Copper Catalysis for Selective Heterocoupling of Terminal Alkynes

Lebin Su,[‡] Jianyu Dong,[‡] Long Liu, Mengli Sun, Renhua Qiu, Yongbo Zhou,* and Shuang-Feng Yin*

State Key Laboratory of Chemo/Biosensing and Chemometrics, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China

S *Supporting Information*

ABSTRACT: A Cu-catalyzed selective aerobic hetero-coupling of terminal alkynes is disclosed, which enables the synthesis of a broad range of unsymmetrical 1,3-diynes in good to excellent yields. The results disprove the long-held belief that homocouplings are exclusively favored in the Glaser–Hay reaction.

The Cu-catalyzed cross-coupling of terminal alkynes (Glaser–Hay reaction) to produce 1,3-diynes is a textbook reaction[1] that has wide applications[2] in organic synthesis[3] and material science.[4] Yet, compared to its extensive application to the synthesis of symmetrical 1,3-diynes via the homocoupling of an alkyne, the preparation of unsymmetrical 1,3-diynes, via the coupling of two different alkynes, is rather limited because of the poor selectivity.[5−8]

Unsymmetrical 1,3-diynes are an important class of inter-mediates in organic synthesis, and they are ubiquitous structural motifs in a large number of natural products and functional materials.[2a,5c,d,9] A landmark contribution to the synthesis of these compounds was made based on the Cadiot–Chodkiewicz reaction,[10a] and the development of its variants was also achieved.[10b,c] Yet, prefunctionalized substrates such as 1-haloalkynes are required. Direct synthetic methods that employ a vast excess of one alkyne were recently developed, but resulting in low total heteroselectivity.[11] Significant progress was recently made by Shi et al. over the Au/phen catalytic system using PhI(OAc)$_2$ as an oxidant, achieving selective heterocoupling of substituted aromatic alkynes with aliphatic alkynes.[12] Nonethe-less, the copper-catalyzed selective heterocoupling of terminal alkynes still remains a big challenge in organic synthesis.[2a,5,12]

Herein, we describe a copper-catalyzed selective heterocou-pling of terminal alkynes using Glaser–Hay-type reaction conditions to produce unsymmetrical 1,3-diynes (eq 1). In

$$R^1 \!\!-\!\!\equiv\!\!-H + H\!\!-\!\!\equiv\!\!-R^2 \xrightarrow[\text{CHCl}_3,\ \text{air}]{\text{Cu}^0,\ \text{TMEDA}} R^1\!\!-\!\!\equiv\!\!-\!\!\equiv\!\!-R^2 \quad (1)$$
$$R^1, R^2 = \text{aryl, alkyl}$$
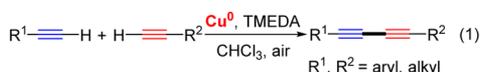
addition to the selective heterocoupling of an aromatic alkyne with an aliphatic alkyne, the copper-catalyzed system allows selective heterocoupling between two different aromatic alkynes and between two different aliphatic alkynes.

Initially, the reaction of 2,2-dimethylpropargyl alcohol (**1a**) with phenylacetylene (**2a**) was tested to optimize the reaction conditions (Table 1; see Supporting Information (SI) for details). For copper catalysts, CuCl, CuBr, Cu$_2$O, and CuF$_2$ showed moderate efficiency (yield: 57−60%, **3a**/**4a** = 4.5−5.7, entries 1−4) in the presence of N^1,N^1,N^2,N^2-tetramethylethylenediamine

Table 1. Optimization of Conditions[a]
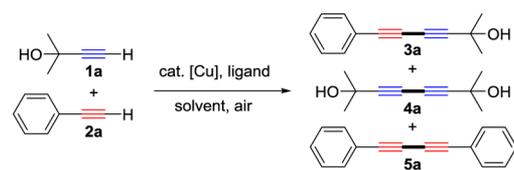
| entry | [Cu] | ligand | solvent | yield (%)[b] | | | 3a/4a/5a |
				3a	4a	5a	
1	CuCl	TMEDA	CHCl$_3$	60	12	18	5.0/1/1.5
2	CuBr	TMEDA	CHCl$_3$	57	10	22	5.7/1/2.2
3	Cu$_2$O	TMEDA	CHCl$_3$	60	12	24	5.0/1/2
4	CuF$_2$	TMEDA	CHCl$_3$	58	13	20	4.5/1/1.5
5	CuI	TMEDA	CHCl$_3$	46	18	29	2.5/1/1.6
6	Cu(OH)$_2$	TMEDA	CHCl$_3$	trace	trace	trace	-
7	Cu(OAc)$_2$	TMEDA	CHCl$_3$	0	0	trace	-
8	Cu(NO$_3$)$_2$	TMEDA	CHCl$_3$	trace	trace	trace	-
9	CuO	TMEDA	CHCl$_3$	trace	0	trace	-
10	Cu^0	TMEDA	CHCl$_3$	74	6	14	12/1/2.3
11	Cu^0	-	CHCl$_3$	0	0	0	-
12	Cu^0	TEEDA	CHCl$_3$	trace	0	trace	-
13	Cu^0	Phen	CHCl$_3$	0	0	0	-
14	Cu^0	TMMDA	CHCl$_3$	0	0	trace	-
15	Cu^0	bpy	CHCl$_3$	trace	0	trace	-
16	Cu^0	DEDMEDA	CHCl$_3$	70	11	18	6.4/1/1.6
17[c]	Cu^0	TMEDA	CHCl$_3$	38	4	13	9.5/1/3.3
18[d]	Cu^0	TMEDA	CHCl$_3$	43	6	11	7.2/1/1.8
19	Cu^0	TMEDA	CH$_3$CN	7	trace	20	-
20	Cu^0	TMEDA	CHBr$_3$	trace	trace	trace	-
21	Cu^0	TMEDA	CH$_2$Cl$_2$	45	14	19	3.2/1/1.4
22[e]	Cu^0	TMEDA	CHCl$_3$/dioxane	78	5	13	16/1/2.6
23[f,g]	Cu^0	TMEDA	dioxane	72	7	16	10/1/2.3
24	Cu^0	TMEDA	dioxane	trace	trace	trace	-
25[h]	Cu^0	TMEDA	CHCl$_3$/dioxane	83	7	16	12/1/2.3
26[h,i]	Cu^0	TMEDA	CHCl$_3$/dioxane	78	14	13	5.5/1/0.9
27[h,j]	Cu^0	TMEDA	CHCl$_3$/dioxane	72	7	13	10/1/1.9
28[g,j]	CuCl	TMEDA	acetone	47	24	25	2.0/1/1

[a]Reaction conditions: 2,2-dimethylpropargyl alcohol, **1a** (0.20 mmol), phenylacetylene, **2a** (0.26 mmol), [Cu] (0.01 mmol, 5.0 mol %), ligand (0.04 mmol, 20 mol %), solvent (0.4 mL), air, 50 °C, 4 h. [b]GC yields of **3a** and **4a** based on **1a**, and **5a** based on **2a**. [c]30 °C. [d]70 °C. [e]CHCl$_3$ (0.3 mL), 1,4-dioxane (0.1 mL). [f]5 equiv of CHCl$_3$ (1 mmol), 1,4-dioxane (0.4 mL). [g]12 h. [h]8 h. [i]**1a** (0.26 mmol), **2a** (0.20 mmol). [j]**1a** (0.20 mmol), **2a** (0.20 mmol).

(TMEDA). In the case of copper powder, there was a significant improvement in both yield and selectivity (74%, **3a**/**4a** = 12, entry 10), whereas Cu(OH)$_2$, Cu(OAc)$_2$, Cu(NO$_3$)$_2$, and CuO were ineffective (entries 6−9).

The replacement of TMEDA with other bidentate ligands, such as N^1,N^1,N^2,N^2-tetraethylethylenediamine (TEEDA), Phen, TMMDA, TMTDA, and bpy, resulted in no yield for the desired product (entries 12−15). Notably, good yield and hetero-

Table 2. Substrate Scope[a,b]

$$R^1\!\!\equiv\!\!-H \;+\; H\!\!-\!\!\equiv\!\!R^2 \xrightarrow[\text{CHCl}_3/\text{1,4-dioxane (3:1), air, 50 °C}]{\text{Cu}^0 \text{ 5 mol \%, TMEDA 20 mol \%}} R^1\!\!\equiv\!\!\equiv\!\!R^2 \;+\; R^1\!\!\equiv\!\!\equiv\!\!R^1 \;+\; R^2\!\!\equiv\!\!\equiv\!\!R^2$$

1 0.20 mmol   **2** 0.26 mmol   **3**   **4**   **5**

R[1], R[2] = aryl, alkyl

3a, 80% (14:1:2.6), 70% (10:1:1.8)[c]   **3b**, 73% (10:1:2.2)   **3c**, 68% (8:1:2)   **3d**, 65% (8:1:2)

3e, 72% (12:1:2.7)   **3f**, 68% (9:1:2.6)   **3g**, 84% (14:1:2.3), 85% (15:1:2.5)[d]   **3h**, 75% (11:1:2.4)

3i, 73% (11:1:2.6)   **3j**, 87% (17:1:2.9)   **3k**, 81% (10:1:2.1)   **3l**, 78% (11:1:2.1)

3m, 74% (11:1:2.1)   **3n**, 72% (9:1:1.9), 74% (9:1:2.2)[d]   **3o**, 70% (10:1:2.6)   **3p**, 72% (8:1:1.9), 62% (6:1:1.4)[c]

3q, 82% (12:1:2.5)   **3r**, 75% (8:1:1.9)   **3s**, 80% (10:1:2.1), 71% (7:1:1.4)[c]   **3t**, 65% (9:1:2.8)

3u, 72% (10:1:2.5)   **3v**, 81% (11:1:2.3)   **3w**, 82% (14:1:2.7)   **3x**, 79% (12:1:2.4)

3y, 83% (13:1:2.3)   **3za**, 91% (30:1:4)   **3zb**, 79% (13:1:2.6)   **3zc**, 90% (27:1:3.9), 80% (20:1:2.3)[c]

3zd, 82% (12:1:2.5)   **3ze**, 69% (8:1:2.2)   **3zf**, 85% (15:1:2.8)   **3zg**, 72% (10:1:2.6)[e]

3zh, 63% (9:1:3), 62% (10:1:3.3)[d]   **3zi**, 63% (8:1:2.7)[e], 58% (4:1:1.5)[c]   **3zj**, 72% (10:1:2.4)   **3zk**, 82% (13:1:2.5), 83% (13:1:2.3)[d]

3zl, 77% (9:1:1.9), 68% (6:1:1.2)[c]   **3zm**, 83% (14:1:3.1), 73% (9:1:1.2)[c]   **3zn**, 87% (14:1:2.4), 75% (8:1:1.3)[c]

3zo, 71% (8:1:2.2)   **3zp**, 71% (8:1:2.4), 63% (5:1:1.2)[c]   **3zq**, 75% (11:1:2.5), 66% (6:1:1.3)[c]

3zr, 72% (10:1:2.6), 76% (13:1:2.9)[d]   **3zs**, 70% (10:1:2.3)   **3zt**, 77% (9:1:2.1), 69% (7:1:1.5)[c]

[a]Reaction conditions: **1** (0.20 mmol), **2** (0.26 mmol), Cu powder (0.01 mmol), TMEDA (0.04 mmol), CHCl₃ (0.3 mL), 1,4-dioxane (0.1 mL), air, 50 °C, overnight. [b]Isolated yield based on **1**, **3**/**4**/**5** in parentheses. [c]**1** (0.20 mmol), **2** (0.20 mmol). [d]Compound **I** (0.01 mmol), TMEDA (0.04 mmol), 1,4-dioxane (0.4 mL). [e]**1** (1.0 mmol), **2** (1.3 mmol).

selectivity were observed (70%, **3a**/**4a** = 6, entry 16) by the use of *N,N′*-diethyl-*N,N′*-dimethylethylenediamine (DEDMEDA) that has only a slightly less steric hindrance than that of TEEDA. The reaction was also sensitive to the reaction temperature, and a low yield of the heterocoupling product (**3a**) was observed at temperatures higher or lower than 50 °C (entries 17 and 18). An investigation of the effect of the solvent showed that a mixture of CHCl₃ and dioxane was the best for reaction performance, producing **3a** in a 78% yield with excellent selectivity (**3a**/**4a** = 16, entry 22). The reaction proceeded smoothly in the presence of only 5 equiv of chloroform in dioxane, producing **3a** in a 72% yield (entry 23), whereas only a trace amount of **3a** was observed in the absence of chloroform (entry 24). By prolonging the reaction time to 8 h, the yield of **3a** slightly increased (83%), but the heteroselectivity decreased due to the homocoupling of redundant **1a** to **4a** (**3a**/**4a** = 12, entry 25). A comparable yield for **3a** (78%) was observed with the inversion of the **1a** to **2a** ratio (1.3:1, entry 26). An equimolar mixture of two alkynes gave a

satisfactory yield of **3a** (72%, **3a**/**4a** = 10, entry 27). In contrast, a low yield of the heterocoupling product[7,12] was observed under Glaser−Hay reaction conditions (47%, entry 28).

As shown in Table 2, the copper catalytic system exhibits a wide scope of substrates and an outstanding tolerance for functional groups, producing various unsymmetrical 1,3-diynes in good to excellent isolated yields (see SI for details). Aromatic alkynes substituted with alkyl (**3b−f**), F (**3g**), Cl (**3h**), Br (**3i**), CF₃ (**3j**), OMe (**3k,l**), aryl (**3m,n**), CN (**3o**), NH₂ (**3p**), CH₃CO (**3q**), and NO₂ (**3r**) worked well to give the corresponding conjugated diynes in 65−87% yields. Steric hindrance has only a slight effect on the reaction (**3b−d**), and the attachment of an electron-withdrawing group on the phenyl ring results in higher yields for the heterocoupling products (**3g−j**). Heteroaromatic alkynes that contain thiophene (**3s**) and pyridine (**3t,u**) also reacted efficiently. Aliphatic alkynes are good substrates, producing the corresponding conjugated diynes in good to excellent yields (63−91%, **3v−zi**). Functional groups, including primary alcohols (**3v**),

secondary alcohols (**3w**), tertiary alcohols (**3x**), benzyl alcohols (**3y**), esters (**3za**, **zf**), ethers (**3zb**), thioethers (**3zc**), acetals (**3zd**), amides (**3ze**), and silicanes (**3zg**), are all tolerated. In the case of ethisterone, being a highly functionalized aliphatic alkyne, the 1,3-diyne-derived drug-like molecule was produced in a satisfactory yield (63%, **3zh**). This clearly demonstrates the great potential of this new methodology for accessing highly function-alized target molecules. Notably, the reaction of phenylacetylene with cyclohexylacetylene, which does not include any functional substituted groups, also proceeded selectively to afford the corresponding product in a 63% yield (**3zi**).

In addition to aromatic and aliphatic alkynes, this Cu-catalyzed reaction is applicable to the heterocoupling between two different aromatic alkynes, and unsymmetrical aryl–aryl 1,3-diynes were selectively produced in 71–87% yields (**3zj**–**zp**). Remarkably, despite slight differences in reactivity for the C(sp)–H bonds, *p*- and *o*-tolyacetylene were well "discriminated" in the catalytic reaction, giving the desired product in a 71% yield (**3zo**), which may have resulted from their different steric hindrance, too. The reaction of two different aliphatic alkynes also resulted in selective formation of heterocoupling products, and a variety of unsym-metrical alkyl–alkyl 1,3-diynes were generated in 70–77% yields (**3zq**–**zt**). Even in the cases of two alkynes in an exact 1:1 molar ratio, satisfactory yields (58–80%) and total heteroselectivity (3/ (3 + 4 + 5), 64–86%) were obtained (**3a**, **3p**, **3s**, **3zc**, **3zi**, **3zl**, **3zm**, **3zn**, **3zp**, **3zq**, and **3zt**).

The method can be applied to the synthesis of unsymmetrical polyynes, such as conjugated triyne and tetrayne. For example, triyne **8** is selectively produced in a 72% yield from buta-1,3-diyn-1-ylbenzene **6** and **1a** (Scheme 1A). Treatment of **3a** with **3p**

Scheme 1. Synthesis of Unsymmetrical Polyynes
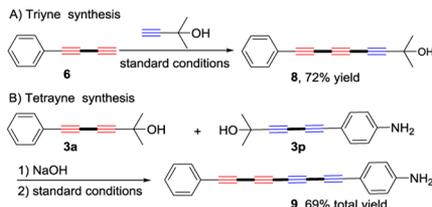
under one-pot deprotection/oxidation conditions produced tetrayne **9** in a 69% yield (Scheme 1B). The gram-scale synthesis of **3a** was successfully achieved (79%; details in SI). Therefore, we envision important applications for this method, especially for the synthesis of electronic, optical, and natural materials.

To gain insights into the mechanism, several control experiments were conducted. The reaction was accomplished in the presence of a catalytic amount of copper powder under N_2, but a longer time was required (eq 2), giving a slightly lower yield and
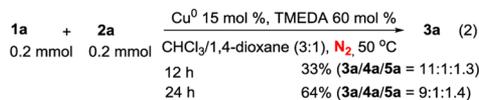
selectivity (**3a**: 64%, **3a**/**4a** = 9:1) than the reaction conducted under air. The results indicate that despite its inferiority to air, chloroform can serve as an oxidant.

After treatment of the Cu powder with TMEDA in chloroform under dry N_2 at 50 °C for 24 h, a pale yellow solid, **I**, was isolated in a 86% yield. The structure of **I** was unambiguously confirmed using single-crystal X-ray crystallography (Figure 1). The X-ray analysis showed that the Cu center was coordinatively saturated
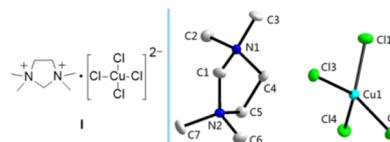
Figure 1. Molecular structure of **I**. Thermal ellipsoids are drawn at 50% probability. H atoms omitted for clarity. Selected bond lengths (Å) and angles (deg): Cu1−Cl1 = 2.2488(8), Cu1−Cl2 = 2.2471(7), Cu1−Cl3 = 2.2559(8), Cu1−Cl4 = 2.2269(9), Cl4−Cu1−Cl2 = 100.35(3), Cl4−Cu1−Cl1 = 101.14(3), Cl2−Cu1−Cl1 = 131.63(3), Cl4−Cu1−Cl3 = 130.36(3), Cl2−Cu1−Cl3 = 99.78(3), Cl1−Cu1−Cl3 = 98.31(3).

inside a tetrahedron structure with similar Cu−Cl distances of 2.2269(9), 2.2471(7), 2.2488(8), and 2.2559(8) Å. Two large Cl−Cu−Cl angles of 131.63(3)° and 130.36(3)° allow attack by alkynes. In the Cu $2p_{3/2}$ XPS spectra of **I** (SI Figure 1), a peak at a binding energy of ∼933.9 eV was accompanied by characteristic Cu(II) shakeup satellites (939−945 eV) that were previously assigned to spinel Cu(II).[13]

In the ESI-MS spectra of **I** in methanol, the peak at *m/z* 367.0 was assigned to $[I + CH_3OH]^+$ (calcd *m/z* 367.6), indicating that the structure of **I** was maintained in solution. Indeed, using **I** as the catalyst in dioxane, the heterocoupling of **1a** and **2a** produced **3a** in a 70% yield in air (eq 3), and comparable results were also

observed in the reaction of other substrates, including that of two aromatic alkynes or two aliphatic alkynes (Table 2, **3g**, **3n**, **3zh**, **3zk**, and **3zr**). The stoichiometric reaction of **1a** with **2a** over copper compound **I** under N_2 produced the heterocoupling product **3a** in a 61% yield. These results suggest that **I** served as the active catalytic species.

By combining an electron-rich aromatic alkyne (**2p**, with a relatively stronger π-electron donating ability) with two electron-deficient aromatic alkynes (**2j** and **2q**, of relatively higher acidity), good heteroselectivity (**3zm**, 72% and **3zl**, 65%) was observed between the electron-rich alkyne and electron-deficient alkynes (eq 4). The selective heterocoupling reaction between **2j** and **2q**
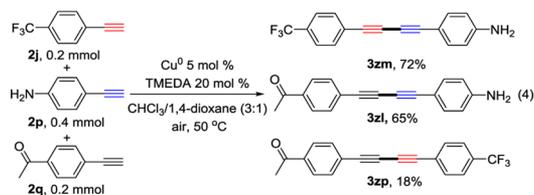
also occurred, giving the heterocoupling product (**3zp**) in an 18% yield. With the dominance of the heterocoupling reactions, the homocoupling reactions of both **2j** and **2q** became minor and produced the homocoupling products in extremely low yields (4% and 7%, respectively; see SI for details). Thus, we deduce that a bigger difference between the reactivity of the alkynes leads to higher heteroselectivity for the desired product.

Regarding the Glaser−Hay coupling mechanism,[1c,14] both the deprotonation and π-complexation of the alkyne with copper are mandatory, and the dimeric copper acetylides are the intermediates that are most currently accepted (Figure 2, left). Obviously, it is difficult to control the chemoselectivity similar to that of the Cadiot−Chodkiewicz reaction (Figure 2, right).[9a,b]
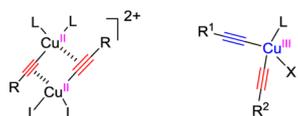
Figure 2. Reaction intermediates in the Glaser coupling reaction (left) and Cadiot−Chodkiewicz coupling reaction (right).

Although the details of the reaction mechanism remain to be clarified, we consider that the good heteroselectivity is perhaps due to the unique structure of Cu complex **I**. It is assumed that the electropositive bis-cation, i.e., the quaternary ammonium of TMEDA, may trap and activate the stronger π-electron donating alkyne (of lower acidity) via a cation−π interaction.[15] The Cu center bonds to four highly electronegative atoms (Cl), and its coordinatively saturated nature resists the π-coordination of the C≡C triple bond to Cu, but it may favor selective ligand exchange with an alkyne of higher acidity. Thus, the two different alkynes could be "discriminated" by the Cu center and bis-cation, respectively.[16] Compared to **I**, Li_2CuCl_4 or $(Et_4N)_2CuCl_4$ provides poor yield and selectivity, which further confirms the above suggestion. In addition, the steric hindrance of both the ligand and alkynes can affect this heteroselectivity, suggesting that it may be another factor for the "discrimination" of two different alkynes.

In summary, we present a new Cu catalysis that leads to selective oxidative cross-coupling of terminal alkynes under mild conditions, enabling the synthesis of a broad range of unsymmetrical aryl−aryl, aryl−alkyl, and alkyl−alkyl 1,3-diynes in good to excellent yields. Both chloroform and TMEDA are essential ingredients for the formation of the Cu(II) catalyst **I**. Catalyst **I** can "distinguish" two different alkynes on the basis of their differences in intrinsic reactivity and steric hindrance, resulting in selective heterocoupling. The present findings not only provide a general, efficient, and simple method for the preparation of unsymmetrical 1,3-diynes and polyynes but also open a new dimension of Cu catalysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b07984.

Experimental procedures and characterization data (PDF)
Crystallographic data for **I** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*zhouyb@hnu.edu.cn
*sf_yin@hnu.edu.cn

Author Contributions

‡L.S. and J.D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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