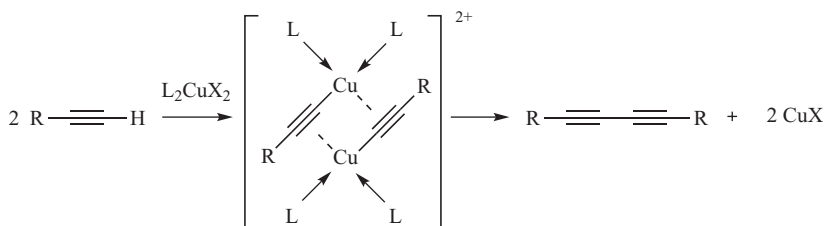

12

COPPER-CATALYZED ALKYNYLATION AND ALKENYLATION REACTIONS OF ALKYNYL DERIVATIVES: NEW ACCESS TO DIYNES AND ENYNES

RUIMAO HUA

12.1 INTRODUCTION

Diynes and enynes represent important classes of organic compounds. In particular, conjugated 1,3-diynes and 1,3-enynes are not only important building blocks in organic synthesis and organic materials^[1] but also are the structural functional units of many natural products.^[2] Therefore, numerous accesses to diynes and enynes have been developed, and the alkynylation and alkenylation reactions of alkynyl derivatives catalyzed by palladium with or without the use of copper salts as cocatalysts have become standard synthetic methods.^[3] In the past decade, cuprous or cupric salts, with or without external ligands, have found widespread applications in carbon–carbon or carbon–heteroatom bond formation.^[2,4] The nontoxicity, ease of handling, and low cost of these versatile catalytic systems make them attractive for the elaboration of sensitive substrates such as diynes or enynes. The formation of these two classes of structural units, catalyzed by copper(I) or copper(II) salts, are reviewed in this chapter.



Scheme 12.1 Bohlmann's dimeric copper acetylides in the Glaser coupling reaction.

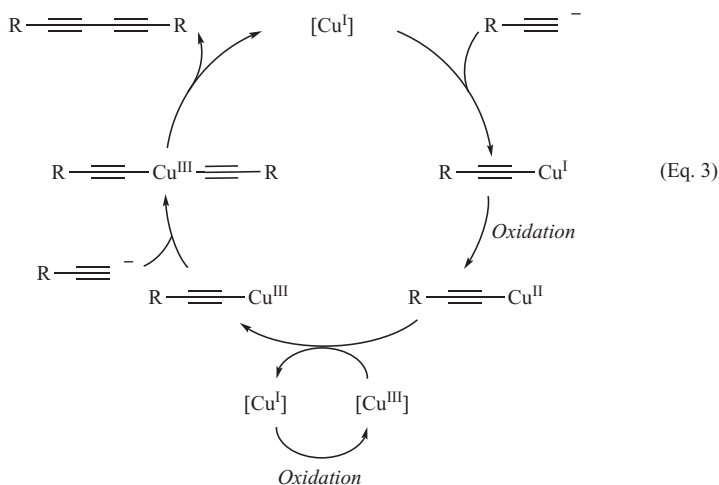
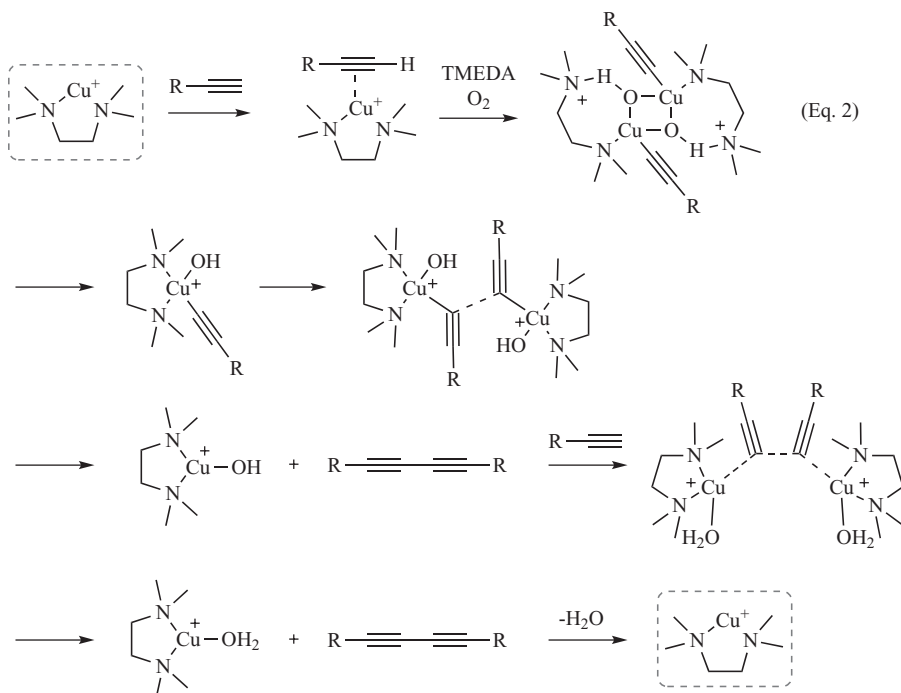
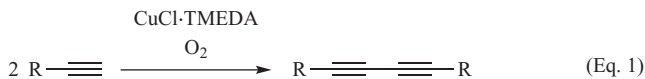
12.2 COPPER-CATALYZED SYNTHESIS OF SYMMETRICAL AND UNSYMMETRICAL 1,3-DIYNES

The homo- and heterocoupling reactions of alkynes is the most efficient and direct route to symmetrical and unsymmetrical 1,3-diynes. The oxidative homocoupling of terminal alkynes is an efficient reaction allowing the synthesis of symmetrical 1,3-diynes, and the first example of such type of coupling reaction was reported by Glaser in 1869 with the use of cuprous chloride as catalyst and aqueous ammonia as the base under an oxygen atmosphere.^[5] A very stimulating historical perspective on this venerable reaction, including a discussion on the different mechanisms, can be found in a 2000 review by Diederich and coworkers.^[1a] Although several mechanisms have been proposed, the most currently accepted one has been reported by Bohlmann and coworkers in 1964 and relies on dimeric copper acetylides as intermediates in the oxidative acetylenic coupling (Scheme 12.1).^[6]

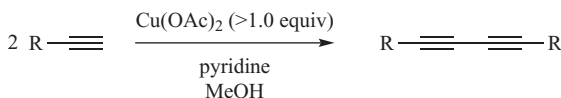
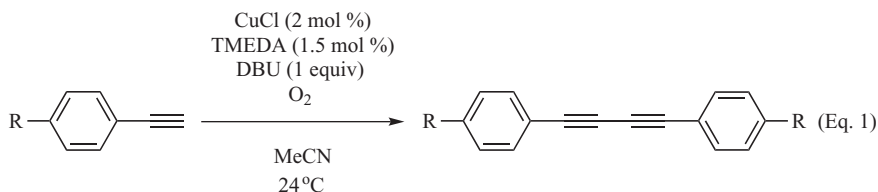
A similar catalytic system for the oxidative homocoupling of terminal alkynes was reported by Hay in 1960 with the use of an atmosphere of oxygen and CuCl-TMEDA (tetramethylethylenediamine [TMEDA]) as the catalyst, which is soluble in a range of organic solvents, resulting in a much more practical coupling reaction (Scheme 12.2, Eq. 1).^[7] Recent density functional theory (DFT) calculations have demonstrated that a bimetallic process relying on copper(I), (II), and (III) oxidation states was operating (Scheme 12.2, Eq. 2).^[6b-d] ¹³C NMR kinetics experiments have also been recently reported supporting a Cu(I)/Cu(II)/Cu(III)/Cu(I) cycle (Eq. 3).^[6e]

In the presence of copper(I), terminal alkynes also underwent the oxidative homocoupling reaction to give symmetrical 1,3-diynes (in the presence of an equivalent or excess amount of copper(II) acetate) (Eglinton coupling reaction) (Scheme 12.3).^[8]

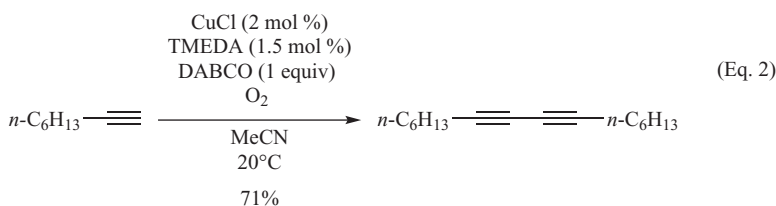
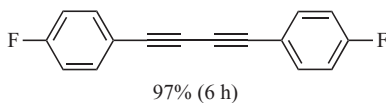
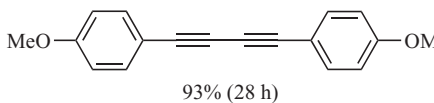
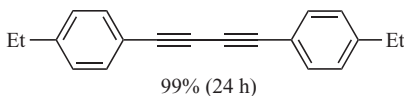
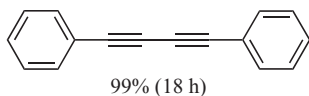
Beifuss and coworkers studied the Glaser-type reaction under different conditions and found that the yields of 1,3-diynes greatly depended on the nature of the base and ligand.^[9] The optimal catalytic system was found to consist of copper(I) chloride (2 mol %), bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO) (1 equiv), and TMEDA (1.5 mol %) as the ligand. Aromatic alkynes could be oxidatively homocoupled in high yields at room temperature in acetonitrile (Scheme 12.4,



Scheme 12.2 The Hay coupling reaction and a proposed mechanism based on DFT and spectroscopic studies.

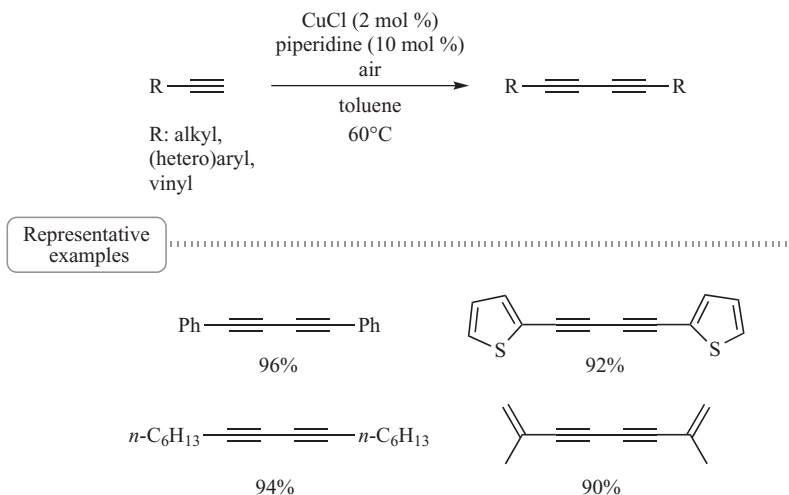
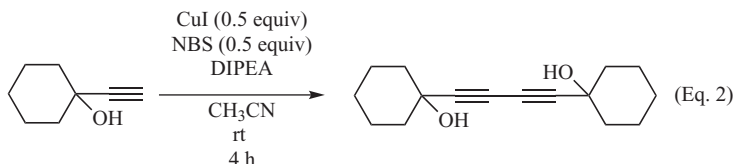
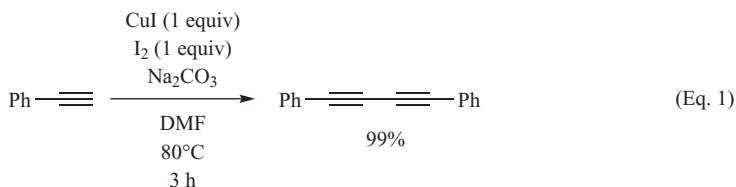
**Scheme 12.3** The Eglinton coupling reaction.

Representative examples

**Scheme 12.4** Influence of the base in the Glaser-type homocoupling reaction.

Eq. 1). Less acidic alkynes, such as aliphatic alkynes that are traditionally less reactive, could also be used in this transformation (Scheme 12.4, Eq. 2).

Hua and coworkers reported that neither copper(I) chloride or iodide nor copper(II) chloride had catalytic activity for the homocoupling of terminal alkynes. However, in the presence of a catalytic amounts of piperidine (10 mol %), copper(I) chloride showed high catalytic activity at 60°C in toluene under an open air atmosphere affording symmetrical 1,4-disubstituted-1,3-diynes in high yields (Scheme 12.5).^[10] Under the optimized reaction

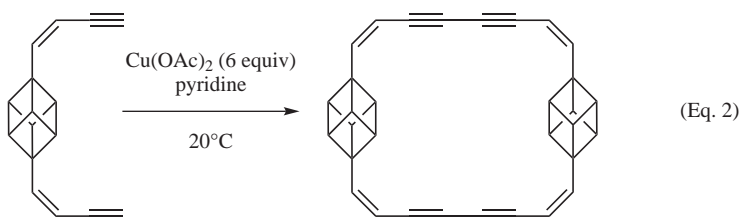
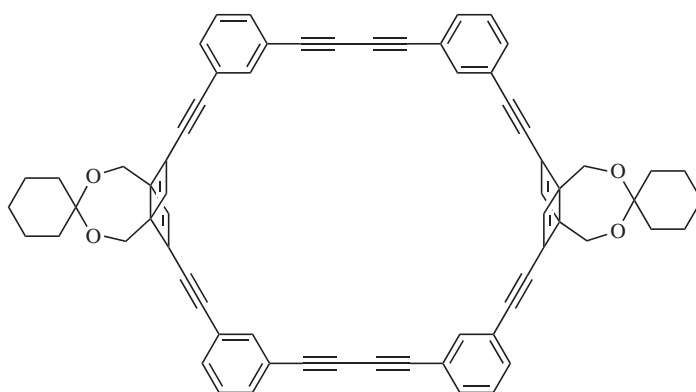
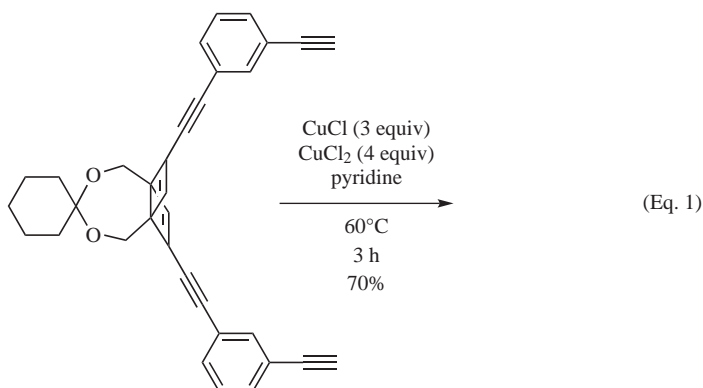
**Scheme 12.5** Hua's copper(I or II)-catalyzed homocoupling of alkynes.**Scheme 12.6** Iodine and *N*-bromosuccinimide as oxidants in Glaser-type reactions.

conditions, copper(II) chloride/piperidine showed low catalytic activity. However, CuCl_2/DBU ,^[11] $\text{CuCl}_2/\text{Et}_3\text{N}$,^[12] and $\text{Cu}(\text{OAc})_2/\text{piperidine}$ ^[13] could efficiently catalyze the homocoupling reactions of terminal alkynes.

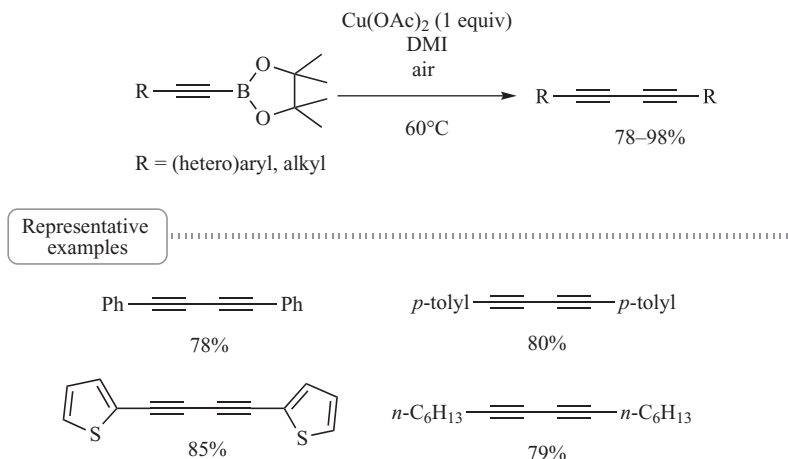
Iodine^[14] and *N*-bromosuccinimide (NBS)^[15] could be also employed as oxidants in the copper(I) iodide-mediated oxidative homocoupling of terminal alkynes (Scheme 12.6). The great attractiveness of this catalytic system is its simplicity and efficiency due to the use of solid oxidants, which are soluble in organic solvents. In the case of NBS as an oxidant, the homocoupling reaction

occurred at ambient temperature, and a variety of functionalized terminal alkynes including sugar- and amino acid-containing alkynes could react smoothly to give functionalized 1,3-diynes in good yields.

Macrocycles linked by acetylenic units are important compounds in supramolecular chemistry and organic materials science, and copper-mediated oxidative homocoupling reaction has become a general synthetic approach to such type of macrocycle. As shown in Scheme 12.7, excess copper(I) chloride



Scheme 12.7 Macrocycle synthesis via terminal alkyne dimerization reaction.

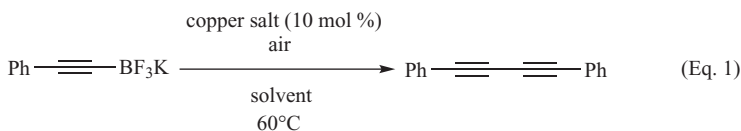


Scheme 12.8 Copper(II)-mediated homocoupling reaction of alkynylboronates.

and copper(II) chloride^[16] or copper(II) acetate^[17] were applied for the dimerization reaction of terminal alkynes, leading to 1,3-diyne-linked macrocycles in good yields.

Besides the oxidative homocoupling of terminal alkynes, both alkynylboronates and alkynyltrifluoroborates were found to be practical and versatile precursors for the synthesis of 1,3-diynes via the activation of the C(*sp*)-B bond in the presence of copper salts under aerobic conditions. As shown in Scheme 12.8, various symmetrical 1,3-diynes could be synthesized by copper(II) acetate-mediated homocoupling reaction of alkynylboronates in good-to-excellent yields in aprotic polar solvents such as 1,3-dimethyl-2-imidazolidinone (DMI). Copper(I) iodide and copper(I) thiophene-2-carboxylate (CuTC) also showed high catalytic activity.^[18]

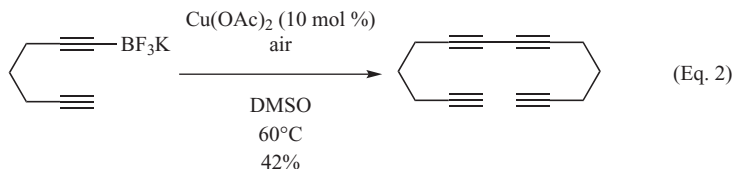
Paixão and coworkers studied the homocoupling reaction of alkynyltrifluoroborates in the presence of a catalytic amount of copper salts under different conditions and found that not only copper(I) and copper(II) salts showed different catalytic activity but also that the homocoupling reaction depended greatly on the solvents.^[19] As shown in Scheme 12.9 (Eq. 1), both copper(II) acetate and copper(I) chloride could efficiently catalyze the homocoupling reaction of potassium phenylethynyltrifluoroborate in DMSO, affording 1,4-diphenyl-1,3-butadiyne in high yield. On the other hand, copper(I) iodide or cyanide and copper(II) chloride showed low catalytic activity. In addition, in *N,N*-dimethylformamide (DMF) and tetrahydrofuran (THF), the catalytic activity of copper(II) acetate decreased significantly, which be due to the lower solubility of the starting trifluoroborates in the solvents. It is interesting to note that under the optimized conditions, the homocoupling reaction occurred at C(*sp*)-B bond selectively and left the C(*sp*)-H bond untouched (Scheme 12.9, Eq. 2).



$\text{Cu}(\text{OAc})_2$ in DMSO: 97%; DMF: 47%; THF: 4%

CuCl_2 in DMSO: 34%; CuCl in DMSO: 89%

CuI in DMSO: 25%; CuCN in DMSO: 4%

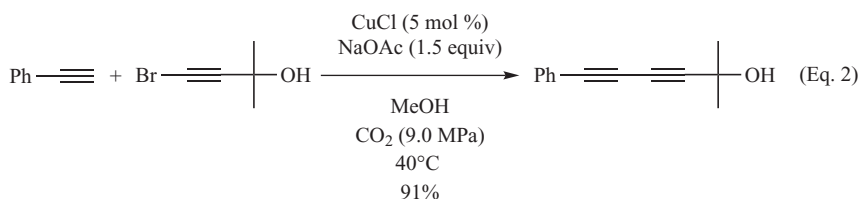
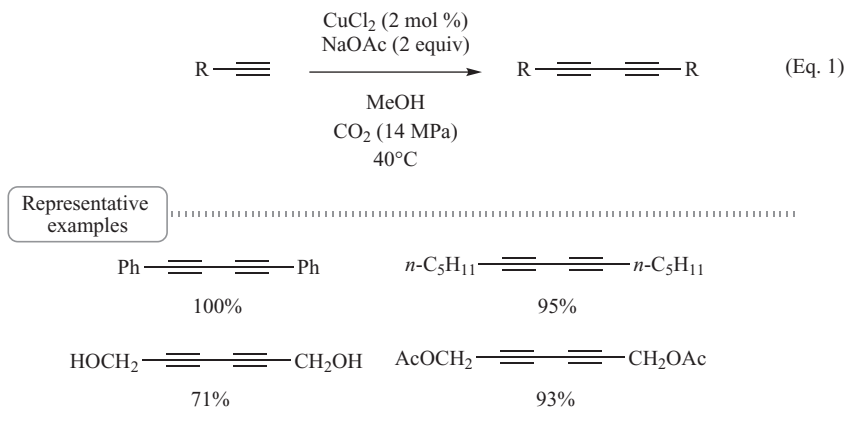


Scheme 12.9 Copper(I or II)-catalyzed homocoupling reaction of alkynyltrifluoroborates.

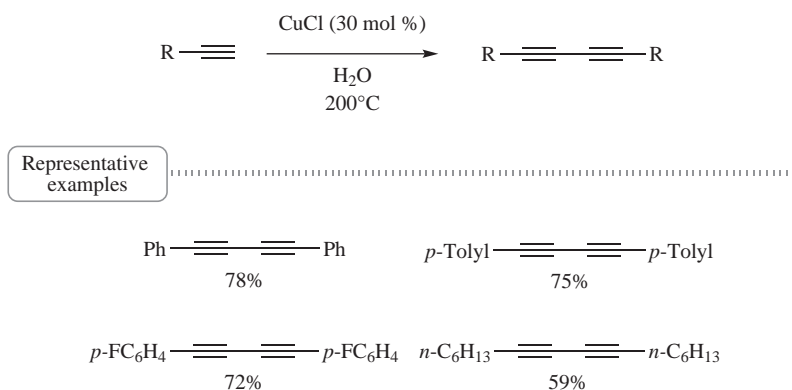
The coupling reaction of terminal alkynes can be also performed in environmentally benign solvents such as supercritical carbon dioxide, water, and ionic liquids. For instance, Jiang and coworkers studied the homocoupling reactions of various terminal alkynes in supercritical carbon dioxide using MeOH as a cosolvent and found that, when sodium acetate was used as a base, 1,3-butadiynes could be obtained in good-to-high yields (Scheme 12.10, Eq. 1).^[20] In order to get a high yield of the desired coupling products, the addition of MeOH was crucial to increase the solubility of reactants. Copper(II) chloride was superior to other cupric salts (i.e., copper(II) sulfate, copper(II) nitrate, copper(II) acetate, and copper(II) bromide) possibly due to its higher solubility in $\text{scCO}_2/\text{MeOH}$ medium. Under similar reaction conditions, copper(I) chloride also showed high catalytic activity for the Cadiot–Chodkiewicz coupling reaction (the heterocoupling process between a 1-bromoalkyne and a terminal alkyne in the presence of a copper(I) catalyst and an amine), giving unsymmetrical 1,3-diynes in high yield (Scheme 12.10, Eq. 2).^[21]

Copper(II) chloride also showed high catalytic activity for the homocoupling of terminal alkynes in near-critical water (200°C) without the use of organic solvent and base, as reported by Wang and coworkers in 2004 (Scheme 12.11).^[22]

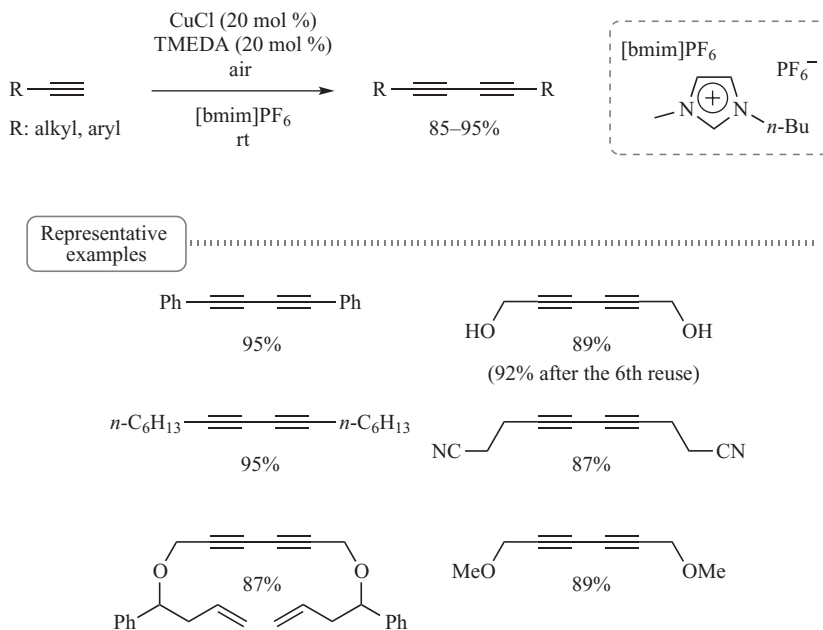
In ionic liquids, cuprous halides could be used as efficient catalysts for the Glaser coupling reaction. As shown in Scheme 12.12, copper(I) chloride catalyzed the homocoupling of terminal alkynes in $[\text{bmim}]\text{PF}_6$, with the use of TMEDA as ligand, at room temperature to afford smoothly 1,3-butadiynes in excellent yields.^[23] The considerable advantages in ionic liquid are enhanced reaction rates and the ease of recovery and reuse of the catalytic system up to six reuses without any noticeable decrease in yield.^[23] Very interestingly,



Scheme 12.10 Copper(I and II)-catalyzed synthesis of 1,3-diynes in supercritical carbon dioxide.



Scheme 12.11 Homocoupling reaction of terminal alkynes in near-critical water.



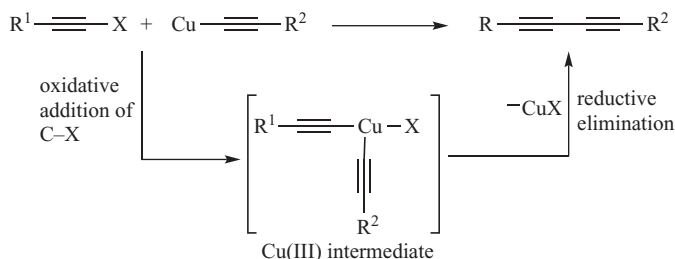
Scheme 12.12 Copper(I)-catalyzed homocoupling of terminal alkynes in ionic liquid.

copper(I) iodide also showed good catalytic activity in [bmim]OH in the absence of both ligand and base.^[24]

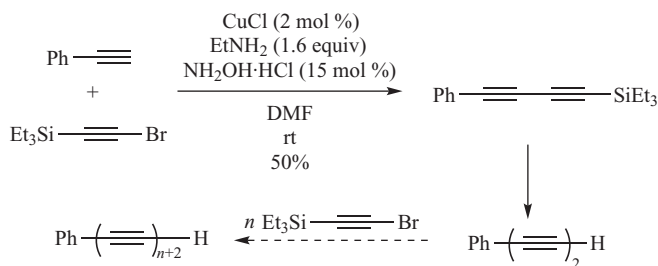
Glaser, Hay, and Eglinton coupling reactions are efficient methods for the synthesis of symmetrical 1,3-diynes, but they are not practical for the preparation of unsymmetrical 1,3-diynes via intermolecular oxidative heterocoupling of two different terminal alkynes due to the difficulty controlling the chemoselectivity of the cross-coupling event. Therefore, the copper-catalyzed cross-coupling reaction of an alkynyl halide with a terminal alkyne is one of the most important and efficient methods in this area.

The pioneering work on the synthesis of unsymmetrical 1,3-diynes was reported by Cadiot and Chodkiewicz in the 1950s through the reaction of an alkynyl halide with a cuprous acetylide (Scheme 12.13).^[25] A base, usually an amine, is also mandatory in this cross-coupling reaction. Hydroxylamine is also often used as an additive to reduce any cupric ions in the reaction media. The proposed mechanism includes the oxidative addition of the haloalkyne to copper(I) to form a copper(III) intermediate,^[25b] and subsequent reductive elimination affords 1,3-diyne.

The preparation of terminal polyacetylenes is not trivial using the classical Cadiot–Chodkiewicz conditions since the acidity of the cross-coupling product is greater than the one of the starting terminal alkyne, and an appropriate protecting group is therefore required.^[26] Walton demonstrated that a triethylsilyl group is particularly well suited in this regard. Copper(I) chloride could



Scheme 12.13 Proposed mechanism for Cadiot–Chodkiewicz coupling reaction.

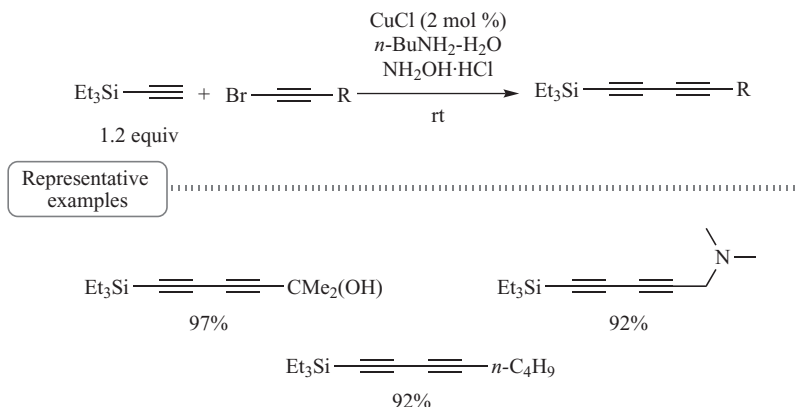


Scheme 12.14 1-Bromo-2-triethylsilyl acetylene in the Cadiot–Chodkiewicz cross-coupling reactions.

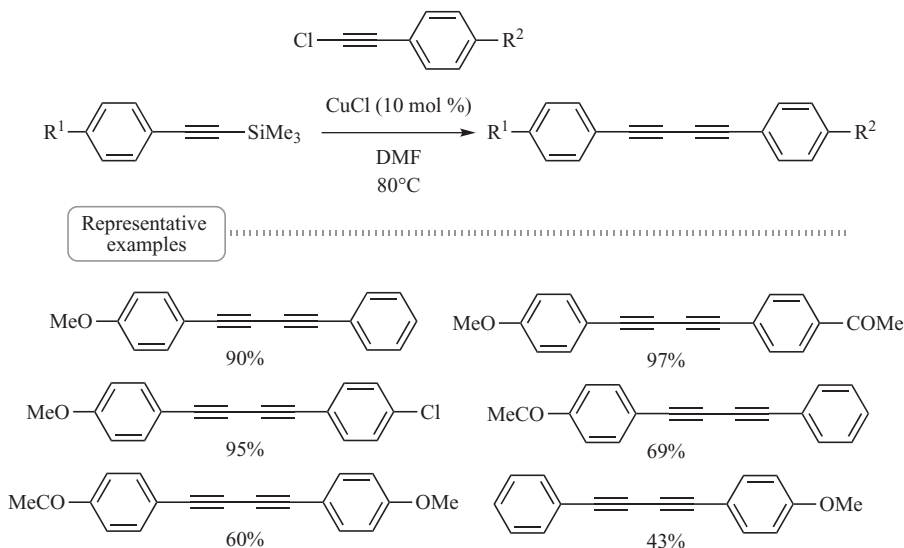
efficiently catalyze the Cadiot–Chodkiewicz cross-coupling reaction of phenylacetylene with 1-bromo-2-triethylsilyl acetylene at room temperature to afford unsymmetrical triethylsilyl-substituted 1,3-diynes in moderate yield (Scheme 12.14).^[27] Since the carbon–silicium bond could be easily converted into a carbon–hydrogen bond, important application of such type of cross-coupling reactions can be envisaged, such as the synthesis of unique linear conjugated polyynes, which possess an interesting potential in electronic and optical materials.

Under essentially similar conditions, Marino and Nguyen studied the cross-coupling reaction of trialkylsilyl acetylenes with different bromoalkynes leaving the carbon–silicium bond intact. A variety of unsymmetrical 1,3-diynes was formed in good yields, providing an efficient route to these synthetically useful motifs (Scheme 12.15).^[28]

Hosomi and coworkers found that the trimethylsilyl group of alkynylsilanes could be smoothly activated by copper(I) chloride to give the corresponding copper(I) acetylides in DMI or DMF.^[29] Similar results were published simultaneously by Mori and coworkers^[30a–c] and based on these observations, they studied the copper(I) chloride-catalyzed cross-coupling reaction of alkynylsilanes with chloroalkynes in DMF, developing an alternative route to synthesize a variety of unsymmetrical 1,4-biaryl-1,3-butadiynes in moderate-to-good yields (Scheme 12.16).^[30d] It is worthy to note that this cross-coupling reaction



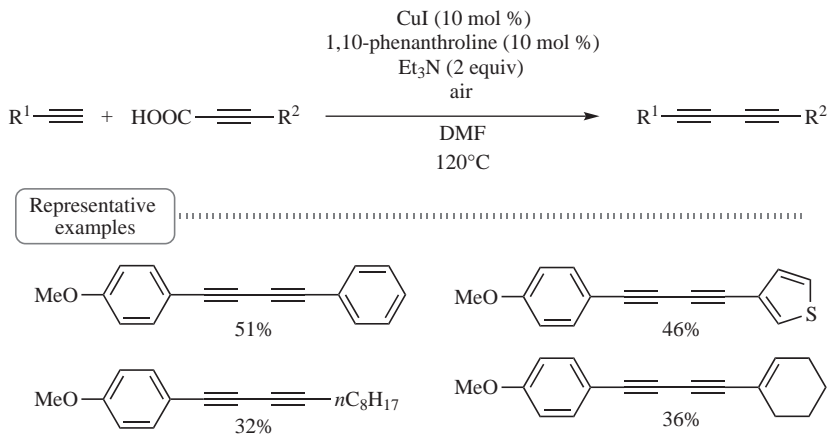
Scheme 12.15 Silylated alkynes in Cadiot–Chodkiewicz cross-coupling reaction.



Scheme 12.16 Copper(I)-catalyzed cross coupling of silylated alkynes with chloroalkynes.

proceeds without any base, which significantly expands the scope of this transformation.

Some natural products containing the 1,3-butadiynyl moiety show interesting important biological and physiological properties.^[2,31] The copper-catalyzed heterocoupling reactions of terminal alkynes have been applied as key steps in the total synthesis of such type of natural products, which is discussed in Chapter 18 in more details.



Scheme 12.17 Copper(I)-catalyzed decarboxylative cross coupling of 3-aryl propiolic acids.

The transition-metal-catalyzed decarboxylative coupling reaction is an efficient carbon–carbon bond formation reaction, which has been recently extensively studied.^[32] Yu and coworkers examined the cross-coupling reaction of 3-aryl propiolic acid with terminal alkynes in the presence of copper(I) iodide (10 mol %) with the use of 1,10-phenanthroline (10 mol %) as ligand, at 120°C under air. This new route allowed the synthesis of unsymmetrical 1,4-disubstituted-1,3-butadiynes in moderate yields via decarboxylation (Scheme 12.17).^[33a] As a logical extension, the use of 1,1-dibromoalkenes instead of terminal alkynes proved possible.^[33b]

In the Cadiot–Chodkiewicz cross-coupling reaction, the formation of symmetrical homocoupled products sometimes is a serious side reaction that decreases the yield of the desired unsymmetrical product and seriously complicates the purification. In order to easily get rid of the dimerization product of the haloalkyne partner, Schore and coworkers developed a copper(I) chloride-catalyzed coupling reaction of polymer-bound bromo- or iodoacetylene with 1-octyne to give unsymmetrical 1,3-diynol after removal from the polymer by hydrolysis. The formation of symmetrical 1,3-diynes is suppressed compared to classical homogeneous conditions.^[34a] As a final note to this section, the synthesis of unsymmetrical 1,3-diynes has been reported from *cis*-styrenyl bromides and terminal alkynes in the presence of copper(I) hydroxyapatite. The use of the *trans*-styrenyl bromides on the other hand delivered the corresponding 1,3-enyne.^[34b]

In order to recover copper catalysts, a variety of heterogeneous copper catalysts such as CuAl hydrotalcite,^[35] Cu(I)-zeolites,^[36] Cu(OH)_x/TiO₂,^[37] and copper nanoparticles^[38] have been successfully applied in the Glaser and Cadiot–Chodkiewicz coupling reactions. An overview of reusable copper-based catalytic systems can be found in Chapter 20.

12.3 COPPER-CATALYZED SYNTHESIS OF 1,4-DIYNES

Copper-mediated cross coupling of acetylenic Grignard reagents with propargyl halides is one of the traditional methods for the formation of 1,4-diynes.^[39] In 1965, Cadiot and coworkers showed that the copper-mediated cross coupling of a terminal alkyne with a propargyl halide provided a direct and efficient method for the synthesis of the corresponding 1,4-diyne (Scheme 12.18, Eq. 1).^[40] However, this transformation was still very limited in scope.^[39,40] More recently, Linstrumelle and coworkers expanded the scope of this reaction by showing that propargylic bromides or iodides or tosylates could react with alkynes in the presence of sodium carbonate and tetrabutylammonium chloride in DMF or acetonitrile as shown in Scheme 12.18 (Eq. 2).^[41] As an example, the copper(I) iodide-mediated cross coupling of 1-heptyne with chloro-2-octyne under basic conditions at room temperature afforded 6,9-pentadecadiyne in an impressive 93% yield (Scheme 12.18, Eq. 3).^[42]

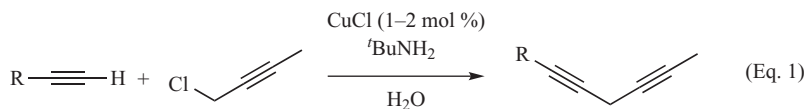
As described in this short subchapter, only a handful of efficient strategies have been developed for the straightforward synthesis of 1,4-diynes using simple reaction conditions. The situation is clearly different for the copper-mediated or copper-catalyzed synthesis of 1,3-enynes. The most representative cross-coupling reactions leading to this central motif are presented in the next chapter.

12.4 SYNTHESIS OF 1,3-ENYNES BY DIRECT REACTION OF VINYL HALIDES WITH ALKYNES

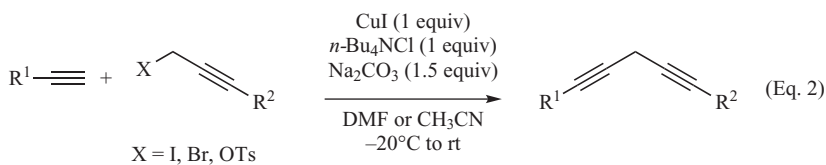
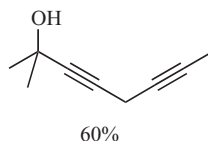
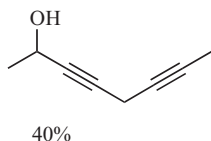
Early examples on the copper-mediated direct cross-coupling reaction of vinyl halides with terminal alkynes were reported by Suzuki and coworkers in 1989.^[43] It was found that in hexamethylphosphoric triamide (HMPA), copper(I) iodide and copper(I) bromide could efficiently mediate the reaction of vinyl iodides with 1-octyne, while copper(I) chloride showed only modest activity (Scheme 12.19, Eq. 1). In the case of vinyl bromides, copper(I) iodide and copper(II) acetate were efficient, but copper(I) bromide and Cu(acac)₂ showed low activity, and CuCl was inefficient (Scheme 12.19, Eq. 2). Under the reaction conditions, all the cross-coupling reactions proceeded with excellent stereoselectivity and with retention of the alkene's configuration.

Three years later, Miura and coworkers reported the copper-catalyzed cross coupling of vinyl halides with terminal alkynes to furnish conjugated 1,3-enynes.^[44] In the presence of a catalytic amount of copper(I) iodide and triphenylphosphine as ligand and with the use of potassium carbonate as base, the coupling reactions occurred smoothly to give 1,3-enynes in good yields (Scheme 12.20).

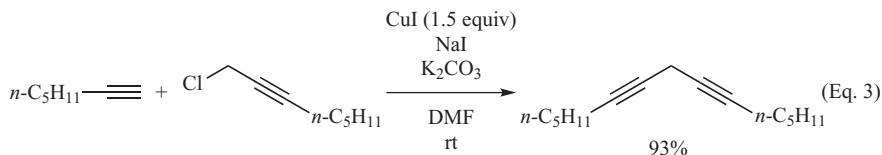
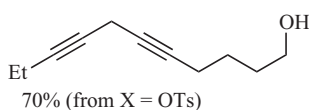
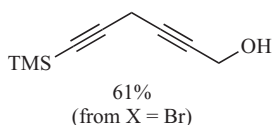
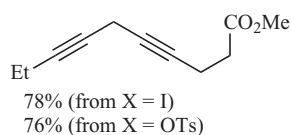
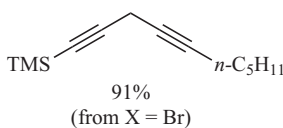
In addition to phosphine ligand, Liu and Ma reported that *N,N*-dimethylglycine·HCl was also an efficient ligand in copper(I) iodide-catalyzed



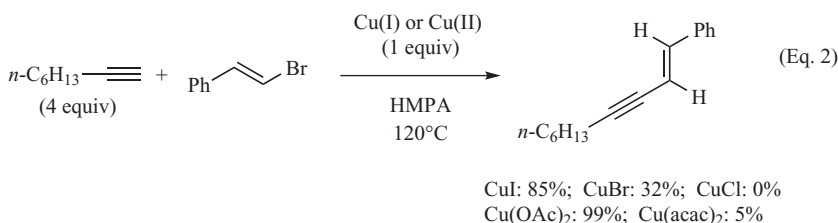
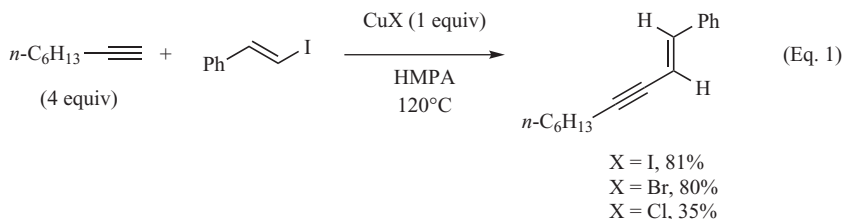
Representative
examples



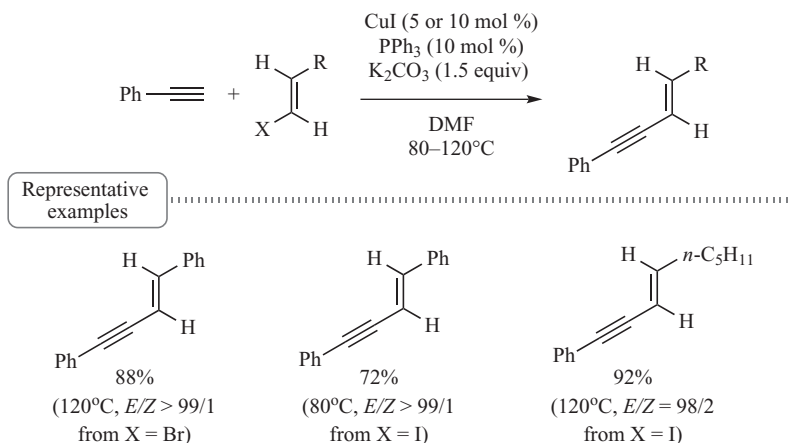
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Scheme 12.18 Cadiot–Chodkiewicz and Linstremelle syntheses of 1,4-diynes.



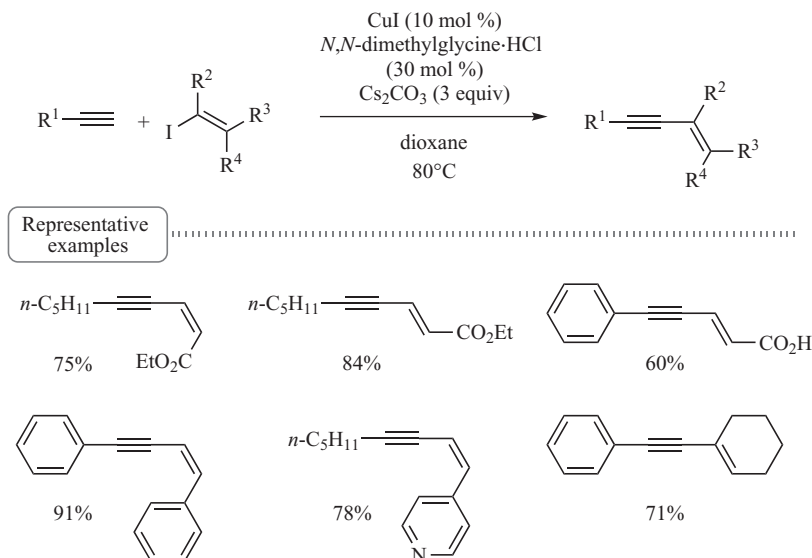
Scheme 12.19 Copper(I or II)-mediated direct vinylation of terminal alkynes.



Scheme 12.20 Copper(I)-catalyzed direct vinylation of terminal alkynes.

cross coupling of terminal alkyne with electron-rich and electron-deficient vinyl iodides in dioxane. The corresponding conjugated 1,3-enynes were obtained in good-to-high yields (Scheme 12.21).^[45] The geometry of the olefin was also generally preserved, leading to *Z*- and *E*-enynes exclusively. Moreover, other catalytic systems, such as copper(I) iodide/8-hydroxyquinoline^[46] or copper(I) iodide/1,10-phenanthroline,^[47] also showed high catalytic activity for the direct cross coupling of vinyl halides with alkynes.

Shao and Shi reported a ligand-free copper(I) iodide-catalyzed cross-coupling reactions of 2,4-halo-but-1-enes with terminal alkynes that provided

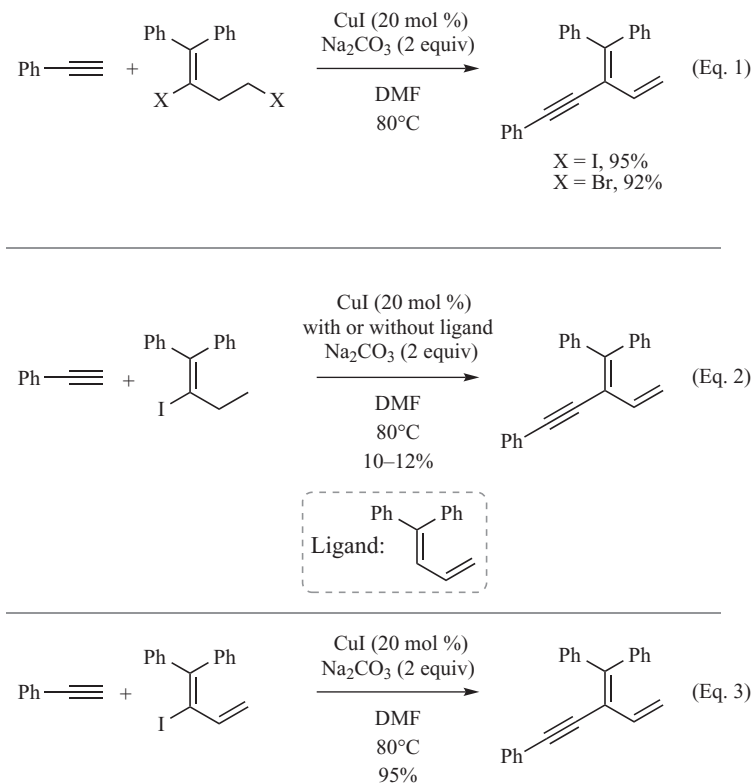


Scheme 12.21 Copper(I) iodide/amino acid-catalyzed synthesis of 1,3-enynes.

a simple and efficient procedure for the synthesis of 2-alkynyl-but-1,3-dienes in high yields (Scheme 12.22, Eq. 1).^[48] To get insights into the reaction mechanism, control experiments were carried out using 1,1-diphenyl-2-iodo-but-1-ene (with or without 1,1-diphenyl-but-1,3-diene as a potential ligand; Scheme 12.22, Eq. 2) or 1,1-diphenyl-2-iodo-but-1,3-diene (Scheme 12.22, Eq. 3). In the former case, only 10–12% of the desired product was obtained, demonstrating that 1,1-diphenyl-but-1,3-diene was not a ligand. In the latter case, the yield of the expected 2-alkynyl-but-1,3-diene reached 95%, indicating that 1,1-diphenyl-2-iodo-but-1,3-diene was a key reaction intermediate.

Venkataraman and coworkers studied the catalytic activity of well-defined copper(I) complexes and copper(I) salts with additives in the cross-coupling reaction of aryl- or alkyl-substituted acetylenes with vinyl iodides (Scheme 12.23).^[49] It was found that $[\text{Cu}(\text{bipy})\text{PPh}_3\text{Br}]$ (bipy = 2,2'-bipyridine) and $[\text{Cu}(\text{phen})(\text{PPh}_3)_2]\text{NO}_3$ (phen = 1,10-phenanthroline) showed much higher catalytic activity than a mixture of CuI/bipy, CuI/phen, and CuI/phen/ PPh_3 . As a general rule, the (*E*)-isomers cross coupled more slowly than the corresponding (*Z*)-isomers (Scheme 12.23, Eq. 2). An enhancement in reaction rate could be obtained when $[\text{Cu}(\text{phen})(\text{PPh}_3)_2]\text{NO}_3$ was used as a catalyst in combination with cesium carbonate as a base. The considerable advantages of this catalytic system include the retention of configuration of alkene, tolerance of a variety of functional groups, and good-to-excellent yields for various enynes.

Miura's catalytic system (copper(I) iodide/ PPh_3) could also promote the intramolecular cross-coupling reaction of vinyl halides with terminal alkynes in DMF to produce macrocyclic compounds embedding a 1,3-enyne moiety in

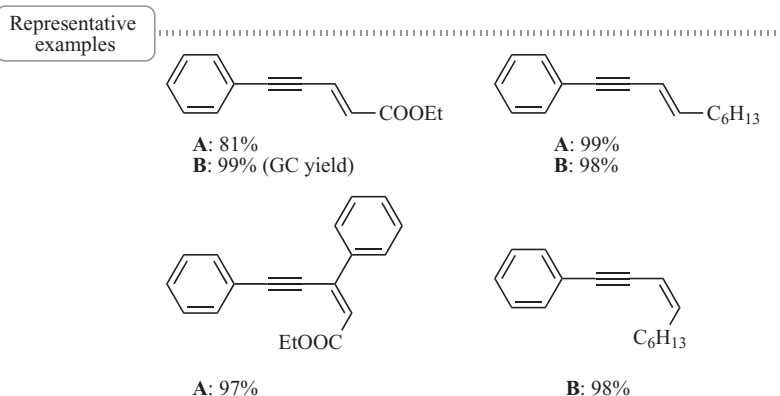
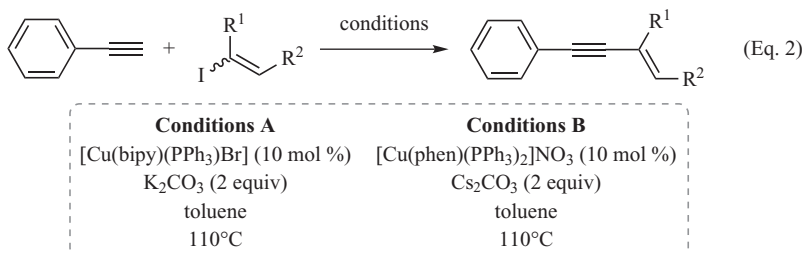
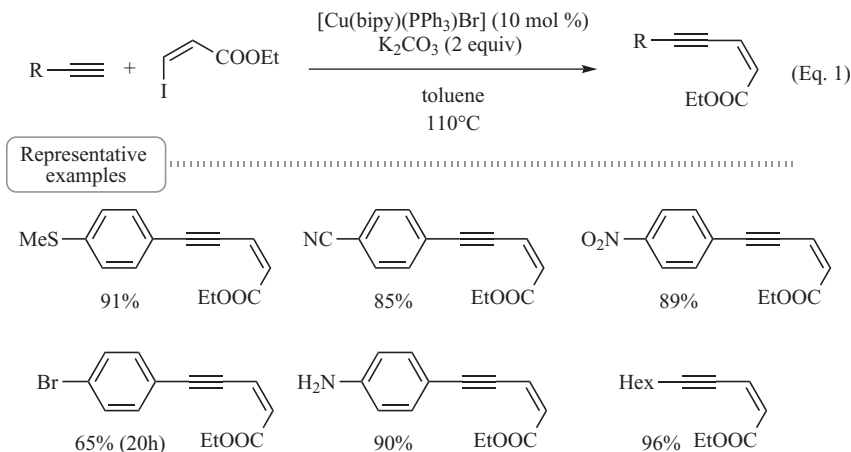


Scheme 12.22 Ligand-free copper(I) iodide-catalyzed of 2-alkynyl-buta-1,3-dienes.

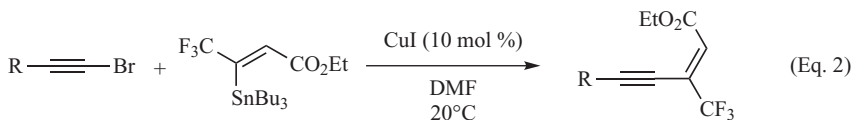
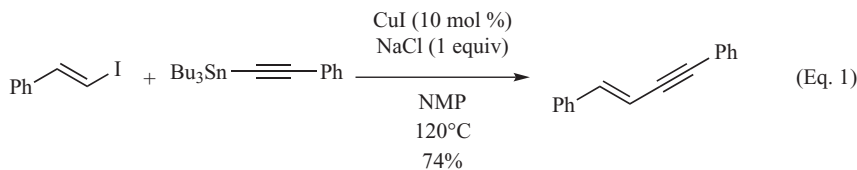
fair yield (Scheme 12.24).^[50] This transformation was used as a key step in model studies toward the total synthesis of oximidines I and II (see Chapter 18 for a more detailed discussion).

In addition, in the presence of an excess of copper(I) chloride, the direct cross coupling of alkynylsilane with vinyl iodides was an alternatively efficient route to 1,3-enynes. As shown in Scheme 12.25, the copper(I) chloride-mediated cross-coupling reaction of 1-trimethylsilyl acetylenes with (*E*)-iodo-alkenes in dimethylimidazolidinone (DMI) gave the corresponding (*E*)-1,3-enynes in good-to-excellent yields.^[51] In order to perform the cross-coupling reaction, an excess of copper(I) chloride (2.2 equiv) was required since when 1 equiv of copper(I) chloride was used, no cross-coupling product could be detected.

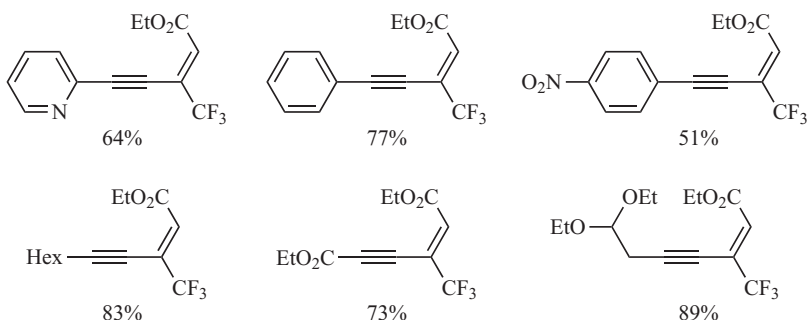
Moreover, 1,3-enynes could also be obtained via a copper(I) iodide-catalyzed cross-coupling reaction of terminal alkynes with very potent electrophiles such as alkenyliodonium salts (e.g., (*E*)- $\text{PhCH}=\text{CHI}^+\text{PhBF}_4^-$) in a mixture of solvents (DME/ H_2O , 4:1) at room temperature.^[52]



Scheme 12.23 Venkataraman's copper(I)-catalyzed synthesis of 1,3-enynes.



Representative
examples



Scheme 12.26 Copper(I)-catalyzed Stille reaction for the synthesis of 1,3-enynes.

chloride and found that the catalytic system was also efficient for the cross coupling of (2-phenylethynyl)tributylstannane with (*E*)- β -styryl iodide in *N*-methyl-2-pyrrolidone (NMP) at 120°C to give the corresponding 1,4-diphenyl-1,3-enyne in 74% yield (Scheme 12.26, Eq. 1).^[53a] More recently, Abarbri and coworkers reported on an easy access to (*E*)-3-trifluoromethylbut-2-en-3-ynoate via a copper(I)-catalyzed Stille coupling of alkynyl bromides and β -tributylstannyl- α,β -acrylates (Scheme 12.26, Eq. 2).^[53b] The excellent stereoselectivity as well as the functional group tolerance should prove very useful for the rapid elaboration of trifluoromethyl-substituted 1,3-enynes. In addition, control experiments demonstrated the tin–copper transmetallation and the relative stability of the *cis* copper intermediate that could be presumably ascribed to a coordination of copper by the ester carbonyl.

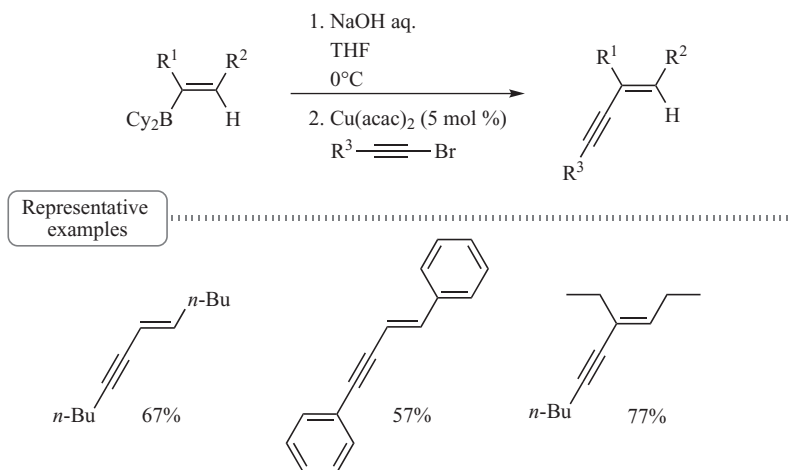
Although only isolated examples of copper-catalyzed synthesis of 1,3-enynes by Stille cross-couplings have been reported, the simplicity of the reaction conditions and the good overall yields are noticeable features of this

transformation. In this context, the Suzuki–Miyaura cross-coupling reaction has also been investigated and will be discussed in the next chapter.

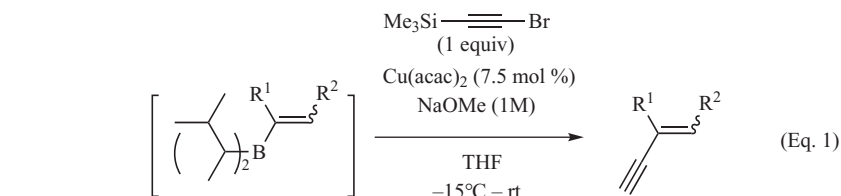
12.6 SYNTHESIS OF 1,3-ENYNES BY THE SUZUKI–MIYAUURA-TYPE CROSS-COUPLING REACTION

The first copper-catalyzed Suzuki–Miyaura-type^[54] cross-coupling reaction to afford 1,3-enyne was reported in 1983 by Arase and coworkers.^[55] They found that copper(II) acetylacetonate showed good catalytic activity for the cross-coupling reaction of alkenyldicyclohexylborane (which was pretreated with sodium hydroxide to generate the corresponding boronate) with 1-bromoalkyne. The conjugated (*E*)-enynes were obtained in moderate-to-good yield in a highly stereoselective manner (Scheme 12.27), similar to the cases where $\text{Pd}(\text{PPh}_3)_4$ was employed as the catalyst.^[56]

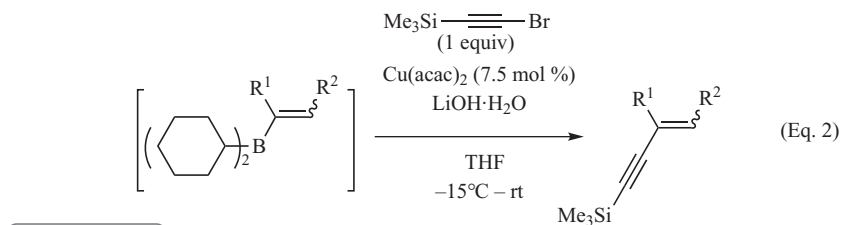
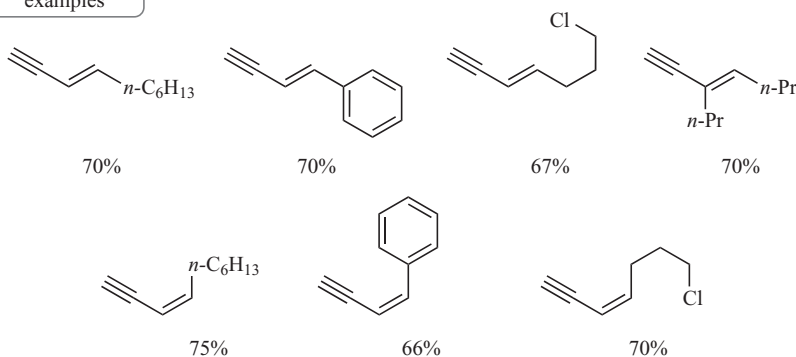
Recently, Hoshi and Shirakawa studied a similar cross-coupling reaction from (*E*)- and (*Z*)-1-alkenyldialkylboranes with (trimethylsilyl)ethynyl bromide in the presence of copper(II) acetylacetonate using sodium methoxide or $\text{LiOH}\cdot\text{H}_2\text{O}$ as the base (Scheme 12.28, Eq. 1 and Eq. 2).^[57] It was found that the nature of the base dramatically influenced the nature of the product. When sodium methoxide was used (Scheme 12.28, Eq. 1), the reaction exclusively afforded both (*E*)- and (*Z*)-3-alken-1-yne with high regio- and stereoselectivity. However, when lithine was employed as a base, the trimethylsilyl group resisted to the reaction conditions and both (*E*)- and (*Z*)-1-trimethylsilyl-3-alken-1-yne were formed regio- and stereoselectively (Eq. 2).^[58]



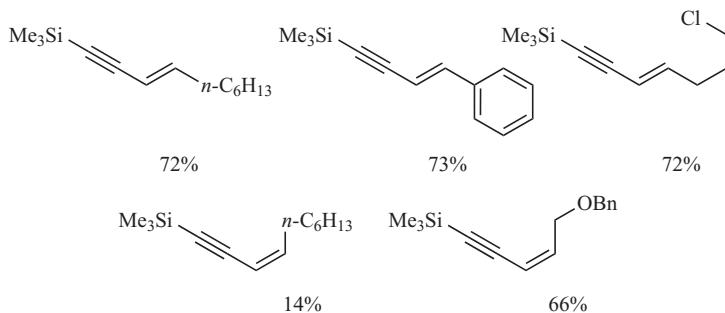
Scheme 12.27 Copper(II)-catalyzed Suzuki–Miyaura cross-coupling reaction with 1-bromoalkyne.



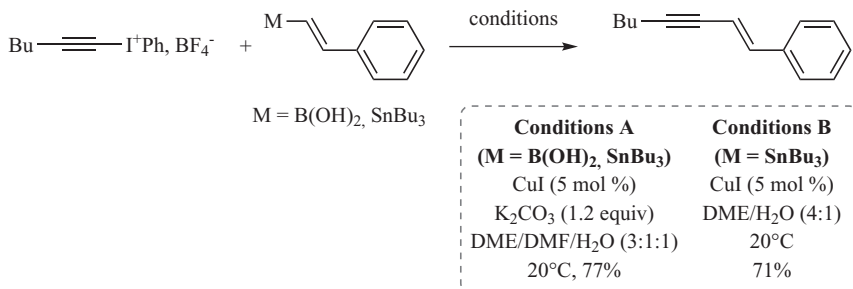
Representative examples



Representative examples



Scheme 12.28 Influence of the base in the copper-catalyzed Suzuki–Miyaura synthesis of 1,3-enynes.



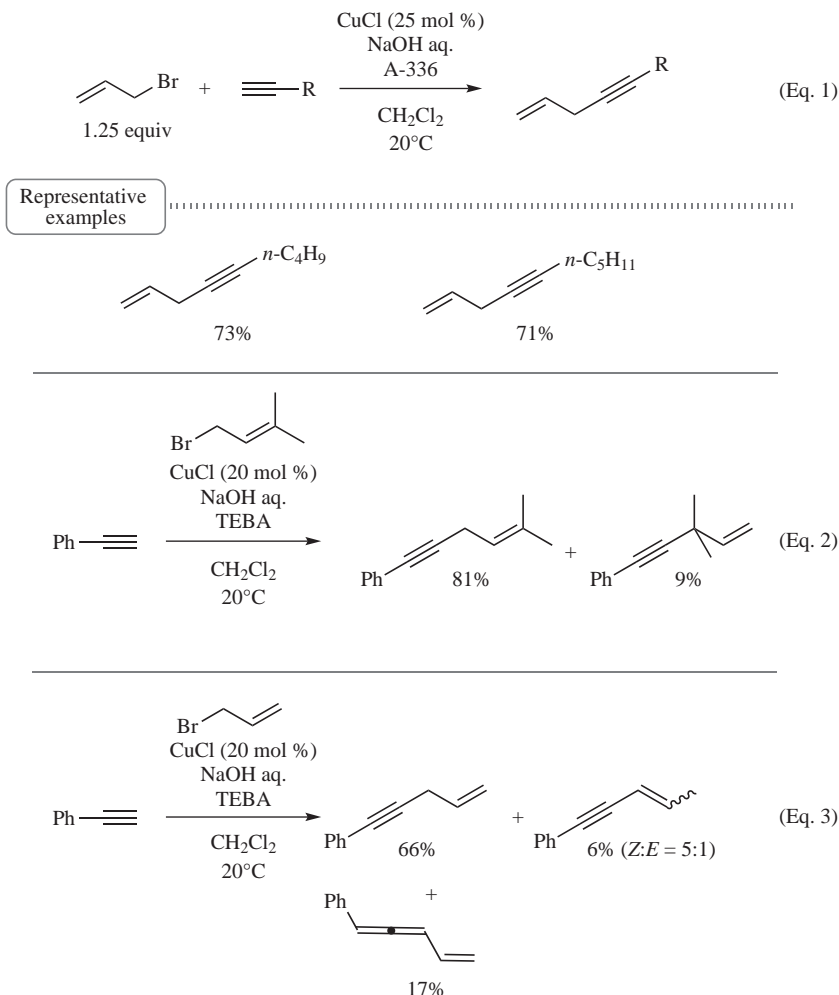
Scheme 12.29 Copper(I)-catalyzed synthesis of 1,3-dienes from alkynyliodonium salt.

Yu and coworkers studied the copper-catalyzed cross coupling of alkynyliodonium tetrafluoroborates with aryl- and vinylboronic acids and vinyltin derivatives under different reaction conditions (Scheme 12.29). It was found that under the optimized conditions, the cross coupling of (*E*)-phenylethenylboronic acid catalyzed by copper(I) iodide in a mixture of solvents (DME/DMF/ H_2O = 3:1:1) at 20°C afforded the corresponding 1,3-enyne derivative in 77% (Scheme 12.29, condition A). Vinyltin derivatives could also be cross coupled with a slightly diminished yield (71%, condition B), although the scope of the reaction was not fully investigated.^[59]

Thus, the copper-catalyzed Suzuki–Miyaura cross coupling proved to be a valuable tool to synthesize 1,3-enynes from 1-bromoalkynes or alkynyliodonium salts and vinylboronate derivatives. The copper-catalyzed synthesis of nonconjugated enynes, such as 1,4-enynes, has also attracted a great deal of attention. A selection of the most relevant examples of this strategy is discussed in the next subchapter.

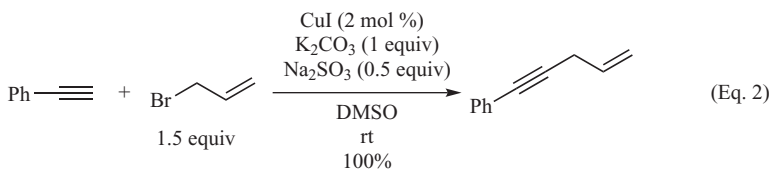
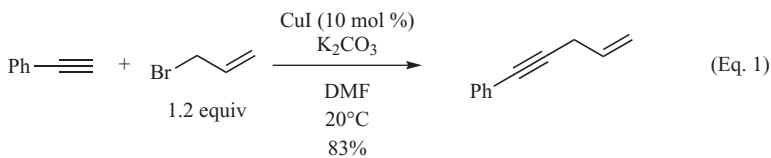
12.7 SYNTHESIS OF 1,4-ENYNES BY ALLYLATION REACTION OF TERMINAL ALKYNES

It is well known that the reaction of alkynylcopper(I) organometallics with allylic halides is an efficient reaction for the synthesis of 1,4-enynes.^[60] Therefore, the copper(I)-catalyzed allylation of terminal alkynes with allylic halides has been extensively studied and became an important process for the synthesis of 1,4-enynes. For instance, Grushin and Alper investigated the cross-coupling reaction of terminal alkynes with allylic bromides in the presence of copper(I) chloride and a phase-transfer catalyst with the use of aqueous sodium hydroxide as a base, and found that the yield of the desired 1,4-enyne depended on the nature of alkyne, the structures of the allylic bromides, and of the phase-transfer catalyst.^[61] As shown in Scheme 12.30 (Eq. 1), the reaction of aliphatic acetylenes with allyl bromide afforded the expected 1,4-enyne derivatives as the exclusive products with the use of A-336 as the



Scheme 12.30 Copper(I)-catalyzed synthesis of 1,4-enynes using phase-transfer catalysis.

phase-transfer catalyst in good yields. On the other hand, the reaction of phenylacetylene with allyl bromide or 1-bromo-3-methyl-2-butene in the presence of triethylbenzylammonium chloride (TEBA) produced a mixture of two or three isomeric products arising from competitive $\text{S}_{\text{N}}2/\text{S}_{\text{N}}2'$ processes or double bond isomerization (Scheme 12.30, Eq. 2 and Eq. 3). However, the use of a relatively weak base such as potassium carbonate (Scheme 12.31, Eq. 1)^[62] and potassium carbonate/sodium sulfite (Scheme 12.31, Eq. 2)^[63] resulted in a significant improvement of the chemoselectivity in the copper(I) iodide-catalyzed reaction of phenylacetylene with allyl bromide. The desired 1,4-enyne derivative was obtained in high or quantitative yield.



Scheme 12.31 Copper(I)-catalyzed synthesis of 1,4-enynes.

12.8 CONCLUSION

Copper salts have recently triggered intense interest as versatile catalysts in organic synthesis.^[4] This chapter gives a summary of recent advances in the application of copper salts as promoters or catalysts in important coupling reactions such as Glaser/Hay/Eglinton coupling, Cadiot–Chodkiewicz coupling, Stille and Suzuki–Miyaura-type cross-coupling reactions, and allylation of terminal alkynes that provide efficient accesses to diynes and enynes. Although significant progresses have been achieved in this field, developing much simpler and much more efficient copper-based catalytic systems for the alkynylation and alkenylation of alkynyl derivatives is still an interesting and challenging research topic since diynes and enynes are important building blocks in organic synthesis and functional organic materials.

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