbonyl and achiral RNH_2 (chirality in C-terminus)***



Type 2. ***Imines derived from chiral R^*NH_2 and achiral carbonyl (chirality in N-terminus)***

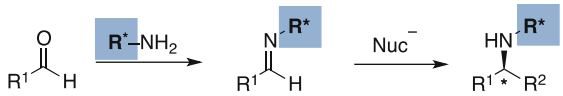


Fig. 4 Diastereoselective addition to chiral imines

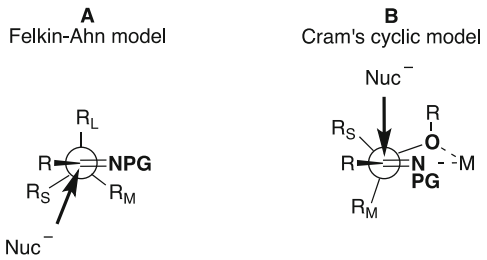
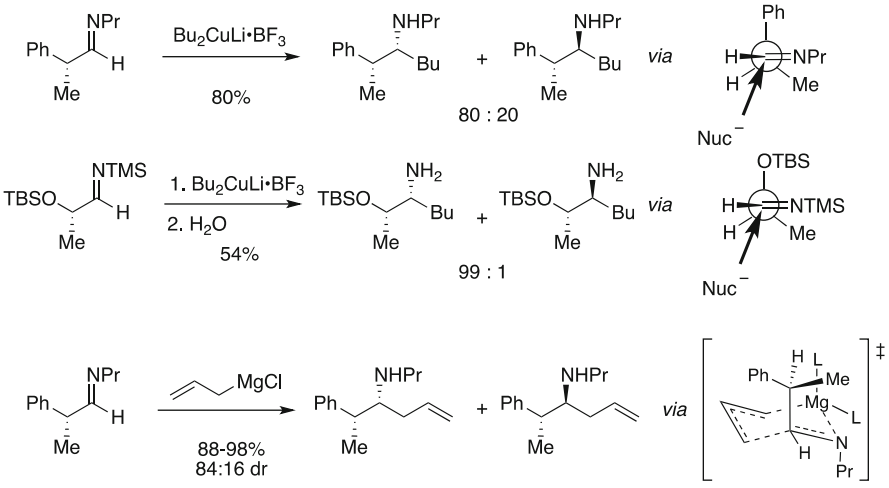
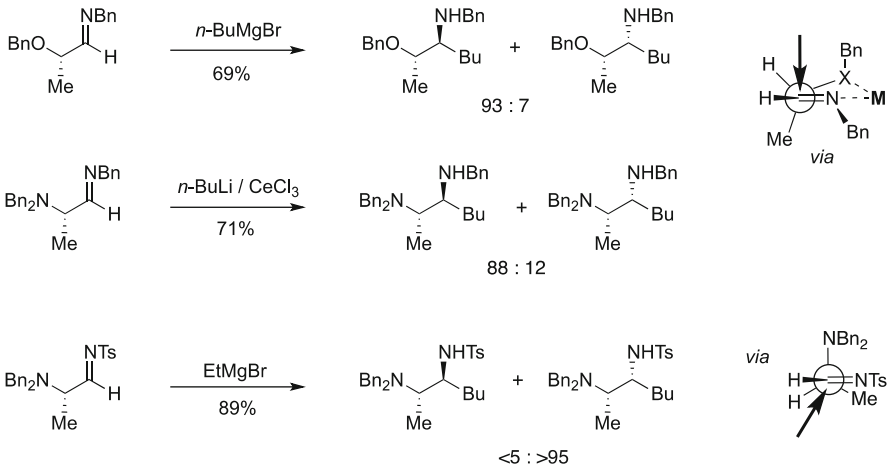


Fig. 5 Diastereoselective addition to chiral imines



Scheme 2 Representative examples of diastereoselective addition to chiral imines

While successful examples of the Felkin–Ahn model with simple alkylmetals and imines remain scarce, alkylcopper or alkylcuprate reagents complexed with BF_3 can usually afford a good diastereoselectivity for the Felkin adduct (Scheme 2)



Scheme 3 Diastereoselective addition reactions to *N*-benzyl and *N*-tosylimines

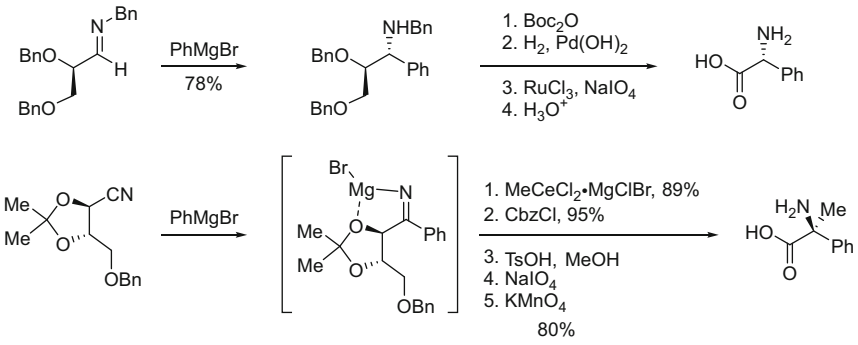
[9, 10]. The use of allyl Grignard reagents is more common and can provide a reasonable level of diastereoselection [9].

The nucleophilic addition reaction under chelation control conditions (see Cram's cyclic model, Fig. 5) is a much more general and widespread means to access α-chiral amines from chiral imines. Various types of α-chiral chelating groups can be used in such processes, including α-chiral benzyl ethers or α-chiral *N*,*N*′-dibenzylamines (Scheme 3) [11, 12]. When the *N*-benzylimine was replaced with *N*-tosylimine the opposite diastereoselectivity issued from a non-chelation control (Felkin–Ahn) was observed for the corresponding 1,2-diamine product [12]. Diastereoselective reactions can also be obtained via chelation control with hydrazones [13–21], oxime ethers [22–24], or nitrones [25–37] derived from chiral aldehydes through an analogous stereoinduction mechanism, where the size of the chelate varies depending on the nature of the imine derivative used.

Diastereoselective addition reactions to imines derived from the chiral pool have provided access to unnatural α-amino acids (Scheme 4) [38, 39].

Alternatively, a chiral acetal, aminal, or thioacetal located at the α-position could be used as removable chiral auxiliaries to provide the corresponding aldehydes after hydrolysis (Fig. 6) [19, 40–42].

The stereocontrol of this strategy relies on a selective chelate formation on one of the Lewis basic sites located on the C-terminus. Both approaches have been shown to lead to very high levels of diastereocontrol for the addition step, with alkyl-, aryl-, or alkynyl-metal nucleophiles.



Scheme 4 Access to α-amino acids

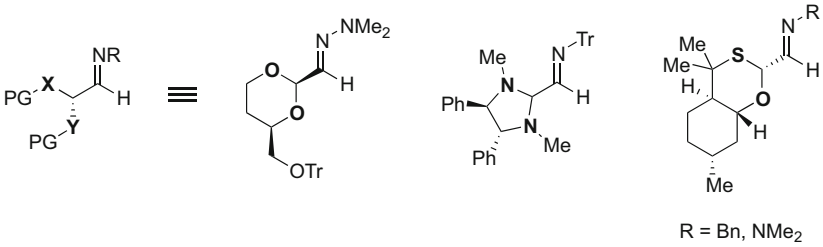


Fig. 6 Representative examples of C-terminus chiral auxiliaries in C=N addition reactions

2.2.2 Chiral Imines and Derivatives Obtained from Chiral Amines

The use of chiral auxiliaries located at the *N*-terminus of the imine substrate is one of the most efficient mean to access α-chiral amines via the addition of organometallic reagents to C=N bonds. Chiral imines derived from *N*-alkylamines, hydrazines, hydroxyamine (oximes and nitrones), and sulfinylamines have been the most widely utilized auxiliaries.

In analogy to the Felkin–Ahn model for C-terminus auxiliaries, a stereochemical model has been proposed to account for the observed diastereoselectivities with N-terminus auxiliaries relying on non-chelation control (Fig. 7a) [9, 43]. Successful examples using these auxiliaries are quite rare [44–47].

The use of α-methyl benzylamine as auxiliary with cuprates/BF_3 mixtures can lead to good diastereoselectivities in certain cases (Scheme 5) [48, 49]. Hydrogenolysis of the benzylic amine leads to the destructive chiral auxiliary cleavage.

Chiral auxiliaries relying on chelation control at the N-terminus are much more widespread and structurally diverse. When the electrophile is an imine, the diastereochemical outcome of the addition can be predicted via a chelation model (Fig. 7b) [50–56].

Several examples of chiral auxiliaries, often derived from amino acids, are illustrated in Fig. 8. While auxiliaries of types I and II are compatible with a variety

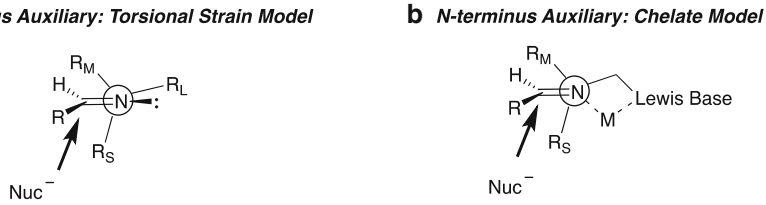
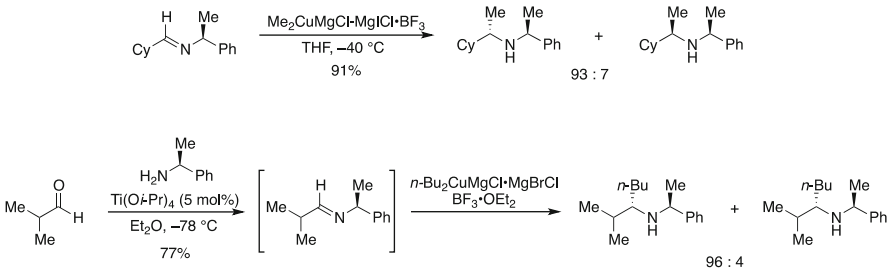


Fig. 7 Torsional vs chelate model in nucleophilic addition reactions



Scheme 5 Example of α-methyl benzylamine as chiral auxiliary

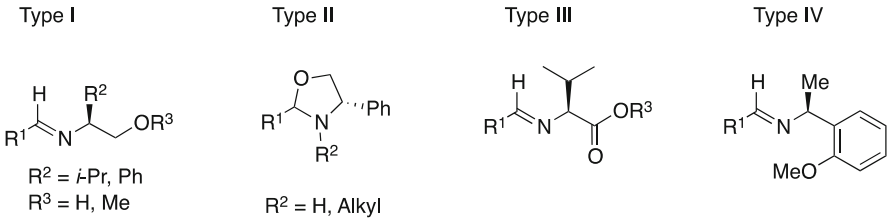
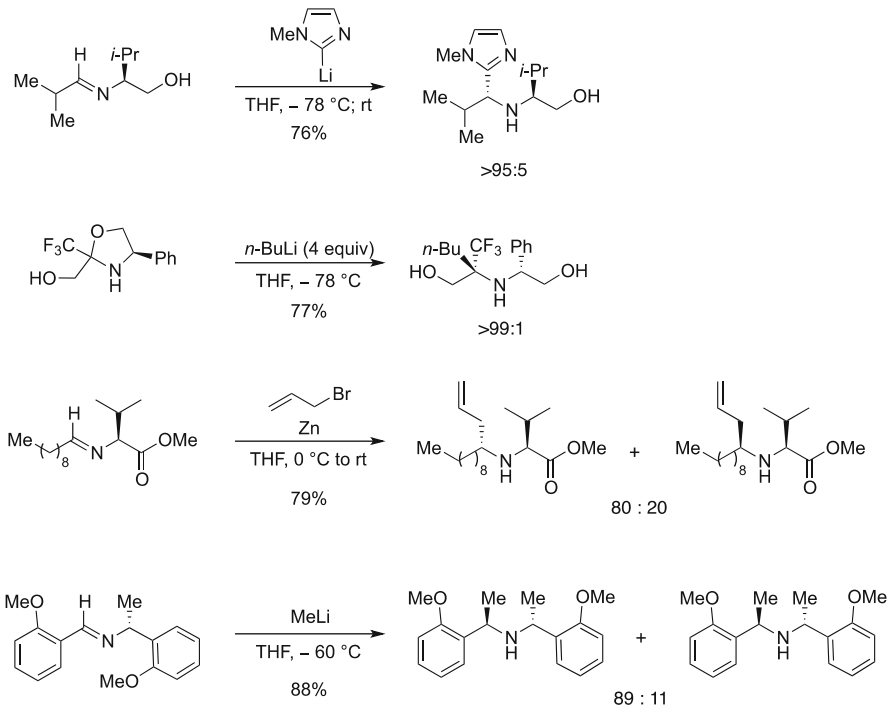


Fig. 8 Imine-derived chiral auxiliaries based on the chelate model

of reagents such as Grignards, organolithium, organozinc, organocuprates, or organocerium nucleophiles [50–59], type III auxiliaries have been limited to allylation reactions under Barbier-type conditions due to ester compatibility issues with more nucleophilic carbanion equivalents [60–68]. The addition of a methoxy group at the ortho position of α-methyl benzylamine leads to high diastereoinduction with alkyl- and allyllithium reagents [69–72]. Recent examples of the use of these auxiliaries are shown in Scheme 6 [70, 73–75].

Chiral hydrazones where the chirality is located on the hydrazine moiety of the precursor have found widespread use for the synthesis of α-chiral amines via the diastereoselective nucleophilic addition of various organometallic reagents. As in the previous case, chelate formation activates the hydrazone towards the nucleophilic addition, which can occur either through an internal or an external delivery,



Scheme 6 Representative examples of N-terminus chiral auxiliaries derived from alkylamines

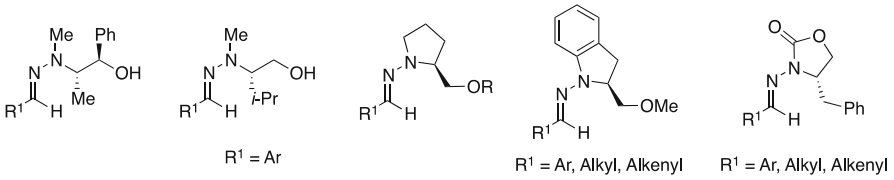
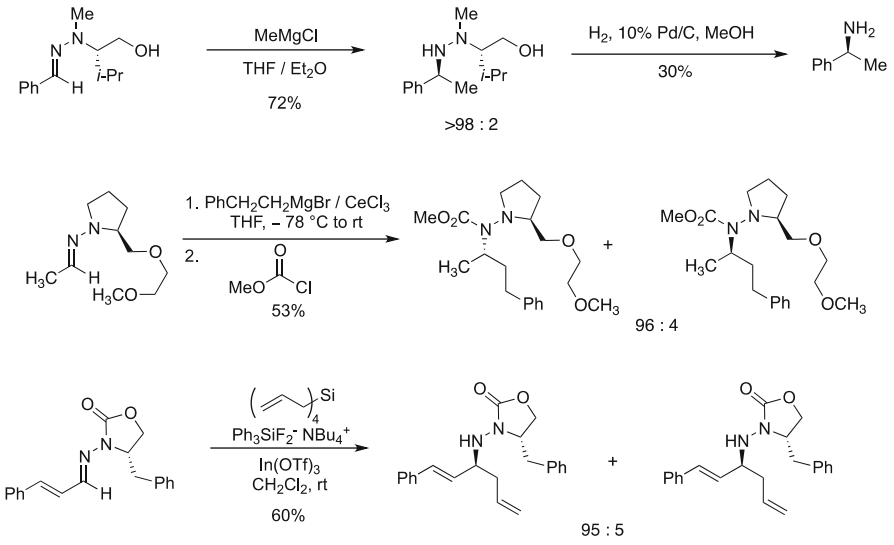


Fig. 9 Representative examples of hydrazone-based chiral auxiliaries

depending on the conditions used. For instance, chiral auxiliaries bearing Lewis basic alkoxides, ethers, and oxazolidinones that are able to form five- or six-membered chelates have been developed (Fig. 9). Chiral hydrazones derived from *N*-aminopyrrolidinol also called SAMP (or RAMP for the *R*-isomer) are general electrophiles for the stereoselective addition of a variety of organometallic reagents including organolithium, Grignards, and organocerium species [76–84]. Several specific transformations are shown in Scheme 7 [84–86]. Hydrazones derived from aliphatic and aromatic aldehydes and protected



Scheme 7 Representative examples of diastereoselective addition using hydrazone based chiral auxiliaries

hydrazinoalcohols are usually tolerated and compatible with both sp^3 and sp^2 nucleophiles. The use of a chiral *N*-acylhydrazone equivalent as auxiliary has been shown to be effective for the indium-mediated addition of allylsilanes to both aromatic and aliphatic electrophiles [86–89]. In addition, nucleophiles for these reactions also includes carbon radicals generated from alkyl iodides [90–101]. In all cases, reductive cleavage of the N–N bond leads to the free α-chiral amine.

Chiral oximes derived from *O*-alkyl hydroxylamines have been used successfully as electrophiles for diastereoselective addition reactions [102–107]. Although these substrates are usually considered to be less general than their hydrazone counterparts, a number of successful examples of their use have been reported [102, 108].

One of the most practical and reliable types of *N*-bound auxiliary for the diastereoselective addition of Grignard reagents to the C=N bond consists of a chiral sulfinyl group directly bound to nitrogen. The most efficient auxiliaries of this type reported to date are definitely **A** [109–114] and **B** [115–129] (Fig. 10), while the parent camphor-derived analogue **C** is not as general and has not been extensively used [130, 131].

The *N*-toluenesulfinylimines (Fig. 10, **A**) are only compatible with allyl- and benzyl-Grignard reagents due to the competitive attack on the sulfinyl group with other nucleophiles such as alkyl-, vinyl-, and arylmetals. Conversely, the use of a much hindered *N-tert*-butanesulfinyl group (Fig. 10, **B**) allows for chemoselective addition reactions to the imine functionality with these nucleophiles, generally with very high diastereocontrol. A chair-like six-membered transition-state where the

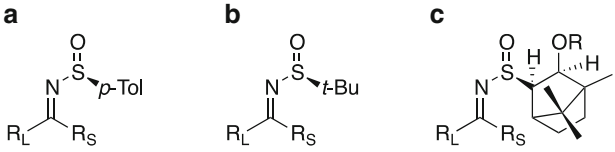


Fig. 10 Most efficient sulfinylimines based chiral auxiliaries

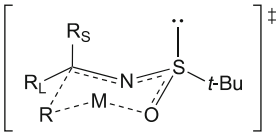
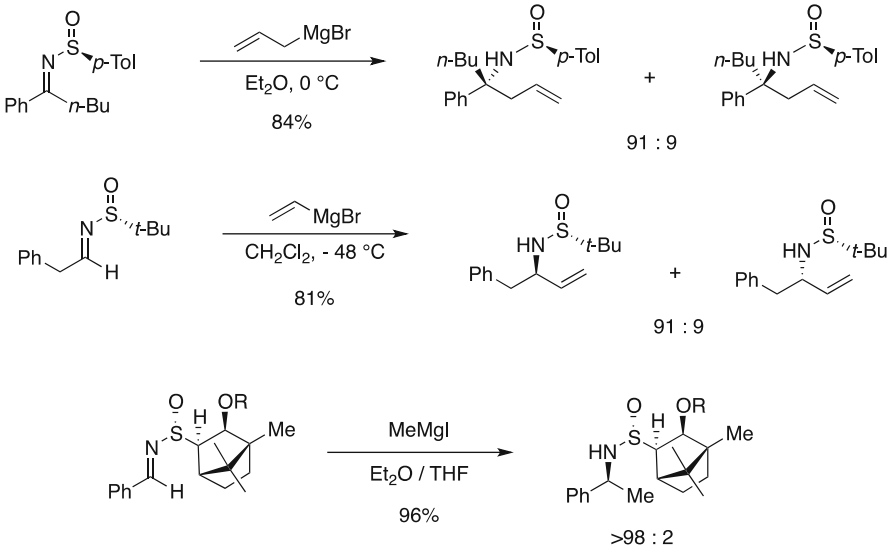


Fig. 11 Chelation model to explain the selectivity with *N-tert*-butylsulfinylimines

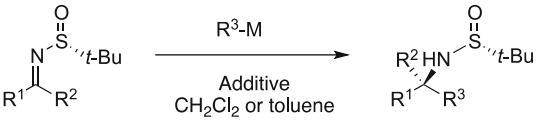


Scheme 8 Representative examples of diastereoselective addition to *N*-sulfinylimines

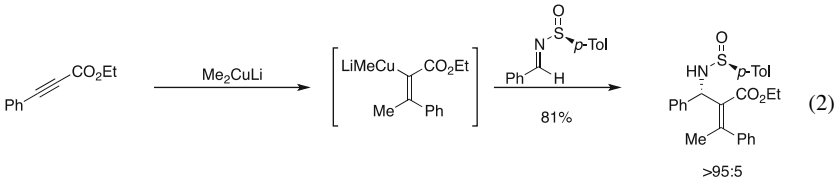
sulfur substituent and the large group of the imine are placed in equatorial positions accounts for the observed relative configuration of the products (Fig. 11). Some additional examples of the use of these auxiliaries are shown in Scheme 8 and in Table 1 [109, 116, 130] (for a review see [132]).

Vinyl-substituted nucleophiles can be generated in situ through carbo- or hydrometallation of alkynes, using organocuprates (2) or Rh-based catalysts (3), respectively, and subsequently react with *N*-sulfinylimines, leading to polysubstituted allylamines in high regio- and stereoselectivity [113, 127]. It should be noted that esters are compatible in the rhodium-catalyzed addition.

Table 1 *N-tert*-Butanesulfinyl group as chiral auxiliary in the stereoselective addition reactions [115–129]



Entry	R^1	R^2	R^3-M	Yield (%)	dr	Additive
1	Et	H	PhMgBr	>99	96:4	–
2	*i*-Pr	H	EtMgBr	>99	97:3	–
3	Ph	H	EtMgBr	98	92:8	–
4	*i*-Pr	Me	PhLi	93	97:3	Me_3Al
5	Ph	Me	*n*-BuLi	86	98:2	Me_3Al
6	Ph	*n*-Bu	MeLi	>99	99:1	Me_3Al
7	2-Naphthyl	Me	PhLi	62	99:1	Me_3Al



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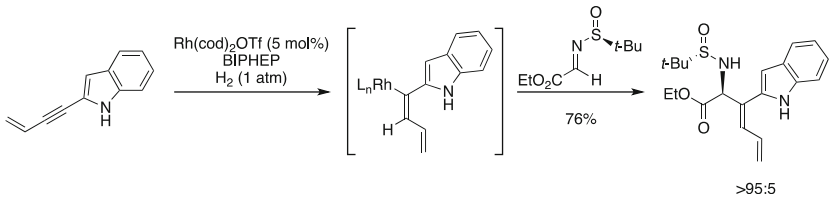
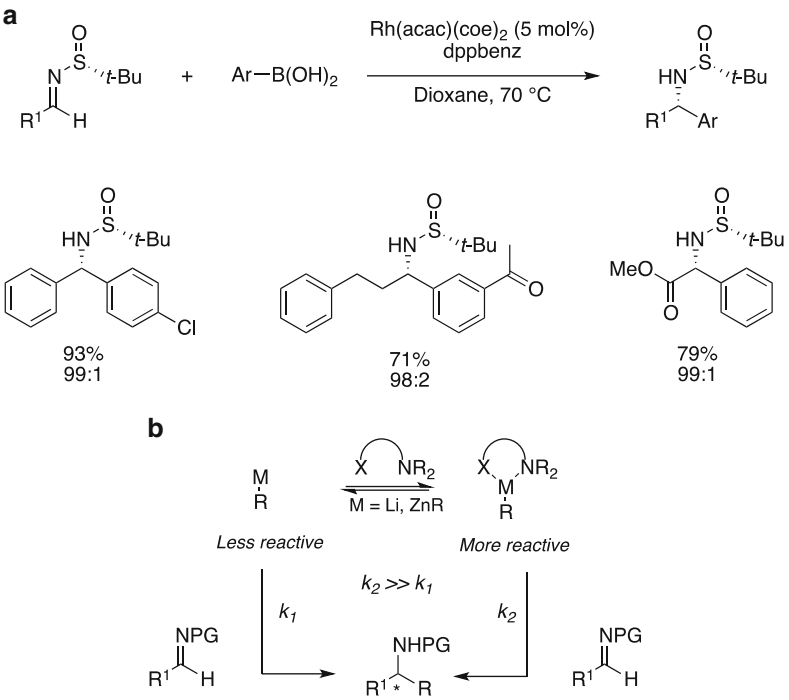


(3)

It is also possible to achieve the diastereoselective addition of arylboronic acids through the use of Rh(I) catalysts, affording a mild and highly chemoselective alternative to aryl-Grignard reagents as stoichiometric nucleophiles (Scheme 9a) [125, 126]. In this type of process, only a catalytic amount of the active arylrhodium nucleophile is generated at once through transmetallation and the reaction tolerates a wide range of imines.

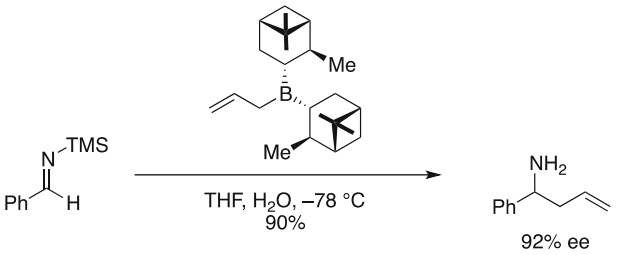
The versatile *N-tert*-butylsulfinamine is readily cleaved to liberate the free amine under a variety of relatively mild acidic conditions, the most widely used being HCl in MeOH.



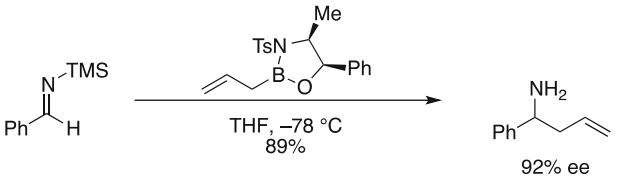
Scheme 9 (**a**) Representative examples of Rh-catalyzed arylboronic acids addition reactions. (**b**) Ligand accelerated nucleophilic addition

2.3 *Stoichiometric Amounts of Chiral Reagents*

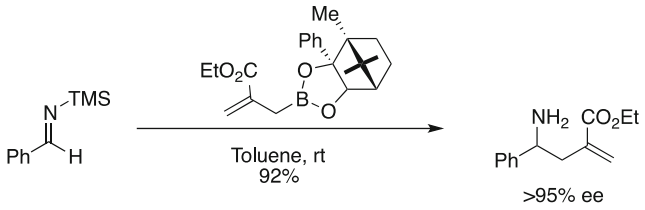
The addition of stoichiometric chiral nucleophiles to achiral imines is not much used in synthesis given the efficiency of chiral auxiliary based and catalytic asymmetric methods. Most of the successful methods reported to date using stoichiometric amounts of chiral nucleophiles are limited to allylation or crotylation reactions. An obvious advantage of such a strategy is the direct formation of enantiopure α-chiral homoallylic amines, without the need for the cleavage of a chiral auxiliary. Several examples of these reactions are provided in (4–6) [133–142]:



(4)

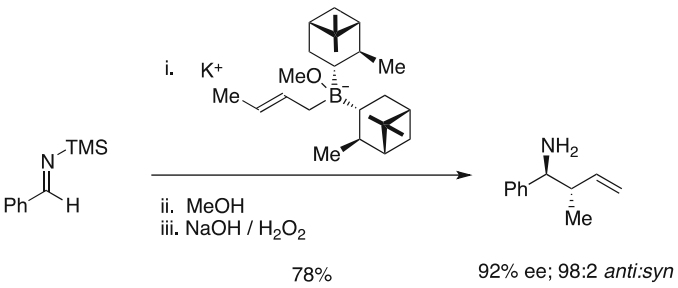


(5)



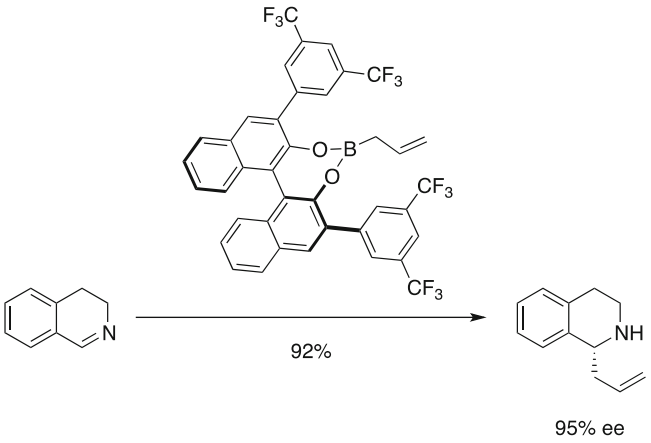
(6)

The addition of a chiral crotylboron reagent bearing diisopinocamphenyl units allows for the stereospecific formation of β-chiral homoallylic amines in good dia- and enantioselectivities (7) [139]:



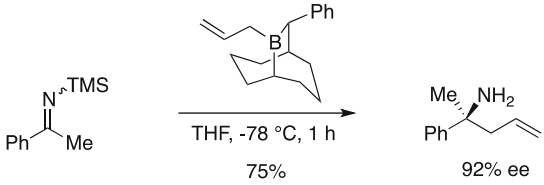
(7)

The allylboration of cyclic *N*-alkylimines was reported to be highly enantioselective when a BINOL-derived allylboron nucleophile was used (8) [140]:



(8)

The enantioselective allylation of ketoimines is also possible with enantiopure *B*-allyl-10-phenyl-9-borabicyclo[3.3.2]-decane, although generally with lower yields than with the parent aldimines (9) [141]:



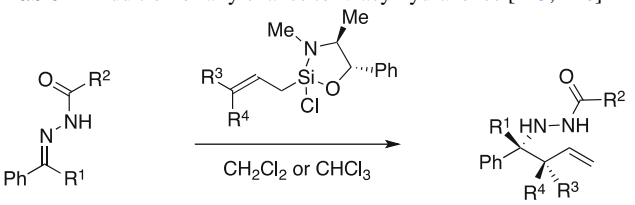
(9)

More recently, several very effective and practical chiral allylsilanes have been reported to add to *N*-acylhydrazones with excellent stereocontrol (Table 2) [143–146]. Good yield and stereoselectivity are typically observed for hydrazones derived from both aldehydes and ketones (entries 1–4). The reaction with crotylsilane reagents also proceeds with high stereocontrol providing either the syn or the anti depending on the configuration of the starting reagent (entries 5, 6).

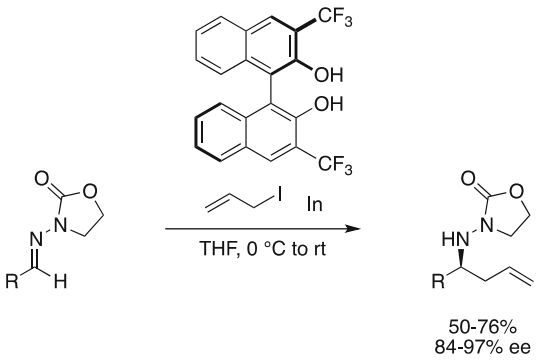
Chiral allyl- or crotylzinc reagents bound to bis(oxazoline) ligands are also competent nucleophiles in this type of process, and the stereoselectivity observed is typically high with a cyclic *N*-alkylimine or glyoxal-derived oximes [147, 148].

N-Acylhydrazones react with a chiral allylindium species formed in situ in a mixture of In(0), allyl iodide, and stoichiometric amounts of a chiral BINOL derivative to afford *N*-acyl homoallylhydrazines (10) [149]. The structure of the BINOL ligand was optimized to allow a highly efficient catalytic asymmetric process, in which only 10 mol% of this chiral ligand is necessary [150].

Table 2 Addition of allylsilanes to *N*-acylhydrazones [145, 146]



Entry	R^1	R^2	R^3	R^4	Yield (%)	dr	*ee* (%)
1	H	Me	H	H	86	–	88
2	Me	Ph	H	H	86	–	90
3	*i*-Pr	Ph	H	H	80	–	97
4	CO_2Me	Ph	H	H	76	–	93
5	H	Ph	Me	H	89	95:5	97
6	H	Ph	H	Me	81	96:4	95

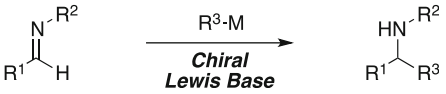


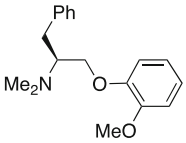
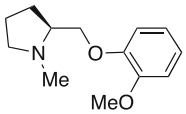
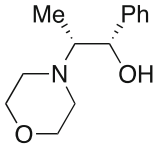
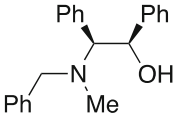
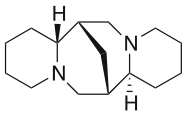
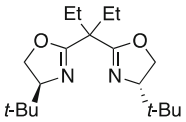
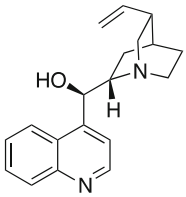
(10)

2.4 Catalytic Asymmetric Nucleophilic Addition

The importance of asymmetric catalysis in the last 40 years and the progress made in a vast array of transformations has stimulated organic chemists to develop new strategies for the synthesis of enantiomerically enriched α-chiral amines via addition reactions. Although the new methodologies have not been published at the same rate as carbonyl addition reactions, a large number of very effective catalytic asymmetric addition reactions to imines are now available. The most efficient and practical methods are summarized in the next sections. Since most methodologies are effective with only one class of carbon nucleophiles, each subsection below will be divided by the type of nucleophile that is used.

Table 3 Early examples of nucleophilic addition reactions to imines employing substoichiometric amounts of a chiral Lewis base



Entry	Chiral Lewis base (mol%)	R^1	R^2	R^3-M	Yield (%)	*ee* (%)	References
1		Ph	PMP	BuLi	99	60	[152]
	(30 mol%)						
2		Ph	Ph	BuLi	44	6	[156]
	(25 mol%)						
3		Ph	$P(O)Ph_2$	Et_2Zn	69	85	[158]
	(50 mol%)						
4		Ph	$P(O)Ph_2$	Et_2Zn	67	90	[159]
	(50 mol%)						
5		$Ph(CH_2)_2$	PMP	BuLi	91	79	[160–163]
	(20 mol%)						
6		Ph	PMP	MeLi	97	69	[164, 165]
	(10 mol%)						
7		Ph	$P(O)Ph_2$	Et_2Zn	77	87	[166]
	(50 mol%)						

2.4.1 Background: Lewis Base Activation of the Nucleophile vs Transition Metal Catalysis

One of the first strategies explored for the synthesis of α-chiral amines through the addition of nonstabilized nucleophiles to imine derivatives consists of using stoichiometric and substoichiometric amounts of a chiral bidentate Lewis base capable of activating the Lewis acidic organometallic reagent via complexation of the metal center (Scheme 9b). The key for the success of this approach mainly resides in the fact that the reagent complexed with the chiral Lewis base is far more nucleophilic than that of the uncomplexed species (R–M). If the rate of the background reaction (k_1) is significantly lower than that of the complexed species (k_2), then one may hope to observe good enantioselectivities if a suitable chiral Lewis base is used. One problem that researchers had faced for many years is the fact that very reactive organolithium or Grignard reagents were always used early on. These reagents react very rapidly with imines even in the absence of a Lewis base. The key issue early on was to discover nucleophiles or reaction conditions in which the rate of the background reaction was suppressed.

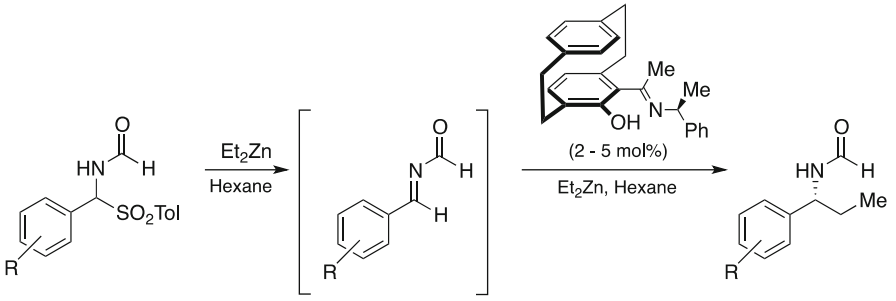
A summary of the early results using organolithium and diorganozinc reagents is shown in Table 3 [151–166]. Most of these methods require a considerable amount of the chiral ligand (10–50 mol%) to be effective and each process is not very general.

One of the rare successful example was reported, using *N*-formylarylimines and chiral [2.2]paracyclophane-based *N*,*O*-ligand as catalyst (Table 4) [167]. Due to the instability of these imines, they had to be formed in situ from their corresponding sulfinate adduct by the addition of 1 equiv. extra of Et_2Zn acting as a base. A related methodology was reported for the addition of Ph_2Zn to these substrates (for other examples of enantioselective addition of diorganozinc reagents to these imines, see [168–170]). The generality of this methodology with regards to nucleophiles that can be used still remains to be established. The formamide is easily hydrolyzed under mild acidic conditions (HCl, MeOH, 50°C).

A second and most successful approach involving nonstabilized nucleophiles and imine derivatives employs a chiral catalyst capable of transmetalation with a non-reactive nucleophilic partner added in stoichiometric amounts (Scheme 10). This active chiral nucleophile formed catalytically is then capable of stereoselective addition reactions to the C=N bond to form enantioenriched α-chiral amine derivatives.

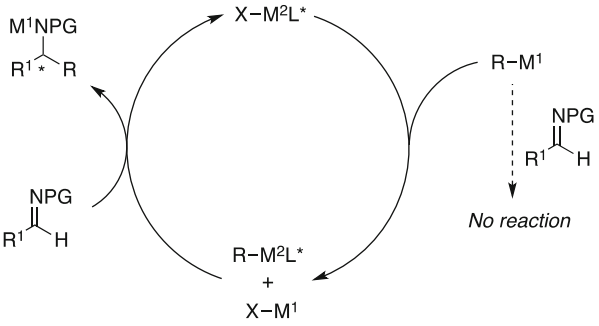
This area of research has generated considerable interest from the synthetic organic community, leading to the development of the most efficient methodologies for the synthesis of α-chiral amine derivatives through addition reactions. These methods will be reviewed in the following sections.

Table 4 Catalytic asymmetric addition to *N*-formylimines.



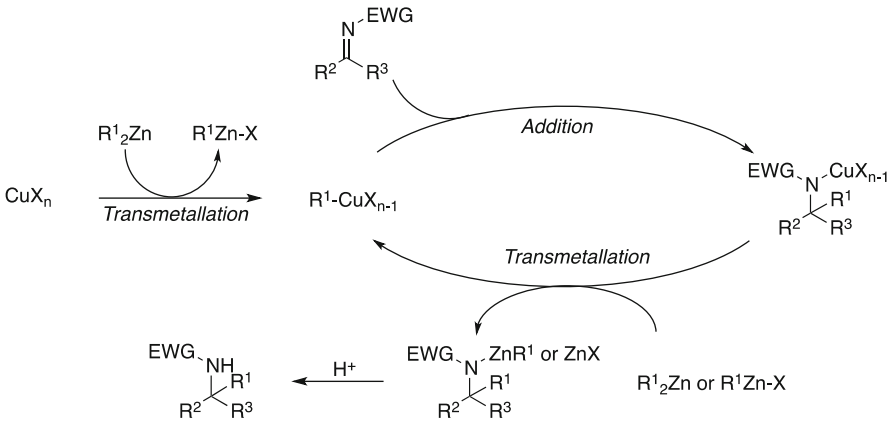
Entry	R	Yield (%)	*ee* (%)
1	H	>99	95
2	4-Cl	97	90
3	4-MeO	97	95
4	4-MeO_2C	90	94
5	2,6-Cl_2	98	95
6	3-Cl	99	93

Scheme 10 Nucleophilic addition reactions involving a transmetalation process



2.4.2 Addition of Alkylmetals (sp^3 Carbon)

One of the first very efficient systems studied is the Cu-catalyzed addition of diorganozinc reagents. In this type of process, imine derivatives bearing either electron-withdrawing groups or arenes are usually required. The practicality of the method often relies on the availability of the chiral ligand, on the generality and accessibility of the nucleophiles used, and on the mildness of the reaction conditions to liberate the free amine following the stereoselective addition. A general mechanism for this reaction is shown in Scheme 11. A diorganozinc species added in stoichiometric amounts is capable of transmetalation with the Cu salt used as catalyst (typically CuOTf or $Cu(OTf)_2$ that is in situ reduced into a Cu(I) species), forming an active Cu-alkyl nucleophile, which adds to the imine derivative. The resulting product can then transmetalate with one of the diorganozinc species,



Scheme 11 Postulated mechanism for the Cu-catalyzed addition of diorganozinc reagents to imine derivatives

regenerating the active nucleophilic catalyst and the zinc salt of the amine product. If a chiral ligand is complexed to the Cu center throughout the process, then a catalytic enantioselective reaction can be envisioned via appropriate control of the chiral environment around the Cu center.

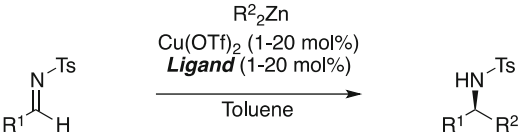
The first successful method of this type employed chiral amido-phosphines ligands for the $Cu(OTf)_2$-based catalyst with *N*-sulfonylimines as electrophiles (Table 5) [171–173]. Further optimization of the chiral phosphine ligand led to three amido-phosphine ligands, which afford a highly enantioselective method for aromatic as well as aliphatic imine derivatives with Et_2Zn, while the addition of Me_2Zn or $(i\text{-Pr})_2Zn$ furnishes slightly lower enantiomeric excesses (for use of a ferrocene-based related ligand see [174]). The *N*-tosyl group can be removed using samarium diiodide in a mixture of THF and HMPA.

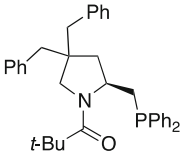
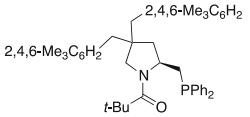
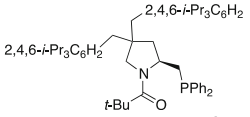
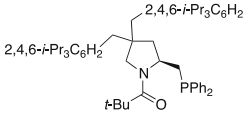
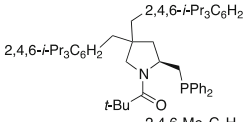
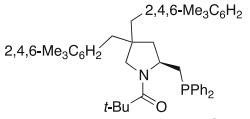
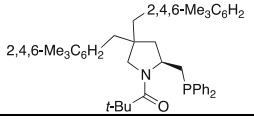
N-Phosphinoylimines are also reactive electrophiles in this type of reaction, and the use of a chiral bis(phosphine) monoxide derived from Me-DuPHOS leads to excellent enantioselectivities for a number of *N*-phosphinoylimine derivatives and diorganozinc reagents (Table 6) [175–184]. Notably, it was found that the phosphine oxide unit does not need to be chiral for high enantioinduction as long as the phospholane unit is chiral [182].

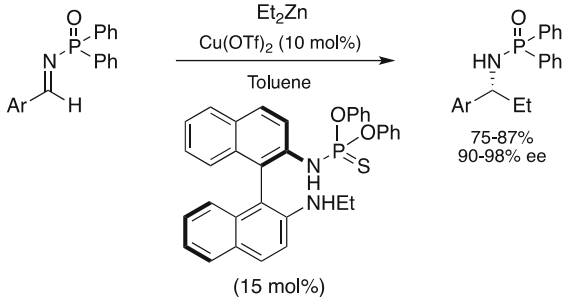
Alkyl-substituted *N*-phosphinoylimines are compatible electrophiles but it is preferable to use their air-stable *p*-toluenesulfinic acid adducts, which get converted to the corresponding imine under the reaction conditions (Scheme 12) [177]. This reaction is also possible with trifluoromethylketoimines as electrophiles, leading to good enantioselectivity for the corresponding *N*-phosphinoylamines (Scheme 12) [183, 184]. In all cases, the *N*-phosphinoyl group is cleaved under mild acidic conditions (HCl, MeOH).

A chiral binaphthylthiophosphoramide ligand also induces high enantioselectivity for this reaction with Et_2Zn and aromatic substrates (11) [185, 186] (for use of related ligands for similar reactions see [187, 188]):

Table 5 Cu-catalyzed enantioselective addition of diorganozinc reagents to *N*-sulfonylimines using chiral amido-phosphine ligands

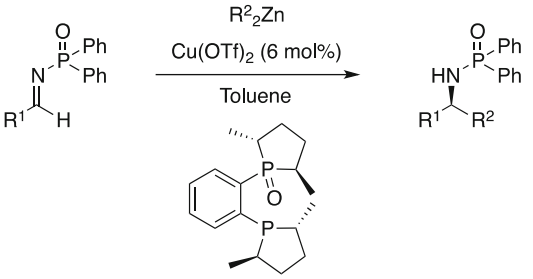


Entry	Ligand	R^1	R^2	Yield (%)	*ee* (%)
1		Ph	Et	98	93
2		Ph	Et	97	96
3		Ph	Et	96	88
4		Ph	Me	97	87
5		Ph	*i*-Pr	92	78
6		c-C_6H_{11}	Et	84	96
7		$Ph(CH_2)_2$	Et	69	93

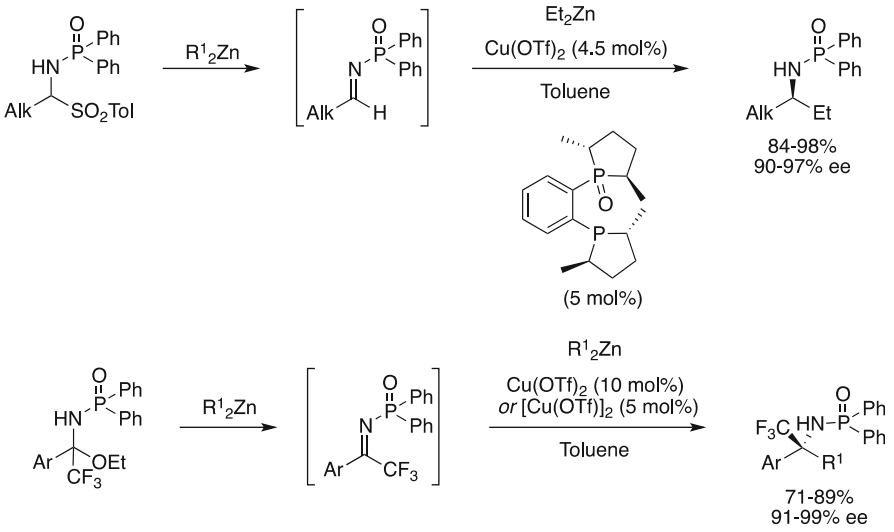


(11)

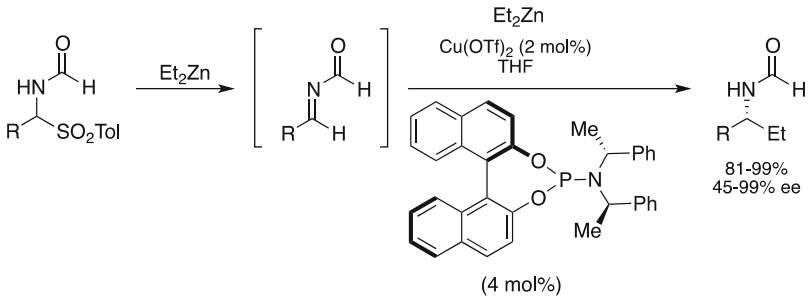
Table 6 Cu-catalyzed enantioselective addition of diorganozinc reagents to *N*-phosphinoylimines using Me-DuPHOS monoxide



Entry	R^1	R^2	Yield (%)	*ee* (%)
1	Ph	Et	96	98
2	1-Naphthyl	Et	96	97
3	2-Furyl	Et	97	96
4	*c*-C_3H_5	Et	95	94
5	Ph	Me	87	97
6	Ph	*i*-Pr	84	95
7	Ph	*n*-$C_{10}H_{21}$	73	97
8	Ph	TBSO-$(CH_2)_6$-	52	90



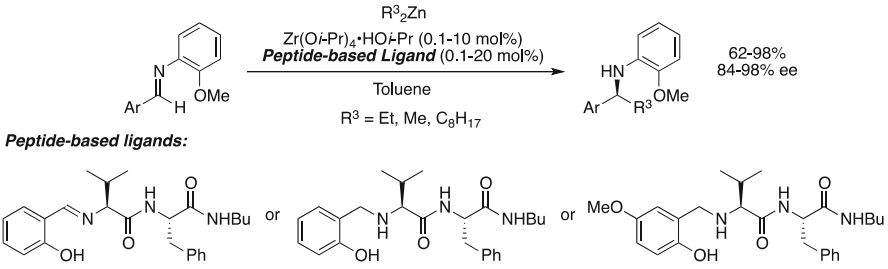
Scheme 12 Enantioselective addition reactions to *N*-phosphinoylimines



Scheme 13 Copper phosphoramide catalyzed dialkylzinc addition

N-Formylimines formed in situ from their corresponding sulfinic acid adducts are also good substrates for these reactions. A monodentate chiral phosphoramidite copper complex can catalyze the addition reaction, producing good enantiomeric excesses with aryl-substituted imines (Scheme 13) [189]. While all imine derivatives tested afforded high yield in this reaction, alkyl-substituted imines afforded only poor enantioselectivity (45–70% *ee*).

Early transition metal complexes derived from zirconium and hafnium are excellent catalysts for the addition of diorganozinc reagents to *N*-*o*-anisidylimines when peptide-based ligands are used [190–194]. Combinatorial screening of peptides led to the discovery that several chiral ligands in combination with $Zr(O\textit{i}\text{-}Pr)_4$ were effective at catalyzing this transformation (12):



(12)

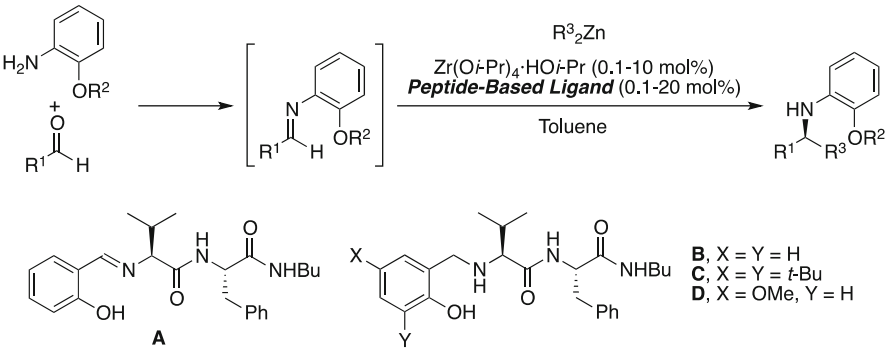
For alkyl-substituted imines, a three-component procedure was developed in which an in situ generation of the imine from the corresponding amine and aldehyde was necessary to get high yields and selectivities (Table 7).

The use of an analogous hafnium-based catalyst instead generally improves the yield while still affording high enantioselectivity (Scheme 14) [193].

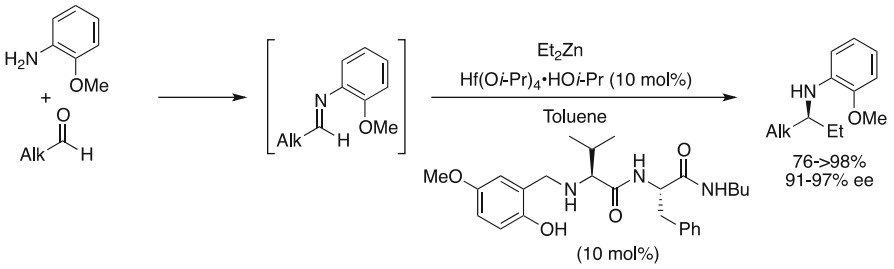
These reactions are also compatible with a variety of electron-poor ketoimine derivatives (13) [194].

The *N*-aryl group can be removed under oxidative conditions such as upon treatment with iodosobenzene diacetate or $AgNO_3/(NH_4)_2S_2O_8$.

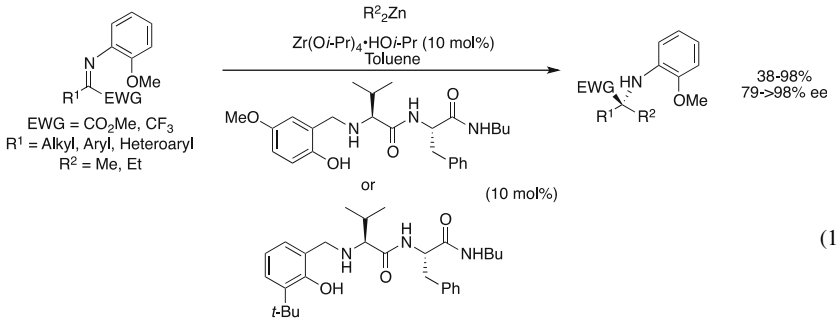
Table 7 Zr-catalyzed enantioselective addition of diorganozinc reagents to *N*-*o*-anisidylimines using peptide-based ligands



Entry	Ligand	R^1	R^2	R^3	Yield (%)	*ee* (%)
1	**A**	Ph	Me	Et	82	93
2	**A**	2-Furyl	Me	Et	87	97
3	**B**	Ph	Me	Me	79	88
4	**B**	Ph	Me	n-C_8H_{17}	63	98
5	**A**	3-Pyridyl	Me	Et	>98	85
6	**D**	n-C_4H_9	Me	Et	69	97
7	**D**	c-C_3H_5	Me	Et	83	98
8	**D**	Br-$(CH_2)_5$-	Me	Et	57	95
9	**C**	$TBSOCH_2CC$	Ph	Et	70	>98

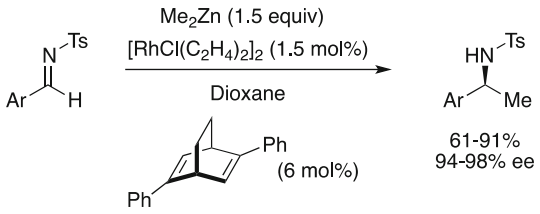


Scheme 14 Addition to *N*-arylimines



(13)

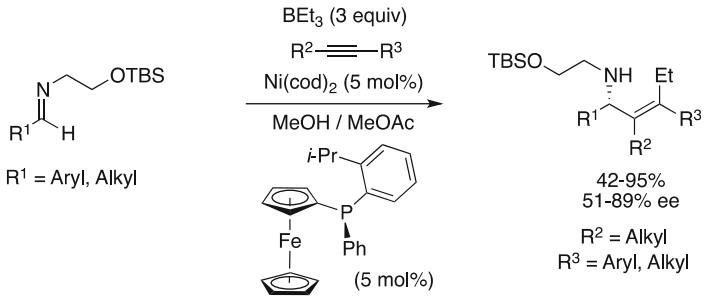
A rhodium-catalyzed dimethylzinc addition to *N*-tosylimine derivatives provides high yields and selectivities of the addition product (14) [195]:



(14)

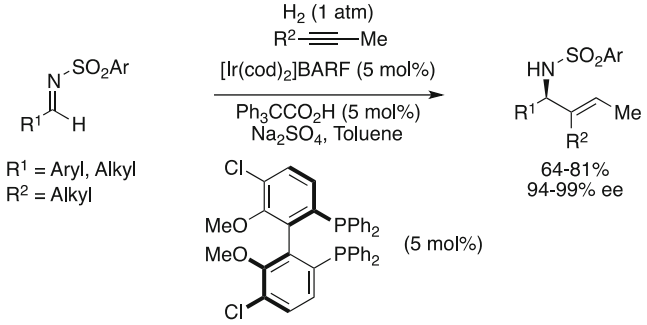
2.4.3 Addition of Alkenyl, Aryl, and Heteroarylmetals (sp^2 Carbon)

The generation of enantiomerically enriched allylic amines by the catalytic asymmetric addition of alkenylmetal to imine derivatives is an extremely important transformation. Since sp^2 hybridized carbon nucleophiles are less reactive than their sp^3 counterparts, one challenge associated with this process is the preparation of not only stereodefined vinylmetals but also those that will be reactive enough to undergo addition reactions with imines. A chiral Ni(0) catalyst can catalyze both, the carbometalation of an alkyne followed by its oxidative coupling with the imine leading to an enantioenriched allylic amine (15) [196, 197]. The process occurs with moderate to good enantioselectivity when a chiral phosphine is added to the reaction mixture:



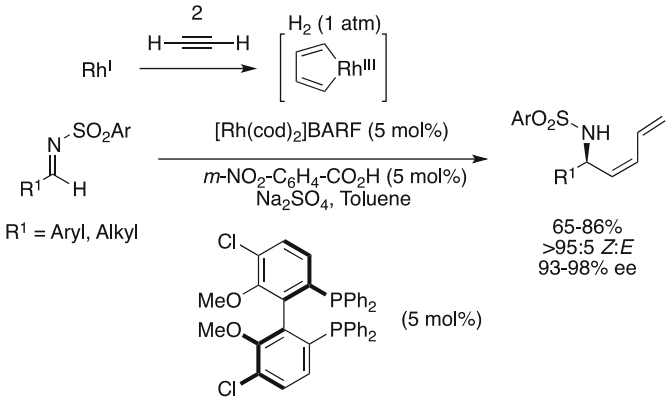
(15)

Alternatively, a chiral Ir(I) catalyst was also found to be competent in effecting an enantioselective oxidative coupling reaction, and the presence of H_2 terminates the catalytic cycle to lead to the synthesis of enantioenriched allylic amines (16) [198]:



(16)

An analogous Rh(I) catalyst allows the use of acetylene to generate a chiral *cis*-dienylmetal equivalent that is capable of undergoing a highly enantioselective alkenylation of *N*-sulfonylimines (17) [199]:



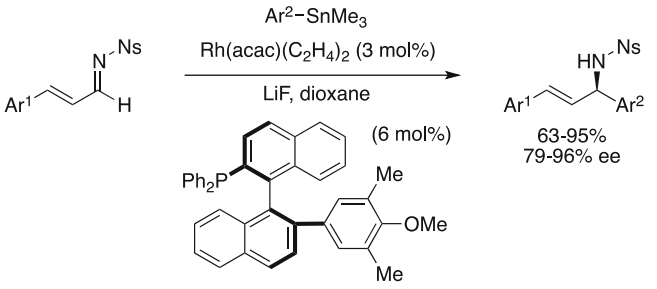
(17)

Vinylboronates can add to α-iminoester intermediates formed in situ through enantioselective organocatalysis with a chiral diol. A wide range of substituents on the amine or the alkenylboronate nucleophile are tolerated (Scheme 15) [200].

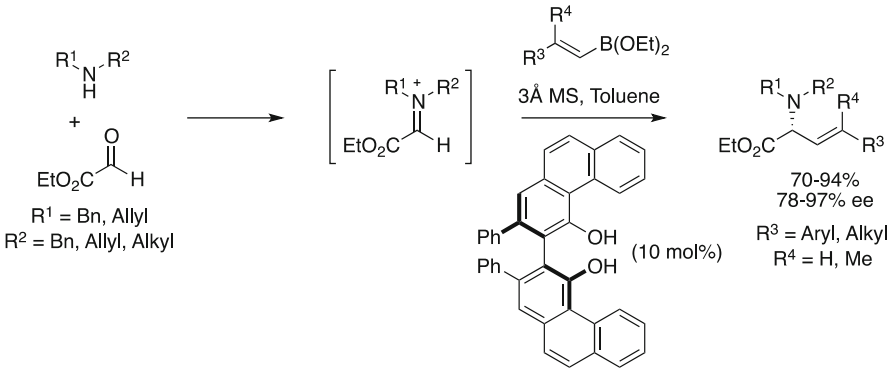
The catalytic asymmetric arylation of imines has emerged as one of the most powerful tools for the synthesis of the biologically important biarylmethylamine derivatives.

The Rh(I)-catalyzed enantioselective addition of arylmetal equivalents to *N*-sulfonylimines has become one the most powerful ways to effect this process. A wide variety of chiral phosphorus-based ligands have been tested for this reaction, and the most efficient methods are summarized in Table 8 [201–209]. Aryltitaniums, arylstannanes, arylboroxines, or arylboronic acid can be used as arylmetal equivalents added in stoichiometric amounts, usually with high yields and enantioselectivities.

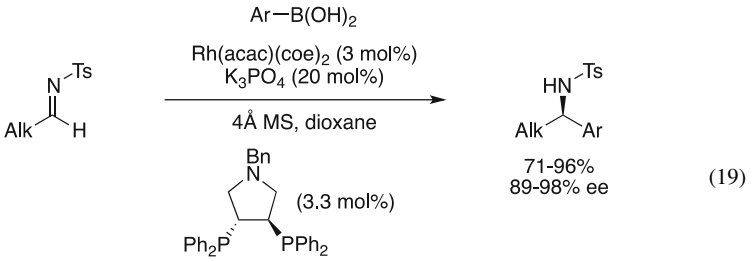
The Rh(I)-catalyzed enantioselective arylation of alkenylimines is also possible under similar conditions (18), and the enantioselective arylation of aliphatic *N*-tosylimines with arylboronic acids is highly efficient using a chiral bis(phosphine) (19). *N*-Boc imines can also be used effectively as electrophiles only if the sulfinate adduct is employed as substrate (20):



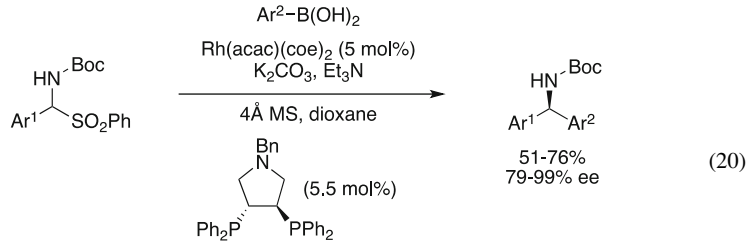
(18)



Scheme 15 Organocatalyzed vinylboronate addition reactions



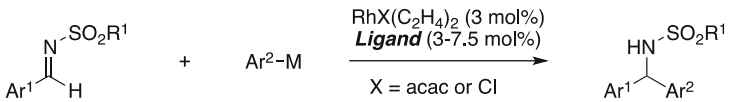
(19)

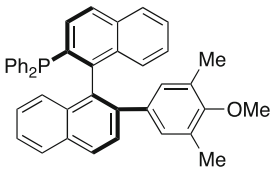


(20)

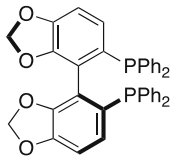
Chiral dienes have been found to be the most powerful ligands for the addition of boroxines to *N*-sulfonylimines, affording yields, enantiomeric excesses, and substrate generality superior to those of most of the other chiral ligands presented above. Selected examples are shown in Table 9 [210, 211].

Table 8 Rh(I)-catalyzed enantioselective arylation of *N*-sulfonylimines using chiral phosphine ligands

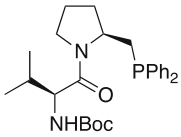




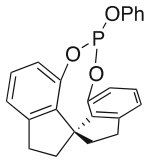
A



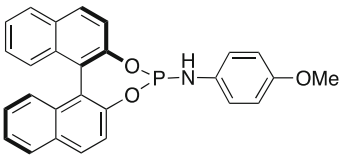
B



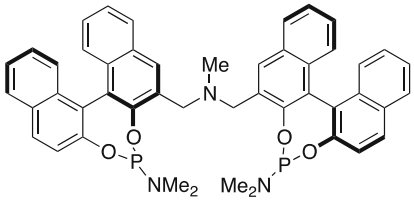
C



D



E



F

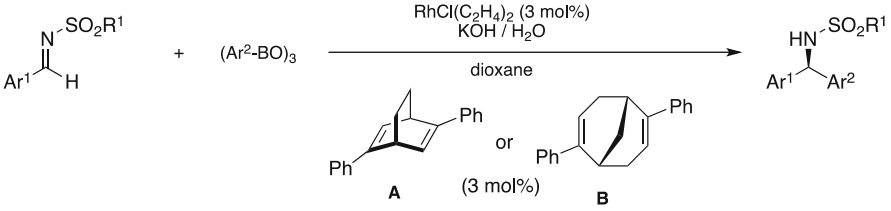
Entry	Ligand	Ar^1	Ar^2-M	R^1	Yield (%)	*ee* (%)	References
1	**A**	4-Cl-C_6H_4	Ph-$SnMe_3$	4-$NO_2C_6H_4$	83	92	[202]
2	**B**	4-Cl-C_6H_4	Ph-Ti(O*i*-Pr)$_3$	2,4,6-(*i*-Pr)$_3C_6H_4$	95	94	[203]
3	**C**	4-Me-C_6H_4	(4-$PhC_6H_4BO)_3$	4-MeC_6H_4	86	72	[204]
4	**D**	4-Cl-C_6H_4	Ph-$B(OH)_2$	4-MeC_6H_4	85	93	[205]
5	**E**	4-Cl-C_6H_4	Ph-$B(OH)_2$	NMe_2	95	95	[206]
6	**F**	4-Cl-C_6H_4	Ph-$B(OH)_2$	4-MeC_6H_4	98	95	[209]

2.4.4 Addition of Alkynylmetals (sp Carbon)

Early success in the enantioselective addition of alkynylmetal equivalents to imine derivatives to form these products in enantioenriched form was only possible using stoichiometric amounts of chiral reagents [212–215]. The synthesis of enantioenriched propargylamines by a catalytic asymmetric alkynylcopper addition reaction can be achieved by a three-component coupling, involving the reaction of an amine, an aldehyde, and a terminal alkyne with a chiral Cu catalyst (Scheme 16) [216–218] (for related methodologies see [219–225]). It is noteworthy that this transformation can be carried out either in toluene or in water with similar efficiency, and the reaction is also possible with preformed α-iminoesters as electrophiles.

Secondary amines, leading to iminium intermediates instead of active electrophiles, can also be used with copper catalysts derived from CuBr and several chiral

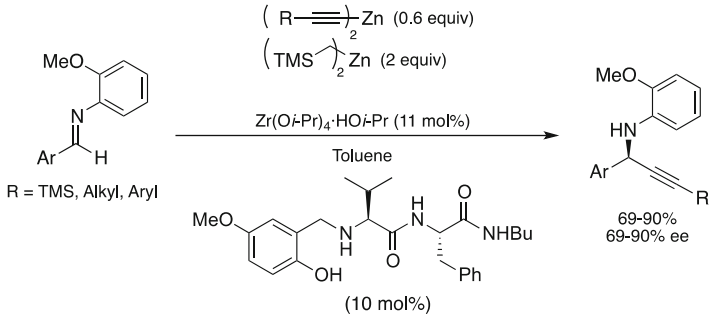
Table 9 Rh(I)-catalyzed enantioselective arylation of *N*-sulfonylimines using chiral diene ligands



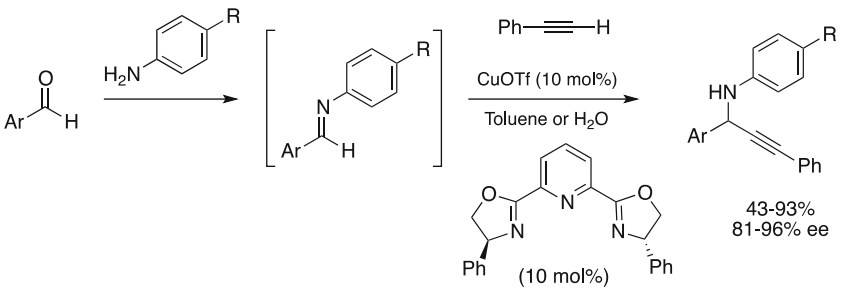
Entry	Ligand	Ar^1	Ar^2	R^1	Yield (%)	*ee* (%)
1	**A**	4-Cl-C_6H_4	Ph	4-Me-C_6H_4	96	98
2	**B**	4-Cl-C_6H_4	Ph	4-NO_2-C_6H_4	96	98
3	**A**	4-CF_3-C_6H_4	Ph	4-Me-C_6H_4	97	95
4	**B**	4-CO_2Me-C_6H_4	Ph	4-NO_2-C_6H_4	95	95
5	**A**	4-MeO-C_6H_4	Ph	4-Me-C_6H_4	96	99
6	**B**	4-MeO-C_6H_4	Ph	4-NO_2-C_6H_4	98	99
7	**A**	1-Naphthyl	Ph	4-Me-C_6H_4	95	98
8	**B**	1-Naphthyl	Ph	4-NO_2-C_6H_4	94	96
9	**A**	Ph	4-Cl-C_6H_4	4-Me-C_6H_4	99	99
10	**B**	Ph	4-Cl-C_6H_4	4-NO_2-C_6H_4	96	99
11	**A**	Ph	4-MeO-C_6H_4	4-Me-C_6H_4	97	96
12	**B**	Ph	4-MeO-C_6H_4	4-NO_2-C_6H_4	94	98

ligands, affording the propargylic amine in excellent enantioselectivity (Scheme 17) [226–234].

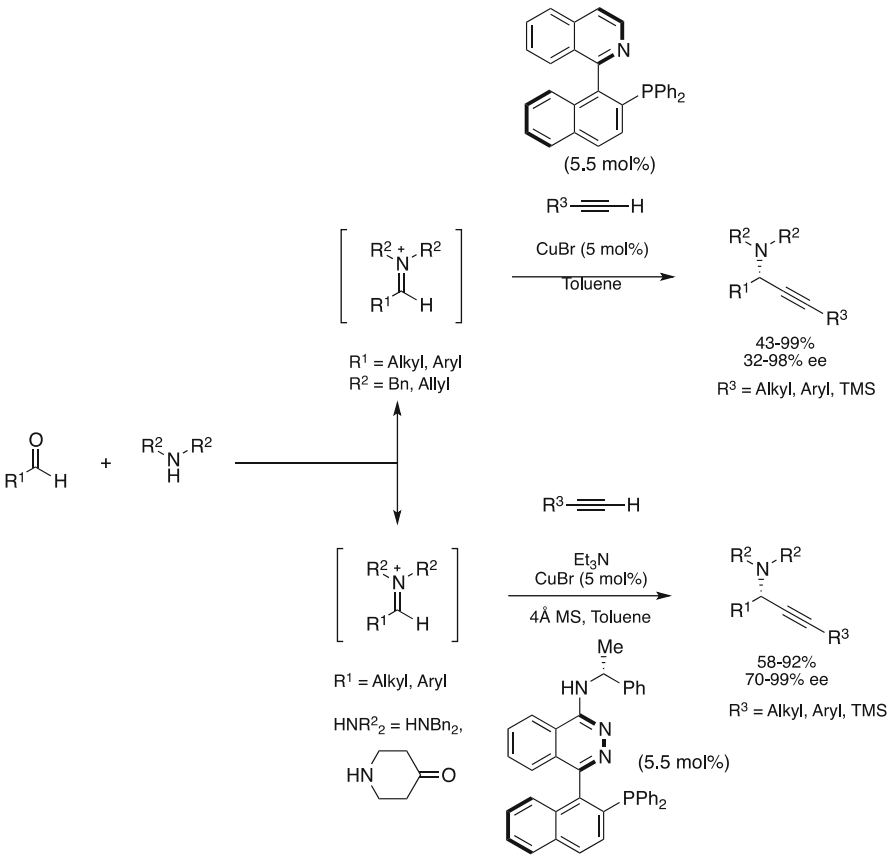
Chiral Zr-catalysts based on peptides can be used with mixed alkynylzinc reagents and *N*-anisidylimines to produce the aryl-protected propargyl amines in good yields and enantioselectivities (21) [235]:



(21)



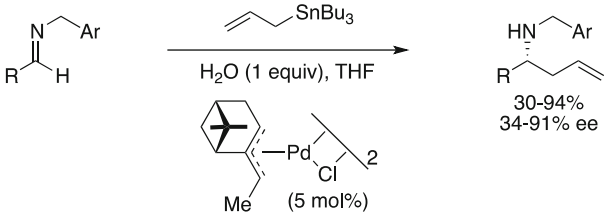
Scheme 16 Copper•pybox catalyzed alkynylation reaction



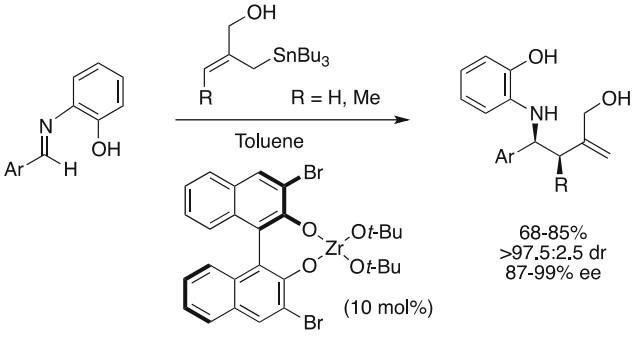
Scheme 17 Enantioselective copper-catalyzed alkynylation of iminium salts

2.4.5 Addition of Allylmetal

Allylmetal nucleophiles display a unique reactivity compared to other types of nucleophiles. If the metal bearing the allyl unit is Lewis acidic, the reaction can occur via an initial Lewis acid/Lewis base interaction followed by an allyl group transfer via a six-membered ring. Chiral Pd- and Zr-based chiral complexes are found to be highly efficient catalysts in the addition of various achiral allylstannanes to *N*-benzyl- and *N*-*o*-anisidylimines, respectively, in good enantioselectivity for aryl-substituted imines (22, 23) [236–241]. The allylstannane can be replaced with an allylsilane reagent with similar efficiency [237, 239], and the analogous carboethoxyallylation is also possible [240].



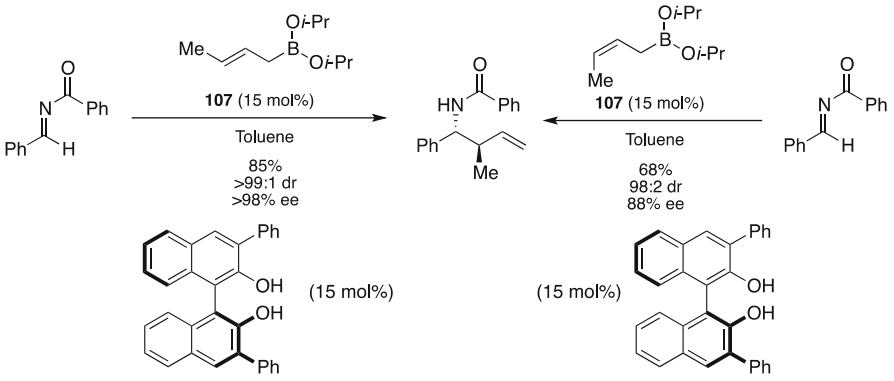
(22)



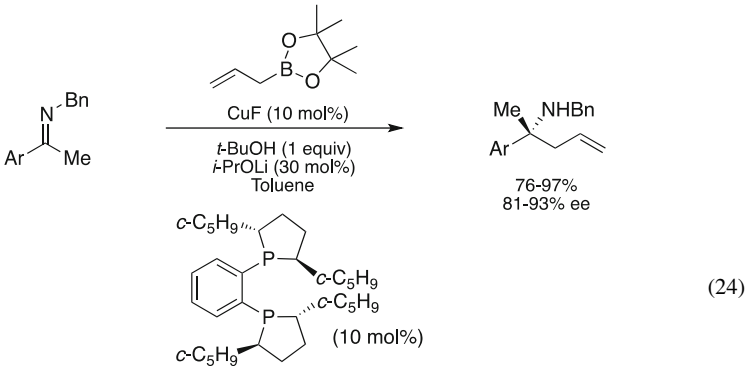
(23)

In addition to these methods, a few other enantioselective methods involving Zn- or Cu-based catalysts were developed for the addition of allylstannane and allylsilane nucleophiles to α-iminoesters, although the enantioselectivities of these processes are modest [242–244].

Allylboronates are found to be good nucleophiles in the enantioselective CuDuPHOS catalyzed allylation of *N*-benzylketoimine electrophiles (24) [245]. It is proposed that the fluoride counterion accelerates the transmetallation of the allyl group from the boronate species to produce the chiral allylcopper complex that later reacts with the imine.

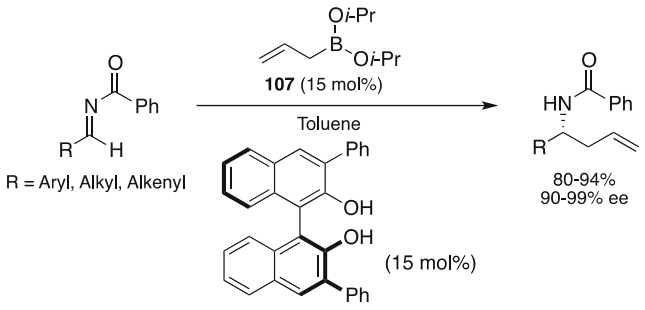


Scheme 18 Crotylation reactions of *N*-acylimines



(24)

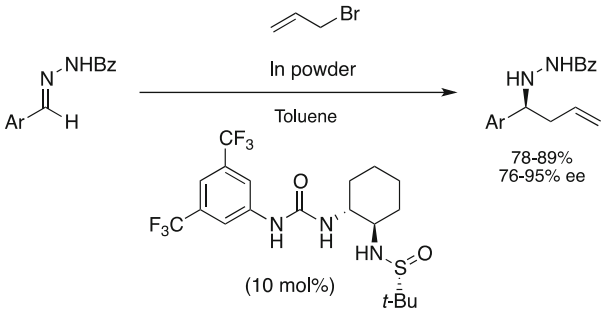
The organocatalyzed enantioselective allylboration of *N*-acylimines is possible with BINOL derivatives (25, Scheme 18) [246]. This reaction is believed to proceed via ligand exchange between an isopropoxy group of the allylboronate and BINOL, followed by allylboration of the imine activated through hydrogen bonding with the remaining free hydroxyl group of the organocatalyst:



(25)

The corresponding *cis*- and *trans*-crotylboronate reagents afford a high diastereo- and enantioselectivity in the process. Quite interestingly, the *anti* product is formed with both reagents. This is in sharp contrast with what is usually observed in uncatalyzed processes. A boat-type transition state is proposed to be favored when the *cis*-crotylboronate is employed, whereas the expected chair-like transition structure is postulated with the *trans*-isomer.

As previously discussed, allylindium species formed in situ from allyl bromide and In(0) are known to add efficiently to *N*-acylhydrazones. Chiral ureas, added in catalytic amounts, have been shown to activate the imine electrophile via hydrogen bonding and allowed for enantioinduction (26) [247]:



(26)

3 Conclusion

The section described above illustrated that the addition of nonstabilized nucleophiles to imine derivatives is one of the most reliable ways to form α-chiral amines. Although chiral auxiliary-based approaches are less atom-economic, they still constitute some of the most widely used methods for the synthesis of a variety of enantioenriched α-chiral amines. In the last decade, tremendous progress has been achieved in the field of asymmetric catalysis in general, and the knowledge acquired during that time is partly due to the continuous efforts devoted to the development of more efficient asymmetric addition reactions to imine derivatives. The catalytic enantioselective addition of sp^3, sp^2, or sp carbon-centered nonstabilized nucleophiles is now available for most nucleophiles (except acetylene) although addition reactions to ketoimine derivatives to generate tertiary carbinylamine still represent a considerable challenge in certain cases.

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