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Palladium-Free Synthesis of Conjugated Enynes by Direct Olefination of Terminal Alkynes Using Vinyl Bromides

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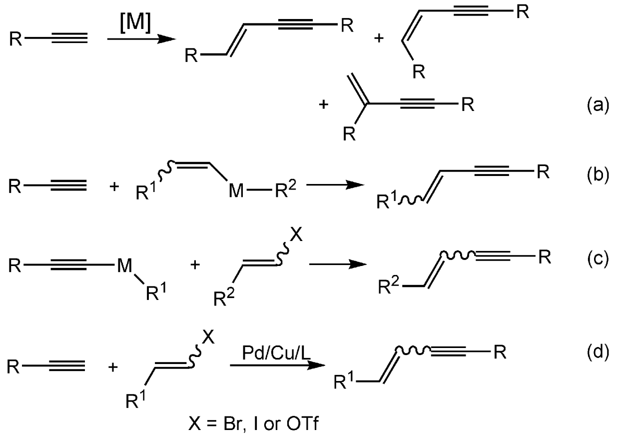
Keywords: Conjugation / Enynes / Alkynes / Copper / Olefination

A series of conjugated enynes were successfully synthesized by the direct copper-catalyzed coupling reaction of vinyl bromides and alkynes. The reaction proceeds smoothly in DMF at 110 °C to give the corresponding products in good to excellent yields. The protocol is tolerant to a broad range of functional groups on the substrates. Moreover, the products were furnished as specific *E* isomers, as the stereochemistry of the vinyl bromides was retained.

Introduction

The conjugated enyne is a structure of high interest owing to its presence in many natural products and biologically active compounds.[1] For example, the Neocarzinostatin chromophore, which contains the central subunit of a conjugated alkyne,[2] is a typical natural product possessing potent antitumor activity and is recognized as the chromoprotein antibiotic. In contrast, as a result of their unique architectural properties, conjugated enynes have been found to be valuable synthons to construct functional chemicals. For example, conjugated enynes are widely employed for the synthesis of polysubstituted benzenes on both the industrial and laboratory scale.[3] Moreover, enynes are excellent precursors for the preparation of stereospecific 1,3-dienes.[4]

With the broad functionalities and utilities embedded in enynes, great efforts have been made to develop practical methods to synthesize this scaffold. Several useful synthetic strategies for enynes have been established during the past decades. Among these known methodologies, the noble-metal-catalyzed dimerization of terminal alkynes is a very straightforward and atom-efficient one (Scheme 1, Equation a).[5] However, the regio- and stereoselectivity of the dimerization process limits this method. In this regard, the metal-catalyzed coupling reaction between an alkyne and a structurally defined organometallic alkene (B,[6] Sn,[7] Te,[8] Cu,[9]) or the alkenylation of alkynylmetals, such as Si[10] and Sb,[11] have been developed to synthesize conjugated enynes in a specific stereoselective manner (Scheme 1, Equations b and c). However, the organometallic substrates are toxic and difficult to prepare.



Scheme 1. Main synthetic routes to conjugated enynes.

The occurrence of palladium complexes and copper-catalyzed Sonogashira-type coupling reactions between vinyl halides and terminal alkynes (Scheme 1, Equation d) offers an elegant solution to overcome the problems involved in the aforementioned methods for the facile synthesis of conjugated enynes of specific stereochemistry.[12]

Nevertheless, the use of two metal catalysts in a coupling reaction of this kind makes the recovery of the costly palladium difficult; this is therefore problematic for large-scale application. Thus, searching for more economical conditions to achieve this kind of transformation is still a significant task. Miura et al.[13] first developed the synthesis of conjugated enynes through the coupling of alkynes and vinyl iodides by using only a copper(I) catalyst. Recently, Venkataraman[14] and co-workers reported a similar conver-

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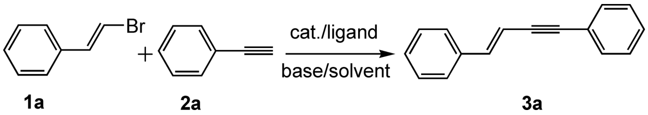
sion catalyzed by a copper(I) complex. However, only vinyl iodides were subjected to the coupling with alkynes in both of the above protocols. To the best of our knowledge, as the equivalent reaction partner of easier access and lower cost, vinyl bromides were not previously claimed to efficiently incorporate into the terminal alkynes to give the targeted conjugated enynes.[15] Following our continuous endeavors to explore the Cu^I-catalyzed transformation of vinyl bromides,[16] herein we wish to report the first simple CuI-catalyzed coupling reaction between vinyl bromides and alkynes to directly provide conjugated enynes.

Results and Discussion

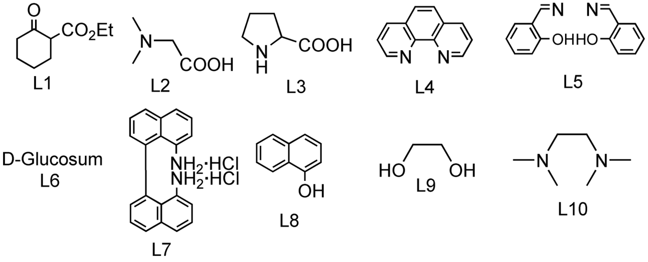
In our preliminary screening experiment, the reaction of vinyl bromide (**1a**) and phenylacetylene (**2a**) was chosen as a model for exploring the suitable reaction conditions (Table 1). A variety of typical ligands were tested to obtain satisfactory result. Among the 10 examined candidates, 1,10-phenanthroline was found as the most effective one (Table 1, Entries 1–10). Subsequently, a brief study on other related reaction conditions was executed. When the temperature was decreased to 90 °C, the product yield decreased (Table 1, Entry 2 vs. 11). In addition, CuI turned out to possess superior catalytic activity over CuBr, Cu_2O, and $FeCl_3$, according to the product yield (Table 1, Entries 4, 12–14). Finally, DMF showed higher efficiency as the reaction medium than all other examined solvents (Table 1, Entries 1, 15–18), and Cs_2CO_3 proved to be a better base than K_2CO_3 and K_3PO_4 (Table 1, Entries 1, 19, 20). Thus, the conditions in Table 1, Entry 4, were found to be optimal for the desired transformation.

On the basis of the above results, the scope and limitations of the coupling reaction were explored by using various vinyl bromides and terminal alkynes, and the results are summarized in Table 2. It was found that the coupling reaction performed well for all substrates examined, affording the corresponding products in moderate to excellent yields. Generally, electron-deficient (*E*)-β-bromostyrenes were superior to electron-rich ones, as evidenced by the better yields (Table 2, Entries 2 and 3 vs. 5 and 6). Similar results were obtained in the coupling of substituted (*E*)-β-bromostyrenes and 1-ethynyl-4-methoxybenzene (Table 2, Entries 12 and 13), but the reaction was slightly disfavored by the steric hindrance of vinyl bromide (Table 2, Entry 6 vs. 7 and Entry 13 vs. 14). Compared to (*E*)-4-methyl-β-bromostyrene, (*E*)-4-methoxy-β-bromostyrene, which contains a strong electron-donating group, gave a considerably lower yield. In contrast, (*E*)-3,4-dimethoxy-β-bromostyrene proved to be a less effective coupling partner, probably owing to its electron-rich properties and steric hindrance (Table 2, Entries 3 and 4). Bromine and chlorine groups are well tolerated on the vinyl bromides (Table 2, Entries 5, 6, 11, 13). In addition, terminal alkynes with an electron-donating group showed higher reactivity than those with electron-withdrawing groups (Table 2, Entries 8–10). Notably, the double-bond geometry of the vinyl halides were retained during the reaction, and the products were obtained specifically as (*E*)-enynes. However, the corresponding product was not observed when (*Z*)-β-bromostyrene was treated with phenylacetylene (Table 2, Entry 15).

Table 1. Optimization of experimental conditions for the formation of enynes.[a]



Entry	Catalyst	Ligand	Base	Solvent	Yield [%][b]
1	CuI	L1	Cs_2CO_3	DMF	83
2	CuI	L2	Cs_2CO_3	DMF	75
3	CuI	L3	Cs_2CO_3	DMF	40
4	CuI	L4	Cs_2CO_3	DMF	88
5	CuI	L5	Cs_2CO_3	DMF	37
6	CuI	L6	Cs_2CO_3	DMF	29
7	CuI	L7	Cs_2CO_3	DMF	62
8	CuI	L8	Cs_2CO_3	DMF	33
9	CuI	L9	Cs_2CO_3	DMF	18
10	CuI	L10	Cs_2CO_3	DMF	trace
11	CuI	L2	Cs_2CO_3	DMF	37[c]
12	CuBr	L4	Cs_2CO_3	DMF	55
13	Cu_2O	L4	Cs_2CO_3	DMF	66
14	$FeCl_3$	L4	Cs_2CO_3	DMF	NR[d]
15	CuI	L1	Cs_2CO_3	DMSO	78
16	CuI	L1	Cs_2CO_3	NMP	54
17	CuI	L1	Cs_2CO_3	DME	40
18	CuI	L1	Cs_2CO_3	toluene	trace
19	CuI	L1	K_2CO_3	DMF	31
20	CuI	L1	K_3PO_4	DMF	56

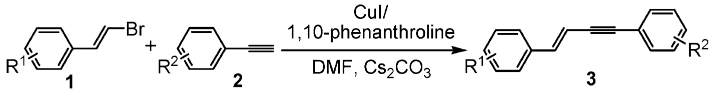


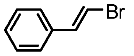
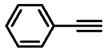
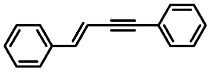
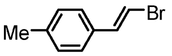
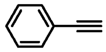
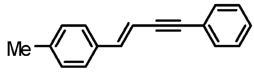
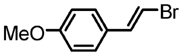
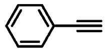
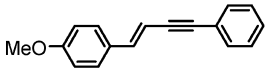
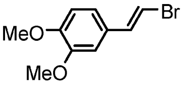
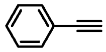
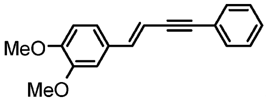
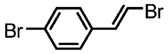
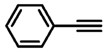
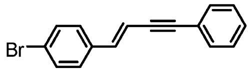
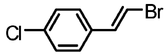
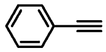
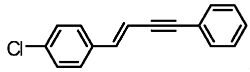
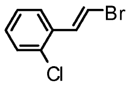
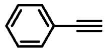
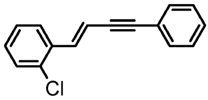
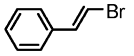
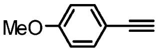
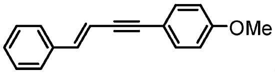
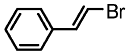
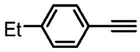
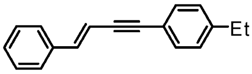
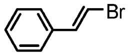
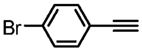
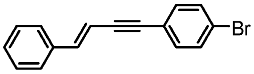
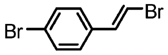
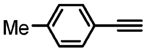
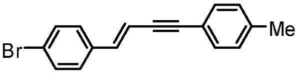
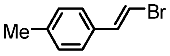
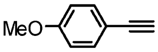
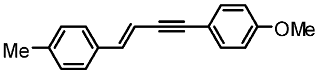
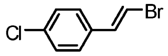
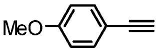
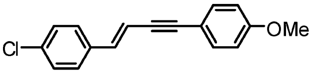
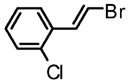
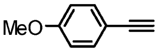
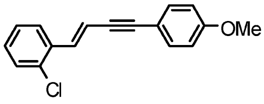
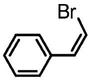
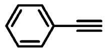
[a] Reaction conditions: catalyst (15 mol-%), ligand (30 mol-%), base (2 mmol), (*E*)-β-bromostyrene (1.0 mmol), phenylacetylene (1.2 mmol), solvent (2 mL), 24 h, 110 °C. [b] Isolated yield. [c] Reaction temperature was 90 °C. [d] No reaction.

Conclusions

In conclusion, we have developed a mild and efficient protocol for the direct synthesis of conjugated enynes by using the CuI-catalyzed coupling of vinyl bromides and alkynes. As the first systematic study on this kind of coupling reaction with the use of only a copper catalyst, this method enjoys broad functional-group tolerance on substrates. This novel methodology provides a very useful supplement to the known methods in terms of economics and workup process for the synthesis of enynes.

Table 2. Preparation of enynes from vinyl bromides with terminal alkynes.[a]



Entry	Vinyl bromide **1**	Alkyne **2**	Product **3**	Yield [%][b]
1			 **3a**	88
2			 **3b**	69
3			 **3c**	52
4			 **3d**	46
5			 **3e**	90
6			 **3f**	91
7			 **3g**	73
8			 **3h**	89
9			 **3i**	90
10			 **3j**	63
11			 **3k**	92
12			 **3l**	78
13			 **3m**	92
14			 **3n**	79
15			–	NR[c]

[a] Reaction conditions: (*E*)-β-bromostyrene (1.0 mmol), phenylacetylene (1.2 mmol), CuI (15 mol-%), 1,10-phenanthroline (30 mol-%), Cs_2CO_3 (2 mmol) in DMF (2 mL) at 110 °C for 24 h. [b] Isolated yield. [c] No reaction.

Experimental Section

General Procedure for the Copper-Catalyzed Coupling of Terminal Alkynes with Vinyl Bromides: A Schlenk tube was charged with CuI (30 mg, 15 mol-%), 1,10-phenanthroline (57 mg, 30 mol-%), and Cs_2CO_3 (650 mg, 2 mmol). The vessel was then evacuated and backfilled with nitrogen. (*E*)-β-Bromostyrene (1.0 mmol), the terminal alkyne (1.2 mmol), and DMF (2 mL) were successively added. The reaction tube was quickly sealed, and the contents were stirred at 110 °C for 24 h. Then, the cooled reaction mixture was dissolved in H_2O and extracted with Et_2O. The combined organic layer was dried ($MgSO_4$). The product was further purified by silica gel column chromatography.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectral data, and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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