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Recent advances in Cu-catalyzed transformations of internal alkynes to alkenes and heterocycles

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Numerous metal-catalyzed reactions involving internal alkynes and aimed towards synthetically and pharmacologically important alkenes and heterocycles have appeared in the literature. Among these, Cu-catalyzed reactions have a special place, which has prompted the investigation and development of carbon–carbon and carbon–heteroatom bond-forming reactions. These reactions possess wide scope, and during the paths of these reactions, either stable or *in situ* intermediates are formed *via* the addition of Cu as a core catalyst or synergistic catalyst. In this review, we aim to report different contributions relating to Cu-catalyzed reactions of internal alkynes for the synthesis of different valuable alkenes and heterocycles which have appeared in the literature in the last decade. We anticipate that this appraisal will deliver basic insights for the further advancement of Cu-catalyzed reactions in organic chemistry.

1. Introduction

Alkyne is a structurally simple and chemically very labile molecule which is the fundamental functional group in organic chemistry. Internal alkynes in particular are more stable than terminal alkynes due to hyperconjugation which makes it easy to handle, store and deal with in reaction environments. The alkyne π-system displays donor–acceptor properties similar to

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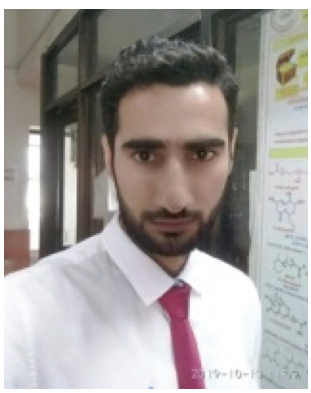

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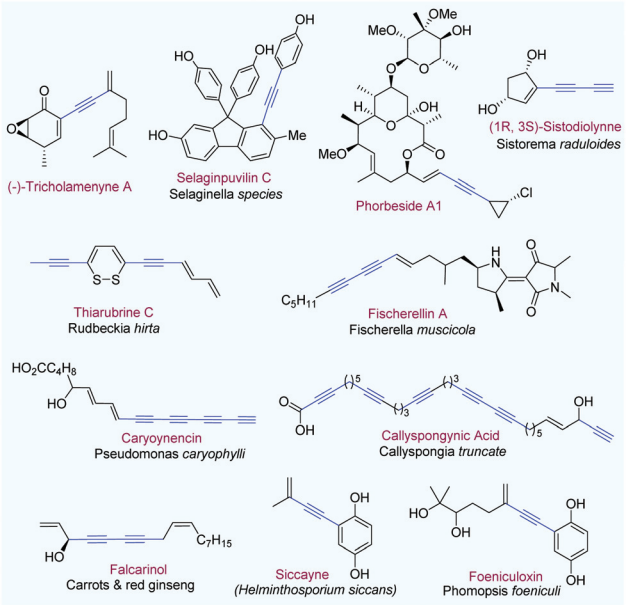


Fig. 1 The alkyne moiety in natural products.

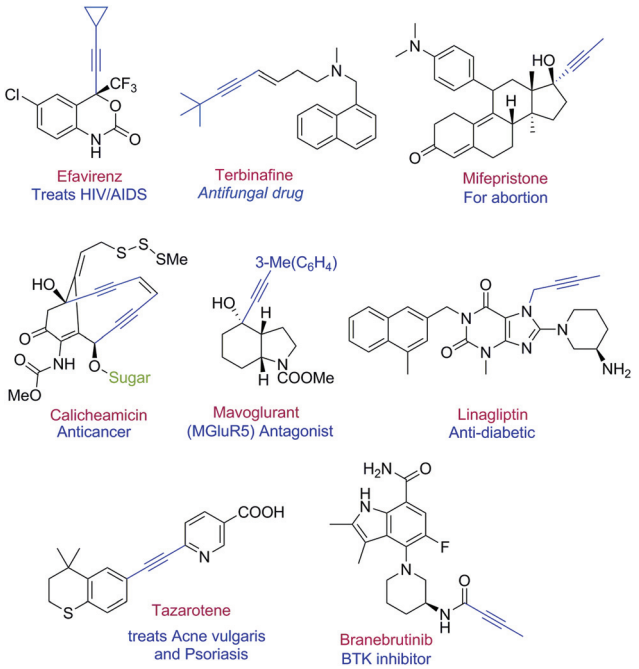


Fig. 2 Alkyne scaffolds in marketed drugs.

those of phenyl, cyano or carbonyl groups, which makes them function as their isostere. In modern organic synthesis internal alkynes have been extensively used for the synthesis of a number of molecules.[1,2] Moreover, the internal alkyne moiety is an active pharmacophore in many natural products[3,4] (Fig. 1) and marketed drugs[5] (Fig. 2). In drug discovery, the ene-diyne unit plays the role of a rigid spacer and bio-isostere and is sometimes referred as a "warhead" because it generates extremely reactive radical species *via* Bergman cyclization to attack DNA inside tumor cells.

Qazi Naveed Ahmed

Qazi Naveed Ahmed is the principal scientist in the Medicinal Chemistry Division at CSIR-Indian Institute of Integrative Medicine (IIIM), Jammu. He obtained his PhD from Kashmir University under the combined supervision of Dr H. M. Sampath Kumar and Prof. M. A. Qureshi at IIIM, Jammu. He completed his post-doctoral fellowship at the University of Paris Sud-XI, France in the CNRS program. He has also served as an assistant professor in the Higher Education Department, Jammu and Kashmir. His research interests include medicinal chemistry and the applications of functional group driven synthetic methodologies across glycochemistry, bio-conjugation/bio-orthogonal chemistry, and the late-stage modification of bioactives.

In synthetic chemistry, the properties of alkynes have spurred the discovery of asymmetric reactions and functional group transformations *via* transition metal catalysis.[6–8] Their applications have also been broadly explored in chemoselective atom economical reactions like alkyne–zipper[9] and click reactions.[10,11] Similarly, benzynes[12a] and cyclohexynes[12b] are cyclic internal alkynes credited as one of the most versatile and valuable reactive intermediates in organic chemistry which can be trapped intra- or intermolecularly with different nucleophiles[13] and natural products[14] (Fig. 3). On the other hand, copper is abundantly present in the earth's crust. Their bio-compatibility, sustainability and low cost make the synthesis of Cu-catalysts very easy, economical and ecofriendly.[15,16] Cu-Based reagents are easily accessible and bear high functional group tolerance and are rendered as first-line catalysts for carrying out any transformation in organic synthesis. In addition, the high extent of tunability in the

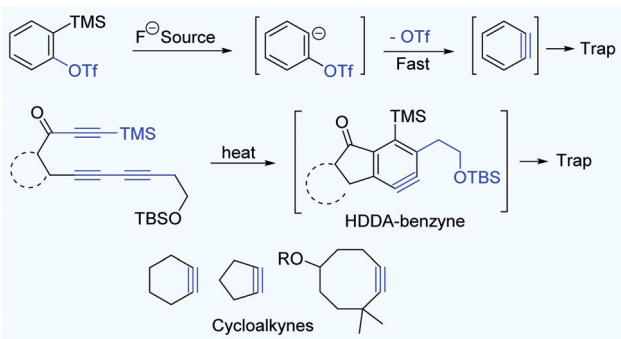


Fig. 3 Highly reactive aryne and cyloalkyne intermediates.

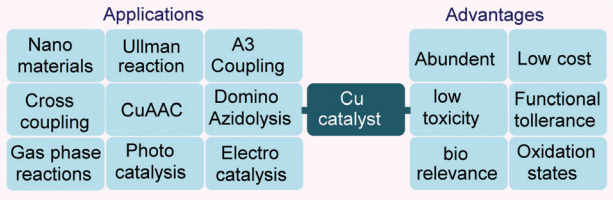


Fig. 4 The applications of Cu-catalyzed reactions.

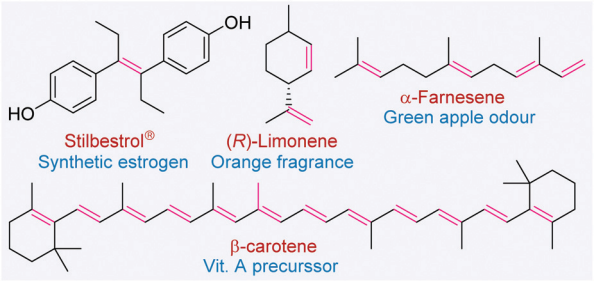


Fig. 5 Substituted alkenes in drugs and plant metabolites.

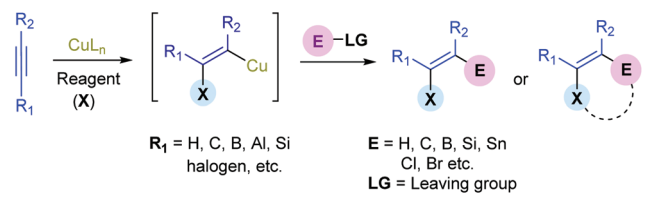
ligand coordination sphere of copper catalysts gives it an edge over other metals for the useful optimization of redox properties.[17] Cu exhibits a range of oxidation states [Cu(0), Cu(I), Cu(II), and Cu(III)] and depending on its oxidation state Cu can catalyze reactions through radical (1e) or polar (2e) pathways. Copper easily coordinates to heteroatoms and π-systems like alkynyl, ally, vinyl or aryl groups and activates them for functionalization by promoting (Fig. 4) selective C–H activation or intramolecular cyclization.[18] A generalized scheme of the copper-catalyzed reaction of internal alkynes is shown in Scheme 1. Apart from long-established Ullmann coupling,[19] internal alkynes have been employed in the chemoselective and direct formation of C–C and C–X (X = O, N, S, P) *via* C–H and C–C bond activation reactions.[20,21a,b] Along these lines, Cu-catalyzed reactions of internal alkynes have been less of a focus compared to the vast study of alkynes in general. Although there have been some selective reviews about Cu-catalyzed alkynes: for example, different metal-catalyzed radical-initiated reactions of internal alkynes have been addressed with some details about alkynoates in the past.[21c,d] Y. Tsuji and co-workers have published a detailed review of the reductive and borylative transformation of alkynes catalyzed by copper hydride and boryl–copper species with many examples related to internal alkynes.[21e] However, alkynoates and propargylic amines turned out to be a separate topic for another review to showcase their progress and synthetic utility. This review particularly aims to cover recent progress in the copper-catalyzed transformation of pure internal alkynes for the synthesis of alkenes and heterocycles which are an essential class of compounds in chemistry.

2. Formation of substituted alkenes

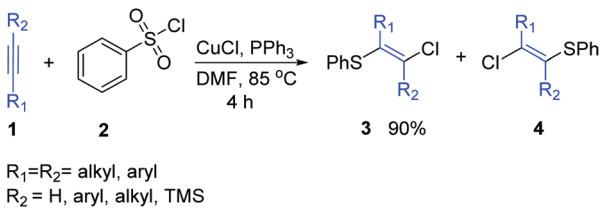
Substituted alkenes are very useful for the synthesis of various starting compounds like natural products (essential oils/terpenes), pharmaceuticals (Fig. 5) and functional polymers.[22] These molecules are available in bulk quantities from petrochemicals to feedstocks and renewable resources.[23] Owing to their unique reactivity and widespread abundance, many processes like coupling, eliminations, cascade, cycloadditions and oxidation/reduction reactions are used for their functionalization. Internal alkynes are specifically the most important resources for the synthesis of substituted alkenes in a myriad of ways. Along these lines, substituted thioalkynes **3** and **4** are formed in a Cu-catalyzed reaction when internal alkyne **1** reacts with benzenesulfonyl chloride **2** in the presence of triphenyl phosphine in DMF.[24] The reaction involves the unprecedented use of commodity materials and is applicable to aryl, alkyl, and TMS-based internal alkynes. The overall process leads to the formation of tetrasubstituted vicinal chlorothiolation of internal alkynes in up to 90% yields. The *E*-selective products can be predicted by *anti*-Markovnikov addition during which a more stable lower energy intermediate is formed. The reaction could be applied for the synthesis of chlorothiolated bioactive natural products. Mechanistically, the reaction is assumed to involve a sulfur radical intermediate generated through copper-catalyzed cleavage of the S–Cl bond followed by the addition of sulfenyl chloride and CuCl to the internal alkyne (Scheme 2).

On the other hand, hydrosulfonylation of internal alkyne **5**[25] occurs through copper catalysis by using sodium sulfinate and an isoxazoline ligand under aerobic conditions in an equal ratio in a trisolvent system. The reaction selectively produces (*E*)-alkenyl sulfone **7** from both internal and terminal alkynes in efficient yields (Scheme 3).

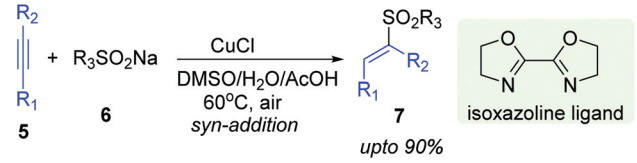
A similar type of reaction was described by G. Lalic and co-workers[26] in which substituted internal alkyne **8** undergoes hydroallylation with allyl phosphates **9** to produce skipped



Scheme 1 The generalized Cu-catalyzed reaction of internal alkynes.



Scheme 2 The chlorothiolation of internal alkynes.



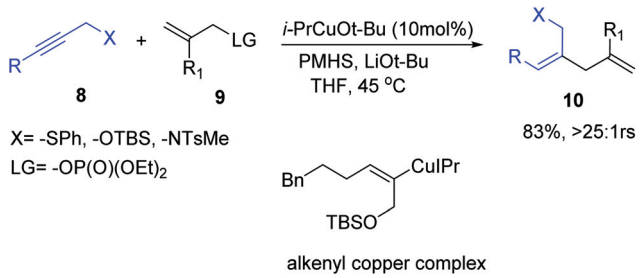
Scheme 3 The Cu-catalyzed hydrosulfonylation of internal alkynes.

dienes **10** and tri-substituted alkenes in a regio- and diastereoselective manner (Scheme 4). The reaction is catalyzed by a copper catalyst iPrCuO*t*-Bu and an H-source like polymethylhydrosiloxane (PMHS) is used along with the additive LiO*t*-Bu which plays a critical role in C–C bond formation and increases the rate of reaction. The regioselectivity is proved on the basis of the alkenyl copper complex after obtaining its X-ray crystal structure.

Another synthesis of skipped dienes can be principally achieved through the Cu-catalyzed allylboration of internal alkynes **11** with allyl carbonates **12** and $B_2(pin)_2$ mediated by a Pd complex.[27] The reaction takes place in the presence of a Pd ligand and base to form borylated skipped dienes **13** in a stereoselective manner. The reaction can be applied to various internal alkynes and allyl carbonates under very mild conditions. The presence of a phenyl or chloro group in the alkyl substituent leads to lower selectivity of the product. The method has been applied in the synthesis of pheromone (*Z,E*)-α-homofarnesene and isosesquilavandulyl alcohol, a key precursor in the synthesis of an active antibiotic agent *Merochlorin A–D* (Fig. 6).[28] Mechanistically, the formation of β-borylalkenylcopper species **III** occurs from the stereoselective borylcuperation of **II** followed by allylic substitution of allyl carbonates catalyzed by palladium (Scheme 5).

Substituted alkenes are also formed by the partial hydrogenation of internal alkynes **16** by using a simple commodity material like N-heterocyclic carbenes (NHC) mediated by an [(SIMes)CuCl] complex at elevated temperature to afford *Z*-alkenes **17** selectively with up to 84% yield.[29] The reaction proceeds efficiently with all the substrates to form *Z*-alkenes selectively; however, with aliphatic terminal alkynes and when R_1 = 4-BrC_6H_4 and R_2 = nonyne, no product formation was observed (Scheme 6).

A new type of reaction was reported by Y. Lee and co-workers[30] in which 1,2-diarylcompounds **20** are prepared from



Scheme 4 The hydroallylation of internal alkynes.

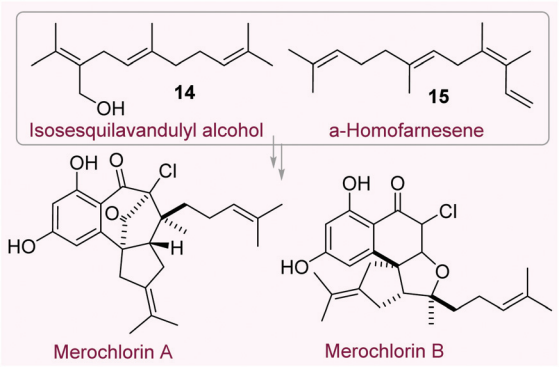
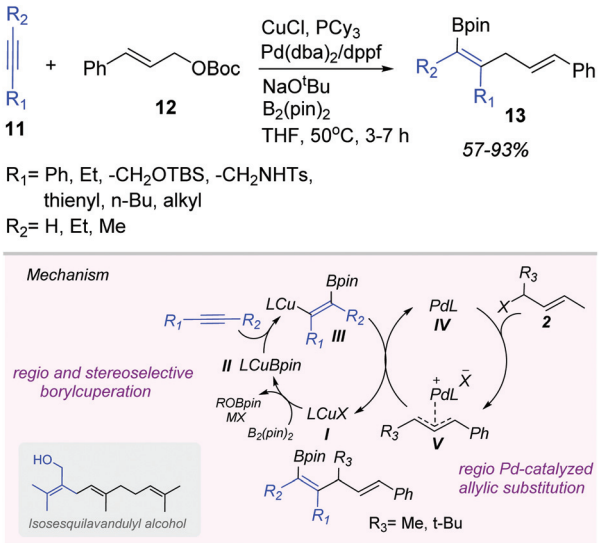
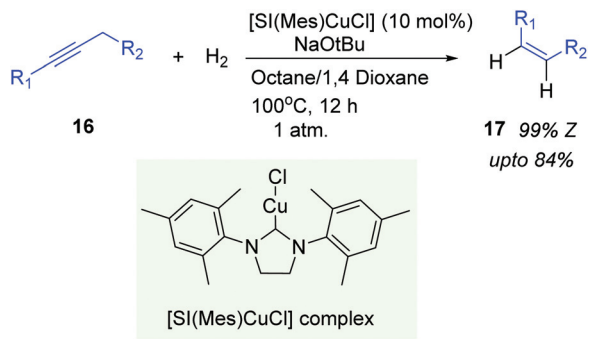


Fig. 6 The Cu-catalyzed hydrosulfonylation of internal alkynes.



Scheme 5 The Cu-catalyzed allylboration of internal alkynes.



Scheme 6 The partial hydrogenation of dodec-6-yne.

internal alkynes **18.** Some enamine products were slightly unstable during the column purification and slowly isomerised into *Z*-isomers. The reaction was applied over a range of *O*-benzoyl hydroxylamine derivatives and the products were subsequently post-modified into the corresponding amines by

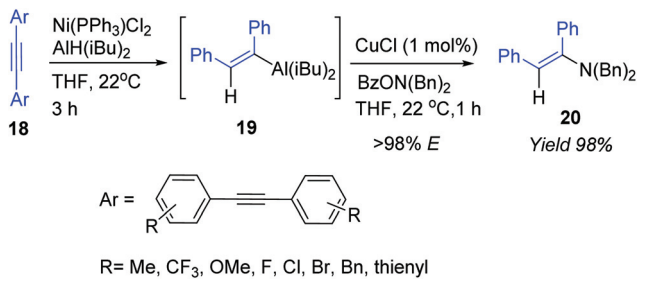
using $NaBH(OAc)_3$ and acetic acid. In the first step, diphenylacetylene reacts with DIBAL-H which generates *in situ trans*-diphenylvinylaluminium intermediate **19** which is then aminated by electrophilic *O*-benzoyl hydroxylamine in the presence of CuCl (1 mol%) as a catalyst and $Ni(PPh_3)_2Cl_2$ as a promoter to form *trans*-substituted aryl compounds **20** with 96% conversion and more than 98% *E*-selectivity (Scheme 7).

Internal alkynes **21** also undergo stereoselective hydroarylation[31] with aryl iodides **22** and polymethylhydrosiloxane (PMHS) **23** as a hydride source assisted by a catalytic amount of $Cu(OAc)_2$ and a dppf ligand to form trisubstituted alkenes **24**. Various symmetrical and unsymmetrical alkyne and aryl iodide substrates can be used in the reaction. Mechanistically, hydrocupration occurs through a 2e oxidative addition followed by reductive elimination and then coupling with alkyne and aryliodide.

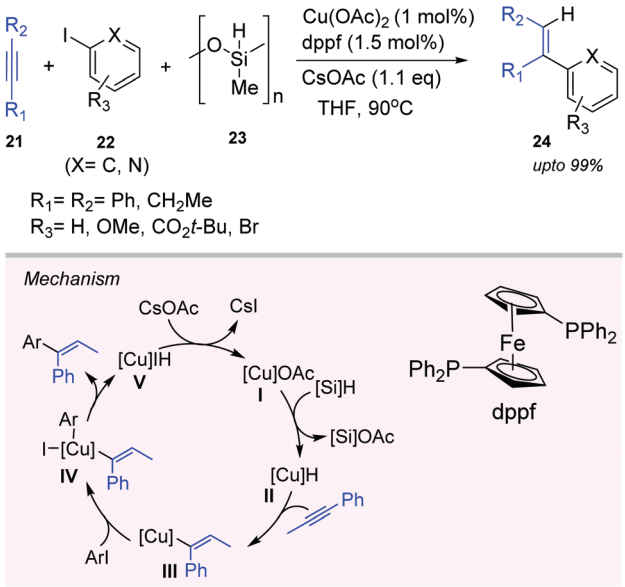
Transmetalation of [Cu]-OAc (**I**) with (PMHS) gives **II** followed by hydrocupration of internal alkyne to form intermediate **III** which after oxidative addition by aryl halide gives Cu^{3+} intermediate **IV**. Finally, after the formation of **V** *via* reductive elimination subsequent transmetalation of **V** with CsOAc regenerates **I** (Scheme 8).

J. C. Carretero and co-workers[32] reported the copper-catalyzed stereoselective and regioselective silylation of 2-pyridylsulfonyl substituted internal alkynes **25** which give rise to α- or β-silyl substituted alkenes **26** on demand. The presence of an SO_2Py moiety on alkyne is very crucial in maintaining the chemoselectivity and efficiency of the reaction and selection of the alkene from the same starting substrate. Alkyne and allene remain in equilibrium before the silylcupration takes place, which is promoted by an *in situ* base. Similar types of silylalkenes **34**, **35**, **38** were formed after the action of silylboronates from simple aryl and electronically biased internal alkynes **33** and **37** catalyzed by copper chloride (Scheme 9).

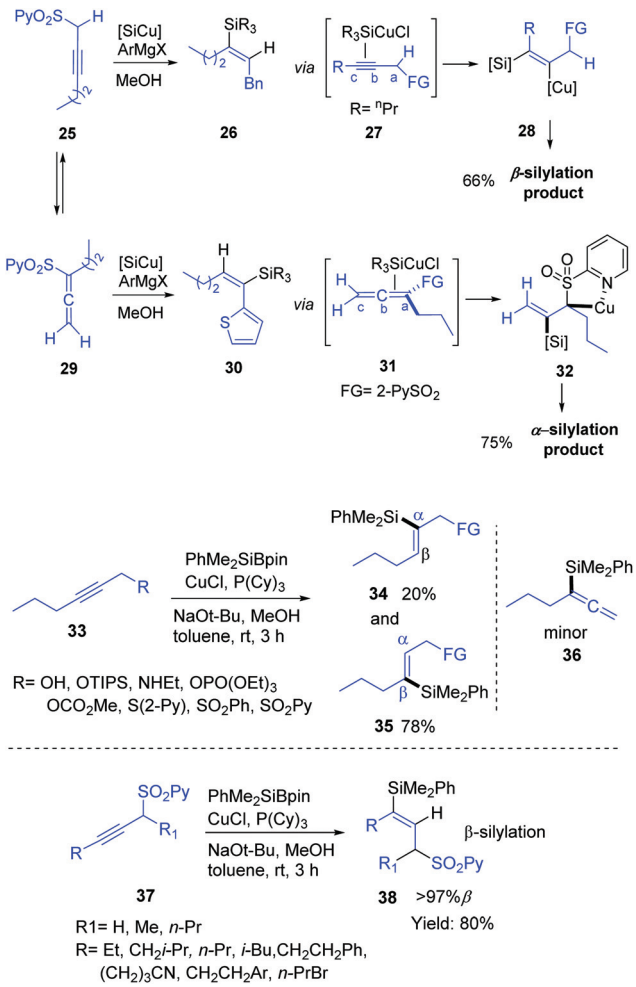
In another method developed by W. L. Santos and co-workers[33] Cu(I), generated from the silicon–boron based pronucleophile, catalyzed the β-silylation of internal alkynes **40** to give vinylsilanes **41**. The reaction secures high regioselectivity in electronically biased substrates like electron-deficient conjugated internal alkynes (*e.g.*, propiolates), 1,3-enynes and aryl alkynes. The mechanism shows the activation of the Si–B bond by a water molecule to generate a nucleophilic silylcopper



Scheme 7 The electrophilic amination of internal alkynes *via* hydroalumination.



Scheme 8 The stereoselective hydroarylation of internal alkynes.

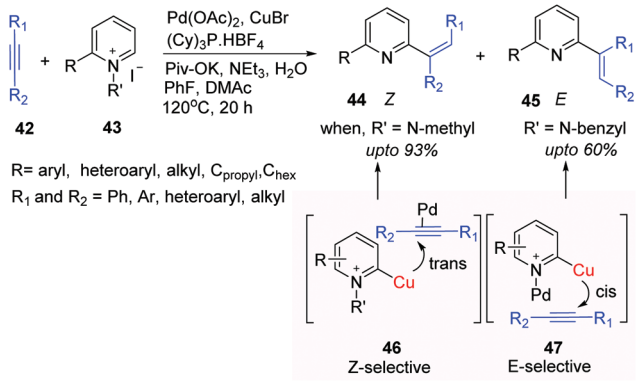


Scheme 9 The chemoselective silylation of 2-pyridylsulfonyl substituted internal alkynes.

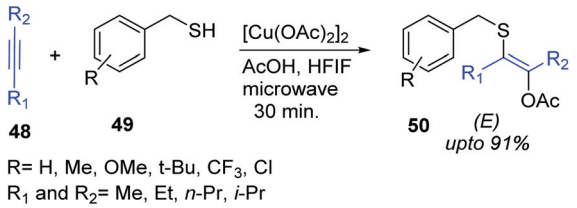
intermediate [LCu^{II}-SiMe$_2$Ph] followed by transmetalation. Whereas in ester substrates, silylcupration across an alkyne **I** takes place in a *syn* manner to form intermediate **II** which is subsequently protonated to yield (*E*)-β-silyl-α,β-unsaturated ester **III** (Scheme 10).

A Pd/Cu-catalyzed *E* and *Z* selective divergent synthesis of alkenylpyridines **44**, **45** takes place when the reaction between internal alkynes **42** and pyridinium salt **43** is carried out at elevated temperature.[34] The presence of the alkyl group on the pyridinyl nitrogen decides the selectivity of the product. R = *N*-methyl on N tends to form *Z*-pyridyl by the *trans* addition of a Cu–pyridyl complex over alkyne whereas R = benzyl type groups tend to form *E*-pyridyl alkenes by the *cis* addition of a Cu–pyridyl complex over alkyne. The Hemmett plot between k_X/k_H and σ^+ gives a ρ value of −0.64, which indicates the accumulation of more positive charge in the transition state and thereby a faster rate of reaction in electronically rich internal alkynes (Scheme 11).

A very simple Cu-catalyzed reaction of internal alkynes **48** with thiols **49** leads to the synthesis of acetate-containing substituted alkenes **50**.[35] The *trans* alkenes are selectively formed and regioselectivity is observed in the case where the alkynes are unsymmetrical in nature. The mechanism shows the involvement of a dimeric copper(II) species which generates a thiyl radical on sulfur. Characterization of the given olefins (*E* isomers) was obtained on the basis of the multiplicity of Me/Et signals at the vinylic carbon and homoallylic $^5J_{H-H}$ values. DFT calculations show that the insertion of sulfide forms a metal-stabilized radical and the dimeric nature of the Cu-reagent is crucial in promoting the reaction (Scheme 12).

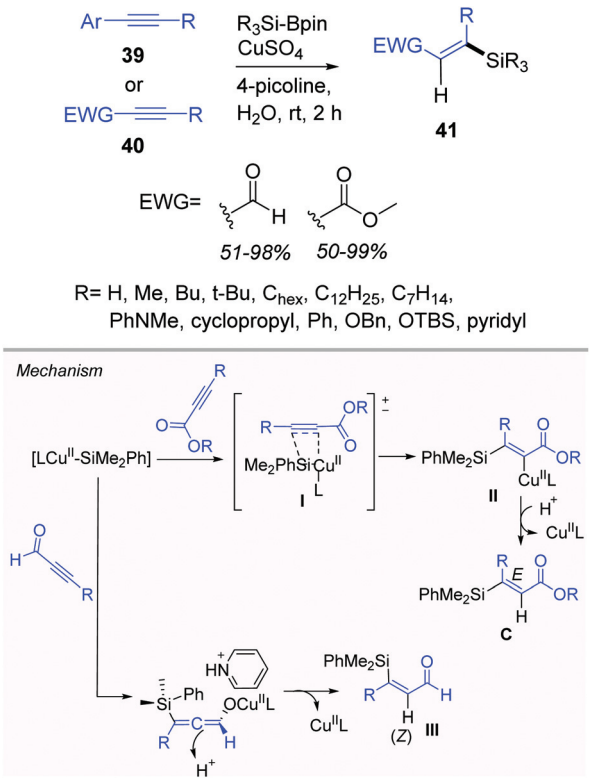


Scheme 11 The *Z*-selective alkenylation of pyridinium salts.

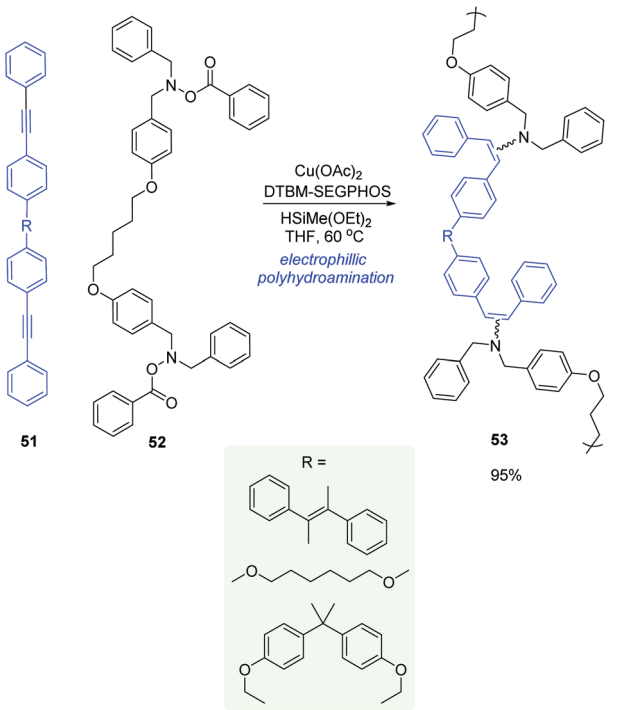


Scheme 12 The acetoxythiolation of internal alkynes.

Most of the poly-hydroamination of alkynes known until recently occurs through nucleophilic addition reactions. B. Z. Tang and co-workers[36] revealed that the Cu-catalyzed electrophilic polyhydroamination of internal alkynes undergoes electrophilic polyhydroamination to yield N-containing polymers. The reaction occurs between internal alkyne **51** and the monomeric form of electrophilic *N,N*-dibenzyl-*O*-benzoylhydroxylamine **52** in the presence of additive (DTBM-SEGPHOS) (R)-5,5′-bis[di(3,5-di-*tert*-butyl-4 methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole and diethoxymethyl silane HSiMe(OEt)$_2$ to yield the desired polymers **53** in 95% yield. The N-containing polymers thus formed are soluble in various solvents like DCM, DMF and THF. A slight increase in temperature increases the yield of the reaction. In addition, the polyenamine(s) polymers are thermally very stable with average weight to molecular weight ratios (M_ws) up to 12 650. The thermal stability of the polymers was calculated by thermo-gravimetric analysis (TGA) and differential scanning calorimetry (DSC), which revealed that the thermal decomposition temperatures (T_d) of all polymers are higher than 330 °C under inert conditions, with glass-transition temperatures (T_g) ranging between 49.80 and 88.30 °C. When phenyl-substituted internal alkynes were switched to alkyl substituents, regioselectivity was also altered. Similarly, by adjusting the tetraphenylethene(s) into the polymer backbone, the resultant polymers exhibited differential emission features which could be used in the detection of explosive materials (Scheme 13).



Scheme 10 The β-silylation of internal alkynes into vinylsilanes.



Scheme 13 The electrophilic polyhydroamination of internal alkynes.

3. Formation of carbonylated alkenes

Carbonylated alkenes are abundantly present in plants as secondary metabolites and used as essential oils, as scents in the perfume industry and for various medicinal purposes (Fig. 7). Carbonylated alkene motifs are also crucial in the biosynthesis of vitamins or their precursors and hormones like progesterone and aldosterone. They commonly exhibit geometrical (*cis*/*trans*) isomerism at the alkene junction as well as chirality at various substituted carbon centers. In general, ketones are of great significance due to their abundance in bioactive scaffolds and applications in organic synthesis.[37] α,β-Unsaturated carbonyl compounds are useful substrates for the formation of C–C bonds through Michael addition. The general mechanism of carboboration involves the formation of Cu-salt and halogen exchange by Bpin. After alkyne insertion, the final product is formed as a result of reductive elimination.

Liu and co-workers[38a] reported the copper-catalyzed reaction for the formation of carbon–vinyl–CF_3 bonds when propargyl alcohol **54** reacts with Togni's reagent **55** to form α-trifluoromethyl α,β-unsaturated enone **56** through a Meyer–Schuster reaction. In a similar way, the construction of tetrasubstituted 3-trifluoromethyl-3-butenal **58** can be accomplished by trifluoromethylation of internal alkynes **57** in the presence of **55**.[38b] The same reagent was utilized in Cu-catalyzed reactions by Hou and co-workers[38c] in the formation of substituted 4-trifluoromethyl substituted dihydro-pyrrolium salt **61** from **59**. Aryl alkynoates **62** also led to the formation of chromen-2-one **63** (Scheme 14). However, the carbon–vinyl CF_3 bond is directly formed as a result of trfluoromethylation cum annulation of internal alkyne **64** by using CuTc (copper(I)thiophene-2-carboxylate) and **65** called Umemoto's reagent to produce **66**.[38d] Product formation can be stopped after adding additives like ethanol or isopropanol with the formation of substituted ethoxy- or isopropoxy derivatives. The product formed after the reaction can be reduced and oxidized to form tetrahydronaphthalene and naphthalene, respectively, and can be easily applied in the synthesis of the antiestrogen molecule, Nafoxidine, an estrogen receptor modulator to treat breast cancer (Scheme 15).

The mechanism shows the formation of the final product through two different pathways. Cu(I) generates CF_3Cu(III) by Umemoto's reagent to give **I** after electrophilic attack by alkyne; species **II** is formed after reductive elimination of **I**. The intramolecular annulation *via* path-*I* gives intermediate **III** which undergoes rearomatization to give product **66**. Path-*II* undergoes an *ipso*-Friedel–Crafts reaction to give MeOH-stabil-

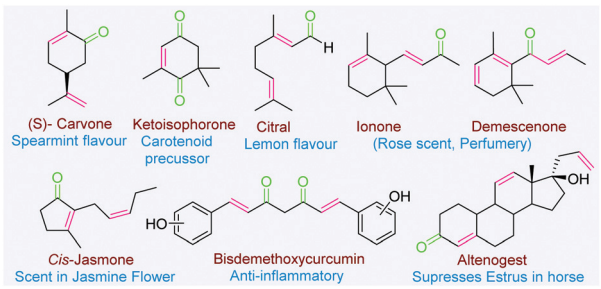
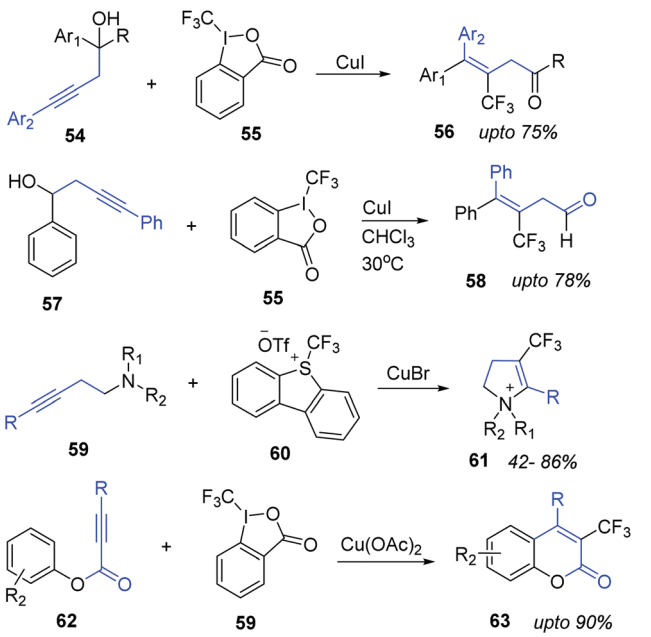
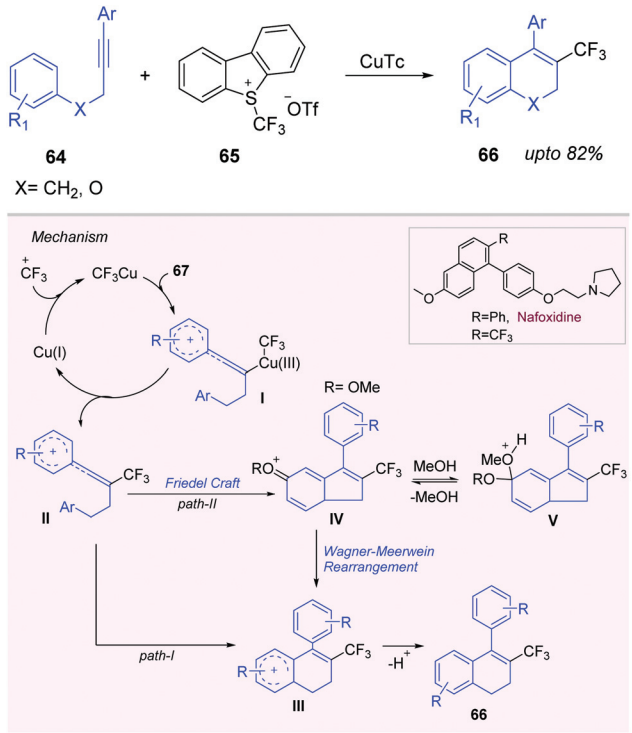


Fig. 7 Examples of carbonylated alkenes in natural products and therapeutics.



Scheme 14 The trifluoromethylation of internal alkynes.

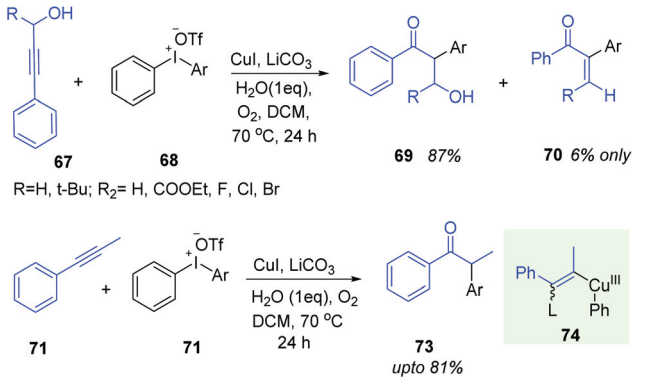


Scheme 15 The mechanism of trifluoromethylation.

ized intermediate **IV** which subsequently passes through Wagner–Meerwein rearrangement to furnish the final product.

Functionalized and simple internal alkynes like **67** and **70** are also exploited for the synthesis of carbonyl compounds. Their reaction with symmetrical and unsymmetrical diaryliodonium salts **68** and **71** proceeds regioselectively to form aryl-substituted ketones **69** and **73** in up to 81% yield.[39] The iodonium salt in the reaction acts both as an oxidant and an arylating reagent and tolerates many functional groups, making further homologation of the products possible. The reaction is catalyzed by 20 mol% CuI species, which are assumed to be formed first followed by their oxidative addition to diphenyliodonium triflate salt to generate a more electrophilic Cu(III)–aryl complex. The more electrophilic Cu(III)–aryl complex undergoes an insertion reaction with the internal alkyne to form alkenyl Cu intermediate **74** which after reductive elimination gives the final product (Scheme 16).

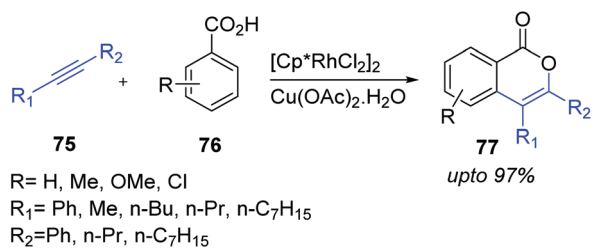
Internal alkynes **75** react with benzoic acids **76** *via* direct Rh-catalyzed and Cu-mediated oxidative coupling to form isocoumarin analogues **77** which are found in various naturally occurring molecules that display a broad range of interesting biological properties.[40a] The reaction takes place in DMF in the presence of air without the formation of any waste material except the liberation of water molecule.[40b] The electron-withdrawing/releasing substrates resulted in the formation of the product in 81–97% yield, whereas phenyl-2-(trimethylsilyl) acetylene only gave a desilylated homocoupled product. On the other hand, substrate 4-methyl benzoic acid (R = 4-Me) exclusively led to the formation of a single regioisomer in the reaction. 1-Phenyl-2-(trimethylsilyl)acetylene employed in the reaction did not couple with alkyne and succeeded only in giving a desilylative homocoupling product which can be detected by GC-MS (Scheme 17).



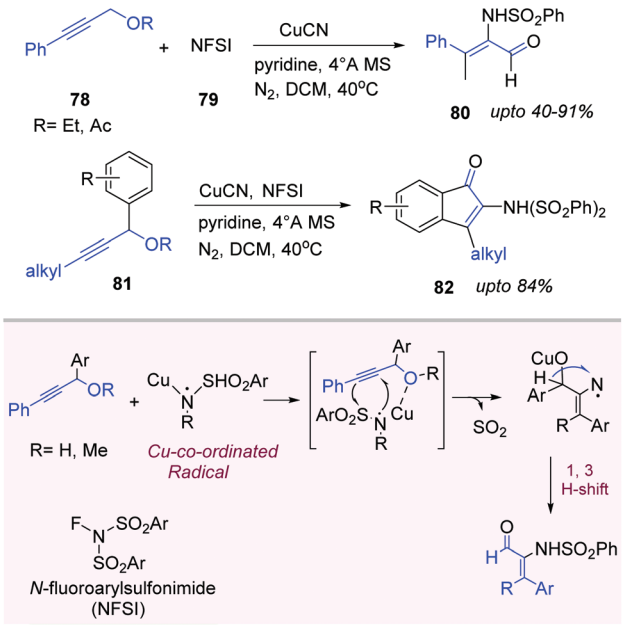
Scheme 16 The regioselective transformation of internal alkynes into α-arylketones.

Aminoarylation of alkynes is used to launch nitrogen and aryl moieties simultaneously into C–C triple bonds.[41] A very simple and mild copper-catalyzed strategy to convert functionalized aryl alkynes into α,β-unsaturated carbonyls is *via* aminoarylation. Different alkynes like **78** and **81** react with *N*-fluoroarylsulfonimides (NFSI) **79** in the presence of copper cyanide in pyridine under anhydrous conditions to yield α,β-unsaturated carbonyl compounds **80** and indenones **82**. The reaction is regioselective in which addition of a Cu-based N-radical adds to the C–C triple bond on the same side. The results indicate that the reaction is more efficient for electron-rich aromatic substrates compared with electron-deficient ones in NFSI derivatives. The Cu-coordinated N-centred radical adds regiospecifically to the internal alkyne to form vinyl radical in an sp-like linear configuration. Later on, 1,4-aryl migration is followed by desulfonylation with subsequent 1,3-hydrogen migration to give α-amino-β-aryl enones (Scheme 18).

An intramolecular oxidative Cu-catalyzed radical cascade cyclization has been developed for the synthesis of biologically important isoxazolidine and 1,2-oxazinane-fused isoquinolin-1(2*H*)-ones **84** in open air conditions.[42a] This takes place between internal alkynes and alkynes tethered with *N*-alkoxyamides **83**. This is yet another example of a very



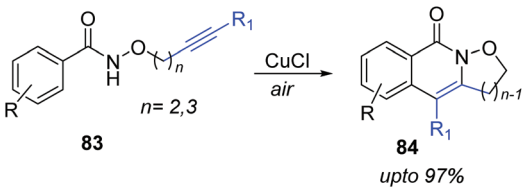
Scheme 17 The Rh/Cu-catalyzed regioselective formation of isocoumarins.



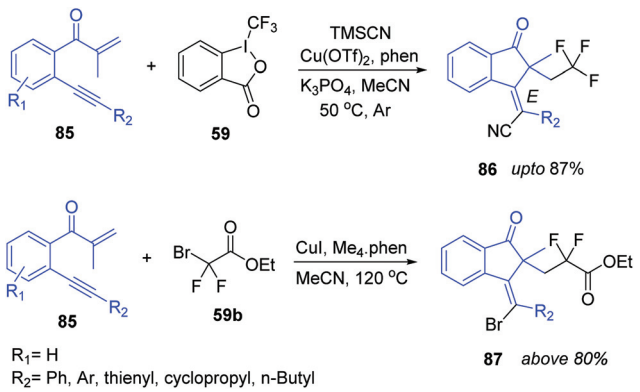
Scheme 18 The hydroxyl-directed aminoarylation of internal alkynes.

cheap, economical process which bears high atom economy and substrate scope and is conducted in one-pot operation without any external additive. In addition, oxazinane-fused isoquinolin-1(2*H*)-one could be obtained when substituted alkynyl-linked *N*-alkoxyamides were allowed to react with alkyne substrates after the length of the tether between the oxygen atom and the alkyne unit was restricted to three carbon atoms (Scheme 19).

Another reaction related to the use of Togni's reagent **59** is the use of $Cu(OTf)_2$ in catalyzing radical cyclization–cyanotrifluoromethylation of 1,6-enynes reported by B. Jiang and co-workers.[42b] In this reaction Togni's reagent is used as a radical initiator along with a CF_3 source and trimethylsilyl cyanide (TMSCN). The reaction leads to the formation of trifluoromethylated indanone derivatives **86** and **87** stereoselectively through a radical-induced cascade reaction promoted by a 1,10-phenanthroline (phen) ligand. The use of α-bromo ester **59b** with **85** gives a bromo indanone derivative **87** in the presence of CuI at elevated temperatures.[42c] The reaction passes through a radical-initiated 5-*exo-dig* cyclization and is only *E*-selective. Other advantages include atom-economical conversion and wide functional group compatibility (Scheme 20).



Scheme 19 Cascade annulations of alkyne-tethered N–alkoxyamides.



Scheme 20 The halofluoroalkylation and cyanotrifluoromethylation of 1,6-enynes.

4. Formation of alkenylboranes

The hydroboration of internal alkynes is a useful strategy for the synthesis of alkenylboron intermediates (Fig. 8).[43a–c] Organoboron compounds have a major role to play in organic synthesis because these molecules can be transformed into a plethora of functional units.[44]

Hence the borylation of alkynes and alkenes is constantly progressing. However, most of their syntheses are basically carried either with organometallic reagents or metal-catalyzed strategies.[45] The hydroboration process is formally initiated by σ-bond metathesis between the diboron reagent and alkyl copper ($Cu–OR_3$) species to form a boryl–copper intermediate.

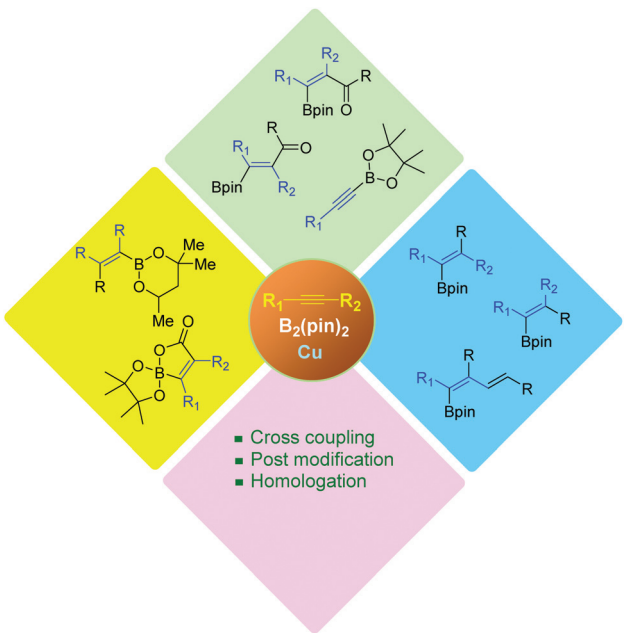
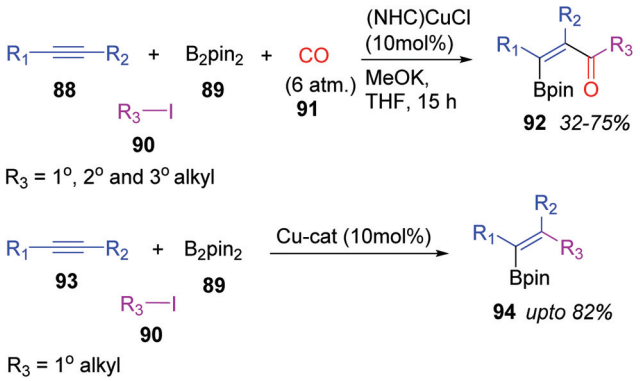


Fig. 8 General structures and applications of vinyl borates generated from internal alkynes.

This intermediate adds across the carbon–carbon triple bond of alkyne to give boryl-substituted alkenyl copper species which finally give the alkynylborane product after protonation (Fig. 9).[45d] Boron-substituted 1,4-dienes are important because of their utility in the Suzuki–Miyaura coupling reaction and conjugate additions and are also versatile building blocks for the synthesis of alkenes. Moreover, boryl–copper species add across the alkyne triple bond to form a more nucleophilic β-borylalkenylcopper intermediate[46a,b] which can further react in a catalytic cycle with nucleophiles like alcohols and amines to yield hydroboration products or may even react with carbon electrophiles to give carboborated products.[46c,d]

All carbon tetrasubstituted alkenylboronates are easily synthesized by carboboration of internal alkynes: for example, tetrasubstituted enones **92** are formed as a result of the reaction between internal alkynes **88**, diborane **89**, alkyl halide **90** and carbon monoxide **91** through a Cu-mediated multi-component coupling reaction in very mild reaction conditions.[47] Tetrasubstituted enones are formed by using β-borylated enones in a Suzuki–Miyaura coupling without the need for any purification. In addition, substituted allylic alcohols and ketones are formed as a result of oxidation, proto-deboration, and halogenation from reduced oxaborole substrates. Another method is the advent of Cu-catalyzed carbo-boration between internal alkyne **93**, B_2pin_2 and alkyl or aryl halides without the use of carbon monoxide to give tetrasubstituted alkenyl-boronate compound **94** (Scheme 21).

A new copper-catalyzed stereo- and regioselective hydroboration of internal alkynes was reported by Y. Tsuji and co-workers.[48] The reaction involves the use of unsymmetrical alkynes **95** and **99** and pinacolboranes **96** and **89** to yield α-substituted alkenes **97** and **100**. Me-Ar-Xantphos was highly efficient in the stereoselective formation of alkene, which could also be controlled in two different catalytic species ([LCuH] and [LCuB]) which are formed from H-Bpin and B_2pin_2. However, when B_2pin_2/MeOH was used in place of H-Bpin keeping CF_3Ar-Xantphos the same, reversal in the regioselectivity was observed to afford mostly the β-products in 74–94% yields. The scope of the reaction ranges from hetero-



Scheme 21 The borocarbonylative coupling of internal alkynes.

cyclic, aromatic and aliphatic substrates with 62–96% overall yields (Scheme 22).

On the other hand, regio-controlled borylated alkenes are formed in up to 81% isolated yields when polar-functionalized internal alkynes **101** react with the bis(pinacolato)diboron **102** in basic conditions in the presence of CuCl and PCy_3.[49] The reaction is driven by the presence of polar functional groups like NHTs, SO_2Py, ArS, OR, OTBS or OH on the internal alkyne part by promoting its Cu^I–PCy_3 complexation and β-site selectivity. The resulting vinylboronates can be further utilized for substitution at the allylic position and cross-coupling reactions. DFT calculations over the entire catalytic system are in accordance with the given regioselectivity and suggest a little orbitalic influence from the propargylic group due to the alkyne when matched with substrate and ligand size effects which is a key reason behind the β-selectivity of this reaction (Scheme 23).

J-Li Chao and co-workers reported the chemoselective formation of bulky silyl-substituted alkenes or vinylsilanes **105** and **106** in aqueous phase by using internal alkyne **103** and silyl-borate substrate $Me_2PhSiBpin$ **104**.[50a] The overall result of the reaction is the hydrosilylation of alkyne catalyzed by Cu $(OTf)_2$ in the presence of a bidentate ligand, 1,10-phenanthro-

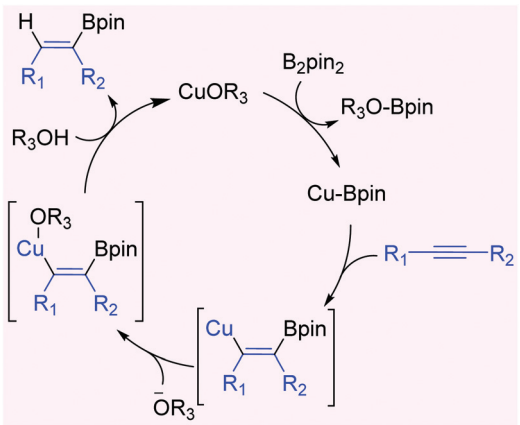
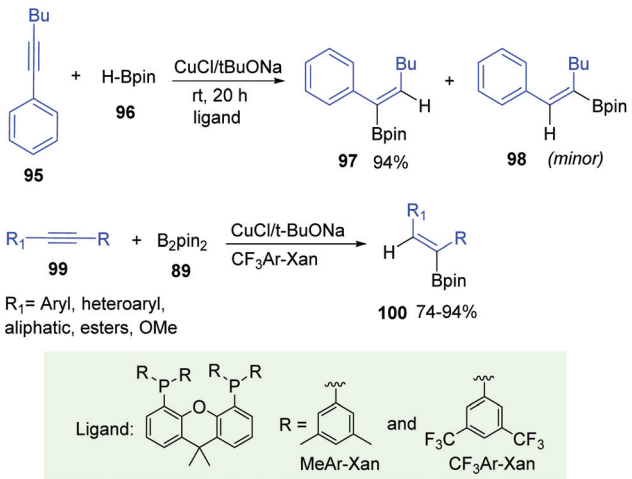
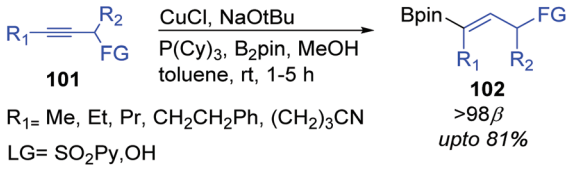


Fig. 9 The proposed catalytic cycle of alkynylboration.



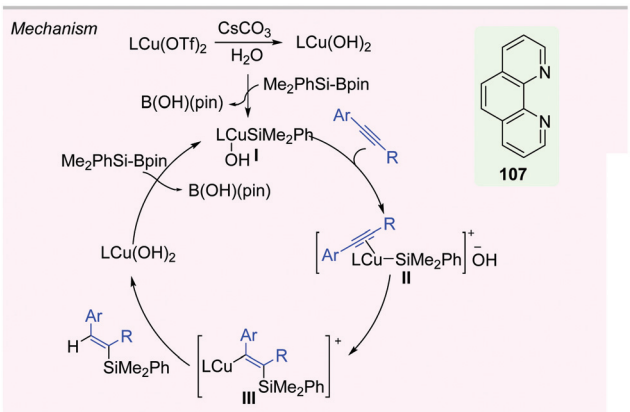
Scheme 22 The selective hydroboration of internal alkynes.



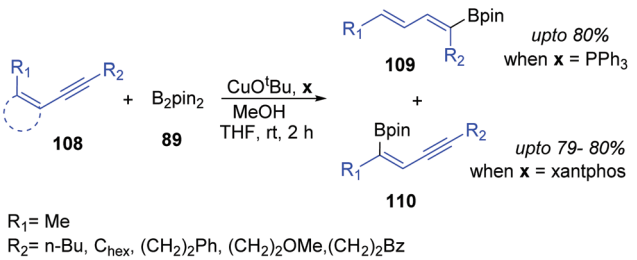
Scheme 23 The Cu^{I}-catalyzed borylation of functionalized internal alkynes.

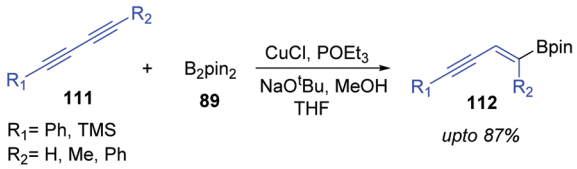
line **107**. Although other biphenyl and pyridyl ligands were used, they were not found to be very successful in product formation. This is another example of the synthesis of multi-substituted alkenes which can be further post-modified at the silyl center. The mechanism involves the silylcupration of the internal alkyne *via* transmetalation in which the complex LCu $(OTf)_2$ is changed to a more labile $LCu(OH)_2$ species by Cs_2CO_3 and H_2O followed by metathesis with silylborate [$Me_2PhSiBpin$] to form **I** which in turn coordinates with alkyne to give species **II**. Species **II** consequently intercepts the C–C triple bond to generate intermediate **III** which is finally hydrolyzed to vinylsilane (Scheme 24).

A regioselective copper-catalyzed borylation of 1,3-enynes was reported by H. Ito and co-workers[50b] for the synthesis of 3-alkynylboronates **110**, **112** and 1,3-dienylboronates **109**. Dienylboronates are formed in 80% yield when PPh_3 is used as a ligand source. In the case of 1,3-enyne **108** substrates the use of xantphos as a ligand selectively produced alkynylboronates **110** in 79–89% yields. The reaction is applied in cross-coupling and cycloaddition reactions. On the other hand, borylation of symmetrical and unsymmetrical conjugated diynes **111** furnishes enynylboronate compounds **112** stereoselectively in the presence of a combination of catalytic $CuCl_2$ and NaO*t*-Bu



Scheme 24 The hydrosilylation of unactivated internal alkynes.



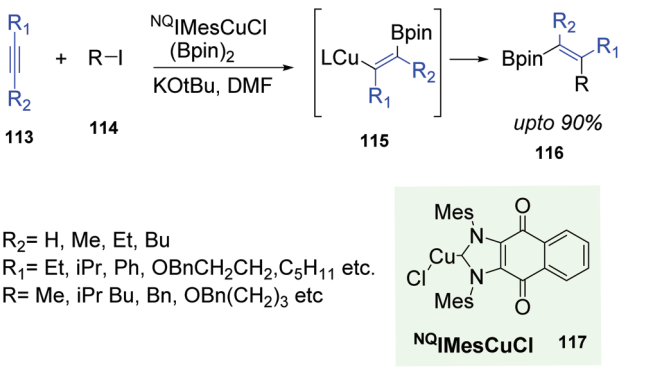


Scheme 25 The regioselective borylation of alkynyl and dienylboronates.

(Scheme 25).[50c] A similar type of stereoselective borylalkylation was reported by M. Kanai and co-workers[51] where internal alkynes **113** react with bis(pinacolato)diboron **89** in combination with butyl iodide **114** to afford trialkyl-substituted alkenylboronates **116**. Boryl copper species with a π-accepting naphthoquinone NHC copper-catalyst (^{NQ}IMesCuCl) **117** are necessary in order to control the chemo- and regioselectivity of the process. This is yet another example where alkenylboronates can easily undergo Suzuki–Miyaura coupling to afford tetrasubstituted alkenes (Scheme 26).

On the other hand, a ligand-free synthesis of tetrasubstituted alkenylboronates takes place *via* a three-component boroylalkylation reaction mediated by copper in the presence of bis(pinacolato)diboron [$(Bpin)_2$] and alkyl iodides.[52]

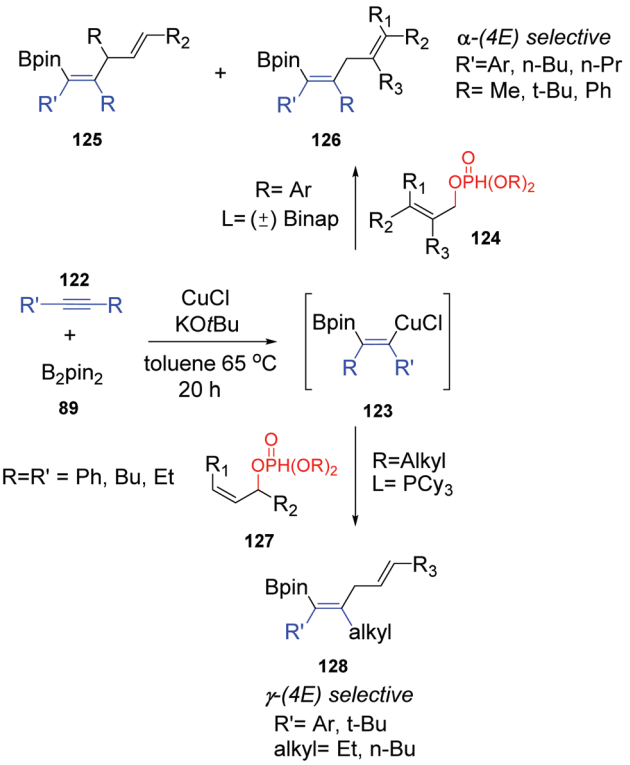
A copper-catalyzed synthesis of substituted vinylboronates was reported from alkyne **118** by C. S. J. Cazin and co-workers[53] in aerobic conditions. The important aspect is that the use of a single catalytic system [Cu(Cl)(IMes)] (IMes = *N*,*N*′-bis-[2,4,6-trimethylphenyl]-imidazol-2-ylidene) delivers carboborated **121**, α-hydroborated **120** and β-hydroborated **119** products in free atmosphere in CPME (cyclopentyl methyl ether) as a solvent. While pinacolboron gave an α-borated product in



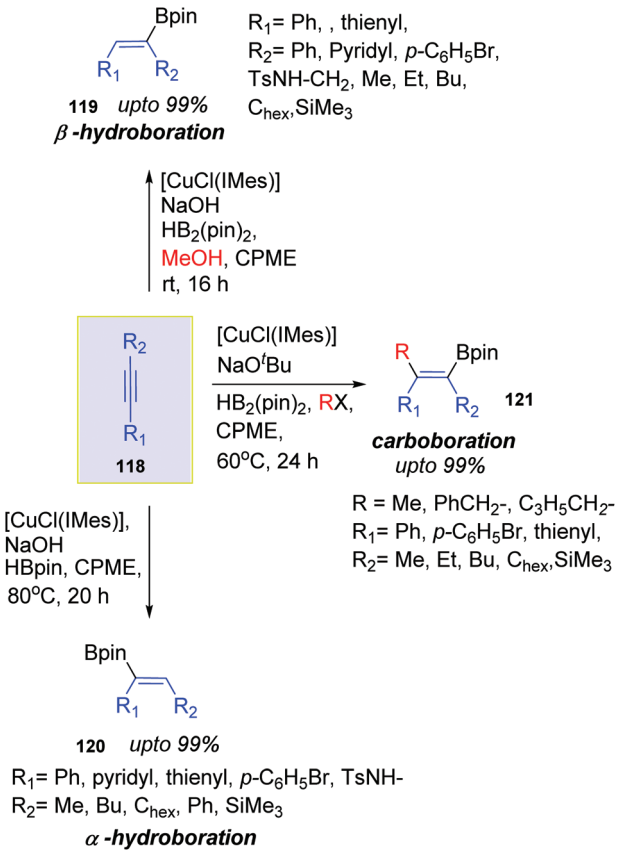
Scheme 26 The borylalkylation of internal alkynes.

basic conditions; bis(pinacolato)diboron afforded the β-hydroborated product in the presence of methanol. Adding an electrophile gave the tetrasubstituted vinylboronate product on (0.04–2 mol%) catalyst loading (Scheme 27). Recently, a new Cu-catalyzed boryl-allylation of alkynes for the synthesis of substituted dienes has been developed by Zhong and co-workers.[54] In this reaction, internal alkynes **122** react with allyl phosphates and bis(pinacolato)diboron **89** to yield boron-substituted 1,4-dienes. The regioselectivity of the new product completely relies upon the structure of the alkyne as well as allyl phosphate. Aryl group containing alkynes generate β-boryl-α-aryl-α-alkenylcopper **123** intermediates which immediately react with allyl phosphates **124** to form γ-(4*E*)-selective boron-substituted 1,4-dienes whereas α-selective boron-substituted 1,4-dienes are formed from primary allyl phosphates **127**. Poor regioselectivity is depicted by α-boryl–α-aryl–β-alkenylcopper species which are produced as a minor intermediate compared to secondary allyl phosphates forming a mixture of α- and γ-selective boron-substituted 1,4-dienes. The reactions with the primary allyl phosphates **127** are γ-selective with the retention of the configuration at the allyl phosphate chain (Scheme 28).

The reactions with the primary allyl phosphates **127** are γ-selective with the retention of the configuration at the allyl

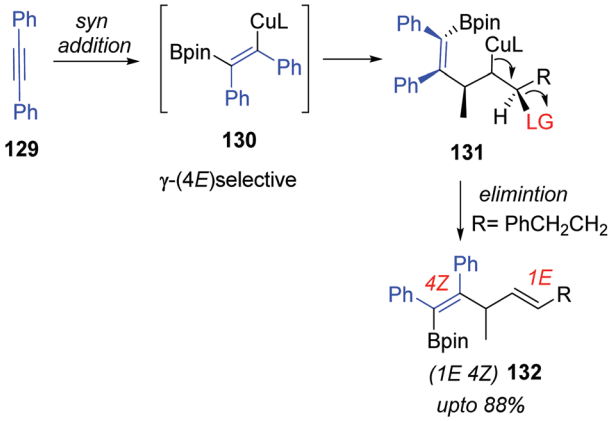


Scheme 28 The stereoselective synthesis of boron-substituted 1,4-dienes.



Scheme 27 The regioselective formation of tri- and tetra-substituted vinylboronates.

phosphate chain (Scheme 28). Basically, this copper-catalyzed reaction proceeds *via* an allylic oxidative addition followed by reductive elimination. The γ-selectivity of the reaction is achieved at the addition–elimination step by the *syn* addition of boryl copper ligands. For the γ-*E*-selective coupling reaction, β-borylalkenylcopper **130** adds across the C–C bond of **129** to form species **131** in a *syn* fashion. Intermediate **131** then affords a product with (1*E*,4*Z*) stereochemistry through stereoselective β-elimination (Scheme 29).



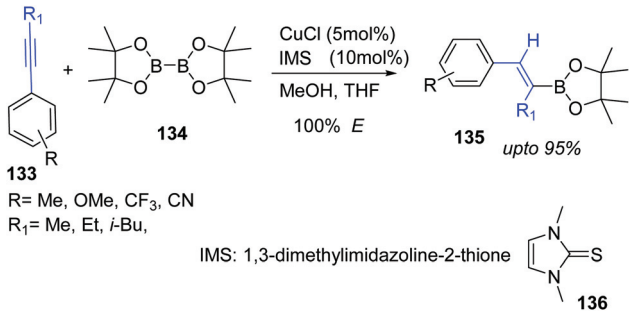
Scheme 29 The possible reaction mechanism of the γ-*E*-selective reaction of secondary allyl phosphates.

S. U. Son and co-workers[55] have developed an efficient and stereoselective boration of internal alkynes **133** by using a bis (1,3-dimethyl imidazoline 2-thione) **136** (**IMS**) based copper reagent system for the synthesis of alkenyl boranes **135**. Steric effects and electronic effects of alkyl and aryl groups influence the selectivity and rate of the reaction, respectively. Again, the alkene substrates so formed can be further utilized in many coupling reactions. Metal–ligand coordination was characterized by a slow diffusion technique in the solution phase to conclude that the Cu-intermediate attains a planar trigonal geometry with a coordination number of 3 and C_2 symmetry (Scheme 30).

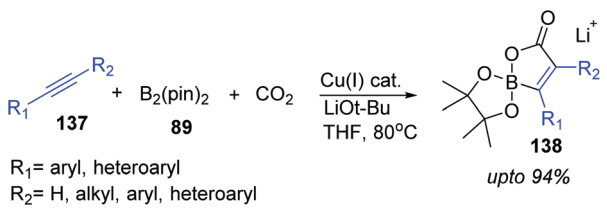
Diaryl alkynes and aryl alkynes **137** undergo boracarboxylation with diborane **89** and carbon dioxide in the presence of an NHC copper catalyst to form unsaturated boralolactone **138**.[56] The reaction is highly regio- and stereoselective and passes through a borylcupration and carboxylation cascade step which was proved by the isolation of the intermediate (Scheme 31).

A similar type of reaction takes place when unsymmetrical internal alkynes **139** undergo borylcupration with $B_2(pin_2)$ catalyzed by $CuCl/K_2CO_3$ and an electron-donating phosphorous ligand tris(*p*-methoxyphenyl) phosphine $P(C_6H_4OMe\text{-}p)_3$.[57] The reaction gives rise to *Z*-alkenyl boron compounds **140** in up to 88% yields stereo- and regioselectively. However, when employing bulky substituents like the *t*-Bu group **141** the yield was enhanced to 92%. In addition, using functionalized substrates like propargylic alkynes, the scope of the reaction also covers aryl, heteroaryl, naphthyl and alkyl substrates each with fixed *Z*-selectivity (Scheme 32).

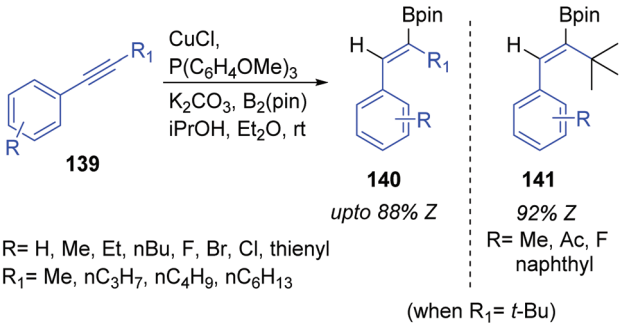
The synthesis of base-promoted Cu-catalyzed formation of alkenes using $B_2(pin)_2$ from internal alkynes has been



Scheme 30 The stereoselective borylation of internal alkynes.

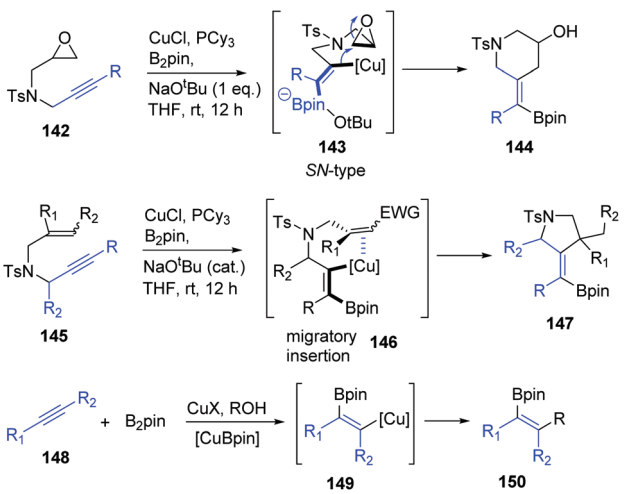


Scheme 31 The boracarboxylation of internal alkynes.



Scheme 32 The CuCl–K_2CO_3-catalyzed selective borylcupration of internal alkynes.

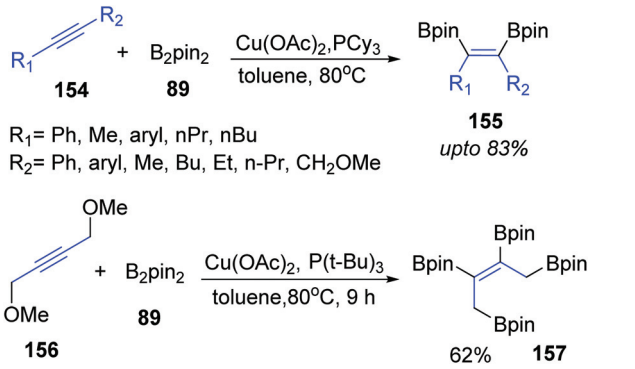
reported by Juan C. Carretero and co-workers.[58] In this reaction unsymmetrical alkyl substituted internal alkynes **142** and **145** react with boronates (B_2pin) in the presence of sodium *tert*-butoxide to form all carbon borylated alkenes. The reaction is highly stereoselective and involves borylcupration and subsequent intramolecular nucleophilic substitution on the epoxide to form the six-membered ring. The reaction may also accompany migratory insertion into alkene to yield **147** containing a five-membered ring. The role of NaO*t*Bu is crucial in generating the alkoxide ion CuOR which leads to the formation of the [RCu(O*t*Bu)-Na] complex. A boryl–copper species that is formed stereo- and regioselectively generates an alkenyl copper complex with more electron density which after SN^2 type nucleophilic attack at C2 gives piperidine analogue **144** *via* a six-membered transition state **143**. In another case, Cu coordinates to alkene through **146** before the migratory insertion takes place without the consumption of a second molecule of NaO^{t}Bu. **146** subsequently reacts with a suitable proton source to form five-membered pyrolidine analogue **147**. In contrast, carboboration of **148** leads to the formation of alkene **150** (Scheme 33).



Scheme 33 The carboboration of alkynes.

M. K. Brown and co-workers[59a] reported the carboboration of internal alkynes **151** for the synthesis of substituted vinylboranes **153** *via* a Cu-catalyzed cross-coupling of boronic esters with aryl iodides **152**. Two regiomers are obtained from unsymmetrical alkynes. The reaction proceeds *via* the insertion of an internal alkyne into the Cu–B bond to form a vinylcopper species followed by reaction with aryl halide **152** to furnish the desired product. Cu activates the alkyne and later on reacts with the arylhalide to form an Ar(HetAr)–Cu complex followed by insertion of the alkyne substrate. The reaction works efficiently for various aryl iodides and arylboronic esters as compared to Pd-catalyzed reactions and also shows orthogonal reactivity for the formation of vinyl boronic esters stereoselectively. The reaction can be used for the synthesis of Tamoxifen, an estrogen receptor antagonist (Scheme 34).

The diborylation of internal alkynes **154** with bis(pinacolato)diboron was reported by K. Takaki and co-workers and occurs in the presence of a PCy_3 ligand to form vicinal *cis*-diborylalkenes **155**.[59b] The method has scope over a range of substrates like aliphatic alkynes, including 2-octyne, 4-methyl-2-pentyne, 5-decyne, as well as aryl–alkylalkynes and diarylalkynes. Aryne substrates were also used in the reaction, which leads to the formation of vicinal *cis*-diborylbenzene products in up to 79% yields. An important characteristic of this catalytic system was observed in the reaction of internal alkyne **156** bearing OMe groups which exclusively formed tetraborylated product **157** in one pot when 3eq. of bis(pinacolato)diboron were used against 7 mol% of P(*t*-Bu)$_3$ (Scheme 35).



Scheme 35 The vicinal *cis*-di and tetraborylation of substituted internal alkynes.

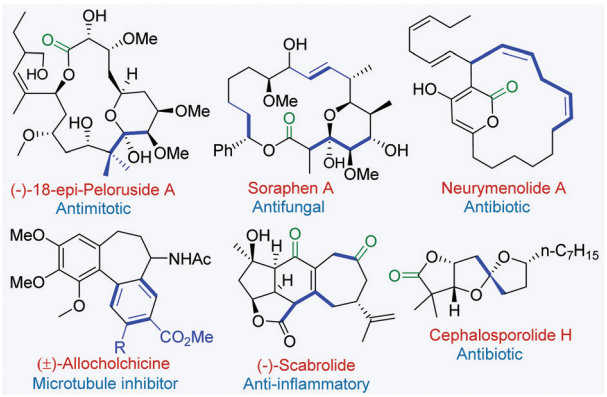
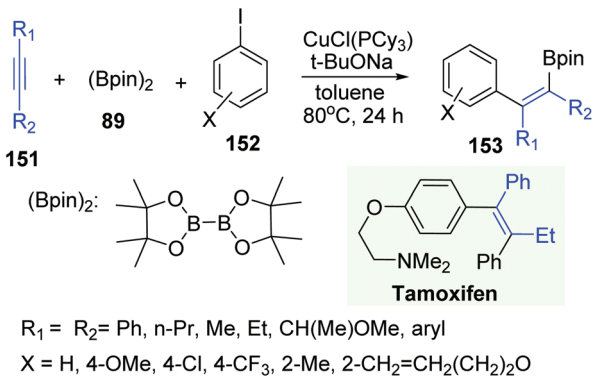


Fig. 10 Natural products synthesized from internal alkynes.

5. Formation of heterocycles

Alkynes are employed in total synthesis for the construction of medicinally important macrolides,[60] spiromolecules[61] and other intricate natural products (Fig. 10). It is not necessary to mention that interesting and highly reactive benzynes like cyclohexyne and the more elusive cyclopentyne intermediates are powerful tools for the synthesis of heterocyclics (Fig. 3).[62]

Mastral and co-workers[63] reported an intramolecular carboarylation cum cyclization of alkyne phosphonates **158** and **161** in the presence of diaryliodonium salts **159** for the preparation of bioactive cyclic phosphonates. These substituted phosphaisocoumarins **160** and **162** bear a structural resemblance to active inhibitors for pancreatic cholesterol esterase (Fig. 11). This reaction forms C–C/C–O bonds and can be used as heteroaryl and vinyl transferring agents. This transformation proceeds through a chemoselective arylation of internal alkyne **B** and then intramolecular trapping of vinyl cation **C** species by the phosphoryl group tethered to alkyne through the carbon chain (Scheme 36 and 37).



Scheme 34 The carboboration of internal alkynes into substituted vinylboranes.

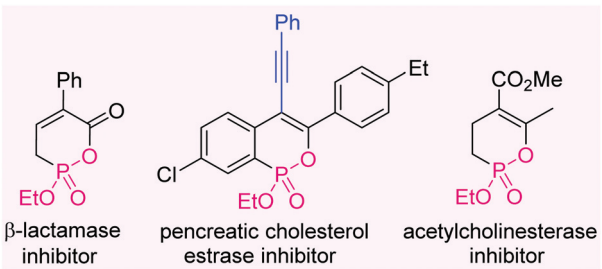
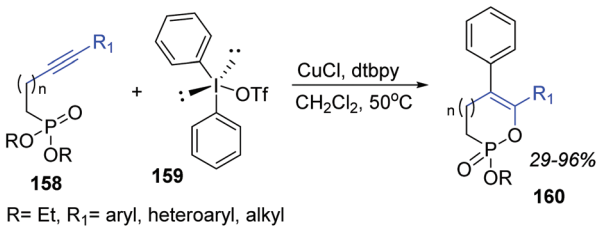
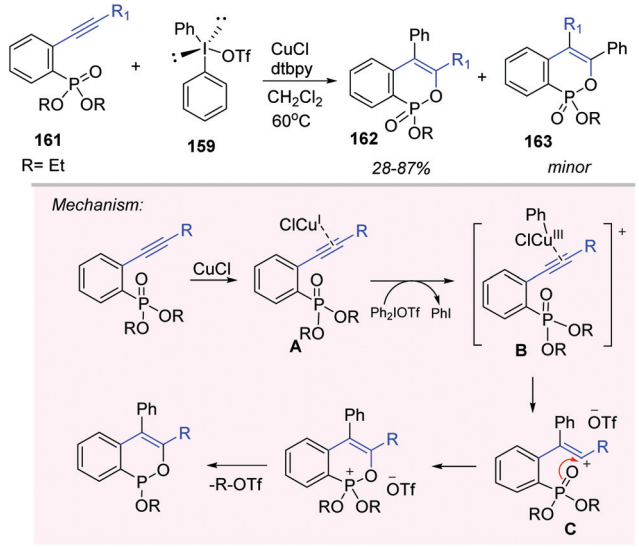


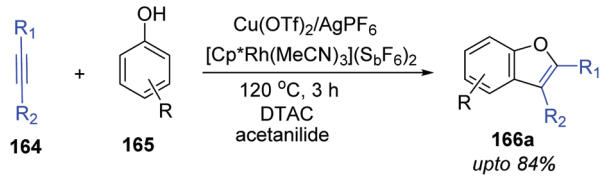
Fig. 11 Biologically active cyclic phosphonates.

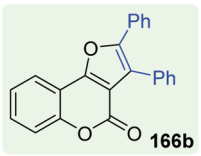


Scheme 36 The intramolecular carboarylation/cyclization of alkynyl phosphonates.

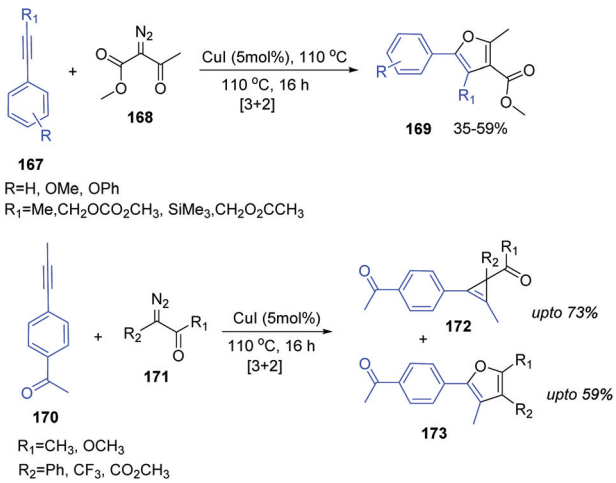


Scheme 37 The intramolecular carboarylation/cyclization of alkynyl phosphonates with diaryliodonium salts.





Scheme 38 Oxidative annulation for the synthesis of benzofurans.



Scheme 39 The [3 + 2] cycloaddition of internal aryl alkynes.

The mechanism involves the coordination of Cu(I) to alkyne to form intermediate **A** which oxidises upon reaction with aryldiazonium salt to form Cu-species **B**.

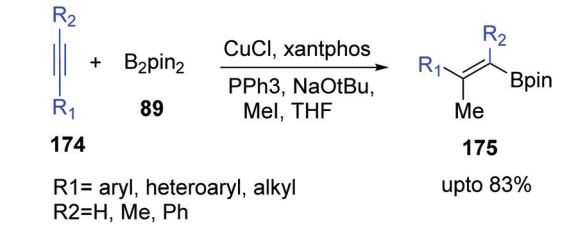
Formation of vinyl cation **C** occurs after intramolecular nucleophilic attack of the internal alkyne. The O-site of the phosphoryl group attacks intramolecularly in an Arbuzov alkyltriflate like elimination to give cyclic enol phosphate.

Work by Z. Shi and co-workers[64] led to the initial formation of benzofuran analogues **166a** and **166b** through Cu-catalyzed oxidative ring formation between phenols **165** and internal alkynes **164**. Different inactivated internal alkynes and phenols were tested with up to 84% product formation. The reaction involves the formation of an electrophilic carbo–cuprate complex with phenol which later on, with the insertion of internal alkyne followed by annulation, yields the desired benzofuran derivatives (Scheme 38).

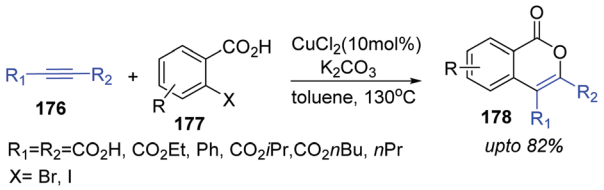
Substituted furans **169**, **172** and cyclopropenes **173** are conveniently formed as a result of [3 + 2] metal carbenoid cycloaddition of internal aryl alkynes **167** and diazoacetates **168** by using Cu(I) N-heterocyclic carbenes in a chemo- and regioselective manner.[65] The acetyl unit of the diazoacetate promotes ring formation in all reported cases. The electronically neutral as well as electron-rich alkyne substrates are able to insert into the C–H bond and silyl substrates and exclusively provide silyl-based furan building blocks. In contrast, the electron-releasing and withdrawing diazoacetates **171** furnish cyclopropenes **172** (Scheme 39).

The formation of pinacol boronic esters takes place in one step by a Cu(I)-catalyzed carboboration of internal alkynes **174** with bis(pinacolato)diboron in the presence of xantphos as a ligand.[66] Multisubstituted *syn* stereoselective vinyl boronic esters **175** can be obtained regioselectively. The products thus formed can further take part in cross-coupling reactions to form more substituted alkene analogues. Electron-releasing groups at *o* and *p* positions lower the rate of carboboration whereas electron-withdrawing groups exhibited excellent reactivity and selectivity. This reaction shows that Cu-catalyzed hydroboration can be trapped by electrophiles to produce substituted alkenes or conjugated alkenes (Scheme 40).

Isocoumarin-based products **178** were obtained when internal alkynes reacted with commercially available 2-iodo- and 2-bromobenzoic acids **177** in the presence of copper chloride.[67] Many activated alkynes are used in the reaction: for example, dimethyl acetylenedicarboxylate, *n*-butyl acetylenedicarboxylate and *n*-propyl acetylenedicarboxylate. The mecha-



Scheme 40 The Cu(I)-catalyzed methylboration of aryl-substituted alkynes.



Scheme 41 The synthesis of isocoumarin derivatives from internal alkynes.

nism is not fully understood, but a dimeric copper(II) carboxylate species is assumed to be the important intermediate associated with this reaction (Scheme 41).

An intramolecular copper-catalyzed cascade radical reaction of β,γ-tethered internal alkyne ketoximes **179** and **181** leads to the formation of isoxazoline derivatives **180** and **182**.[68] A library containing phenylacetylenes bearing electron-releasing and electron-withdrawing groups including naphthalein and thiophene substrates was used in the reaction which successfully led to the formation of corresponding isoxazolines **180** and **182**. During this reaction, an oxygen molecule is cleaved to generate iminoxyl radical **A** which then undergoes O/N 5-*exo-dig* cyclization to give **B** as they carry single-electron spin density delocalization on O as well as on the N atom (Fig. 12). ^{18}O isotopic labeling studies show that the O atoms of the

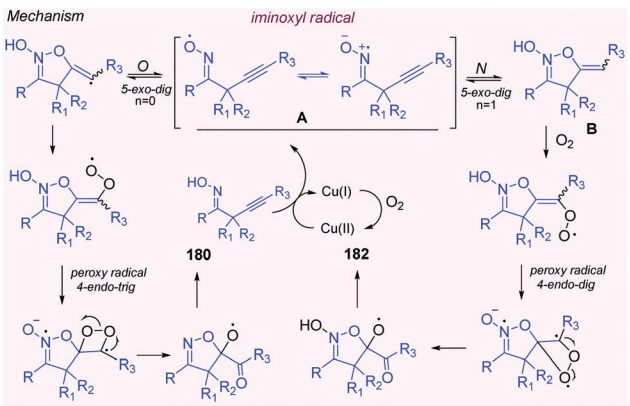
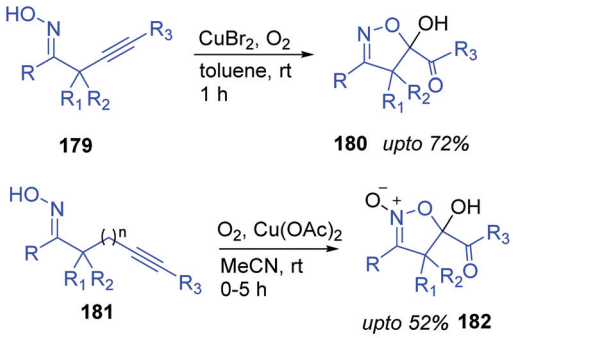
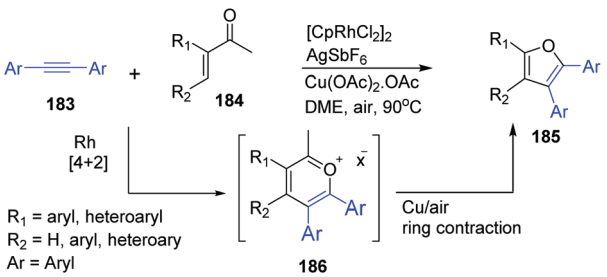


Fig. 12 The proposed cascade radical reaction mechanism for the synthesis of isoxazoline derivatives.



Scheme 42 The Cu-catalyzed cascade radical reaction for the synthesis of isoxazoline derivatives.



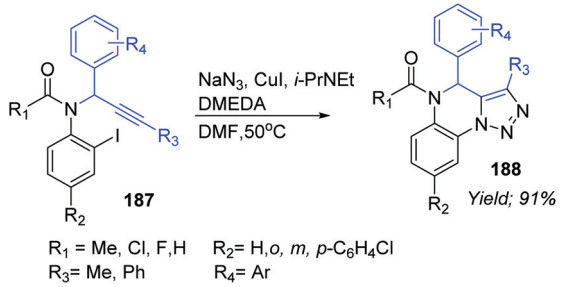
Scheme 43 The vinylic C–H activation of internal alkynes to substituted furans.

hydroxyl and carbonyl groups come from the oxygen molecule (Scheme 42).

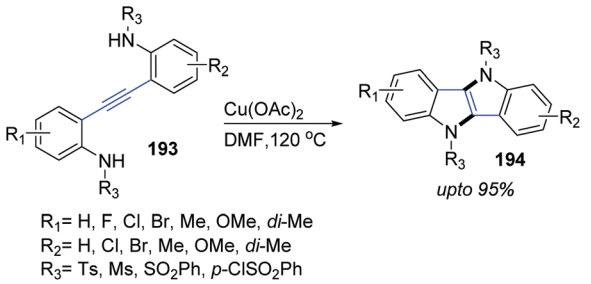
The formation of substituted furans **185** may take place through vinylic C–H activation when internal alkynes **183** react with α,β-unsaturated ketones **184** in a [4 + 2] cycloaddition manner.[69] According to the ^{18}O-labelling studies the O atom in furan is delivered from α-aryl-enones. However, the O atom from H_2O may also be transferred into the product through oxygen interchange with α-aryl-enones. The first process generates a pyrylium intermediate catalyzed by an Rh-catalyst and a Lewis acid followed by ring contraction in the next step that is catalyzed by $Cu(OAc)_2$ (Scheme 43).

Quinoxalines have been studied for their importance in antiviral, anticancer, antibacterial, anti-inflammatory and kinase-inhibiting properties. Y. Zhu and co-workers[70] reported an intramolecular reaction of aryl iodide tethered internal alkynes **187** and sodium azide catalyzed by copper iodide for the construction of [1,2,3]triazolo[1,5-*a*]quinoxalines **188**. This is basically the combined application of azide–alkyne cycloaddition (CuAAC) and Ullmann-type coupling. A triazole–copper or an arylazide are assumed to be the intermediates involved during the processes (Scheme 44).

Internal alkynes **189** may react through Cu-catalyzed N-heterocyclic carbenes to form triazoles **190** and **191**, a well-



Scheme 44 Copper(I) iodide catalyzed reactions of *N*-propargyl-*N*-(2-iodoaryl)amides.



Scheme 46 The cascade annulation of diarylalkyne sulfonamides through dual C–N bond formation.

known pharmacophore with a range of interesting biological properties.[71]

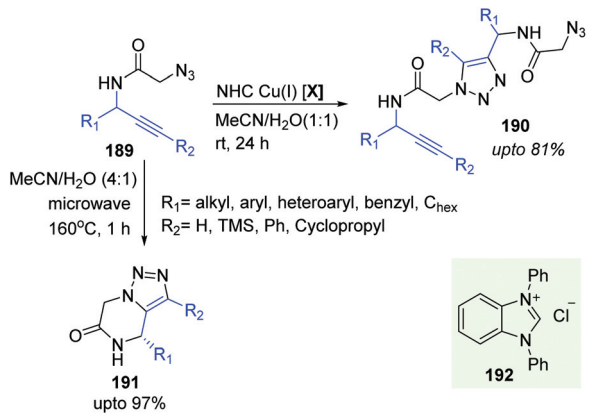
This is an example of cycloaddition of 2-azidoacetamides on alkynes assisted by microwaves to form trisubstituted triazole skeleton derivatives with an amino methyl group at the stereocenter. This is an important example demonstrating the use of silyl alkynes as unique substrates for CuAAC with suitable coupling partners. The products thus formed may be transformed into unnatural peptides and can be applied to study conformationally constrained peptides in medicinal chemistry (Scheme 45).

A Cu-catalyzed reaction involving intramolecular cyclization of diarylalkyne sulphonamides **193** leads to the formation of biologically important indole derivatives **194**.[72] The presence of a sulfonyl functional group is crucial in accelerating the nucleophilic reaction as well as providing protection for the amide moiety. This process is a two-step cascade reaction involving the ligation of Cu to the alkyne function followed by the loss of an acetate ion and a subsequent intramolecular nucleophilic reaction by nitrogen (Scheme 46).

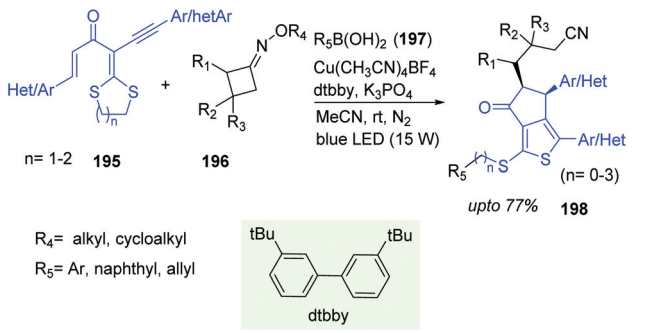
An interesting light-induced multicomponent reaction between alkylthio alkynes **195**, cycloxime esters **196** and boronic acids **197** was reported by Z. Yu and co-workers to produce aryl 2-thienyl sulfides **198**.[73] This is a Cu-catalyzed chemo- and diastereoselective reaction and takes place in the presence of 10 mol% $Cu(CH_3CN)_4BF_4$, dtbbpy, and K_3PO_4 irradiated by blue LED. The process is assumed to be controlled by electronic factors and steric constraints of the substrate. The reaction bears a wide scope for internal alkynes, oxime esters and boronic acids and the products can be post-modified easily into other useful derivatives. Steric and electronic effects control the diastereoselectivity of the reaction with heteroaryl boronic acids like 2-thienyl and 2-furyl boronic acids furnishing trace quantities of the desired products (Scheme 47).

Another Cu-catalyzed base-mediated intramolecular hydroamination reaction of internal alkynes **199** for the construction of tricyclic indole derivatives **200**, **201** and **202** was reported by M. Jha and co-workers.[74] The reaction takes place in the presence of CuI and triethylamine after alkynes tethered with indole sulfides **199** are heated to 100 °C. The formation of a five- to eight-membered ring can occur depending upon the alkyne moiety through hydroamination to yield an exocyclic and internal pi-bond containing indole tricycles (Scheme 48).

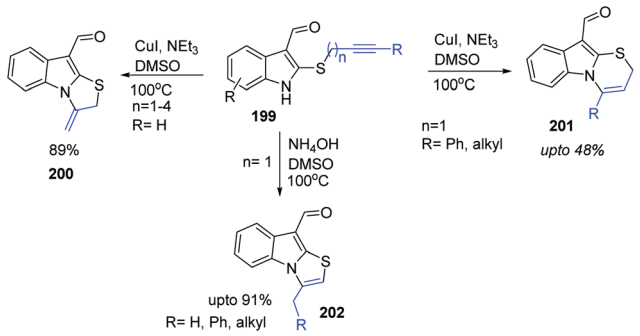
The insertion of non-toxic and abundant CO_2 into C–C bond formation is usually challenging. In this respect, Y. Tsuji and co-workers[75] reported a copper-catalyzed selective synthesis of α,β-unsaturated silalactone **205**, **209** which is a rare heterocycle formed as a result of silacarboxylation of internal alkynes **203**, **207** in the presence of carbon dioxide and silylborane **204**, **208** with $[CuCl(PCy_3)]_2$. The reaction proceeds with aryl, substituted aryl and aliphatic type substrates with 94–84% yield in 1-phenyl-1 propyne and up to 92% yield (ee =



Scheme 45 The Cu-NHC-catalyzed cycloaddition of azido-substituted internal alkynes.



Scheme 47 The three-component annulation of *gem*-dialkylthio enynes.

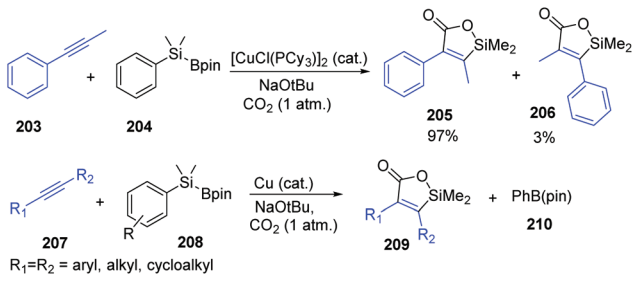


Scheme 48 The hydroamination of alkynes to give indoles.

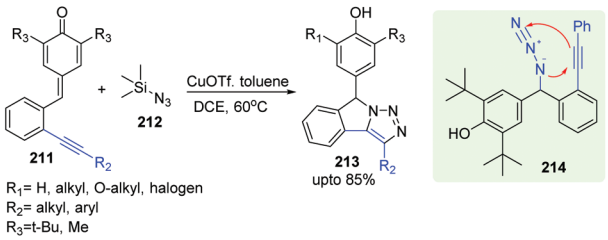
98 : 2) with other internal alkynes. The reaction of an alkoxo-copper complex with silylboranes affords silylcopper species which add to the alkyne in a *syn*-addition fashion to generate β-silylalkenylcopper species. As a result insertion of CO_2 into the Cu–C(vinyl) bond takes place to give a copper carboxylate intermediate which subsequently undergoes intramolecular cyclization to form a phenylcopper species by extrusion of silalactone. The application of such silalactone substrates can be highlighted in Hiyama cross-coupling reactions (Scheme 49).

In yet another Cu-catalyzed reaction, quinone-based internal alkynes **211** react *via* [3 + 2] cycloaddition with trimethylsilyl azide **212** to yield triazoles **213**.[76] This reaction takes place when Michael addition of trimethylsilyl azide occurs on *o*-alkynylated *p*-quinone methide which later on undergoes [3 + 2]-intramolecular cycloaddition. Various tricyclic fused 1,2,3-trazoles and isoindoline derivatives are formed in good yields. Mechanistically, *o*-alkynylated *p*-quinone methide is most likely to undergo 1,6-conjugate addition with Me_3SiN_3 which after an intramolecular click reaction through azide intermediate **214** (confirmed by NMR and IR studies) furnishes triazole-fused isoindoline analogues (Scheme 50).

Internal alkynes **215** and terminal alkynes **218** react in 1,4-dioxane under reflux in microwave conditions to form five-, six- and seven-membered N-heterocycles.[77] The reaction is actually hydroamination/alkynylation and simply occurs in the presence of eco-friendly copper bromide (5 mol%). Attempts to form three- and four-membered rings were unsuccessful and mechanistic understanding highlights that hydroamination



Scheme 49 The silacarboxylation of internal alkynes into silalactones.



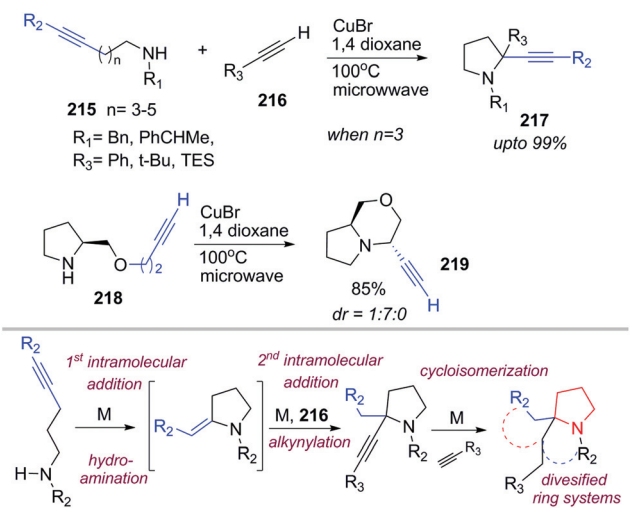
Scheme 50 The [3 + 2] cycloaddition of internal alkynes to obtain 1,2,3-triazole-fused isoindolines.

and alkenylation steps involve two intramolecular additions followed by isomerization. This method provides direct formation of functionalized 1,*n*-enynes **217** and fused-ring systems **219** with secondary cyclic amines (Scheme 51).

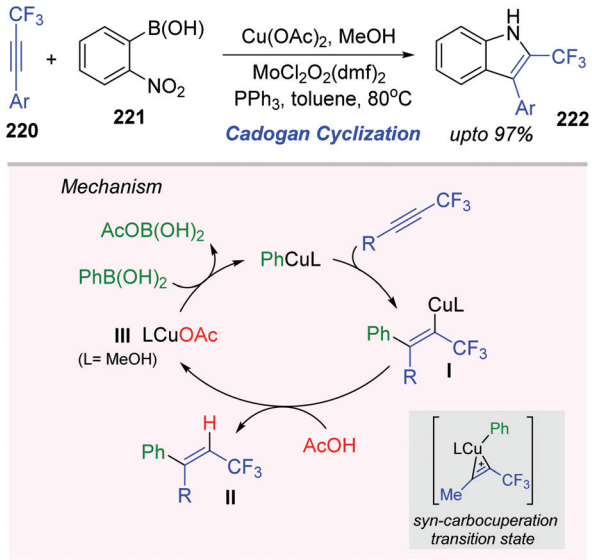
In another similar approach, trifluoromethane-substituted alkynes **220** react with aryl boronic acids **221** through hydroarylation in a Cu-catalyzed transformation to form indole analogues **222.** Arylboronic acid with *o*-nitro substitution drastically controls regioselectivity during carbometalation after which the nucleophilic addition of the resulting alkenyl-metal intermediate takes place followed by Cadogan reductive cyclization mediated by a triphenylphosphine and molybedinium complex.[78]

This reaction is useful for the synthesis of biologically active substituted indoles (Scheme 52).[79]

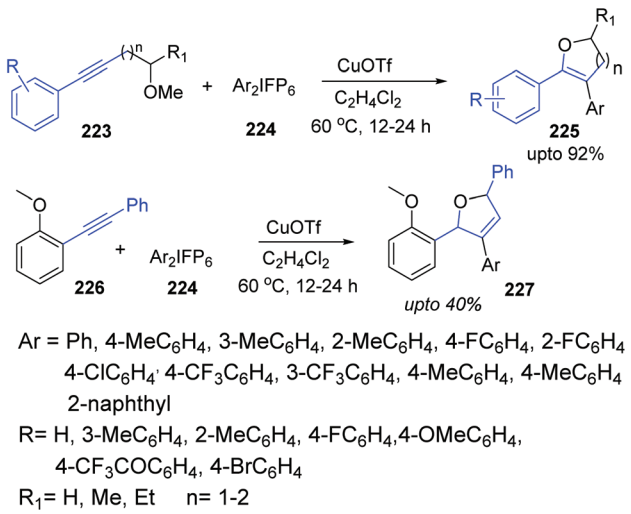
Qu H. and co-workers[80a] have developed a copper-catalyzed intramolecular aryl-etherification of a remotely situated alkoxy group containing internal alkynes **223** and **226** with diaryliodonium salt **224** through the cleavage of a stable C–O bond to form oxoheterocycles **225** and **227**. The vinyl cation generated in the process undergoes copper-catalyzed alkoxylation to form benzofurans, dihydrofurans and dihydropyrans (Scheme 53). Similarly, a single-step Cu-catalyzed cyclization–halogenation–



Scheme 51 The cyclization-triggered addition of internal alkynes into N-heterocycles.

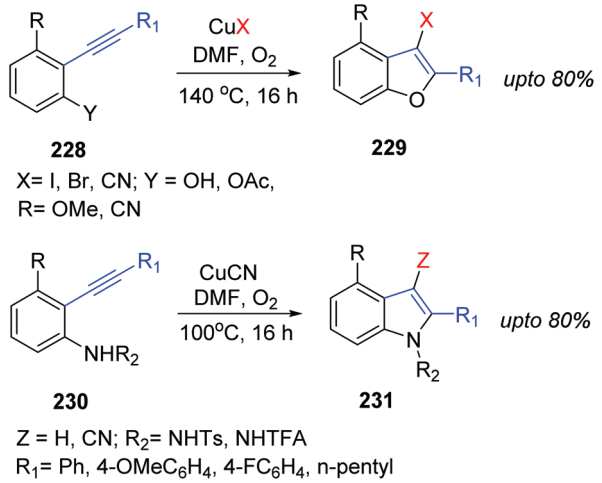


Scheme 52 The hydroarylation of internal alkynes with aryl boronic acids.



Scheme 53 The aryl-etherification of internal alkynes.

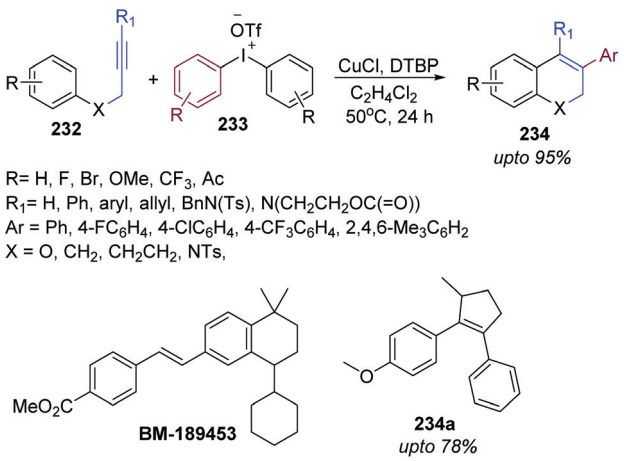
cyclization reaction was reported by Stephen G. Pyne and co-workers[80b] in which *o*-alkynylphenols and their acetyl derivatives **228** yielded 3-substituted benzofurans **229**. When the reaction is carried out in presence of CuCN at a slightly lower temperature *o*-alkynyl aniline substrates **230** yield cyanoindoles **231** in up to 84% yields. All the substrates employed in the reaction gave quantitative yields, but the methoxy derivative (R = OMe) produced too many by-products during the reaction. Only soft amine nucleophiles underwent fast annulation with the Cu–alkyne complex intermediate which is a relatively soft electrophile. Non-aromatic substrates (R = *n*-pentyl) gave iodinated and cyanated derivatives in the presence of copper iodide and copper cyanide (Scheme 54).



Scheme 54 The synthesis of 3-substituted benzofurans and cyanoindoles.

Gaunt M. J and co-workers[81a] reported the alkenylation of C–halogen bonds through copper-catalyzed carboarylation of internal alkyne **232** and $Ph_2I(OTf)$ **233** to give 1,2-dihydronaphthalenes or chromenes **234**. This is an intramolecular annulation that takes place in DTBP (2,6-di-*tert*-butylpyridine) as a base and anisole as a nucleophile. Mechanistically, Cu(I) activates diaryliodonium salt to generate a tri-substituted vinyl cationic intermediate (Scheme 55). The same research group reported a Cu-catalyzed cascade process for the synthesis of cyclopentenes **234a** and BMS-189453, a retinoid receptor agonist that shows a male contraceptive property.[81b]

Synthesis of substituted pyranes **237** through cyclization can be initiated by the activation of carbon–halogen bonds.[82] For instance, 3-iodo-indole-2-carboxylic **236** acid reacts with internal alkynes **235** through a copper-catalyzed reaction to give tricyclic indolopyranone and thienopyranone **237** with tolerance for various functional groups. When the iodo group in



Scheme 55 The carboarylation of internal alkynes *via* the alkenylation of C–halogen bonds.

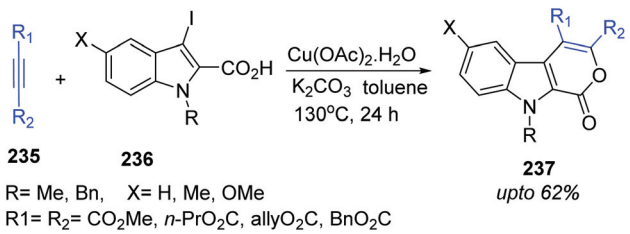
indole-2-carboxylic acid is replaced by a bromo group, the same product is formed in a very limited quantity (42%) (Scheme 56).

A unique asymmetric borylalkenylation of internal alkynes **238** with cyclohexadienone at one of its sp^3 carbons and bis (pinacolato)diboron takes place through a Cu-catalyzed cyclization process.[83a] The reaction takes place in the presence of a chiral naphthyl based phosphorous ligand **I** and selectively carries β-borylation followed by 1,4-addition to the cyclohexadienone moiety. As a result, optically pure *cis*-hydrobenzofuran derivative **239** is formed in an *enantio*- and regioselective manner, which can be further transformed into other bridged and tricyclic compounds like methyl ketones without the loss of enantiomeric excess (Scheme 57).

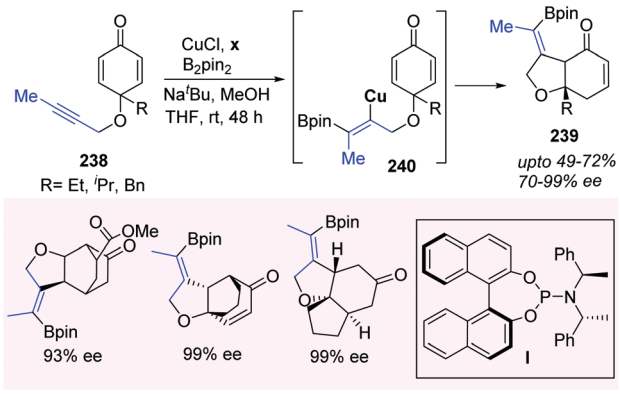
A copper-mediated mild cyclization of aminoalkynes **240** with terminal alkynes **241** for the synthesis of tetrahydropyrroloquinoline derivatives **242** was reported by Z. H. Yong and co-workers.[83b] Many substituted tetrahydropyrroloquinoline scaffolds were synthesized under microwave irradiation in 84–91% yield. Steric effects rather than electronic effects are known to facilitate the regioselectivity in this reaction (Scheme 58).

A reaction highlighting the role of 1-iodoalkynes **243** and **244** azides in the formation of triazoles **245** was reported by V. V. Fokin and co-workers.[83c] In this reaction, 5-iodo-1,2,3-triazoles **245** are formed in up to 98% yield and can be further post-functionalized into useful molecules. Uses of starting substrates are advantageous in many ways because of their increased stability, accessibility and their reactivity, which surpasses that of the terminal alkynes. In addition, products can be obtained in gram-scale quantities with tolerance to many sensitive functional groups. The overall reaction is azide–iodoalkyne cycloaddition, which is similar to the conventional CuAAC reaction and is also a desirable method for orthogonal chemical ligation (Scheme 59).

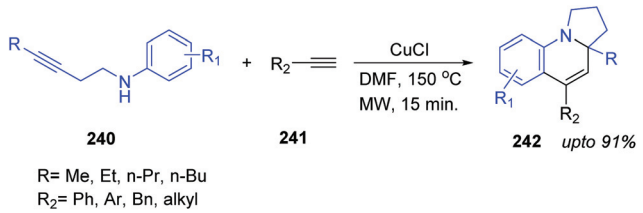
Recently, a radically induced novel Cu-catalyzed reaction of enyne nitrile **245a** (R = N) and enediyne **245a** (R = C–R) led to difluoromethylation and trifluoromethylation with subsequent spirotricyclization processes and produced *para*-quinone methide (*p*-QM) compounds.[83d] This method is used for the synthesis of very useful cyclohexadienone-based five-membered cyclic spiroindene substrates **245b** and **245c** in a regioselective manner in very efficient yields (Scheme 60). The mechanism of the reaction shows the formation of a complex trifluoromethyl or difluoromethyl radical induced 1,6-addition through Baldwin rules like 6-*exo-dig*, 6-*endo-trig* and 5-*exo-dig* tricyclization. The construction of an additional three rings takes place directly by the formation of four new chemical bonds through a single electron transfer (SET) mechanism in one step. The reaction is also distinguished by excellent substrate scope with respect to aryl groups and its multiple bond-forming capability, cyclization process, and regioselectivity.



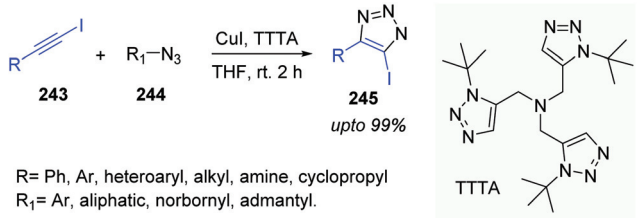
Scheme 56 The activation of carbon–halogen bonds to give pyranes from internal alkynes.



Scheme 57 The Cu-catalyzed asymmetric borylative cyclization of 1,6-enynes.



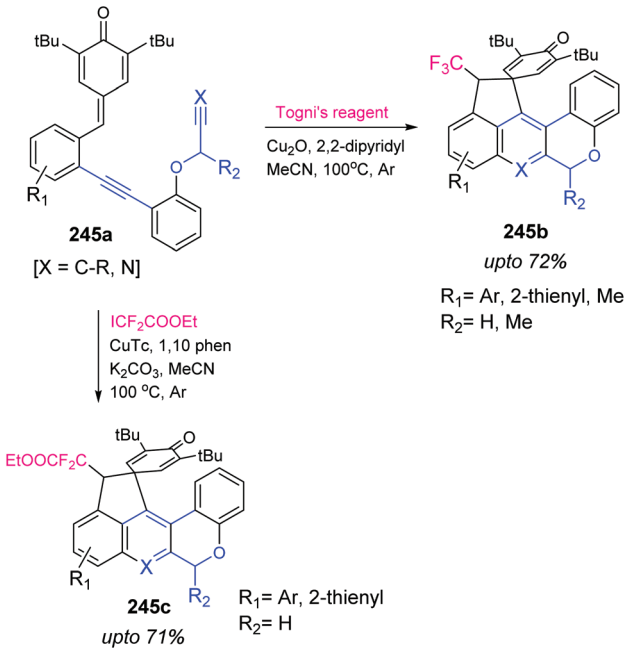
Scheme 58 The synthesis of tetrahydropyrroloquinolines.



Scheme 59 Copper(I)-catalyzed azide–iodoalkyne cycloaddition.

6. Cu as a co-catalyst/synergic catalysis

Cu has been employed as a co-catalyst in a number of reactions with different metals: *e.g.* Ni, Zn, Pd, Rd, and Rh[84] During these reactions, Cu may work as a cross-coupling agent, Lewis acid, oxidizing agent or activating agent for the nucleophilic attack. Furthermore, co-metals taking part in the



Scheme 60 Copper-catalyzed spirotricyclization for the synthesis of pentacyclic spiroindenes.

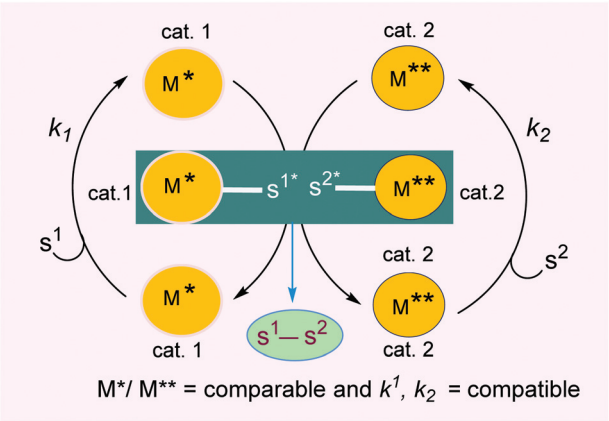


Fig. 13 A general representation of synergistic dual-metal catalysis.

reaction must activate the substrates [S^1] and [S^2] into cat.1 M*-[S^1] and cat.2 M**-[S^{2*}] with similar activation rates (k_1 and k_2) so that the reaction performance can be significantly improved by the catalysts, which could lower the activation energy barrier to achieve high selectivity and yields, thereby reducing the possibility of decomposition of the reactants (Fig. 13).

Transformation of alkynes into allenes was described by C. Li and co-workers.[85] The reaction starts with 1,3-enyne system **246** to afford corresponding bis-trifluoromethylated allenes **247** stereoselectively through a Cu-mediated allenyl radical pathway.

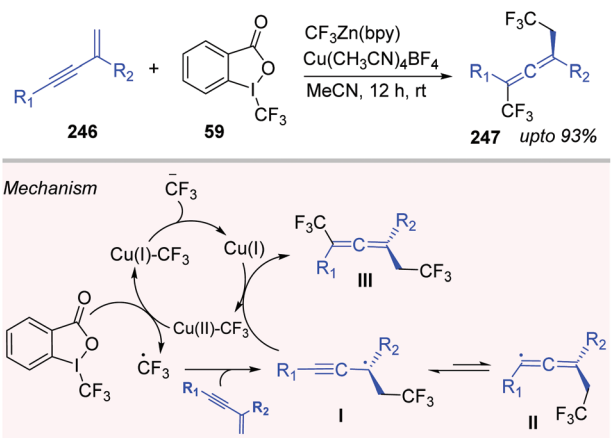
The catalyst, $Cu(CH_3CN)_4BF_4$ was employed along with Togni-II-CF_3 reagent **59** and (bpy)$Zn(CF_3)_2$ reagents were used during the reaction. Besides showing good reaction scope, the reaction also proceeds with overall 93% isolated yields. Although excellent stereochemistry was observed in most of the substrates employed in the reaction, alkyl-substituted alkyne substrates exhibited poor efficacy and stereoselectivity (Scheme 61).

Mechanistically, (bpy)$Zn(CF_3)_2$ and $Cu(CH_3CN)_4BF_4$ are assumed to generate a Cu(I)–CF_3 complex which undergoes single-electron transfer SET with Togni-II-CF_3 reagent to generate a CF_3 radical and Cu(II)–CF_3 species. 1,3-Enyn undergoes addition by a CF_3 radical to form **I** which is in equilibrium with more reactive allenyl radical **II**. Finally propargyl radical **I** or **II** is intercepted by Cu(II)–CF_3 *via* the tautomeric form of **I** to yield the bis(trifluoromethylation) product **III**.

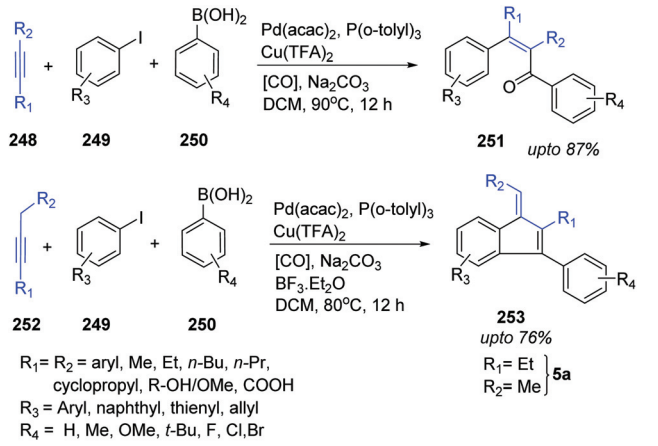
A multicomponent copper-mediated and Pd-catalyzed carbonylation[86] takes place between internal alkynes **248** and **252** with substituted aryl boronic acids **250** and aryl halides **249** to give substituted α,β-unsaturated ketones **251** and benzofulvenes **253** when carbon monoxide is pumped into the reaction mixture. The reaction occurs in the presence of catalytic amounts of $Pd(acac)_2$ and $Cu(TFA)_2$ as an additive and proceeds stereo- and regioselectively.

The addition of more $Cu(TFA)_2$ led to the formation of indene in small quantities. Mechanistically, there was no interchange between benzofulvene and enone and the reaction between phenylboronic acid and indenone did not lead to the formation of benzofulvene (Scheme 62).

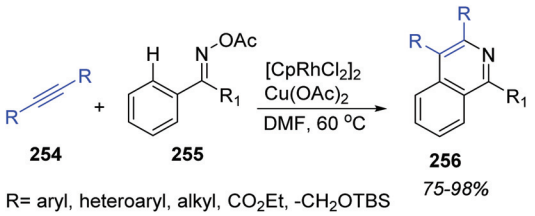
Isoquinoline derivatives **256** are formed when diphenyl acetylenes **254** react with aryl *O*-acetyl oximes **255** by employing $Cu(OAc)_2$ and chiral ligand $[Cp^*RhCl_2]_2$ as relay catalysts (Scheme 63).[87] The reaction is applicable to both *E* and *Z*-oximes and heterocycles like indole, benzofuran, furan and thiophene based oximes including aromatic and aliphatic alkyne substrates. Oxidative addition of *O*-acetyl generates iminyl Cu(III) followed by the reduction of oxime through Cu(I)



Scheme 61 The Cu-catalyzed radical bis(trifluoromethylation) of internal alkynes.



Scheme 62 The four-component carbonylative synthesis of enones and benzofulvenes.



Scheme 63 The Cu–Rh-mediated synthesis of azaheterocycles from internal alkynes.

species to give **III** which further undergoes N–O bond cleavage to generate N-radical species **IV** to form iminyl Cu(II) intermediate **V** after reduction by Cu(I). As a result, the five-membered rhodacycle **VII** is formed from iminyl Cu(I) species **V** with Rh(III) iminyl rhodium **VI** *via* the loss of a proton. The insertion of alkyne into **VII** followed by reductive elimination *via* C–N bond cleavage gave the final isoquinoline product **256** (Fig. 14).

The late-stage synthesis of three-membered mesoionic heterocycles **259** through C–H activation of internal alkynes **257** and sydnones **258** has been reported by Xingwei Li and coworkers.[88] The reaction is catalyzed by Rh(III) and $Cu(OAc)_2$ and is very efficient, taking place under mild conditions. A high catalyst loading and temperature in MeOH are important for the reaction. The C–H activation is assumed to occur competitively at the hindered *o*-site by dehalogenation. The product can also be modified in the late-stage process with excellent yield up to 98%. The catalytic cycle initiated by cyclometalation of sydnone by [RhCp*X_2] (X = SbF_6 or OAc) to give species **I** which after rollover C–H activation forms Rh(III) intermediate **II** followed by the insertion of an internal alkyne to give rhodacycle **III**. Reductive elimination of seven-membered rhodacycle **III** affords the final quinoline-fused sydnone product (Scheme 64).

Construction of substituted furans **262** may take place through vinylic C–H activation when internal alkynes **260** react

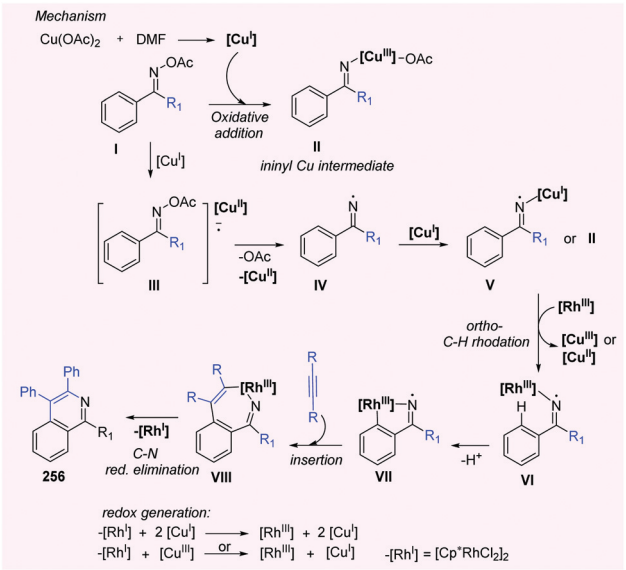
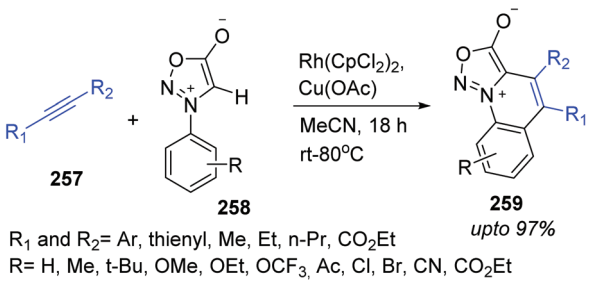
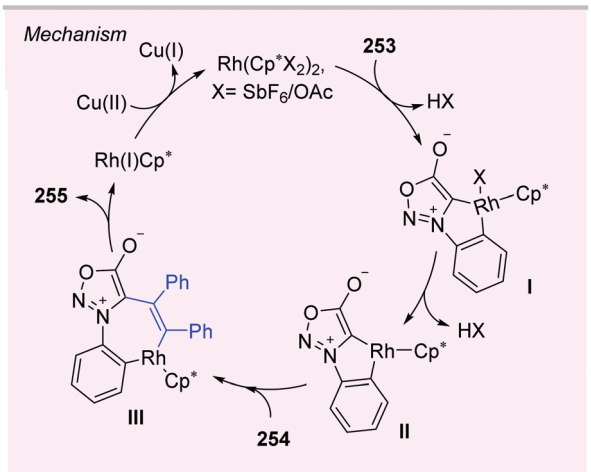


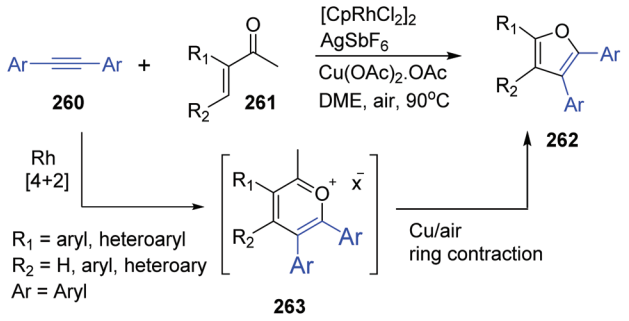
Fig. 14 The proposed reaction pathway for the synthesis of azaheterocycles.





Scheme 64 The oxidative synthesis of quinoline-fused sydnones *via* 2-fold C–H activation.

with α,β-unsaturated ketones **261** in a [4 + 2] cycloaddition manner. The first process generates the pyrylium intermediate **263** catalyzed by a Rh-catalyst and Lewis acid followed by ring contraction in the next step catalyzed by $Cu(OAc)_2$ (Scheme 65).[89]



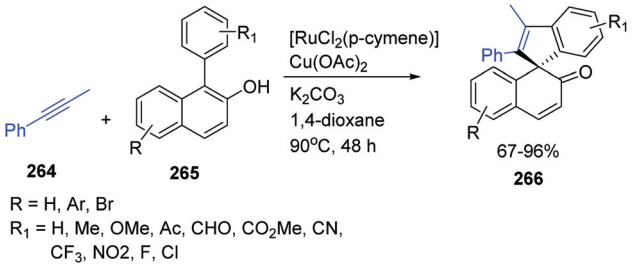
Scheme 65 Cascade [4 + 2] vinylic C–H *O*-annulation and ring contraction with internal alkynes.

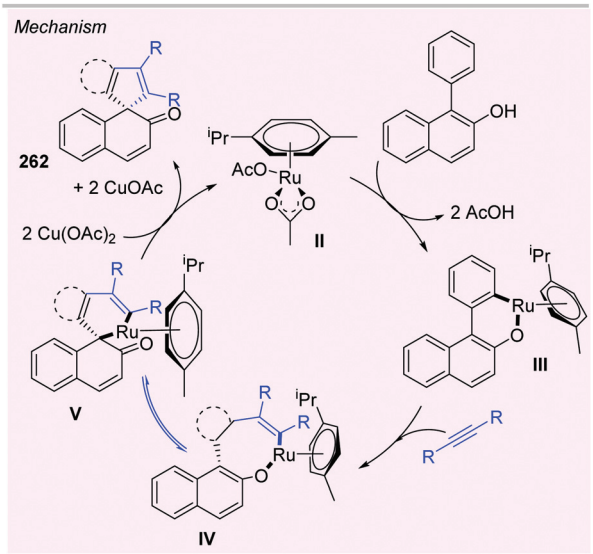
A very important protocol for the construction of all carbon containing spirocyclic compounds **266** is the reaction between internal alkynes **264** and α-aryl β-naphthols **265** catalyzed by an Ru/Cu catalytic system.[90] The stepwise cleavage of the sp^2 C–H bond occurs is followed by insertion of internal alkyne **264** with the loss of aromaticity in β-naphthol. The presence of EWGs on aryl substrates helps to increase product formation. Initially, C–C bond formation in the alkyne insertion step occurs favorably at the alkyne carbon bearing the alkyl substituents. Coordination of internal alkyne with species **III** which is formed after deprotonation and fission of the C–H bond forms strained eight-membered cyclic intermediate **IV** after regioselective migratory insertion. Finally the keto–enol tautomerization of phenol gives carbon–Ru intermediate **V** which after reductive elimination gives the desired spirocyclic product **262** (Scheme 66).

Internal alkynes **267** also react with electronically scarce naphthoquinone derivatives **268** in a single-pot reaction to furnish substituted tetracyclic naphthoxazoles **269**.[91] This reaction is catalyzed by Cu(II) and Rh(III) along with copper acetate in the presence of a Lewis acid. This is a tandem cascade reaction in which naphthoquinone undergoes tautomerization before sp^2 C–H activation. The oxidative addition occurs followed by cyclization and restoration of the aromatic nature of the product (Scheme 67).

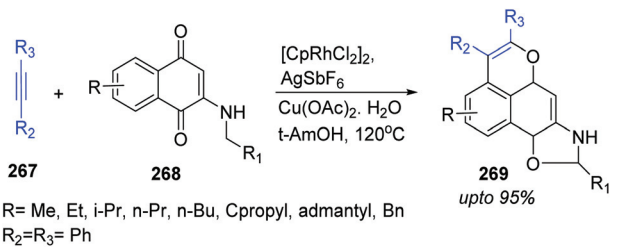
The formation of fluorescent indazoles **272**, **275**, **279** takes place when internal alkynes like **270**, **273**, **276** and pyrazoles **271**, **274** and **277** react in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ at elevated temperatures.[92] The process occurs *via* simultaneous C–H activation on two adjacent carbon centers of pyrazole as a directing group that leads to cyclization to form the product as a novel fluorophore (Scheme 68).

Jingsong You and co-workers[92] revealed the Rh/Cu-mediated formation of functionalized quinolizinones **282**, **284** as a result of the cyclization of internal alkynes **280** and pyridinones **281**, **283** through a double-rollover C–H activation method (Scheme 69). The reaction occurs in the presence of $[Cp^*RhCl_2]_2$ $Cu(OAc)_2$ at high temperature with a scope extending to *N*-pheylpyridinones and various *N*-arylpyridinones including alkynes can be utilized in the reaction. Initially, cyclometalation of pyridines gives rhodacycle **I** followed by cyclometalation to form intermediate **II**.





Scheme 66 The vinylative dearomatization of naphthols with internal alkynes.

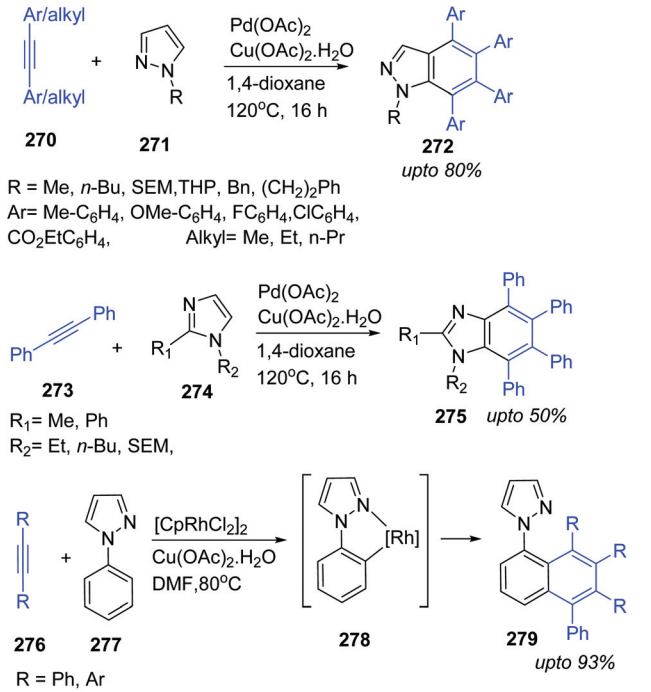


Scheme 67 The synthesis of naphthoxazole *via* directed C–H annulation and Csp^3–H bond cleavage.

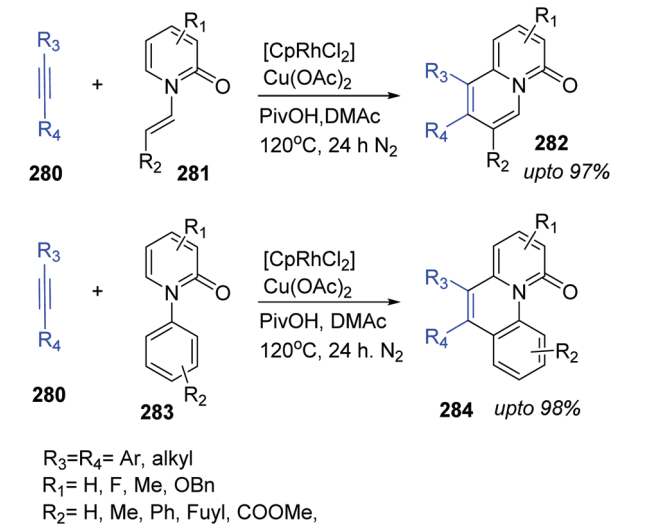
Coordination of alkyne to intermediate **II** gives species **III**. Subsequent migratory insertion produces **V** or **VI** which after reductive elimination leads to the formation of the final product. Whereas in *path b*, an alkyne insertion takes place followed by a double cyclo-rhodation step to form seven-membered rhodacycle species **V** (Fig. 15).

There is a similar type of Rh/Cu-catalyzed cyclization reaction in which internal alkynes **285** and arylthiophenes **286** react to produce conjugated tetracyclic naphthothiophene analogues **287**.[93]

Electron-deficient substrates (R = *p*-Cl, *m*-F) prefer to react more quickly and give exclusively single products compared to electron-rich substrates (R = *p*-Me, *p*-OMe) in which the formation of minor products may also take place. Hence, the



Scheme 68 The synthesis of fluorescent indazoles *via* the benzannulation of pyrazoles with internal alkynes.



Scheme 69 The annulation of pyridinones with internal alkynes *via* double C–H activation.

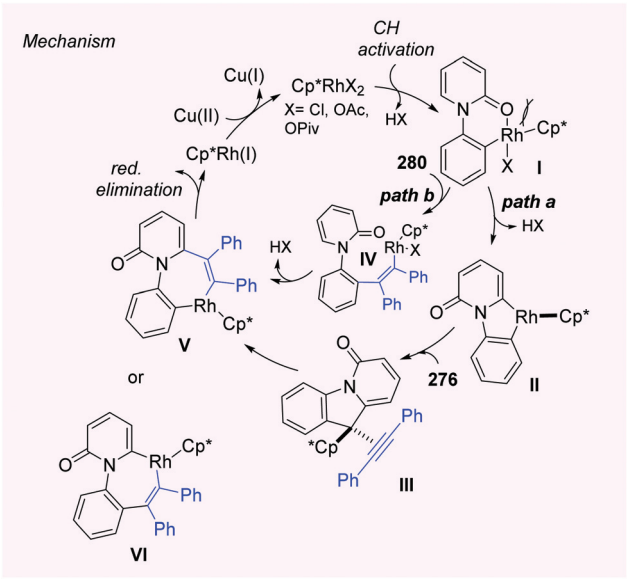
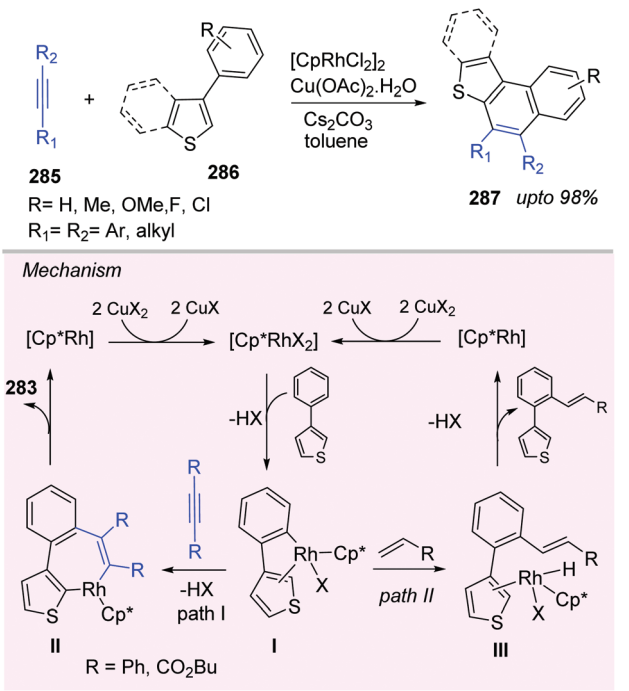


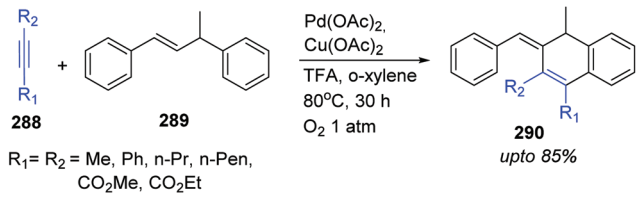
Fig. 15 A plausible reaction mechanism for the annulation of pyridinones *via* double C–H activation.



Scheme 70 The annulative coupling of 3-phenylthiophenes with internal alkynes.

cyclization preferentially takes place at the electron-deficient site. The reaction again involves double C–H activation and simply operates by using catalytic amounts of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ in the presence of a base (Scheme 70).

The formation of substituted naphthyl products **290** takes place when symmetrical and unsymmetrical alkynes **288** react with allylarenes **289** in the presence of a catalytic amount of Pd and copper acetate at 80 °C in an oxygen atmosphere (Scheme 71).[94] Ring formation occurs after the *ortho*-C–H activation by Pd(II) species. Mechanistically, the rate-determining step is the fission of the C–H bond. An ample difference of 3.76 between the intra- and intermolecular KEA data suggests that pi-coordination to the allylic C=C double bond takes place before the carbopalladation can take place. The electro-



Scheme 71 The synthesis of naphthalenes from internal alkynes.

philic palladium complex $[Pd(TFA)]^+$ is assumed to facilitate the coordination of the pi-bonds to give intermediate **I** which immediately undergoes cyclometalation to give Pd(II) complex **II**. Coordination of internal alkyne to **II** generates vinylpalladium intermediate **III** which further undergoes *cis*-addition into the neighbouring allylic pi-bond to generate alkyl-Pd species **IV**. β-Hydride elimination of **IV** with subsequent isomerization gives the final naphthalene product (Fig. 16).

A very simple Pd/Cu-catalyzed reaction of internal alkynes **291** to give 1,2-dicarbonyl compounds **292** was described by Yangjie Wu and co-workers.[94] The reaction occurs mostly with diphenyethyne to yield specifically benzil in DMSO. The mechanism was also studied before using DMSO as an oxidant where diphenyl sulfide was formed as a byproduct (Scheme 72).

In other similar processes, internal alkynes **293** were transformed into 1,2-diketones **294** through oxidation by Pd/Cu catalysis in PEG-400 and water.[95] Various alkynes were employed

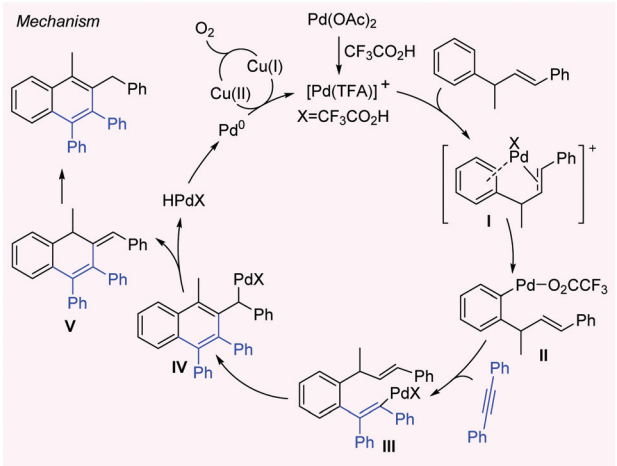
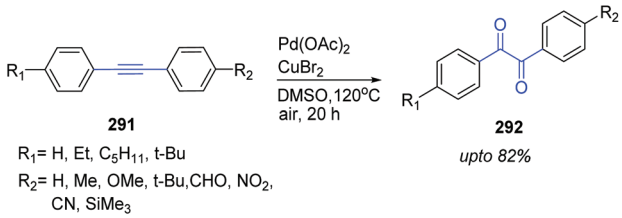


Fig. 16 A plausible reaction pathway.



Scheme 72 The oxidation of internal alkynes into 1,2-diketones.

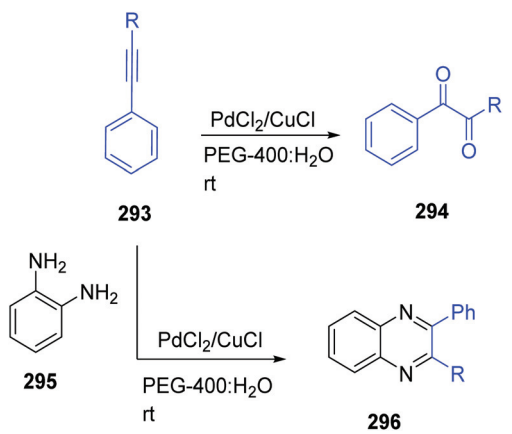
during these reactions to improve the yields of the corresponding products. In addition, the strategy was successfully involved in the synthesis of 2,3-disubstituted quinoxalines **295** from 1,2-diamines **295** (Scheme 73).

Orthoalkynyl anilines **297** and arylboronic acids **298** produce substituted indole derivatives **299** in a Pd/Cu-promoted transformation reported by Lee and co-workers.[95]

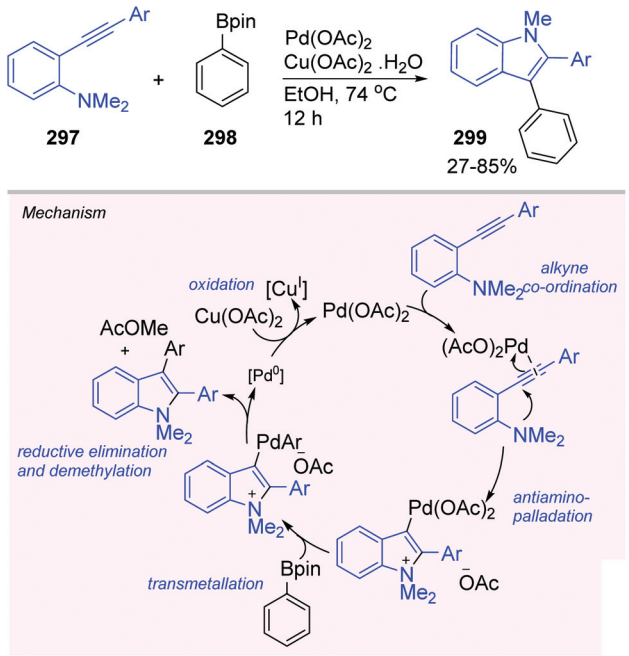
The reaction takes place by aminopalladation which initiates an intramolecular cascade reaction over alkyne to form 2,3-diaryl indoles. In this reaction, Pd acts as a π-acidic Lewis catalyst which initiates anti-aminopalladation of the alkyne and generates Pd^{II} after reacting with the arylboronic ester through transmetalation. Subsequent reductive elimination yields the corresponding substituted indole derivatives with the regeneration of Pd^0 species (Scheme 74). A similar type of Rh/Cu-catalyzed reaction between internal alkynes **300** and triazoles **301** was reported by P. N. Liu and co-workers.[96] The reaction is a C–H activation process that leads to the formation of alkenes **302** in the presence of catalytic $[Ru(p\text{cymene})Cl_2]_2/Cu(OAc)_2{\cdot}H_2O$ and $AgSbF_6$. The reaction has a wide scope and many mono- and di-substituted alkenes can be formed in sufficient yields.

Diaryl-substituted internal alkynes bearing electron-withdrawing groups like Cl or CF_3 at the *para* position of the aryl ring exhibited better reactivity (77 to 83%) than diarylalkynes bearing electron-releasing groups like Me/OMe and furnished 63 to 52% of the product (Scheme 75).

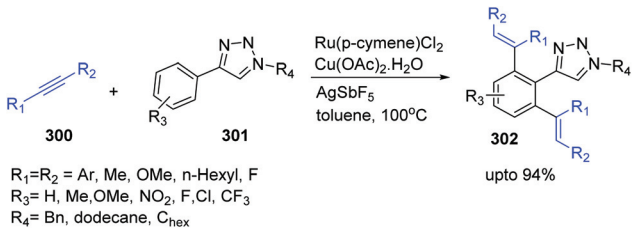
A stereoselective conversion of internal alkynes **303** into conjugated borylated alkenes **305** in the presence of bis(pinacolato)diboron **89** and alkenyl bromides **304** was developed by F. M Martın and co-workers.[97] The reaction shows regio- and stereo-control with different substrates under mild conditions. Partial decomposition of the alkenyl bromide substrate is seen when *trans* bomopropene was employed in the reaction. The products serve as linchpin substrates for the synthesis of polyene chains. Mechanistically, catalytic β-boryl substituted $C(sp^2)$–Cu intermediate is formed which undergoes a palladium-catalyzed cross-coupling reaction between alkynylboron



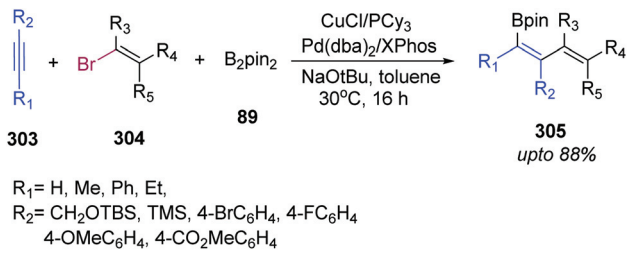
Scheme 73 The oxidation of internal alkynes into 1,2-diketones and quinoxalines.



Scheme 74 The formation of indoles *via* amino-palladation over an internal alkyne.



Scheme 75 The Rh/Cu-catalyzed alkenylation of arenes with internal alkynes.



Scheme 76 The Cu/Pd-catalyzed alkenylboration of internal alkynes.

and alkenyl bromide to form the required products in up to 88% yields (Scheme 76).

7. Summary and outlook

This review has summarized detailed perspectives about copper-catalyzed reactions involving internal alkynes for the synthesis of various types of substituted, carbonylated, boron-containing alkenes and heterocycles with mechanistic insights in many important cases. In addition, many reactions involving Cu as a synergistic catalyst with other metals like Ni, Zn, Pd, Ru, Rh, or Ag were also discussed. These reactions show useful applications in medicinal chemistry and technology. Previous developments on Cu catalysis and internal alkynes have profoundly evolved and are continuously tending to unveil new reactions for the construction of intricate heterocyclic molecules in catalysis and organic synthesis. In coming times this combination is going to be further explored and consequently, imperative developments in this field are definitely going to have an impact in the areas of organic synthesis, material science, and pharmaceutical chemistry. However, the relationship between internal alkynes and Cu catalysis still needs to be strengthened by addressing challenges, especially in the field of natural product synthesis.

8. Conclusions

In summary, the chemistry of internal alkynes plays a very crucial role in the formation of C–C and C–X (X = O, N, S, and P) bonds in organic chemistry. These reactions are stereoselective and are mostly driven under normal conditions. Internal alkynes are versatile substrates for carrying out useful chemical transformations aimed towards functionalized alkenes and the synthesis of heterocycles. In addition, Cu exists as a cost-effective and sustainable first-line catalyst for cross-coupling and C–H activation reactions, and it can also catalyze reactions in a synergistic manner in the presence of other metals.

Conflicts of interest

There are no conflicts to declare.

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