1
Stereoselective Synthesis of α-Branched Amines by Nucleophilic Addition of Unstabilized Carbanions to Imines

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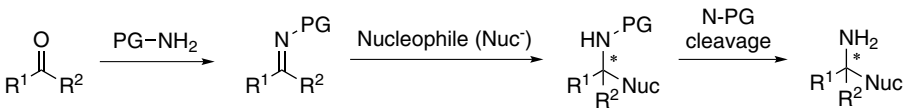
1.1
Introduction

Amines bearing a stereocenter α to the nitrogen atom are among the most commonly found subunits in bioactive molecules, natural products, and chiral ligands. As such, there has been much interest in developing methods for their synthesis. Of these methods, the addition of nonstabilized carbanions to activated imines constitutes one of the most reliable ways for synthesizing this important class of compounds [1, 2].

The preparation of α-branched amines from the corresponding carbonyl derivatives typically requires three steps: (1) imine formation; (2) nucleophilic addition; and (3) protecting or activating group (PG) cleavage (Scheme 1.1). Over the past 25 years, numerous variants of this process allowing the preparation of a large variety of substituted α-branched amines have been developed.



Scheme 1.1 Preparation of chiral amines from carbonyl derivatives.

As oxygen is more electronegative than nitrogen, *N*-alkyl-substituted imines are less electrophilic but more Lewis basic than their carbonyl counterparts. For this reason, only very reactive nucleophiles, such as organolithium [3], Grignard [4], organocuprate/BF_3 [3], and organocerium reagents [3], have been reported to react with *N*-alkyl imines (Scheme 1.2). Conversely, *N*-alkyl-substituted imines are usually the candidates of choice for Lewis acid-catalyzed processes, such as the Strecker reaction [5], Mannich condensation [6], and Ugi condensation [7].

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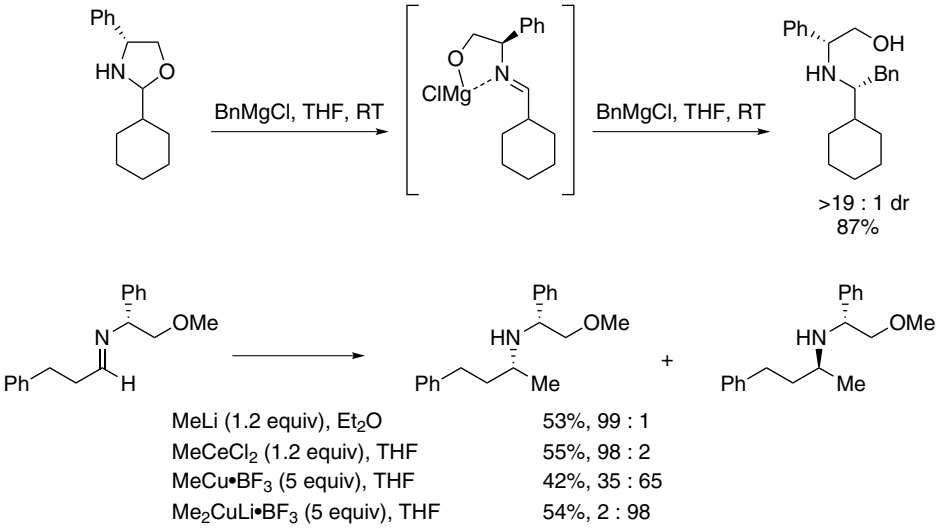


Scheme 1.2 Types of nucleophiles that add to *N*-alkyl-substituted imines.

The electrophilicity of these imines can be increased via the selection of an appropriate electron-withdrawing *N*-substituent, a strategy that has been quite important in increasing the scope of potential nucleophiles suitable for this chemistry. With the appropriate activating group (phosphinoyl, sulfonyl, etc.), Grignard reagents add smoothly in high yields to various imines. This method of activation is especially important in the catalytic asymmetric addition of nonstabilized carbanion reagents, where several activated imines have been reported. This modification opened the door to copper-, rhodium-, iridium-, and palladium-catalyzed nucleophilic addition chemistry. The increase in electrophilicity as a function of the electron-withdrawing ability of the activating group can be appreciated by comparing the *ab initio* calculations of the LUMO energy of various electrophiles to that of the imine derived from benzaldehyde and *N*-methylamine (Figure 1.1) [8]. These results suggest that *N*-acyl imines are substantially more electrophilic than the other types of imines bearing alkyl or aryl groups.

This chapter will discuss methods for the preparation of these electrophiles as well as their applications in various stereoselective transformations.

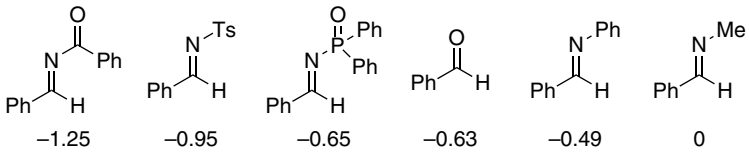
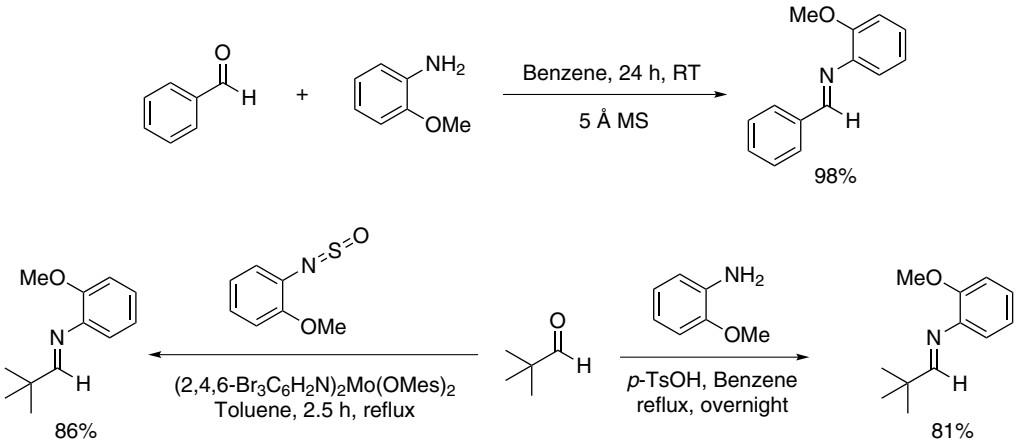


Figure 1.1 Calculations of the LUMO energy in eV (geometry optimized at B3LYP/6-31G(d)) relative to *N*-methyl imine derived from benzaldehyde.

1.2
Overview of the Methods for the Preparation of Imines

1.2.1
N-Aryl and *N*-Alkyl Imines and Hydrazones

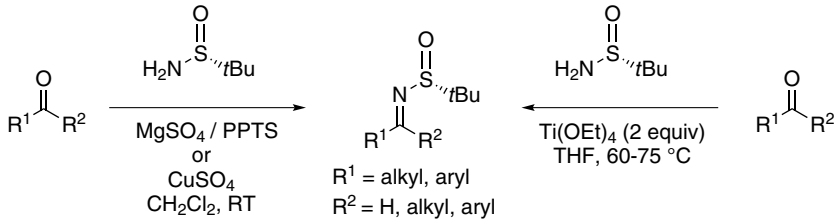
The method most commonly used for the preparation of imines derived from aldehydes and anilines [9], primary amines, or hydrazines [10] consists in mixing a nucleophilic amine with the corresponding carbonyl derivative under Dean–Stark conditions or in the presence of a dehydrating agent, such as magnesium sulfate or molecular sieves. For example, the preparation of the imine derived from benzaldehyde and *o*-anisidine is accomplished by stirring both reagents in benzene in the presence of molecular sieves (Scheme 1.3). Conversely, the imine derived from pivalaldehyde requires heating the reagents in benzene in the presence of a catalytic amount of *p*-TsOH. Alternatively, it is also possible to use *N*-sulfinyl amines as precursors to generate *N*-aryl imines [11].



Scheme 1.3 Preparation of *N*-aryl imines.

1.2.2
N-Sulfinyl Imines

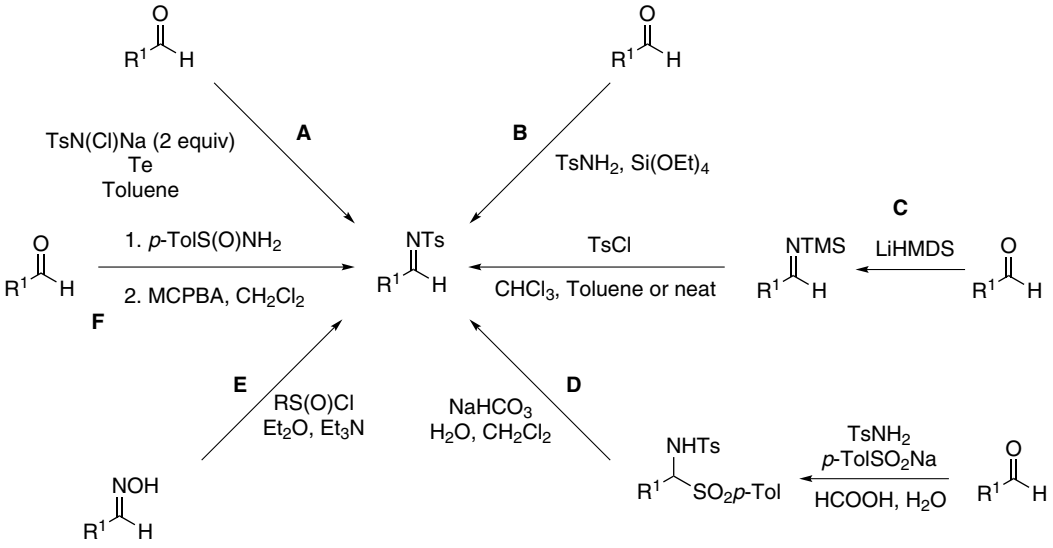
Although *N*-sulfinyl imines can be prepared by several other methods (oxidation of sulfenimines [12] and iminolysis of sulfinates [13]), they are most conveniently synthesized by condensing aldehydes with *tert*-butanesulfinamide in the presence of copper(II) sulfate or magnesium sulfate/pyridinium *p*-toluenesulfonate as a Lewis acid catalyst and water scavenger (Scheme 1.4) [14]. When ketones, more sterically hindered aldehydes or even electronically deactivated aldehydes are used, titanium tetraethoxide is the preferred Lewis acid and water scavenger. These methods are convenient to synthesize both alkyl- and aryl-substituted imines.



Scheme 1.4 Preparation of *N*-sulfinyl imines.

1.2.3
N-Sulfonyl Imines

A plethora of methods are available for the preparation of *N*-sulfonyl imines (Scheme 1.5). However, some are only compatible when R^1 is an aryl group or when the starting carbonyl compound is nonenolizable. Trost reported that aldehydes could be treated with the reagent obtained by mixing chloramine-T and tellurium to generate *N*-tosyl imines in high yields (method A) [15]. Alternatively, the direct condensation of an aldehyde and *p*-toluenesulfonamide is greatly facilitated by the addition of a strong Lewis acid, such as $TiCl_4$ [16] or $Si(OEt)_4$ [17] (method B). *N*-Sulfonylation of *N*-(trimethylsilyl) imines conveniently leads to *N*-tosyl imines when aryl-substituted aldehydes are used (method C) [18]. One of the most general methods compatible with both nonenolizable and enolizable aldehydes involves the initial formation of the sulfinic acid adduct of the imine from an aldehyde and *p*-toluenesulfinic acid formed *in situ* from formic acid and sodium benzene sulfinate

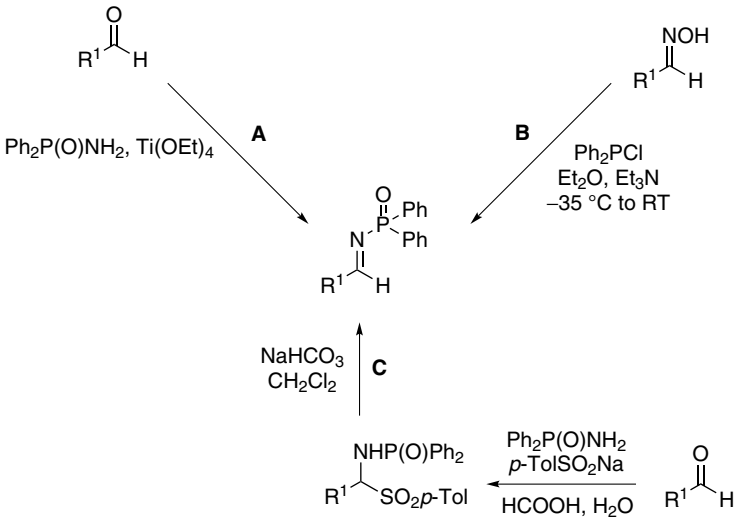


Scheme 1.5 Methods for the preparation of *N*-sulfonyl imines.

(method D) [19]. A subsequent base treatment generates the *N*-tosyl imines. Oximes can be treated with a sulfinyl chloride and undergo the Hudson reaction to generate the *N*-tosyl imine (method E) [20]. Finally, it is also possible to initially prepare the *N*-sulfinyl imine from the more nucleophilic sulfinamide and oxidize it with MCPBA to generate the *N*-tosyl imine (method F) [21]. Along method D, this route is the most effective in generating *N*-tosyl imines derived from either enolizable or nonenolizable aldehydes.

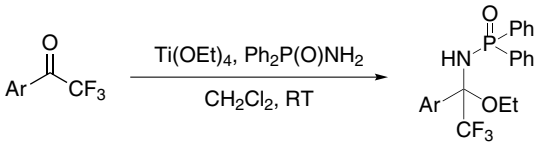
1.2.4
N-Phosphinoyl Imines

Although *N*-phosphinoyl imines can be prepared by most of the methods applied in the synthesis of *N*-tosyl imines, the most commonly used methodologies are illustrated in Scheme 1.6. The direct condensation of diphenylphosphonamide with an aldehyde is efficient in the presence of a titanium Lewis acid that also acts as a water scavenger (method A) [16]. The carbonyl moiety can also first be treated with hydroxylamine to generate the corresponding oxime, which is then treated with chlorodiphenylphosphine. The *O*-phosphinoyl oxime undergoes a spontaneous N−O bond homolytic cleavage followed by a radical pair recombination to yield the corresponding *N*-phosphinoyl aldimine (method B) [22]. One of the most reliable procedures for generating *N*-diphenylphosphinoyl imines from enolizable and nonenolizable aldehydes is a two-step sequence involving the initial formation of the *p*-toluenesulfinic acid adduct of the imine (method C) [23, 24], and subsequent base treatment leads to the readily isolable imine. Depending on the structure of the imine and the reaction in which it is used, it is sometimes possible to use the sulfinic acid adduct directly in the nucleophilic addition reaction.



Scheme 1.6 Most widely described methods for the preparation of *N*-phosphinoyl imines.

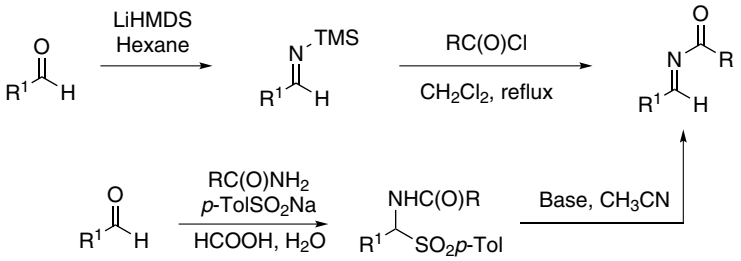
The Kresze reaction has also been used in the synthesis of *N*-phosphinoyl imines derived from nonenolizable aldehydes, although usually in modest yields [25, 26]. The *N*-phosphinoyl imine derived from trifluoromethyl ketones can be prepared via the ethanolate intermediate (Scheme 1.7) [27]. This adduct is directly used in the subsequent nucleophilic addition reaction.



Scheme 1.7 Preparation of trifluoromethyl-substituted ketimines via the ethanolate adduct.

1.2.5
N-Acyl and *N*-Carbamoyl Imines

N-Acyl imines can be achieved from nonenolizable aldehydes by the formation of *N*-silyl imines obtained through treatment of the carbonyl derivative with lithium hexamethyldisilazide [28]. The resulting *N*-silyl imines can be reacted with an acylchloride to generate the corresponding *N*-acyl imines. Due to the instability of the latter imines, they must be reacted directly with a nucleophile without further purification (Scheme 1.8). In addition, it is also possible to prepare *N*-acyl and *N*-carbamoyl imines via the following two-step sequence [29]. The treatment of an aldehyde with the corresponding amide in the presence of an arenesulfinic acid and formic acid in water generates the corresponding α-acyl [30] or α-carbamoyl sulfone [31]. Subsequent basic treatment leads to *N*-acyl or *N*-carbamoyl imines.



Scheme 1.8 Preparation of *N*-acyl imines from nonenolizable aldehydes.

1.3
Chiral Auxiliary-Based Approaches

The nucleophilic addition to imines bearing a chiral auxiliary is an extremely reliable, efficient, and powerful strategy to generate α-branched amines [32]. Imines are structurally unique, as the chirality can reside on either terminus of the imine double bond (Figure 1.2). Both strategies are complementary and will be reviewed separately in the following two sections.

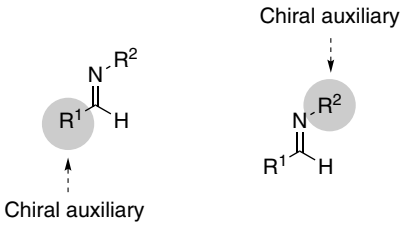
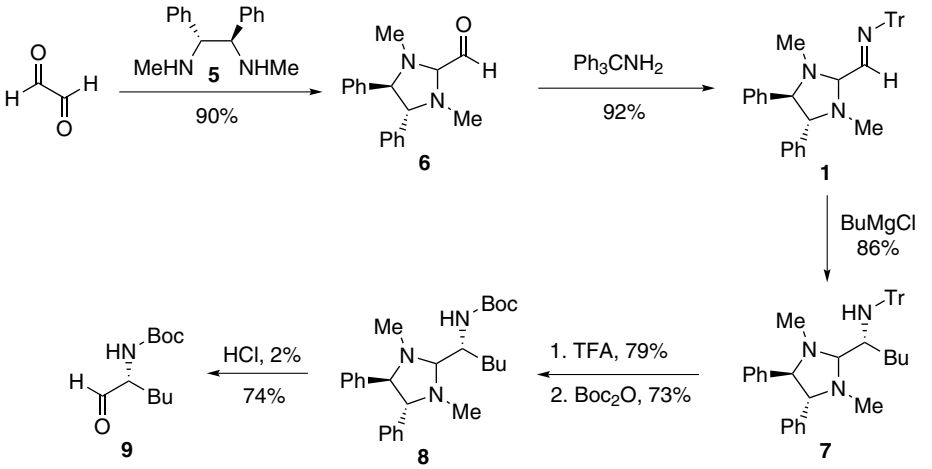


Figure 1.2 Complementary approaches for the incorporation of a chiral auxiliary.

1.3.1
Imines Derived from Chiral Aldehydes

Masked forms of the monoimine from glyoxal have been extensively used as chiral precursors to α-amino acids and α-amino aldehydes (Figure 1.3) [33]. For example, glyoxal can be converted into aminal **6** in 90% yield upon treatment with diamine **5** (Scheme 1.9) [33b]. Imine formation, followed by Grignard addition, leads to amine **7** in 86% yield as a single diastereomer. Acid hydrolysis affords the α-amino aldehyde **9** in good yields.



Scheme 1.9 Preparation of α-amino aldehydes from glyoxal.

An alternative strategy to the recoverable chiral auxiliary utilizes chiral α-hydroxy aldehydes as starting materials. For example, 2,3-di-*O*-benzyl-D-glyceraldehyde (**10**) is converted to the imine **11** (Scheme 1.10) [33e] and treatment with phenylmagnesium bromide leads to amine **12** as a single diastereomer. Phenylglycine **14** is obtained following protecting group cleavage and oxidation of the resulting diol.

Reports of diastereoselective additions to chiral ketimines are much more rare. One example describes the sequential addition of two different nucleophiles (Grignard and organocerium reagents) to the tartaric acid-derived nitrile **15** (Scheme 1.11) [34]. The second addition proceeds with good yields and excellent

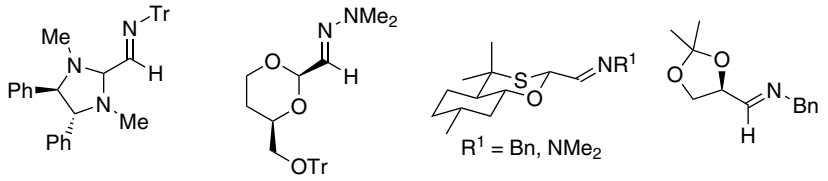
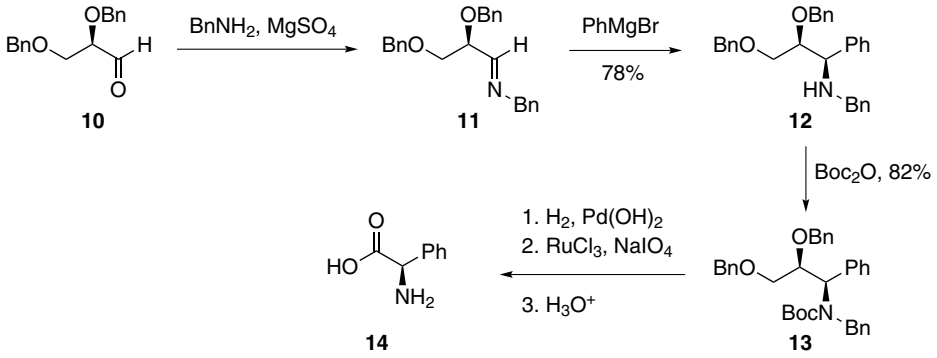
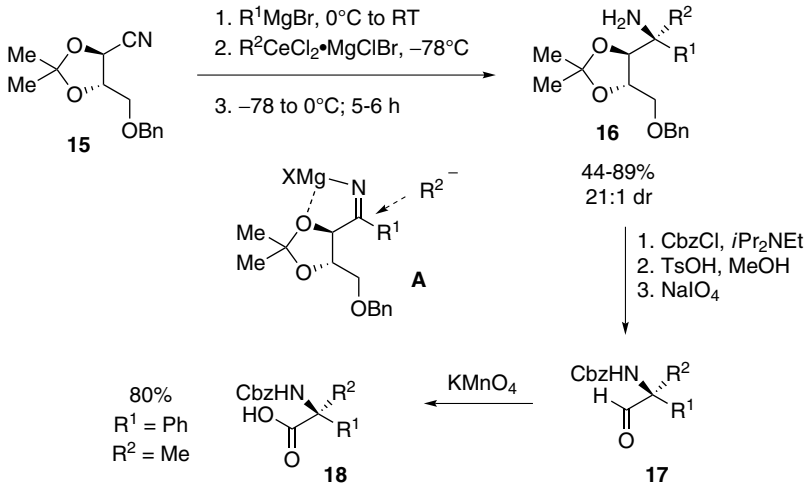


Figure 1.3 Selected chiral imines derived from glyoxal (**1**–**3**) and chiral α-hydroxyaldehydes **4**.



Scheme 1.10 Preparation of α-amino acids from protected glyceraldehyde.



Scheme 1.11 Sequential diastereoselective addition to chiral nitriles.

diastereocontrol that can be explained through nucleophilic addition from the least hindered face of the postulated magnesium chelate **A** (Scheme 1.11). The reaction products are converted into α,α-disubstituted α-amino aldehydes and α,α-disubstituted α-amino acids [35].

1.3.2
Imines Bearing a Chiral Protecting/Activating Group

One of the most practical methodologies used to generate α-branched amines relies on the stoichiometric use of covalently bonded chiral auxiliaries on the nitrogen substituent. As such, a large number of chiral amines have been applied toward the generation of chiral imines suitable for nucleophilic addition chemistry (Figure 1.4).

The imine **19** derived from α-phenylethylamine has been reported to react with various nucleophiles, such as organolithium reagents and cuprates, to generate the diastereoenriched amine following hydrogenolysis (H_2/Pd) of the chiral auxiliary. However, the diastereoselectivities of these reactions are typically modest [36–38]. The seminal works of Takahashi [39] and later Pridgen [40] demonstrated that higher

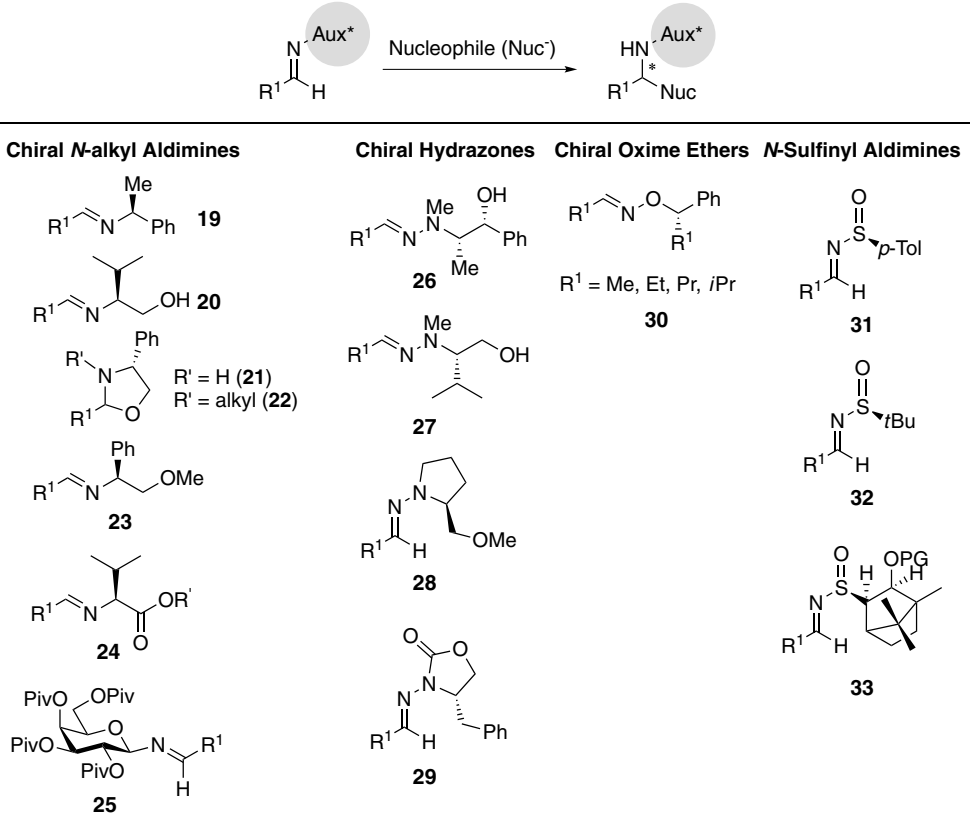
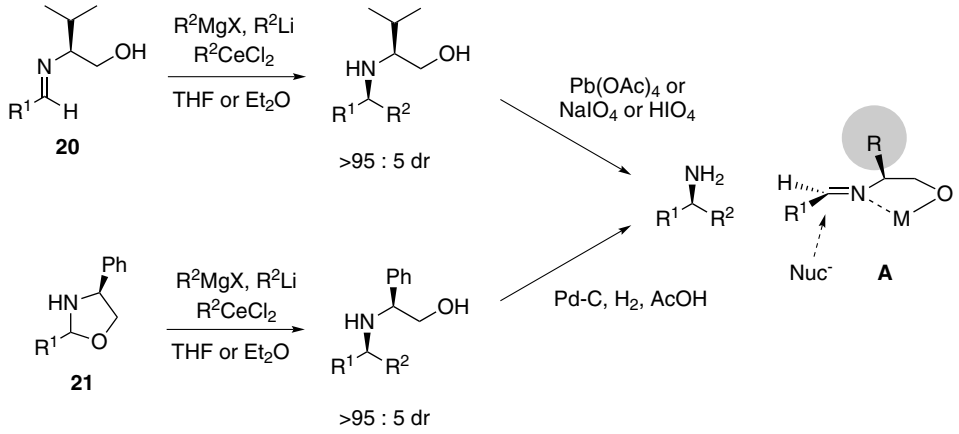


Figure 1.4 Some chiral auxiliaries for the nucleophilic addition to imines.

diastereoselectivities are observed when Grignard, organolithium, allylzinc halides, or organocerium reagents are added to the imine **20** or the oxazolidine **21** bearing a chiral auxiliary derived from either valine or phenylglycine (Scheme 1.12). The imine derived from phenylglycinol spontaneously cyclizes to the oxazolidine **21** upon formation. Further treatment of **21** with excess Grignard or organolithium reagent induces the ring opening to generate a chelated imine–metal alkoxide intermediate (**A**, Scheme 1.12) that undergoes the nucleophilic addition to yield the desired product. In addition, high diastereocontrol is observed with *N*-alkylated oxazolidines (**22**). The cleavage of the auxiliary is achieved through either hydrogenolysis conditions (phenylglycinol auxiliary) or oxidative conditions (valinol or phenylglycinol auxiliaries). Other chiral moieties, such as the imine **23** bearing an amino ether chiral auxiliary, have been developed that behave in a similar fashion [3]. Several other chiral auxiliaries bearing ester groups (**24** [41] and **25** [42]) have been reported, although the scope is typically limited to allylation reactions.

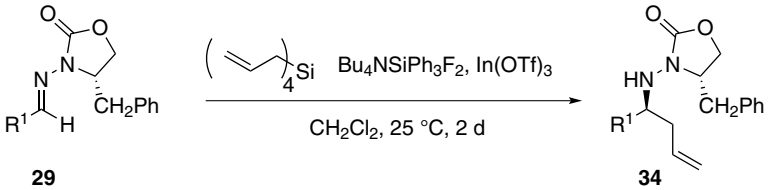


Scheme 1.12 Takahashi's valinol and phenylglycinol chiral auxiliaries.

Hydrazones derived from chiral hydrazines have also been applied as auxiliaries for the nucleophilic addition chemistry. Takahashi [43] reported that chiral hydrazones prepared from L-ephedrine (**26**) and L-valinol (**27**) react with Grignard reagents with good to excellent diastereoselectivities. Following the addition, the N−N bond cleavage can be achieved by hydrogenolysis (H_2, Pd). Both RAMP and SAMP hydrazines [44] have been developed and used by the Enders [45] and Denmark [46] groups as hydrazone **28** precursors. These groups have demonstrated that both organolithium reagents and organocerium reagents (prepared from Grignard or organolithium reagents) can be added to the hydrazone in high yields and excellent diastereocontrol. The cleavage of the N−N bond is accomplished either with hydrogenolysis, with H_2/Raney Ni, or with radical cleavage by lithium in ammonia.

Friestad's auxiliary **29** has been applied in diastereoselective indium(III) triflate-mediated allylation reactions with tetraallylsilane (Table 1.1) [47, 48]. The reaction proceeds with high diastereocontrol with imines derived from aryl-substituted

Table 1.1 Diastereoselective allylation of hydrazone **29**.



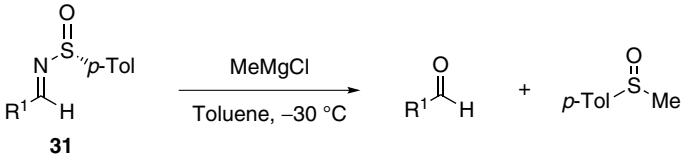
29 **34**

R^1	Yield (%)	dr
p-Tolyl	94	98 : 2
m-Nitrophenyl	71	>99 : 1
2-Naphthyl	82	98 : 2
2-Furyl	58	96 : 4
Phenyl	78	>99 : 1
(*E*)-PhCH=CH	60	95 : 5
Et	51	82 : 18

aldehydes. The reductive cleavage of the N−N bond is accomplished upon treating the resulting product with samarium diiodide.

Several oxime ethers (i.e., **30**) have been used as chiral auxiliaries; however, the diastereoselectivities for the nucleophilic addition reactions are usually modest [49].

Chiral *N*-sulfinyl imines **31**–**33** are among the most popular and widely used chiral auxiliaries in the preparation of α-branched amines. Although the *p*-tolylsulfinyl group **31** has been sporadically used for the addition of Grignard reagents, the transformation generally suffers from an important side reaction resulting from an undesired attack of the nucleophile on the electrophilic sulfur atom [50] (Scheme 1.13).

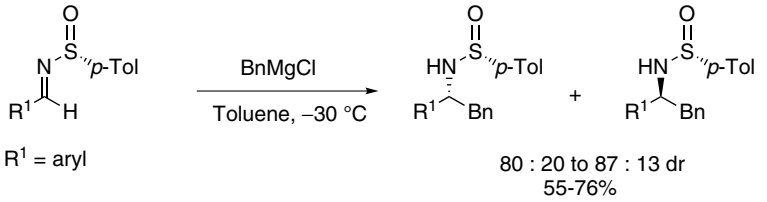


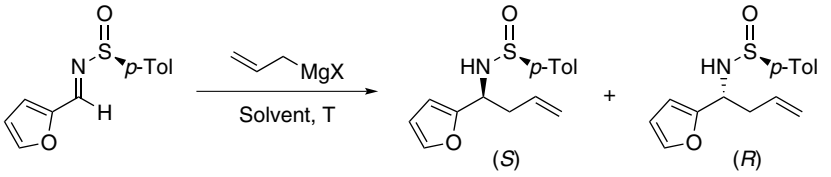
31

Scheme 1.13 Addition of methylmagnesium chloride to *N*-sulfinyl imines.

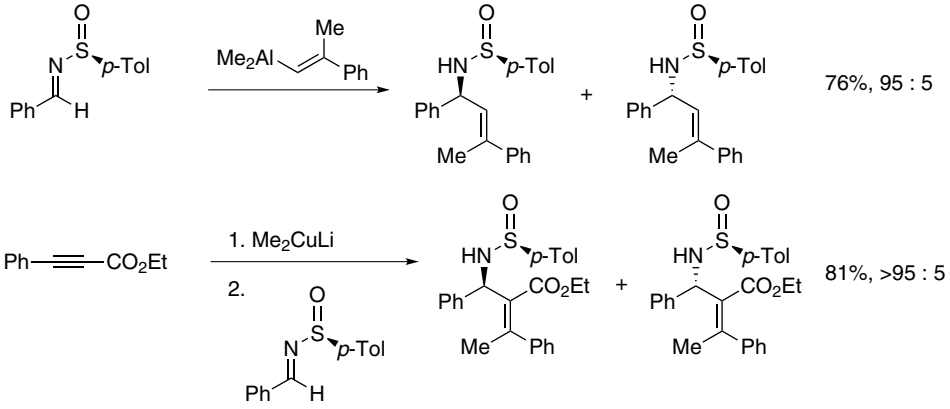
As seen in Scheme 1.14, exceptions to this are when benzyl- [50], allylmagnesium chloride [51], vinylaluminum [52, 53], or vinylcopper reagents are used as nucleophiles [54].

The *N*-*tert*-butanesulfinyl chiral auxiliary **32** has become the reagent of choice for the preparation of α-branched amines due to its excellent level of diastereocontrol and the fact that the steric hindrance caused by the *tert*-butyl group aids in the minimization of side reactions [32d]. The preparation of this chiral auxiliary in enantiomerically pure form is easily achieved in two steps and 65% overall yield starting from di-*tert*-butyl disulfide (Scheme 1.15) [55]. The nucleophilic addition of

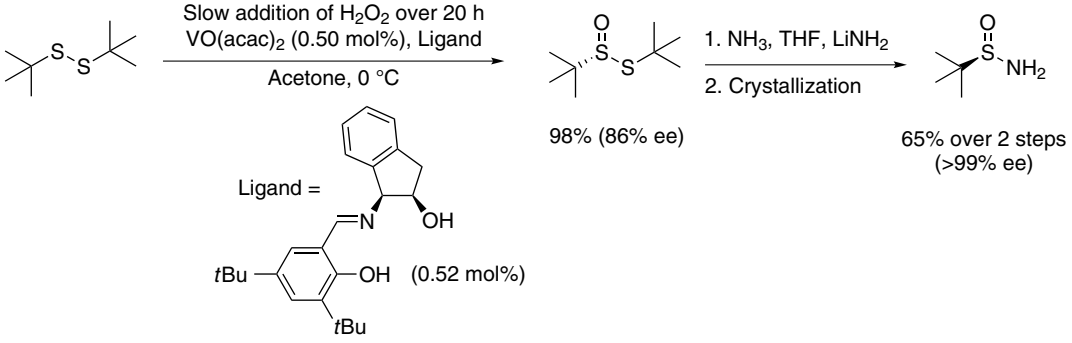




X	Additive	Solvent	T	Yield [%]	dr [(*S*) : (*R*)]
Br	—	CH_2Cl_2	−78 °C	98	9 : 91
Cl	BF_3•OEt_2	Et_2O	−78 to −40 °C	83	>99 : 1

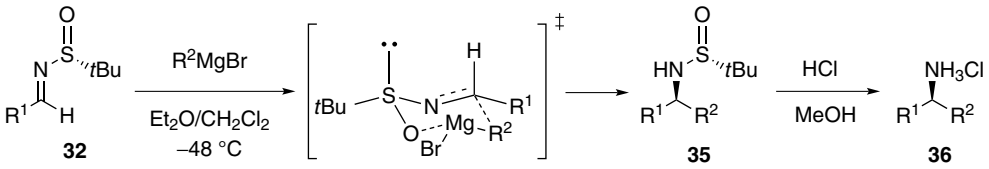


Scheme 1.14 Allylation, benzylation, and alkenylation of *N*-sulfinyl imines.



Scheme 1.15 Preparation of *tert*-butanesulfinamide.

Table 1.2 Diastereoselective addition to *N-tert*-butanesulfinyl imines derived from aldehydes.

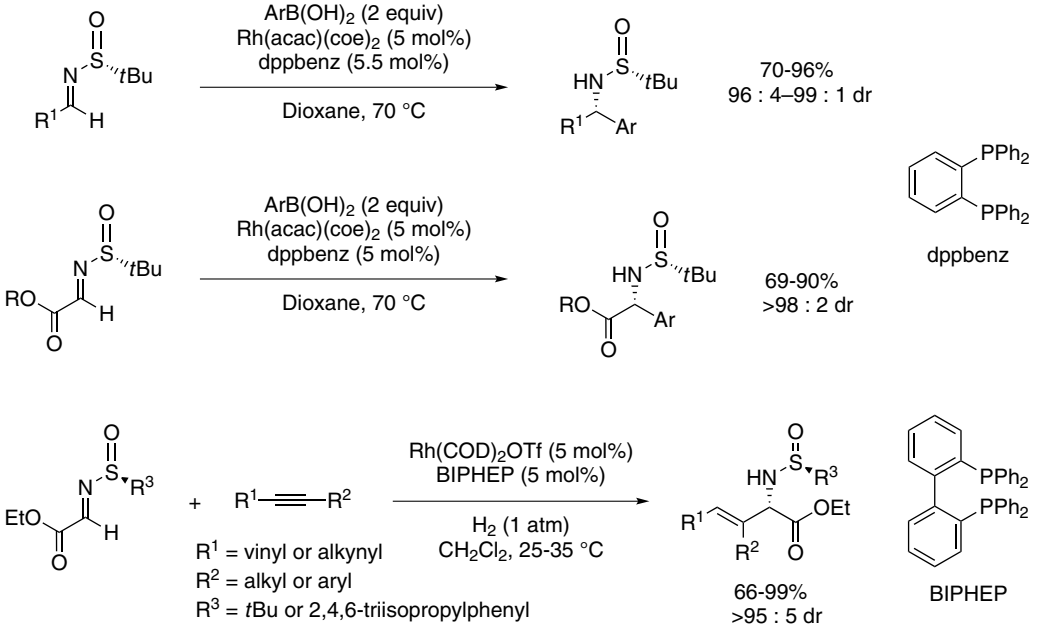


Entry	R^1	Nucleophile	Yield 35 (%)	dr	Yield 36 (%)
1	Et	MeMgBr	96	93 : 7	97
2	Et	*i*PrMgBr	97	98 : 2	92
3	Et	PhMgBr	>98	96 : 4	90
4	*i*-Pr	MeMgBr	97	98 : 2	97
5	*i*-Pr	EtMgBr	>98	97 : 3	93
6	*i*-Pr	PhMgBr	98	89 : 11	91
7	*i*-Pr	VinylMgBr	90	88 : 12	78
8	Ph	MeMgBr	96	97 : 3	88
9	Ph	EtMgBr	98	92 : 8	94
10	Ph	*i*PrMgBr	29	—	—
11	Ph	VinylMgBr	79	94 : 6	93
12	Bn	MeMgBr	89	95 : 5	95
13	Bn	EtMgBr	85	92 : 8	98
14	Bn	VinylMgBr	81	91 : 9	97
15	Bn	PhMgBr	81	95 : 5	99
16	*p*-MeOPh	EtMgBr	88	99 : 1	>98
17	*p*-MeOPh	PhCCLi	93	98 : 2	—
18	*p*-MeOPh	TMSCCLi	75	98 : 2	—
19	*p*-MeOPh	*n*BuCCLi	88	94 : 6	—
20	*n*-Bu	PhCCLi	76	97 : 3	—

Grignard reagents to these imines proceeds very efficiently and generally with high diastereocontrol [56]. The reaction is thought to proceed via the chair transition-state intermediate depicted in Table 1.2, in which the Lewis acidic magnesium atom is believed to activate the imine. In addition, cleavage of the chiral auxiliary occurs under mild acidic conditions to generate α-branched amines **36** [57]. It is also possible to add sp^2 hybridized carbanions (see Table 1.2, entries 3, 6, 7, 11, 14, and 15) [58] as well as substituted lithium acetylides to these chiral electrophiles with high diastereocontrol (Table 1.2, entries 17–20) [59, 60].

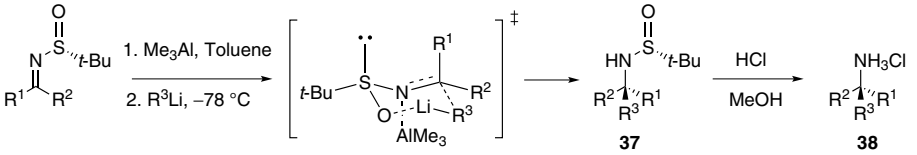
Imines derived from *N-tert*-butanesulfinamide also undergo diastereoselective rhodium(I)-catalyzed addition of arylboronic acids [61] (Scheme 1.16), a reaction that has been primarily developed for catalytic asymmetric processes (see below).

The hydrogenation of 1,3-enynes or 1,3-diynes in the presence of *N*-sulfinyl-iminoesters enables highly regio- and stereoselective reductive coupling to afford diene- and enyne-containing α-amino acid esters [62]. The reaction has been extended to include ketimines used in the synthesis of tertiary carbinamines [63] with excellent diastereoselection (Table 1.3) [64, 65]. As with the aldimines, one key



Scheme 1.16 Rhodium(I)-catalyzed arylboronic acid diastereoselective addition.

Table 1.3 Diastereoselective addition to *N*-sulfinyl ketimines.

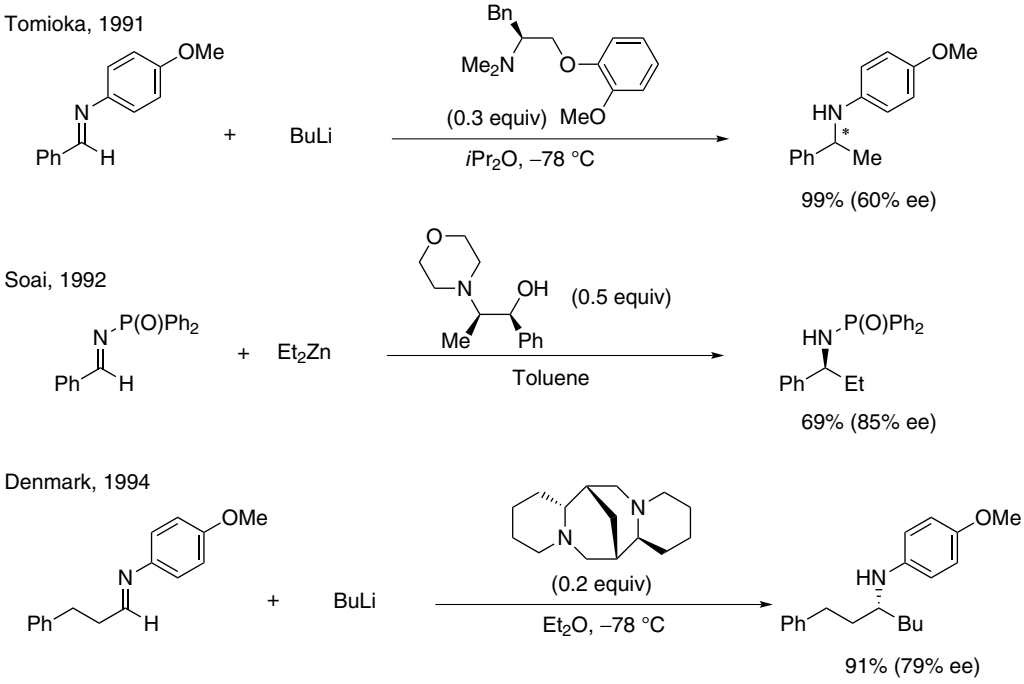


Entry	R^1	R^2	R^3Li	Yield **37** (%)	dr
1	Me	*i*-Pr	BuLi	61	99 : 1
2	Me	*i*-Pr	PhLi	93	97 : 3
3	Bu	*i*-Pr	MeLi	82	91 : 9
4	Bu	*i*-Pr	PhLi	82	91 : 9
5	Me	Ph	BuLi	86	98 : 2
6	Me	Bu	PhLi	93	89 : 11
7	Me	*i*-Bu	PhLi	62	85 : 15
8	Me	2-Naphthyl	PhLi	62	99 : 1
9	Bu	Ph	MeLi	>98	99 : 1
10	Me	Ph	AllylMgBr (no $AlMe_3$)	85	>99 : 1
11	Me	*i*-Pr	AllylMgBr (no $AlMe_3$)	93	>95 : 5
12	Me	*i*-Pr	*n*-PrCCLi	71	>99 : 1
13	Me	*t*-Bu	TMSCCLi	81	>99 : 1

feature of this methodology is the ability to generate the starting imine as a major diastereomer. The reaction can also be applied to the preparation of α,α-dibranched propargylamines (Table 1.3, entries 12 and 13) [66].

1.4
Catalytic Asymmetric Nucleophilic Addition to Achiral Imines

The first catalytic asymmetric addition of organolithium reagents to imines in the presence of a chiral amino alcohol was reported by Tomioka in 1991 (Scheme 1.17) [67]. This report was quickly followed by Soai [68], who showed that a chiral amino alcohol can also be used in the nucleophilic addition of diorganozinc to *N*-diphenylphosphinoyl imines. Four years after Tomioka's seminal report, Denmark disclosed that sparteine [69] and bisoxazolines [70] can be used in catalytic amounts in the transfer of organolithium reagents to *N*-aryl imines. All three approaches are founded on the concept that the chiral ligand RMet complex should be more reactive than the corresponding uncomplexed organometallic reagent. These initial results provided the foundation for the development of new, effective, and more practical methods for the transition metal-catalyzed asymmetric alkylation of imines, which will be discussed in the following sections.



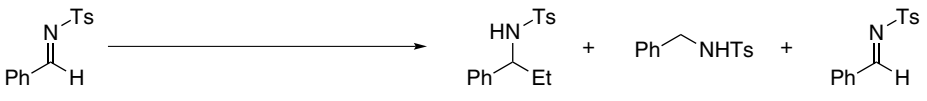
Scheme 1.17 Initial reports of the catalytic asymmetric addition of organometallic reagents to achiral aldimines.

1.4.1 Catalytic Asymmetric Addition of sp^3 Hybridized Carbanions

Several transition metal-based catalysts have been developed for the addition of sp^3 hybridized carbanions to imines (Cu, Zr/Hf, Ti, Zn, and Rh). Since most of these reactions are mechanistically different, they will be addressed separately.

1.4.1.1 Copper-Catalyzed Dialkylzinc Additions

The breakthrough for the efficient development of a catalytic asymmetric addition of nucleophiles to imines was first made by Tomioka [71], when he reported that the conditions developed by Feringa and Alexakis for conjugate addition chemistry [72] were very effective in minimizing background reactions observed with uncatalyzed nucleophilic additions to the imine (Scheme 1.18). Treatment of **39** with diethylzinc in toluene leads to a mixture of the starting material (50%), the ethyl addition product **40**, and the reduction product **41**. The addition of copper(II) trifluoromethanesulfonate triphenylphosphine complex improves the yield of **40**, while minimizing the yield of the reduced imine **41**. The substitution of triphenylphosphine with chiral ligands **42**–**44** provided excellent yields and selectivities for the addition of diethylzinc to *N*-tosyl imines (Table 1.4).



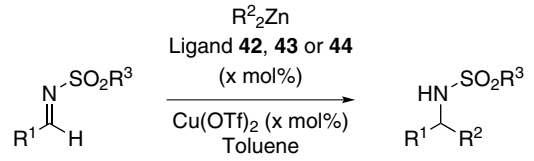
39 **40** **41** **39**

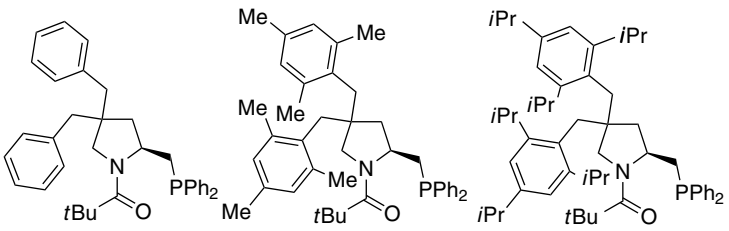
Et_2Zn, Toluene, 0 °C, 4 h	10%	40%	50%
Et_2Zn, $Cu(OTf)_2$, Toluene, RT, 12 h	46%	32%	18%
Et_2Zn, $Cu(OTf)_2$•2 PPh_3 Toluene, 0 °C, 4 h	57%	15%	22%

Scheme 1.18 Conditions to minimize the uncatalyzed background reaction.

The addition of dimethyl- or diisopropylzinc proceeds with much lower efficiency, requiring higher catalyst loading and producing lower enantioselectivities (Table 1.4, entries 3 and 4). The ethyl transfer process is very efficient with aryl- and alkyl-substituted *N*-mesyl (Ms), *N*-trimethylsilylethanesulfonyl (SES), or *N*-tosyl imines (Ts). The cleavage of the sulfonyl group is accomplished with standard conditions; however, some racemization is observed when the methanesulfonyl group is cleaved using RedAl (Table 1.5). Although extensive studies to elucidate the reaction mechanism have not yet been completed, it is likely that the reaction proceeds via a pathway similar to that postulated for conjugate additions. The reaction of a dialkylzinc with copper(I) or copper(II) triflate affords an alkylcopper(I) species that is complexed to the chiral ligand. This species then undergoes an enantioselective nucleophilic attack to the imine. A final copper–zinc transmetallation completes the catalytic cycle and regenerates the nucleophile (Figure 1.5).

Table 1.4 Catalytic asymmetric addition to *N*-tosyl imines.

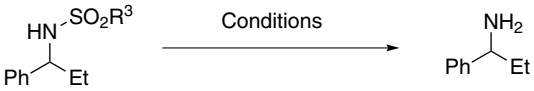




42 **43** **44**

Entry	R^1	R^2	R^3	Ligand	Loading *x* (mol%)	Yield (%)	ee (%)
1	Ph	Et	Tol	**42**	8	98	93
2	Ph	Et	Tol	**43**	5	97	96
3	Ph	Me	Tol	**43**	19.5	39	82
4	Ph	*i*Pr	Tol	**44**	19.5	92	78
5	Ph	Et	Ms	**42**	1	97	94
6	Ph	Et	SES	**42**	8	98	90
7	1-Naphthyl	Et	Ms	**42**	5	79	92
8	2-Naphthyl	Et	Ms	**42**	1	94	93
9	4-(MeO)C_6H_4	Et	Ms	**42**	5	83	92
10	4-ClC_6H_4	Et	Ms	**42**	1	95	94
11	2-Furyl	Et	Ms	**42**	1	98	93
12	*c*-C_6H_{11}	Et	Ts	**43**	5	84	96
13	Ph$(CH_2)_2$	Et	Ts	**43**	5	69	93

Table 1.5 Cleavage of the *N*-sulfonyl group.



Entry	R^3	Conditions	Yield (%)	ee (%) (starting material)	ee (%) (product)
1	Ts	SmI_2, THF-HMPA, reflux, 5 h	84	89	89
2	SES	CsF, DMF, 95 °C, 40 h	84	86	86
3	Ms	RedAl, C_6H_6, reflux, 12 h	87	94	72

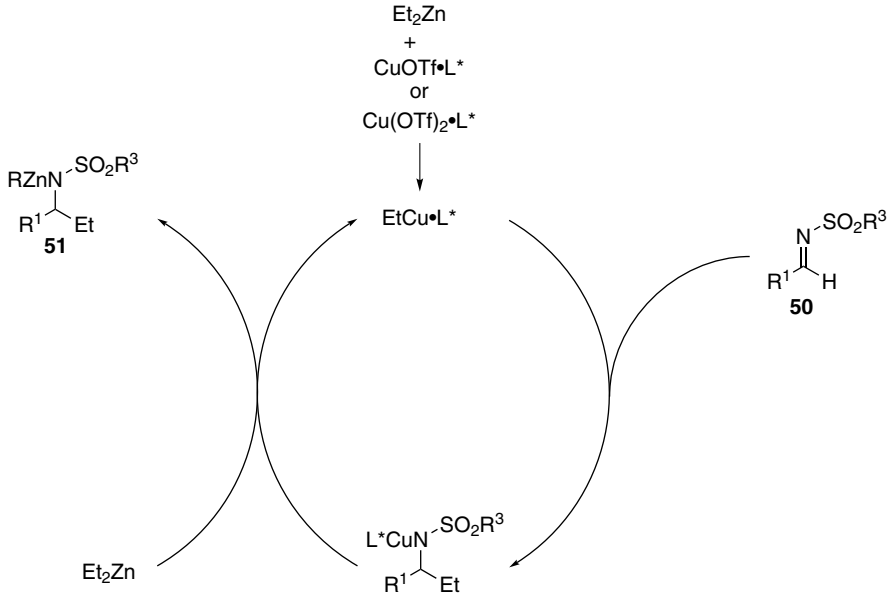


Figure 1.5 Possible catalytic cycle for the copper-catalyzed diorganozinc addition to imines.

Related chiral ligands have been developed for the copper-catalyzed addition to *N*-sulfonyl imines, but the enantioselectivities are usually lower and/or the scope is more limited (Figure 1.6) [73].

A copper-catalyzed catalytic asymmetric addition of diorganozinc reagents to *N*-phosphinoyl imines was developed by Charette [74, 75]. The most effective ligand was determined to be the Me-DuPHOS monoxide, a hemilabile, bidentate ligand prepared in two steps from Me-DuPHOS. The scope of the reaction is quite large, and this method offers the advantage of facile cleavage of the *N*-phosphinoyl group under mild acidic conditions (HCl, MeOH) (Table 1.6). In addition, Charette also reported that diorganozinc reagents prepared from a reaction between Grignard reagents and zinc methoxide produce chiral amines with high yields and enantiomeric excesses [76].

Since the stability of *N*-phosphinoyl imines derived from enolizable aldehydes can be problematic, an *in situ* formation of the *N*-phosphinoyl imine from its

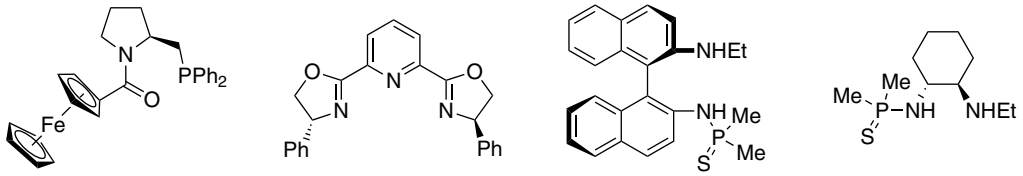
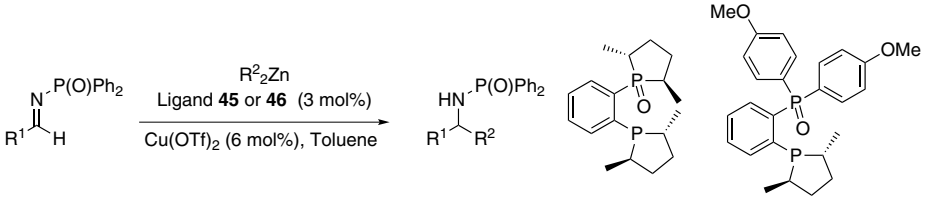


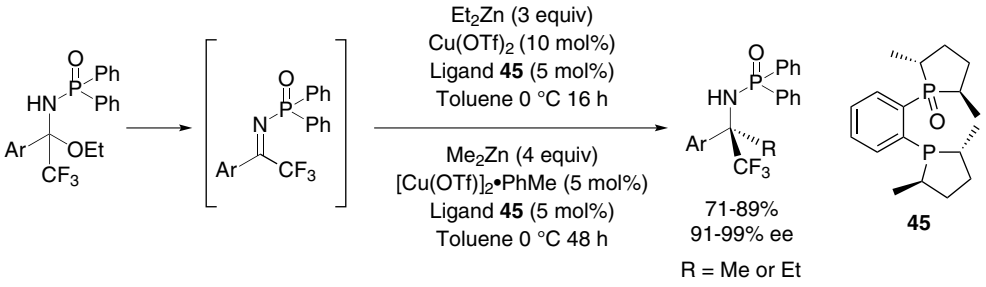
Figure 1.6 Other chiral ligands tested in the copper-catalyzed diorganozinc addition to *N*-sulfonyl imines.

Table 1.6 Selected examples of catalytic asymmetric addition of diorganozinc reagents to *N*-phosphinoyl imines.



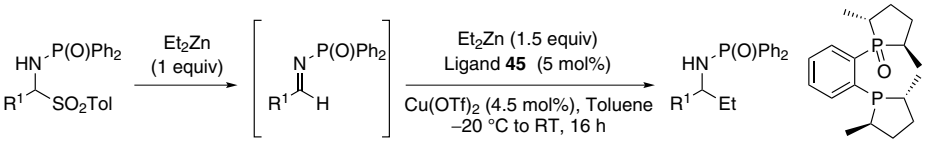
Entry	R^1	R^2	Ligand	Loading (mol%)	Yield (%)	ee (%)
1	Ph	Et	**45**	3	96	98
2	Ph	Et	**46**	5	84	94
3	4-MeC_6H_4	Et	**45**	3	94	98
4	3-MeC_6H_4	Et	**45**	3	96	97
5	4-$(MeO)C_6H_4$	Et	**45**	3	91	98
6	1-Naphthyl	Et	**45**	3	93	97
7	2-Naphthyl	Et	**45**	3	96	97
8	2-Furyl	Et	**45**	3	97	96
9	Cyclopropyl	Et	**45**	3	95	94
10	2-$(MeO)C_6H_4$	Et	**45**	3	98	98
11	Ph	Me	**45**	5	87	97
12	Ph	*n*Bu	**45**	5	92	96
13	Ph	*i*Pr	**45**	5	84	95
14	Ph	$nC_{10}H_{21}$	**45**	10	73	97

corresponding *p*-toluenesulfonic acid adduct has been developed (Table 1.7), again obtaining the products in high yields and enantiomeric excesses [23, 74d]. A procedure for the one-pot preparation of α-branched amines from aldehydes and the corresponding amine has also been developed using the stable precatalyst CuOTf (Me-DuPHOS(MO))$_2$ [74c]. In addition, this catalytic system is effective for the preparation of chiral α,α,α-trifluoromethylamines (Scheme 1.19) [27].



Scheme 1.19 Preparation of α,α,α-trifluoromethylamines.

Table 1.7 Enantioselective addition to alkyl-substituted *N*-phosphinoyl imines.



45

Entry	R^1	Yield (%)	ee (%)
1	Ph	87	97
2	cC_5H_{11}	92	95
3	$PhCH_2CH_2$	98	96
4	cC_6H_{11}	89	96
5	C_6H_{13}	98	95
6	*i*Pr	86	96
7	Me	97	90
8	*i*Bu	97	96
9	$TrOCH_2$	84	97

Feringa has reported a Cu phosphoramidite-catalyzed addition of diorganozinc and organoaluminum reagents to *N*-acyl imines [77]. The imines are generated *in situ* from aromatic and aliphatic α-amidosulfones. The reaction proceeds with high yield and a high degree of enantiocontrol (Table 1.8). However, the scope of the reaction is limited to aryl-substituted imines.

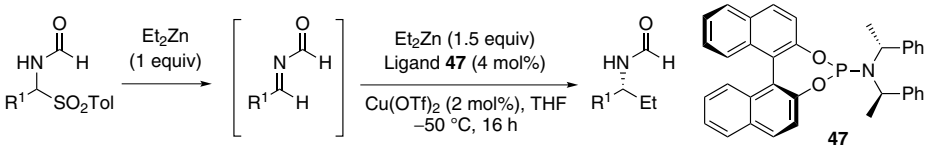
1.4.1.2 Zinc Alkoxide-Catalyzed Dialkylzinc Additions

Since the first report by Soai, which suggested that zinc alkoxides derived from amino alcohols could be used as substoichiometric additives to induce the nucleophilic attack of diorganozinc reagents to *N*-phosphinoyl imines, limited success has been achieved in developing a catalytic process using these electrophiles [78]. A breakthrough in this area was reported by Bräse in 2002 when it was found that substitution of the electrophile for a *N*-formyl imine led to a very efficient catalytic reaction when the chiral paracyclophane **48** [79] was employed as a catalyst [80]. Although the stability of *N*-acyl imine precluded their use as starting materials, they could be readily generated *in situ* from their corresponding sulfinic acid adducts (Table 1.9). Furthermore, hydrolysis of the *N*-formyl amide to the free α-branched amine is accomplished under mild acidic conditions (HCl, MeOH, 50 °C, 1.5 h).

1.4.1.3 Early Transition Metal (Zr, Hf)-Catalyzed Dialkylzinc Additions

Hoveyda and Snapper reported an alternative approach to the preparation of α-branched amines. Through the screening of parallel libraries of peptide-based ligands, they discovered that Schiff base dipeptide ligands were quite effective in mediating zirconium-catalyzed dialkylzinc addition to *N*-aryl imines (Table 1.10) [81]. The chiral catalyst complex is believed to increase the electrophilicity of the imine

Table 1.8 Copper-catalyzed diethylzinc addition to *N*-formyl imines.

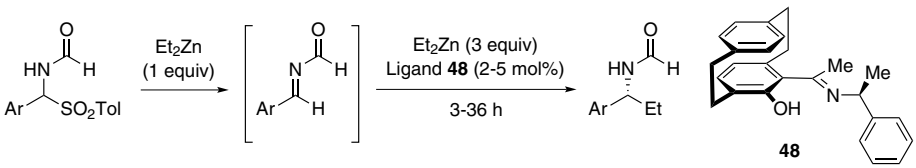


Entry	R^1	Yield (%)	ee (%)
1	Ph	99	96
2	4-ClC_6H_4	94	97
3	4-BrC_6H_4	94	99
4	3-MeC_6H_4	99	95
5	3-(MeO)C_6H_4	96	95
6	2-(MeO)C_6H_4	99	47
7	*c*Hexyl	99	45
8	*n*Hexyl	99	70

through a Zr imine complex and to increase the nucleophilicity of the dialkylzinc through complexation (Figure 1.7). When dimethyl zinc is employed as the nucleophile, a large excess (15 equiv) is required for the reaction to proceed in good to excellent yields (Table 1.10, entries 8 and 9).

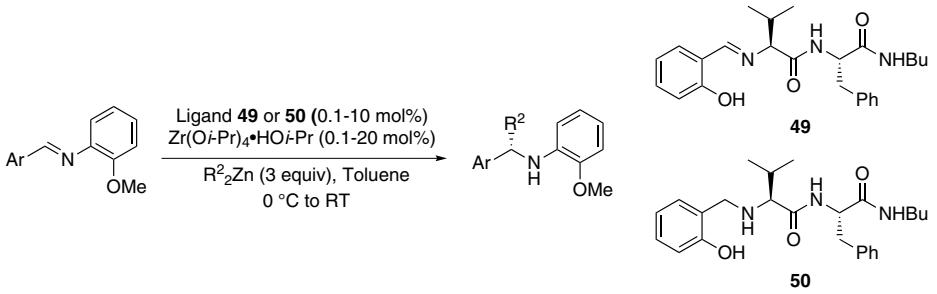
To extend this methodology to *N*-aryl imines derived from alkyl-substituted aldehydes, they developed a three-component approach involving *in situ* imine formation from an appropriate aldehyde and *o*-anisidine followed by the alkylation

Table 1.9 Diethylzinc addition to *N*-formyl imines.



Entry	Ar	Loading (mol%)	Yield (%)	ee (%)
1	Ph	2	>99	95
2	4-ClC_6H_4	2	>99	89
3	4-ClC_6H_4	5	97	90
4	4-(MeO)C_6H_4	2	97	95
5	4-(MeOOC)C_6H_4	2	90	94
6	2,6-$Cl_2C_6H_3$	2	98	95
7	4-*t*BuC_6H_4	2	>99	75
8	4-MeC_6H_4	2	>99	95
9	3-ClC_6H_4	5	99	93

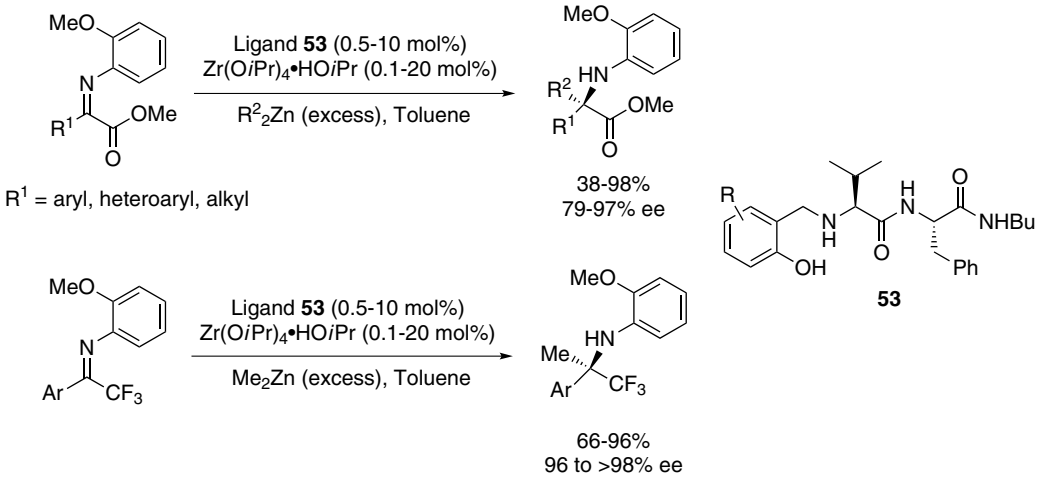
Table 1.10 Zirconium-catalyzed alkylation of *N*-aryl imines.



Entry	Ar	R^2	Ligand	Yield (%)	ee (%)
1	Ph	Et	**49**	82	93
2	1-Furyl	Et	**49**	87	97
3	2-Naphthyl	Et	**49**	67	92
4	1-Naphthyl	Et	**49**	86	91
5	4-$(CF_3)C_6H_4$	Et	**50**	87	88
6	2-BrC_6H_4	Et	**50**	62	90
7	4-$(MeO)C_6H_4$	Et	**50**	71	91
8	Ph	Me	**50**	79	88
9	1-Furyl	Me	**50**	98	84

reaction (Table 1.11) [82]. While the more Lewis acidic zirconium alkoxide afforded lower yields, higher yields with equally good or slightly lower enantioselectivities were obtained using hafnium tetraisopropoxide [83].

These conditions using the same family of chiral ligands have been recently applied to the enantioselective synthesis of *N*-substituted quaternary carbon centers derived from ketoimines (Scheme 1.20) [84, 85].



Scheme 1.20 Zirconium-catalyzed addition to *N*-aryl imines.

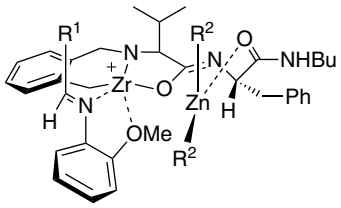
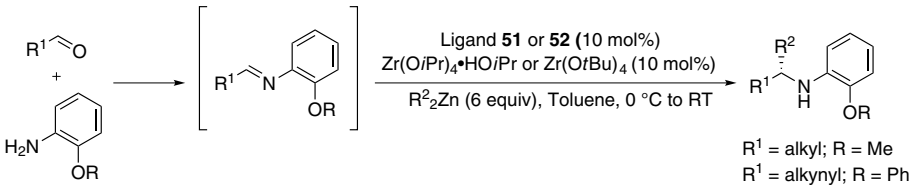


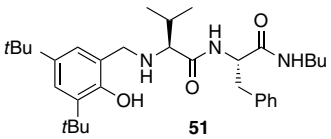
Figure 1.7 Model for the zirconium-catalyzed diorganozinc addition to *N*-aryl imines.

1.4.1.4 **Rhodium-Catalyzed Dialkylzinc Addition Reactions**

As mentioned, in most copper- and zirconium-catalyzed alkylations of imines, the addition of less reactive dimethylzinc (relative to diethylzinc) usually requires a large excess of the organometallic reagent. Hayashi reported that the methylation of *N*-tosyl imines could be achieved using only 1.5 equiv of dimethylzinc in the presence of a chiral rhodium complex that is coordinated with chiral diene **54** [86]

Table 1.11 Three-component synthesis of α-branched amines.





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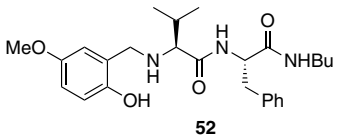

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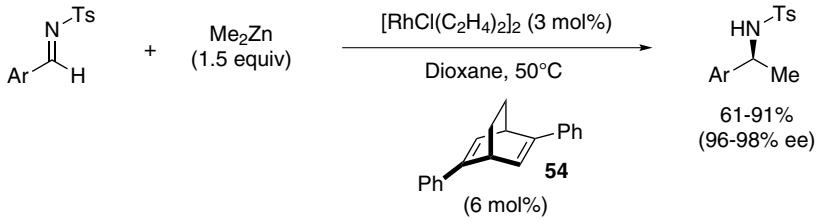
Entry	R^1	R^2	Ligand	Yield (%)	ee (%)
1	C_4H_9	Et	**52**	69	97
2	C_6H_{13}	Et	**52**	62	97
3	$PhCH_2CH_2$	Et	**52**	>98	94
4	(*E*)-$C_5H_{11}CH{=}CHCH_2CH_2$	Et	**20**	60	>98
5	*i*$PrCH_2$	Et	**52**	58	95
6	*c*C_3H_5	Et	**52**	83	98
7	$Br(CH_2)_5$	Et	**52**	57	95
8	*n*$C_5H_{11}CC$	Me	**51**	87	82
9	$TBSOCH_2CC$	Me	**51**	75	92
10	$TBSOCH_2CC$	Et	**51**	70	>98
11	PhCC	Me	**51**	84	80
12	PhCC	Et	**51**	85	>98
13	$TMSOC(Me_2)CC$	Et	**52**	86	84

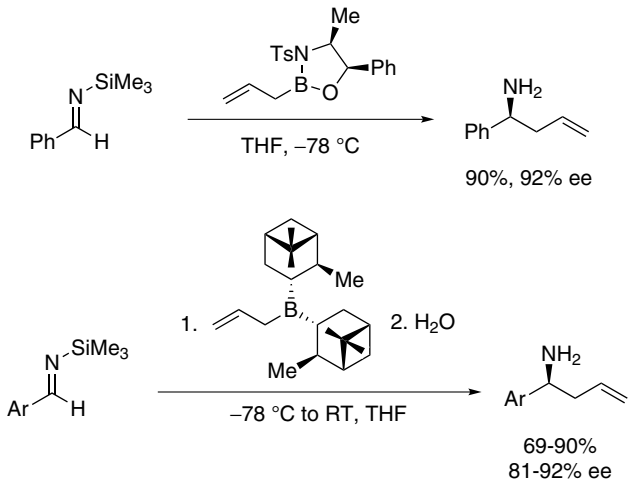


Scheme 1.21 Rhodium-catalyzed dimethylzinc addition to *N*-tosyl imines.

(Scheme 1.21). This catalyst provides the addition product derived from the *N*-tosyl imines of aryl-substituted aldehydes in high yield and enantiocontrol. It is believed that the addition proceeds via the formation of a methylrhodium species obtained by the reaction between the rhodium catalyst and dimethylzinc.

1.4.2
Catalytic Asymmetric Allylation of Imines

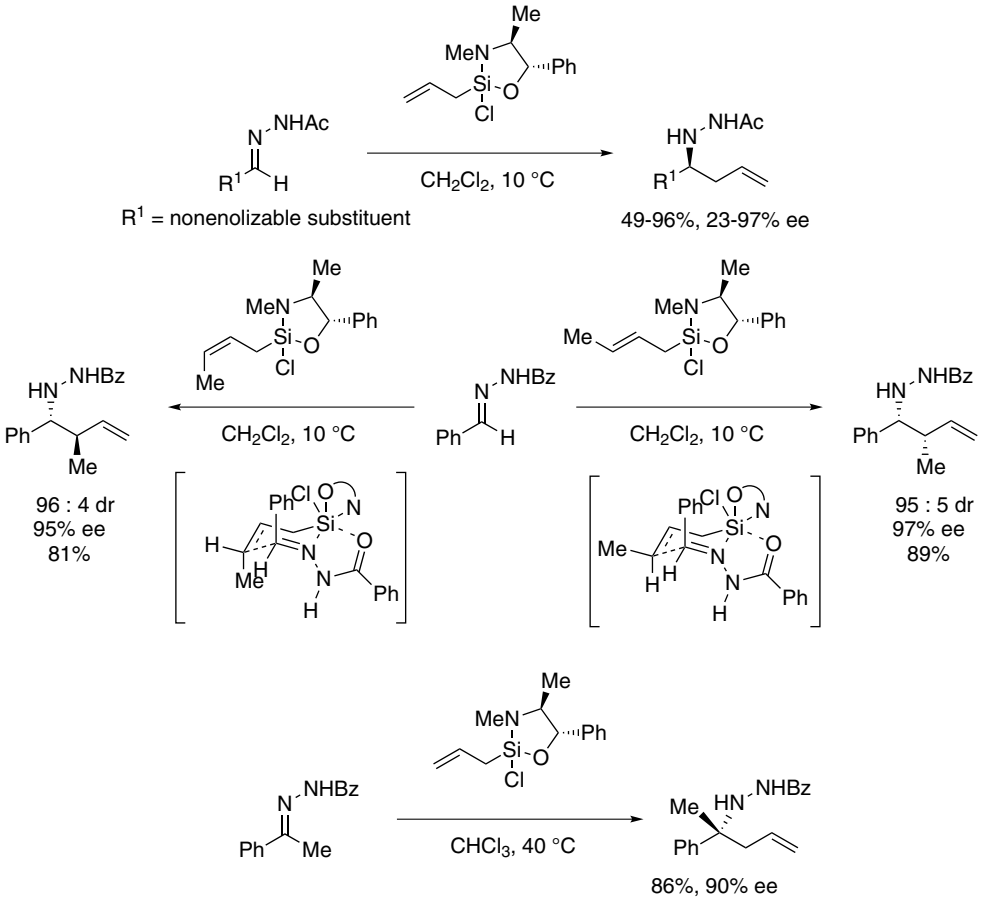
The enantioselective asymmetric allylation of imines has been a synthetic challenge, the initial solutions of which required stoichiometric amounts of chiral allylboron [87], allylsilane [88], allylzinc [89], or allylindium reagents [90]. Itsuno showed that a chiral *B*-allyloxazaborolidine derived from norephedrine could add to the *N*-trimethylsilyl imine prepared from benzaldehyde in high yield and enantiomeric excess (Scheme 1.22) [91]. Brown later reported that *B*-allyldiisopinocamphenylborane is also very effective for the allylation of the same electrophiles, but the addition of a molar amount of water is necessary to obtain high yields [92]. The diastereo- and



Scheme 1.22 Allylation of *N*-silyl imines.

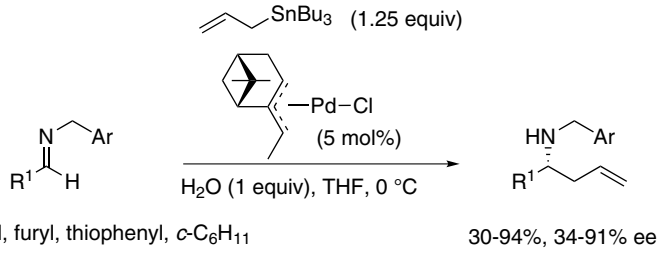
enantioselective crotylation of *N*-alumino imines (obtained by the DIBAL-H reduction of the nitrile) using the related *E*- or *Z*-crotylboranes has also been reported [93].

An interesting methodology employing the related allylsilane chemistry has been reported by Leighton [88c,d]. Chiral allylsilanes derived from pseudoephedrine are reacted with aldehyde- and ketone-derived hydrazones to generate the homoallylic hydrazide in good to excellent enantioselectivities and yields (Scheme 1.23). *cis*-Crotylsilanes and *trans*-crotylsilanes react with the hydrazone to afford the *anti*-hydrazide and the *cis*-hydrazide, respectively, with high enantio- and diastereocontrol. The stereochemistry is the opposite to that observed for the addition of crotylboranes to aldehydes. That is why a two-point binding/double activation has been proposed to account for these observations. Reductive cleavage of the N−N bond is accomplished in high yield using samarium diiodide.



Scheme 1.23 Allylation of hydrazones.

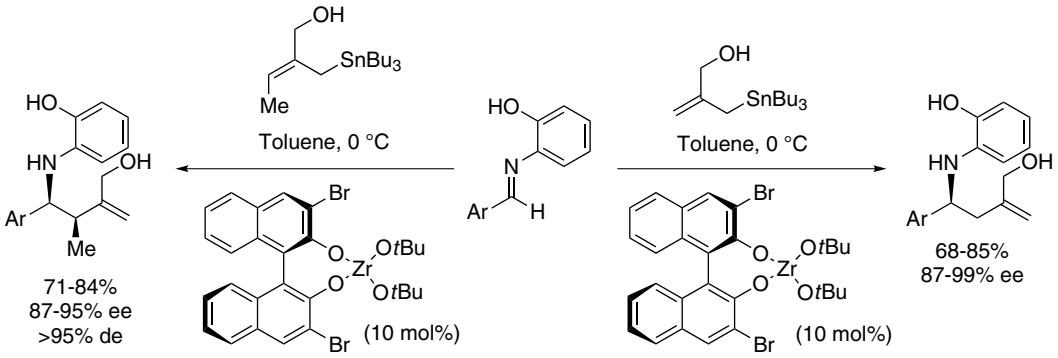
Yamamoto reported the first palladium-catalyzed addition of allyltributyltin or allyltrimethylsilane to *N*-benzyl imines [94]. Higher enantioselectivities are obtained if the reaction is performed in the presence of 1 equiv of water (Scheme 1.24).



Scheme 1.24 Palladium-catalyzed allylation of *N*-benzyl imines.

The first step of the catalytic cycle reaction is presumably an initial tin to palladium transmetallation to generate an η^3 allylpalladium species that adds on the imine. The catalyst is then regenerated following a second *N*-Pd to *N*-Sn transmetallation.

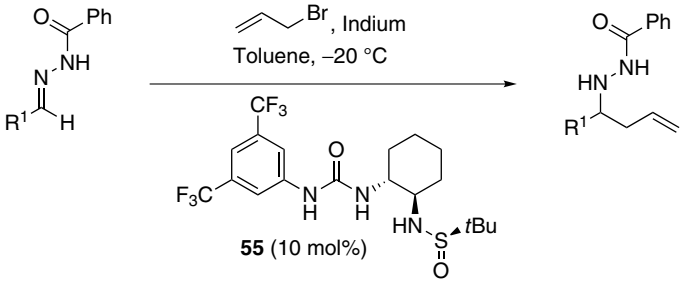
Kobayashi has demonstrated that a chiral zirconium catalyst derived from 3,3′-dibromo- or 3,3′-dichloro-BINOL can catalyze the addition of substituted allylstannanes to the imines derived from 2-hydroxyaniline and aryl- or hetereoaryl-substituted aldehydes (Scheme 1.25) [95]. The active catalyst is possibly generated by the bonding of the alcohol functionalities of the imine and of allylstannane to the zirconium center.



Scheme 1.25 Zirconium-catalyzed allylation of *N*-aryl imines.

Cook reported that a 3,3′-bis(trifluoromethyl)-BINOL-catalyzed asymmetric addition of allylindium to hydrazones proceeds in modest to good enantioselectivities (10–92% ee) [90]. The stoichiometric version of this reaction yields much higher enantioselectivities (84–97% ee). Jacobsen later found that a chiral urea catalyst is effective in catalyzing a similar transformation [96]. The bifunctional catalyst **55** bearing a hydrogen-bond donor and a Lewis base that are properly

Table 1.12 Allylation of hydrazones.



Entry	R	Yield (%)	ee (%)
1	C_6H_5	87	92
2	$pClC_6H_4$	83	92
3	2-Furyl	90	87
4	2-Thienyl	82	93
5	$p(MeOOC)C_6H_4$	92	76
6	$oBrC_6H_4$	78	93
7	$oMeC_6H_4$	89	95
8	1Naphthyl	89	95
9	$p(MeO)C_6H_4$	79	93

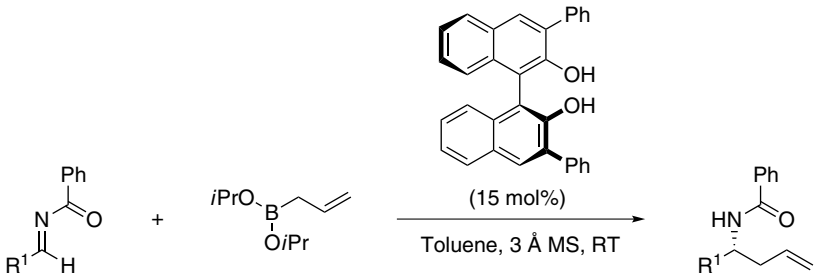
positioned is very effective in catalyzing the allylindium addition to *N*-acylhydrazones (Table 1.12).

The last class of allylation reactions that are amenable to asymmetric catalysis employs allylboronate derivatives. Schaus reported that several chiral BINOL derivatives catalyze the enantioselective asymmetric allylboration of acyl imines [97]. This reaction is most effective when 3,3′-diphenyl-BINOL acts as the catalyst and allyldiisopropoxyborane is the nucleophile. The allylation products are obtained in good yields (75–94%) and excellent enantiomeric excesses (>90% ee) for both aromatic and aliphatic imines (Table 1.13).

The reactions of both isomers of the corresponding crotyldiisopropoxyboranes are stereoconvergent, giving the *anti*-isomer with excellent diastereocontrol (Scheme 1.26). Mechanistic studies suggest that a facile exchange between an isopropoxy group of the nucleophile and a BINOL unit takes place to give the active allylation reagent. Two transition states have been proposed for the reaction of *E*-crotyl- and *Z*-crotylboronates (Figure 1.8).

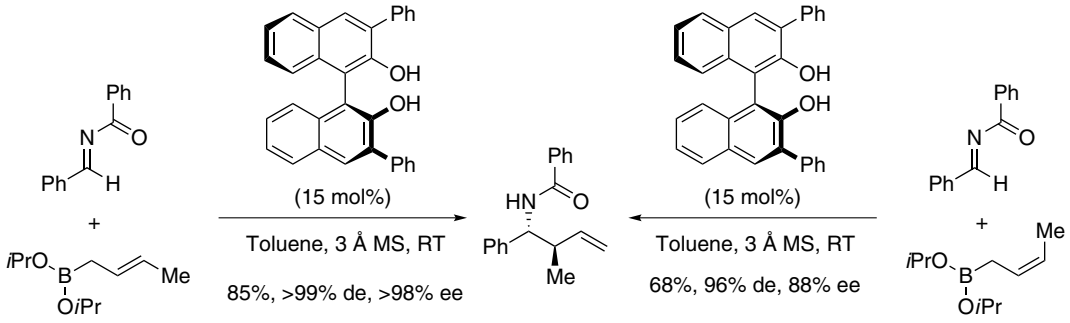
Shibasaki also reported related allylation chemistry using allylboronic acid pinacol ester [98], where an allylation procedure of ketoimines using 10 mol% of CuF cyclopentyl-DuPHOS, 30 mol% of lithium isopropoxide, and *t*-butanol was developed. High enantiocontrol is observed with a variety of aryl methyl ketoimines (Table 1.14). The enantioselectivity decreases with dialkyl-substituted ketoimines. Mechanistic studies suggest that lithium isopropoxide accelerates the reaction rate by increasing the concentration of the allylcopper species.

Table 1.13 Allylation of *N*-benzoyl imines.



Entry	R^1	Yield (%)	ee (%)
1	C_6H_5	87	98
2	*p*MeC_6H_4	83	96
3	*p*BrC_6H_4	86	95
4	*p*(MeO)C_6H_4	85	90
5	*p*FC_6H_4	94	96
6	*o*FC_6H_4	91	91
7	*m*$(CF_3)C_6H_4$	89	95
8	2-Furyl	83	92
9	2-Thienyl	81	90
10	2-Naphthyl	88	92
11	(*E*)-PhCH=CH	82	91
12	$PhCH_2CH_2$	83	99
13	*c*C_6H_{11}	80	96
14	*t*Bu	81	99
15	$BnOCH_2$	84	93
16	(*Z*)-EtCH=$CH(CH_2)_2$	82	91

Several catalytic asymmetric allylation reactions have been developed specifically for iminoester derivatives, but the level of enantioselection remains typically only in the low to high 80s (Table 1.15). Allylstannanes [99], allylsilanes [100], allyltrimethoxysilanes [101], and allylboronates [102] are suitable nucleophiles in these copper- or zinc-catalyzed processes.



Scheme 1.26 Crotylation of *N*-acyl imines.

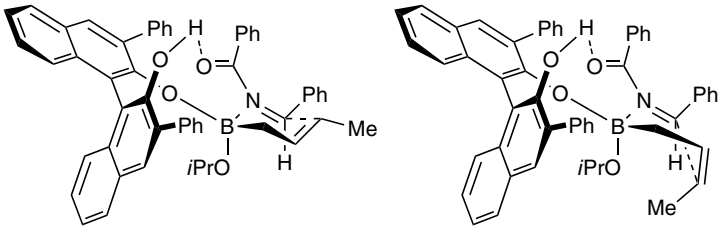
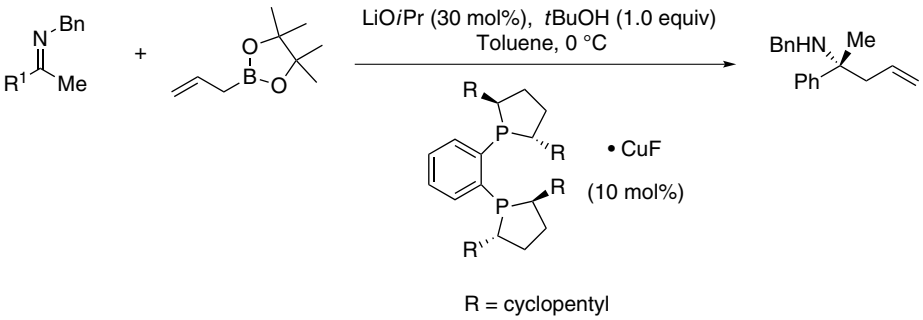


Figure 1.8 Transition-state models for the crotylation of *N*-acyl imines.

1.4.3
Catalytic Asymmetric Addition of sp^2 Hybridized Carbanions

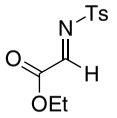
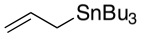
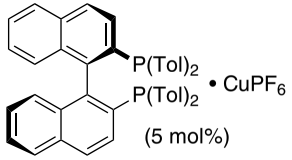
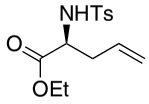
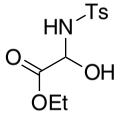
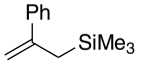
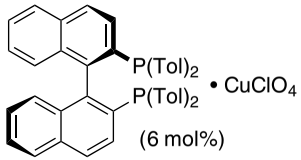
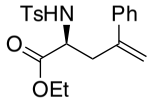
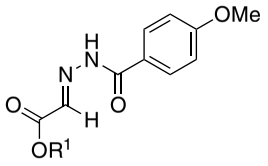
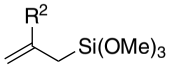
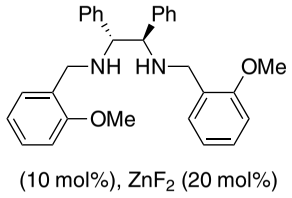
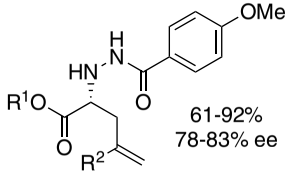
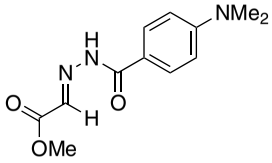
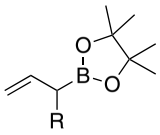
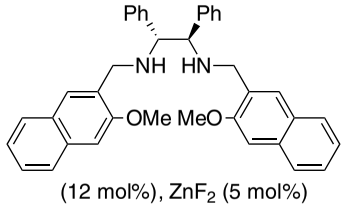
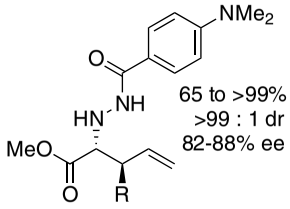
The various possibilities for the preparation of chiral allylic amines or α-aryl-substituted amines are outlined in Figure 1.9. Although the addition reaction of a carbon nucleophile to an imine derived from an aryl-substituted aldehyde is very efficient (**B**), the related addition to an α,β-unsaturated imine (**A**) can sometimes proceed via a 1,4-addition pathway. Similarly, the asymmetric C=N reduction reaction (**C** and **D**) is sometimes hampered by the possibility of either obtaining conjugate reduction (in the case of **C**) or low enantioselectivities (in **D** when R = aryl). The addition of sp^2 hybridized carbanions to imines (**E**) is a particularly effective

Table 1.14 Allylation of *N*-benzyl ketimines.



Entry	R^1	Yield (%)	ee (%)
1	Ph	92	89
2	3-MeC_6H_4	96	91
3	3-$(MeO)C_6H_4$	97	93
4	3-FC_6H_4	89	87
5	4-$(MeO)C_6H_4$	76	85
6	4-ClC_6H_4	82	81
7	2-Naphthyl	88	92
8	$PhCH_2CH_2$	98	23

Table 1.15 Selected catalytic systems for the allylation of imines.

Electrophile	Nucleophile	Catalyst	Product	Author, year
				Jørgensen, 1999
				Lectka, 1999
				Kobayashi, 2003
				Kobayashi, 2008

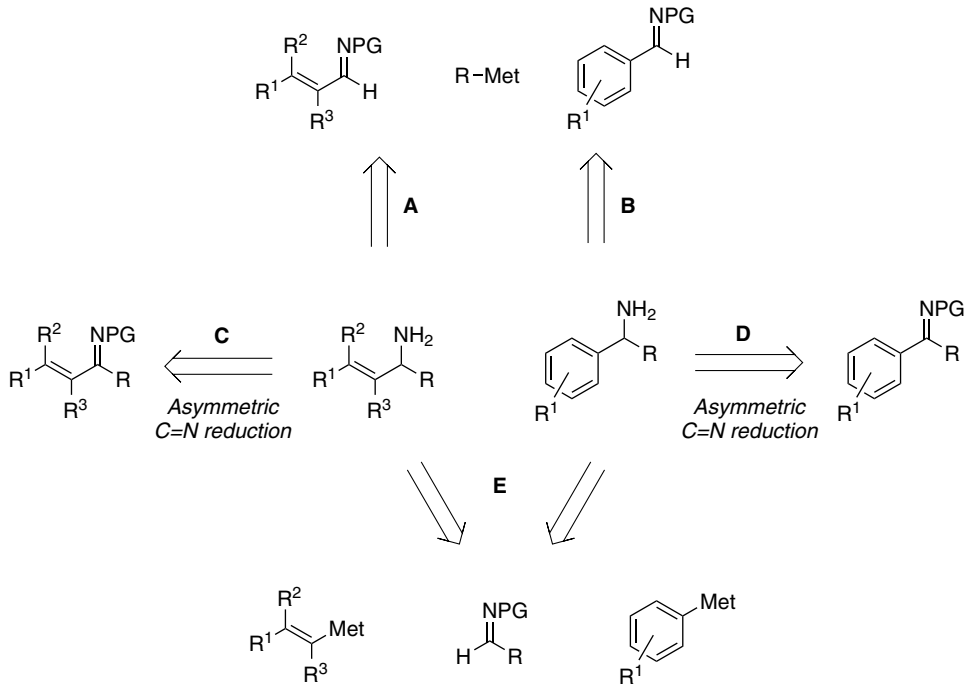


Figure 1.9 Various approaches to allylic and benzylic amines.

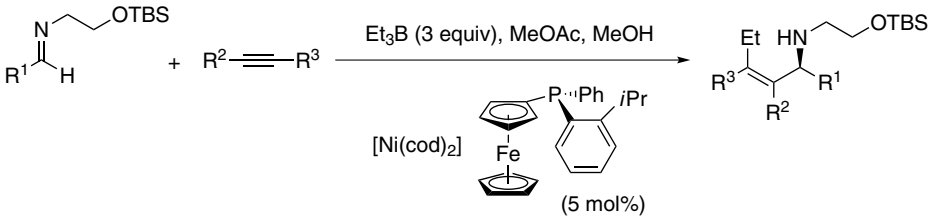
method to generate chiral allylic amines or diarylcarbinamines when the other strategies outlined in Figure 1.9 are not appropriate.

1.4.3.1 **Catalytic Asymmetric Vinylation**

The catalytic asymmetric addition of an unsubstituted vinylorganometallic reagent to an imine remains an important synthetic challenge and, to date, only limited success has been reported with appropriately substituted vinyl units. Jamison has reported a nickel-catalyzed three-component coupling of alkynes, imines, and organoboron reagents to afford tetrasubstituted allylic amines in a single step as well as high reaction yields and good enantioselectivities (Table 1.16) [103]. When unsymmetrical alkynes are used, a regioisomeric mixture of allylic amines is usually obtained unless both substituents on the alkyne are sterically or electronically significantly different (Table 1.16, entry 10 versus entry 11). The removal of the (*tert*-butyldimethylsilyloxy)ethyl protecting group is achieved using a two-step process (Bu_4NF then H_5IO_6).

An enantioselective iridium-catalyzed hydrogenative coupling of alkynes to aromatic and aliphatic *N*-arylsulfonyl imines has been reported by Krische (Table 1.17) [104]. The reaction is very efficient with a wide range of imines and alkynes. When unsymmetrical alkynes are used, the carbon–carbon bond forming process occurs at the more substituted position (Table 1.7, entries 17–21).

Table 1.16 Vinylation of imines.



Entry	R^1	R^2	R^3	Yield (%)	ee (%)
1	Ph	*n*Pr	*n*Pr	85	89
2	Ph	*n*Bu	*n*Bu	83	89
3	Ph	Et	Et	89	83
4	*o*MeC_6H_4	*n*Pr	*n*Pr	74	85
5	*p*$(MeO)C_6H_4$	*n*Pr	*n*Pr	75	82
6	*p*$(CF_3)C_6H_4$	*n*Pr	*n*Pr	91	85
7	2-Naphthyl	*n*Pr	*n*Pr	90	73
8	2,3-$(OCH_2O)C_6H_3$	*n*Pr	*n*Pr	95	73
9	*c*C_6H_{11}	Et	Et	53	51
10	Ph	Ph	Et	62	71
11	Ph	2-Naphthyl	Me	42 (85 : 15 rr)	70

The reaction is believed to proceed via the formation of an aza-iridacyclopentene that undergoes protolytic cleavage of the nitrogen–iridium bond (Scheme 1.27). Subsequent reductive elimination leads to the product.

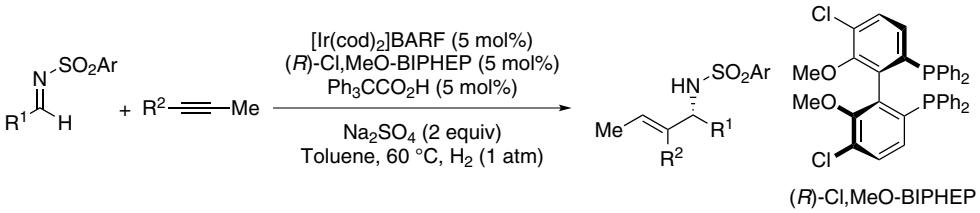
A related rhodium-catalyzed enantioselective reductive coupling of acetylene to *N*-arylsulfonyl imines leads to the formation of (*Z*)-dienyl allylic amines (Scheme 1.28) [105]. The scope of the reaction is comparable to that demonstrated for the analogous iridium-catalyzed process. The reaction between the acetylene and rhodium leads to the oxidative dimerization of acetylene to form a cationic rhodacyclopentadiene that then reacts with the imine to generate the product after the protolytic cleavage and reductive elimination.

The Petasis reaction is a mild multicomponent reaction that allows the condensation of a boronic acid, an amine, and a carbonyl derivative to generate an allylic amine. Although several diastereoselective Petasis reactions have been reported [106], the first catalytic asymmetric reaction was described in 2008 (Scheme 1.29) [107]. It was shown that the condensation proceeds in high yields and enantiomeric excesses, affording the corresponding protected α-vinylglycine derivatives.

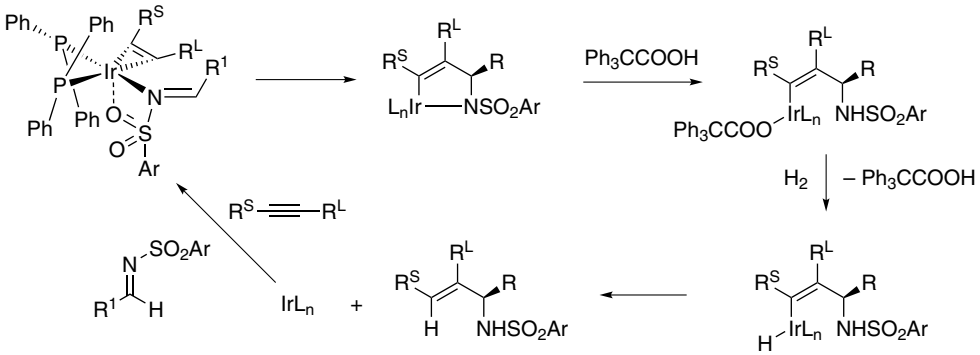
1.4.3.2 Catalytic Asymmetric Arylation

1.4.3.2.1 **Amino Alcohol-Catalyzed Addition of Organozinc Reagents** Despite the relatively large number of efficient catalytic asymmetric methods available for alkyl group transfer from diorganozinc reagents to imines, the analogous reaction employing a diarylzinc reagent is much more difficult to achieve. A major obstacle

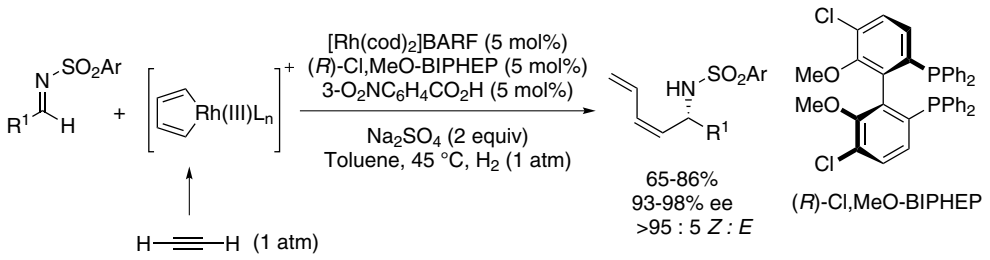
Table 1.17 Iridium-catalyzed vinylation of *N*-sulfonyl imines.



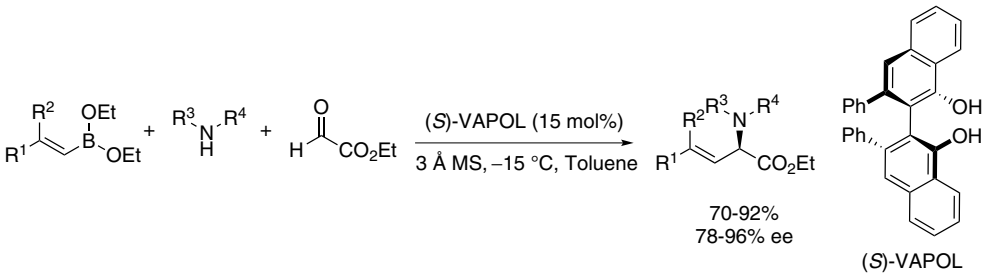
Entry	R^1	Ar	R^2	Yield (%)	ee (%)
1	C_6H_5	Ph	Me	70	98
2	4-(MeO)C_6H_4	Ph	Me	64	99
3	3-(MeO)C_6H_4	Ph	Me	72	98
4	4-ClC_6H_4	4-Tol	Me	67	97
5	4-(MeOOC)C_6H_4	4-Tol	Me	72	97
6	2-Naphthyl	Ph	Me	64	94
7	(*E*)-PhCH=CH	Ph	Me	76	99
8	1-Furyl	Ph	Me	80	97
9	1-Thienyl	Ph	Me	81	98
10	*c*C_6H_{11}	4-Tol	Me	74	98
11	*c*C_5H_9	Ph	Me	66	99
12	*c*C_3H_5	Ph	Me	80	92
13	Me	4-Tol	Me	67	97
14	*n*Pr	Ph	Me	70	97
15	*i*Pr	Ph	Me	69	94
16	*i*Bu	4-Tol	Me	70	99
17	1-Furyl	Ph	*n*Pr	78	97
18	*c*C_3H_5	Ph	*n*Pr	65	99
19	1-Furyl	Ph	*i*Pr	80	97
20	*c*C_3H_5	Ph	*i*Pr	66	94
21	1-Furyl	Ph	CH_2CH_2OTBS	69	98



Scheme 1.27 Proposed mechanism for the iridium-catalyzed vinylation.

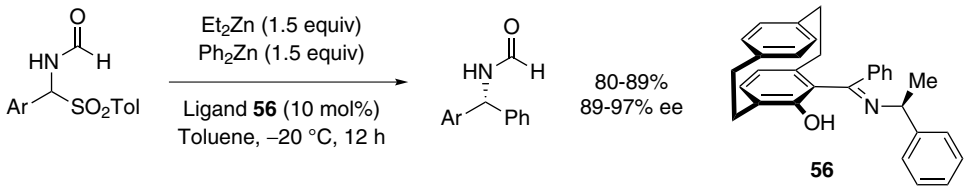


Scheme 1.28 Rhodium-catalyzed vinylation of *N*-arenesulfonyl imines.



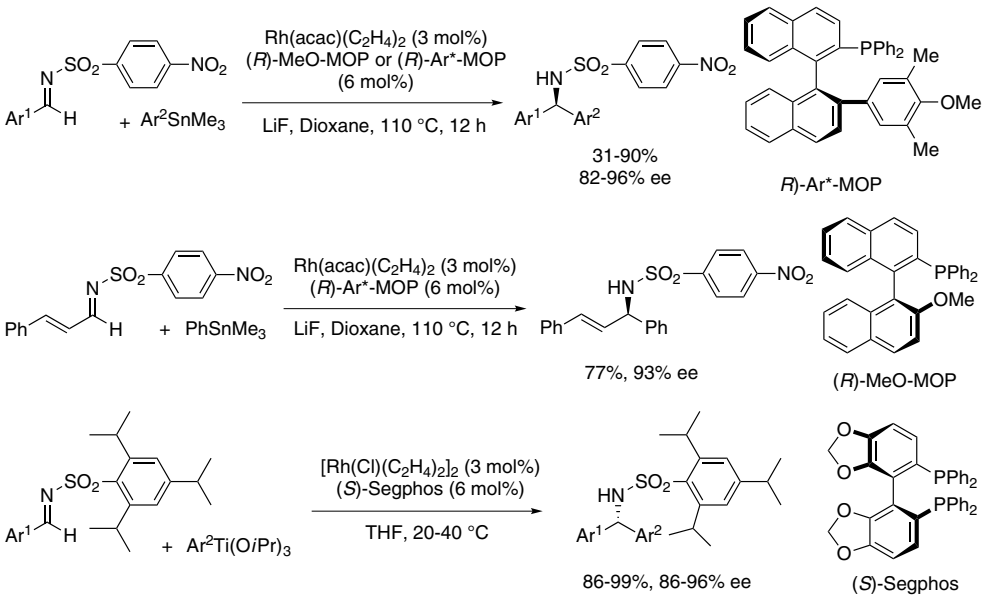
Scheme 1.29 Asymmetric Petasis reaction.

resides in the fact that the aryl group transfer from a diarylzinc reagent to an imine is a more facile process, thus rendering the uncatalyzed aryl group transfer competitive with the catalyzed asymmetric process. A solution to overcome this problem is to apply mixed diorganozinc reagents that possess lower levels of reactivity [108]. Bräse and Bolm have reported that the *in situ* preparation of a mixed diorganozinc leads to increased enantioselectivities for the phenyl group transfer to *N*-formyl imines catalyzed by cyclophane **56** [109] (Scheme 1.30). Thus far, the reaction has not been applied to the transfer of other aryl groups.



Scheme 1.30 Arylation of *N*-formyl imines.

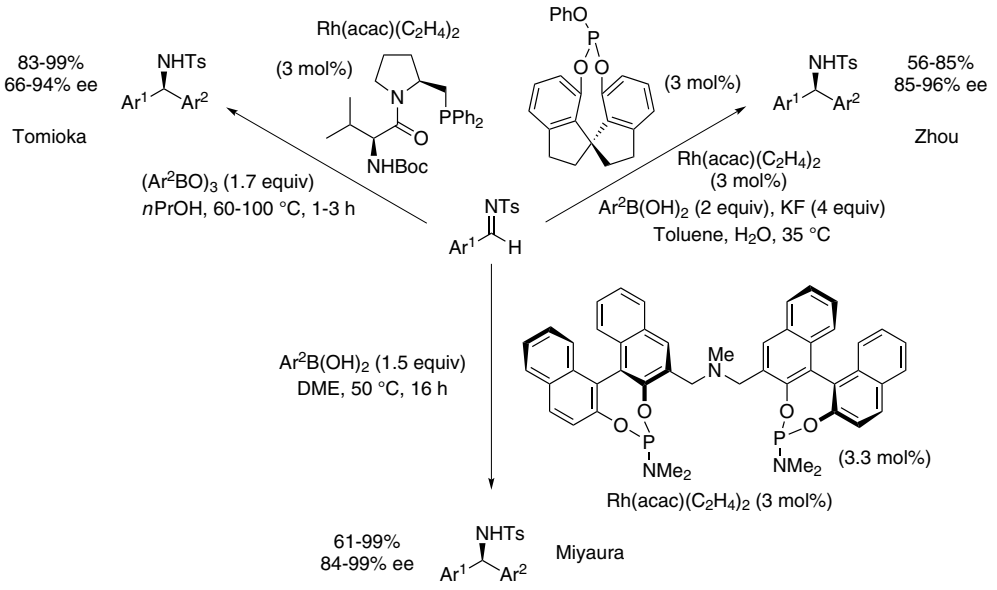
1.4.3.2.2 **Rhodium Phosphine-Catalyzed Arylation of Imines** The asymmetric rhodium-catalyzed arylation of imines is among the most efficient methods for the preparation of α-aryl chiral amines. Hayashi first reported that arylstannane [110] and



Scheme 1.31 Rhodium-catalyzed arylation of *N*-arenesulfonyl imines.

aryltitanium [111] reagents can be used as stoichiometric nucleophiles in the rhodium-catalyzed addition to *N*-sulfonyl imines (Scheme 1.31). Both reactions presumably proceed via the formation of an arylrhodium species that is complexed to the chiral ligand. Several aryl sulfonyl groups were screened, and the *p*-nitro derivatives gave not only the highest ee's when (*R*)-Ar*-MOP was used as the ligand but also the highest yields when 4 equiv of various arylstannanes were employed. The cleavage of the sulfonyl group to liberate the free amine is accomplished in high yields upon treating the product with thiophenol and potassium carbonate. Interestingly, the arylation of an α,β-unsaturated imine leads to the 1,2-addition product in high ee's under these reaction conditions. The arylation of *N*-sulfonyl imines with 2 equiv of an aryltitanium reagent leads to the product in good yields and ee's. SEGPHOS was determined to be the optimal ligand with this nucleophile, but the sterically hindered 2,4,6-triisopropylbenzenesulfonyl group afforded the highest enantioselectivities. The cleavage of the bulky group could be accomplished with no epimerization with samarium diiodide in HMPA, lithium in ammonia, or with RedAl.

Building upon Miyaura's pioneering work on the rhodium-catalyzed addition of organoboron reagents to *N*-tosyl imines [112], Tomioka reported [113] the first catalytic enantioselective version of the reaction involving several chiral phosphines (Scheme 1.32). The enantiomeric excesses are usually >90% when Ar^1 is an *o*-trimethylsilylphenyl. Although the enantioselectivities were good, several more effective phosphorus-based ligands were since developed to give high enantioselectivities and yields. Zhou later found that a rhodium complex bearing a chiral monophosphite ligand gave good enantioselectivities [114].



Scheme 1.32 Arylation of *N*-tosyl imines.

Finally, a chiral *N*-linked C_2-symmetric bidentate phosphoramidite was developed by Miyaura for the arylation of *N*-sulfonyl imines [115]. Over 38 different chiral *N*-tosyl amines were prepared in high yields and enantiomeric excesses using this novel ligand. These conditions were also quite effective (72–99% yield and 93–98% ee) for the arylation of *N*-*p*-nitrobenzenesulfonyl imines, which can be cleaved under mild conditions to liberate the free amine.

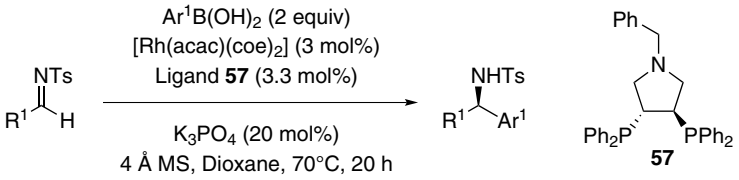
The catalytic enantioselective addition of arylboronic acids to aliphatic imines proceeds with broad substrate scope, high yields, and enantiocontrol (Table 1.18) [116]. In this case, DeguPHOS (**57**) was found to be the optimal chiral ligand.

The nature of the activating group on the imine can also be modified to facilitate its cleavage after the addition. Again, DeguPHOS (**57**) was found to be equally effective for the nucleophilic addition to both aryl- [61a] and alkyl-substituted *N*-phosphinoyl imines [116]. The diphenylphosphinoyl group was easily cleaved using HCl/MeOH to afford high yield of the pure amine hydrochloride (Scheme 1.33).

Alternatively, it is also possible to use *in situ* generated *N*-Boc imines as electrophiles [117]. When α-carbamoyl sulfones are treated under the rhodium-catalyzed addition of arylboronic acids, the imine is formed *in situ*, and the nucleophilic addition proceeds smoothly to generate the *N*-Boc-protected amine (Scheme 1.34).

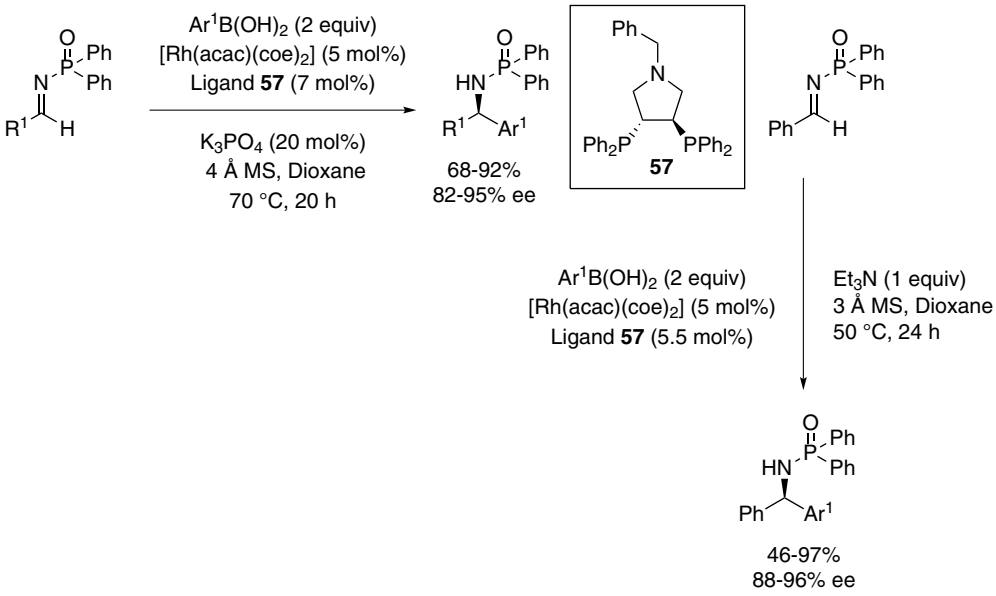
The catalytic asymmetric synthesis of diarylmethylamines by a rhodium/phosphoramidite-catalyzed addition of arylboronic acids to *N*,*N*-dimethylsulfamoyl-protected aldimines has been reported by de Vries and Feringa [118]. The reaction produces very high yields and high enantioselectivities of the protected amine. Deprotection of the amine is achieved without any racemization upon heating the product in the microwave with 1,3-diaminopropane (Scheme 1.35).

Table 1.18 Addition of arylboronic acids to *N*-tosyl imines.

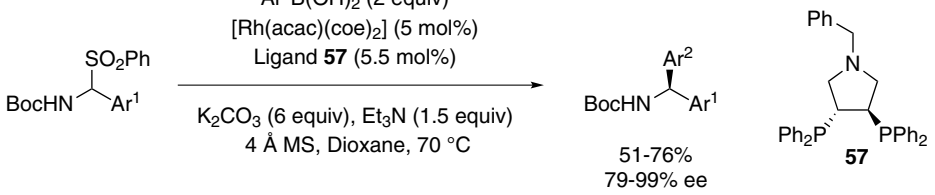


Entry	R^1	Ar^1	Yield (%)	ee (%)
1	$PhCH_2CH_2$	4-ClC_6H_4	94	95
2	$CH_3CH_2CH_2$	4-ClC_6H_4	89	93
3	$(CH_3)_2CHCH_2$	4-ClC_6H_4	96	91
4	$CH_2{=}CHCH_2CH_2$	4-ClC_6H_4	87	98
5	cC_6H_{11}	4-ClC_6H_4	80	96
6	cC_6H_{11}	4-MeC_6H_4	71	96
7	cC_6H_{11}	4-$MeOC_6H_4$	74	90
8	cC_6H_{11}	4-$CF_3C_6H_4$	89	91
9	cC_6H_{11}	3-ClC_6H_4	75	90
10	cC_6H_{11}	3-AcC_6H_4	81	89

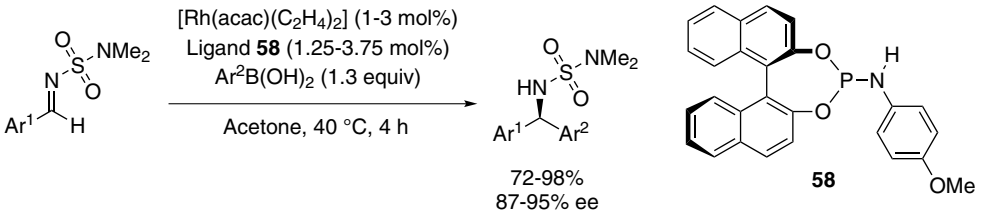
The mechanism of the rhodium-catalyzed arylation of imines presumably occurs via an initial transmetallation to produce the arylrhodium species **59** (Figure 1.10). Aryl transfer followed by a second rhodium–boron transmetallation (or protonation by water) completes the catalytic cycle.



Scheme 1.33 Addition of arylboronic acid to *N*-phosphinoyl imines.



Scheme 1.34 Arylation of *N*-Boc imines.



Scheme 1.35 Arylation of *N*-sulfamoyl imines.

1.4.3.2.3 **Rhodium Diene-Catalyzed Arylation of Imines** Hayashi has shown that the asymmetric synthesis of diarylmethylamines could be realized with high enantiocontrol by the rhodium-catalyzed arylboronic acid addition to *N*-tosyl imines [119]. The rhodium catalyst bears the C_2-symmetrical bicyclo[2.2.1]heptadiene ligand **54**.

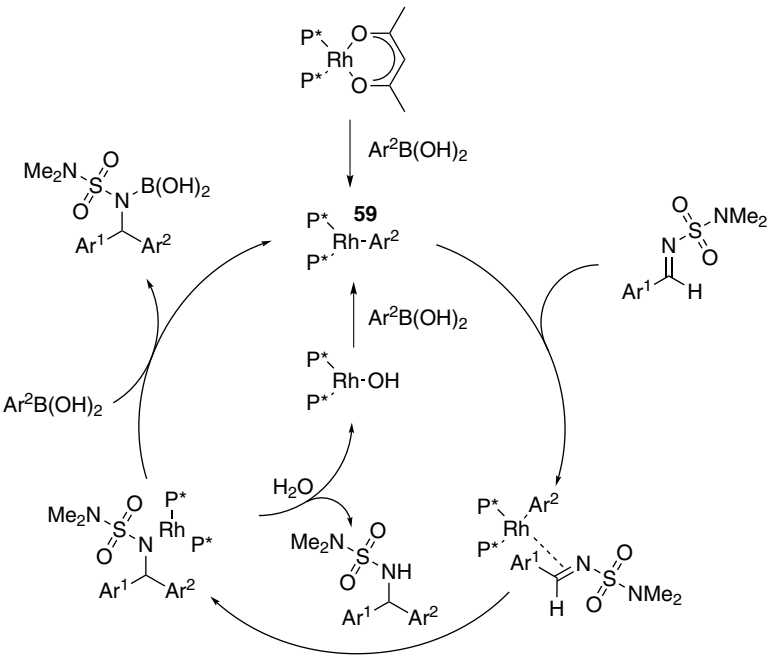
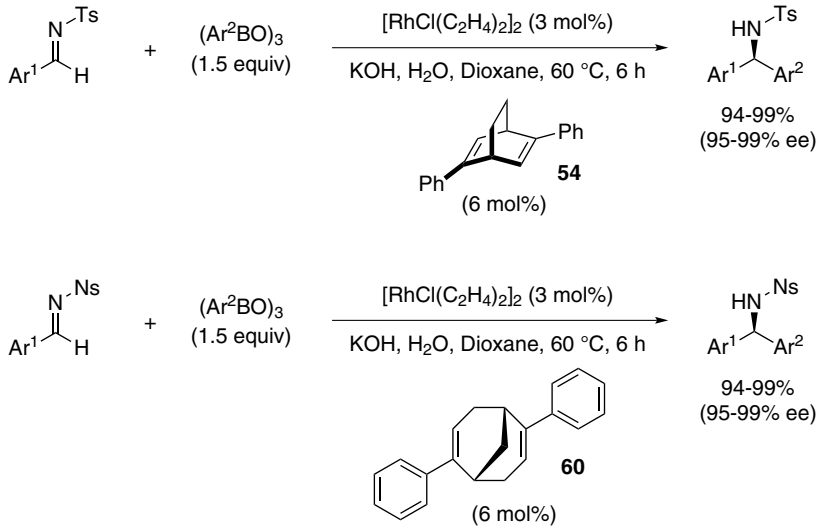


Figure 1.10 Proposed mechanism for the rhodium-catalyzed arylation of imines.



Scheme 1.36 Rhodium-catalyzed arylation of *N*-arenesulfonyl imines.

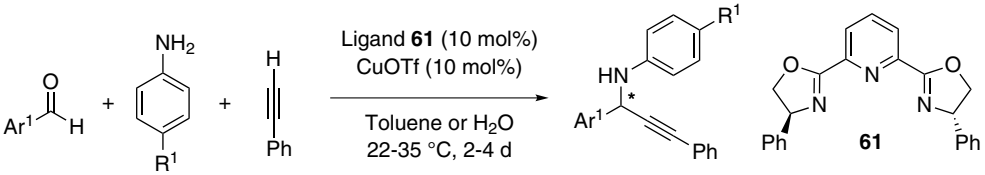
This chiral diene ligand displays a clear superiority over chiral phosphorus ligands in both enantioselectivity and catalytic activity. A second-generation catalytic system was later reported for the highly enantioselective addition to *N*-nosyl imines, for which the product is more easily converted into the free amine than that bearing a *N*-tosyl group [120]. The more effective chiral ligand **60** had to be used (Scheme 1.36).

1.4.4
Catalytic Asymmetric Addition of sp Hybridized Carbanions

The first examples of enantioselective alkynylation of imines relied on the use of stoichiometric chiral additives [121] or chiral reagents [122]. It was only in 2002 that the first reports of catalytic asymmetric copper-catalyzed terminal alkyne addition to imines appeared. Li reported that a three-component approach, in which *N*-aryl imines are generated *in situ* from an aldehyde and aniline, leads to propargylamines in excellent yields and enantioselectivities (Table 1.19) [123, 124]. Quite remarkably, the reaction can be carried out either in toluene or in water, with the yields and enantioselectivities being slightly higher in toluene. However, the scope is limited to aryl-substituted aldehydes. The reaction presumably involves the *in situ* formation of an alkynylcopper nucleophile that adds to the imine. Several similar chiral bidentate ligands were developed, but they offer little advantages over the original pybox ligand derived from phenylglycinol [125].

An enantioselective copper-catalyzed addition of alkynes to enamines was reported by Knochel [126]. The reaction was later extended to an enantioselective three-component reaction for the synthesis of *N,N*-disubstituted propargylamines (Scheme 1.37) [127].

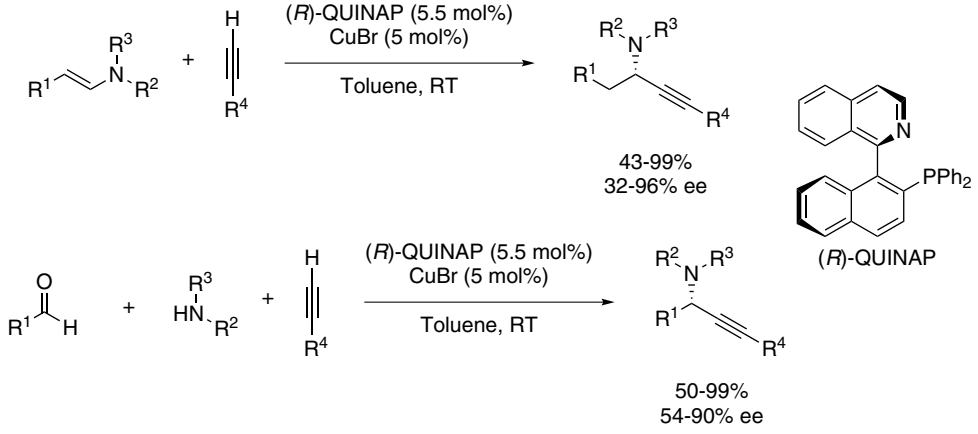
Table 1.19 Copper-catalyzed alkynylation of *N*-aryl imines.



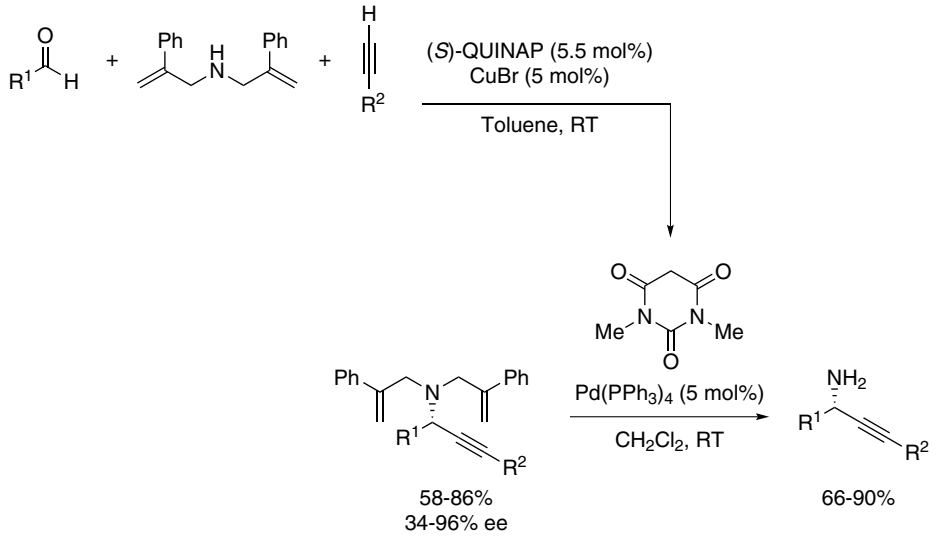
(1 equiv) (1.2 equiv) (1.5 equiv)

Entry	Ar^1	R^1	Toluene		H_2O	
			Yield (%)	ee (%)	Yield (%)	ee (%)
1	Ph	H	78	96	71	84
2	4-MeC_6H_4	H	85	92	86	81
3	4-ClC_6H_4	H	85	94	70	87
4	4-PhC_6H_4	H	81	94	48	84
5	2-Naphthyl	H	63	88	57	86
6	4-$(CF_3)C_6H_4$	H	71	93	56	87
7	Ph	Br	93	91	82	83
8	Ph	Cl	92	91	77	84
9	Ph	Me	93	94	68	91

Although the level of enantioselectivity depends upon the dialkylamine used for the enamine precursor, the reaction is highly divergent, as four different substituents can be modified in one step. Although the use of the dibenzylamine generally provides the highest enantioselectivities, its removal under hydrogenolysis conditions also leads to the reduction of the alkyne. The deprotection of the protected propargylamine is possible using palladium(0) when diallylamine or bis(phenallyl) amine is used (Scheme 1.38) [128]. However, the enantioselectivity of the conden-



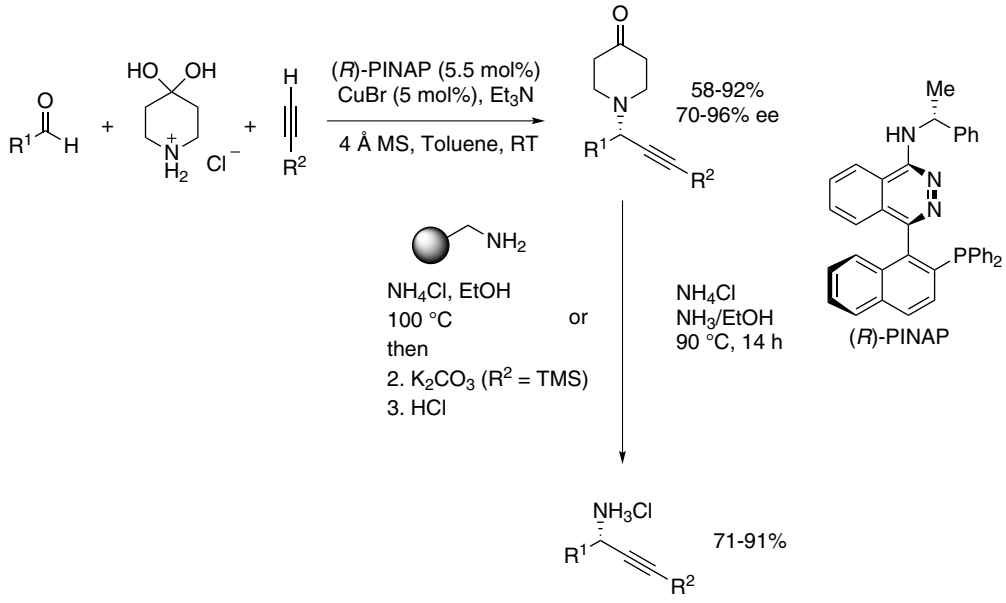
Scheme 1.37 Alkynylation of enamines.



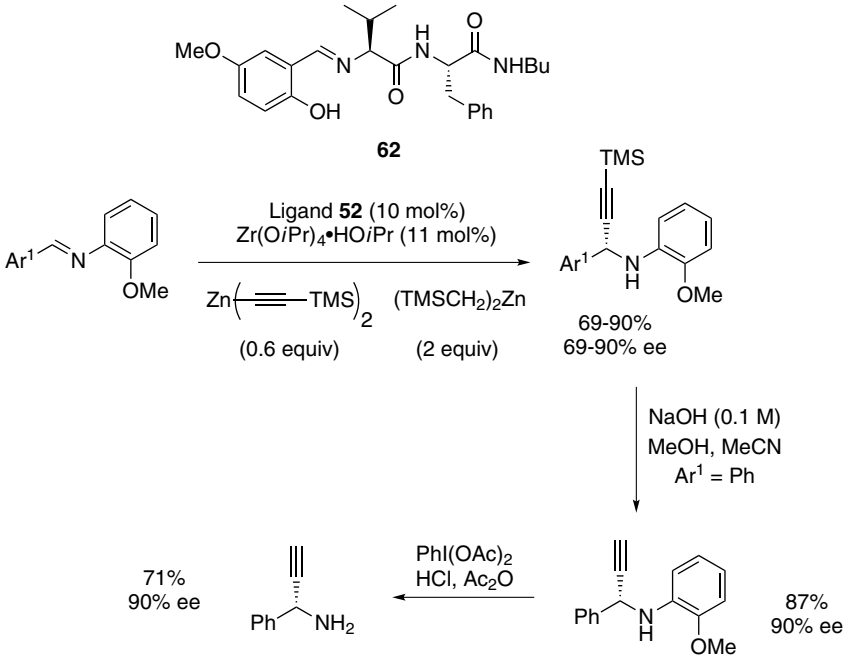
Scheme 1.38 Three-component synthesis of propargylamines.

sation reaction is usually higher with bis(phenallyl)amine than with diallylamine or bis(methallyl)amine.

A variant of this reaction has been reported by Carreira using a novel PINAP ligand [129]. The use of 4-piperidone hydrochloride hydrate affords the tertiary amine in good yield and enantioselectivity (Scheme 1.39). The deprotection of the amine can



Scheme 1.39 Preparation of unprotected propargylamines.



Scheme 1.40 Zirconium-catalyzed alkynylation of *N*-aryl imines.

be accomplished in high yield upon treatment with ammonia or, more conveniently, a polystyrene-supported scavenger amine.

Hoveyda and Snapper reported that the addition of mixed alkynylzinc reagents to various aryl imines can be catalyzed by Schiff base ligand **52** and zirconium tetraisopropoxide to afford the protected propargylamines in good yields and enantioselectivities [130]. The oxidative removal of the *o*-anisidyl group affords the propargylamine without any racemization (Scheme 1.40).

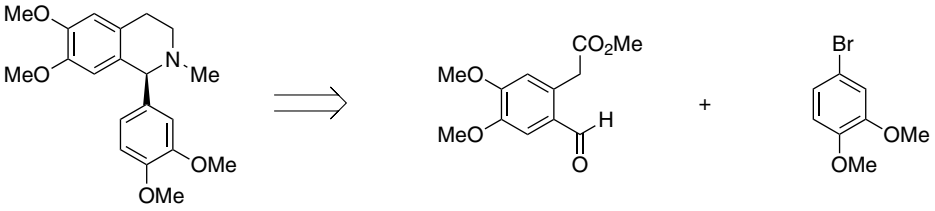
1.5 Conclusion

The importance of α-branched chiral amines in nature and as substructures in biologically active unnatural products led to the rapid development of an impressive number of methods to synthesize this class of compounds in enantiomerically enriched forms. It is quite spectacular to see how many very efficient methods have appeared since the early twenty-first century. Furthermore, catalytic asymmetric methods now exist to transfer sp^3, sp^2, or sp nonstabilized carbanion nucleophiles to a wide range of activated imines. Even if the past 10 years have witnessed phenomenal advances in this area, Ellman's chiral auxiliary method is still very attractive. Indeed, it is the only one that allows the addition of the three kinds of nucleophiles using the same class of reagents and it also possesses numerous other

advantages (easy hydrolysis of the auxiliary and commercial availability of numerous Grignard reagents and of *tert*-butanesulfonamide's chiral auxiliary). These features make this process even more attractive when large amounts of an α-branched chiral amines are needed.

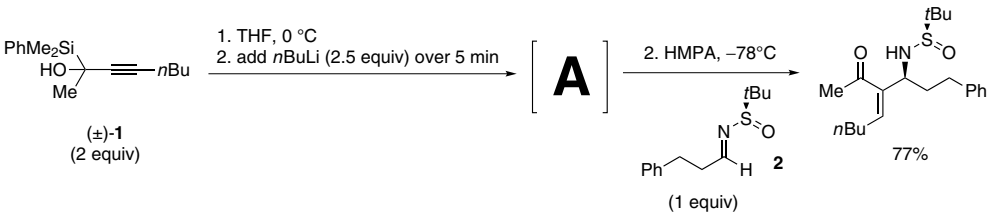
Questions

1.1. The cryptostylines and their analogues have been used as pharmacological probes, such as the D_1 dopamine receptor, an antagonist of substance P, and a peptide neurotransmitter. Propose a catalytic asymmetric synthesis of (*S*)-(+)-cryptostyline II starting from methyl 2-(2-formyl-4,5-dimethoxyphenyl)acetate and 4-bromo-1,2-dimethoxybenzene.

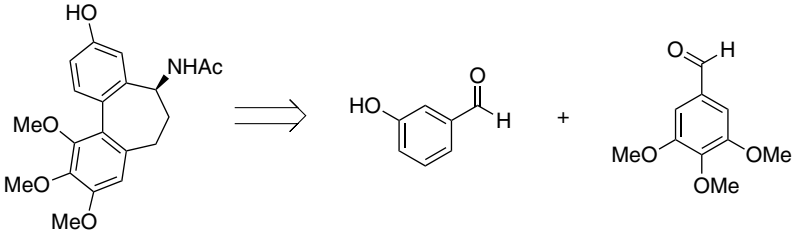


(*S*)-(+)-cryptostyline II

1.2. Propose a mechanism for the following formation of the aza-Morita–Baylis–Hillman reaction product that is obtained from an α-hydroxypropargylsilane (**1**) and the *N*-*tert*-butanesulfinyl imine. Provide the structure of intermediate **A** obtained upon slow addition of *n*-BuLi to (±)-**1**.



1.3. Propose a catalytic asymmetric synthesis of *N*-acetylcolchinol starting from 3-hydroxybenzaldehyde and 3,4,5-trimethoxybenzaldehyde.



N-acetylcolchinol

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