Direct addition of alkynes to imines and related C=N electrophiles: A convenient access to propargylamines

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Propargylic amines are highly useful building blocks in organic synthesis, and the corresponding structural motif has been found in various natural products and compounds of pharmaceutical relevance. This article provides an overview of the most significant advances in the preparation of propargylic amines *via* the direct addition of alkynes to imines and related carbon–nitrogen electrophiles in the presence of metal catalysts or promoters.

1 Introduction

In recent years, propargylic amines have found broad application as precursors for the synthesis of various nitrogen-containing compounds, such as allylamines, pyrrolidines, oxazoles and pyrroles.[1] Furthermore, they have often been used as intermediates in the preparation of complex natural products,[2] such as dynemicines,[2a–c] pharmaceuticals[3] and plant protectives (herbicides and fungicides).[4]

In addition to their synthetic utility, some propargylic amine derivatives were found to possess interesting biological properties,[5] for example as inhibitors of the enzyme monoamide oxidase B (MAO-B).[6]

To date, efforts to develop reliable procedures for the synthesis of these important compounds have primarily focused on the addition of suitable organometallic species to imines.[7]

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Despite that, while the addition of acetylenes to carbonyl compounds has been the subject of a large number of publications, the use of imines and related C=N electrophiles as substrates has been much less developed, mostly as a result of the reduced reactivity of these compounds compared to aldehydes and ketones.[8] To overcome this problem of reactivity, activated substrates, such as nitrones or *in situ*-generated iminium ions, have often been employed instead of simple imines.

Classical methodologies for the preparation of propargylic amines have usually exploited the relatively high acidity of a terminal acetylenic C–H bond to form alkynyl-metal reagents by reaction with strong bases. Typically, compounds such as butyllithium,[9] organomagnesium compounds[10] or LDA[11] were used for this purpose. The so-formed organometallic compounds were then able to undergo nucleophilic addition to imines and similar C=N electrophiles to form the desired products.[12]

Clearly, the strongly basic reagents employed in such reactions are incompatible with sensitive substrates, and therefore alkyne deprotonation often had to be carried out

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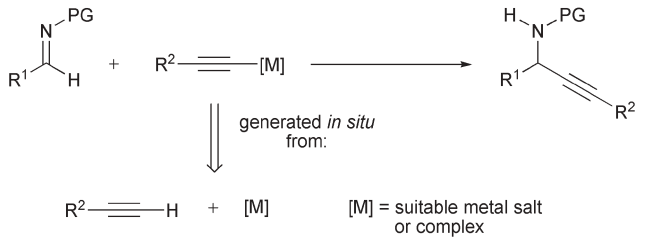


Scheme 1 Direct addition of *in situ*-generated metal alkynylides to imines.

in a separate step. In addition, the reactivity of the resulting polar lithium-, magnesium- and, in some cases, aluminum-alkynylides is, in general, too high to allow the reaction to proceed in a stereocontrolled manner under mild conditions, which, for a long time, precluded the development of efficient enantioselective alkynylation processes.[13]

A solution to this problem has been identified by the introduction of synthetic methodologies capable of performing the direct addition of acetylenes to imines, using organometallic reagents generated *in situ* from alkynes and suitable metal precursors, under conditions compatible with electrophilic reaction partners (Scheme 1).

In the last few years, considerable progress has been made in expanding the scope of the direct addition of alkynes to carbon–nitrogen double bonds, and the first examples of enantioselective processes have been reported. Despite that, it must be recognised that this area remains underdeveloped compared to the related field of the direct alkynylation of aldehydes. This article will highlight the most significant contributions that have appeared in the literature so far, with particular emphasis being placed on catalytic enantioselective methodologies.

2 Non-asymmetric and diastereoselective metal-promoted direct alkynylation of C=N electrophiles

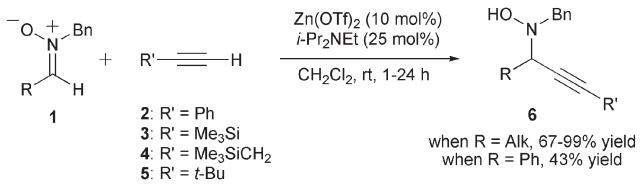
2.1 Zinc-mediated alkyne additions

The first zinc-catalysed addition of alkynes to a C=N electrophile was reported in 1999 by Carreira and co-workers, who used nitrones **1** as starting materials due to their ease of preparation and superior reactivity in comparison to imines. The use of 10 mol% $Zn(OTf)_2$ in combination with 25 mol% *i*-Pr_2NEt (Hünig's base) afforded *N*-hydroxy propargylamines **6** in moderate to excellent yields (up to 99%).[14] Interestingly, the authors observed that metal alkynylides, generated from Cu(I) salts and other metal sources such as $Mg(OTf)_2$, $Mn(OTf)_2$ and ZnX_2 (X = Cl, I), failed to add to the substrates. Only a partial addition was obtained when $Sn(OTf)_2$ was employed.

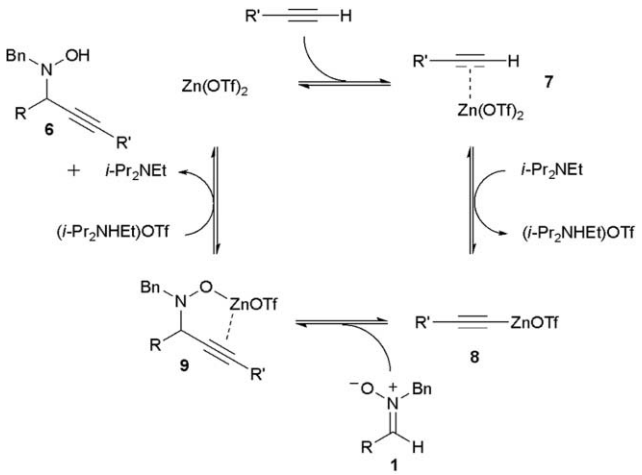
Various alkynes **2–5** could be used in the process, and nitrones derived from aliphatic aldehydes proved to be more reactive than their corresponding aromatic counterparts (Scheme 2).

The same procedure could also be applied to phenyl *N*-tosylimine as the substrate (**20a**, see Scheme 8), but the yield in this case was only moderate (43%).

The commonly accepted mechanistic picture of this reaction can be summarised as follows (Scheme 3). The zinc salt initially



Scheme 2 Zinc-catalysed direct alkynylation of nitrones by Carreira *et al.*



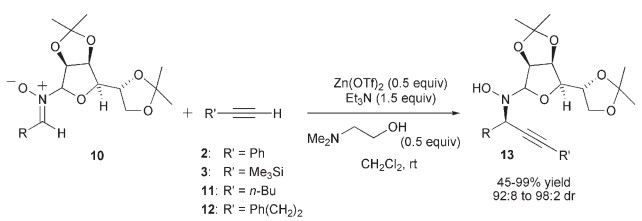
Scheme 3 Mechanism of the $Zn(OTf)_2$-catalysed direct alkynylation of nitrones.

forms a π-complex **7** with the terminal acetylene. As a result of coordination, the C_{sp}–H bond is labilised, so that even a weak base, such as a tertiary amine, can effect deprotonation of the alkyne, with concomitant formation of the corresponding metal alkynylide, **8**. The latter reacts with electrophile **1** to produce a zinc hydroxylamide **9**, from which the catalyst is regenerated by the action of the *in situ*-formed ammonium triflate.

The formation of zinc acetylenides under these conditions was confirmed by ^{13}C NMR[14] and later *in situ*-IR[15] studies of the corresponding alkynylation of aldehydes.[16]

The $Zn(OTf)_2$-catalysed direct alkynylation of nitrones was subsequently applied, with some modifications to its stoichiometry, by the same research group to the preparation of optically active *N*-hydroxylamines **13** using nitrones **10**, bearing a mannose-derived chiral auxiliary, as substrates (Scheme 4).[17]

A large number of combinations of various alkynes and nitrones were tested, and the diastereomeric ratios of the products, **13**, were found to be very high in each case (ranging from 92 : 8 to 98 : 2 dr, in favour of the diastereomer shown in Scheme 4). Interestingly, during the course of optimisation



Scheme 4 Diastereoselective direct alkynylation of nitrones.

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studies, it was found that addition of a sub-stoichiometric quantity (0.5 equiv.) of a ligand such as *N*,*N*-dimethyl-2-aminoethanol had a doubly-beneficial effect on the reaction; on one hand, it caused a five-fold increase in the reaction rate, and on the other, it allowed a homogeneous solution to be retained throughout the course of the reaction.

Once again, aromatic derivatives were less reactive than aliphatic ones, and stoichiometric conditions were required to achieve their full conversion into the products. A convenient aspect of the process was represented by the ease of removal of the chiral auxiliary. Thus, treatment of adducts **13** with a small excess of hydroxylamine (or hydrazine) hydrochloride in the presence of sodium acetate led to the isolation of the corresponding enantioenriched NH propargylic hydroxylamines in high overall yields.

An extension of this work was recently reported by the same group that makes use of rigorously dried $ZnCl_2$ to promote the addition of alkynes to mannofuranosylnitrones **10**,[18] to afford products **13** in excellent yields with high diastereoselectivity (up to 98 : 2 dr). This time, the conditions were stoichiometric, and 1.5 equiv. of each of the zinc salt, triethylamine and alkyne [mostly trimethylsilylethyne (**3**)] had to be used. Since, under these conditions, the reaction mixture was homogeneous, no additional ligand was required. An additional improvement was the possibility of using toluene as a solvent instead of the environmentally less friendly dichloromethane.

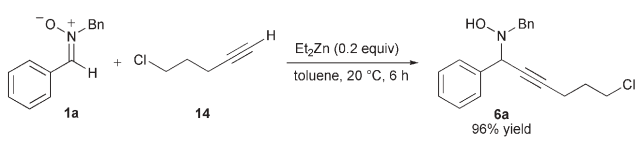
A further protocol for the addition of *in situ*-generated zinc alkynylides to nitrones was published in 2002 by Vallée and co-workers, who generated the reactive nucleophiles by mixing terminal alkynes with diethylzinc in the presence of the substrate.[19] Notably, under these conditions, the reaction did not require any additional base.

While initial experiments were conducted using a stoichiometric quantity of Et_2Zn, changing the solvent from dichloromethane to toluene allowed a reduction in the amount of the organozinc species used to 0.2 equiv. (Scheme 5).

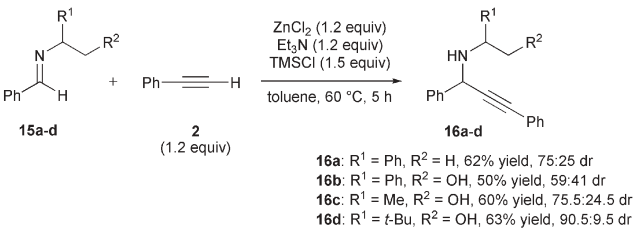
After optimisation, various alkynes could be added to four different nitrones to afford the products in good to high yields, even though, in some cases, 2,3-dihydroisooxazoles were detected as side-products, resulting from the cyclisation of the formed *N*-hydroxypropargylamines.

The authors also conducted detailed NMR studies with the aim of elucidating the reaction mechanism. The results suggested that intermediate zinc bis-hydroxylamides could be involved as metallating agents, which would explain why only a sub-stoichiometric amount of the initial dialkylzinc species is needed to induce the transformation.

A zinc-mediated, diastereoselective addition of alkynes to *N*-alkylimines was described in 2003 by Jiang and Si.[20] Inspired by the work of Carreira, the authors investigated the use of $ZnCl_2$ as a promoter, employed in a stoichiometric quantity, in the presence of triethylamine as the base. The



Scheme 5 Diethylzinc-promoted alkynylation of a nitrone.



Scheme 6 Diastereoselective addition of phenylacetylene to *N*-alkylimines.

reduced reactivity of the substrates compared to nitrones made it necessary to use a Lewis acid, such as TMS-Cl, to activate them and obtain satisfactory yields of the products.

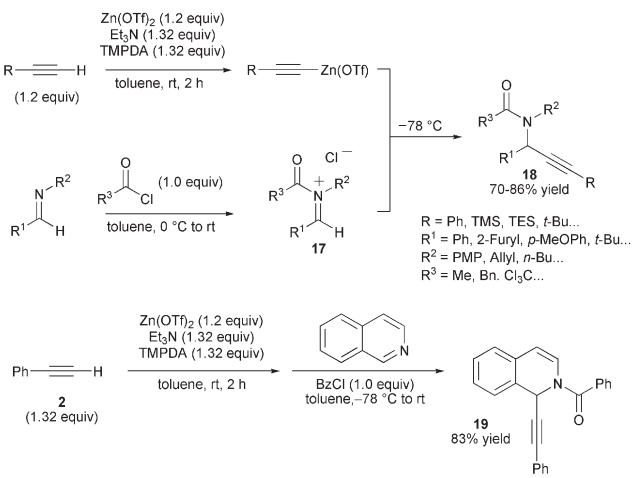
The use of enantiopure substrates derived from benzaldehyde and a chiral amine allowed the products to be obtained in moderate yield with up to a 90.5 : 9.5 diastereomeric ratio (Scheme 6).

Some other achiral imines derived from benzylamine and various aldehydes could also be converted using the same methodology, giving products in 62–93% yield.

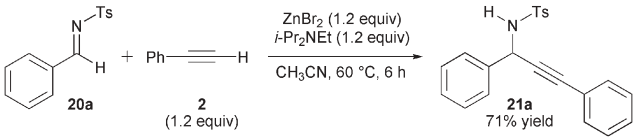
An alternative strategy to perform a zinc-mediated addition of terminal alkynes to activated C=N electrophiles was recently reported, in which the treatment of *N*-alkyl or *N*-arylimines with an acyl chloride led to the formation of acyliminium species **17**. These reactive intermediates were subsequently able to rapidly undergo addition, *via* a zinc acetylenide, to furnish a propargylic *N*-alkyl or *N*-arylamide **18** as the product.[21]

Following this methodology, several alkynes could be added to acyliminium ions, obtained from various imines and acyl chlorides, to give the products in 70–86% yield (Scheme 7). The reaction was also applicable to cyclic substrates such as isoquinoline, furnishing the resulting 1-substituted *N*-benzoyl-1,2-dihydroisoquinoline (**19**) in 83% yield.

Interestingly, diphenylphosphinoyl chloride ($Ph_2P(O)Cl$) could also be employed to generate the iminium ions, giving access to *N*-diphenylphosphinoylamides. These compounds are useful synthetic intermediates, since the phosphorous-based protecting group can easily be removed by treatment with Brønsted acids.



Scheme 7 Addition of zinc alkynylides to *N*-acyliminium ions.



Scheme 8 Zinc-promoted addition of phenylacetylene to a *N*-tosylimine.

As well as already mentioned for the reaction in Scheme 4, in this case, addition of a ligand (TMPDA = *N*,*N*,*N*′,*N*′-tetramethylpropylene diamine) was necessary to obtain a homogeneous mixture and therefore enhance the rate of the reaction.

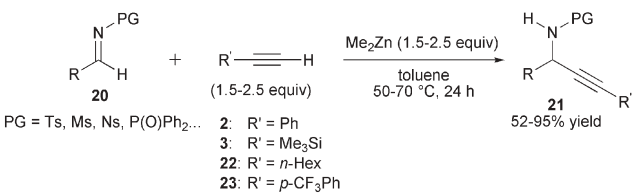
The first systematic study on the use of *N*-activated imines (*i.e.*, imines bearing an electron-withdrawing group on the nitrogen atom) as substrates for zinc-mediated direct alkynylation reactions was published in 2005 by Kim and co-workers, who employed *N*-tosyl or *N*-mesylimines **20** as starting materials.[22] In this case, the zinc alkynylide was generated by mixing a terminal acetylene with $ZnBr_2$ and *i*-Pr_2NEt (1.2 equiv. each). No additional Lewis acid was needed for the reaction to occur, as a consequence of the superior reactivity of the substrates in comparison to simple, non-activated imines.

The *N*-sulfonyl propargylic amine products, **21**, could be isolated in 60–81% yield. In particular, *N*-benzylidene *para*-toluenesulfonamide (**20a**) reacted with phenylacetylene (**2**) to furnish sulfonamide **21a** in 71% yield, superior to the 43% yield reported earlier by Carreira *et al.* (Scheme 8).[14]

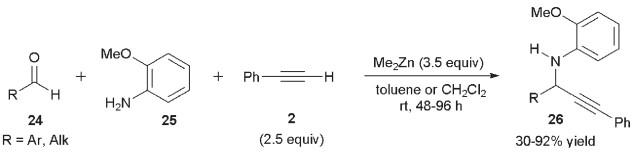
A variation of the latter methodology was published by the same group, which this time examined the addition of phenylacetylene to cyclic substrates, such as quinoline, pyridine and isoquinoline.[23] Addition of an acyl chloride (or ethyl chloroformate) to an acetonitrile solution of these species generated strongly electrophilic acyliminium ions, which readily reacted with the zinc acetylenide, generated from **2** and $ZnBr_2$ in the presence of Hünig's base. The resulting *N*-acyl (or *N*-ethoxycarbonyl) cyclic propargylamines were isolated in 63–79% yield.

The first dialkylzinc-mediated alkynylation of imines was recently reported by Bolm and co-workers, who employed a mixture of an alkyne and dimethylzinc (1.5–2.5 equiv. each), in the absence of an additional base, to convert various *N*-activated imines into the corresponding protected propargylamines (Scheme 9).[24]

Reaction of imine **20a** with **2** provided *N*-tosyl amine (**21a**) in 80% yield, superior to the values previously reported by Carreira *et al.*[14] and Kim *et al.*[22] Interestingly, when diethylzinc was used instead of dimethylzinc for the conversion of **20a**, *N*-tosylbenzylamine, resulting from its reduction, was



Scheme 9 Dimethylzinc-mediated direct alkynylation of *N*-activated imines.



Scheme 10 Me_2Zn-mediated one-pot synthesis of propargylamines.

the major product of the reaction, in a ratio of 3 : 1 to the expected protected propargylic amine **21a**.

Imines bearing aromatic groups are the substrate of choice, but α-branched aliphatic imines are also applicable, as exemplified by the reaction of *N*-tosyl cyclohexylimine with **2**, which furnished the corresponding addition product in 84% yield.

Since it is usually believed that dimethylzinc can only deprotonate terminal alkynes in the presence of appropriate ligands,[25] the authors suggested that, in this case, the substrate behaved in a "ligand like" fashion, coordinating Me_2Zn with its heteroatoms and thus enhancing its basicity. This observation was in agreement with the results of a previous study concerning the alkyne addition reaction to carbonyl compounds, in which it was demonstrated by DFT calculations that the activation energy of the deprotonation step could be greatly reduced by the presence of coordination by the substrate.[26]

In the same study, the authors also developed a one-pot synthesis of *N*-aryl propargylic amines starting from the corresponding aldehydes **24** (Scheme 10).[24]

In the first step, aldehyde **24** reacts with *ortho*-methoxyaniline (**25**) to give an *ortho*-methoxyphenylimine, which then undergoes nucleophilic addition *via* the *in situ*-generated zinc alkynylide to form the product. The reaction is general with respect to the aldehyde, since by means of small modifications in the practical procedure, not only aromatic, but also aliphatic aldehydes could be converted in satisfactory yields.

An activation process through coordination of dimethylzinc by the substrate, similar to that already described for the reaction in Scheme 9, is also supposed to be operating in this case.

Although initially only phenylacetylene (**2**) was employed, further studies suggest that other terminal acetylenes, including trimethylsilylethyne (**3**), can be applied to this reaction.[27]

2.2 Copper-catalysed alkyne additions

Copper-catalysed reactions have a prominent role in the field of metal-promoted additions of terminal acetylenes to C=N electrophiles. In analogy to zinc salts, copper salts are also able to form π-complexes with terminal alkynes, which can subsequently react with a weak base to afford the corresponding copper acetylenides. Although the use of copper salts as catalysts was ineffective in promoting the reaction of alkynes with aldehydes,[8a] it was recently applied to the analogous reaction featuring C=N electrophiles as substrates.

The first report on the use of a mixed Ru/Cu catalytic system for the addition of terminal acetylenes to imines appeared in 2002.[28] Shortly before, in the same year, a similar methodology for the addition to aldehydes, making use of iridium instead of

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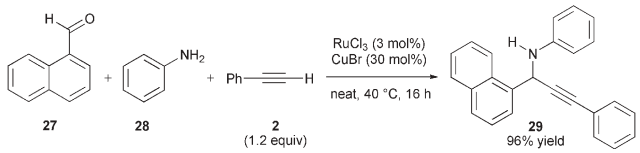


Scheme 11 Ru/Cu-based catalytic system for the addition of phenylacetylene to imines.

copper, was published.[29] In this study, $RuCl_3$ (3 mol%) and CuBr (30 mol%) were used to catalyse the addition of alkynes **2**, **3** and **11** to *N*-arylimines, generated *in situ* from various aldehydes and anilines. Interestingly, the reactions were conducted in water or under solvent-free conditions (Scheme 11).

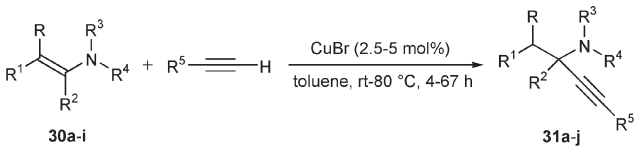
The use of both metal salts proved crucial for obtaining the products in high yields (77–96%). While CuBr alone was able to induce the reaction, albeit with reduced efficiency, no product could be isolated in the presence of only $RuCl_3$. A mechanistic proposal, involving the formation of a ruthenium alkynylide and activation of the imine by the copper salt, was formulated by the authors, but no experimental evidence was provided.

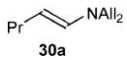
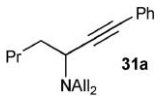
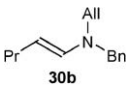
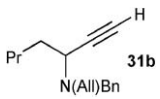
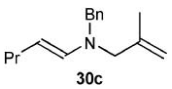
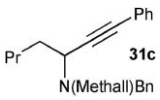
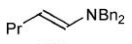
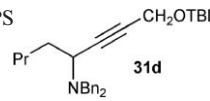
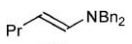
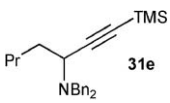
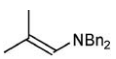
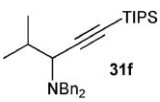
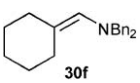
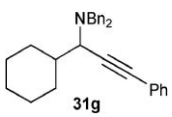
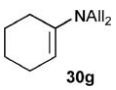
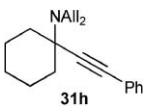
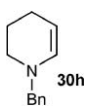
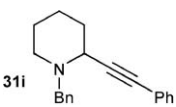
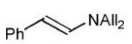
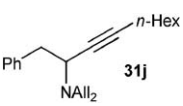
Another copper-promoted alkynyl addition to imines and iminium ions has been described that takes place in an aqueous medium.[30] In this reaction, the substrate is generated *in situ* starting from α-phenylsulfonylamines, in the presence of CuBr as the metal mediator. Since the products could only be obtained in low yield by using 10–30 mol% of the copper(I) salt, an excess of the latter (2–3 equiv.) was required to afford propargylic amines in good yields.

Copper-catalysed additions of terminal alkynes to enamines,[31] through the intermediacy of the corresponding iminium species, were described by Knochel and co-workers, who employed Cu(I) or Cu(II) bromide as a catalyst (max. 5 mol%).[32] The reactions were performed in toluene at rt–80 °C. Under these conditions, *N*,*N*-disubstituted propargylic amines were obtained in good to excellent yields. The only serious limitation of this protocol consists of the necessity to use enolisable aldehydes to generate the enamines. As a consequence, no aromatic derivatives could be prepared. Some of the products obtained by this methodology are reported in Table 1.

Almost contemporary with the studies by Fischer and Carreira on the $Zn(OTf)_2$-mediated alkynylation of acyliminium ions,[21] the same transformation was reported by Black and Arndtsen, who employed a catalytic amount of copper(I) iodide as the promoter.[33] Under optimised conditions, 10 mol% of CuI was enough to obtain satisfying yields (76–99%) of *N*-acyl propargylamines (**18**, essentially the same compounds as those resulting from Carreira's reaction, see Scheme 7). In this process, 1.5 equiv. of a weak base (*i*-Pr_2NEt or Et_3N were preferable to K_3PO_4) had to be used. When the reactions were run in acetonitrile, full conversion of the starting material was usually observed within a 15 min reaction time. The authors also demonstrated the possibility of using ethyl chloroformate instead of an acyl chloride to generate the iminium ion, in order to obtain *N*-propargyl carbamates as the products. Heterocyclic substrates were also applicable, and pyridine

Table 1 Copper-catalysed addition of terminal acetylenes to enamines



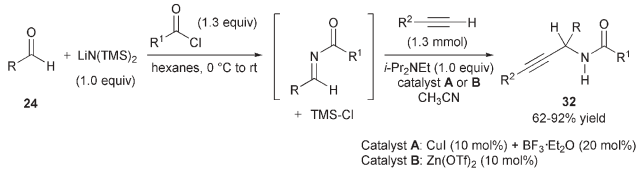
Entry	Enamine	R^5	Product	Yield *t*/h	(%)[a]
1	 **30a**	Ph	 **31a**	16	98
2	 **30b**	H	 **31b**	4	69
3	 **30c**	Ph	 **31c**	20	91
4	 **30d**	$CH_2OTBDPS$	 **31d**	24	93
5	 **30d**	TMS	 **31e**	16	70
6	 **30e**	TIPS	 **31f**	7	88
7	 **30f**	Ph	 **31g**	27	94
8	 **30g**	Ph	 **31h**	24	75
9	 **30h**	Ph	 **31i**	3	86
10	 **30i**	*n*-Hex	 **31j**	18	79

[a] Yield of analytically pure product.

reacted with benzoylchloride and phenylacetylene (**2**) to afford *N*-benzoyl-2-phenylethynyl-1,2-dihydropyridine in 73% yield.

Later, the same authors extended the scope of the reaction to include *N*-trimethylsilylimines as substrates, either under copper or zinc catalysis.[34] *N*-Trimethylsilylimines could be prepared in a separate step or directly generated *in situ* by reaction of aldehydes with $LiN(TMS)_2$ (Scheme 12). In the presence of an acyl chloride, *N*-acyl imines are generated, which are the actual substrates of the reaction.

Cleavage of the N–Si bond during the course of the reaction, with the contemporary elimination of TMS-Cl, allows the



Scheme 12 One-pot synthesis of propargylamides from aldehydes, acyl chlorides, a silylamide and alkynes.

preparation of secondary propargylamides **32**, which could not be accessed using the previous methodology. The authors demonstrated that treatment of amides **32** with a strong base, such as NaH, induces cyclization to form synthetically useful 2,4,5-trisubstituted oxazoles.[34]

The possibility of performing the alkyne addition reaction on acyliminium ions, prepared from aromatic heterocycles such as pyridines and quinolines, has already been mentioned. This transformation was studied in detail by Yadav and co-workers, who, once again, employed a combination of CuI and Hünig's base to induce the reaction.[35] Several 2-alkynyl-substituted heterocycles could be prepared by following this protocol, generally in good yields (70–90%). The reaction displayed a remarkable functional group tolerance, and compounds bearing unprotected hydroxy groups, as well as halogen atoms, nitro groups and even carboxylic acids could be employed without modifying the practical procedure. A representative example is shown in Scheme 13.

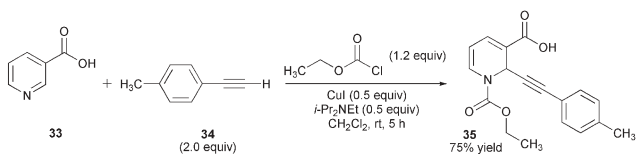
Finally, the first example of a copper-catalysed synthesis of propargylic amines in ionic liquids has recently been reported.[36] Four different acetylenes were added to the iminium ion, generated *in situ* from an aldehyde and a secondary amine, using 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) as the solvent. Various copper sources were tested for their ability to catalyse the reaction, the best results being obtained with CuI and CuBr.

With as little as 2 mol% of catalyst, full conversion of the aldehydes was obtained within 4 h at 120 °C. The corresponding propargylic amines could then be isolated in pure form in 68–98% yield, simply by extraction with an organic solvent. The authors demonstrated that the catalyst could be re-used up to five times without any significant decrease in the yield, although, in the last cycle, longer reaction times were generally needed to reach full conversion of the substrate.

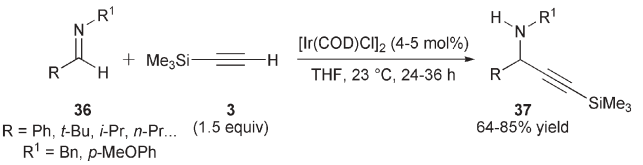
2.3 Iridium-, gold- and silver-catalysed alkyne additions

Further metal salts or complexes that have been used to catalyse the direct addition of alkynes to C=N electrophiles include those of iridium, gold and silver.

An iridium-catalysed addition of trimethylsilylethyne (**3**) to *N*-benzyl and *N*-(*para*-methoxy)phenylimines was reported as



Scheme 13 Copper-mediated alkynylation of an *aza*-heterocycle.



Scheme 14 Iridium-catalysed addition of **3** to imines.

early as 2001 by Fischer and Carreira.[37,38] They showed that treatment of the substrates with 4–5 mol% $[Ir(COD)Cl]_2$ in the presence of 1.5 equiv. of **3** led to the formation of the corresponding propargylic amines in synthetically useful yields of 64–85% (Scheme 14).[37]

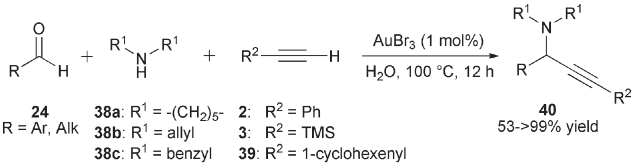
The authors demonstrated that the reaction also proceeds under solvent-free conditions, which could be useful in view of possible large-scale applications, and that the addition of some ligands, such as tri-*tert*-butylphosphine, increased the reaction rate. Although this observation was considered by the authors as a starting point for the identification and development of an asymmetric process, no report concerning such a transformation has yet appeared in the literature.

More recently, an iridium-catalysed addition of **3** to various acylquinolinium and acylisoquinolinium ions, similar to the protocols involving zinc or copper catalysis discussed above,[21,33,35] was reported.[39] The authors noted that the addition of 5–10 mol% AgOTf to the reaction mixture increased the efficiency of the process in comparison to the reaction run in the absence of the additive.

The first gold-catalysed, three-component synthesis of propargylamines from aldehydes, secondary amines and alkynes was described in 2003 by Wei and Li.[40] In this reaction, the iminium ion, generated by condensation of the aldehyde with the amine, undergoes addition by an alkynyl-gold species, formed by reaction of a gold salt with the alkyne.

Interestingly, both Au(I) and Au(III) salts, but not elemental gold, were active catalysts for the reaction, the best one being $AuBr_3$. Surprisingly, the use of water as the solvent afforded the best results,[41] while employment of organic reaction media, such as THF, toluene or DMF, usually led to incomplete conversion and the formation of by-products. Under optimised conditions, the adducts resulting from the combination of three different alkynes, three different secondary amines and several aldehydes could be prepared in yields ranging from 53 to >99% (Scheme 15).

The catalyst loading was generally low (typically 1 mol%, but full conversion could also be obtained with 0.25 mol%) and a temperature of 100 °C was required. The authors reported that aromatic aldehydes usually reacted better than aliphatic ones. Moreover, this methodology is limited by the



Scheme 15 Gold-catalysed three-component synthesis of propargylic imines.

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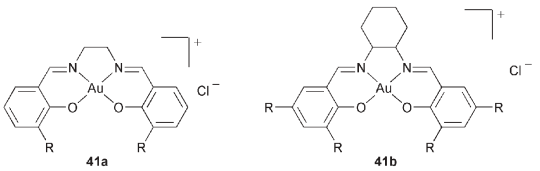


Fig. 1 Au(III)/salen complexes for the three-component synthesis of propargylamines.

impossibility of using anilines or primary amines to generate the products.

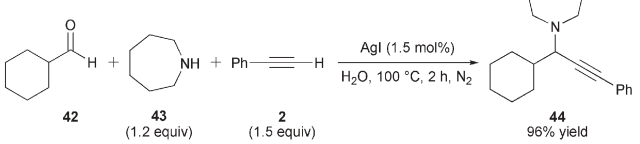
A variation of the same protocol has been reported recently, in which some Au(III)/salen complexes **41a,b** (Fig. 1) were used as catalysts in the three-component synthesis of propargylamines.[42] The new catalytic system allowed products to be obtained with consistently high yields. Employment of chiral, enantiopure, proline-derived cyclic amines resulted in the preparation of the corresponding propargylic amines with excellent diastereomeric ratios (up to 99 : 1 dr).

The same reaction has been described, in which a heterogeneous gold catalyst was used as the promoter.[43] Layered double hydroxide-supported gold tetrachloride (LDH-$AuCl_4$) catalysed the reaction of secondary amines with aliphatic or aromatic aldehydes and **2** in refluxing THF, and furnished propargylamines with up to 93% yield. However, when alkyl monosubstituted acetylenes were employed instead of **2**, the yields were much lower (up to 55%). Due to the heterogeneous nature of the catalyst, it could be easily recovered and re-used. However, partial reduction of the gold ions on its surface led to a strong reduction in the yield of the product after only the third cycle.

In an effort to identify a better catalyst for the conversion of aliphatic aldehydes, Li and co-workers found that the above-described three-component synthesis of propargylamines (see Scheme 15) could also be promoted by Ag(I) salts.[44] Again, water was used as the solvent.

Various silver compounds, such as AgCl, AgI, AgBr, AgOTf, Ag_2O and others, were tested as catalysts for the reaction of benzaldehyde, piperidine and phenylacetylene. All proved able to induce the formation of the product, the best one being silver iodide. Under silver catalysis, aliphatic aldehydes reacted better than aromatic ones, and, after optimisation, the use of 1.5–3 mol% AgI allowed good yields of *N*,*N*-dialkyl propargylamines to be obtained (up to 99%). Cyclic secondary amines reacted particularly well in this coupling. A representative example is shown in Scheme 16.

Finally, a silver-catalysed alkynylation of an α-iminoester was reported in 2004 by Chan and co-workers.[45] In this work, various silver salts, among which AgOTf was found to be the best, were used to promote the addition of terminal acetylenes to *N*-PMP-α-iminoethyl glyoxalate (**45**, PMP = *para*-methoxyphenyl) in hexane at ambient temperature. The reactions were usually complete within 30 min, affording the corresponding propargyl amino esters **46** in 79–93% yield (Scheme 17).



Scheme 16 Ag(I)-catalysed three-component synthesis of propargylic amines.

3 Enantioselective metal-promoted direct alkynylation of C=N electrophiles

Despite the substantial amount of work dedicated to the development of efficient methodologies for the metal-mediated or metal-catalysed direct addition of acetylenes to C=N electrophiles, the enantioselective version of this transformation has not yet been fully developed. Although excellent protocols have already been reported, they still lack generality, and only some of them employ catalytic quantities of metal complexes or chiral ligands, while in other cases, stoichiometric amounts of such promoters are still needed.

In most of the enantioselective processes reported so far, copper species are used as the catalysts, but protocols based on the use of other metals, such as zinc and zirconium, or chiral boronates, have also been published.

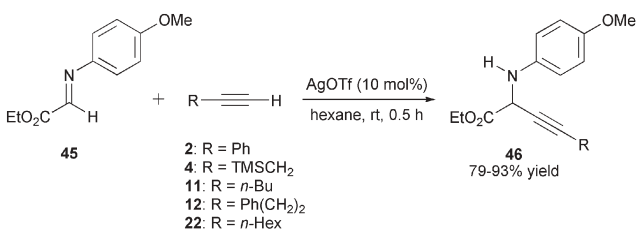
3.1. Copper-catalysed enantioselective alkyne additions

The first copper-catalysed enantioselective addition of phenylacetylene (**2**) to *N*-arylimines was described in 2002 by Wei and Li,[46] who employed Cu(I) salts, in combination with nitrogen-containing ligands, to generate the catalytic species. The substrates were generally formed *in situ* by pre-mixing the appropriate aldehyde and aniline, before addition of the catalyst and alkyne.

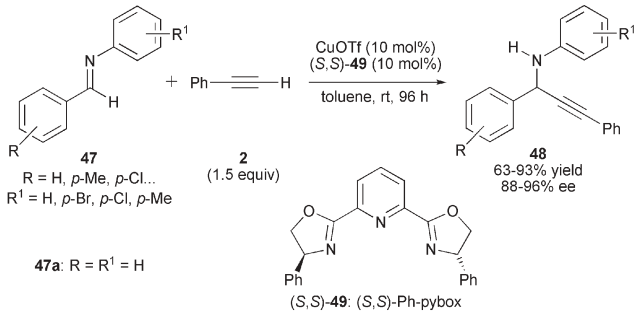
After some unfruitful efforts, the authors found that use of tridentate *bis*(oxazolinyl)pyridine (pybox) ligands, such as (*S*,*S*)-**49**, in combination with CuOTf, led to products with high yields and high enantioselectivity at room temperature. Interestingly, both toluene and water could be used as solvents, with the former giving slightly better results in terms of selectivity.

Under optimised conditions, several aromatic imines could be alkynylated with **2**, furnishing the corresponding propargylamines in up to 93% yield and 96% ee (Scheme 18). Some of the most significant results are listed in Table 2.

The long reaction time of 4 days could be shortened to 2 days by performing the reactions at 35 °C instead of at room temperature, but generally a slight reduction in the enantiomeric excesses of the products were observed under these conditions (Table 2, entry 1 *vs.* entry 2 and entry 5 *vs.* entry 6). At this stage, the reaction suffered from two considerable



Scheme 17 Ag(I)-catalysed alkynylation of an α-iminoester.



Scheme 18 Catalytic, enantioselective alkynylation of *N*-arylimines.

Table 2 Scope of the enantioselective addition of alkynes to imines in toluene and water

Entry	Aldehyde	Aniline	Solvent	*T*/°C	*t*/d	Yield (%)	ee (%)
1	PhCHO	$PhNH_2$	Toluene	22	4	78	(+) 96
2	PhCHO	$PhNH_2$	Toluene	35	2	83	(+) 93
3	PhCHO	$PhNH_2$	Water	22	4	71	(+) 84
4	4-MeC_6H_4CHO	$PhNH_2$	Toluene	35	2	85	(+) 92
5	4-EtC_6H_4CHO	$PhNH_2$	Toluene	22	4	70	(+) 96
6	4-EtC_6H_4CHO	$PhNH_2$	Toluene	35	2	73	(+) 95
7	4-EtC_6H_4CHO	$PhNH_2$	Water	22	4	68	(+) 89
8	4-ClC_6H_4CHO	$PhNH_2$	Toluene	22	4	85	(+) 94
9	2-NaphCHO	$PhNH_2$	Toluene	22	4	63	(+) 88
10	2-NaphCHO	$PhNH_2$	Water	22	4	57	(+) 86
11	PhCHO	4-BrC_6H_4CHO	Toluene	35	2	93	(+) 91
12	PhCHO	4-BrC_6H_4CHO	Water	35	2	82	(+) 83
13	PhCHO	4-MeC_6H_4CHO	Toluene	35	2	93	(+) 94
14	PhCHO	4-MeC_6H_4CHO	Water	35	2	68	(+) 91

limitations: firstly, **2** was the only alkyne employed, and secondly, the use of imines stemming from enolisable, aliphatic aldehydes was not reported.

Later, the same research group demonstrated that alkyl-substituted terminal acetylenes were also applicable, although the enantiomeric excesses of the corresponding propargylamines did not exceed 85%.[47] In addition, it was also found that the reaction of *N*-benzylidene aniline (**47a**) with **2** could be performed in as many as 16 different solvents without the enantioselectivity being significantly affected (the only exception being protic solvents, such as water or methanol, which gave slightly reduced ee values). The best result was obtained in 1,2-dichloroethane, with the product being isolated in 71% yield and 99.5% ee (compared to 96% in toluene: Table 2, entry 1). On the other hand, the applicability of this reaction to convert imines derived from aliphatic aldehydes has not yet been demonstrated.

A modification of the reaction shown in Scheme 18 has been described, which makes use of a pybox derived from (*S*)-1,1-diphenyl-2-*iso*-propyl-2-aminoethanol as the ligand. Under conditions similar to those reported by Li,[46] employment of 10 mol% of this ligand, in combination with $CuPF_6$, led to various propargylic amines of type **48** being obtained in high yields with up to 99% ee.[48]

Recently, a series of polymer-bound pybox ligands, having structures similar to that of (*S*,*S*)-**49**, with different substituents on the oxazoline rings, have been synthesised on a solid phase and treated with CuOTf to form the corresponding Cu(I) complexes **50a–f** (Fig. 2).

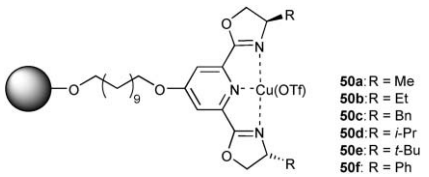


Fig. 2 Solid-supported Cu(I)/pybox complexes.

The complexes shown in Fig. 1 have been used as catalysts for the enantioselective addition of **2** to *N*-benzylidene aniline (**47a**).[49] Interestingly, all the complexes proved able to promote the reaction, the only exception being **50f**, *i.e.*, the solid-supported analogue of the CuOTf/(*S*,*S*)-**49** complex, which, according to Li, was the most efficient homogeneous catalyst.[46] The ee values of the products were generally lower than those of the propargylic amine prepared using the homogeneous catalytic system, and did not exceed 83% ee. The authors demonstrated the possibility of re-using the catalysts for at least three consecutive runs.

A protocol, similar to that of Li,[46] employing chiral binaphthyl-based diimines **51**[50] or diamines **52** and **53**[51] (Fig. 3) as ligands, has been recently reported by Benaglia and co-workers, who worked on pre-formed *N*-aryl imines **47**. Generally, complexes obtained from Cu(I) salts and compounds **51** gave products with higher yields and enantioselectivities than those resulting from diamines **52** and **53**.

Although use of a catalytic quantity (1–10 mol%) of diimine **51** (Ar = pentafluorophenyl), in combination with an equimolar amount of CuOTf, gave a good result for the addition of phenylacetylene (**2**) to *N*-benzylidene aniline (**47a**), affording product **48a** with 85% ee, application of the same catalytic system to the reaction of other *N*-aryl imines and acetylenes generally yielded products with lower ee values, not exceeding 80%. Variation of the reaction conditions (solvent, temperature, catalyst concentration) and copper source (CuBr, CuCl, $CuPF_6$) did not lead to improvements. The authors demonstrated that enantiomerically enriched propargylamine **48a** could be subjected to a partial or complete hydrogenation, or to Hg(II)-catalysed hydrolysis (to furnish the corresponding β-amino ketone **57**) without a loss of stereochemical integrity (Scheme 19).[50b]

The combination of a Cu(I) salt with a pybox ligand was recently found by Chan and co-workers to be effective in catalysing the asymmetric direct alkynylation of α-iminoester **45** to yield optically active propargylic α-amino acid derivatives of type **46**.[52] As already mentioned above, Ag(I) salts were competent catalysts for the corresponding racemic transformation (Scheme 17),[45] but when the authors employed

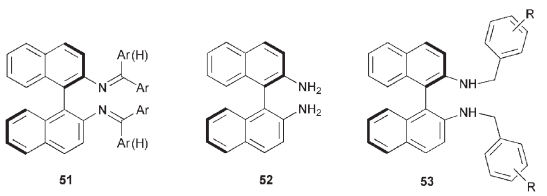


Fig. 3 Chiral diimines and diamines for the Cu(I)-catalysed enantioselective alkynylation of imines.

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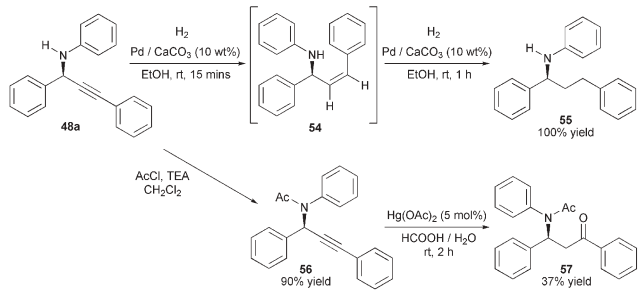


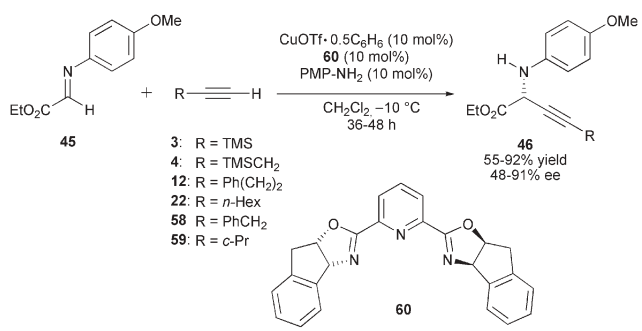
Scheme 19 Synthetic elaborations of propargylamine **48a**.

them in combination with chiral ligands, no conversion of the starting material was observed. After an extensive optimisation effort, a catalytic system consisting of the combination of CuOTf·0.5C_6H_6/pybox **60** was found to afford the best results in terms of yield and selectivity (Scheme 20).

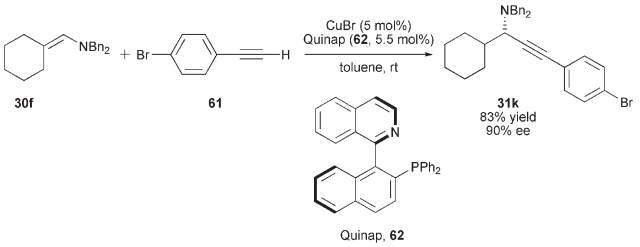
Interestingly, the addition of a small (0.1 equiv.) quantity of *para*-anisidine to the reaction mixture led to an increase in the reaction rate, without affecting the enantioselectivity. The best result was obtained when 1-octyne was used as the alkyne (91% ee), while employment of a bulkier acetylene, such as trimethylsilylethyne (**3**), gave a much less efficient and selective reaction (55% yield, 48% ee). Compound **46** (R = $PhCH_2$) could be further elaborated to a fully saturated, free α-amino ester with no loss in optical purity.

As already mentioned, an efficient protocol for the addition of alkynes to enamines (derived from aliphatic aldehydes) by means of a Cu(I) catalyst has recently been discovered by Knochel (see section 2.2., Table 1). Addition of a suitable chiral ligand allowed the development of an enantioselective version of this reaction. After an extensive screening, axially chiral Quinap (**62**)[53] was found to give the best results in terms of yield and selectivity. Its use in combination with CuBr provided access to a large array of propargylamines with ee values up to 90% (Scheme 21).[32]

To overcome the limitations related to the use of enamines as starting materials, a three-component procedure was subsequently introduced by the same research group, in which the reactive iminium intermediate was generated by reaction of an aldehyde with a secondary amine (generally dibenzyl or diallylamine).[54–59] Higher enantioselectivities were typically obtained in comparison to the previous methodology (up to 96% ee) and, more importantly, the new protocol also allowed



Scheme 20 Catalytic, enantioselective alkynylation of α-iminoester **45**.

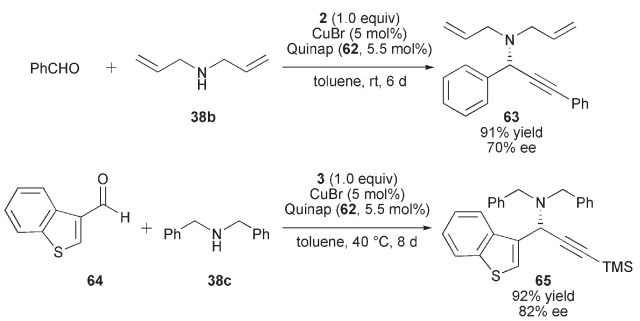


Scheme 21 Copper-catalysed enantioselective addition of an alkyne to an enamine.

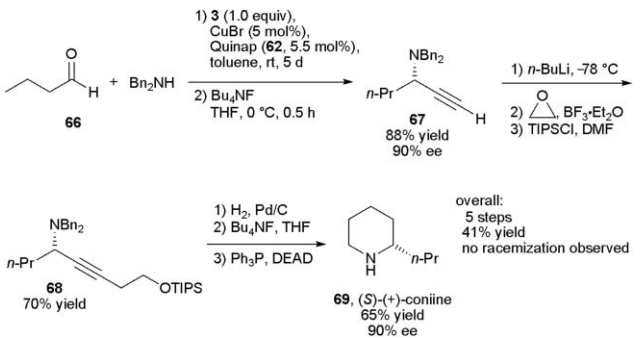
the conversion of substrates stemming from aromatic aldehydes.[54,58] Unfortunately, however, the enantioselectivity of reactions in which such compounds are used as starting materials is still largely inferior to that of reactions in which aliphatic aldehydes are employed and, to date, only enantiomeric excesses in the range of 70–80% have been obtained, with heteroaromatic aldehydes being slightly superior to the others (Scheme 22).

In the same study, the authors examined the reaction of 2-ethylbutanal, dibenzylamine (**38c**) and **3** in the presence of CuBr and scalemic **62**, and found the presence of a considerable positive non-linear effect (ligand **62** with 10% ee afforded the product of the reaction with 68% ee). As a consequence, the participation of more than one molecule of **62** in the transition state of the reaction's enantioselective step was proposed.[54]

The synthetic utility of the propargylamines obtained from the enantioselective direct alkyne addition described above was demonstrated by Gommermann and Knochel through a straightforward synthesis of (*S*)-(+)-coniine (**69**, Scheme 23).[55]



Scheme 22 Copper-catalysed, enantioselective three-component synthesis of propargylamines.



Scheme 23 Enantioselective synthesis of (*S*)-(+)-coniine (**69**).

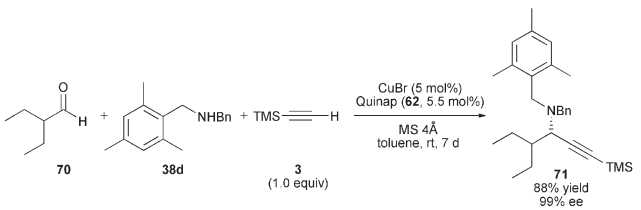
The same group subsequently reported further applications of this powerful enantioselective transformation, which included the synthesis of variously functionalised, enantioenriched, terminal propargylic amines and their conversion into α-aminoalkylpyrimidines,[56] their further deprotection and elaboration at the triple bond,[57] and the synthesis of chiral triazoles *via* a Cu(0)-catalysed 1,3-dipolar cycloaddition between the triple bond and various azides.[58] Furthermore, it was discovered that the employment of a bulkier secondary amine, such as (mesitylmethyl)benzylamine (**38d**), instead of diallyl or dibenzylamine, led to an increase in the enantiomeric excess of the corresponding propargylamines, which were isolated with up to 99% ee (Scheme 24).[59]

Recently, Knochel's method found application in the enantioselective alkynylation of isolated isoquinolinium ions,[60] which was applied to the asymmetric synthesis of (*S*)-(−)-homolaudanosine (**75**), an isoquinoline-based natural product possessing neurological activity (Scheme 25).[60a]

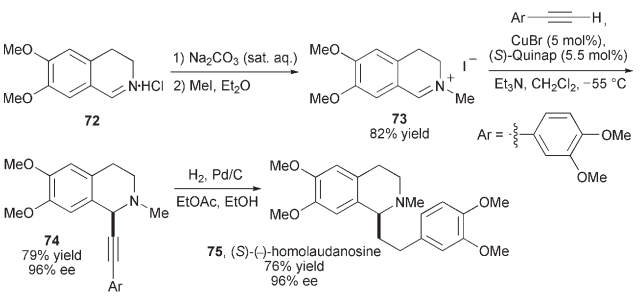
A major drawback of the methodology developed by Knochel was the necessity to use **62** as a chiral ligand. The preparation of this compound is costly in time and includes a resolution step.[53] Today, **62** is commercially available but rather expensive.[61] For this reason, various research groups have focused on the development of alternative *P*,*N*-ligands that are structurally related to it.

In 2004, Carreira and co-workers reported the synthesis and application of a new family of such compounds, which they named Pinap (**76–77**, Fig. 4).[62]

The syntheses of compounds **76** and **77** comprise only four steps. The presence of an element of central chirality, in addition to the axially chiral binaphthyl unit, allows the easy separation of the two diastereomers of **76** or **77** by flash chromatography or crystallisation. The authors reported that the use of compounds **77a,b** as ligands in the three-component synthesis of propargylic amines, as described by Knochel,[54]



Scheme 24 Enantioselective three-component synthesis of (mesitylmethyl)benzyl-substituted propargylamines.



Scheme 25 Enantioselective total synthesis of (*S*)-(−)-homolaudanosine (**75**).

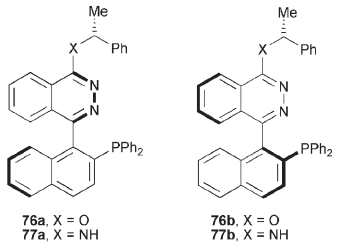


Fig. 4 Diastereomeric Pinap ligands.

generally furnished products with higher ee values compared to the reaction with Quinap (**62**). Some of the results are reported in Table 3.

Table 3 shows that products with enantiomeric excesses up to 99% could be obtained by the application of compounds **77a,b** as ligands. Moreover, a slight match/mismatch effect was observed, with **77b** generally providing the products with a better enantioselectivity than its diastereomer **77a**.

Recently, the same reaction was conducted using 4-piperidinone hydrochloride hydrate instead of dibenzylamine as the amine component. The resulting propargylic imines were obtained in good yields with up to 96% ee. Selective cleavage of the piperidone protecting group by the use of $EtOH/NH_3$ or a polymer-supported scavenger amine allowed the isolation of enantioenriched primary propargylamines.[63]

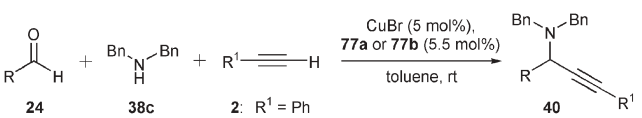
3.2. Other metal-mediated enantioselective alkyne additions

To date, only a few examples of enantioselective direct additions of alkynes to C=N electrophiles which do not make use of copper complexes as catalysts have been described.

In 2003, Hoveyda *et al.* utilised peptide-based ligand **82**, in combination with $Zr(O\textit{i}\text{-Pr})_4 \cdot HO\textit{i}\text{-Pr}$, to catalyse the addition of a mixed alkynylzinc reagent to various *N*-aryl aromatic imines (Scheme 26).[64]

Although products with good to high enantiomeric excesses could be prepared by following this protocol, the necessity of using pre-formed organometallic species **79** and **80** to generate the reactive mixed zinc alkynylide renders the methodology less attractive. Moreover, when dialkynylzinc reagents bearing groups other than trimethylsilyl on the triple bond were used, much lower enantioselectivities were observed (up to 79% ee).[65]

Table 3 Cu(I)/Pinap-catalysed synthesis of propargylamines



Entry	R	R^1	Ligand	Yield (%)	ee (%)	ee with **62**[54] (%)
1	*i*-Pr	TMS	**77a**	84	98 (*R*)	92
2			**77b**	82	99 (*S*)	
3	*i*-Pr	Ph	**77a**	88	90 (*R*)	84
4			**77b**	82	95 (*S*)	
5	*i*-Bu	*n*-Bu	**77a**	74	91 (*R*)	82
6			**77b**	72	94 (*S*)	

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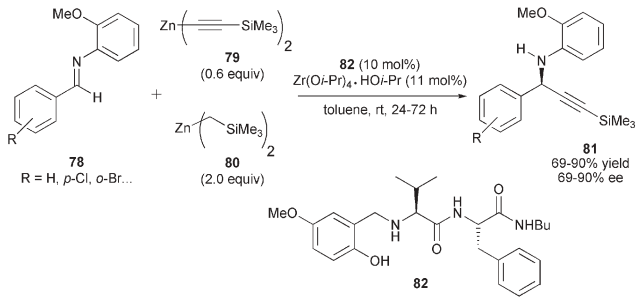


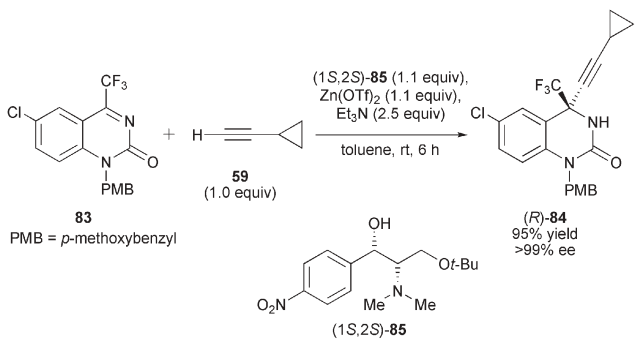
Scheme 26 Zr-catalysed enantioselective alkynylation of aromatic imines.

In 2004, Jiang and Si described the application of amino alcohol (1*S*,2*S*)-**85** as a stoichiometric ligand for the addition of alkynes to a cyclic trifluoromethyl-activated cyclic imine **83**.[66] This reaction is the key step in the synthesis of DPC-961,[13] an aza analogue of the famous anti-AIDS drug Efavirenz (Sustiva®, Bristol–Myers–Squibb).[67] The use of (1*S*,2*S*)-**85**, in combination with $Zn(OTf)_2$ and triethylamine, furnished the addition product **84** in high yield with an extremely high enantiomeric excess (Scheme 27).

The applicability of this methodology to the large-scale production of DPC-961 was demonstrated by the authors, who carried out the reaction on a 100 g scale, with a result comparable to that of the small-scale reaction. Alkynes other than **59** could be applied, and the resulting cyclic propargylamides were always obtained in good yields with 98 → 99% ee. The chiral amino alcohol could be recovered after the reaction and re-used at least three times with no loss of yield or selectivity (although the reaction time had to be increased to 10 h).

A zinc-mediated enantioselective alkynylation has also been described by Inomata and co-workers, who employed alkynylzinc reagents, prepared *in situ* from terminal alkynes and dialkylzinc species, in combination with di-(*tert*-butyl)zinc tartrate for the addition to nitrones. In order to obtain a good enantioselectivity, a stoichiometric quantity of the chiral auxiliary was needed. Addition of product-like *N*-hydroxylamine to the reaction mixture provoked an increase in the enantiomeric excess of the products, and propargyl *N*-hydroxylamines with up to 95% ee could be prepared.[68]

Finally, the use of binaphthol-based alkynylboronates **88** was reported by Wu and Chong to perform the enantioselective alkynylation of *N*-acylaldimines.[69] In their approach, the



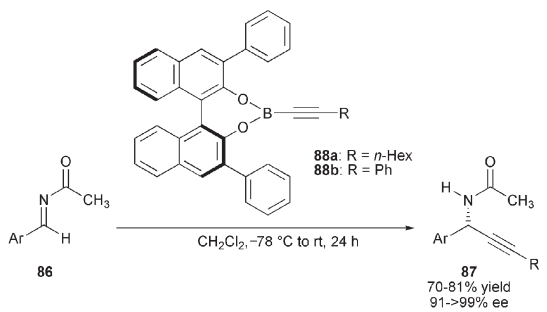
Scheme 27 Enantioselective addition of alkyne **59** to a DPC-961 precursor.

chiral alkynylboron reagent, as well as the aldimine, has to be prepared and isolated prior to the reaction. The reaction then proceeds in a similar way to a conjugate addition, with initial coordination of the alkynylboron species by the oxygen of the substrate and subsequent alkynyl transfer. The authors found that substitution at the 3,3′-position of the binaphthol unit was essential to obtain products with a high degree of enantioselectivity (Scheme 28).

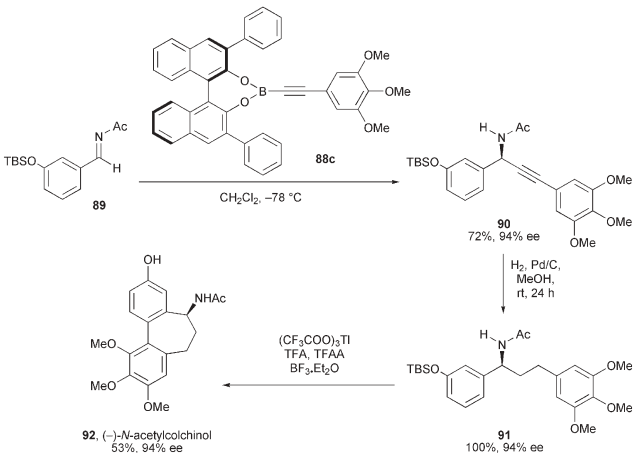
N-Acylpropargylamines **87** derived from various aromatic imines could be prepared in good yields with high enantioselectivities. The synthetic utility of this protocol was demonstrated by the synthesis of (−)-*N*-acetylcolchinol (**92**), whose *O*-phosphate, also known as ZD6126, is useful in the treatment of cancer (Scheme 29).[69] While racemic *N*-acetylcolchinol had already been prepared by total synthesis, the levorotatory enantiomer could previously only be obtained in enantiomerically pure form by degradation of natural (−)-colchicine.

4. Conclusions

In this review, the currently available methods to achieve a metal-promoted direct addition of acetylenes to C=N electrophiles have been described. Many different protocols can be applied to the synthesis of racemic propargylamines, employing various metal promoters, either in stoichiometric or catalytic amounts. Although some aspects of the reaction still need to be improved, in particular concerning substrate and



Scheme 28 Enantioselective synthesis of *N*-acyl propargylamines.



Scheme 29 Enantioselective total synthesis of (−)-*N*-acetylcolchinol (**92**).

alkyne scope, conversion of less reactive, unactivated imines and efficiency of the catalysts, this methodology already constitutes a new and efficient alternative way to construct carbon–carbon single bonds.

On the other hand, the development of reliable methods to effect this transformation in an enantioselective manner is still in its infancy. Whereas excellent enantiomeric excesses in the synthesis of some classes of propargylamines have already been reported, especially by use of copper-based catalysts, a truly general catalytic system still does not exist.

Despite these limitations, the metal-mediated asymmetric alkynylation of C=N electrophiles has already demonstrated a remarkable synthetic utility, as exemplified by the straightforward syntheses of such natural products as (*S*)-(+)-coniine (**69**),[55] (*S*)-(−)-homolaudanosine (**75**)[60] and (−)-*N*-acetylcolchinol (**92**).[69] Given the considerable attention received by this transformation in recent years, further improvements are soon expected to be reported in the literature.

Footnote added in proof

Since the submission of this manuscript, a highly enantioselective alkynylation of *N*-acylimines has been described by Soderquist and co-workers that makes use of chiral *B*-alkynyl borabicyclononanes as reagents. *N*-acetyl propargylic amines could therefore be obtained in good yields with a high enantiomeric excess (up to 99% after recrystallization).[70]

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