Copper-Catalyzed Coupling of Alkynes with Alkenyl Halides

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Received 1 December 2011

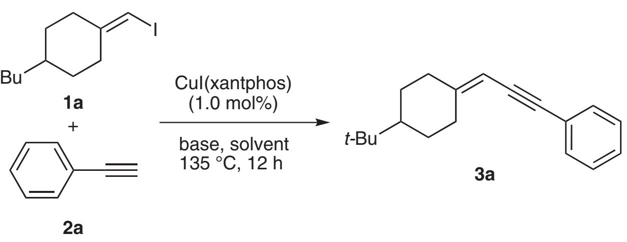
Abstract: The synthesis of enynes from the coupling of terminal alkynes with alkenyl iodides and bromides is described. This system employs 1.0–5.0 mol% of CuI(Xantphos) as a catalyst. A variety of alkenyl iodides and bromides are coupled smoothly with terminal alkynes, affording enynes in good to excellent yields.

Key words: copper, cross-coupling, terminal alkyne, alkenyl halide, enyne

Enynes are important skeletons in organic synthesis, materials science, and the pharmaceutical industry.[1,2] Many strategies have been achieved for preparing enynes, but the transition-metal-catalyzed dimerization of two terminal alkynes is one of the more popular methods.[3] This method is an excellent example of the atom-economy concept, however, it sometimes suffers from a lack of regioselectivity, leading to undesirable regioisomers.[3a,e,g,i] The metal-catalyzed coupling reaction of alkynyl halides with organometallic alkenes is another route to enynes and eliminates the ailment of regioselectivity,[4] however, tedious procedures are required for synthesizing alkynyl halides and organometallic alkenes limiting the popularity of this approach. The Sonogashira coupling reaction of aryl and alkenyl halides with alkynes in the presence of palladium and copper as the co-catalyst is well known and has been widely applied for the formation of Csp^2–Csp bond.[5,6] Indeed, adding a copper salt as the sole metal source has gained significant attention in the Sonogashira-type reaction because of the low cost of copper.[7] As a result, the copper-catalyzed coupling reaction of alkynes and alkenyl halides is an alternative way for constructing enynes.[8,9] For example, the combination of CuI (5 mol%) with Ph_3P (10 mol%) has been reported as the first example of a copper-catalyzed coupling reaction of terminal alkynes with alkenyl halides, however, few cases have been described by this work.[8f] Elegant work published by Venkataraman et al. using 10 mol% of well-defined copper complex [Cu(bipy)PPh_3Br] as the catalyst has also been described.[8d] More recently, Bao et al. demonstrated that a system using 15 mol% of CuI and 30 mol% of 1,10-phenanthroline (30 mol%) is reactive for coupling the (*E*)-β-bromostyrene derivatives with alkynes, however, no alkyl alkynes were presented in their work.[8a] Despite these recent advances, lower catalyst (and ancillary ligand) loading, and greater variety of substrates are desired in the preparation of enynes.

Recently, we communicated a catalytic system comprising of a copper salt with Xantphos as a very efficient method of coupling aryl iodides with alkynes.[7a] Herein, we report that the well-defined CuI(Xantphos) complex[10] also represents a powerful catalyst for the coupling reaction of alkynes with alkenyl halides, affording the enynes in good to excellent yields.

Table 1 Optimization of the Copper-Catalyzed Coupling Reaction of 1-(Iodomethylidene)-4-*tert*-butyl-cyclohexane (**1a**) with Phenylacetylene[a]



Entry	Base	Solvent	Yield (%)[b]
1	Cs_2CO_3	DMSO	44
2	Cs_2CO_3	NMP	68
3	Cs_2CO_3	DMF	–
4	Cs_2CO_3	DME	83
5	Cs_2CO_3	dioxane	99
6	Cs_2CO_3	toluene	42
7[c]	Cs_2CO_3	dioxane	–
8	K_3PO_4	dioxane	75
9	K_2CO_3	dioxane	74
10	KO*t*-Bu	dioxane	–
11	Na_2CO_3	dioxane	43
12	Cs_2CO_3	dioxane	72[d]

[a] Reaction conditions (unless otherwise stated): CuI(Xantphos) (0.005 mmol, 1.0 mol%), base (1.0 mmol), phenylacetylene (0.75 mmol), 1-(iodomethylidene)-4-*tert*-butylcyclohexane (0.5 mmol) in solvent (0.5 mL).

[b] Isolated yield.

[c] No catalyst.

[d] 120 °C

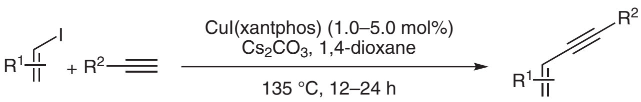
SYNLETT 2012, 23, 930–934
Advanced online publication: 15.03.2012
DOI: 10.1055/s-0031-1290502; Art ID: W74011ST

Initially, 1-(iodomethylidene)-4-*tert*-butylcyclohexane and phenylacetylene were selected as the substrates to optimize the reaction conditions. The results are summarized in Table 1. After screening the effect of solvent (Table 1, entries 1–6), dioxane was found to be the best (Table 1, entry 5). Lower yield of product was observed when the reaction was carried out without catalyst (Table 1, entry 7). Other bases such as K_3PO_4, K_2CO_3, KO*t*-Bu, and Na_2CO_3 could not give satisfying results (Table 1, entries 8–11). Lower temperature will decrease the yield of the product (Table 1, entry 12).

In order to explore the scope of the system, a variety of alkyl and aryl alkynes were reacted with alkenyl iodides (Table 2, entries 1–23), giving the corresponding enynes in good to excellent yields. The results are summarized in Table 2. Functional groups such as free amine (Table 2, entry 5), amino (Table 2, entry 6), and nitro (Table 2, entry 7) all tolerated the reaction conditions. Sterically demanding aryl alkynes also underwent the cross-coupling reaction, affording the products in good to excellent yields (Table 2, entries 3 and 11). (*E*)-β-bromostyrene can also be coupled using this catalytic system (Table 2, entries 24–27).

In summary, we have demonstrated that the CuI(Xantphos) is an active catalyst for the coupling reaction of alkynes with alkenyl iodides and bromides; a variety of alkyl and aryl alkynes with substituted aromatics are involved, giving the corresponding enynes in good to excellent yields.

Table 2 Copper-Catalyzed Coupling Reaction of Alkenyl Halides with Alkynes[a]



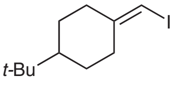
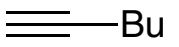
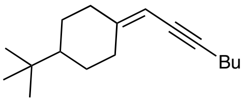
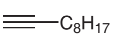
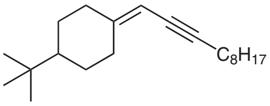
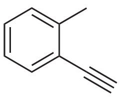
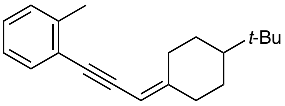
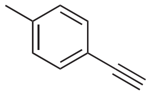
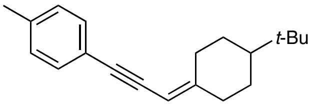
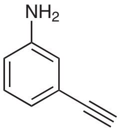
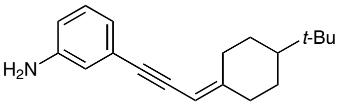
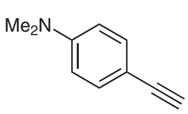
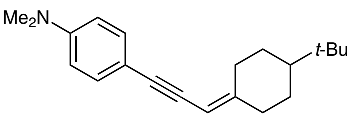
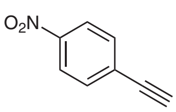
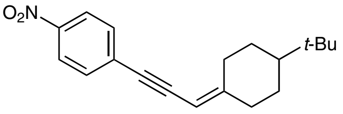
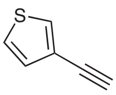
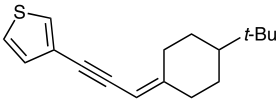
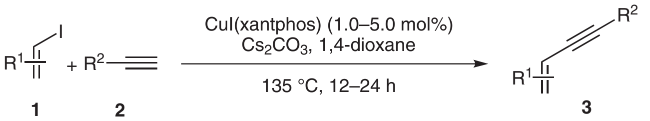
Entry	1	2	Product		Yield (%)[b]	Ratio (*E*/*Z*)[d]
1	 **1a**			**3b**	76	
2	**1a**			**3c**	77	
3	**1a**			**3d**	81	
4	**1a**			**3e**	99	
5	**1a**			**3f**	97	
6	**1a**			**3g**	94	
7	**1a**			**3h**	78	
8	**1a**			**3i**	86	

Table 2 Copper-Catalyzed Coupling Reaction of Alkenyl Halides with Alkynes[a] (continued)



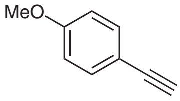
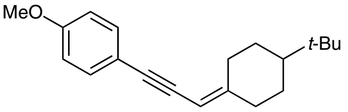
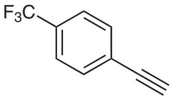
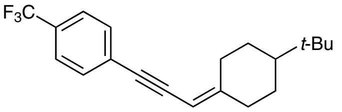
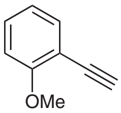
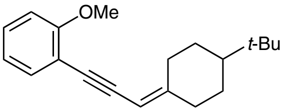
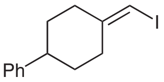
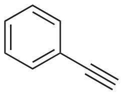
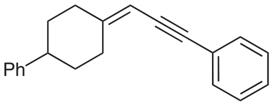
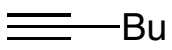
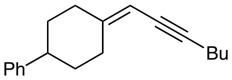
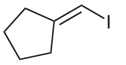
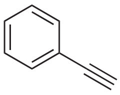
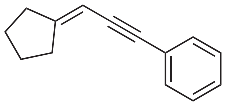
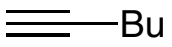
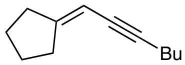
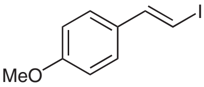
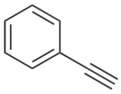
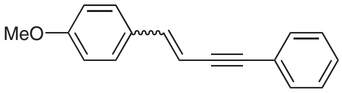
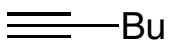
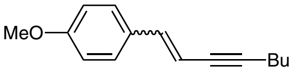
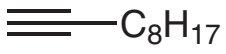
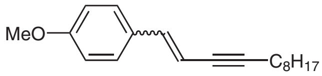
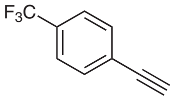
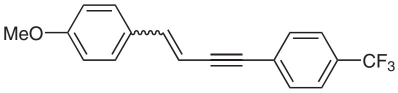
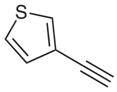
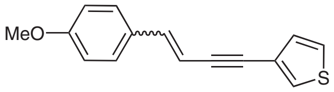
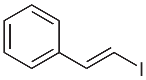
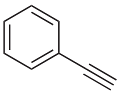
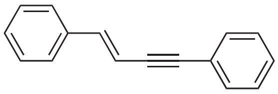
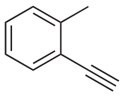
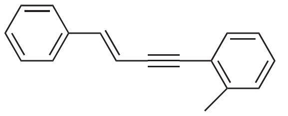
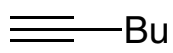
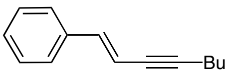
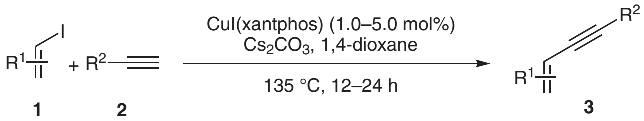
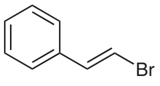
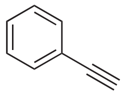
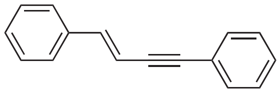
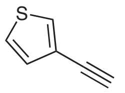
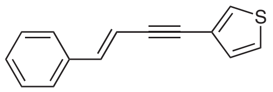
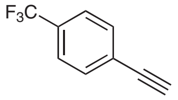
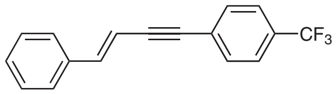
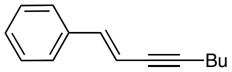
Entry	1	2	Product		Yield (%)[b]	Ratio (*E*/*Z*)[d]
9	**1a**			**3j**	97	
10	**1a**			**3k**	99	
11	**1a**			**3l**	98	
12	 **1b**			**3m**	67	
13	**1b**			**3n**	76[c]	
14	 **1c**			**3o**	79	
15	**1c**			**3p**	98[c]	
16	 **1d**			**3q**	92	4.6:1
17	**1d**			**3r**	90	8.2:1
18	**1d**			**3s**	90[c]	6.5:1
19	**1d**			**3t**	99	4.3:1
20	**1d**			**3u**	99	7.6:1
21	 **1e**			**3v**	67	
22	**1e**			**3w**	68	
23	**1e**			**3x**	98[c]	

Table 2 Copper-Catalyzed Coupling Reaction of Alkenyl Halides with Alkynes[a] (continued)



Entry	1	2	Product		Yield (%)[b]	Ratio (*E*/*Z*)[d]
24	 **1f**			**3v**	98[c]	
25	**1f**			**3y**	88[c]	
26	**1f**			**3z**	90[c]	
27	**1f**	≡—Bu		**3x**	75[c]	

[a] Reaction conditions (unless otherwise stated): CuI(Xantphos) (0.005 mmol, 1.0 mol%), Cs_2CO_3 (1.0 mmol), alkenyl halide (0.5 mmol), alkyne (0.75 mmol) in dioxane (0.5 mL).

[b] Isolated yield.

[c] CuI(Xantphos) (0.025 mmol, 5.0 mol%), 24 h.

[d] The ratios of *E*/*Z* were determined by GC–MS and ^{1}H NMR techniques. The starting 1-(2-iodovinyl)-4-methoxybenzene (**1d**) contains a ratio of *E*/*Z* = 8:1; 1-(2-iodovinyl)benzene (**1e**) contains a ratio of *E*/*Z* = 9:1; 1-(2-bromovinyl)benzene (**1f**) contains a ratio of *E*/*Z* = 10:1. Only the *E* products were detected in entries 21–27.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

Financial support by the National Science Council, Taiwan (NSC99-2113-M-005-004-MY2) and the National Chung Hsing University are gratefully acknowledged. We thank Prof. Fung-E. Hong for generously sharing his GC–MS instruments. C.F.L. is a Golden-Jade Fellow of Kenda Foundation, Taiwan.

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