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Copper-Catalyzed Synthesis of 1,3-Enynes

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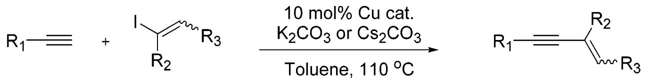
ABSTRACT



We report a copper(I)-catalyzed procedure for the synthesis of 1,3-enynes. This method affords a variety of enynes in good to excellent yields. This method can tolerate a variety of functional groups, does not require the use of expensive additives, and is palladium-free.

1,3-Enynes can be found in many naturally occurring and biologically active compounds.[1] Terbinafine, which is commonly known as Lamisil, contains the 1,3-enyne moiety and is a pharmaceutically important compound used in the treatment of superficial fungal infections.[2] Another pharmaceutically important compound is Calicheamicin $\gamma_1{}^{I}$, which has been shown to be an effective antitumor antibiotic.[3] 1,3-Enynes are also important precursors to polysubstituted benzenes[4] and conjugated dienes via hydroboration-protonolysis.[5]

Among the methods developed to synthesize 1,3-enynes, the Pd-Cu-catalyzed Sonogashira coupling reaction between an alkyne and a vinyl halide is most prevalent.[6] Other methods include the Pd-catalyzed coupling between a terminal organometallic alkyne (Cu, Mg, Si, Zn, Sn)[6a,7] and an alkene or the alkynylation of alkenylmetals (Al, B, Cu, Mg, Zr).[6a,8] The latter methods do suffer from some drawbacks such as toxic reagents, the need to prepare an organometallic alkyne or alkene, poor functional group tolerance, and undesired side-products resulting in low yields.[9]

The use of copper has also been shown to mediate the synthesis of conjugated enynes. Marshall and co-workers synthesized 1,3-enynes by coupling trimethylsilyl alkynes with vinyl iodides.[10] However, this procedure requires the use of a greater than stoichiometric amount of CuCl and is limited to propargylic alcohol derivatives. Hoshi synthesized

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10.1021/ol049706e CCC: $27.50

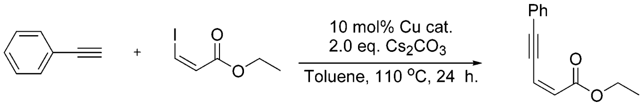
conjugated enynes through the coupling of alkenyldialkylboranes and (trimethylsilyl)ethynyl bromide using strong bases such as NaOMe and LiOH and a catalytic amount of Cu(acac)$_2$.[11]

In recent years, there has been a resurgence in the development of copper-based protocols for a variety of cross-coupling reactions.[12−14] These newly developed protocols have been shown to be mild and tolerate a wide variety of functional groups and substrates. On the basis of these precedences, we now report a Cu(I)-catalyzed cross-coupling reaction of vinyl iodides and acetylenes for the synthesis of 1,3-enynes.[15]

To optimize the reaction protocol we chose the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate as the test reaction. We examined a variety of copper(I) complexes, copper(I) salts, and copper(I) salts with certain additives in toluene at 110 °C with 2.0 equiv of Cs_2CO_3 as the base (Table 1). It was found that both [Cu(phen)(PPh$_3$)$_2$]NO$_3$ and [Cu(bipy)PPh$_3$Br] were effective at catalyzing the reaction.

Using these two complexes as potential catalysts, we then screened a variety of bases for the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate in toluene at 110 °C for 24 h. It was found that the optimal base for [Cu(phen)(PPh$_3$)$_2$]NO$_3$ remained to be Cs_2CO_3. This afforded the desired product with a yield of 76% by GC. However, with [Cu(bipy)PPh$_3$Br] as the catalyst and K_2CO_3 as the base, the yield was improved to 99%. Lowering the amount of base to 1.5 equiv resulted in lower yields. Other bases such as K_3PO_4, Na_2CO_3, KO*t*Bu, NaO*t*Bu, Et_3N, and DBU were ineffective with this reaction. When this reaction was monitored over a period of time, it was discovered that the reaction was complete within 8 h. Lowering the catalytic loading of [Cu(bipy)PPh$_3$Br] to 2.5 mol % for the cross-coupling of phenylacetylene and (*Z*)-ethyl-3-iodoacrylate using 2.0 equiv of K_2CO_3 as the base decreased the yield to 51% in 24 h. When the reaction was run either in the absence of catalyst or in the absence of base, the product was not observed by GC. On the basis of the results of the optimization and control experiments, we decided to use 10 mol % [Cu(bipy)PPh$_3$Br] as the catalyst and 2.0 equiv of K_2CO_3 as the base in toluene at 110 °C for the standard protocol for synthesizing 1,3-enynes.

Table 1. Comparison of *Well-Defined* Copper(I) Complexes, Copper(I) Salts, and Additives as Catalysts for the Cross-Coupling of Phenylacetylene and (*Z*)-Ethyl-3-iodoacrylate[a]



catalyst	GC yield
well-defined complexes	
[Cu(phen)(PPh$_3$)$_2$]NO$_3$	76%
[Cu(bipy)PPh$_3$Br]	74%
[Cu(phen)PPh$_3$Br]	69%
[Cu(PPh$_3$)$_3$Br]	51%
[Cu(neocup)PPh$_3$Br]	34%
[Cu(acac)(PPh$_3$)$_2$]	21%
[Cu(neocup)$_2$Br]H$_2$O	7%
[Cu(CH$_3$CN)$_4$]PF$_6$	4%
copper(I) salts	
CuCl	2%
CuI or CuBr or Cu$_2$O	0%
copper(I) salts/additives	
CuI/phen/PPh$_3$ (1:1:2)	53%
CuI/phen (1:1)	36%
CuI/bipy (1:1)	16%

[a] Reaction Conditions: 1.00 mmol phenyl acetylene, 1.00 mmol (*Z*)-ethyl-3-iodoacrylate, 10 mol % Cu(I) catalyst, 2.0 equiv Cs_2CO_3, toluene, 110 °C, 24 h (phen = 1,10-phenanthroline, bipy = 2,2′-bipyridine, neocup = 2,9-dimethyl-1,10-phenanthroline, acac = acetylacetonate).

We first chose to examine the efficacy of coupling a variety of acetylenes to (*Z*)-ethyl-3-iodoacrylate (Table 2). It was found that a wide-range of aryl acetylenes could be coupled in good to excellent yields with complete retention of stereochemistry. This method tolerated both electron-rich and electron-poor aryl acetylenes. Sterically hindered aryl acetylenes (Table 2, entries 3 and 13) are also successfully coupled in good to excellent yields. Notably, base-sensitive functional groups such as methyl ketones (Table 2, entry 11) and methyl esters (Table 2, entries 12 and 13) are also tolerated by this method. A free aniline group (Table 2, entry 6), a terminal alkene (Table 2, entry 7), and a bromine (Table 2, entry 17) all proved to be compatible functional groups. Heterocyclic acetylenes such as a pyridine moiety and a thiophene (Table 2, entries 15 and 16, respectively) were also compatible substrates with this protocol. However, for 3-ethynylpyridine, the use of [Cu(phen)(PPh$_3$)$_2$]NO$_3$ as the catalyst and Cs_2CO_3 as the base was needed to obtain the cross-coupled product in a moderate yield. The cross-coupling of *n*-octyne and (*Z*)-ethyl-3-iodoacrylate demon-

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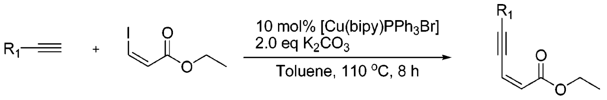
(15) We are aware of only one account of a copper(I)-catalyzed cross-coupling of vinyl iodides and acetylenes. However, this method requires the use of DMF or DMSO as the solvent at 120 °C. Furthermore, the scope and limitations of this reaction have not been fully explored. See: Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716.

Table 2. Copper-Catalyzed Cross-Coupling of Various Acetylenes with (*Z*)-Ethyl-3-iodoacrylate Using the Standard Protocol



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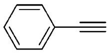
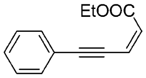
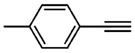
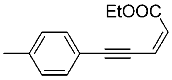
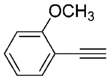
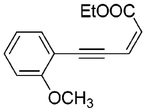
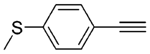
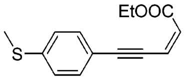
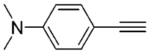
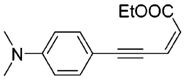
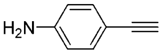
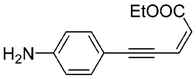
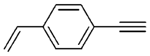
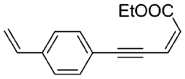
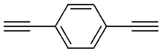
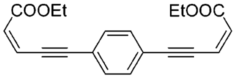
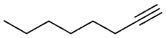
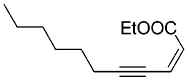
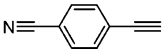
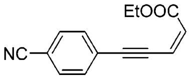
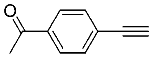
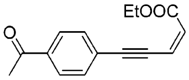
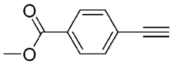
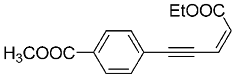
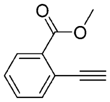
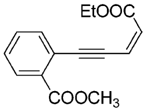
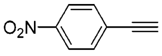
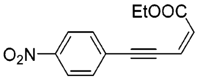
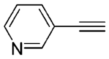
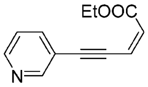
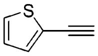
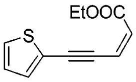
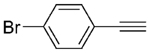
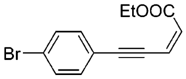
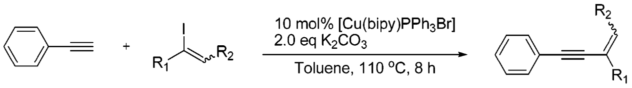
1			99
2			85
3			98
4			91
5			88
6			90
7			95
8			87[a]
9			96
10			85
11			92
12			88
13			77
14			89
15			51[a,b]
16			62
17			65[c]

[a] Reaction run for 12 h. [b] [Cu(phen)(PPh$_3$)$_2$NO$_3$] (10 mol %) as catalyst and 2.0 equiv of Cs$_2$CO$_3$ used as base. [c] Reaction run for 20 h.

Table 3. Copper-Catalyzed Cross-Coupling of Phenylacetylene with Various Vinyl Iodides Using the Standard Protocol



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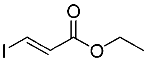
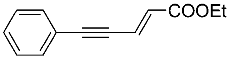
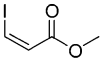
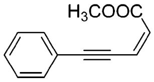
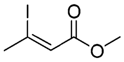
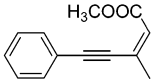
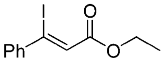
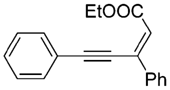
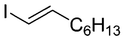
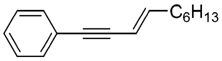
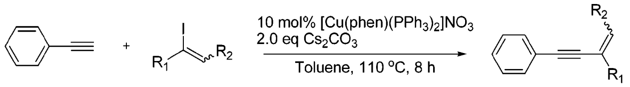
1			81[a]
2			90
3			97
4			97
5			99[a]

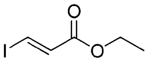
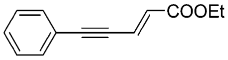
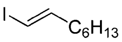
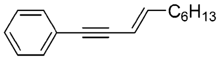
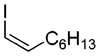
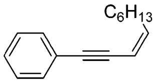
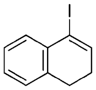
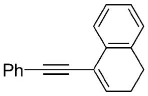
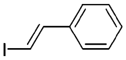
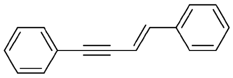
[a] Reaction run for 24 h.

strated that this procedure was not specific to aryl acetylenes (Table 2, entry 9).

We then chose to examine cross-coupling of phenyl acetylene to a variety of vinyl iodides (Table 3). The standard protocol worked well for a variety of β-(*Z*)-iodo-α,β-unsaturated esters (Table 3). When (*E*)-ethyl-3-iodoacrylate was used as the vinyl iodide, the reaction yield after 8 h was only 55% when [Cu(bipy)PPh$_3$Br] was used as the catalyst and K$_2$CO$_3$ was used as the base. However, allowing the reaction continue for 24 h improved the yield to 81%. A similar observation was made when (*E*)-1-iodo-octene was

Table 4. Copper-Catalyzed Cross-Coupling of Phenylacetylene with Various Vinyl Iodides Using 10 Mol % [Cu(phen)(PPh$_3$)$_2$]NO$_3$ as the Catalyst and Cs$_2$CO$_3$ as the Base



entry	vinyl iodide	product	yield
1			99[a]
2			98
3			98
4			78[b]
5			98

[a] GC yield. [b] Reaction run for 24 h.

used as the vinyl iodide (Table 3, entry 5). This reaction also required 24 h to afford the desired product in excellent yield.

For reactions that were difficult using our standard protocol, we found that when the catalyst was changed to $[Cu(phen)(PPh_3)_2]NO_3$ and the base changed to Cs_2CO_3, the yields were greatly improved (Table 4). We were now able to successfully couple electron-rich vinyl iodides in excellent yields. (*E*)-Ethyl-3-iodoacrylate can now be coupled to phenyl acetylene with a near quantitative yield in 8 h (Table 4, entry 1). The cross-coupling of both (*E*)-1-iodo-octene and (*Z*)-1-iodo-octene to phenyl acetylene (Table 4, entries 2 and 3, respectively) were complete in 8 h with retention of stereochemistry. We did find that the use of a cyclic vinyl iodide resulted in slightly lower yields and longer reaction times (Table 4, entry 4).

In conclusion, we have developed a mild protocol for the synthesis of 1,3-enynes via a copper(I)-catalyzed cross-coupling reaction between an acetylene and a vinyl iodide. For most substrates, we recommend the use of $[Cu(bipy)PPh_3Br]$ as the catalyst and K_2CO_3 as the base. In cases where the vinyl halide is an (*E*)-alkene, we recommend the use of $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and Cs_2CO_3 as the base. Our protocol tolerates a wide-range of substrates and functional groups affording the desired enynes in high yields. The cross-coupled products retain the stereochemistry of the starting vinyl iodides. Furthermore, this protocol is palladium-free, does not rely on the use of expensive and air-sensitive additives, and eliminates the need for an organometallic alkene or alkyne species.

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Supporting Information Available: Synthetic procedures and complete characterization data for entries in Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

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