With compliments of the Author

The Development of A³-Coupling (Aldehyde-Alkyne-Amine) and AA³-Coupling (Asymmetric Aldehyde-Alkyne-Amine)

Chunmei Wei,[a] Zigang Li,[a] Chao-Jun Li*[a,b]

[a] Department of Chemistry, Tulane University, New Orleans, Louisiana 70118, USA

[b] Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec H3A 2K6, Canada
   Fax +1(514)3983797; E-mail: cj.li@mcgill.ca

Abstract: This account briefly describes the authors' recent efforts to develop the catalytic coupling of aldehyde, alkyne, and amine, as well the asymmetric catalytic coupling of aldehyde, alkyne, and amine.

Key words: aldehyde-alkyne-amine coupling, asymmetric, catalysis

1   Introduction

Chiral nitrogen-containing compounds are widely found in nature and many of them show important biological properties. Hence, the development of methods for synthesizing diastereomerically and enantiomerically pure amines is a major objective for organic chemists. Traditionally, similar to the addition of carbanions to the carbonyl group of aldehydes and ketones,[1] the addition of organometallic reagents to the C=N bonds of imines or imine derivatives is an important and efficient process to afford many useful nitrogen-containing building blocks. Furthermore, a new stereogenic center and a C−C bond are formed in a single step in such an addition reaction. The formation of propargyl amines via the addition of acetylenic moiety to a C=N bond is a useful method in synthesis.[2] The resulting alkynyl addition derivatives can undergo further transformations and are versatile synthetic tools.[3]

Optically active propargyl amines are important synthetic intermediates for the synthesis of various nitrogen-con-

taining compounds and are components of bioactive compounds (such as pharmaceutical agents) and natural products.[4] However, the reactive metal alkynilides are often prepared by deprotonation of terminal alkynes by using highly reactive organometallic reagents such as BuLi,[5] EtMgBr[6] or LDA[7] in a separate step. In addition, many metal alkynilides are usually not easy to handle because the reaction must be carried out under anhydrous solvent, inert atmosphere, and low temperature conditions. Therefore, development of a method for the direct alkynylation of imines and their derivatives performed under mild conditions without utilizing a stoichiometric amount of a highly reactive organometallic reagent would be highly desirable. It would be even more desirable to develop the asymmetric version of such a reaction. Additionally, there has been greater interest in recent years in developing organic reactions in aqueous media which has the potential of simplifying synthesis (e.g. elimination of protection-deprotection steps) and minimizing environmental impacts.[8] With these combined objectives in mind, we recently developed a highly efficient direct coupling of aldehyde, alkyne, and amine (Scheme 1) as well as the asymmetric coupling of aldehyde, alkyne, and amine (Scheme 2). Such reactions were found to be successful in organic solvents, in water, in ionic liquids, and under neat conditions.
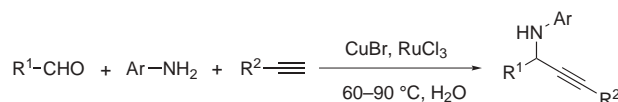
Scheme 1
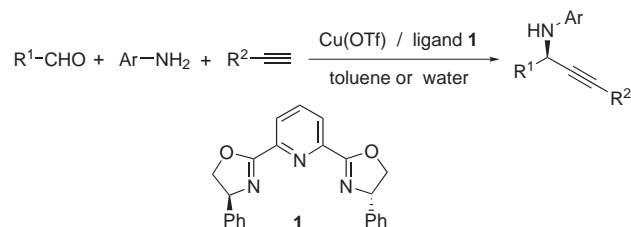
Scheme 2

2 Background

Our investigation of such reactions stemmed from our long-term objective of developing Barbier−Grignard-type reactions in water[9] and our interest in green chemistry.[10] Prior to this study, Barbier−Grignard-type carbonyl (and imine) allylation,[11] propargylation-allenylation,[12] alkenylation and arylation,[13] as well as related aldol-type reactions[14] (Scheme 3) have been developed under aqueous conditions through the efforts of various laboratories, including ours.[15] Very recently, we and others have also developed the addition of a simple alkyl group to aldehydes and imines in water by using reacting metal with unactivated alkyl halides.[16] However, we have met with continuous failure over the last decade in developing a Barbier−Grignard-type coupling reaction between carbonyl compounds (and imines) with alkynyl halides in water. In fact, such a reaction has never been successful until recently and the failure of the reaction was attributed to the strong sp-hybridized C−X bond.

Recently, our interest in the further greening of Barbier−Grignard-type reactions in water led us to develop related reactions that use only a catalytic amount of metals instead of a stoichiometric amount. The ruthenium-catalyzed olefin migration[17] and the subsequent tandem olefin migration-aldol reaction[18] provided us with significant impetus in this endeavor. This then led us to consider the

Biographical Sketches

Chunmei Wei received her B.Sc. from Peking University, M.Sc. from Zhongshan University, and Ph.D. from the Chinese University of Hong Kong (with T. L. Chan). She has been a postdoctoral fellow in Professor C. J. Li's group since 2001. Her current research interests include green chemistry, transition-metal catalyzed organic reactions in water, and development of new stereoselective methods in organic synthesis.
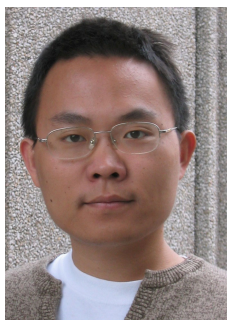
Zigang Li was born in 1978 (Hefei, China). He received his bachelor degree from the University of Science and Technology of China in 2001. Subsequently, he began his Ph.D. studies under the direction of Dr. Chao-Jun Li at Tulane University in New Orleans. His current research mainly focuses on environmentally-benign catalytic carbon-hydrogen activation reactions and their further applications.

Chao-Jun Li (born in 1963) received his B.Sc. at Zhengzhou University in 1983, M.Sc. (with T. H. Chan) at the Chinese Academy of Sciences in Beijing in 1998, and Ph.D. (with honor) at McGill University in 1992 under the direction of T. H. Chan and D. N. Harpp. After a NSERC Postdoctoral Fellow (1992−1994) in B. M. Trost's laboratories at Stanford University, he started his independent career in 1994 at Tulane University as an Assistant Professor, promoted to Associate Professor with tenure in 1998 and Full Professor in 2000. While at Tulane, he received a NSF Early Career Award (1997), an Outstanding Young Scientist Award (Overseas) from NSF of China (2000), a Presidential Green Chemistry Challenge Award by the US EPA (2001), a LAS Annual Faculty Research Award at Tulane (2002), an Eli Lilly Teaching Fellow (1995), and a Japan Society for Promotion of Science (Senior) Fellow (2002). He is an honorary research professor at the Chemistry Institute of Chinese Academy of Science in Beijing (since 1996) and was a visiting professor (with R. G. Bergman) at the University of California at Berkeley (2002). In 2003, he became a Canada Research Chair (Tier I) in Green Chemistry and a Professor of Chemistry at McGill University in Canada. His current research efforts are on developing catalytic organic reactions for 'Green Chemistry' and on synthesizing biologically important compounds.

Barbier−Grignard-type addition of a terminal alkyne to aldehyde and imine via the activation of the C−H bond, instead of the C−X bond, in water. It should be noted that within the past few years, there have been great developments by Knochel,[19] Carreira,[20] Jiang,[21] and others[22] in the direct addition of terminal alkynes to aldehydes by using various Lewis acids and bases in anhydrous organic solvent (Scheme 4). For example, InBr$_3$·Et$_3$N was used as a catalyst by Sakai to promote alkynylation of aldehyde and N,O-acetals.[23] Related asymmetric additions have also been developed by a number of groups.[24] In our own work, we focused on developing transition metal-catalyzed alkyne-aldehyde and alkyne-imine additions, with the expectation that the reactions developed will be able to survive in aqueous conditions. Late transition metals such as copper, gold, silver, and platinum metals were our focus because of their softness, which is less affected by 'hard' water. Subsequently, we developed a direct addition of terminal alkynes to aldehydes in water by using a ruthenium/indium bicatalyst system (Scheme 5).[25] This catalytic system can be applied to substituted aromatic aldehydes and aliphatic aldehydes without an α-hydrogen.
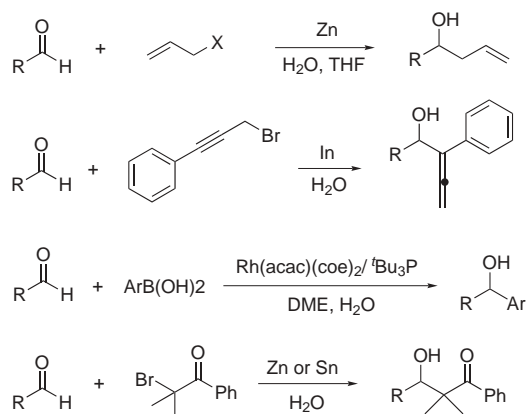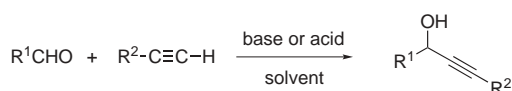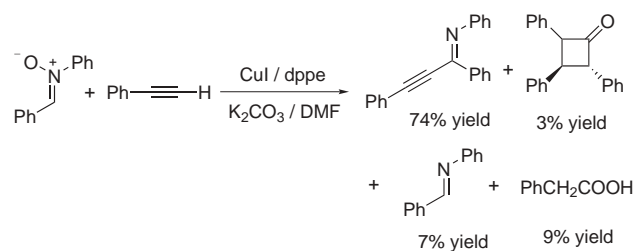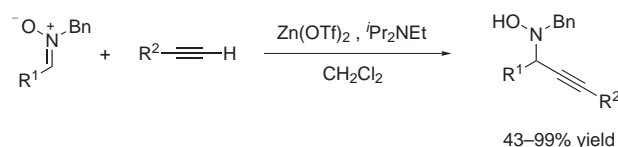

Scheme 3

Scheme 4
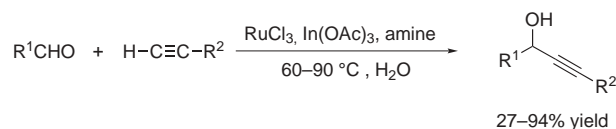
Scheme 5

3 The Development of Aldehyde-Alkyne-Amine Coupling (A^3-Coupling)

Recently, significant efforts have been made to develop methodologies to generate propargyl amines.[26] The direct 1,2-addition of terminal alkynes to the C=N double bond

in imines and their derivatives via activation of C−H bond in the terminal alkynes is a convenient route to synthesize propargyl amines. Prior to our studies, there had been no report of an effective direct addition of a terminal alkyne to an imine. Miura reported the addition of acetylene to nitrones through the initial formation of a dipolar cycloaddition (Scheme 6)[27] while Carreira had used a Zn(II)-catalyzed process in CH$_2$Cl$_2$ for the addition of terminal alkynes to nitrones to form propargyl N-hydroxyl amine adducts (Scheme 7).[28] Knochel reported an enantioselective synthesis of propargyl amines by copper-catalyzed addition of alkynes to enamines (Scheme 8).[29]
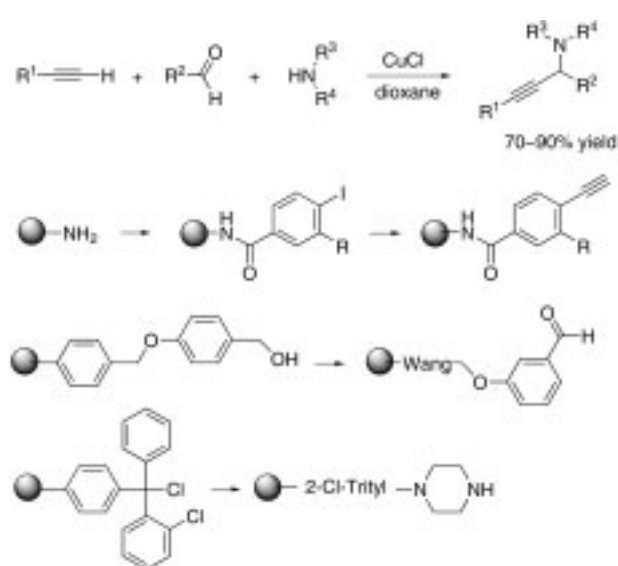

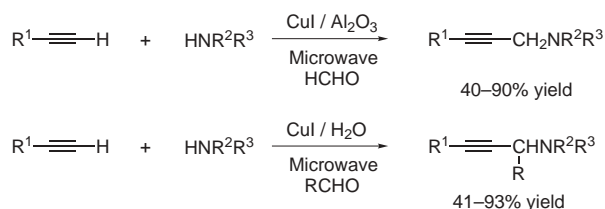**Scheme 6**

Scheme 7
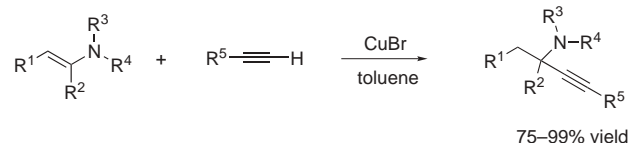
Scheme 8

3.1 Catalyzed by Cu (I)

For the direct addition of an alkyne to an imine, the difficulty lies in the stronger coordination between the Lewis acid and the product (amine) than between the Lewis acid and the starting material (imine). This stronger coordination implies that a catalytic amount of Lewis acid may not be enough for the reaction. On the other hand, a transition-metal catalyst that can coordinate the C=N bond may offset such an unfavorable factor. Recently, late-transition-metals have been found to be successful as catalysts in direct alkyne-imine additions. During our own investigations of catalytic alkyne-imine additions, Dax and coworkers reported the usage of copper as a transition metal catalyst for a solid-phase Mannich condensation of amines, aldehydes, and alkynes (Scheme 9).[30] This solid-phase Mannich reaction is an efficient method for the rapid synthesis of propargyl amines. The polymer-supported three-component Mannich condensation of acetylenes, aldehydes and secondary amines, similarly afforded the de-

sired Mannich adducts when one of the reactants was immobilized on a resin. In these cases, a copper (I) salt is needed to promote the reaction. Any single component can be attached to an appropriate solid support to make the methodology versatile from a synthetic perspective. The process did not require pre-preparation of the iminium species, and isolated products are usually of high purity. A microwave-assisted Mannich reaction of terminal alkynes, amines and formaldehyde in the presence of Cu(I) on Al_2O_3 was reported by Pagni[31] (Scheme 10) and others.[32] The microwave-enhanced Mannich condensations of aliphatic or aromatic terminal alkynes, secondary or primary amines with paraformaldehyde or formaldehyde, in the presence of CuI or CuCl doped Al_2O_3 without any organic solvent as a reaction medium, produced the corresponding amino-methylated adducts in good yields. The reaction can be promoted by microwave irradiation and is complete within several minutes. The process is highly efficient and is not hampered by the heterogeneity of the reaction. A similar reaction with aliphatic and aromatic aldehydes was also carried out in water under microwave irradiation to afford the coupling products.[33]
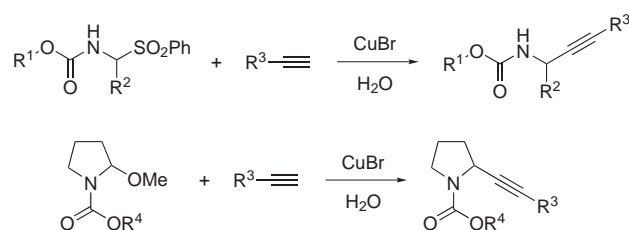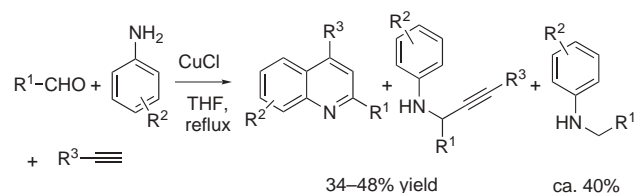

Scheme 9

Scheme 10

We had reported a copper-mediated coupling of alkynes with *N*-acylimines and *N*-acyliminium ions in water to generate propargyl amide derivatives[34] (Scheme 11). *N*-Acylimines or *N*-acyliminium ions can be generated in situ from amines containing a good leaving group at α-position − for example, α-phenylsulfonyl *N*-acyl amine and

α-methoxy *N*-(alkoxycarbonyl)pyrrolidine − and the products can be modified easily for various synthetic purposes. α-Phenylsulfonyl *N*-acyl amine can be prepared conveniently by the reaction of carbamate derivatives with aldehydes and sodium phenylsulfinate in the presence of formic acid.[35] Subsequent elimination of sulfinic acid under very mild conditions will generate an acylimine, which can been reacted with various nucleophiles. α-Methoxy *N*-(alkoxycarbonyl)pyrrolidine and its analogues can be prepared by electrochemical or organic synthetic methods.[36] It was found that the products could be obtained in good yield when an excess amount of CuBr (2−3 equivalents) was employed to ensure the complete consumption of the starting material. The reaction is highly sensitive to the carbamate structural portion of starting material. The α-phenylsulfonyl amines derived from aromatic aldehydes provide higher yields than those derived from aliphatic aldehydes, and both a strong electron-withdrawing group and a strong electron-donating group on the aromatic ring led to decreased yield of the product, possibly due to the hydrolysis of the acylimines.

Scheme 11

Recently, Iqbal[37] reported a general method for the synthesis of 2,4-disubstituted quinolines in one-pot from an aryl amine, an aldehyde, and an aliphatic terminal alkyne in dry THF using CuCl (Scheme 12). Benzaldehyde and *p*-anisidine reacted with 1-hexyne or 1-octyne to give the corresponding disubstituted quinolines in good yields. Benzyl amine was formed as a by-product (about 40%) along with the desired quinoline derivatives.


Scheme 12
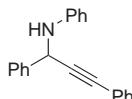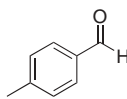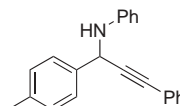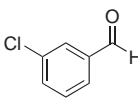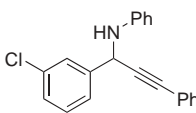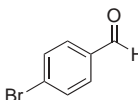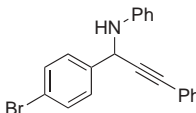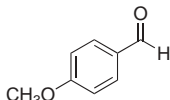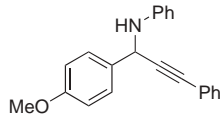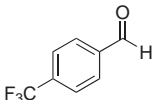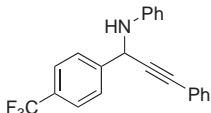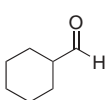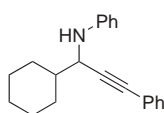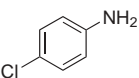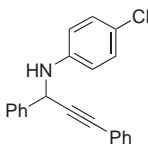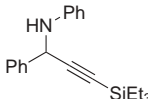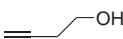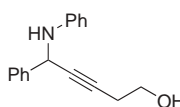
3.2   Catalyzed [Ru-Cu]

Our success in the direct addition of phenylacetylene to aldehydes catalyzed by Ru/In in a mildly basic aqueous media led us to explore a similar catalytic system both in organic solvents and in water. In the alkynylation of aldehydes to give Grignard-type nucleophilic addition products, a bicatalyst system was required in which ruthenium was proposed to catalyze the overall reaction and indium

to activate the carbonyl group. For the corresponding addition of alkynes to the C=N double bond in imines to generate propargylic amines, we decided to use arylimines as the electrophiles because they are easily synthesized and stable in water. Initially, we reacted arylimines, which were readily accessible by the in situ condensation of an aldehyde with aniline, with phenylacetylene by using a Ru/In catalytic system in water. Although this catalytic system was very effective for alkyne-carbonyl additions, it did not provide any desired product. Subsequently, we observed that phenylacetylene can react with an arylimine in the presence of a catalytic amount of Cu(I) in aqueous media to give the desired adducts but in low conversions.[38] We initially attributed the low reactivity to the conversion of the C–H bond in the terminal alkyne to a C–Cu bond. To increase the reactivity, a more effective catalyst would be required. Subsequently, we found that by using $RuCl_3$ as a co-catalyst, the reaction was more efficient. However, no desired product was found with $RuCl_3$ alone as the catalyst. We carried out this addition with a broad range of substituted aromatic and aliphatic imines (Scheme 13). In a few cases, the imines were found to be unstable and easily hydrolyzed in water. For those compounds, the additions were found to be highly effective under neat conditions. This simple process provides a convenient and efficient method for the preparation of propargyl amines (Table 1). This work (submitted in 2001) was the first general method for the catalytic addition of terminal alkynes to imines in the literature.

Table 1 The Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes Catalyzed by $CuBr/RuCl_3$

Entry	Aldehyde	Amine	Alkyne	Product	Yield (%)
1	PhCHO	$Ph-NH_2$	≡—Ph	$Ph-CH(NHPh)-C≡C-Ph$	91
2	4-methylbenzaldehyde	$Ph-NH_2$	≡—Ph	4-methylphenyl-CH(NHPh)-C≡C-Ph	87
3	3-chlorobenzaldehyde	$Ph-NH_2$	≡—Ph	3-chlorophenyl-CH(NHPh)-C≡C-Ph	89
4	4-bromobenzaldehyde	$Ph-NH_2$	≡—Ph	4-bromophenyl-CH(NHPh)-C≡C-Ph	95
5	4-methoxybenzaldehyde	$Ph-NH_2$	≡—Ph	4-methoxyphenyl-CH(NHPh)-C≡C-Ph	52
6	4-(trifluoromethyl)benzaldehyde	$Ph-NH_2$	≡—Ph	4-CF_3-phenyl-CH(NHPh)-C≡C-Ph	87
7	cyclohexanecarbaldehyde	$Ph-NH_2$	≡—Ph	cyclohexyl-CH(NHPh)-C≡C-Ph	58
8	PhCHO	4-chloroaniline	≡—Ph	Ph-CH(NH-4-Cl-C6H4)-C≡C-Ph	87
9	PhCHO	$Ph-NH_2$	≡—$SiEt_3$	Ph-CH(NHPh)-C≡C-$SiEt_3$	83
10	PhCHO	$Ph-NH_2$	≡—CH_2OH	Ph-CH(NHPh)-C≡C-CH_2CH_2OH	82

Scheme 13

3.3 Catalyzed by Ir(I)

Iridium has also been shown to be effective as a catalyst for the direct addition of alkyne to imines. Ishii found that a new type of C−H bond activation adjacent to the nitrogen atom of imines by [Ir(COD)Cl]$_2$ in THF led to a three-component coupling reaction of aldehydes, amines and alkynes to generate substituted allyl imines (Scheme 14, Table 2).[39] In most cases the reaction produced the corresponding coupling products in fair to good yield. In only one 'failed' case, the reaction of trimethylsilylacetylene with amine and aldehyde with [Ir(COD)Cl]$_2$ afforded the undesired adduct propargyl amine (Scheme 14). This alkyne was added to the double bond of the initially formed imine, in contrast to the reaction of other aliphatic alkynes.
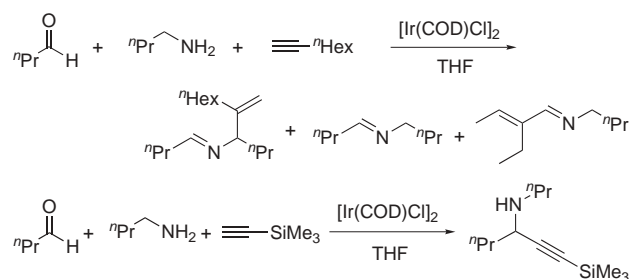
Scheme 14

Carreira reported a process to prepare propargyl amine involving the direct addition of trimethylsilylacetylene to *N*-alkyl or *N*-aryl aldimines in the presence of the same [Ir(COD)Cl]$_2$ catalyst (Scheme 15).[40] An initial screening of transition-metal complexes led them to identify [Ir(COD)Cl]$_2$ as the catalyst for the addition of trimethylsilylacetylene to aldimines at room temperature. *N*-Benzyl aldimines derived from aromatic as well as aliphatic aldehydes participating in the Ir-catalyzed addition reaction (Table 3). The additions can be carried out under neat conditions to provide a highly atom-economical process. However, only silylacetylenes were reactive for this addition reaction.
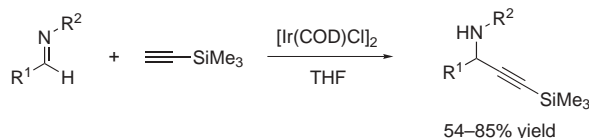
Scheme 15

Table 2 The Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes Catalyzed by [Ir(COD)Cl]$_2$

Entry	Aldehyde	Amine	Alkyne	Product	Yield (%)
1					68
2					74
3					0
4					73
5					62
6					60
7					45
8					0

Table 3 The Addition Reaction of Imines and Me$_3$SiC≡CH Catalyzed by [Ir(COD)Cl]$_2$

Entry	Imine	Product	Yield (%)
1			76
2			84
3			69
4			65
5			54
6			85

3.4   Catalyzed by [Au]

There are some limitations to the methods mentioned above: (1) the polymer-supported Cu(I)-catalyzed method does not easily generate simple propargyl amines that have other functional groups; (2) the microwave-assisted method is limited to the aminomethylation of alkynes; (3) Ir(I)-catalyzed method is limited to silylacetylenes; and (4) our Cu/Ru-catalyzed method is largely limited to imines generated from aryl amines and aryl aldehydes. Due to our continued interest in extending the scope of the synthesis of propargyl amines via activation of alkynes, we examined a three-component coupling of aldehydes, dialkyl amines, and terminal alkynes by other catalysts. We found that the reaction is highly efficient and general with gold as the catalyst (Scheme 16).[41] When compared to other transition metals, gold has not been used extensively as a catalyst. Only recently it has been shown by Ito,[42] Hashmi,[43] and others[44] that gold has some unique catalytic activities.

We found that no co-catalyst or activator is needed for the gold-catalyzed reaction. Less than 1 mol% of catalyst is enough to generate an excellent yield of the corresponding propargyl amine products. Both aromatic and aliphatic aldehydes were able to undergo this three-component coupling with alkyne and amine. Dialkyl amines are good for the reaction, whereas anilines gave the corresponding products in lower yields and *N*-alkylanilines did not form the desired products. Aromatic aldehydes reacted more efficiently and nearly quantitative yields were obtained in most cases. Aliphatic aldehydes can also be used; however, some trimerizations of aldehydes were observed that decreased the yields of the propargyl amine products. The properties of solvents significantly affect the reaction. Water is the best solvent and the reaction is very clean with almost quantitative yield while the use of organic solvents such as THF, toluene, and DMF resulted in low conversions and more by-products.

$$R^1CHO + H-C\equiv C-R^2 + (R^3)_2NH \xrightarrow[100\ °C,\ H_2O]{AuBr_3} $$

47–99% yield (see scheme)

53–99% yield
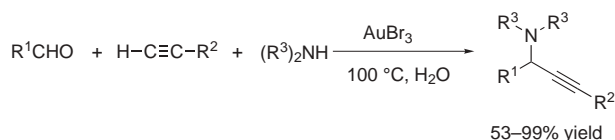
Scheme 16

3.5   Catalyzed by Ag(I)

Silver complexes are rarely considered to be 'transition metal catalysts'. Although some silver-catalyzed reactions have been reported, the silver species often served as either a co-catalyst or a Lewis acid.[45] The high efficiency of gold as a catalyst for the three-component coupling of aldehydes, amines, and alkynes in water led us to examine Ag catalysts for the related coupling. Initially, we focused our attention on water-soluble silver salts. The water-soluble or partially soluble salts such as $AgNO_3$, Ag_2O, $AgOAc$, Ag_2SO_4, $AgOTf$, and $AgBF_4$ were all found to catalyze the reaction of benzaldehyde, piperidine, and

phenylacetylene with a low conversion (ca. 25−45%) together with the formation of some carboxylic acid. The low yields were attributed to the deactivation of the silver catalyst due to its reduction to silver metal and when silver metal was used, it showed no catalytic activity. It was found that AgCl, AgBr and AgI all showed good catalytic activity for the three-component coupling (Scheme 17),[46] and AgI was found to be the most effective. Additionally, no other additive was needed for this reaction. Only a trace amount of product was obtained with acyclic amines (such as diallyl amine), whereas cyclic amines reacted well in these conditions. Both aromatic and aliphatic aldehydes were able to undergo addition to afford the corresponding propargyl amines. Interestingly, in this reaction, aromatic aldehydes had a decreased reactivity whereas aliphatic aldehydes displayed higher reactivity and cleaner reactions. The reactions involving aliphatic aldehydes gave both higher conversions and better yields. The reactions proceeded well in either water or an organic solvent such as toluene and DMF. When 0.2 mol% AgI was used as a catalyst, the reaction in water generated more than 92% isolated yield of the desired product.

$$R^1CHO + H-C\equiv C-R^2 + (R^3)_2NH \xrightarrow[100\ °C,\ H_2O]{AgI} $$

47–99% yield
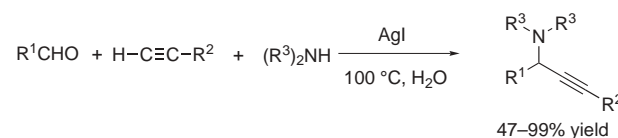
Scheme 17

4   The Development of Asymmetric Aldehyde-Alkyne-Amine Coupling (AA³-Coupling)

Asymmetric synthesis is among the most important recent developments in organic chemistry.[47] Our original highly effective ruthenium/copper-catalyzed direct addition of alkyne to imine in water and under neat conditions[48] led us to explore the corresponding asymmetric coupling. Within the past few decades numerous phosphine-based chiral catalysts have been synthesized, leading to the development of various chiral catalysts for asymmetric reactions.[49] Initially we focused on investigating a chiral ruthenium catalyst with various chiral phosphine ligands, with or without a copper co-catalyst, to investigate the asymmetric alkyne-imine addition. Unfortunately, our investigations with these chiral catalysts did not generate any significant enantioselectivity in these additions, although in most cases the reaction proceeded smoothly to generate the propargyl amines. Therefore, we decided to look for alternative catalytic systems for the asymmetric addition.

4.1   Catalyzed by [Cu]

When we reexamined our original investigation of the racemic alkyne-imine addition, we noticed that CuBr alone also afforded the desired product, albeit in low conver-

sions. We then hypothesized that the low conversion when using CuBr as a catalyst may in fact provide us with a rare opportunity to develop highly efficient enantioselective alkyne-imine additions. We postulated that the low conversion with CuBr may be due to the low reactivity of the alkynyl C−Cu bond rather than due to the low reactivity of C−H to C−Cu conversion as we thought originally. If that is the case, then a strongly coordinating ligand with copper (nitrogen-based) may increase the reactivity by weakening the C−Cu bond. Furthermore, a chiral nitrogen-based ligand will produce a chiral environment around the C−Cu bond, which may lead to asymmetric in-

duction during the imine addition. With this objective in mind, various nitrogen-based chiral ligands were examined. Among the ligands investigated, the desired enantioselective addition product of terminal alkynes to imines was found in low ee when the bidentate bis(oxazoline) (box) with CuBr in water was used. The use of the tridentate bis(oxazolinyl)pyridines (pybox) with CuBr resulted in increased enantioselectivities. Using CuOTf instead of CuBr afforded the product in both high yield and enantioselectivity. The enantioselectivity and reactivity were further increased by carrying out the addition in toluene – up to 96% ee and 92% yield with CuOTf-pybox as the

Table 4 Enantioselective Three-Component Coupling Reaction of Aldehydes, Amines, and Alkynes at Room Temperature in Toluene

Entry	Aldehyde	Amine	Alkyne	Product	Yield (%)	OR/ee (%)
1	Ph-CHO	Ph−NH$_2$	≡−Ph		78	(+) 96
2	Et-C$_6$H$_4$-CHO	Ph−NH$_2$	≡−Ph		70	(+) 96
3	Cl-C$_6$H$_4$-CHO	Ph−NH$_2$	≡−Ph		85	(+) 94
4	Br-C$_6$H$_4$-CHO	Ph−NH$_2$	≡−Ph		87	(+) 94
5	Br-C$_6$H$_4$-CHO	Ph−NH$_2$	≡−Ph		85	(+) 95
6	F$_3$C-C$_6$H$_4$-CHO	Ph−NH$_2$	≡−Ph		71	(+) 93
7[a]	Ph-CHO	Me-C$_6$H$_4$-NH$_2$	≡−Ph		93	(+) 94
8[a]	Ph-CHO	Cl-C$_6$H$_4$-NH$_2$	≡−Ph		92	(+) 91
9	Ph-CHO	Ph−NH$_2$	≡−SiEt$_3$		53	(+) 60
10	Ph-CHO	Ph−NH$_2$	≡−(CH$_2$)$_4$OH		62	(+) 85

[a] Reaction temperature is 35 °C.

catalyst.[50] In most cases, imines were formed in situ, and the addition was very simple: mixing an aldehyde, an aniline, and an alkyne with the catalyst in one-pot (Scheme 18). This catalytic system could be extended to aliphatic alkynes to afford the corresponding propargyl amines. As shown in Table 4, various alkynes add to imines in toluene with good yields and enantioselectivity. Phenylacetylene afforded better yields and enantioselectivity than other aliphatic alkynes. The effect of solvent on the yield and enantioselectivity of the addition of phenylalkyne to *N*-benzylideneaniline was examined (Table 5). Both the yield and %ee are strongly affected by the reaction solvent.
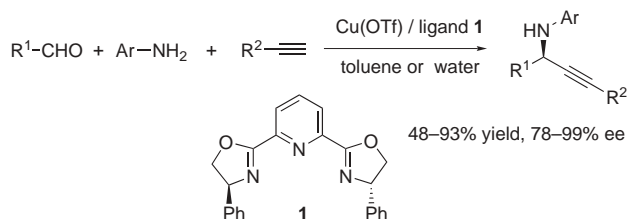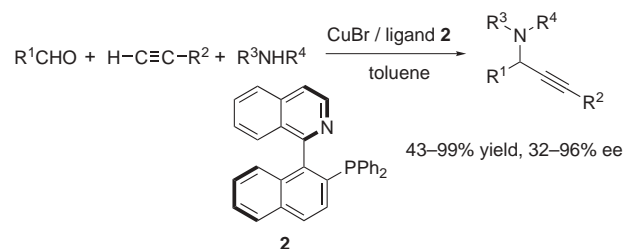

Scheme 18

Table 5 Enantioselective Addition of Phenylacetylene to *N*-Benzylideneaniline in Various Solvents

Entry	Solvent	Yield (%)	ee (%)
1	toluene	78	96
2	benzene	74	97
3	heptane	80	99
4	CH_2Cl_2	79	98
5	$CHCl_3$	81	97
6	1,4-dioxane	82	98
7	THF	65	96
8	EtOAc	53	98
9	acetone	80	99
10	CH_3CN	82	99
11	MeOH	85	88
12	H_2O	71	84

To determine our product with greater certainty, we wanted to ascertain the absolute configuration of the propargyl amine. We tried to correlate our products with known compounds in which the absolute configuration was determined, but only racemic amines were found. With a bromine atom in the molecule serving as a structure marker, the absolute configuration of one of our products was conveniently established as *R* by X-ray crystallographic structure analysis.

4.2 Catalysis as Reported by Others

Subsequent to our report, other novel processes of three-component reactions of aldehydes, amines and alkynes were reported. In order to avoid the generation of sensitive enamines, an enantioselective process of three-component reactions of an alkyne, an aldehyde, and a secondary amine in toluene at room temperature in the presence of CuBr, (*R*)-quinap, and 4Å molecular sieves to afford propargyl amines in both good yields and good enantioselectivities, was recently published by Knochel's group.[51] For the racemic reaction without ligand, the reaction was usually complete within 12 to 48 hours; for the enantioselective reaction, it was complete in 1 to 6 days. The alkyne could have either an aryl substituent or an alkyl substituent. Branched aliphatic aldehydes led to the desired products in high yields and trimethylsilylacetylene had increased enantioselectivity. The presence of either an electron-donating or electron-withdrawing group in the *para* position on the aromatic aldehydes had only moderate influence on the enantioselectivities. The yield was reduced in the aromatic aldehyde with an electron-withdrawing group. Heterocyclic aldehydes were also viable substrates. This reaction was highly diastereoselective if a chiral amine or aldehyde was used (Scheme 19).

Scheme 19

DuBois and co-workers reported a stereocontrolled synthesis of functionalized propargylic amine derivatives from *N,O*-acetals and alkynylzinc reagent (Scheme 20).[52] They described the preparation of new iminium ion equivalents of heterocyclic *N,O*-acetals with varying substitution patterns by Rh-catalyzed C–H insertion. With Lewis acid $BF_3 \cdot OEt$ as the optimal promoter for this coupling process, the reaction of a chiral *N,O*-acetal and alkynylzinc chloride (generated from trans-metalation of the lithium acetylide with $ZnCl_2$) in THF at 40 °C, afforded diastereomers of desired product in high yield and high stereoselectivity. They also confirmed the *cis* product stereochemistry by X-ray structure analysis of the intermediate.
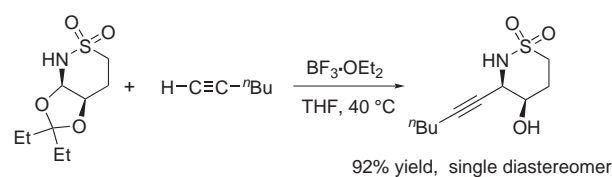
Scheme 20

Hoveyda and Snapper reported a catalytic enantioselective method to afford propargyl amines by addition of alkynylzinc reagents to arylimines by using chiral ligands and Zr salt as the catalyst (Scheme 21).[53] They synthesized propargyl amines by the addition of alkynylzinc to arylimines or alkylzinc to alkynylimines. The enantioselective additions of trimethylsilylacetynylzinc to a variety of *ortho*-anisidylimines are promoted by a peptidic chiral ligand in the presence of Zr(O*i*-Pr)₄·HO*i*-Pr at room temperature, to generate the derived alkynyl amines in up to 90% ee and 69% isolated yield. Elevated reaction temperatures gave lower enantioselectivity and yield. Arylimines with different steric and electron attributes can be converted efficiently into alkynyl amines, but an arylimine from *ortho* substituent aromatic aldehyde can reduce the asymmetric induction. Imine substrates do not require initial preparation. The *o*-anisidyl group can be removed efficiently to generate the corresponding amines or other related derivatives. With Zr(O*i*-Pr)₄·HO*i*-Pr salt and some similar peptidic chiral ligands, the alkylation of alkynylimines were also efficient and generated a range of enantiomerically enriched propargyl amines.
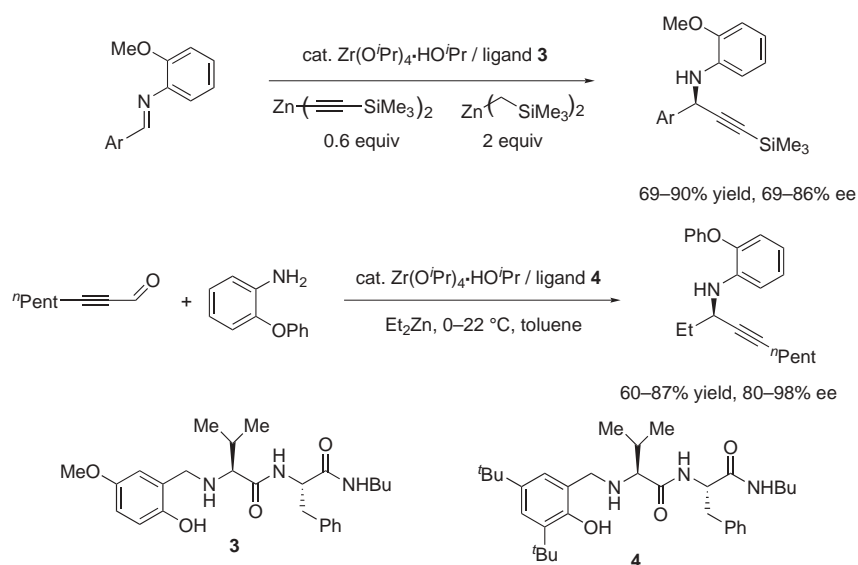
Jiang reported the addition of terminal alkynes to imines by using ZnCl₂ and Et₃N as catalysts and TMSCl as the Lewis acid for the activation of imines (Scheme 22).[54] The reaction of an alkyne with *N*-benzylimine did not proceed by using ZnCl₂/Et₃N as the catalyst. After the addition of chlorotrimethylsilane as an activator, the reaction was dramatically improved and generated the desired product in high yield. The imines can be derived from alkyl or aromatic aldehydes and the aromatic imines with electron-withdrawing groups are more reactive than the ones with electron-donating groups. In the reaction, phenylacetylene gives a higher yield than other alkyl acetylenes. The use of chiral imines as starting material, derived from chiral amines, also afforded the corresponding adducts with moderate diastereoselectivity.

50–93% yield, 18–91% de
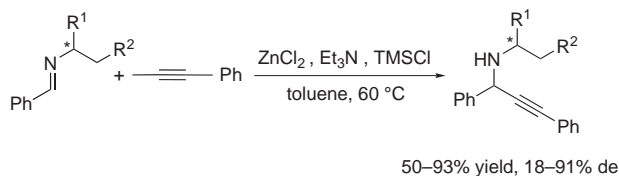
Scheme 22

5   Conclusion

The catalytic direct addition of alkyne to imine and its related three-component coupling of aldehydes, amines and alkynes produced propargyl amines in the most direct and economical manner. Our initial studies involved metal-mediated activation of terminal alkynes and their reaction with aldehydes to generate propargyl alcohols. In developing this conceptual framework further, we found a novel reaction in which a terminal alkyne was activated by a transition metal, which then reacted with an imine, that was form in situ, to generate propargyl amines under mild conditions. The use of late transition metals to catalyze such a reaction in water allows the direct use of compounds bearing hydroxyl groups without the necessary derivatization. The utilization of transition metals as catalysts allows for the asymmetric alkyne-imine addition and the three-component aldehyde-alkyne-amine addition by means of a chiral ligand. The addition reaction of alkynes to arylimines in the presence of chiral pybox was shown to be highly enantioselective and efficient to provide a practical method for the preparation of optically active propargyl amines. We also developed a highly efficient three-component coupling of aldehydes, dialkyl amines, and alkynes with gold and silver as catalysts, which showed complementary chemistry.

69–90% yield, 69–86% ee

60–87% yield, 80–98% ee

Scheme 21

References

(1) (a) McMurry, J. *Organic Chemistry*, 5th Ed.; Brooks/Cole: Pacific Grove, **2000**. (b) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th Ed.; Kluwer Academic: New York, **2000**. (c) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407. (d) Frost, C. G.; Willis, M. C. *Organic Aspects in Organometallic Chemistry,* In *Organometallic Chemistry*, Vol. 29; RSC: London, UK, **2001**, 170. (e) Goldfuss, B. *Top. Organomet. Chem.* **2003**, *5 (Organolithiums in Enantioselective Synthesis)*, 21.

(2) (a) Lu, G.; Li, X.; Jia, X.; Chan, W. L.; Chan, A. S. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5057. (b) Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. *Tetrahedron Lett.* **2003**, *44*, 6755.

(3) (a) Mori, Y.; Hayashi, H. *Tetrahedron* **2002**, *58*, 1789. (b) Galliford, C. V.; Beenen, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487. (c) Garcia, C. I.; Tillack, A.; Hartung, C. G.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 3217.

(4) (a) Kauffman, G. S.; Harris, G. H.; Dorow, R. L.; Stone, B. R. P.; Parsons, R. L.; Pesti, J. J. A.; Magnus, N. A.; Joseph, M.; Confalone, F. P. N.; Nugent, W. A. *Org. Lett.* **2000**, *2*, 3119. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(5) (a) Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* **2003**, *5*, 3479. (b) See ref. 1d. (c) See ref. 1e.

(6) (a) Umeno, M.; Suzuki, A. *Chemical Industries (Handbook of Grignard Reagents)*, Vol. 64; Dekker: New York, **1996**, 645–666. (b) Tuulmets, A.; Pallin, V.; Tammiku-Taul, J.; Burk, P.; Raie, K. *J. Phys. Org. Chem.* **2002**, *15*, 701.

(7) (a) Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* **2000**, *2*, 1855. (b) Rosas, N.; Sharma, P.; Alvarez, C.; Gomez, E.; Gutierrez, Y.; Mendez, M.; Toscano, R. A.; Maldonado, L. A. *Tetrahedron Lett.* **2003**, *44*, 8019.

(8) (a) Miyamoto, H.; Daikawa, N.; Tanaka, K. *Tetrahedron Lett.* **2003**, *44*, 6963. (b) Manabe, K.; Kobayashi, S. *Chem.–Eur. J.* **2002**, *8*, 4094.

(9) (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, **1997**. (b) Li, C. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4856. (c) Li, C. J.; Wang, D. *Chemtracts* **2003**, *16*, 59. (d) Li, C. J. *Acc. Chem. Res.* **2002**, *35*, 533. (e) Li, C. J.; Huang, T. S.; Venkatraman, S.; Meng, Y.; Kort, D.; Ding, R.; Wang, D.; Nguyen, T. *Pure Appl. Chem.* **2001**, *73*, 1315. (f) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (g) Zhang, W. C.; Hua, X. G.; Meng, Y.; Venkatraman, S.; Keh, C. C. K.; Li, C. J. In *Recent Research Developments in Organic Chemistry*, Vol. 4, Part II.; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, India, **2000**, 397. (h) See also: *Organic Synthesis in Water*; Greico, P. A., Ed.; Thomson Science: Glasgow, **1998**.

(10) (a) Li, C. J. *Green Chem.* **2002**, *4*, 1. (b) Li, C. J.; Haberman, J. X.; Keh, C. C. K.; Yi, X. H.; Meng, Y.; Hua, X. G.; Venkatraman, S.; Zhang, W. C.; Nguyen, T.; Wang, D.; Huang, T. S.; Zhang, J. H. In *Cleaner Media*; Moen, L.; Abraham, M., Eds.; ACS Symposium Series, Oxford University Press: Cambridge, **2001**.

(11) (a) Nokami, J.; Otera, J.; Sudo, T.; Okawara, R. *Organometallics* **1983**, *2*, 191. (b) Petrier, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 910. (c) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017.

(12) (a) Issac, M. B.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003. (b) Yi, X. H.; Meng, Y.; Li, C. J. *J. Org. Chem.* **1998**, *63*, 7472.

(13) (a) Ueda, M.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 4450. (b) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976. (c) Li, C. J.; Meng, Y. *J. Am. Chem. Soc.* **2000**, *122*, 9538.

(14) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505.

(15) (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (c) Keh, C. C. K.; Li, C. J. *Chemtracts* **1999**, *12*, 813.

(16) (a) Keh, C. C. K.; Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 4062. (b) Huang, T. S.; Keh, C. C. K.; Li, C. J. *Chem. Commun.* **2002**, 2440. (c) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131.

(17) (a) Li, C. J.; Wang, D.; Chen, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 12867. (b) Wang, D.; Chen, D. L.; Haberman, J. X.; Li, C. J. *Tetrahedron* **1998**, *54*, 5129.

(18) Wang, M. W.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 3589.

(19) Tzalis, D.; Knochel, P. *Angew. Chem. Int. Ed.* **1999**, *38*, 1463.

(20) (a) Diez, R. S.; Adger, B.; Carreira, E. M. *Tetrahedron* **2002**, *58*, 8341. (b) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687.

(21) (a) Jiang, B.; Wang, Q.; Xiong, W.; Zhang, M. *Faming Zhuanli Shenqing Gongkai Shuomingshu* **2001**, 8. (b) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 8323.

(22) (a) Ishikawa, T.; Mizuta, T.; Hagiwara, K.; Aikawa, T.; Kudo, T.; Saito, S. *J. Org. Chem.* **2000**, *68*, 3702. (b) Lu, G.; Li, X.; Chen, G.; Chan, W. L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 449. (c) Braga, A. L.; Appelt, H. R.; Silveira, C. C.; Wessjohann, L. A.; Schneider, P. H. *Tetrahedron* **2002**, *58*, 10413. (d) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555.

(23) Sakai, N.; Hirasawa, M.; Konakahara, T. *Tetrahedron Lett.* **2003**, *44*, 4171.

(24) (a) Reber, S.; Knopfel, T. F.; Carreira, E. M. *Tetrahedron* **2003**, *59*, 6813. (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605. (c) Jiang, B.; Xiong, W.; Chen, Z. *Faming Zhuanli Shenqing Gongkai Shuomingshu* **2001**, 10. (d) Chen, Z.; Xiong, W.; Jiang, B. *Chem. Commun.* **2002**, 2098. (e) Gao, G.; Moore, D.; Xie, R.-G.; Pu, L. *Org. Lett.* **2002**, *4*, 4143.

(25) Wei, C. M.; Li, C. J. *Green Chemistry* **2002**, *4*, 39.

(26) (a) Imada, Y.; Yuassa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282. (b) Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, *42*, 1655. (c) Caporusso, A. M.; Geri, R.; Polizzi, C.; Lardicci, L. *Tetrahedron Lett.* **1991**, *32*, 7471.

(27) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

(28) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245. (b) Carreira, E. M. *Chimia* **2001**, *55*, 818. (c) Carreira, E. M.; Frantz, D. E.; Fässler, R.; Tomooka, C. S. *Acc. Chem. Res.* **2000**, *33*, 373.

(29) (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.

(30) (a) Youngman, M. A.; Dax, S. L. *J. Comb. Chem.* **2001**, *3*, 469. (b) Dax, S. L.; Youngman, M. A.; Kocis, P.; North, M. *Solid-Phase Organic Syntheses* **2001**, *1*, 45. (c) Dyatkin, A. B.; Rivero, R. A. *Tetrahedron Lett.* **1998**, *39*, 3647. (d) McNally, J. J.; Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1998**, *39*, 967. (e) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347.

(31) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 676.

(32) (a) Sharifi, A.; Farhangian, H.; Mohsenzadeh, F.; Naimi-Jamal, M. R. *Monatsh. Chem.* **2002**, *133*, 199. (b) Wang, L.; Li, P.-H. *Chin. J. Chem.* **2003**, *21*, 710.

(33) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001.

(34) Zhang, J. H.; Wei, C. M.; Li, C. J. *Tetrahedron Lett.* **2002**, *43*, 5731.

(35) (a) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. (b) Kanazawa, A. M.; Denis, J. N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238.

(36) (a) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Syntheses*, Vol. 7; Wiley: New York, **1990**, 307. (b) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Fujita, K. *Chem. Commun.* **1999**, 2213. (c) Hernandez, B. R.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 4930. (d) Matsumura, Y.; Shirakawa, Y.; Satoh, Y.; Umino, M.; Tanaka, T.; Maki, T.; Onomura, O. *Org. Lett.* **2000**, *2*, 1689.

(37) Huma, H. Z. S.; Halder, R.; Kalra, S. S.; Das, J.; Iqbal, J. *Tetrahedron Lett.* **2002**, *43*, 6485.

(38) Li, C. J.; Wei, C. M. *Chem. Commun.* **2002**, 268.

(39) Satoshi, S.; Takashi, K.; Ishii, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 2534.

(40) Carreira, E. M.; Fischer, C. *Org. Lett.* **2001**, *3*, 4319.

(41) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9584.

(42) (a) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247. (b) Sawamura, M.; Nakayama, Y.; Kato, T.; Ito, Y. *J. Org. Chem.* **1995**, *60*, 1727. (c) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*,

6405. (d) Ito, H.; Yajima, T.; Tateiwa, J.-I.; Hosomi, A. *Chem. Commun.* **2000**, 981.

(43) (a) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*, 3. (b) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553.

(44) (a) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron* **1992**, *48*, 1999. (b) Mizushima, E.; Hayashi, T. i.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349. (c) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 4399.

(45) (a) Patmore, N. J.; Hague, C.; Cotgreave, J. H.; Mahon, M. F.; Frost, C. G.; Weller, A. S. *Chem.–Eur. J.* **2002**, *8*, 2088. (b) Yanagisawa, A. In *Lewis Acids in Organic Synthesis*, Vol. 2; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, **2000**, 575. (c) Bertus, P.; Pale, P. *J. Organomet. Chem.* **1998**, *567*, 173. (d) Loncaric, C.; Manabe, K.; Kobayashi, S. *Adv. Synth. Catal.* **2003**, *345*, 475.

(46) Wei, C. M.; Li, Z. G.; Li, C. J. *Org. Lett.* **2003**, *5*, 4473.

(47) (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: New York, **1999**. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, **2000**. (c) Noyori, R. *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.

(48) Li, C. J.; Wei, C. M. *Chem. Commun.* **2002**, 268.

(49) (a) Colacot, T. *Chem. Eng.* **2001**, *108*, 73. (b) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354.

(50) (a) Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C. M.; Mague, J. T.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749.

(51) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.

(52) James, J. F.; Kristin, W. F.; DuBois, J. D. *J. Am. Chem. Soc.* **2003**, *125*, 2028.

(53) (a) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273. (b) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4244.

(54) Jiang, B.; Si, Y.-G. *Tetrahedron Lett.* **2003**, *44*, 6767.