Synthesis of Propargylamines by Cross-Dehydrogenative Coupling

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Abstract: Propargylamines are versatile compounds for heterocyclic synthesis, some of which are current drugs prescribed to treat patients with Parkinson's disease. There are different methods to synthesize propargylamines; however, modern chemistry has moved progressively demanding to rely on new strategies that meet the principles of Green Chemistry. In this context, propargylamines are readily accessible by the cross-dehydrogenative coupling (CDC) of two C-H bonds (i.e., $NCsp^3$-H and Csp-H bonds); surely, CDC can be considered the most atom-economic and efficient manner to form C-C bonds. The aim of this review is to provide a comprehensive survey on the synthesis of propargylamines by the CDC of amines and terminal alkynes from three fronts: (a) transition-metal homogeneous catalysis, (b) transition-metal heterogeneous catalysis and (c) photoredox catalysis. A section dealing with the asymmetric synthesis of chiral propargylamines is also included. Special attention is also devoted to the proposed reaction mechanisms.

Keywords: asymmetric synthesis, cross-dehydrogenative coupling, green chemistry, homogeneous catalysis, heterogeneous catalysis, photoredox catalysis, propargylamines, tetrahydroisoquinolines.

1. INTRODUCTION

Propargylamines are useful synthetic scaffolds broadly exploited as precursors of heterocyclic compounds, such as quinolones [1a], phenanthrolines [1b], pyrroles [1c], pyrrolidines [1d], indolizines [1e] or oxazolidinones [1f], among others [2]. They have also been utilized as starting materials for transition-metal catalyzed Csp^3-H and Csp^3-Csp activation [3], and as intermediates in the total synthesis of some natural and pharmaceutical products [4]. The propargylamine unit can be found in diverse bioactive compounds [5], some of which have been proven to be potent anti-apoptotic agents that protect neurons against cell death in cellular and animal models of neurodegenerative disorders. Indeed, they have been shown to delay the necessity for symptomatic therapy in untreated Parkinson's disease patients, results that are consistent with the neuroprotection role of this type of compounds [6]. For instance, selegiline (Anipril®) and rasagiline (Azilect®) are current propargylamine-containing drugs for monotherapy in patients with early Parkinson's disease and for adjunctive therapy in patients with moderate-to-advanced disease [6c]. Pargyline (Eutonyl®) is an irreversible inhibitor of monoamine oxidase (MAO) with antihypertensive properties [6d] (Figure 1).
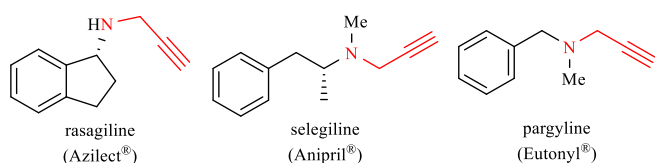

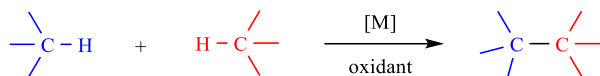**Figure 1.** Some examples of bioactive propargylamines.

Standard procedures for the construction of the propargylamine moiety are based on the direct amination of propargyl halides [7a], triflates [7b], phosphates or acetates [7c], or on the more widely practiced addition of alkynylmetal reagents to imines [Scheme 1, eq. (1) and (2), respectively] [8]. The latter option, normally involving stoichiometric amounts of lithium or magnesium acetylides, demands strict control of the reaction conditions and its application is hampered by the presence of reactive functional groups. The metal-catalyzed multicomponent coupling of aldehydes, amines, and alkynes (A^3 coupling) [9] or the nucleophilic substitution of *in-situ* generated chloromethyl amines catalyzed by copper or silver [Scheme 1, eq. (3) and (4), respectively] [10] are more interesting approaches.
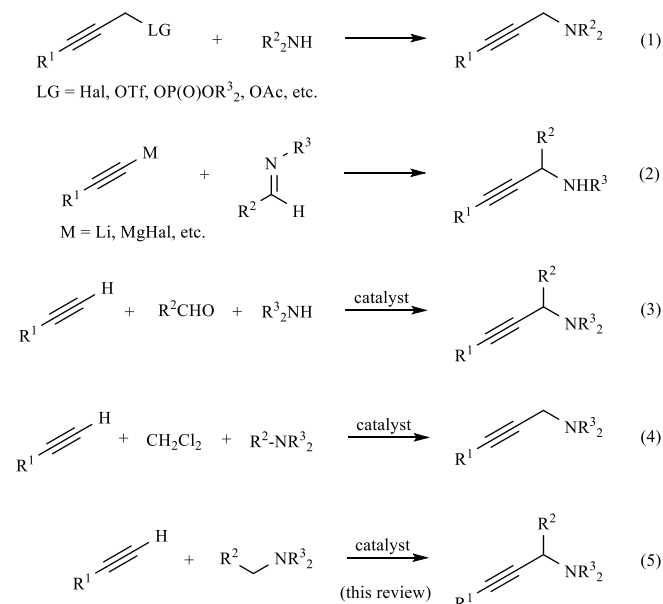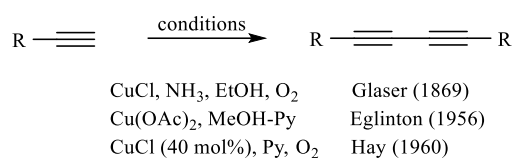

Scheme 1. Some general methods for the synthesis of propargylamines.

On the other hand, a C-C bond should be ideally built from two C-H bonds (Scheme 2). Historically, the oxidative homocoupling of alkynes promoted by copper can be considered the first reaction of this type; originally discovered by Glaser in 1869 utilizing CuCl and ammonia in the presence of oxygen [11a], it was upgraded almost a century later by Eglinton [11b] [excess of $Cu(OAc)_2$ in MeOH-Py] and Hay with the introduction of pyridine or TMEDA (Scheme 3) [11c].

Scheme 2. Carbon-carbon bond formation from C-H bonds.

conditions	
$CuCl$, NH_3, EtOH, O_2	Glaser (1869)
$Cu(OAc)_2$, MeOH-Py	Eglinton (1956)
CuCl (40 mol%), Py, O_2	Hay (1960)

**Scheme 3.** Oxidative alkyne homocoupling.

The conversion of two C-H (or C-H and Het-H) bonds into a C-C (or C-Het) bond is nowadays known as the cross-dehydrogenative coupling (CDC). This is a powerful atom-economy tool to efficiently design organic molecules, that has become one of the most active research areas in chemistry [12]. We present herein a comprehensive review on the synthesis of propargylamines by the catalytic coupling of Csp^3-H bonds adjacent to nitrogen with Csp-H bonds of terminal alkynes [Scheme 1, eq. (5)].

2. TRANSITION-METAL CATALYSIS

2.1. Homogeneous catalysis

In 1993, Miura *et al.* published the synthesis of *N*-methyl-*N*-propargylamines from *N,N*-dimethylanilines and terminal alkynes catalyzed by $CuCl_2$, under an oxygen atmosphere in acetonitrile (Scheme 4) [13]. Besides using 2 equiv. of the alkyne, the reaction was little selective, producing substantial amounts of the *N*-methyl- and *N*-formyl-*N*-methylanilines as by-products. The reaction mechanism set forth involved the aminomethyl radical of the *N,N*-dimethylamine (generated either by one-electron oxidation/deprotonation or by hydrogen abstraction), the corresponding benzyl organocopper and its complex with the arylacetylene. However, the authors stated that the role of the copper species in this reaction was dubious (Scheme 4). This can be considered the first synthesis of propargylamines through CDC. Copper catalysis has been most applied to this reaction ever since.

A major breakthrough was achieved by Li *et al.* with the introduction of CuBr as catalyst and *tert*-butylhydroperoxide (TBHP) as an oxidant (Scheme 5) [14]. Not only *N,N*-dimethylanilines but other amines also underwent this reaction. The process was especially straightforward in the case of arylacetylenes, whereas the aliphatic counterparts were found to be more reluctant to react. In a tentative reaction mechanism, the participation of an iminium ion complexed to copper was propounded together with the *in-situ* generation of the copper acetylide, followed by coupling of these two intermediates (Scheme 5).
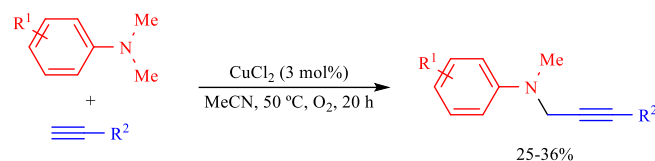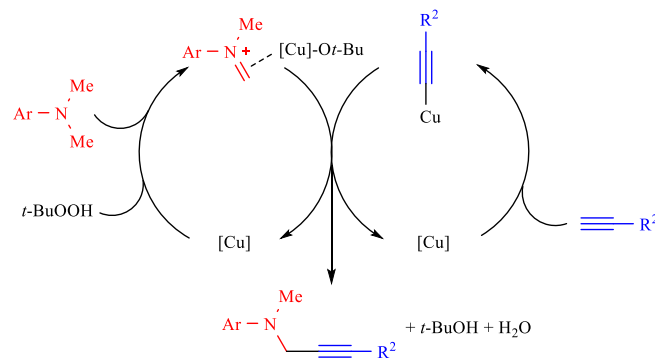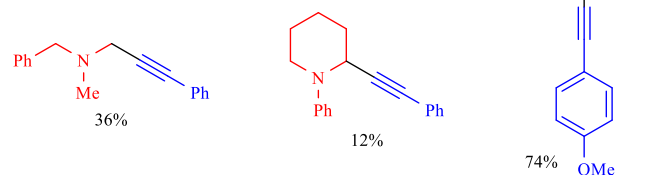

R^1 = 4-Me, 4-OMe, 4-OEt, 3,4-Me$_2$,
R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, *n*-Pent
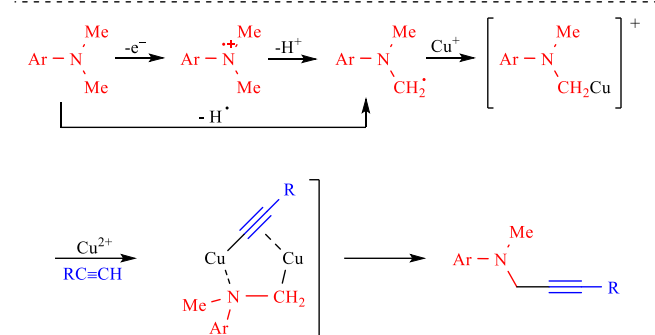
Scheme 4
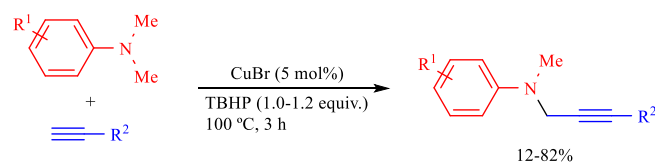
R^1 = H, 2-Me, 4-Me, 4-Br
R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-PhC$_6$H$_4$,
      2-pyridyl, CH$_2$OH, CH$_2$CO$_2$Et, CO$_2$Me, *n*-Bu

Scheme 5

Fu *et al.* replaced TBHP by the safer NBS as an alternative oxidant or free radical initiator [15]. The optimized reaction conditions required a larger amount of catalyst (40 mol% CuBr) and 2 equiv. of amine in MeCN as solvent, at 80 °C under a nitrogen atmosphere (Scheme 6). The procedure was mostly employed in the coupling of tertiary benzylic amines and aromatic alkynes; *N,N*-dimethylanilines as well as aliphatic (non-benzylic) amines were more resistant to react. Lower yields were also attained in the case of aliphatic

alkynes. The authors proposed that the intermediate amine radical cation was formed by the action of the free radicals derived from NBS on the tertiary amine, followed by hydrogen abstraction to produce the iminium ion, which would, eventually, undergo the attack of the copper acetylide.

R = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-BrC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, 1-naphthyl, cyclopropyl, 1-hexyl

44%   41%
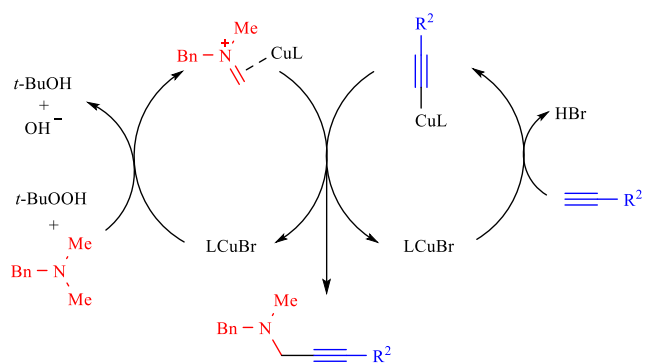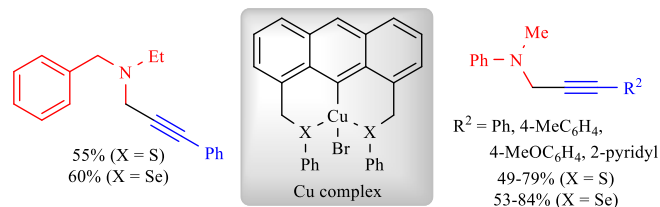
29%   43%
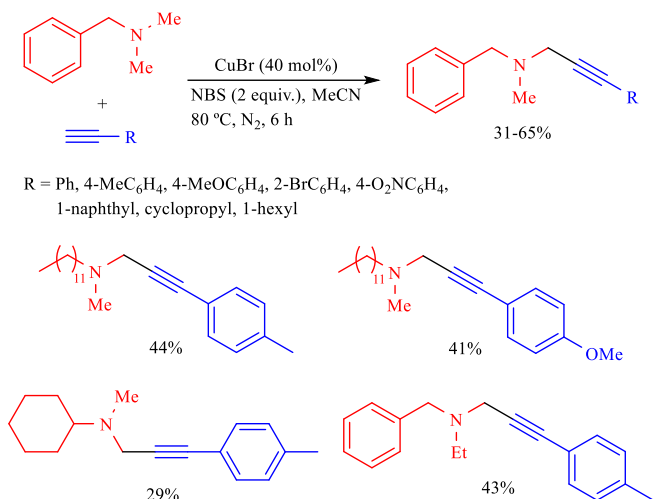
Scheme 6

Very recently, the same type of tertiary benzylic amines have been coupled with aromatic alkynes employing Cu(I) complexes of 4,5-bis[(phenylthio/seleno)methyl]-acridine as catalysts [16]. In general, electron-rich substrates led to better yields of the desired propargylamines (Scheme 7). Contrary to the previous catalytic system commented, *N,N*-dimethylanilines reacted under equal conditions as the *N,N*-dimethylbenzylamines in moderate-to-good yields. Aliphatic (non-benzylic) amines were not covered in this study, whereas the only propargylamine tested derived from an aliphatic alkyne was obtained in modest yield (46%, X = S; 51%, X = Se). In spite of being a homogeneous catalytic system, it could be recycled in five runs by adding, every time, a fresh lot of reactants to the flask, though with limited effectiveness (73-45% yield). A close reaction mechanism to that of Li *et al.* was invoked.

The alkynylation of aliphatic tertiary amines through CDC was improved by introducing DEAD as a dehydrogenating agent of the amines [17]. In this way, there was no need to exclude air and moisture from the reaction flask, with the reactions proceeding under mild conditions in good-to-excellent yields. Moreover, the method was applicable to the less reactive aliphatic alkynes and trimethylsilylacetylene (Scheme 8). The reaction was advocated to take place through an ionic pair comprised of the iminium cation of the amine and the hydrazine anion derived from DEAD.
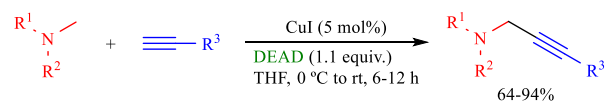
The crucial role of the oxidant in these reactions was clearly demonstrated by J.-X. Li *et al.* in the coupling of TMEDA with terminal alkynes [18]. The expected CDC products were produced when using CuCl$_2$ (10 mol%) in DMSO at 80 °C in air; however, cleavage of the C-C bond of TMEDA took place when switching to TBHP at room temperature, leading to propargylamines derived from a formal alkyne aminomethylation reaction (Scheme 9).
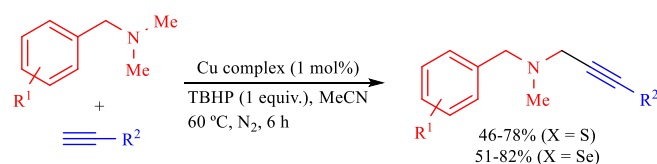
R^1 = Ph, 4-YC$_6$H$_4$ (Y = Me, MeO, Cl, Br), 3-ClC$_6$H$_4$
R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, CF$_3$, 2-pyridyl, *n*-Pent

55% (X = S)   60% (X = Se)

Cu complex

R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-pyridyl
49-79% (X = S)
53-84% (X = Se)

Scheme 7

R^1 = Me; R^2 = *c*-hexyl; R^3 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-F$_3$CC$_6$H$_4$, 3-FC$_6$H$_4$, 3-ClC$_6$H$_4$, Bn, PhCH$_2$CH$_2$, 3-pyridyl, 3-thienyl, Bu, TMS
R^1 = Me, R^2 = *c*-pentyl, R^3 = Ph
R^1 = Me, R^2 = *c*-heptyl, R^3 = Ph
R^1 = R^2 = *c*-hexyl, R^3 = Ph
R^1 = *i*-Pr, R^2 = *t*-Bu, R^3 = Ph
R^1 = Me, R^2 = Bn, R^3 = Ph
R^1 = Me, R^2 = *i*-Pr, R^3 = 4-Me(CH$_2$)$_4$C$_6$H$_4$

via
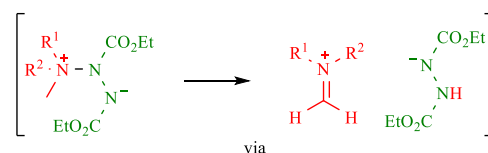
Scheme 8

In 2011, Bao *et al*. disclosed the synthesis of *N,N*-dimethylpropargylamines by the Cu(II)-catalyzed CDC of terminal alkynes and tertiary amine *N*-oxides, instead of the typically studied tertiary amines [19]. A clear advantage was the fact that the reactions proceeded in the absence of an external oxidant, using Cu(acac)$_2$ in DME at 110 °C. However, one additional step was required, as the amine *N*-oxides had to be prepared by amine oxidation; this, together with the usage of two equiv. of the amine *N*-oxide and the necessity for a nitrogen atmosphere, can be considered the weak points of this approach. Both, aromatic and aliphatic alkynes reacted with excellent functional group compatibility
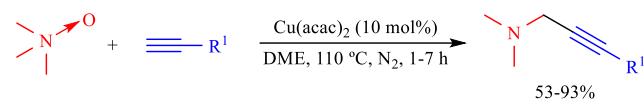
32-89%

91-67%
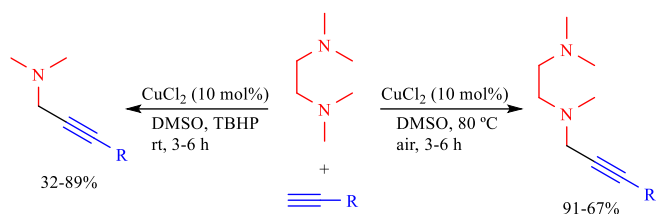
R = Ph, *n*-Bu, *t*-Bu, 2-thienyl, 3-MeC$_6$H$_4$, 4-YC$_6$H$_4$ (Y = *t*-Bu, MeO, F)

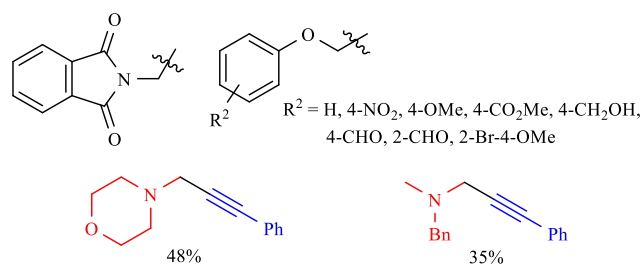Ar = Ph, 4-YC$_6$H$_4$ (Y = Me, MeO, I)
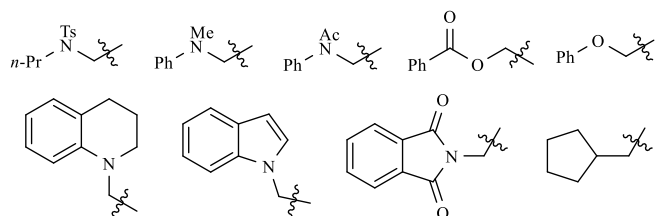
Scheme 9

and in moderate-to-high yields (Scheme 10). Trimethylamine *N*-oxide gave the best results, whereas modest yields were noted for *N*-methylmorpholine *N*-oxide and benzyldimethylamine *N*-oxide. The authors advocated iminium ions coordinated to copper hydroxide and copper acetylide as intermediates.


53-93%

R^1 = Ph, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, *c*-Hex, *n*-Oct, PhCH$_2$CH$_2$,

R^2 = H, 4-NO$_2$, 4-OMe, 4-CO$_2$Me, 4-CH$_2$OH, 4-CHO, 2-CHO, 2-Br-4-OMe

48%   35%
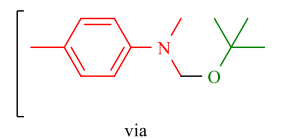
Scheme 10

The CDC of tertiary amines and terminal alkynes is not limited to copper catalysis; catalytic systems based on iron and zinc have also been shown to be efficient in this transformation. For instance, in 2009, Vogel *et al.* introduced FeCl$_2$ as an alternative to copper catalysts for the CDC of *N,N*-dimethylanilines, as well as benzyl and aliphatic tertiary amines with terminal alkynes [20]. *t*-Butyl peroxide (TBP) was used as the oxidant in air at 100 °C, under solvent-free conditions, with relatively long reaction times (18–30 h) (Scheme 11). The catalytic system was effective for aromatic, heteroaromatic and aliphatic alkynes, with the latter requiring prolonged heating. An unsymmetrical propargyldiamine could be obtained from two different amines and trimethylsilylacetylene, following a CDC-desilylation-CDC sequence. Control experiments in the absence of the alkyne supported the formation of an intermediate hemiaminal ether derived from the amine and TBP, which couples with the alkyne under the action of FeCl$_2$.

13-93%
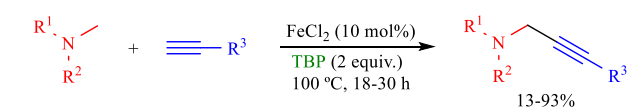
R^1 = 4-MeC$_6$H$_4$; R^2 = Me; R^3 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, PhCH$_2$CH$_2$, 2-pyridyl, 3-pyridyl, *n*-Hex, TMS, 1-cyclohexenyl, CO$_2$Et, Cl(CH$_2$)$_3$, PhOCH$_2$

R^1 = Me; R^2 = Ph, 2-MeC$_6$H$_4$, 4-BrC$_6$H$_4$; R^3 = Ph, 4-MeC$_6$H$_4$

R^1 = Me, Ph; R^2 = Bn, *c*-Hept, *n*-Oct; R^3 = Ph, 3-pyridyl


via

Scheme 11

Nakamura *et al.* described the redox CDC of propargylamines and terminal alkynes catalyzed by ZnBr$_2$ in toluene at 100 °C, under nitrogen for 24 h [21]. The carbon-carbon triple bond of the starting propargylamine was reduced, acting as an internal oxidant. The resulting N-tethered 1,6-enynes were produced in modest-to-good yields, in most cases using 3 equiv. of the alkyne (Scheme 12). A reaction mechanism was put forward in which alkynylzinc bromide species added to *in-situ* generated iminium ions by a 1,5-hydride shift.


73%

via
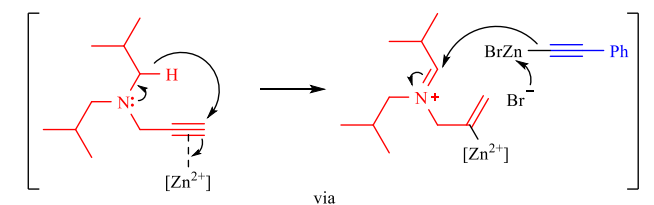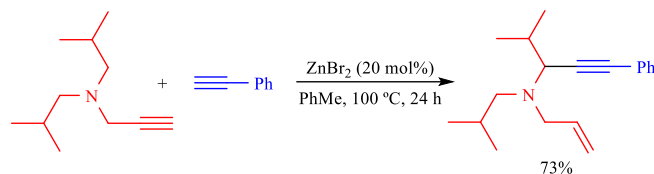
Scheme 12

The group of Mizuno also made use of ZnBr$_2$ for the CDC of terminal alkynes and tertiary amines, in this case, in combination with a manganese oxide-based octahedral molecular sieve (OMS-2) [22]. Reactions were conducted with 2 equiv. of the tertiary amine, 5 mol% ZnBr$_2$, 100 mg/mmol OMS-2, in CPME at 100 °C under oxygen (1 atm) for 8–24 h (Scheme 13). Aliphatic and benzylic *N*-methyl tertiary amines were successfully coupled with aromatic alkynes; the aliphatic counterparts provided the CDC products in lower yields. The OMS-2 could be reused in four cycles with a gradual loss of activity (85–72% yield). In the suggested reaction mechanism, alkynylzinc bromide species add to the iminium ion derived from the tertiary amine, which appears by OMS-2-promoted SET processes.

The α-functionalization of α-amino acids has attracted a great deal of attention in recent years [23]. Already in 2008, Li's group demonstrated that their copper-catalyzed CDC strategy developed for tertiary amines could be successfully extended to glycine amides [24]. In this case, the CuBr-TBHP system was utilized at room temperature in CH$_2$Cl$_2$ under argon. The installation of a *N-p*-methoxyphenyl group
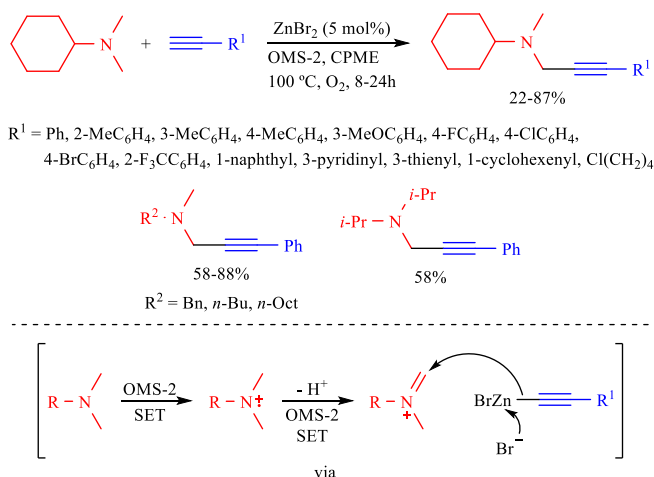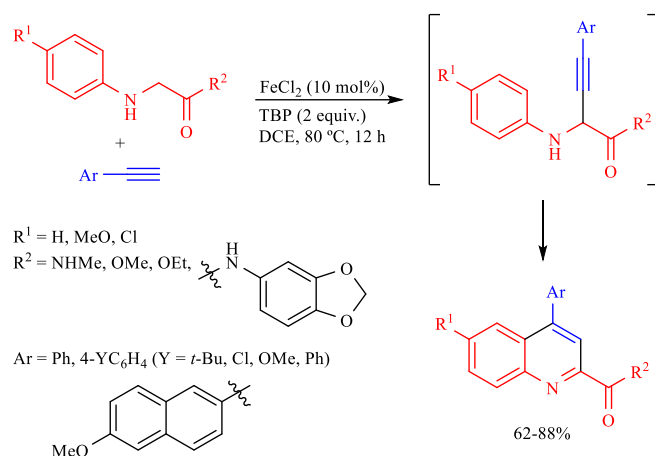
Scheme 13

(PMP) was found to be essential for the reaction to occur. Aryl alkynes were coupled with secondary and tertiary glycine amides in moderate-to-good yields (Scheme 14). Glycine esters did not react under these conditions, what allowed the selective alkynylation of a small peptide. Furthermore, a homophenylalanine derivative was synthetized by catalytic hydrogenation of the alkyne moiety of one of these compounds.
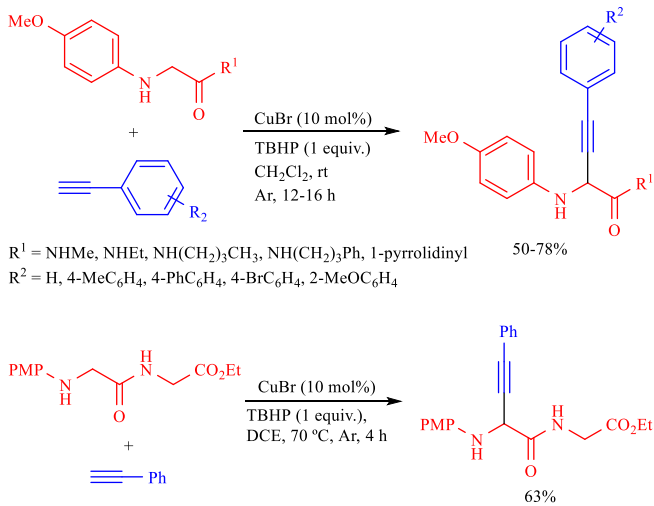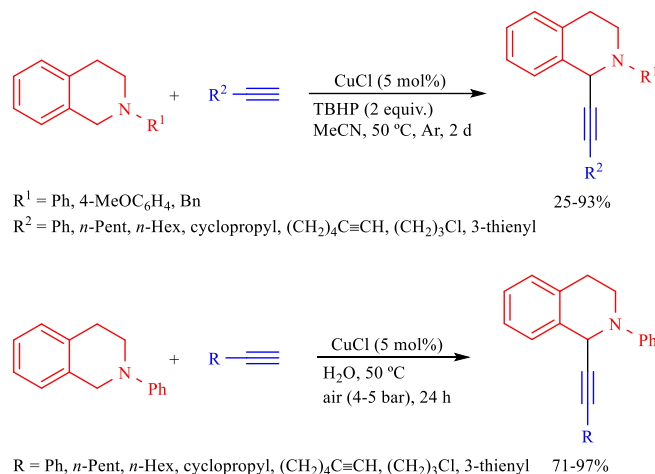
Scheme 14

It is noteworthy that, under very similar conditions but using iron instead of copper catalysis, the propargylamines derived from the coupling of the aforementioned glycine derivatives with aromatic alkynes evolved into quinolines in moderate-to-good yields (Scheme 15) [25].

The tetrahydroisoquinoline (THIQ) skeleton is ranked 19th as the most recurrent nitrogen heterocycle in the FDA list of approved drugs [26]. It can be also found in natural alkaloids, such as in noscapine, which reduces tubulin polymerization without serious side effects. Waldman *et al.* discovered that some alkynylated THIQs exhibit equivalent or more potent antimitotic activity than noscapine [27]. *N*-aryl THIQs are especially activated substrates towards CDC, that is why they have been widely studied as electrophilic partners in this reaction. Recently, Schnürch *et al.* studied in detail the alkynylation of THIQs through CDC [28]: *N*-

Scheme 15

phenyl, *N*-*p*-methoxyphenyl and *N*-benzyl THIQs were coupled with aromatic and aliphatic alkynes using CuCl and TBHP in MeCN at 50 °C under argon (Scheme 16). Notably, the CDC with *N*-phenyl THIQs could be carried out faster in water and in air (4-5 bar) at the same temperature, giving the products in good-to-excellent yields.

Scheme 16

In 2012, Klussmann *et al.* presented the first systematic and thorough study on the reaction mechanism of the CDC with THIQs (Schemes 17 and 18) [29]. Two catalytic systems were compared: CuCl$_2$·2H$_2$O-O$_2$ and CuBr-TBHP. The authors concluded that, in the first case, Cu(II) was the real
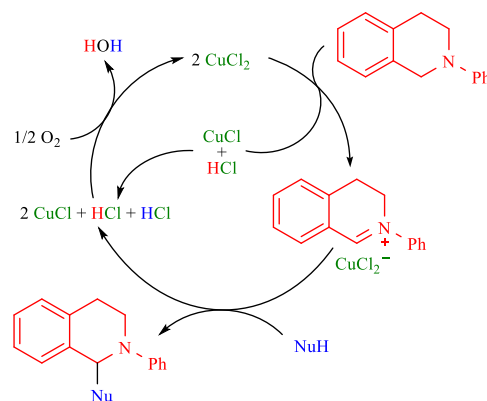
Scheme 17

oxidant for the THIQ, whereas O_2 was the terminal oxidant to reoxidize Cu(I) to Cu(II) (Scheme 17). In the second case, the iminium ion of THIQ was not detected by NMR but the *t*-butoxyperoxyl derivative instead, emerging in substantial quantities at the outset of the reaction. This derivative was postulated to be generated by a radical mechanism and to be a precursor of the iminium ion in the catalytic cycle (Scheme 18).
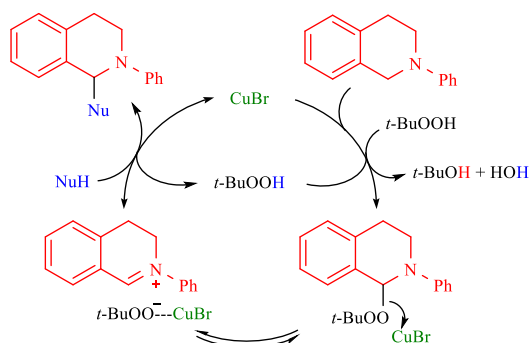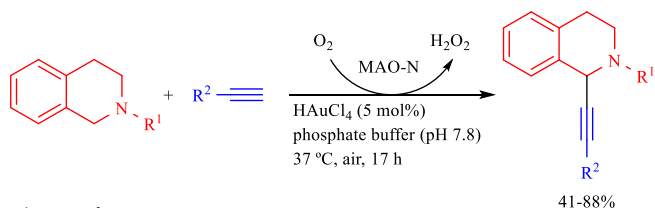

Scheme 18

The presence of an *N*-aryl fragment is normally mandatory for the alkynylation of THIQs by CDC, what facilitates the proper activation of the substrate by generation of the corresponding intermediate iminium ion. In a recent study, Turner *et al.* combined biocatalysis and metalocatalysis to couple *N*-alkyl THIQs with terminal alkynes [30]. The enzymatic oxidation of the THIQs was accomplished with monoamine oxidase type N (MAO-N), whereas the creation of the C-C bond was catalyzed by gold. Reactions were effected in one pot with 2 equiv. of the alkyne and $HAuCl_4 \cdot H_2O$ (5 mol%) in a phosphate buffer (pH 7.8) at 37 ºC in air for 16 h (Scheme 19). In a few cases, better yields were achieved when a one-pot two-step method was put into practice, in which the alkyne and gold catalyst were added in the second step (60 ºC for additional 16 h). The standard protocol was applicable to *N*-methyl, *N*-ethyl, *N*-allyl and *N*-(3-butenyl) THIQs; *N*-acetyl, *N*-benzyl or *N*-unsubstituted THIQs did not give the expected products.


R^1 = Me; R^2 = Ph, 4-YC_6H_4 (Y = Me, MeO, *n*-Bu, NEt_2),
2-YC_6H_4 (Y = Me, MeO, NH_2, F), 3-MeC_6H_4, 1-naphthyl, 3-thienyl
R^1 = Et, 2-allyl, 3-butenyl; R^2 = Ph
Two-step method:
R^1 = Me; R^2 = 4-ClC_6H_4, 4-HC≡CC_6H_4, 3-pyridyl, cyclopentyl, 2-Pent

Scheme 19

2.2. Heterogeneous catalysis

Heterogeneous catalysis is advantageous with respect to the homogeneous counterpart in terms of sustainability (i.e., catalyst recovery and reuse), generally, minimizing the metal leaching into solution and product contamination [31]. In this sense, Che *et al.* prepared a SBA-15-supported iron terpyridine complex that served as catalyst in the CDC coupling of *N,N*-dimethylanilines and *N*-phenyl-1,2,3,4-tetrahydroisoquinoline with arylacetylenes [32]. TBHP was

deployed as an oxidant in toluene at reflux to furnish the desired propargylamines in moderate-to-good yields (Scheme 20). Catalyst recycling was studied in a related CDC reaction, showing demetalation under the same reaction conditions as above. The SBA-15-supported ligand, however, could be recovered by filtration and reutilized in five consecutive cycles, with a slight loss of activity (79–72% yield), upon the addition of $Fe(ClO_4)_2 \cdot 6H_2O$ and *in situ* regeneration of the complex.
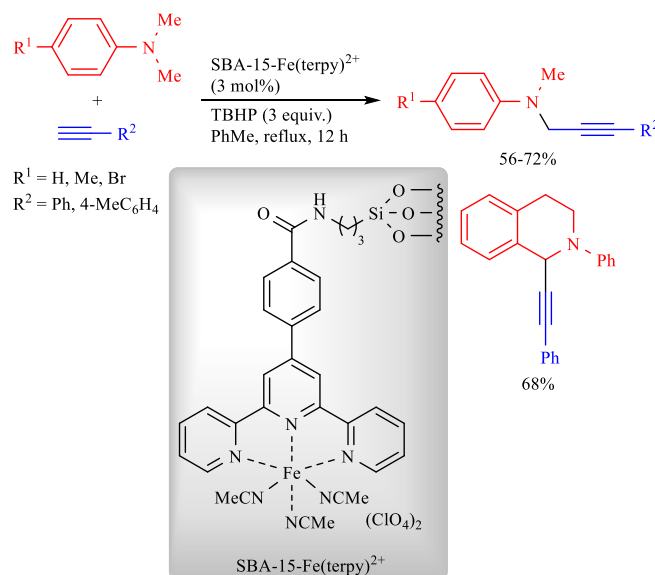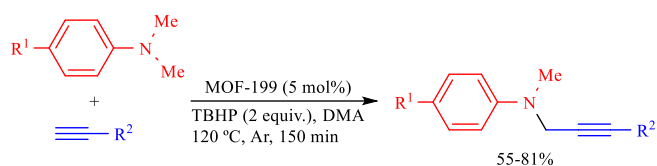

Scheme 20

In 2013, Li and Moores *et al.* compared the catalytic activity of magnetite nanoparticles (Fe_3O_4) with that of copper ferrite nanoparticles ($CuFe_2O_4$) in CDC reactions; only copper ferrite was found to catalyze the CDC of THIQs with arylacetylenes [33]. Reactions were carried out using 10 mol% $CuFe_2O_4$ and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1 equiv.) in decane at 100 ºC for 24 h (Scheme 21). The CDC of other tertiary amines or aliphatic terminal alkynes was not explored. The catalyst could be efficiently recovered magnetically and reutilized in ten cycles with no apparent loss of activity. A heterogeneous reaction mechanism was suggested based on the low leaching measured (0.39 ppm) in the supernatant and the invariable size and morphology of the nanoparticles upon reuse. A reaction mechanism was set forth in which the alkyne is activated by ferrite lattice Cu, while a neighboring Cu or Fe atom could coordinate the THIQ iminium ion, followed by coupling of these two moieties.

In 2014, Truong and Phan *et al.* made an important contribution to the heterogeneous synthesis of propargylamines through CDC reactions. They first exploited the copper-based metal-organic framework MOF-199 for the CDC of *N,N*-dimethylanilines (2 equiv.) with aromatic and aliphatic alkynes [34]. The optimized conditions involved 5 mol% MOF-199 and TBHP in dimethylacetamide (DMA) at 120 ºC for 150 min under Ar (Scheme 22). The catalyst was recovered by filtration and subjected to washing with abundant amounts of DMF and EtOH, and to drying at 170 ºC under vacuum for 6 h prior to reutilization. In this way, the catalyst could be reused in ten consecutive cycles with near quantitative conversion and no appreciable loss of crystallinity.
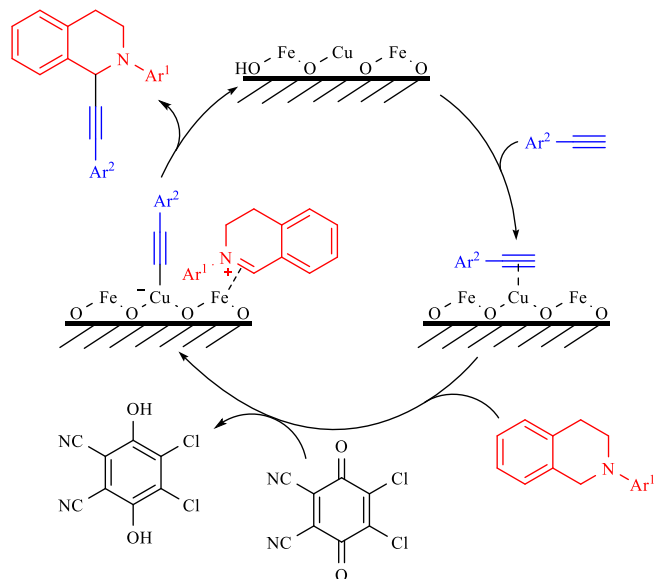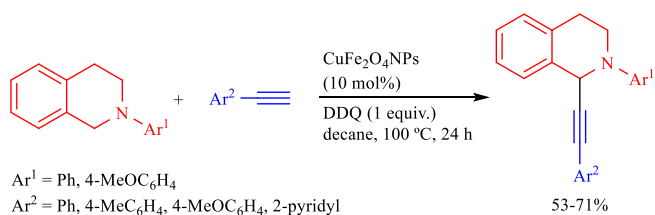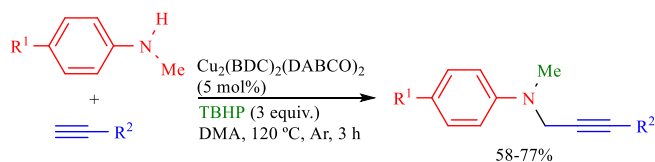
Scheme 21

R[1] = H, Me, Br
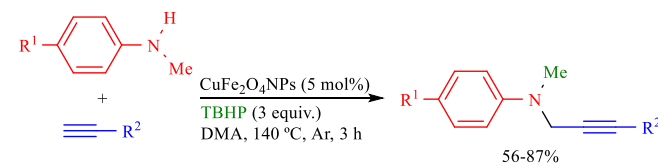R[2] = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, *n*-Hex

Scheme 22

Under analogous reaction conditions as above, but using MOF Cu$_2$(BDC)$_2$(DABCO)$_2$ (5 mol%), the same group described the conversion of *N*-methylanilines (2 equiv.) into *N*-aryl-*N*-methylpropargylamines [35] (Scheme 23). TBHP was used as an oxidant and methylating agent in dimethylacetamide (DMA) at 120 °C. The process could be scaled up to 20 mmol. The catalyst was isolated by filtration, washed with large amounts of DMF, dried at 140 °C under vacuum (6 h) and recycled in ten runs maintaining a high performance with negligible leaching. Copper salts such as Cu(NO$_3$)$_2$ and Cu(OAc)$_2$ showed comparable catalytic activity to that of the MOF.


R[1] = H, MeO, Cl
R[2] = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, *n*-Hex

Scheme 23

The same type of transformation was reported under the catalysis of superparamagnetic CuFe$_2$O$_4$ nanoparticles [36] (Scheme 24). The catalyst was recovered by magnetic separation and recycled (after washing and drying) in six runs with constant conversion, unchanged crystallinity and negative leaching test (30 ppm in the filtrate). It must be mentioned that 3 equiv. of the *N*-methylaniline are required with respect to the alkyne in an Ar atmosphere. TBHP was considered the source of Me radical, after previous Cu-promoted decomposition into *t*-butoxyl radical and further evolution of the latter. Reaction of Me radical with *N*-methylaniline would lead to *N,N*-dimethylaniline, which would undergo the standard CDC pathway.

R[1] = H, MeO, Cl
R[2] = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, *n*-Hex
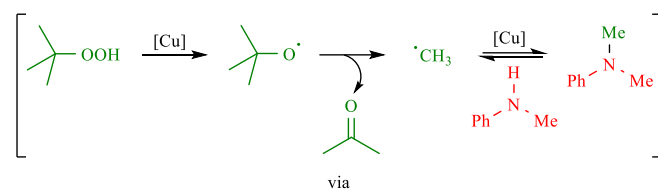
Scheme 24

Alonso *et al.* presented a new heterogeneous catalyst for the CDC of tertiary amines and terminal alkynes comprised of oxidized copper nanoparticles on sodium Y zeolite [37]. The catalyst, in the presence of aqueous TBHP, was applied at 1.5 mol% loading to make an array of propargylamines in moderate-to-excellent yields (Scheme 25). Contrary to other previously reported methodologies, it was demonstrated that the copper-catalyzed CDC could be conducted under solvent-free conditions and without the requirement of an inert atmosphere. The reaction conditions were compatible with the presence of different functionalities such as methoxy, ester, cyano, hydroxy, halogen and ketone. Not only activated *N,N*-dimethylanilines were covered in this study but benzyl and aliphatic amines. The catalyst was successfully both reutilized in seven successive runs and adapted to a 12 mmol scale. Moreover, its catalytic activity surpassed that of various commercially available copper catalysts, depleting the formation of 1,3-diynes as by-products. The propounded reaction pathway discloses the pivotal role of free radicals (methyl radical, in particular) and that of the Cu(I)/Cu(II) redox couple (Scheme 25). In addition, the methylation-alkynylation of the secondary amine *N*-methylaniline took place quantitatively, under the same conditions, to furnish the expected tertiary propargylamine. The results of this study also highlight the utility of nanosized copper in catalysis when compared with bulk copper sources.
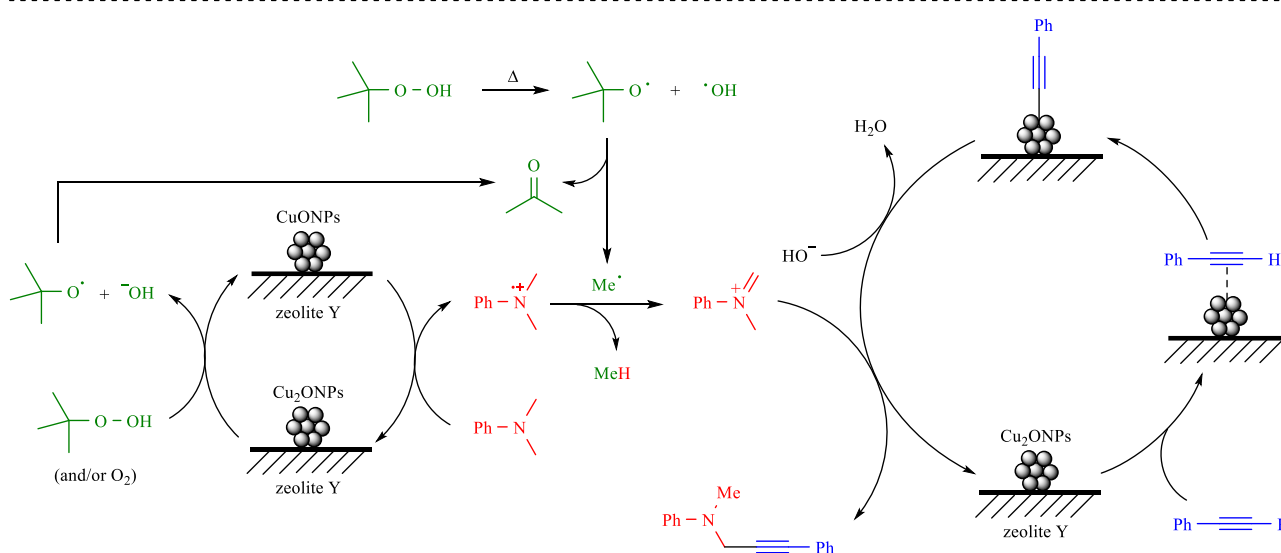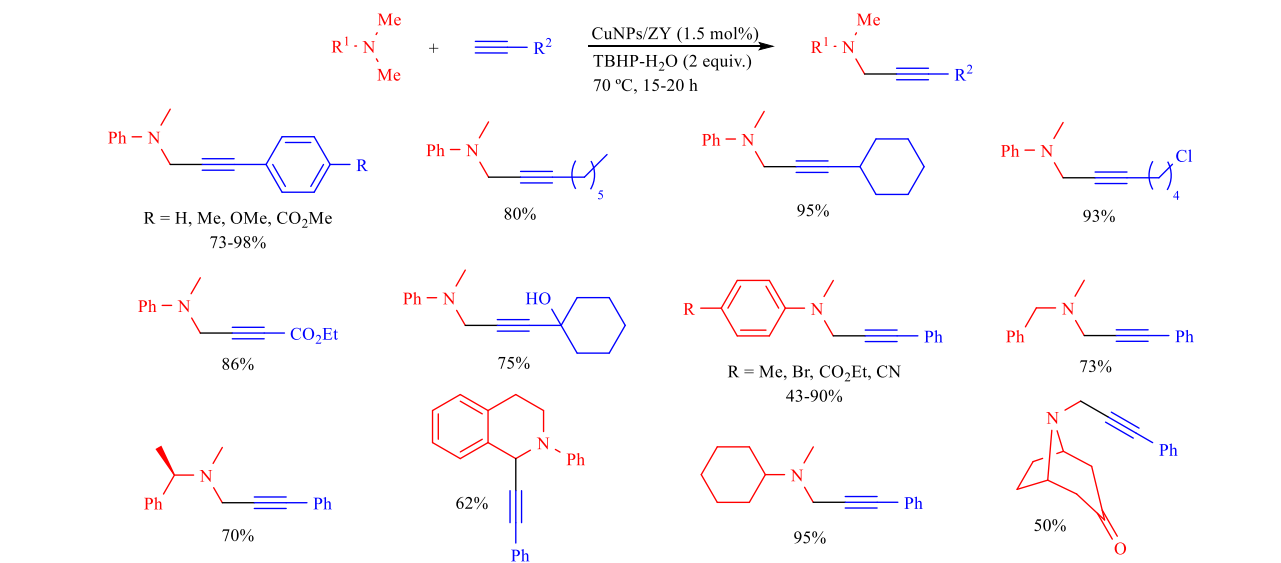
Scheme 25

Singh and Jain *et al.* prepared $Cu_6Se_{4.5}NPs$ from CuSePh and applied them to the CDC of *N,N*-dimethylbenzylamines and *N,N*-dimethylanilines with terminal alkynes [38]. Reactions occurred in the presence of TBHP under nitrogen, with the latter preventing the oxidation of the benzylic amines to benzaldehydes. In general, lower yields were attained when the aryl moieties were substituted with electron-withdrawing groups as well as for aliphatic and heterocyclic alkynes (Scheme 26). The catalyst was reused in four cycles with a decrease in the yield that was attributed to partial agglomeration of the nanoparticles and some leaching of the catalyst. An analogous reaction mechanism to those previously published with TBHP as the oxidant was invoked.
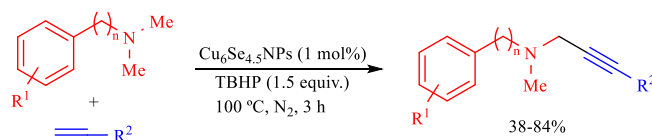
n = 0; R^1 = H; R^2 = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 2-pyridyl
n = 1; R^1 = H, 4-Cl, 4-Br, 4-MeO, 4-NO$_2$, 2-Cl, 3-Cl
    R^2 = H, 4-YC$_6$H$_4$ (Y = Me, MeO, CF$_3$), 2-pyridyl, *n*-Pent
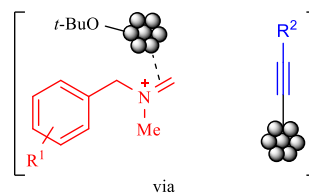
Scheme 26

More recently, Gómez and Favier *et al.* disclosed the first application of zero-valent CuNPs to the synthesis of propargylamines through CDC [39]. The Cu(0)NPs (1.7–2.4 nm) were prepared by reduction of Cu(I) and Cu(II) precursors in glycerol, in the presence of PVP as stabilizer under H_2. *N,N*-Dimethylanilines, *N,N*-dimethylbenzylamine and *N*-methylaniline were subjected to CDC with both aromatic and aliphatic alkynes; 2 equiv. of the amine and TBHP were used in glycerol at 100 ºC for 2 h (Scheme 27). Due to the relatively narrow substrate scope studied, it is difficult to assess the functional group compatibility of this catalytic system. Reusability of the catalyst was not tested in this particular reaction but was found to be effective in the amination of iodobenzene, included in the same publication.

n = 0; R^1 = H; R^2 = H; R^3 = Ph, 4-MeC$_6$H$_4$, *n*-Pent
n = 0; R^1 = Me; R^2 = H, 4-Br, 3-Me; R^3 = Ph, 4-MeC$_6$H$_4$, 4-MeO$_2$CC$_6$H$_4$, *n*-Pent
n = 1; R^1 = Me; R^2 = H; R^3 = Ph

Scheme 27

3. PHOTOREDOX CATALYSIS

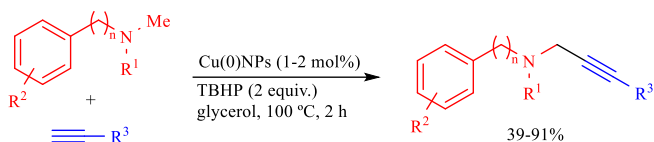In recent years, photoredox catalysis has gained considerable interest as a sustainable and green synthetic tool, making use of low-energy renewable light sources to promote organic transformations [40]. In 2012, the groups of Stephenson and Rueping pioneered the synthesis of propargylamines by CDC with a dual catalytic system consisting of a photoredox catalyst and a metal catalyst. Stephenson *et al.* alkynylated THIQs using the photoactive metal complex Ru(bpy)$_3$Cl$_2$ (1 mol%) in combination with BrCCl$_3$ as the oxidant, under the action of blue LEDs in DMF for 3 h, and subsequent addition of the alkyne, CuBr (15 mol%) and Et$_3$N in the absence of light (Scheme 28) [41]. The success of this reaction is undebatable but this approach cannot be considered green and sustainable because of the large amount of reagents deployed [BrCCl$_3$ (3 equiv.), Et$_3$N (5 equiv.) and alkyne (5 equiv.)]. In addition, the procedure was not straightforward and required control of the THIQ oxidation prior to the C-C bond forming step under an argon atmosphere. The reaction was largely accelerated by carrying out the experiment in a continuous-flow photoreactor [42]: the 3 h batch reaction time for the THIQ iminium formation was reduced to a residence time of only 0.5 min when the reaction was performed in flow.


R^1 = H; R^2 = Ph   82%
R^1 = H; R^2 = CH$_2$CH$_2$Ph   53%
R^1 = MeO, R^2 = Ph   89%
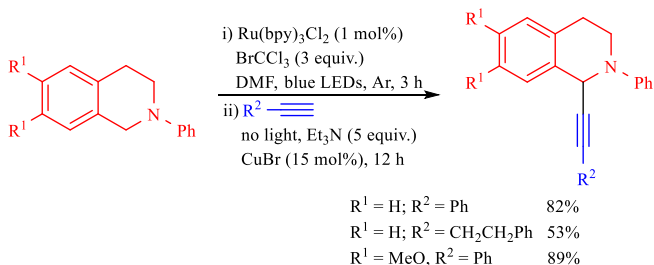
Scheme 28

In parallel to the aforementioned work, Rueping *et al.* thoroughly studied the CDC of N-substituted THIQs and

terminal alkynes utilizing [Ru(bpy)$_2$(dtbbpy)](PF$_6$)$_2$ as photocatalyst and (MeCN)$_4$CuPF$_6$ as the metal catalyst under the radiation of a 5 W fluorescent bulb [43]. A wide range of *N*-aryl THIQs was alkynylated in moderate-to-excellent yields (50–95%) with aromatic and aliphatic alkynes, as well as with triphenylsilylacetylene (Scheme 29). Furthermore, the procedure was not restricted to *N*-aryl THIQs but it was equally effective for THIQ-derived glycine esters (43–73%). In both cases, an excess of the alkyne (5 equiv.) was employed. The authors noted that Ag(O$_2$CCF$_3$) was an alternative salt to (MeCN)$_4$CuPF$_6$ in cases where the latter was less effective. Two catalytic cycles were proposed to participate in the reaction mechanism. On one hand, the photoredox cycle activates the amine, with the intervention of the Ru complex, to form the amine radical cation and the iminium ion with reoxidation of the photocatalyst by O$_2$. The transmutation of the amine radical cation into the iminium ion might occur by abstraction of H• by the superoxide anion or by deprotonation by the amine or superoxide radical anion, with the concomitant electron transfer to Ru(II), Ru(II)* or HOO•. On the other hand, the Cu acetylide is formed in the metal catalytic cycle to, ultimately, add to the iminium ion and give the propargylamine.
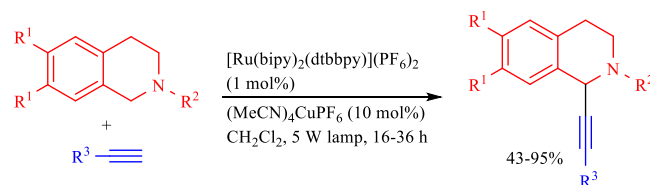
R^1 = H; R^2 = Ph, 4-YC$_6$H$_4$ (Y = Me, Et, Cl), 2-MeC$_6$H$_4$, 2-naphthyl;
R^3 = Ph, 4-YC$_6$H$_4$ (Y = Me, *t*-Bu, *n*-Pent), 6-MeO-2-naphthyl, cyclopropyl, cyclohexyl, *n*-Bu, Ph$_3$Si, CO$_2$Et
R^1 = MeO; R^2 = Ph; R^3 = Ph
R^1 = H, MeO; R^2 = CH$_2$CO$_2$Me, CH$_2$CO$_2$(*t*-Bu); R^3 = Ph, 4-MeC$_6$H$_4$, 4-(*t*-Bu)C$_6$H$_4$, 1-cyclohexenyl
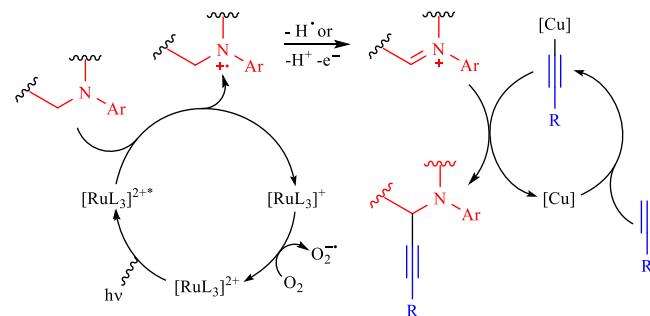
Scheme 29

4. ASYMMETRIC SYNTHESIS

The alkynylation involving one of the two enantiotopic hydrogens of CH$_2$N in substrates such as THIQs and glycine derivatives leads to chiral propargylamines. That is why different research groups have attempted the asymmetric alkynylation of THIQs through CDC, primarily, under copper catalysis [44]. The copper-catalyzed enantioselective CDC of THIQs and terminal alkynes was pioneered by the group of Li [45]. CuOTf in the presence of TBHP and Pybox ligand promoted this coupling in moderate yields and up to 74% e.e. (Scheme 30). The THIQ was used in two-fold excess, with the conditions including prolonged heating (2 d) under a nitrogen atmosphere. In general, the yield (11-65%) and e.e. (30%) recorded were lower for aliphatic alkynes.
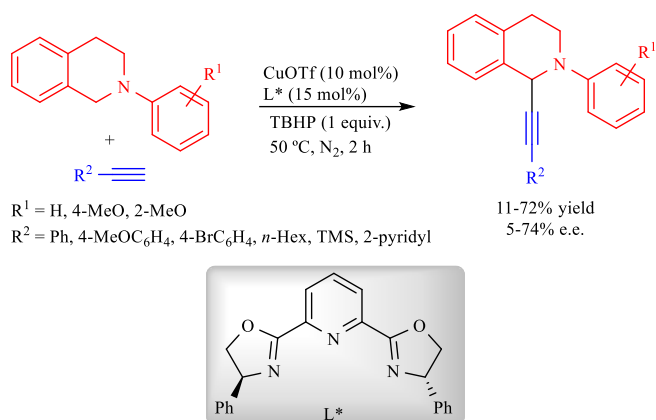
Scheme 30

In 2013, Su *et al.* described the asymmetric CDC of THIQs and terminal alkynes under solvent-free high-speed ball-milling conditions [46]. Pybox was the optimized chiral ligand, which in the presence of DDQ, silica gel and two copper steel balls led to the corresponding enantiomerically enriched propargylamines in up to 77% yield and 79% e.e. (Scheme 31). The substituent on the N atom of the THIQs did not have any significant influence in the enantioselectivity, whereas the latter was rather low in the case of using aliphatic alkynes. Some of the yields could be enhanced by the addition of 5 mol% Cu(OTf)$_2$, albeit the e.e.'s still were low (20-22% e.e.). The method was extended to a 10 mmol scale in reasonably good yield (69%) and e.e. (70%). What is more, the copper balls, acting as catalyst and milling balls, could be easily recovered from the reaction medium, though no studies on the nature of the catalysis and potential degradation of the balls were undertaken.
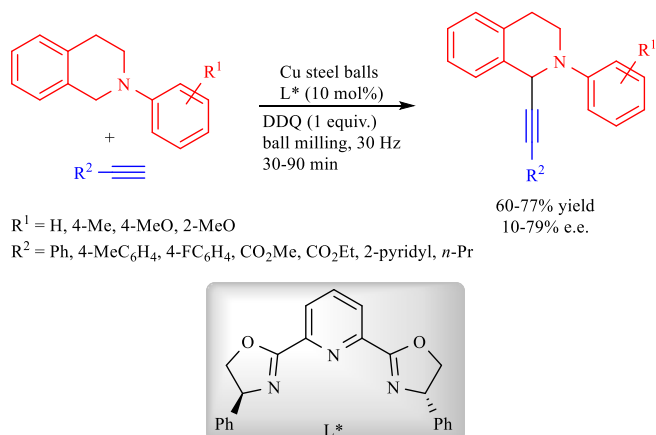
Scheme 31

Liu *et al.* managed to augment the e.e.'s of the THIQ alkynylation by changing the typical aryl group on the N atom into the Cbz group [47]. A rather complex catalytic system had to be developed, including: Ph$_3$CBF$_4$, a Pybox-type ligand, CuBr, EtOH, Yb(OTf)$_3$, KOH and H$_2$O in a CH$_2$Cl$_2$-PhMe solvent mixture. High enantioselectivities were reached for aromatic alkynes at room temperature though, once more, low yield and e.e. were noted for aliphatic alkynes (Scheme 32). The reactions were relatively slow (48 h) and required 2 equiv. of the alkyne. The authors postulated the concurrence of two hemiaminals in the process, though the role of water was not clarified. It must be remarked that the procedure was successfully implemented

for the synthesis of homoprotoberberine and an intermediate in the synthesis of emetine.
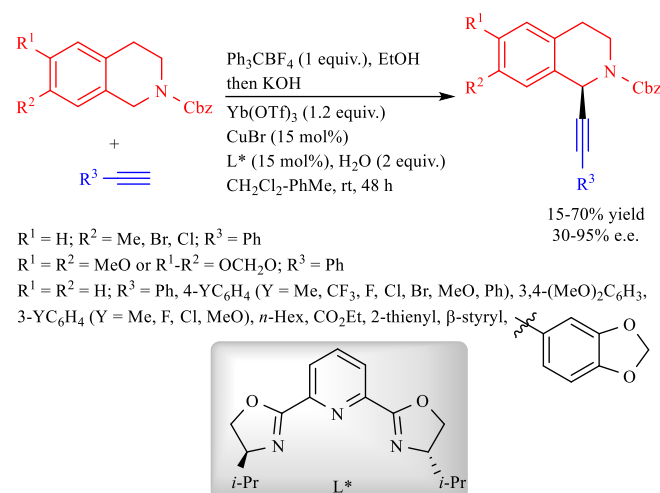
Scheme 32

In 2015, Li's group combined photoredox catalysis with a chiral copper complex to substantially increase both, the yield and enantioselectivity previously reported under only copper catalysis (Scheme 33) [48]. Very mild conditions were practiced in the presence of an Ir complex as photocatalyst, CuBr, a bynaphthyl-type chiral ligand and (BzO)$_2$, under visible light irradiation (Scheme 33). It must be highlighted that, for the first time, the e.e.'s of the CDC products derived from aliphatic alkynes were high (up to 90% e.e.), though the yields were low-to-moderate (20-57%). The reaction mechanism put forward contains two
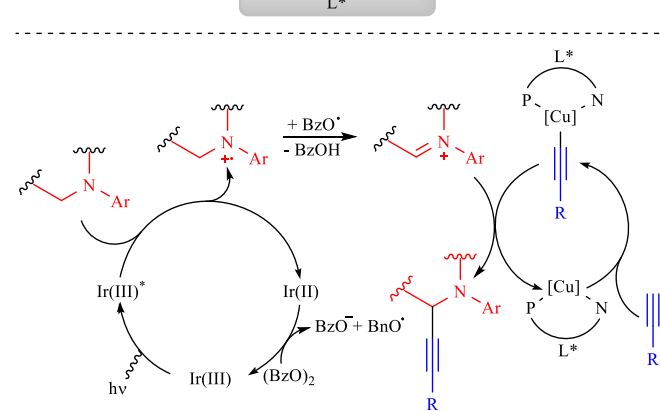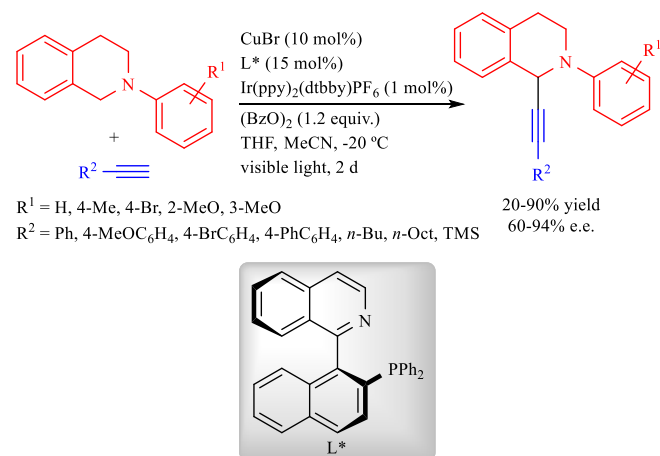
Scheme 33

catalytic cycles resembling those depicted in Scheme 29 but, in which, Ir(II) is reoxidized to Ir(III) by the SET reduction of $(BzO)_2$ to BzO^- anion and $BzO\cdot$ radical.

Khan *et al.* also made use of dual catalysis (i.e., photoredox and transition-metal catalysis) for the enantioselective CDC of THIQs and terminal alkynes [49]. In this case, a Cu(I) complex with a C_2-symmetric iminoalcohol-based ligand was combined with Rose Bengal as photoredox catalyst under visible light and with molecular oxygen as the terminal oxidant. The chiral propargylamines were obtained in moderate-to-good yields and excellent enantioselectivities, even for the more problematic alkynes, such as trimethylsilylacetylene, alkyl- and cycloalkyl-substituted alkynes (Scheme 34). In the reaction mechanism, excited Rose Bengal was considered to oxidize the THIQ to the corresponding radical cation, with the former going back to the ground state by the action of molecular oxygen. Hydrogen abstraction of the mentioned radical cation by superoxide radical anion would generate the iminium ion of the THIQ, that would enter the copper cycle similarly to as stated by others.

R^1 = H, 4-Me, 4-Cl, 4-MeO, 2-MeO
R^2 = Ph, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 3-ClC$_6$H$_4$, *c*-Pr, *n*-Oct, TMS
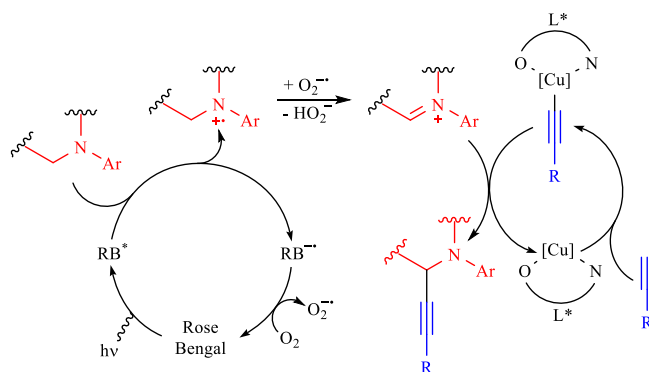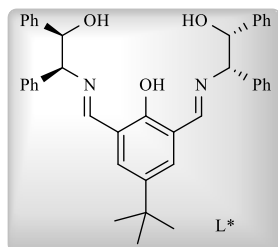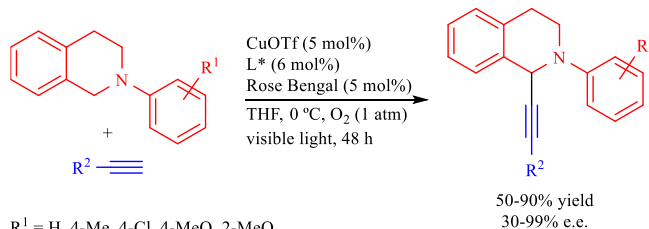
Scheme 34

Recently, Feng *et al.* introduced a chiral *N,N*'-oxide ligand, together with a Zn(II)-Fe(II) bimetallic cooperative catalytic system, for the asymmetric alkynylation of *N*-PMP-substituted THIQs under a molecular oxygen atmosphere and mild conditions [50]. The presence of both, 5 Å molecular sieves NaB[3,5-(F$_3$C)$_2$C$_6$H$_3$]$_4$ was found to be crucial to attain higher yields and e.e.'s. Aromatic alkynes

led to moderate-to-good yields of the CDC products and excellent enantioselectivities; aliphatic alkynes, however, gave the products with poor-to-moderate enantioselectivities (Scheme 35). Differently substituted THIQs on the N atom and on the aromatic ring were also explored, in general, with good results. The process could be successfully scaled to a gram production (70% yield, 93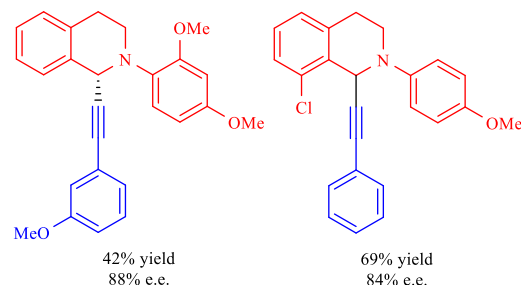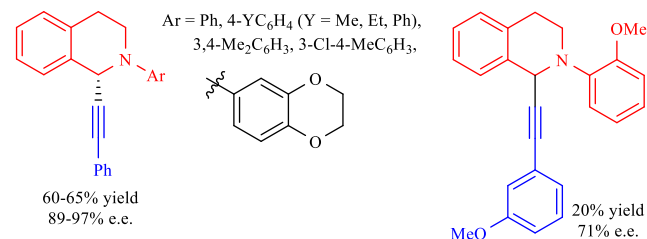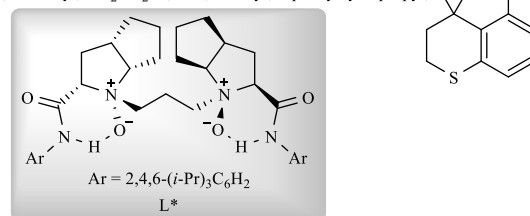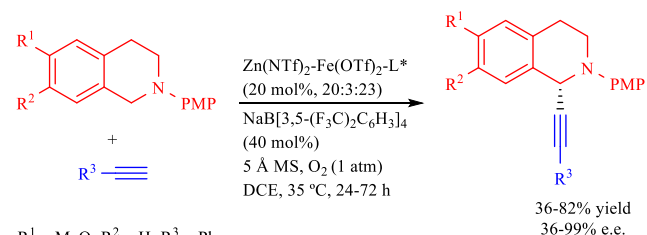% e.e.). Mechanistic studies seem to support the cooperation of Fe(II) and oxygen in the oxidation of the THIQ and the assistance of Zn(II) in the formation of the metal acetylide.

R^1 = MeO; R^2 = H; R^3 = Ph
R^1 = R^2 = MeO or R^1-R^2 = OCH$_2$O; R^3 = Ph
R^1 = R^2 = H; R^3 = Ph, 4-YC$_6$H$_4$ (Y = Me, Et, Cl, Br, *n*-Pr, *n*-Bu, *n*-Pent, MeO, MeCO$_2$, NC), 2-YC$_6$H$_4$ (Y = F, Cl), 3-YC$_6$H$_4$ (Y = F, Cl, Me, MeO, O$_2$N), 3,5-F$_2$C$_6$H$_3$, 1-naphthyl, 2-thienyl, CH$_2$CH$_2$Ph, *c*-Pr, *n*-decyl, 1-phenylcyclopropyl,

$Ar = 2,4,6-(i$-Pr$)_3$C$_6$H$_2$
L*

Ar = Ph, 4-YC$_6$H$_4$ (Y = Me, Et, Ph), 3,4-Me$_2$C$_6$H$_3$, 3-Cl-4-MeC$_6$H$_3$,

Scheme 35

Although most of the studies on the asymmetric synthesis of propargylamines by CDC have focused on THIQs as substrates, Liu *et al.* published a survey on the copper-catalyzed aerobic CDC of *N*-aryl glycine esters and terminal alkynes [51]. The catalytic system was composed of Cu(OTf)$_2$ and a Pybox-type chiral ligand which, in a first step reacted with the *N*-aryl glycine ester under molecular oxygen, whereas the alkyne was added in a second step under a nitrogen atmosphere. The resulting α-alkynyl amino acid derivatives were produced in moderate-to-good yields and fair-to-high enantiomeric ratios, including those derived from aliphatic alkynes (Scheme 36). The aryl group bonded

to the N atom was found to be decisive for the reaction to occur. The participation of a copper complex was suggested, in which the imino ester and the chiral ligand were coordinated to the metal of the copper acetylide.

R^1 = Me, MeO, Br
R^2 = Et, *i*-Pr, *i*-Bu
R^3 = Ph, 4-YC_6H_4 (Y = Me, MeO, Cl, Br), 3-MeC_6H_4, *n*-Bu, *n*-Hex, *n*-Oct, *c*-Pr, CH_2CH_2OTBS, CH_2CH_2OBn
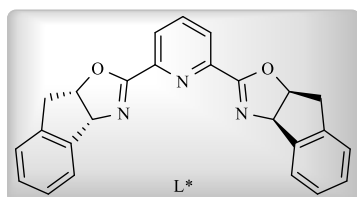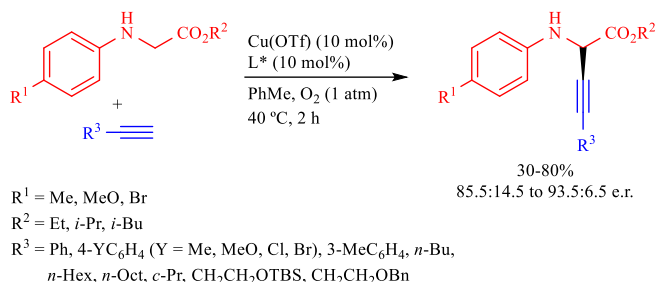
Scheme 36

5. CONCLUSION

Concluding this review, we can say that the CDC of amines and terminal alkynes is a convenient and green approach to the synthesis of propargylamines. The high atom economy of the process, without any pre-functionalization, makes of this coupling a competitive tool to make NCsp^3-Csp bonds. Homogeneous catalytic CDC works with 5-40 mol% catalyst at 60-110 °C, commonly, for *N,N*-dimethyl-substituted anilines and benzylamines, in the presence of a peroxide, under an inert atmosphere in an organic solvent. The protocols involving air or molecular oxygen as the terminal oxidants are particularly interesting. The reaction has been upgraded in terms of sustainability by introducing heterogeneous catalysts, which are recyclable and work with lower metal loading (1-10 mol%), albeit at higher temperature (mostly, 100-140 °C). Reactions at room temperature have been performed through photoredox catalysis; this is an underdeveloped approach, so far conditioned to the use of expensive ruthenium complexes and applicable exclusively to tetrahydroisoquinolines. Moreover, the fact that propargylamines can be obtained in a chiral non-racemic fashion by asymmetric synthesis, makes this strategy additionally attractive. In our opinion, there is still room for research in this area, as some aspects are partially unresolved or pending solution. Further investigation should be focused on reducing the amount of catalyst (particularly in homogeneous catalysis), as well as on the use of environmentally benign solvents or solvent-free protocols under aerobic conditions, and on the activation of the more demanding unreactive aliphatic (non-benzylic) amines and alkynes. The exploration of metals other than copper and ruthenium in the catalytic systems might open new ventures in the synthesis of propargylamines by CDC.

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LIST OF ABBREVIATIONS

BDC: 1,4-benzenedicarboxylate
bpy: 2,2'-bipyridine
Cbz: benzyloxycarbonyl
CDC: Cross-Dehydrogenative Coupling
CPME: cyclopentyl methyl ether
DABCO: 1,4-diazabicyclo[2.2.2]octane
DEAD: diethyl azodicarboxylate
DMA: *N,N*-dimethylacetamide
dtbppy: 4,4'-di-*tert*-butyl-2,2'-bipyridine
equiv.: equivalent
L*: chiral ligand
MAO-N: monoamine oxidase type N
MS: molecular sieves
NBS: *N*-bromosuccinimide
OMS-2: oxide-based octahedral molecular sieve
PVP: poly(*N*-vinylpyrrolidin-2-one)
Py: pyridine
Pybox: 2,6-bis[(4*S*)-4-phenyl-2-oxazolinyl]pyridine
TBHP: *tert*-butylhydroperoxide
TBP: *tert*-butylperoxide
THIQ: 1,2,3,4-tetrahydroisoquinoline
TMEDA: *N,N,N',N'*-tetramethylethylenediamine

CONFLICT OF INTEREST

The authors declare no conflict of interests. The manuscript was written through contributions of all authors, who have given approval to the final version of the manuscript.

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