Heterocycle synthesis by copper facilitated addition of heteroatoms to alkenes, alkynes and arenes

Sherry R. Chemler* and Peter H. Fuller

The *de nouvo* synthesis of small organic heterocyclic molecules has benefited from recent protocols for copper-facilitated additions of heteroatoms to alkenes, alkynes and arenes. This *tutorial review* summarizes a number of these recent contributions. Copper salts can facilitate bond formations due to their ability to serve as Lewis acids, oxidizing agents and transition metal catalysts. The current understanding of the mechanisms of these reactions is presented. This review should be of interest to chemists involved in the synthesis of heterocycles and those investigating transition metal facilitated reactions.

1 Introduction

Copper-facilitated reactions have a long history in organometallic chemistry and new reactions continue to be discovered and developed. In recent years, the area of heterocycle synthesis has especially benefited from novel copper facilitated transformations. The chemistry of copper is rich in mechanistic possibilities, oxidation states 0–3 are accessible, and two-electron, as well as one-electron transfer processes are possible. Copper salts can act as catalytic cross-coupling agents, Lewis acids and oxidizing agents. The relatively low cost of copper and the realization of catalysis in many instances makes it an attractive reagent. Copper has a high affinity for both polar functional groups such as amines and alcohols as well as π-bonds, making it a logical tool for advancing the reactions of these functional groups.

A number of recent reviews that illustrate the wide range of copper-facilitated organic transformations have appeared.[1–5] This tutorial review covers recent developments in the area of

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copper facilitated additions of heteroatoms (N, O, S) to unsaturated carbons (alkenes, alkynes, arenes) with an emphasis on heterocycle formation. Not covered in this review are copper-catalyzed hetero-Diels–Alder reactions.[6]

2 Unsaturated heterocycles *via* additions to alkenes and arenes

2.1 Cross-coupling reactions—The intramolecular Ullmann condensation (IUC)

The copper-catalyzed reaction of heteroatoms (O, N, S) and aryl halides or arylorganometallics (stannanes, silanes, boranes) fall under the category of the Ullmann condensation. This topic has been extensively reviewed,[3–5] so this review will highlight only recent contributions where a new heterocycle is formed in the copper-catalyzed reaction (intramolecular Ullmann condesation or IUC). The recent use of copper-coordinating ligands in these reactions has enabled a broad substrate scope (*vide infra*).

A mechanism for the intramolecular copper(I)-catalyzed coupling of aryl- and vinyl halides with heteroatoms (N, O, S) is shown in Scheme 1.[3] Ligand exchange of the heteroatom

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Peter Fuller
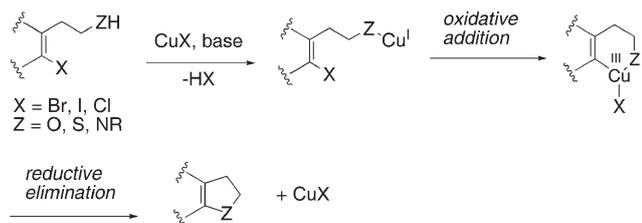
**Scheme 1** Mechanism of the intramolecular Ullmann condensation (IUC).

functional group with the copper(I) ligand provides a new copper(I) intermediate that may then undergo oxidative addition into the aryl halide bond, thereby generating a Cu(III) intermediate. Subsequent reductive elimination provides the observed products and regenerates the Cu(I) catalyst.

Several syntheses of nitrogen heterocycles *via* the copper(I)-catalyzed coupling of nitrogen functional groups and aryl- and vinyl halides have been reported. The amino variant of the Ullmann condensation was first reported by Goldberg and is often referred to as the Goldberg reaction.[7]

Kwong and Buchwald reported an efficient intramolecular copper(I)-catalyzed amination of aryl halides and primary amines (*e.g.* **1**) for the synthesis of five- and six-membered nitrogen heterocycles (*e.g.* **2**, Scheme 2).[8] The use of diethylsalicylamide as ligand was important to the success of the reaction, and other ligands have subsequently demonstrated even greater catalyst activation.[9] Kinetic evidence suggests the ligands in these reactions are important for preventing and reversing multiple substrate ligation as the multi-ligated complex, $[R_2N–Cu–NR_2]^-$, is an unproductive reaction intermediate.[10] The ligand may also increase the oxidation potential of the Cu(I) complex, making the oxidative addition into the aryl halide bond, which results in a Cu(III) complex, more facile.[11]

The intermolecular coupling of amides and carbamates with vinyl halides was reported by Buchwald and co-workers in 2003.[12] The use of N,N'-dimethylethylenediamine was important to the reaction efficiency. Hu and Li subsequently reported the synthesis of various cyclic enamine lactams, *e.g.* **4**, through a copper-catalyzed intramolecular vinylation of amides (Scheme 3).[13,14]
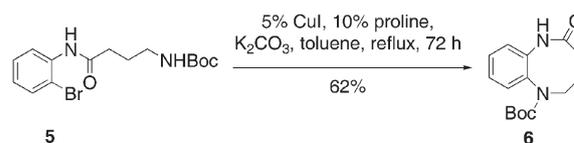
A copper-catalyzed synthesis of medium- and large-sized nitrogen heterocycles, *e.g.* **6**, *via* N-arylation of phosphoramidates and carbamates with aryl bromides has also been
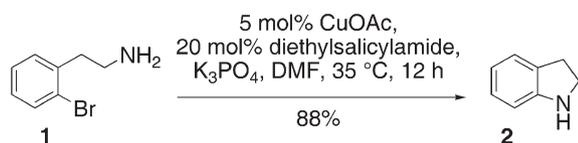
Scheme 2 Primary amines can be effective coupling partners.
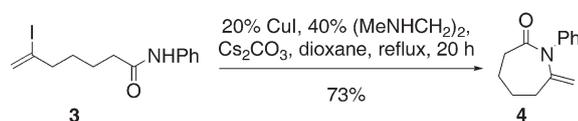
Scheme 3 Synthesis of cyclic enamines *via* IUC.

Scheme 4 Synthesis of nitrogen-containing macrocycles *via* IUC.

reported (Scheme 4).[15] Copper(I)-catalyzed reactions of other nitrogen functional groups and aryl halides have also been reported for the synthesis of 2-aminobenzimidazoles,[16] dipyridoimidazoles,[17] oligo(*p*-aniline)s[18] and indoles.[19]
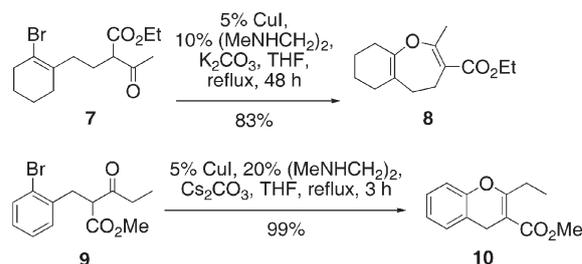
For the synthesis of oxygen heterocycles, alcohols, ketones, amides and the ketone of β-keto esters can all provide an oxo unit in an intramolecular Ullmann condensation.[20–24] Surprisingly, phenols have not been reported for use as the oxo component in IUCs with aryl- or vinyl halides even though they have been used extensively in the intermolecular Ullmann reaction.[3]

Fang and Li reported the synthesis of five-, six- and seven-membered cyclic enol ethers, *e.g.* **8**, *via* the coupling of β-keto esters with vinyl halides[20] and the synthesis of 4*H*-1-benzopyrans, *e.g.* **10**, *via* the coupling of β-keto esters with aryl halides (Scheme 5).[21]

Evindar and Batey reported the parallel synthesis of a library of benzoxazoles and benzothiazoles **12** using a copper(I) catalyzed cyclization of *ortho*-halobenzanilides **11** (Scheme 6).[22]

Kobayashi and co-workers recently reported an interesting application of the IUC for the synthesis of spirocyclic oxindoles (Scheme 7).[23] The IUC of haloindoles, *e.g.* **13**, bearing an allylic alcohol established allyl vinyl ether adducts, *e.g.* **14**. Subsequent Claisen rearrangement provided the spirocyclic oxindoles, *e.g.* **15**.

The Chan–Evans–Lam-modified Ullmann condensation reaction between arylboronic acids and heteroatomic functional groups provides for the formation of C(aryl)–O, C(aryl)–N and C(aryl)–S bonds.[3] The copper(II) acetate mediated intramolecular O-arylation of phenols with phenylboronic acids provides a direct route to complex macrocycles
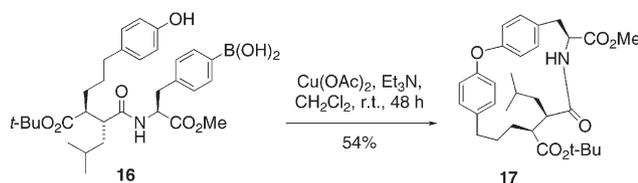

Scheme 5 Oxygen heterocycles *via* IUC with β-keto esters.
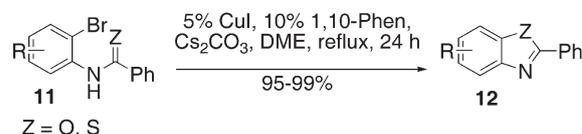
Scheme 6 Synthesis of benzoxazoles and benzthiazoles *via* IUC.
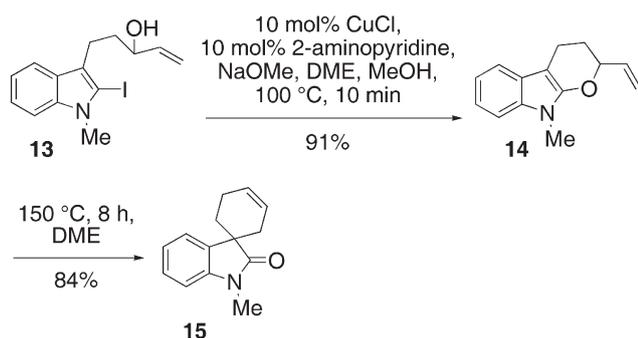
Scheme 7 Synthesis of spirocyclic oxindoles *via* IUC–Claisen combination.


Scheme 8 Macrocyclization of a phenol and arylboronic acid.

and is significant in that no reports of the IUC reaction of phenols and aryl halides have appeared.[25] Decicco, Song and Evans developed this reaction for application to the synthesis of matrix metalloproteinase (MMP) inhibitors (Scheme 8). Notably, the reaction occurs under mild conditions at room temperature, making it suitable for sensitive substrates. This method was also applied as a key step in the synthesis of the anti-HIV agent chloropeptin I.[26]

A mechanism of the reaction proposed by Evans is illustrated in Scheme 9. The oxidation state of the copper intermediate prior to reductive elimination (Cu^{2+} *vs.* Cu^{3+}) has not been studied in detail. It is also feasible that ligand exchange (ArO– for X) occurs prior to transmetallation.
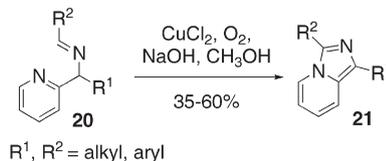
2.2 Oxidative cyclizations

Copper salts can facilitate the synthesis of heterocycles by serving as Lewis acid activators and oxidizing agents. Noto *et al.* used copper(II) as a two-electron oxidant in the
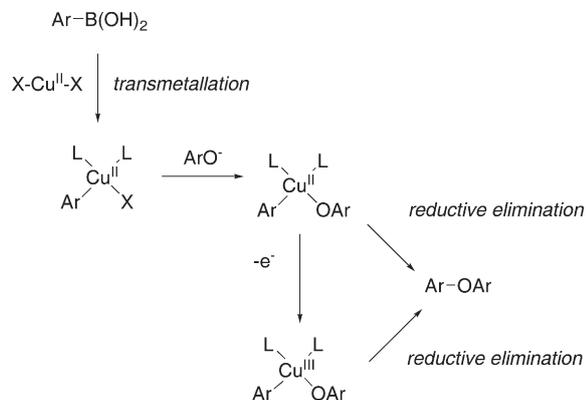
Scheme 9 Proposed mechanism for the coupling of arylboronic acids with phenols.
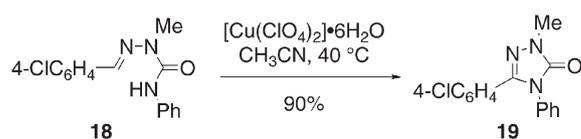
Scheme 10 Oxidative cyclization of a benzaldehyde semicarbazone.

R^1, R^2 = alkyl, aryl

Scheme 11 Oxidative cyclization for the synthesis of imidazoles.

cyclization of benzaldehyde semicarbazones (*e.g.* **18** → **19**, Scheme 10).[27]

A similar reaction involving the cyclization of a pyridine onto an imine catalyzed by copper(II) chloride in the presence of oxygen was subsequently reported by Döring and co-workers (Scheme 11).[28] Copper(II) first acts as a Lewis acid to coordinate the imine nitrogen of **20**, thereby promoting nucleophilic attack onto the imine carbon. It then serves to oxidize the resulting amine intermediate through either a one- or two-electron process, thereby providing bicyclic imidazole **21**. Copper(II) is an efficient oxidant of aliphatic amines.[29–31]

Junjappa and co-workers reported a related copper(II) chloride promoted oxidative cyclization of 2-aminopyridines that provides acylimidazo[1,2-*a*]pyridines efficiently (Scheme 12).[32] The electron-rich 2-aminopyridines **22** are thought to undergo one-electron oxidation followed by cyclization and loss of another electron to allow for rear-omatization, thereby forming acyl[1,2-*a*]pyridines **23**.

## 3 Saturated heterocycles *via* addition of heteroatoms to alkenes

A variety of nitrogen heterocycles can be synthesized *via* addition of a nitrogen nucleophile to an unactivated alkene. Recent developments in this field have shown that copper is capable of promoting such transformations with high regio- and stereoselectivity. The reactions that fall under this category are net hydroamination, carboamination, diamination and aminohalogenation.

3.1 Intramolecular hydroaminations

The catalytic intramolecular addition of N–H bonds across alkenes is an atom economic process for the production of nitrogen heterocycles. Takaki and co-workers reported the synthesis of five- and six-membered nitrogen heterocycles *via*

X = SMe, OMe, NR$_2$
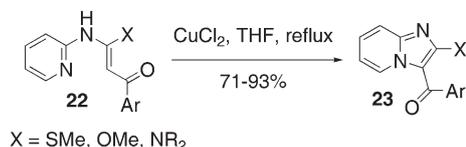
Scheme 12 Synthesis of acyl[1,2-*a*]pyridines.
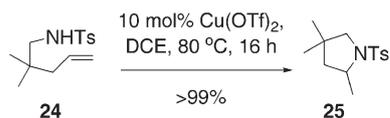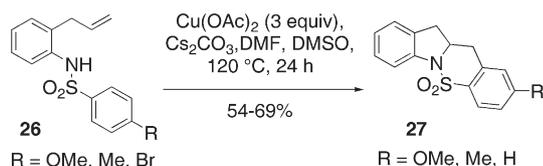
Scheme 13 Intramolecular hydroamination.

the intramolecular hydroamination of γ- and δ-alkenyl sulfonamides catalyzed by a iron, copper and silver salts.[33] Included in the variety of transition-metal chloride and triflate salts tested, Cu(OTf)$_2$ in dichloroethane (DCE) at 80 °C for 16 h promoted the cyclization of **24** in nearly quantitative yield (Scheme 13).

The triflic acid (TfOH) catalyzed hydroamination reactions of γ- and δ-alkenyl sulfonamides have been reported to occur under nearly identical reaction conditions, implying the above reaction may proceed *via* a Brønsted acid catalyzed process.[34] The Cu(OTf)$_2$ catalyzed intermolecular hydroamination reactions of styrenes, norbornenes and dienes with sulfonamides have also been reported; the alkene substrate is thought to undergo Brønsted acid catalyzed addition by a copper-coordinated sulfonamide nucleophile.[35]

3.2 Carboamination of alkenes

The intramolecular carboamination reaction of unactivated alkenes, a net N–C and C–C bond forming process, can provide rapid construction of polycyclic nitrogen heterocycles. We recently reported a copper(II) carboxylate promoted intramolecular carboamination reaction of arylsulfonyl-*o*-allyl-lanilines **26** for the synthesis of polycyclic sultams **27** (Scheme 14).[36] In general, electron-rich arylsulfonamides (R = Me, OMe, Cl) reacted efficiently to provide carboamination adducts in respectable yields (54–69%). While the chloro-substituent (Scheme 15) survived the reaction conditions, the bromide was removed (Scheme 14). Electron-withdrawing groups (NO$_2$) diminish the substrate reactivity substantially.

meta-Substituted arylsulfonyl-*ortho*-allylanilines **28** provided a roughly 2 : 1 mixture of regioisomeric carboamination
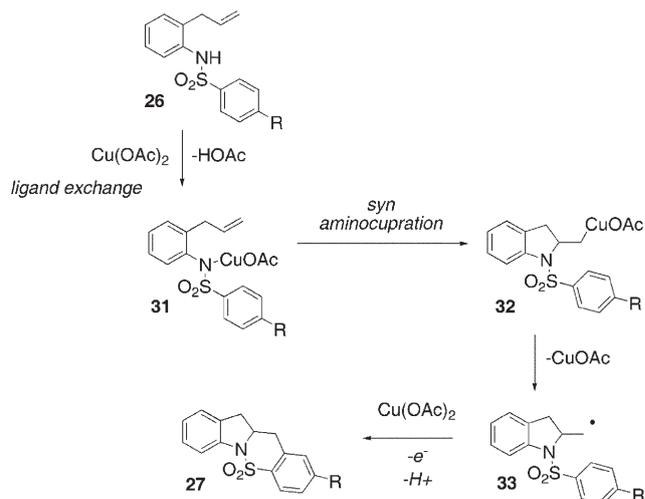

Scheme 14 Copper(II) acetate promoted intramolecular carboamination.
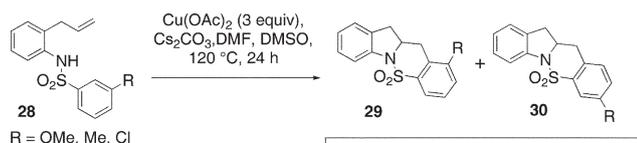
R	yield (%)	selectivity (**29** : **30**)
OMe	62	2.7 : 1
Me	67	2.3 : 1
Cl	60	1.8 : 1

Scheme 15 Regioselectivity in the carboamination.

Scheme 16 Proposed mechanism for the copper(II) facilitated carboamination.

adducts **29** and **30** where the more sterically hindered *ortho*-adduct **29** predominated (Scheme 15).

This surprising preference for the *ortho* adduct indicated that the C–C bond might be formed *via* addition of a primary radical to the aryl ring (Scheme 16). Previous studies have found that the addition of radicals to substituted aryl rings can occur with a preference for the *ortho*-adduct.[37,38] Our working mechanistic hypothesis is illustrated in Scheme 16. We believe that the copper(II) carboxylate promoted carboamination reaction proceeds *via* ligand exchange, *syn* aminocupration and subsequent homolytic cleavage of the resulting unstable C–Cu(II) bond (Scheme 16). Evidence for the *syn* aminocupration mechanism is based upon stereochemical studies.[39] The resulting primary radical then cyclizes onto the aromatic ring of the tosyl group, leading, after [Cu]-facilitated one-electron oxidation and loss of H$^+$, to the carboamination adduct. The mechanism is currently under intensive investigation.[39] We do not, however, believe a nitrogen radical is involved in the reaction pathway.

A mechanistically distinct copper promoted net carboamination reaction was reported by Clark and co-workers.[40] During their investigation of amidyl radical tandem cyclization reactions catalyzed by AIBN in the presence of Bu$_3$SnH, Clark observed that the *N*-benzyl substituted *O*-acyl hydroxamic acid **34** yielded only the monocyclized hydroamination product (not shown) and none of the carboamination product **35**. In order to optimize for the carboamination product, the substrate was treated with Cu(OTf)$_2$/DBN in acetonitrile at 120 °C for 48 h, resulting in a 93% overall yield of a 57 : 43 ratio of carboamination and reduced products, **35** and **36**, respectively (Scheme 17). Clark *et al.* proposed that the reaction occurs *via* an amidyl radical, created upon copper promoted homolysis of the N–O bond.

3.3 Copper promoted intramolecular diamination of unactivated alkenes

We recently reported the first copper-promoted olefin diamination reaction.[41] Treatment of variously substituted γ- and
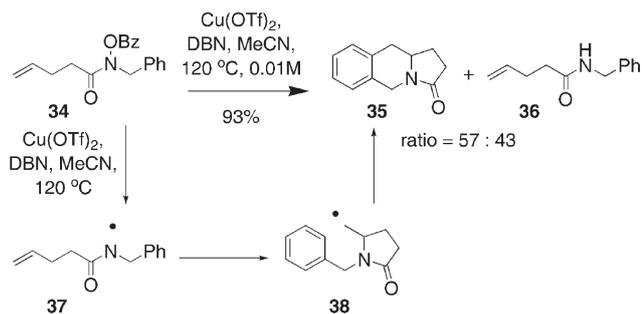
Scheme 17 Carboamination *via* amidyl radical.

δ-alkenyl sulfamides with Cu(OAc)$_2$ in the presence of K$_2$CO$_3$ at 90–120 °C in a DMF/DMSO solvent system readily provided several diamination adducts in good to excellent yield (Table 1).

The mechanism of the reaction is thought to be similar to the copper(II) carboxylate-promoted carboamination reaction (Scheme 16). *Syn* aminocupration to generate **42**, followed by homolysis of the unstable carbon–copper(II) bond would generate primary radical intermediate **43** (Scheme 18). A copper salt (CuL$_n$) could then facilitate the coupling of the carbon radical and the second nitrogen *via* ligation and reductive elimination, possibly *via* a copper(III) intermediate.[42] The presence of the carbon radical intermediate **43** was implicated by stereochemical studies.[43] It is known that carbon
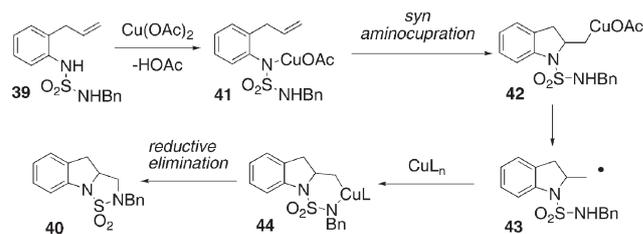
Scheme 18 Postulated mechanism of the copper-promoted alkene diamination reaction.

radicals can react rapidly with copper(II) salts to generate organocopper(III) intermediates that subsequently undergo reductive elimination.[42]

3.4 Aminohalogenation

Aminohalogenation of γ-alkenyl sulfonamides as well as atom-transfer reaction of γ-alkenyl *N*-chloroamines can be promoted by copper halide salts. We recently reported that CuBr$_2$ (3 equiv.) in CH$_3$CN at room temperature converts the *N*-tosyl-*o*-allylaniline **26a** into a mixture of aminohalogenation adduct **45**, 54% yield, and dibromination adduct **46**, 22% yield (Scheme 19).[44] The reaction was not inhibited upon addition of a radical scavenger such as hydroquinone. Thus, it is likely that this reaction proceeds through a polar reaction mechanism (electrophilic addition of Br$_2$ formed *via* 2 CuBr$_2$ → 2 CuBr + Br$_2$) rather than a radical pathway.

A mechanistically distinct copper promoted aminohalogenation reaction was developed by Stella and co-workers.[45] In this reaction, *cis* and *trans N*-chloropentenyl amines, *e.g.* **47**, undergo the radical cyclization upon treatment with CuCl, CuCl$_2$ to yield chloromethyl pyrrolidines, *e.g.* **48**, in good to high yield and almost exclusive diastereomeric purity depending on pre-existing olefin geometry (Scheme 20). The stereospecificity of this reaction suggests a mechanism involving a concerted trans addition of the aminyl radical and chlorine atom across the alkene.

Gottlich and co-workers observed that a catalytic amount of CuCl enables a similar transformation (Scheme 21).[46] In their study, the authors observed a range of diastereoselectivities (3 : 1 to complete diastereomeric purity) depending on
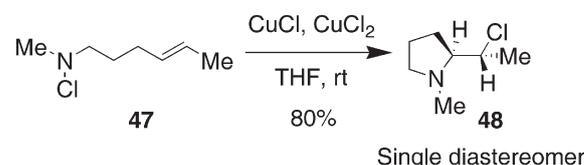
Table 1 Copper(II) acetate promoted alkene diamination

Entry[a]	Substrate	Product(s)	Yield (%)
2[b]			73
3[b]			56
4			57
5		*selectivity = >20:1*	71
6[b]			83

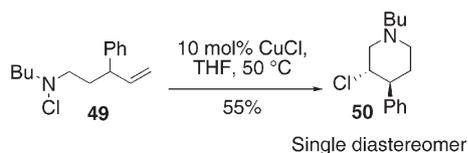[a] *Reaction conditions*: 3 equiv. Cu(OAc)$_2$, 2 equiv. K$_2$CO$_3$, DMF (0.08–0.1 M), DMSO (10 equiv.), 90 °C, 48 h. [b] Reaction was conducted at 120 °C.
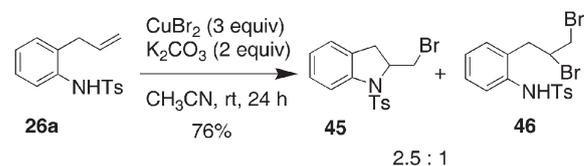
Scheme 19 Copper(II) bromide promotes aminobromination.

Scheme 20 Copper-facilitated atom transfer *via* aminyl radical.

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Chem. Soc. Rev., 2007, **36**, 1153–1160 | 1157

Scheme 21 Piperidine formation *via* atom transfer reaction.

substitution pattern. They proposed that the initial five-membered ring aminochlorination product undergoes a ring expansion through an aziridinium intermediate to provide the thermodynamically favored piperidine ring, *e.g.* **50**.[47]

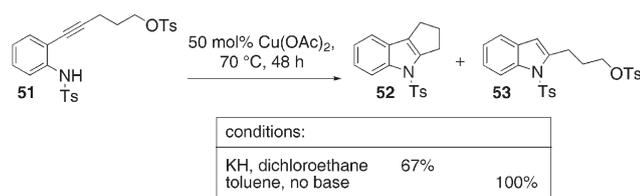# 4 Intramolecular reactions of heteroatoms and alkynes

Copper salts have a high affinity for alkynes and promote additions of heteroatoms to them. The reactions of terminal and internal alkynes differ in that the former can form a copper acetylide intermediate.

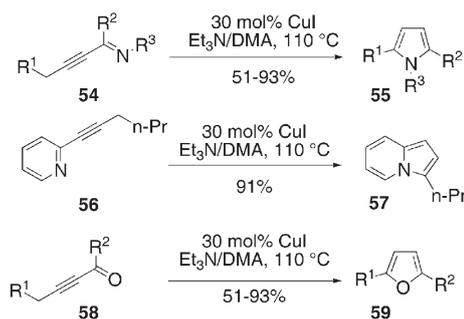## 4.1 Copper-catalyzed intramolecular reactions of heteroatoms and alkynes

The copper(II)-catalyzed cyclization of 2-ethynylanilines to indoles, *e.g.* **51**, has been reported by Hiroya *et al.* (Scheme 22).[48,49] The corresponding oxygen heterocycle can also be formed from the cyclization of 2-ethynylphenol catalyzed by copper(II). It is thought that the copper(II) activates the alkyne and *trans* addition occurs. The resulting organocopper intermediate can act as a vinyl carbanion to protonate to give indole **53** or, in the presence of KH (ensuring the absence of an acidic proton), the carbanion can perform an intramolecular S_N2 to form an additional ring, *e.g.* for the formation of indole **52**. It is interesting that the vinyl carbanion is sufficiently electronegative as to prevent its oxidation to a vinyl radical by the copper(II) salt. The synthesis of nitrogen heterocycles has also been accomplished *via* the copper(I) catalyzed intramolecular hydroamination of alkynes.[50,51]

Gevorgyan and co-workers have developed novel copper(I) catalyzed cycloisomerizations of alkynyl imines and alkynyl ketones for the synthesis of pyrroles **55** and **57** and furans **59**, respectively (Scheme 23).[52,53]

The mechanism is thought to involve an allene intermediate (Scheme 24). Deuterium labeling studies and anion trapping experiments support the involvement of base-induced deprotonation–protonation sequences in the reaction pathway.[52]

Scheme 22 Intramolecular carboamination and hydroamination of alkynes.

**Scheme 23** Cycloisomerizations of alkynyl imines and ketones.
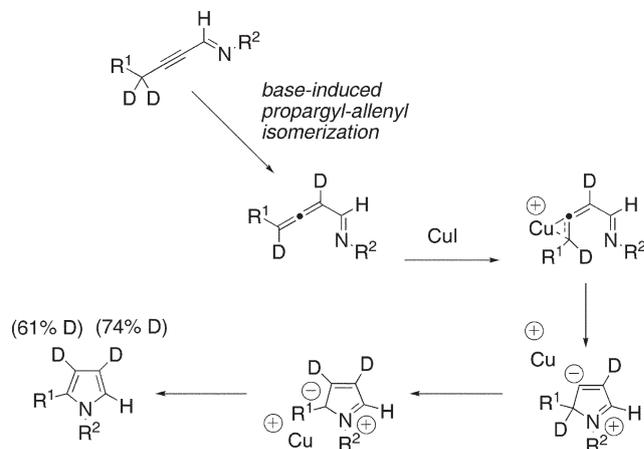
**Scheme 24** Mechanism of the cycloisomerization reaction.

4.2 Intermolecular reactions: [3 + 2] cycloadditions

Copper catalyzed [3 + 2] cycloaddition reactions can provide valuable unsaturated heterocyclic compounds such as 1,2,3-triazoles and β-lactams under mild conditions. Azides, nitrones and azomethine imines can all serve as the dipole component in these copper(I) catalyzed 1,3-dipole cycloaddition reactions. These reactions are thought to proceed through a copper acetylide dipolarophile intermediate (*e.g.* **63**, Scheme 25). The regioselectivity in these reactions is consistent with the negatively charged end of the dipolarophiles bonding to the copper-substituted carbon of the acetylides.

The first copper(I) catalyzed [3 + 2] cycloaddition reported was the reaction of terminal acetylenes with nitrones to produce β-lactams.[54,55] The *cis vs. trans* diastereoselectivity in these reactions is dependent on both the alkyne and nitrone
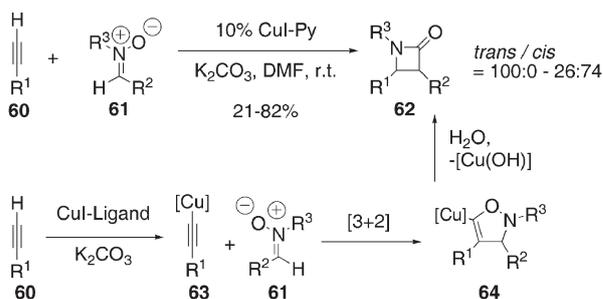
Scheme 25 Synthesis of β-lactams.
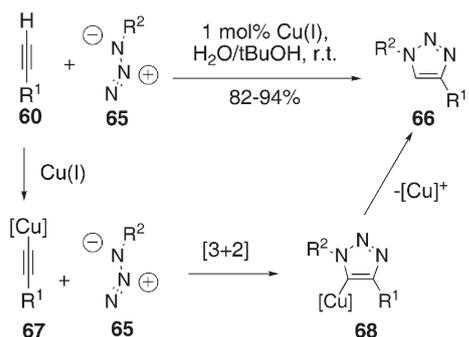
Scheme 26 [3 + 2] Cycloaddition of azides and terminal alkynes.

substituents but in most cases the selectivity is moderate (Scheme 25). Use of chiral bisoxazoline ligands and (−)-sparteine provided β-lactams with moderate levels of enantiomeric excess (23–68%).[55]
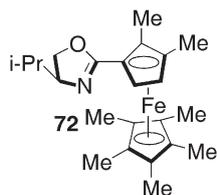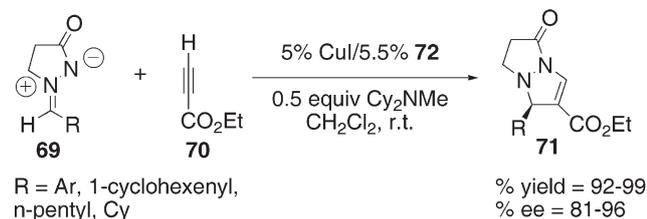
The copper(I) catalyzed [3 + 2] cycloaddition of azides and terminal alkynes for the synthesis of 1,2,3-triazoles was reported independently by the labs of Sharpless[56] and Meldal[57] in 2002. Although the thermal, uncatalyzed [3 + 2] cycloaddition of azides and alkynes was previously known, the copper catalyzed variant provides a lower temperature and highly regioselective protocol (Scheme 26).

Due to the mild, room temperature conditions, the high regioselectivity and chemoselectivity and the tolerance for aqueous ambient conditions and a broad range of functional groups, this reaction quickly found broad application in bioorganic chemistry.[58]

Shintani and Fu recently reported the first copper catalyzed [3 + 2] cycloaddition of terminal alkynes and azomethine imines (Scheme 27).[59] This reaction provided a highly regioselective synthesis of heterocycles 71. The researchers were able to obtain high levels of enantioselectivity in this reaction when they used a catalytic amount of chiral P,N-ligand 72.

4.3 Copper facilitated reactions of nitriles and isocyanides

Yamamoto and co-workers reported that electron-deficient internal alkynes 73 react with isocyanides 74 under copper

R = Ar, 1-cyclohexenyl,
n-pentyl, Cy

% yield = 92-99
% ee = 81-96

Scheme 27 Catalytic asymmetric [3 + 2] cycloaddition of terminal alkynes and azomethine imines.
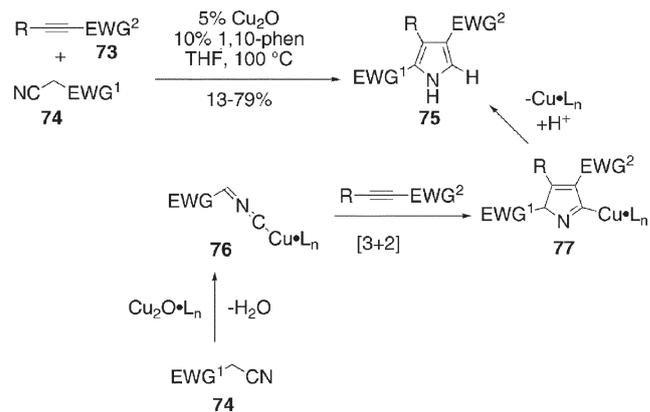
Scheme 28 Synthesis of pyrroles *via* copper catalyzed condensation of isocyanides and alkynes.

catalysis to afford 2,3-di-EWG-substituted pyrroles 75 (Scheme 28).[60] The reaction is thought to occur *via* copper(I) promoted 1,3-dipole formation from the isocyanide followed by [3 + 2] cycloaddition with the alkyne.
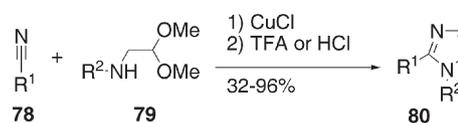
4.3 Nitriles and isocyanides for imidazole synthesis

Frutos *et al.* developed a one-pot procedure for the synthesis of substituted imidazoles from the copper(I) promoted reaction of nitriles with α-amino acetals (Scheme 29).[61]

Yamamoto and co-workers designed and developed a copper-catalyzed cross-cycloaddition between arylisocyanides 81 and isocyanides with electron withdrawing groups 74 (enolizable isocyanides), producing 1,4-disubstituted imidazoles 82 in high yields (Scheme 30).

5 Summary and outlook

From the reactions summarized in this tutorial review it is obvious that copper salts are valuable reagents and catalysts for the synthesis of nitrogen heterocycles. The use of ligands for tuning the reactivity of copper has significantly advanced the range of transformations enabled by this metal. Although few examples of ligand-based asymmetric induction for these reactions have been reported, it is clear that catalysis and asymmetric catalysis will be important frontiers for this chemistry in the coming years.

Scheme 29 Synthesis of imidazoles.
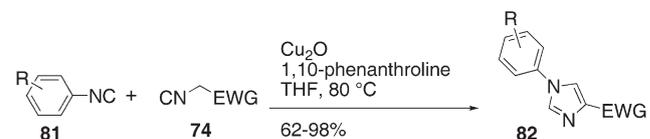
Scheme 30 Cross condensation of isocyanides for imidazole synthesis.

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Note added in proof: The synthesis of 9–19 membered macrocycles via copper-catalyzed intramolecular condensation of alkynyl bromides with carbamates and sulfonamides was recently reported by Hsung and co-workers.[62]

The copper-catalyzed rearrangement of vinyl oxiranes to 2,5-dihydrofurans was reported by Njardarson and co-workers shortly after this review was prepared.[63]

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