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Copper-Catalyzed Alkyne−Aryne and Alkyne−Alkene−Aryne Coupling Reactions

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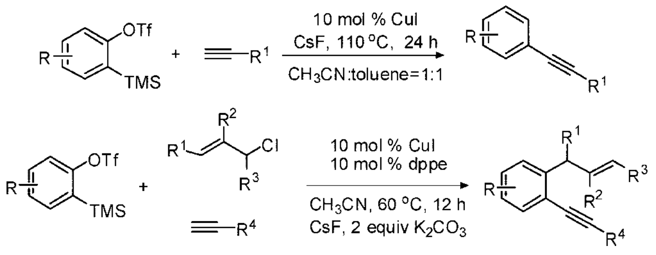
ABSTRACT



The efficient copper-catalyzed two-component coupling reaction of alkynes with arynes and the three-component coupling reaction of alkynes with allylic chlorides and arynes have been developed. Copper acetylide was postulated as a transient intermediate for the initiation of the coupling reactions.

Alkynes have been widely used as substrates in transition metal-mediated C−C bond-formation processes.[1] However, arynes are seriously limited as components of catalytic reactions due to their high reactivity and the harsh conditions required to prepare them. In 1983, a mild method for the preparation of arynes in situ at moderate temperatures from commercially available *o*-silyl aryl triflates[2] promoted the exploration of the reactions with arynes as substrates,[3] and the transition metal-catalyzed reaction sequences indeed occurred with arynes in high efficiency.[4] For example, the cyclotrimerization of arynes,[5] the cocyclization of arynes with alkynes,[6] and the multicomponent reactions involving arynes[7] have been reported in the presence of palladium catalysts, which have demonstrated great potential in organic synthesis with selectivities. Copper is one of the most efficient catalysts for the construction of carbon−carbon and carbon−heteroatom bonds,[8] and in particular, the copper acetylide species are active intermediates in organic transformations.[9] However, to the best of our knowledge, there is no report based on the copper-catalyzed strategy of arynes.[10] Our ongoing research program on employing arynes as useful substrates in organic

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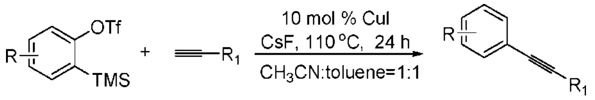
synthesis[11] prompted us to explore the function of copper in the reaction of arynes. Herein, we report the first example of a copper-catalyzed two-component coupling reaction of alkynes with arynes and a three-component coupling reaction of alkynes with allylic chlorides and arynes.

Initially, we performed the reaction of benzyne generated in situ from 2-(trimethylsilyl)phenyl triflate[2] and phenyl acetylene in the presence of copper catalysts. After certain optimization work on the reaction, to our delight, the coupling product of diphenyl acetylene was obtained in an 87% yield without the use of any ligands (Table 1, entry 1). A trace of self-coupling product from phenyl acetylene was observed, but the cocyclization product of arynes and alkynes that often form in palladium catalysis[6a,b] was not detected. Both alkyl and aryl alkynes afforded the desired coupling products in good yields, and the various aryl substituents in aryl alkynes tolerated well the reaction conditions (Table 1, entries 2−5). A good yield was obtained for ethyl propiolate (Table 1, entry 6) and the substituted benzyne gave comparable yields with benzyne (Table 1, entries 7 and 8).

Table 1. The Copper-Catalyzed Two-Component Coupling Reaction



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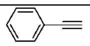
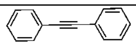
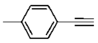
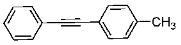
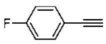
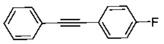
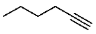
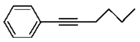
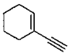
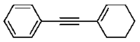
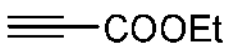
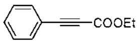
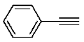
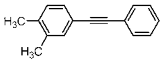
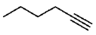
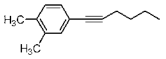
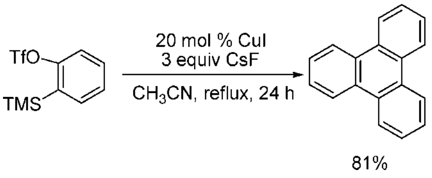
1	H			87
2	H			82
3	H			72
4	H			85
5	H			87
6	H			83
7	3,4-dimethyl			89
8	3,4-dimethyl			92

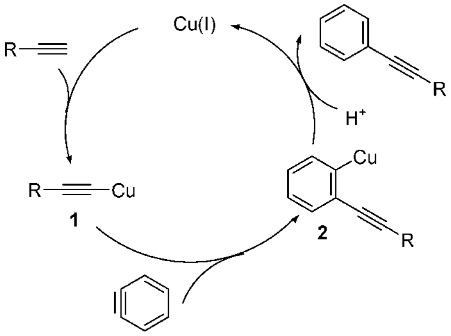
^{a} Reaction conditions: benzyne precursor (1.2 mmol), terminal alkyne (1.0 mmol), CsF (365 mg, 2.4 mmol), CuI (19 mg, 0.05 mmol), toluene: CH$_3$CN = 3:3 mL, 110 °C (bath temperature), 24 h. ^{b} Isolated yield.

Quite interestingly, the cyclotrimerization of benzyne took place in the absence of alkynes, and a high yield of triphenylene was isolated in the presence of 20 mol % CuI in refluxing CH$_3$CN for 24 h (Scheme 1). This result implied that the copper acetylide, which was possibly generated in situ under the reaction conditions, might be a very active intermediate for the initiation of the coupling reaction of alkynes and arynes. A tentative mechanism was proposed for the above coupling reaction as presented in Scheme 2. First, the copper acetylide **1** is formed from the terminal alkyne and copper(I), and the subsequent insertion of benzyne into the copper acetylide **1** produces the carbocopper

Scheme 1



Scheme 2



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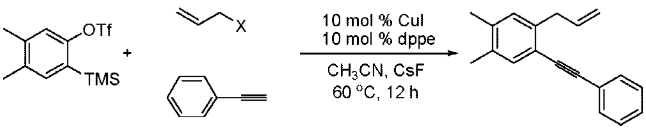
intermediate **2**, which undergoes protonolysis to liberate the coupling product and copper catalyst.

It should be noted that the carbocopper intermediate **2** should also be active and might react with another suitable reagent. Therefore, allyl acetate, allyl chloride, and allyl bromide, which are general allylating reagents used in metal catalysis, were chosen as the third component for the reaction. We were very delighted to find that both allyl chloride and allyl bromide underwent the three-component coupling reaction and yielded the useful 1,6-enyne product (Table 2, entries 1 and 2), while allyl acetate was inactive (Table 2, entry 3). A number of Cu sources were tested, including CuCl, CuBr, $CuCl_2$, and $CuBr_2$, and CuI showed the best reactivity (Table 2, entries 4−7). In these cases, however, the phosphine ligands such as 1,3-bis(diphenylphosphino)propane (dppp) and 1,2-bis(diphenylphosphino)ethane (dppe) were required. No reaction was observed in the absence of copper catalysts (Table 2, entry 8). When the substituted internal alkynes were used as the substrates, a small amount of triphenylene was isolated. Phenanthrene derivatives, which were formed in palladium-catalyzed systems,[6a,b] were not found.

Table 2. Screen for Reaction Conditions[a]

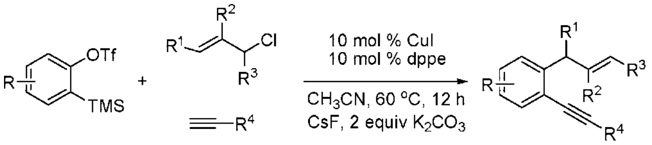


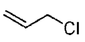
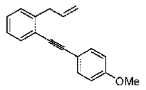
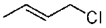
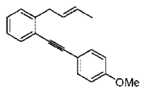
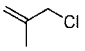
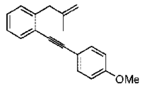
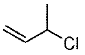
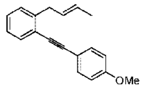
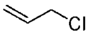
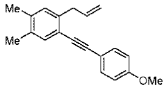
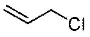
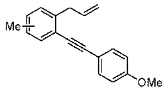
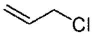
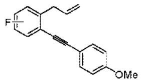
entry	X	cat.	yield (%)[b]
1	Cl	CuI	73
2	Br	CuI	58
3	OAc	CuI	trace
4	Cl	CuCl	53
5	Cl	CuBr	57
6	Cl	$CuCl_2$	60
7	Cl	$CuBr_2$	61
8	Cl	-	NR

[a] Reaction conditions: 4,5-dimethyl-2-(trimethylsilyl)phenyl triflate (163 mg, 0.5 mmol), phenyl acetylene (51 mg, 0.5 mmol), allyl chloride (76 mg, 1.0 mmol), CsF (228 mg, 1.5 mmol), copper catalysts (0.05 mmol), ligands (0.05 mmol), CH_3CN (5 mL), 60 °C (bath temperature), 12 h [b] Isolated yields.

During further studies, we found that a trace of two-component coupling products from alkynes and arynes was always formed in the three-component coupling product as determined by GC-MS analysis, and it was very difficult to separate these byproducts. We felt that we might be able to suppress it by adjusting the reaction conditions, for example, using a base or increasing the amount of allyl chloride to promote the ensuing transformations over the protonolysis of intermediate **2** (Scheme 2). We then performed the reaction using 4 equiv of allyl chloride, and the amount of the two-component coupling product from alkynes and arynes was indeed decreased. The coupling product from alkynes and arynes was fully suppressed by using 2 equiv of K_2CO_3, which probably retarded the protonolysis of intermediate **2**. In conclusion, the optimal reaction conditions for this three-component reaction utilized 10 mol % CuI, 10 mol % dppe, 1.5 equiv of CsF, and 2 equiv of K_2CO_3 in CH_3CN solvent at 60 °C for 12 h.

Table 3. Copper-Catalyzed Three-Component Couplings[a]



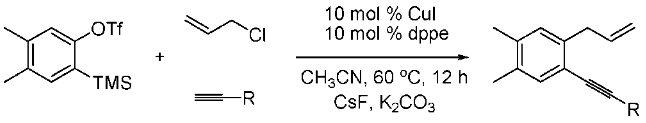
entry	R	allylic chloride	product	yield (%) [b]
1	H			70
2	H			64
3	H			66
4	H			67
5	3,4-dimethyl			71
6	4-Me			82 [c]
7	5-F			75 [c]

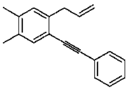
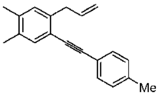
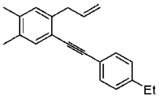
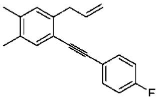
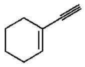
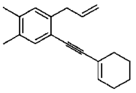
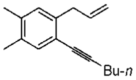
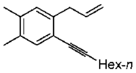
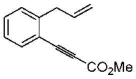
[a] Reaction conditions: benzyne precursors (0.5 mmol); 4-methoxy phenyl acetylene (66 mg, 0.5 mmol), allylic chlorides (2.0 mmol), CsF (228 mg, 1.5 mmol), CuI (10 mg, 0.05 mmol), dppe (25 mg, 0.05 mmol), K_2CO_3 (138 mg, 1.0 mmol), CH_3CN (5 mL), 60 °C (bath temperature), 12 h. [b] Isolated yields. [c] Two isomers are nearly 1:1.

The scope and limitations of this copper-catalyzed three-component coupling reaction were studied as shown in Table 3. Under the standard reaction conditions, a variety of substituted allylic chlorides underwent the reaction smoothly and delivered good yields (Table 3, entries 1−4). Interestingly, we found that the reaction of 3-chlorobut-1-ene afforded the same product as that of chlorobut-2-ene with high regioselectivity at the less substituted carbon in 67% yield (Table 3, entry 4). Benzyne with two methyl groups on the phenyl ring showed comparable reactivity with benzyne and gave the three-component coupling product in 71% yield (Table 3, entry 5). It should be noted that 4-methyl-substituted aryne led to two regioisomers in a ratio of 1:1, indicating that the reaction process was through

4-methylbenzyne (Table 3, entry 6). Similarly, a mixture of regioisomers was obtained in the case of 5-fluoro-substituted benzyne precursor (Table 3, entry 7).

Table 4. Copper-Catalyzed Three-Component Couplings[a]

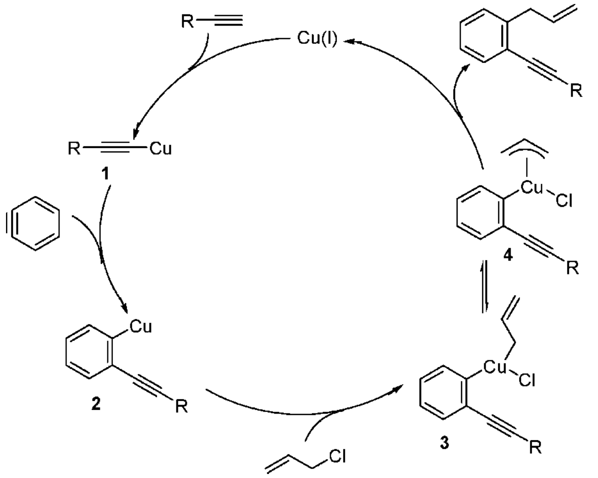


entry	R	product	yield (%)[b]
1	C_6H_5		73
2	4-Me-C_6H_4		76
3	4-Et-C_6H_4		80
4	4-F-C_6H_4		72
5			81
6	*n*-Bu		77
7	*n*-Hex		81
8	≡—COOMe		46

[a] Reaction conditions are the same as for Table 3. [b] Isolated yield.

The optimized reaction conditions could be applied to a variety of terminal alkynes (Table 4). Electronic variation on aryl acetylenes causes no appreciable change in the efficiency of the three-component couplings (Table 4, entries 1−4). The conjugated enyne readily participated in the reaction (Table 4, entry 5). The aliphatic terminal alkynes exhibited comparable reactivity with phenylacetylene (Table 4, entries 6 and 7). Methyl propiolate, which is inactive in some of the coupling reactions,[12] underwent this three-component aryne coupling process, and a 46% yield was obtained (Table 4, entry 8). However, no product was found for TMS acetylene and 2-methylbut-3-yn-2-ol.

Scheme 3. Proposed Mechanism and Intermediates



On the basis of these results, we proposed a plausible mechanism for this useful 1,6-enyne synthesis (Scheme 3). Initially, the copper acetylide **1** is formed from the terminal alkyne and copper(I), following insertion of benzyne generated in situ from *o*-(trimethylsilyl)phenyl triflate to afford carbocopper intermediate **2**. Subsequent oxidative addition of allyl chloride to carbocopper intermediate **2** results in the intermediate **3**, which might rearrange to allylcopper complex **4**.[13] The reductive elimination of intermediate **3** or **4** affords the 1,6-enyne product. In the case of substituted allylic chlorides, the reductive elimination of intermediate **4** determines the regiochemistry, and the elimination takes place at the less hindered end of the π-allylic system. Accordingly, 3-chlorobut-1-ene afforded the same product as that of chlorobut-2-ene in the reaction (Table 3, entries 2 and 4). In addition, the phosphine ligands should play a role in the reactivity of intermediate **2**, **3**, and **4**. One other possible pathway is that the nucleophilic attack of carbocopper intermediate **2** to allyl chloride generates the final 1,6-enyne product via an S_N2 or S_N2' reaction due to the allylic rearrangement.

In summary, the present process demonstrates the first example of aryne reactions with copper catalysts and terminal alkynes. The efficient copper-catalyzed three-component coupling of arynes with terminal alkynes and allylic chlorides provides a facile and novel route for the synthesis of 1,6-enynes. Further studies to elucidate the reaction mechanism and extend the scope of the reactions are in progress.

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Supporting Information Available: The experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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