Review

Copper-Catalyzed Asymmetric Alkylation of Imines with Dialkylzinc and Related Reactions

Ken-ichi Yamada, and Kiyoshi Tomioka

Chem. Rev., **2008**, 108 (8), 2874-2886 • DOI: 10.1021/cr078370u • Publication Date (Web): 25 July 2008

Copper-Catalyzed Asymmetric Alkylation of Imines with Dialkylzinc and Related Reactions

Ken-ichi Yamada and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo, Kyoto 606-8501, Japan

Received January 9, 2008

Contents

1. Introduction

The catalytic asymmetric addition reactions of organometallic reagents to C=N double bonds of imines are fundamentally important processes, which provide convenient and versatile routes to optically active amines bearing a stereogenic center at the α-position. Optically active α-branched amines are important chiral building blocks, and are abundantly present in biologically active compounds, such as methoxyphenamine (a β_2-adrenergic antagonist for treatment of asthma), rivastigmine (an AcCh esterase inhibitor for treatment of Alzheimer's disease), tamsulosin (a selective α_1-adrenergic antagonist to improve urinary trouble due to prostatic hyperplasia), and repaglinide (a blocker of ATP-dependent K^+ channels in β cells used as a hypoglycemic agent) (Figure 1).

Asymmetric addition to C=N double bonds has been achieved based on the use of a chiral auxiliaries[1] or chiral ligands.[2] In 1982, Takahashi and co-workers reported the pioneering work of a chiral auxiliary-controlled asymmetric addition of organolithium reagents to imines **1** derived from aldehydes and valinol or phenylglycinol (Scheme 1).[3,4]

The chiral auxiliary strategy is still an important technology from a practical point of view because separation of the diastereomeric products prior to cleavage of the chiral auxiliary provides enantiomerically pure products. In the past two decades, the asymmetric additions of organometallic reagents to the C=N double bonds of imines in the presence of a stoichiometric or catalytic amount of a chiral ligand have been developed as a new technology for the synthesis of optically active amines, including alkaloids. The ligand-induced enantioselective synthesis has the potential for direct recovery and reuse of the unchanged chiral ligands. In 1990, Tomioka and co-workers reported the first chiral ligand-controlled asymmetric addition reaction of organometallic compounds to C=N double bonds of imines with organolithium reagents activated by a chiral amino ether ligand **5** (Scheme 2).[5] Even with 5 mol % of ligand **5**, enantiomerically enriched amine **6** was produced, though with moderate ee, opening up the door to catalytic asymmetric addition reactions of organometallic reagents to a C=N double bond of an imine.[6]

Denmark and co-workers also showed the excellent ability of asymmetric induction of (−)-sparteine and bisoxazoline ligands and the catalytic use of these ligands for addition of organolithium reagents to imines (Scheme 3).[7]

In 1992, Soai and co-workers reported the first catalytic asymmetric addition reaction of a dialkylzinc reagent to a C=N double bond.[8] In the presence of chiral amino alcohol **11**, addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines proceeded with high enantioselectivity (Scheme 4). Surprisingly good enantioselectivity was observed even with 10 mol % of the amino alcohol, although the chemical yield was not satisfactory.

Since these early examples, considerable energetic approaches toward the catalytic asymmetric addition of organometallic reagents to C=N double bonds of imines have appeared. Among these, chiral π-allylpalladium-catalyzed allylation with allylstannane[9] or allylsilane,[10] and rhodium-MOP-based phosphine-catalyzed arylation with arylstannanes[11] showed impressive early success. A key concept is catalytic generation of reactive organometal−chiral ligand complexes from corresponding less reactive organometallic reagents in situ. Excellent feature articles have been published on this exciting topic.[1f,h,12] However, in great contrast to the chiral amino alcohol catalyzed asymmetric alkylation of aldehydes with organozinc reagents, which has become a very effective and general method,[13] the catalytic asymmetric

* To whom correspondence should be addressed. Tel: 81-(0)75-753-4553. Fax: 81-(0)75-753-4604. E-mail: tomioka@pharm.kyoto-u.ac.jp.

10.1021/cr078370u CCC: $71.00
Published on Web 07/25/2008

Ken-ichi Yamada was born in 1973 in Tokyo, Japan. He completed his Ph.D. under the supervision of Professor Masakatsu Shibasaki in 2001 (University of Tokyo, Japan). He joined Kyoto University as an Assistant Professor in 2001 and has worked in the laboratory of Professor Kiyoshi Tomioka since then. He was promoted to Associate Professor in 2006. He received the Pharmaceutical Society of Japan Award for Young Scientists in 2007. His research interests are in synthetic organic chemistry, asymmetric synthesis, and organometallic chemistry.

Kiyoshi Tomioka, born in 1948 in Tokyo, Japan, is a Professor of the Graduate School of Pharmaceutical Sciences, Kyoto University. He received his Ph.D. from the University of Tokyo in 1976 under the direction of Prof. S. Yamada. He worked as a postdoctoral fellow with Prof. A. I. Meyers at Colorado State University in 1976−1978. He joined the University of Tokyo as a Research Associate in 1978 and was promoted to Associate Professor in 1983. He moved to Osaka University as a Professor in 1992. He has been a Professor at Kyoto University since 1996. He received The Pharmaceutical Society of Japan Award in 2003. His research interests are in synthetic organic chemistry, asymmetric synthesis, organometallic chemistry, and molecular architecture.

addition of simple alkylmetals to imines that satisfies high catalytic performance in chemical yield and enantioselectivity had not been achieved until very recently copper-catalyzed asymmetric addition of dialkylzinc to imines appeared.[14] In this review, we focus on these recently developed copper-catalyzed asymmetric reactions and some related reactions including other copper-catalyzed asymmetric addition reactions of imines. For the reactions of stabilized carbanions, such as enolates, nitronates, and cyanide, the previous report is recommended as an excellent review.[12d]

2. Reactivity of Imine

The addition to imines has been limited by the poor electrophilicity of the azomethine carbon atom, in comparison with that of a carbonyl group.[1f] This poor electrophilicity is attributable to the less polarity of C=N double bonds (C=N 0.9 D vs C=O 2.3 D) due to the smaller electronegativity

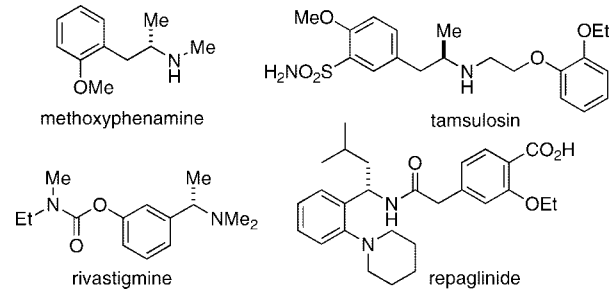
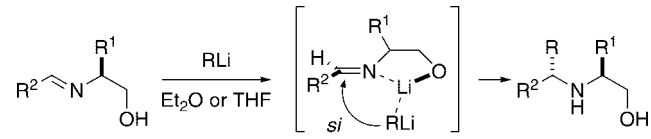


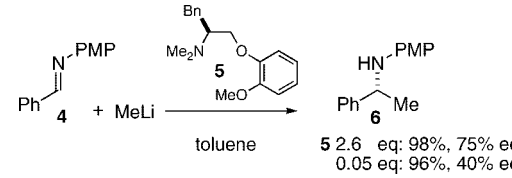
Figure 1. Selected examples of biologically significant α-chiral amines.

Scheme 1

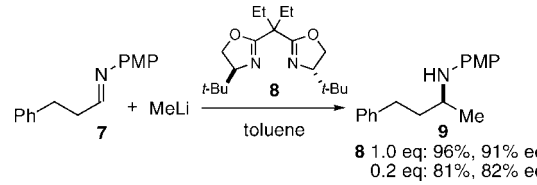


R^1 = *i*-Pr, Ph
R^2 = Et, Bn, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-furyl, 2-thienyl, 3-thienyl, ferrocenyl
R = Me, Bu, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4

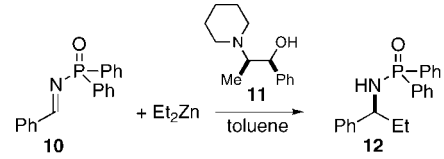
Scheme 2



Scheme 3



Scheme 4



of nitrogen (Pauling 3.0) than that of oxygen (Pauling 3.5).[15] This difference in electronegativity also results in the less stability of amide (p*K*a for H_2N-H ca. 38)[16] than hydroxide (p*K*a for HO−H ca. 16),[17] which are formed by addition of organometallic reagents to C=N and C=O double bonds, respectively, suggesting the addition reaction to C=N double bonds should be thermodynamically much more disfavored than that to C=O double bonds.

The lower electrophilicity of imines has been overcome by attaching activating substituents on the imine nitrogen atom as well as by a Lewis acid activation of imines. Also, increased nucleophilicity of the organometallic reagents has been utilized. A nonsubstituted imine **13** and frequently used activated imines **14**−**18** are shown in Figure 2 along with

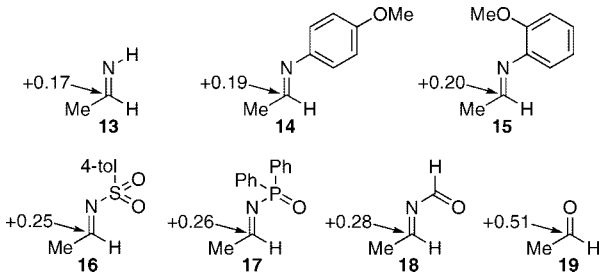


Figure 2. Structure of acetaldehyde (**19**) and its imines **13**−**18**, and the natural atomic charges in electrons on the carbonyl or azomethine carbons.

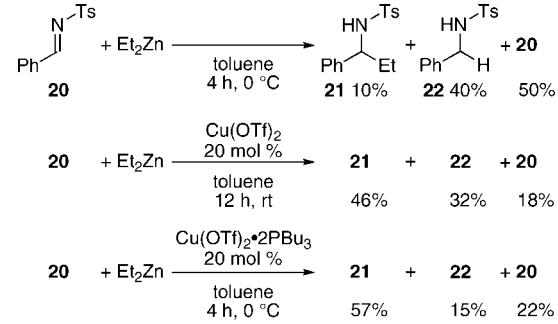
the corresponding aldehyde **19**. All these substituents on the imine nitrogen atoms have the ability to stabilize a negative charge on the nitrogen atom, resulting from addition of organometallic reagents, by delocalization over the aromatic rings or on the electronegative oxygen atoms. The atomic charges of the azomethine carbons, given by the HF/6-31G* level molecular orbital calculations, are shown in Figure 2, suggesting increased electrophilicity of imines **14**−**18**.

3. Dialkylzinc Reagents

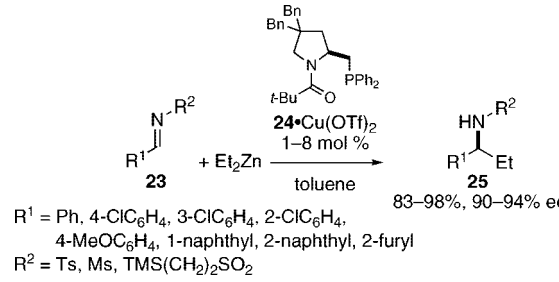
Dialkylzinc reagents are less nucleophilic organometallic compounds and, without any activation, react slowly with aldehydes and very slowly or not at all with imines and nitriles because the C−Zn bond is rather nonpolar due to relatively large electronegativity of zinc (Pauling 1.6) and an sp-hybridized linear geometry at the zinc.[18] From a viewpoint of functional group tolerance, the mild reactivity of dialkylzinc reagents is advantageous as an alkyl group donor if an appropriate activation is possible. Although commercially available dialkylzinc reagents are so far limited to those having C_1 to C_4 alkyl groups, several practical preparation methods have been developed especially by Knochel and co-workers.[19] A variety of functionalized dialkylzinc reagents can be prepared via iodine−zinc exchange without[20] or with copper salt[21] or irradiation,[22] boron−zinc exchange,[23] or nickel-catalyzed hydrozincation.[24]

The successful applications of dialkylzinc reagents in organic synthesis have been summarized in several reviews.[19] Dialkylzinc reagents have been efficiently activated by transmetalation or complexation with a variety of transition metal salts. In 1993, this strategy was nicely applied to copper-catalyzed asymmetric conjugate addition reactions[25,26] by Alexakis and co-workers.[27] Activation of dialkylzinc was also achieved by coordination of a Lewis basic ligand that forces a bent geometry at the zinc, where the increased polarity of C−Zn bond makes the alkyl group more nucleophilic and the zinc more Lewis acidic.[18] The catalytic asymmetric alkylation of aldehydes with dialkylzinc reagents using catalytic amount of chiral amino alcohol ligands is one of the most successful asymmetric catalytic reactions.[13] Soai and co-workers showed this amino alcohol strategy was applicable to the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines as shown in Scheme 4. However, due to lower electrophilicity of the imines, the catalyst efficiency was not as good as the corresponding reaction with aldehydes. Recently, chiral ligand complexes of certain metals, such as copper, zirconium, or hafnium, were found to accelerate the addition reaction of dialkylzinc reagents to C=N double bonds of imines. In the next section, the copper-catalyzed reactions will be discussed. The other

Scheme 5



Scheme 6



metals-catalyzed asymmetric addition reactions as well as recent progress of the chiral Lewis base strategy will also be introduced in section 6.

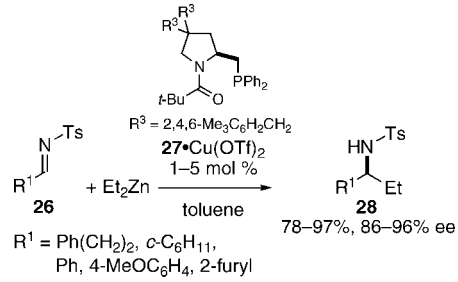
4. Copper-Catalyzed Asymmetric Addition of Dialkylzinc to Imines

4.1. Addition to C=N Double Bonds of Imines

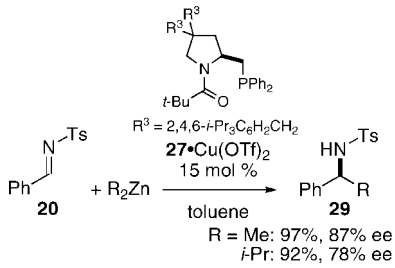
As shown in section 3, enhancement of nucleophilicity of alkyl groups of dialkylzinc reagents has been realized by transmetalation or complexation with transition metal salts.[19−24] Among these transition metal salts, a copper salt with an appropriate chiral phosphine ligand has been widely studied and utilized as an excellent catalyst for asymmetric conjugate addition of dialkylzinc and other organometallic reagents.[25] In 2000, Tomioka and co-workers first reported the acceleration effect of a copper−phosphine complex on the addition reaction of dialkylzinc reagents to imines, and developed a catalytic asymmetric reaction using a chiral amidophosphane ligand.[14a] The addition of diethylzinc to *N*-tosyl imine **20** was a sluggish reaction which gave adduct **21** in low yield along with significant amounts of reduced product **22** and recovered imine **20** after 4 h at 0 °C (Scheme 5). The addition of copper(II) triflate accelerated the addition, and **21** was obtained in improved yield with decreased amounts of **22** and **20** after 12 h at room temperature. A complex of the copper salt and a phosphine further enhanced the reaction rate as well as suppressed the production of **22** to give **21** in further improved yield after 4 h at 0 °C.

The first asymmetric addition of diethylzinc to imines has been achieved by using chiral amidophosphane **24** as a ligand.[14a] Imines **23** bearing tosyl, mesyl, or 2-trimethylsilylethanesulfonyl groups on the nitrogen atom were good acceptors to give the addition products with high enantioselectivity up to 94% in high yield using 1 mol % of **24**−copper complex (Scheme 6). It is noteworthy that only a negligible amount of reduced products were observed in this asymmetric version. Other *N*-substituents were also

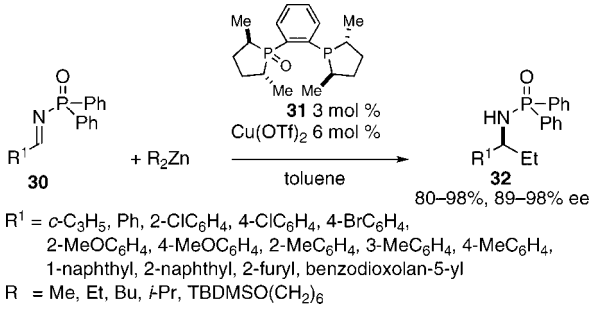
Scheme 7



Scheme 8



Scheme 9



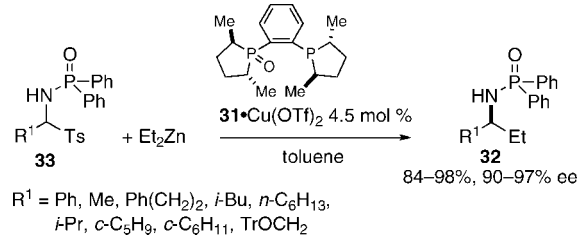
tested.[28] *N*-(Diphenylphosphinoyl) imine **23** (R^1 = Ph, R^2 = $Ph_2P(O)$) was found to be less effective, giving product **25** with lower enantioselectivity and yield (38%, 34% ee). In contrast, the reaction of *N*-methoxycarbonyl imine **23** (R^1 = Ph, R^2 = MeO_2C) took place smoothly, but almost racemic **25** (90%, 3% ee) was obtained. The addition to *N*-PMP imine **23** (R^1 = Ph, R^2 = 4-$MeOC_6H_4$) failed to proceed.

The modification of ligand **24** revealed that a bulkier substituent on the pyrrolidine ring improves the catalyst efficiency in chemical yield and enantioselectivity. The best ligand for the addition of diethylzinc was found to be amidophosphane **27** (R^3 = 2,4,6-$Me_3C_6H_2CH_2$) to afford adducts **28** with increased enantioselectivity and yield (Scheme 7).[14b,c] Enolizable aliphatic imines were also applicable in this reaction.

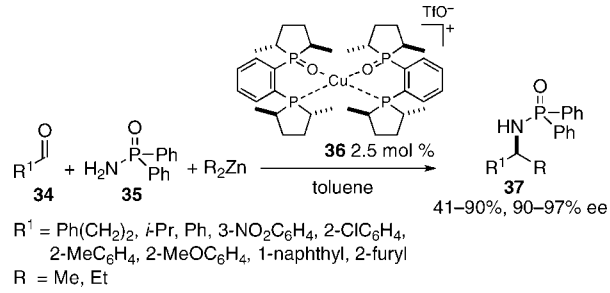
The previous limitation on the use of other dialkylzinc reagents was overcome also by a bulky amidophosphane. Generally, dimethylzinc shows less donor ability in addition reactions. The asymmetric addition of dimethylzinc as well as diisopropylzinc to *N*-tosyl imine **20** was catalyzed by more bulky amidophosphane **27** (R^3 = 2,4,6-*i*-$Pr_3C_6H_2CH_2$) to give adducts **29** with good enantioselectivity in high yield (Scheme 8).[14c]

Charette and co-workers reported another example of this copper-catalyzed reaction with a unique chiral bisphosphine monoxide ligand **31** (Scheme 9).[29] A wide range of *N*-(diphenylphosphinoyl) imines **30** derived from aromatic aldehydes were converted into the corresponding adducts **32** with high enantioselectivity in high chemical yield. Facile

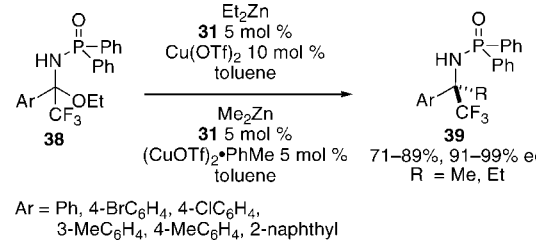
Scheme 10



Scheme 11



Scheme 12

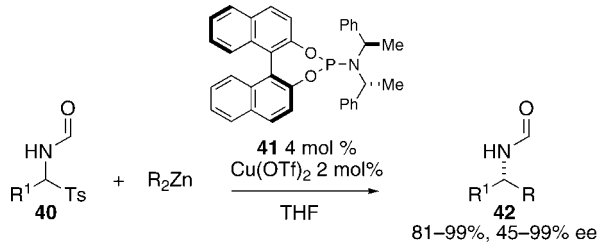


cleavage of a diphenylphosphinoyl group from a nitrogen atom under mildly acidic conditions, e.g., methanolic HCl at room temperature,[30] is an advantage of the use of the *N*-(diphenylphosphinoyl) activating group. Dialkylzinc having siloxy group was shown to be applicable, highlighting an advantage of the functional group tolerance of diorganozinc reagents. Only non-enolizable imines were applicable to this reaction.

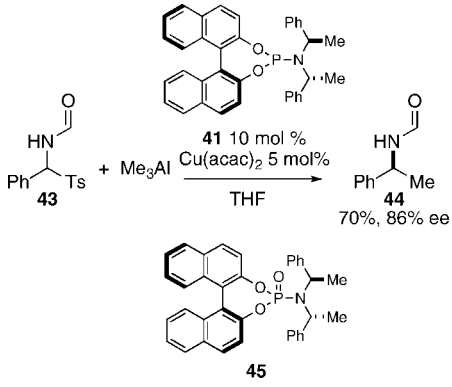
Instead of the direct use of unstable enolizable aliphatic *N*-(diphenylphosphinoyl) imines, two alternatives were proven to be effective. Sulfinate adducts **33** generates the corresponding imines in situ, which then underwent ethylation to produce adducts **32** with high enantioselectivity and yield (Scheme 10).[31] Three-component type reaction of aldehyde **34**, phosphinamide **35**, and dialkylzinc also worked for enolizable aldehydes to produce adducts **37** with high enantiomeric excess (Scheme 11).[32] Methylation with dimethylzinc was also possible. In this reaction, copper complex **36** was employed as a precatalyst.

Development of asymmetric addition reaction to ketimines is generally more difficult than that to aldimines because of lower electrophilicity of the C=N double bonds as well as difficulty of discrimination between two alkyl groups more than that between an alkyl group and a hydrogen atom.[33] Charette and a co-worker reported the copper-catalyzed asymmetric addition of dialkylzinc reagents to ketimines with high enantioselectivity, though non-enolizable rather activated electron-deficient ketimines were used (Scheme 12).[34] In this reaction, the hemiaminal derivatives **38** served as an imine precursor. The best copper source was different for diethyl and dimethylzinc, respectively.

Scheme 13



Scheme 14

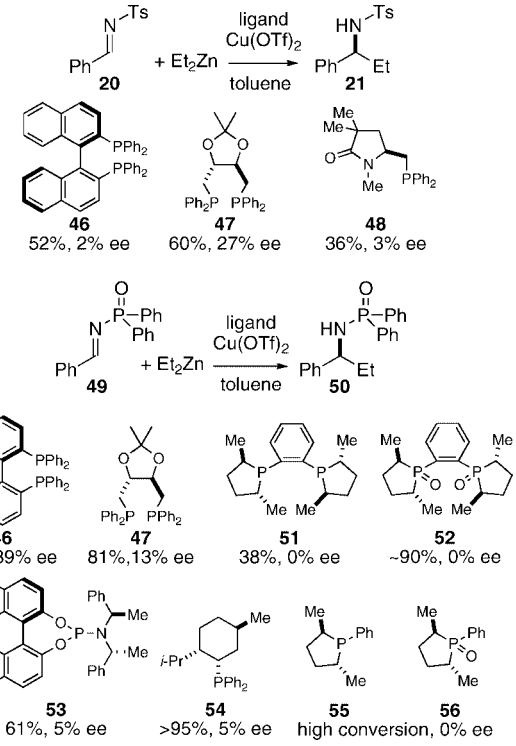


Recently, Feringa, Minnaard, and a co-worker reported an efficient copper-catalyzed addition of dialkylzinc reagents to *N*-formyl imines generated in situ from their sulfinate adducts **40** (Scheme 13).[35] Monodentate phosphoramidite ligand **41** was an effective chiral ligand for this reaction. A variety of sulfinates **40** including those derived from enolizable aliphatic aldehydes were applicable to the reaction.

In a methylation reaction, trimethylaluminum showed better ability of enantioselective transfer of a methyl group to imine than dimethylzinc and copper acetoacetonate was the copper source of choice (Scheme 14). In the reaction with trimethylaluminum, phosphoramide **45**, generated by in situ oxidation of **41**, was found to play an important role as a chiral analog of HMPA to modify a structure of the actual catalyst that gives the product with good ee. Actually, racemic **44** was obtained under conditions where no oxidation of **41** to **45** took place. In contrast, neither the presence of nor the absence of phosphoramide **45** much affected the result of the reaction using diethylzinc as an alkylating agent. It is also interesting that the observed sense of facial selectivity was opposite to each other for dialkylzinc and trimethylaluminum reagents.

In contrast to the well-studied mechanisms for the copper-catalyzed conjugate addition reactions,[25] that for the copper-catalyzed addition reactions of dialkylzinc reagents to imines has not been fully discussed or documented yet. Possibly, the reaction proceeds via metal exchange leading to the formation of a zinc cuprate−ligand complex based on analogy to the conjugate addition reactions. The ligand effects on the reactions showed that the oxygen functionalities of ligands **24**, **27**, and **31** play important role in enantioselectivity as well as an efficient transfer of an alkyl group to *N*-tosyl and *N*-(diphenylphosphinoyl) imines. As shown in Scheme 5, the tributylphosphine−copper complex accelerated the addition of diethylzinc to *N*-tosyl imine **20**,

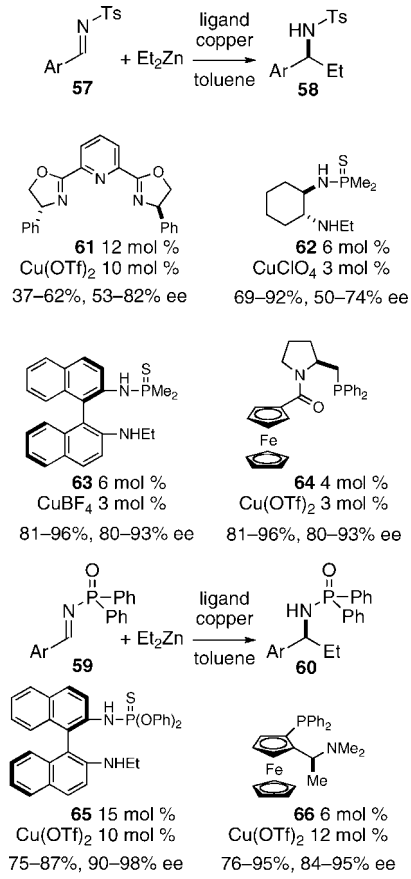
Scheme 15



giving adduct **21** in 57% yield. Chiral bis(phosphine oxide) **52**, monophosphine oxide **56**, and monophosphines **54** and **55** also showed an ability to accelerate the addition to *N*-(diphenylphosphinoyl) imine **49**, but without any enantioselectivity (Scheme 15).[29a] Interestingly, phosphoramidite **53** that gave excellent results in the copper-catalyzed asymmetric conjugate addition reaction to enones[36] failed to promote the addition reaction to imine **49** efficiently with meaningful stereocontrol, though its diastereomer **41** gave excellent results for the addition to *N*-formyl imines (Scheme 13). Conventional chiral bisphosphine ligands (*R*)-BINAP (**46**), (−)-DIOP (**47**), and Me-DuPHOS (**51**)[37] were found to be less effective in the reaction of *N*-tosyl and *N*-(diphenylphosphinoyl) imines **20** and **49**, giving adducts **21** and **50** with lower enantioselectivity, respectively.[29a] Another type of chiral amidophosphane **48** had poor catalytic performance, producing almost racemic **21** in low chemical yield. These results may suggest the importance of coordination to zinc and/or hemilabile chelation to copper, by the oxygen moieties of **24**, **27** and **31** in the addition reactions to *N*-tosyl and *N*-(diphenylphosphinoyl) imines. The asymmetric addition of diethylzinc to imines **23** (R^1 = Ph) bearing a bulky substituent (R^2 = 2,4,6-$Me_3C_6H_2SO_2$) or an electron-deficient sulfonyl group (R^2 = $C_6F_5SO_2$ or 4-$NO_2C_6H_5$) was significantly retarded.[14a] This observation implies that coordination to copper or zinc by a sulfonyl oxygen followed by conjugate addition-type alkylation takes place. In contrast, an electron-withdrawing substituent on the phosphorus atom of *N*-phosphinoyl imine slightly improved an enantioselectivity of the addition reaction using bisphosphine monoxide **31**.[29c]

Other ligands were also reported for asymmetric addition of diethylzinc (Scheme 16). Although bisoxazoline ligands **61**[38] and 1,2-cyclohexanediamine-based amino thiophosphoramide ligand **62**[39] were less efficient for this reaction, binaphthyl-based amino thiophophoramide ligands **63** and **65**[40] were reported to give good results for *N*-tosyl[41] and

Scheme 16

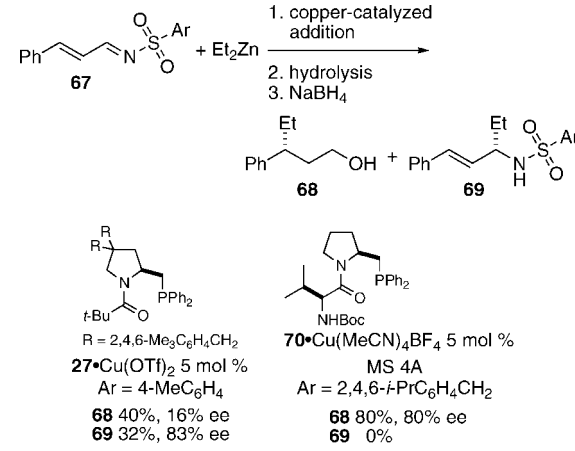


N-(diphenylphosphinoyl)[42] aromatic imines, respectively. Recently, ferrocene-connected amidophosphane **64**[43] and ferrocene-based[44] aminophosphane **66**[45] were reported as a new ligand for the reaction of *N*-tosyl and *N*-(diphenylphosphinoyl) imines **57** and **59**, respectively. In the reaction of *N*-(diphenylphosphinoyl) imines, amidophosphane **64** was less effective.[46]

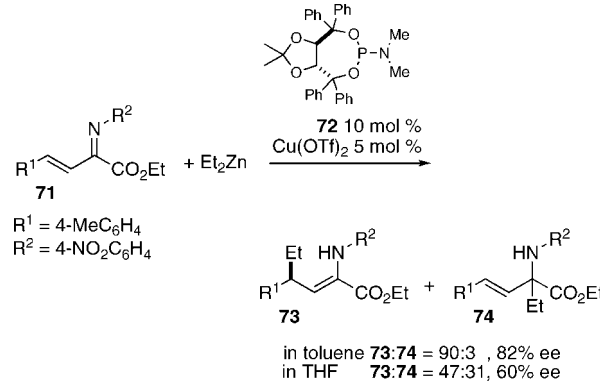
4.2. Conjugate Addition to α,β-Unsaturated Imines

When α,β-unsaturated imines are the substrate for the addition reaction, the selectivity between 1,2-addition and 1,4-conjugate addition is a matter of concern. For the asymmetric conjugate addition of Grignard reagents and organolithium reagents, α,β-unsaturated aldimines were shown to be good Michael acceptors.[47] Besides, a copper catalyst with dialkylzinc reagents is the established combination of reagents for the asymmetric conjugate addition of alkyl groups to enones.[25] Accordingly, one may expect the copper-catalyzed asymmetric addition of dialkylzinc reagents to α,β-unsaturated imines to proceed in quite 1,4-selective manner. Interestingly, however, the regioselectivity of the reaction with diethylzinc and imine **67** derived from cinnamaldehyde was found to depend on a substituent on imines and a phosphane ligand, and under the standard conditions for saturated imines, 1,4-adduct **68** and 1,2-adduct **69** were obtained in 4:3 ratio after hydrolysis and reduction (Scheme 17).[48] Under the conditions optimized for the conjugate addition, where molecular sieves 4A slightly improved the enantioselectivity, only 1,4-adduct **68** was obtained with good enantiomeric excess. Even with α,β-unsaturated ketimine **71**, the regioselectivity was reported to be solvent dependent.[49]

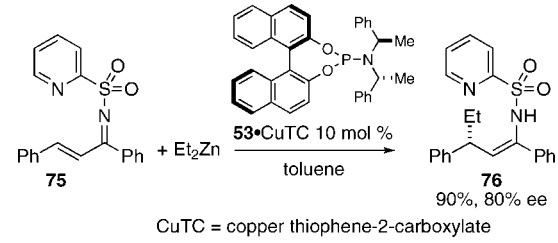
Scheme 17



Scheme 18



Scheme 19



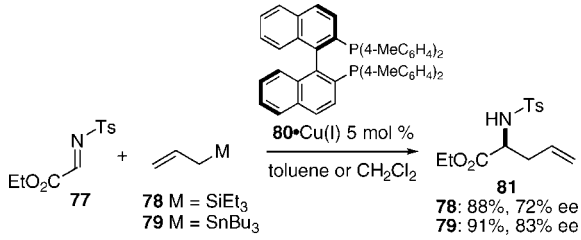
In contrast to the preferred 1,4-conjugate addition in toluene, a significant amount of 1,2-adduct **74** was produced in THF (Scheme 18). In the reaction of ketimine **75** having an internal Lewis basic functionality, the 1,4-conjugate addition proceeded exclusively with good enantioselectivity in the presence of chiral ligand **53**, probably via pseudointramolecular delivery of alkylmetal species by the pyridine functionality to the β-position (Scheme 19).[50] Interestingly, the reaction of the corresponding imine derived from cinnamaldehyde under the same conditions proceeded in completely 1,2-selective manner, though the enantioselectivity was not reported.

5. Copper-Catalyzed Asymmetric Allylation, Arylation, and Alkynylation Reactions of Imines

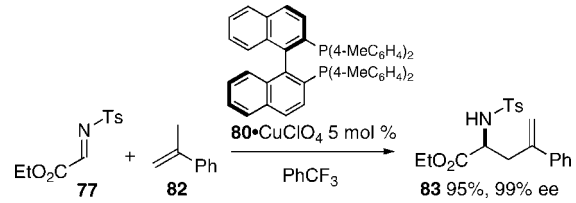
5.1. Copper-Catalyzed Asymmetric Allylation of Imines

In 1998, the first catalytic asymmetric addition of an allyl group to imines was achieved by Yamamoto and co-workers

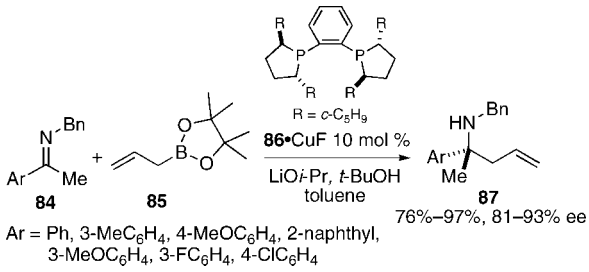
Scheme 20



Scheme 21



Scheme 22



using chiral π-allyl palladium complex as a catalyst with allylstannane[9] or allylsilane.[10] Afterward, many stoichiometric or catalytic asymmetric allylation reactions of imines have been developed,[51] including addition of chiral allylzinc species.[52]

Soon after the first report by Yamamoto, it was shown that copper catalysis is also effective for allylation reactions. Lectka's group and Jørgensen's group independently developed the tol-BINAP (**80**)−copper(I)-catalyzed asymmetric allylation of *N*-sulfonyl glyoxylate imine **77** with allylsilane **78**[53] and that with allylstannane reagent **79**,[54] respectively (Scheme 20).

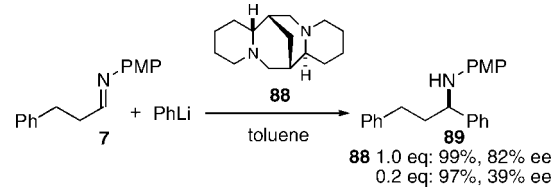
tol-BINAP (**80**)−copper also catalyzed asymmetric allylation of imine **77** via ene reaction to provide homoallylic amine **83** with very high enantioselectivity and yield (Scheme 21).[55,56] This result clearly shows that copper(I) can efficiently activate C═N double bonds of imines as a Lewis acid catalyst and not only increase the donor ability of carbonucleophiles by transmetalation or complexation.

The copper catalysis showed its efficacy when Shibasaki and co-workers developed the first catalytic asymmetric allylation of ketimines.[57] *N*-Benzyl ketimines **84** were allylated with good to high enantioselectivity with allylboronate **85** using DuPHOS **86**−CuF as a catalyst (Scheme 22). The alkoxide additive facilitates the boron−copper transmetalation as is usually the case in the transition metal-catalyzed reactions with organoborane species.[58]

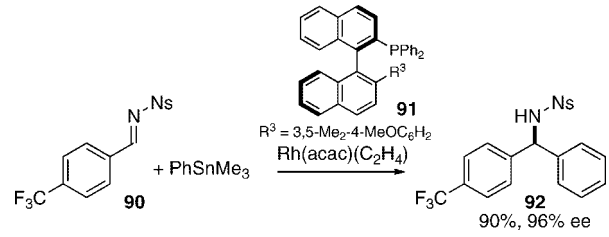
5.2. Copper-Catalyzed Asymmetric Arylation of Imines[59]

In 1994, Denmark and co-workers showed that (−)-sparteine (**88**) was a suitable chiral ligand to control enantioselectivity in the addition of phenyllithium to imine

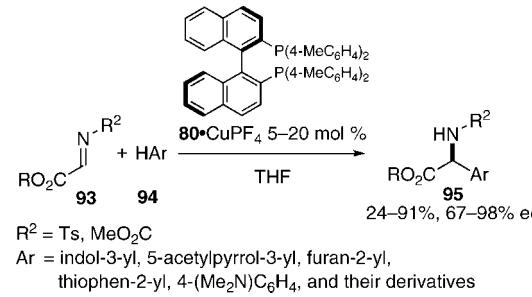
Scheme 23



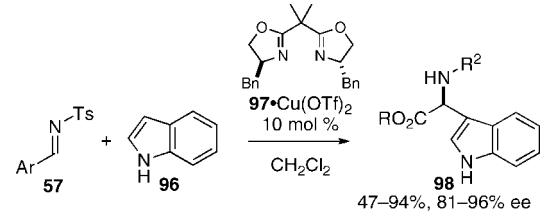
Scheme 24



Scheme 25



Scheme 26

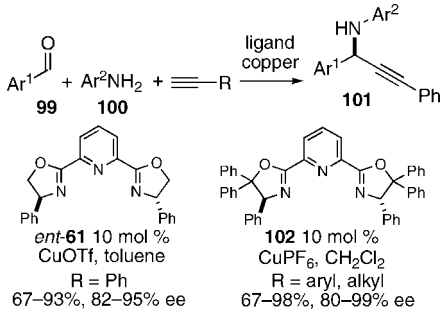


(Scheme 23).[7a] Although selectivity decreased, enantiomerically enriched amine **89** was obtained with a substoichiometric amount of ligand **88**.

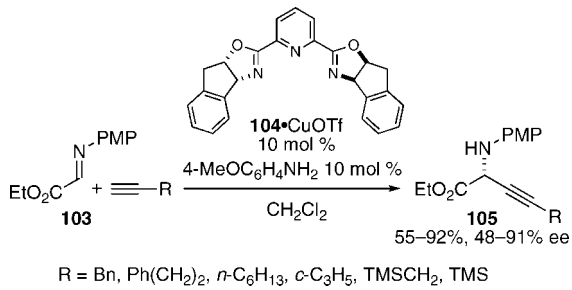
The first catalytic asymmetric arylation of imine was achieved by Hayashi and a co-worker in 2000 with a chiral phosphine **91**−rhodium catalyst and arylstannane species (Scheme 24).[11] Recently, the aryl group donor has been replaced by less toxic aryltitanium[60] or arylboron[61] reagents.

Copper also catalyzes the arylation of glyoxylate imine **93** via Friedel−Crafts-type reaction as a Lewis acid.[62] Electron-rich aromatic compounds **94**, such as indole, pyrrole, furan, thiophene, and *N,N*-dimethylaniline derivatives, underwent addition to the C═N double bond of imine **93** to provide amino ester derivatives **95** with good to very high enantioselectivity (Scheme 25).[63,64] *N*-Tosyl imines **57** were also good substrate for the asymmetric Friedel−Crafts-type reaction catalyzed by a bisoxazoline **97**−copper complex (Scheme 26).[65] Recently, a gold−silver-catalyzed Friedel−Crafts-type reaction of imine was reported, though the asymmetric version has not been developed.[66] A catalytic amount of chiral Brønsted acid[67,68] and chiral thiourea,[69] or a stoichiometric amount of chiral chlorosilane[70] were also reported as promoters of this type of asymmetric transformation.

Scheme 27



Scheme 28



5.3. Copper-Catalyzed Asymmetric Alkynylation of Imines[71]

The activation of terminal alkynes as zinc acetylide nucleophiles followed by their asymmetric addition to C═O double bonds of carbonyl compounds with chiral amino alcohol ligands is a well-established methodology.[72] Carreira and co-workers first showed applicability of this methodology to addition to C═N double bonds in the racemic addition to nitrones.[73] A few asymmetric versions have been developed using a stoichiometric amount of chiral amino alcohol[74] or chiral dialkoxide as a Lewis base.[75] Recently, a catalytic reaction has been reported using a chiral amino alcohol though the lowest catalyst loading was 40 mol %.[76] Until now, copper played a major role also in this type of asymmetric reactions. As is the case in zinc salts, copper salts also form π-complexes with terminal alkynes, which are converted into the corresponding copper acetylide nucleophiles upon treatment with a weak base, such as an amine. Other metals, such as iridium,[77–79] gold,[80–82] and silver[83,84] are also known to catalyze racemic addition of a terminal alkyne to imine.

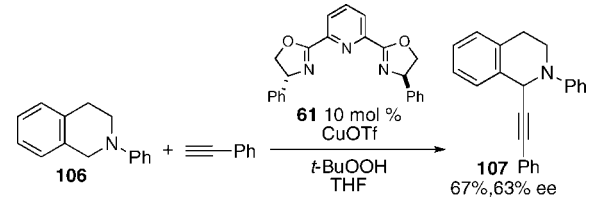
The first catalytic asymmetric addition of terminal alkynes to C═N double bonds was achieved by Li and a co-worker in 2002, using chiral bisoxazoline *ent*-**61**−copper complex with imines generated in situ from aromatic aldehydes **99** and amines **100** (Scheme 27).[85] The enantioselectivity and yield as well as generality of alkyne were improved by using modified ligand **102**.[86]

Bisoxazoline **104** was also reported to be a better ligand than **61** for the addition to glyoxylate imine **103** (Scheme 28).[87] Interestingly, the reaction rate was accelerated in the presence of 10 mol % of *p*-anisidine. Not only simple 1-alkynes and arylethyne, but synthetically useful trimethylsilylethyne also afforded the corresponding product, though yield and enantioselectivity were moderate (55%, 48% ee).

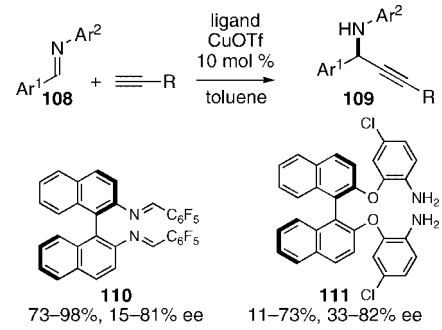
Direct asymmetric alkynylation at the benzylic position of tetrahydroisoquinoline **106** was demonstrated using this catalyst via oxidation (Scheme 29).[88]

Binaphthyl-based ligands were also utilized for this catalysis. Several substituents of 1,1′-binaphthyl-2,2′-diamine-derived diimine ligands were examined for this copper-catalyzed reaction, and pentafluorophenyl-substituted ligand **110** was found to be the best (Scheme 30).[89] Recently, new binaphthyl-based diamino diether ligand **111** was also developed for catalytic asymmetric addition of terminal alkynes to imine.[90]

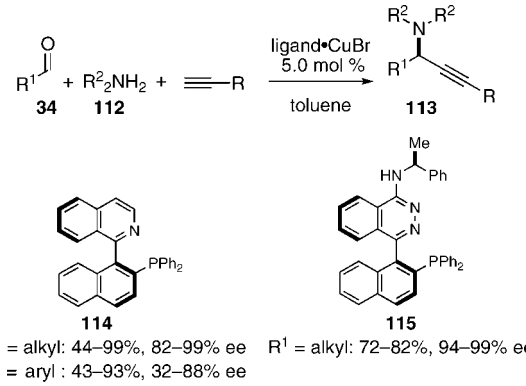
Scheme 29



Scheme 30

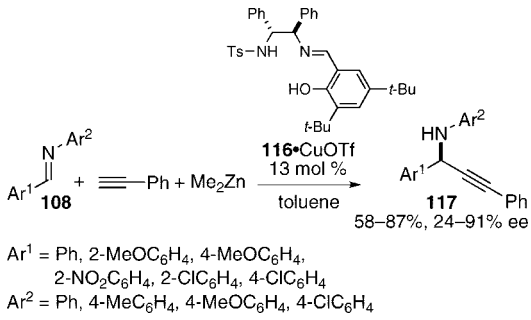


Scheme 31

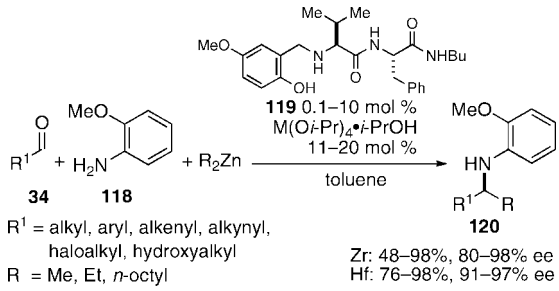


The above-mentioned reactions were not compatible with enolizable imines. In 2002, Knochel and co-workers succeeded in the catalytic asymmetric alkynylation of enamines, thus enolizable imines. Metal salts and chiral ligands were screened and the combination of copper(I) bromide[91] and Quinap (**114**) was found to be the best. A variety of enamines were converted into propargylamines with good enantioselectivity (up to 90% ee).[92] It was proposed that the reaction proceeded via in situ generated iminium species followed by addition of an alkynyl group to the C═N double bond. The limitation of this reaction, that only enolizable aldehydes are applicable, was overcome by utilizing a three-component protocol. Iminium species, generated in situ from an aldehyde and a secondary amine, underwent the asymmetric alkynylation reaction under the same conditions.[93] Generally, higher enantioselectivity was observed compared to the previous enamine protocol, and non-enolizable aromatic aldehydes were also applicable, though usually the enantioselectivity was lower than those of aliphatic aldehydes (Scheme 31). It is noteworthy that synthetically useful trimethylsilylethyne also provided corresponding propargylamine with high yield

Scheme 32



Scheme 33



and enantioselectivity. Improvement of enantioselectivity was achieved with a new ligand **115**.[94]

Recently, copper-catalyzed asymmetric alkynylation of aromatic *N*-aryl imines **108** with terminal alkynes, dimethylzinc, and the catalytic amount of chiral tridentate *N,O*-ligand **116** was reported (Scheme 32).[95] In this reaction, addition of dimethylzinc improved enantioselectivity as well as chemical yield. Diastereoselective addition of a chiral alkynylboron reagent to achiral imine[96,97] and aluminum acetylides to chiral *N*-sulfinyl imines were also reported.[98] As we mentioned above, diorganozinc reagents were not popular donors of allyl, aryl, and alkynyl groups, so far.

6. Other Catalysts for Asymmetric Alkylation of Imines with Diorganozinc Reagents

6.1. Asymmetric Addition of Diorganozinc to Imines Catalyzed by Group 4 Metals

Hoveyda, Snapper, and co-workers reported that dipeptide **119**−zirconium[99] and hafnium[100] complexes catalyzed asymmetric addition of dialkylzinc reagents to *N*-(2-methoxyphenyl) imines with high efficiency. These zirconium and hafnium catalyst were successfully applied to three-component reaction of aldehyde, arylamine, and dialkylzinc. A broad range of imines, derived from aromatic, aliphatic, and propargyl aldehydes, including further functionalized aldehydes, were generated in situ and converted into the corresponding adducts **120** in good to very high yield with high enantioselectivity (Scheme 33).

According to the observation that the sense of facial selectivity in the addition depends on the stereochemistry of the phenylalanine moiety of ligand **119**, it was proposed that the terminal amide carbonyl of phenylalanine acts as a Lewis base to deliver the dialkylzinc reagent to the *si* face of the imine that is fixed and activated by coordination to the zirconium or hafnium moiety (Figure 3, above). The approach of a dialkylzinc reagent that is coordinated to the amide carbonyl oxygen, to the *re* face of the imine is unfavorable (Figure 3, below): for

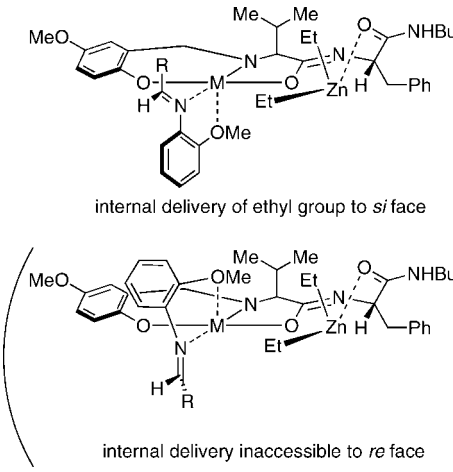
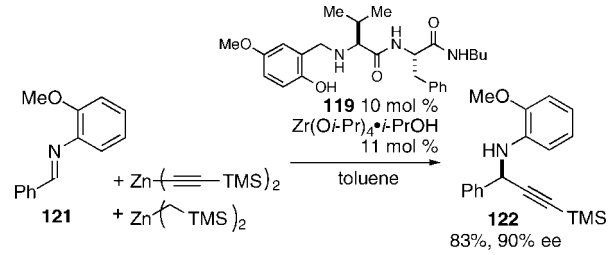
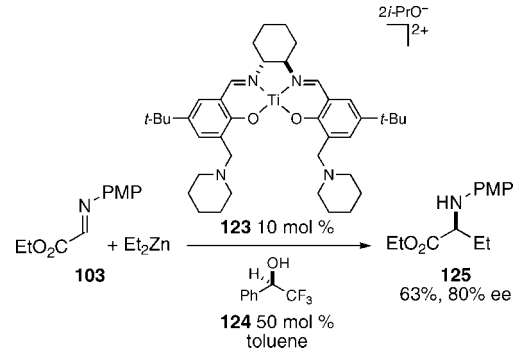


Figure 3. Proposed rationale for stereochemical outcomes.

Scheme 34



Scheme 35

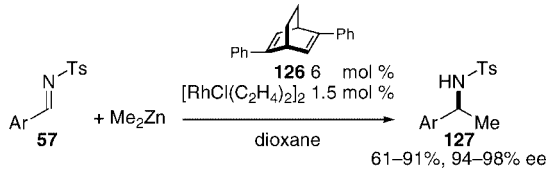


the delivery to the *re* face, the phenylalanine moiety with the opposite stereochemistry should be favorable.

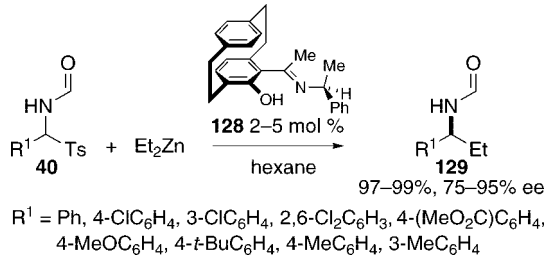
The chiral zirconium complex also catalyzed asymmetric alkynylation of aromatic *N*-aryl imines **121** with a mixed alkynylzinc reagent (Scheme 34).[101] Solubility of the dialkynylzinc reagent was much improved by being mixed with the dialkylzinc, without which conversion was only 5−10% under the conditions similar to those of Scheme 34. Only the alkynyl group was transferred to the C=N double bond to give selectively propargylamine **122**, implying higher donor ability of the alkynyl group than that of the alkyl group.

Asymmetric addition of diethylzinc to imine **103** derived from glyoxylate was catalyzed by a titanium−salen complex **123** bearing piperidine moieties in the presence of chiral alcohol **124** as an additive to produce α-amino acid derivative **125** with 80% ee (Scheme 35).[102] Although the role was not clear,[103] alcohols with a pK_a between 12 and 14 were found to be effective additives, among which **124** was the best. Internal delivery of diethylzinc by a coordination of the piperidine moiety was proposed also for this example.

Scheme 36



Scheme 37



6.2. Asymmetric Addition of Dialkylzinc to Imines Catalyzed by Late Transition Metals

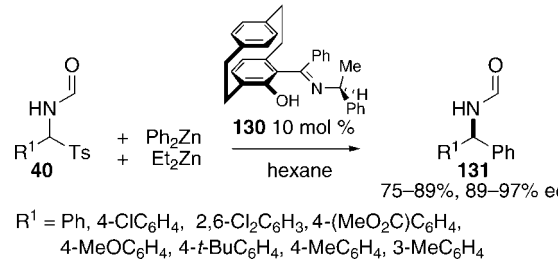
Recently, Hayashi and co-workers showed that rhodium−chiral diene **126** catalyst is applicable to the asymmetric addition of dimethylzinc to *N*-tosyl imines **57** with high enantioselectivity (Scheme 36).[104] Because dimethylzinc generally shows smaller donor ability in the copper-catalyzed reactions, this rhodium-catalyzed reaction may be a useful alternative. It is also reported that a catalytic amount of nickel complexes extremely promote addition of dialkylzinc reagents to C=N double bonds of *N*-sulfonyl and *N*-(diphenylphosphinoyl) imines.[105] Although the reported examples were racemic catalysis, an asymmetric version with an appropriate chiral ligand would be the next entry of this topic.

6.3. N,O-Ligand Catalysis

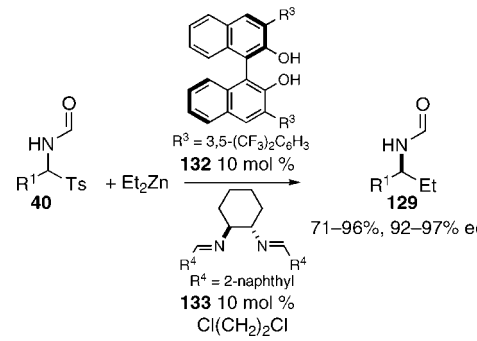
Since Soai and co-workers reported the chiral amino alcohol-controlled asymmetric addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines in 1992 (Scheme 4),[8a] many types of *N*,*O*-ligands have been introduced to the addition reaction of dialkylzinc reagents to C=N double bonds of imines. Among these were norephedrine,[106] 2-amino-1,2-diphenylethanol,[107] 9-aminofulorene-9-methanol,[108] cinchona alkaloid,[109] oxazoline-4-methanol,[110] and prolinol[111] derivatives. These *N*,*O*-ligands form a zinc alkoxide *N*,*O*-chelate with dialkylzinc reagents, and increase polarity of the zinc−alkyl bond and, hence, nucleophilicity of the alkyl group as well as Lewis acidity of the zinc.[13a] However, efficient catalysis with less than 10 mol % of *N*,*O*-ligands had hardly been achieved. This lower efficiency of the Lewis base catalysis has recently been overcome by using more electrophilic *N*-formyl imine as an acceptor. Bräse and a coworker reported that in the presence of the chiral [2,2]paracyclophane-based imino alcohol ligand **128** (1−5 mol %), dialkylzinc reagents underwent asymmetric addition to *N*-formyl imines, generated in situ from the corresponding sulfinate adduct **40**, with high enantioselectivity and chemical yield (Scheme 37).[112]

The [2,2]paracyclophane-based *N*,*O*-ligand strategy was nicely applied to asymmetric phenylation of aromatic *N*-formyl imines using a mixed organozinc reagent generated from diethylzinc and diphenylzinc (Scheme 38).[113] The use of diphenylzinc alone led to lower enantioselectivity, which the authors attributed to competitive uncatalyzed background

Scheme 38



Scheme 39



reaction of diphenylzinc. It is speculated that mixing diphenylzinc and diethylzinc should result in a diorganozinc species with less donor ability. Interestingly, no ethylated product was observed in this reaction, indicating transfer of a phenyl group is much faster than that of an ethyl group.

Combination of chiral binaphthol-based ligand **132** and 1,2-diimine **133** was also reported as an effective promoter for the asymmetric addition of diethylzinc to *N*-formyl imines (Scheme 39).[114]

7. Incorporation of Radical Pathways

It has been reported that dialkylzinc reagents could initiate and mediate a radical process.[115] When dialkylzinc reagents react with molecular oxygen[105a,116–122] or are heated with a copper salt,[19b] alkyl radicals are formed and radical chain processes are initiated. Accordingly, asymmetric reaction with a dialkylzinc reagent sometimes suffers from side reactions through radical pathways.[121a,123] These side reactions may be prevented by strictly controlled conditions under inert gas[121a] or by a radical scavenger as an additive.[123]

8. Conclusions

In the past decade, methodology for asymmetric C−C bond formation by an addition reaction to a C=N double bond has been greatly improved and many catalytic reactions have been developed. Copper catalysis plays one of the most important parts in this field because of its high ability to activate a C=N double bond of an imine as well as to facilitate alkyl group transfer from organometallic reagents. In spite of many developed efficient catalyses, application of enolizable imines is still sometimes problematic, and few asymmetric catalysts are available for ketimines. Widening the applicability of these substrates would be the target of the next decade. Apparently, dialkylzinc reagents are one of the ideal organometallic reagents as a functionalized alkyl group donor because of their mild reactivity. We believe that further development of this field will provide a convenient approach to a variety of chiral nitrogen-containing molecules.

9. References

(1) Reviews for addition to C═N controlled by chiral auxiliary: (a) Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157. (b) Zhou, P.; Chen, B.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (c) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253. (d) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (e) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651. (f) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (g) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13. (h) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(2) (a) Tomioka, K. *Synthesis* **1990**, 541. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (d) Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull.* **2000**, *48*, 315. (e) Iguchi, M.; Yamada, K.; Tomioka, K. In *Organolithiums in Enantioselective Synthesis*; Hodgson, D. M., Ed.; Springer, Berlin, 2003; p 22.

(3) (a) Takahashi, H.; Suzuki, Y.; Inagaki, H. *Chem. Pharm. Bull.* **1982**, *30*, 3160. (b) Takahashi, H.; Chida, Y.; Suzuki, T.; Yanaura, S.; Suzuki, Y.; Masuda, C. *Chem. Pharm. Bull.* **1983**, *31*, 1659. (c) Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull.* **1983**, *31*, 2183. (d) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 2895. (e) Takahashi, H.; Chida, Y.; Yoshii, T.; Suzuki, T.; Yanaura, S. *Chem. Pharm. Bull.* **1986**, *34*, 12071.

(4) (a) Wu, M.-J.; Pridgen, L. N. *Synlett* **1990**, 636. (b) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (c) Pridgen, L. D.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237. (d) Mokhallalati, M. K.; Pridgen, L. N. *Synth. Commun.* **1993**, *23*, 2055. (e) Muralidharan, K. R.; Mokhallalati, M. K.; Pridgen, L. N. *Tetrahedron Lett.* **1994**, *35*, 7489. (f) Pridgen, L. D.; Mokhallalati, M. K.; McGuire, M. A. *Tetrahedron Lett.* **1997**, *38*, 1275.

(5) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681.

(6) (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095. (b) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603. (c) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron* **1994**, *50*, 4429. (d) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527. (e) Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Chem. Pharm. Bull.* **1997**, *45*, 1705. (f) Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Heterocycles* **1997**, *46*, 165. (g) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533. (h) Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153.

(7) (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. *J. Am. Chem. Soc.* **1994**, *116*, 8797. (b) Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884. (c) Denmark, S. E.; Sttif, C. M. *J. Org. Chem.* **2000**, *65*, 5875.

(8) (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097. (b) Soai, K.; Suzuki, T.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1994**, 317. (c) Hayase, T.; Inoue, Y.; Shibata, T.; Soai, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2509. (d) Suzuki, T.; Narisada, N.; Shibata, T.; Soai, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2519. (e) Sato, I.; Kodaka, R.; Soai, K. *J. Chem. Soc., Perkin Trans 1* **2001**, 2912. (f) Sato, I.; Hosoi, K.; Kodaka, R.; Soai, K. *Eur. J. Org. Chem.* **2002**, 3115. (g) Soai, K.; Sato, I. C. R. *Geoscience* **2003**, *6*, 1097.

(9) (a) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (b) Bao, M.; Nakamura, H.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 131. (c) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.

(10) (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614. (b) Fernendes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735.

(11) (a) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (b) Hayashi, T.; Ishigetani, M. *Tetrahedron* **2001**, *57*, 2589.

(12) (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (e) Bäse, S.; Baumann, T.; Dahmen, S.; Vogt, H. *Chem. Commun.* **2007**, 1881.

(13) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382. (d) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(14) (a) Fujihara, H.; Nagai, K.; Tomioka, K. *J. Am. Chem. Soc.* **2000**, *122*, 12055. (b) Nagai, K.; Fujihara, H.; Kuriyama, M.; Yamada, K.; Tomioka, K. *Chem. Lett.* **2002**, 8. (c) Soeta, T.; Nagai, K.; Fujihara, H.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2003**, *68*, 9723.

(15) Brown, B. R. In *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Oxford University Press: Oxford. 1994.

(16) Buncel, E.; Menon, B. *J. Organomet. Chem.* **1977**, *141*, 1.

(17) Harned, H. S.; Robinson, R. A. *Trans. Faraday Soc.* **1944**, *36*, 973.

(18) Boersma, J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds; Pergamon Press: New York, 1982; p 823.

(19) Reviews: (a) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117. (b) Knochel, P. *Synlett* **1995**, 393. (c) Nakamura, M.; Nakamura, E. *J. Synth. Org. Chem., Jpn.* **1998**, *56*, 632. (d) Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275. (e) Boudier, A.; Bromm, L. O.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414.

(20) (a) Rozema, M. J.; Sidduri, A. R.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956. (b) Micouin, L.; Knochel, P. *Synlett* **1997**, 327. (c) Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 1017.

(21) (a) Rozema, M.; Eisenberg, C.; Lütjens, H.; Ostwald, R.; Belyk, K.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 3115. (b) Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 5849.

(22) Charette, A. B.; Beauchemin, A.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1998**, *120*, 5114.

(23) (a) Langer, F.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *Synlett* **1994**, 410. (b) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229. (c) Boudier, A.; Darcel, C.; Flachsmann, F.; Micouin, L.; Oestreich, M.; Knochel, P. *Chem. Eur. J.* **2000**, *6*, 2748. (d) Boudier, A.; Hupe, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2294. (e) Hupe, E.; Knochel, P. *Org. Lett.* **2001**, *3*, 127.

(24) (a) Vettel, S.; Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 1023. (b) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473.

(25) Reviews for copper-catalyzed asymmetric conjugate addition reactions: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Krause, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 283. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (d) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (e) López, F.; Minnaard, A. J.; Feringa, B. L. *Acc. Chem. Res.* **2006**, *40*, 179.

(26) Reviews for enantioselective conjugate addition reactions: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, Chapter 31. (b) Tomioka, K. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 12. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Tomioka, K. In *Comprehensive Asymmetric Catalysis;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 2004; Supplement to Chapter 31.1, p 109. (e) Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M. *Synthesis* **2007**, 1279.

(27) Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.

(28) Fujihara, H. Ph.D. Thesis, Kyoto University, Japan, 2001.

(29) (a) Boezio, A. A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 1692. (b) Boezio, A. A.; Pytkowitz, J.; Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 14260. A review: (c) Charette, A. B.; Boezio, A. A.; Côte, A.; Moreau, E.; Pytkowicz, J.; Desrosiers, J.-N.; Legault, C. *Pure Appl. Chem.* **2005**, *77*, 1259.

(30) (a) Ramage, R.; Atrash, B.; Hopton, D.; Parrott, M. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1217. (b) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357.

(31) (a) Côté, A.; Coezio, A. A.; Charette, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5405. (b) Desrosiers, J.-N.; Côté, A.; Charette, A. B. *Tetrahedron* **2005**, *61*, 6186.

(32) Côté, A.; Charette, A. B. *J. Org. Chem.* **2005**, *70*, 10864.

(33) Riant, O.; Hannedouche, J. *Org. Biomol. Chem.* **2007**, *5*, 873.

(34) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743.

(35) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940.

(36) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Varis, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865.

(37) Bisphosphine **51** can serve as a precursor of monoxide **31** when **51** is premixed with a copper salt before the addition of dialkylzinc reagent: Côte, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6525.

(38) Li, X.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Tetrahedron: Asymmetry* **2003**, *14*, 3819.

(39) Shi, M.; Zhang, W. *Tetrahedron: Asymmetry* **2003**, *14*, 3407.

(40) A review: Zhang, W.; Shi, M. *Synlett* **2007**, 19.

(41) Wang, C.-J.; Shi, M. *J. Org. Chem.* **2003**, *68*, 6229.

(42) (a) Shi, M.; Wang, C.-J. *Adv. Synth. Catal.* **2003**, *345*, 971. (b) Shi, M.; Lei, Z.-Y.; Xu, Q. *Adv. Synth. Catal.* **2006**, *348*, 2237.

(43) Wang, M.-C.; Xu, C.-L.; Zou, Y.-X.; Liu, H.-M.; Wang, D.-K. *Tetrahedron Lett.* **2005**, *46*, 5413.

(44) A review: Arrayás, R. G.; Adrio, J.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7674.
(45) Wang, M.-C.; Liu, L.-T.; Hua, Y.-Z.; Zhang, J.-S.; Shi, Y.-Y.; Wang, D.-K. *Tetrahedron: Asymmetry* **2005**, *16*, 2531.
(46) Wang, M.-C.; Xu, C.-L.; Cheng, F.; Ding, X. *Tetrahedron* **2006**, *62*, 12220.
(47) (a) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951. (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732. (d) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351. (e) Tomioka, K.; Shioya, Y.; Nagaoka, Y.; Yamada, K. *J. Org. Chem.* **2001**, *66*, 7051.
(48) Soeta, T.; Kuriyama, M.; Tomioka, K. *J. Org. Chem.* **2005**, *70*, 297.
(49) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405.
(50) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 7451.
(51) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815.
(52) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1995**, *37*, 8997.
(53) (a) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67.
(54) Fang, X.; Johannsen, M.; Yao, S.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 4844.
(55) Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006.
(56) Yao, S.; Fang, X.; Jørgensen, K. A. *J. Chem. Soc., Chem. Commun.* **1998**, 2547.
(57) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687.
(58) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(59) A review for the asymmetric arylation reactions: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.
(60) Hayashi, T.; Kawai, M.; Tokunaga, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6125.
(61) (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (d) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789. (e) Duan, H.; Jia, Y.; Wang, L.; Zhou, Q. *Org. Lett.* **2006**, *8*, 2567.
(62) Reviews: (a) Jørgensen, K. A. *Synthesis* **2003**, 1117. (b) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550.
(63) Johannsen, M. *Chem. Commun.* **1999**, 2233.
(64) (a) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4114. (b) Saaby, Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352.
(65) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621.
(66) Luo, Y. M.; Li, C. J. *Chem. Commun.* **2004**, 1930.
(67) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *45*, 629.
(68) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086.
(69) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558.
(70) Shirakawa, S.; Berger, R.; Leighton, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 2858.
(71) A review for asymmetric addition of an alkynyl group to C═N double bonds: Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263.
(72) Reviews: (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095.
(73) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245.
(74) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.
(75) Wei, W.; Kobayashi, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2006**, *35*, 176.
(76) Zani, L.; Eichhorn, T.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 2587.
(77) Sakaguchi, S.; Kubo, T.; Ishii, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2534.
(78) (a) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (b) Fischer, C.; Carreira, E. M. *Synthesis* **2004**, 1497.
(79) Yamazaki, Y.; Fujita, K.; Yamaguchi, R. *Chem. Lett.* **2004**, *33*, 1316.
(80) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.
(81) Kantam, M. L.; Prakash, B. V.; Reddy, C. R. V.; Sreedhar, B. *Synlett* **2005**, 2329.
(82) Lo, V. K.-Y.; Liu, Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2006**, *8*, 1529.
(83) Wei, C.; Li, Z.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473.
(84) Ji, J.-X.; Au-Yeung, T. T.-L.; Wu, J.; Yip, C. W.; Chan, A. S. C. *Adv. Synth. Catal.* **2004**, *346*, 42.
(85) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C.; Mague, J. T.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (c) Rosa, J. N.; Santos, A. G.; Afonso, C. A. M. *J. Mol. Catal. A* **2004**, *214*, 161. (d) McDonagh, C.; O'Conghile, P.; Gebbink, R. J. M. K.; O'Leary, P. *Tetrahedron Lett.* **2007**, *48*, 4387.
(86) Bisai, A.; Singh, V. *Org. Lett.* **2006**, *8*, 2405.
(87) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 11196.
(88) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.
(89) (a) Benaglia, M.; Negri, D.; Dell'Anna, G. *Tetrahedron Lett.* **2004**, *45*, 8705. (b) Orlandi, S.; Colombo, F.; Benaglia, M. *Synthesis* **2005**, 1689. (c) Colombo, F.; Benaglia, M.; Orlandi, S.; Usuelli, F.; Celentano, G. *J. Org. Chem.* **2006**, *71*, 2064.
(90) Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379.
(91) Early report on CuCl-catalyzed alkynylation of enamine: Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1462.
(92) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797.
(93) (a) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (b) Gommermann, N.; Knochel, P. *Chem. Commun.* **2004**, 2324. (c) Dube, H.; Gommermann, N.; Knochel, P. *Synthesis* **2004**, 2015. (d) Gommermann, N.; Gherig, A.; Knochel, P. *Synlett* **2005**, 2796. (e) Gommermann, N.; Knochel, P. *Synlett* **2005**, 2799. (f) Gommermann, N.; Knochel, P. *Tetrahedron* **2005**, *61*, 11418. (g) Gommermann, N.; Knochel, P. *Chem. Eur. J.* **2006**, *12*, 4380.
(94) Thomas, F.; Knöpfel, T. F.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.
(95) Liu, B.; Liu, J.; Jia, X.; Huang, L.; Li, X.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2007**, *18*, 1124.
(96) Wu, T. R.; Chong, J. M. *Org. Lett.* **2006**, *8*, 15.
(97) Gonzalez, A. Z.; Canales, E.; Soderquist, J. A. *Org. Lett.* **2006**, *8*, 3331.
(98) Turcaud, S.; Berhal, F.; Royer, J. *J. Org. Chem.* **2007**, *72*, 7893.
(99) (a) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 984. (b) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409. (c) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244.
(100) Akullian, L.; Porter, J.; Traverse, J.; Snapper, M.; Hoveyda, A. *Adv. Synth. Catal.* **2005**, *347*, 417.
(101) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3237.
(102) Basra, S.; Fennie, M.; Kozlowski, M. *Org. Lett.* **2006**, *8*, 2659.
(103) A review on additives in asymmetric catalysis: Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570.
(104) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979.
(105) (a) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87. (b) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron* **2007**, *63*, 1167.
(106) El-Shehawy, A. A. *Tetrahedron: Asymmetry* **2006**, *17*, 2617.
(107) (a) Zhang, X.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Let.* **2001**, *42*, 6369. (b) Zhang, H.-L.; Zhang, X.-M.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 1399. (c) Zhang, H.-L.; Jiang, F.; Zhang, X.-M.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *Chem. Eur. J.* **2004**, *10*, 1481.
(108) Jimeno, C.; Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 3157.
(109) (a) Beresford, K. J. M. *Tetrahedron Lett.* **2002**, *43*, 7175. (b) Beresford, K. J. M. *Tetrahedron Lett.* **2004**, *45*, 6041.
(110) (a) Zhang, X.; Lin, W.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron Lett.* **2002**, *43*, 1535. (b) Zhang, X.-M.; Zhang, H.-L.; Lin, W.-Q.; Gong, L.-Z.; Mi, A.-Q.; Cui, X.; Jiang, Y.-Z.; Yu, K.-B. *J. Org. Chem.* **2003**, *68*, 4322.
(111) Almansa, R.; Guijarro, D.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 896.
(112) Dahmen, S.; Bräse, S. *J. Am. Chem. Soc.* **2002**, *124*, 5940.
(113) Hermanns, N.; Dahmen, S.; Bolm, C.; Bräse, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3692.
(114) (a) Zhang, H.-L.; Liu, H.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Synlett* **2005**, 615. (b) Liu, H.; Zhang, H.-L.; Wang, S.-J.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2005**, *16*, 2901.
(115) Reviews: (a) Yamada, K.; Yamamoto, Y.; Tomioka, K. *J. Synth. Org. Chem., Jpn.* **2004**, *62*, 1158. (b) Bazin, S.; Feray, L.; Bertrand, M. P. *Chima* **2006**, *60*, 260.
(116) Miyano, S.; Hashimoto, H. *J. Chem. Soc. D: Chem. Commun.* **1971**, 1418.
(117) Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335.

(118) (a) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (b) Bertrand, M. P.; Feray, R.; Nouguier, R.; Perfetti, P. *J. Org. Chem.* **1999**, *64*, 9189. (c) Bertrand, M. P.; Coantic, S.; Feray, L.; Nouguier, R.; Perfetti, P. *Tetrahedron* **2000**, *56*, 3951. (d) Bazin, S.; Feray, L.; Siri, D.; Naubron, J.-V.; Bertrand, M. P. *Chem. Commun.* **2002**, 2506. (e) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261. (f) Bazin, S.; Feray, L.; Vanthuyne, N.; Siri, D.; Bertrand, M. P. *Tetrahedron* **2007**, *63*, 77.

(119) (a) Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 176. (b) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. (c) Miyabe, H.; Asada, R.; Yoshida, K.; Takemoto, Y. *Synlett* **2004**, 540. (d) Miyabe, H.; Asada, R.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 385.

(120) Feringa, B. L.; Kellog, R. M.; van der Deen, H. *Org. Lett.* **2000**, *2*, 1593.

(121) (a) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509. (b) Yamada, K.; Yamamoto, Y.; Tomioka, K. *Org. Lett.* **2003**, *5*, 1797. (c) Yamamoto, Y.; Yamada, K.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 795. (d) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *64*, 1531. (e) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Chen, J.-B.; Tomioka, K. *Tetrahedron Lett.* **2004**, *45*, 6595. (f) Yamamoto, Y.; Maekawa, M.; Akindele, T.; Yamada, K.; Tomioka, K. *Tetrahedron* **2005**, *61*, 379. (g) Akindele, T.; Yamamoto, Y.; Maekawa, M.; Umeki, H.; Yamada, K.; Tomioka, K. *Org. Lett.* **2006**, *8*, 5729.

(122) (a) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043. (b) Denes, F.; Cutri, S.; Perez-Luna, A.; Chemla, F. *Chem. Eur. J.* **2006**, *12*, 6506.

(123) Li, K.; Alexakis, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7600.

CR078370U