ORGANIC LETTERS

2004
Vol. 6, No. 6
1001−1003

# Microwave-Promoted Three-Component Coupling of Aldehyde, Alkyne, and Amine via C–H Activation Catalyzed by Copper in Water

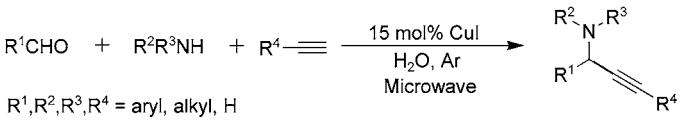
**Lei Shi, Yong-Qiang Tu,* Min Wang, Fu-Min Zhang, and Chun-An Fan**

*Department of Chemistry and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China*

*tuyq@lzu.edu.cn*

**Received January 12, 2004**

## ABSTRACT




**An efficient three-component coupling of aldehyde, alkyne, and amine to generate propargylamines has been effected under microwave irradiation in water using only CuI catalyst without the noble metal cocatalyst. This method has proved to be applicable to a wide range of substrates. In addition, the preliminary experiment using (*S*)-proline methyl ester as a chiral source demonstrated that it could be developed to be a direct and highly diastereoselective method for construction of chiral propargylamines.**

Microwave (MW)-promoted reactions, especially those run in water, have been attracting increasing research interest from chemists in recent years, not only because these reactions exhibit some particular or unexpected reactivities in some cases but also because they are significantly useful for green chemistry.[1] In our corresponding investigations, we have reported a MW-promoted coupling reaction of two components (aromatic halide and amine).[2] As a continued interest, we recently have developed another MW-promoted procedure in a water system of three-component coupling of aldehyde, alkyne, and amine ($A^3$ coupling).[3] We chose this reaction because it produces important propargylamines,[3−5] which are major skeletons[6] or synthetically versatile and key intermediates[7] for preparation of many biologically active nitrogen compounds such as conformationally restricted peptide isosteres, oxotremorine analogues, and $\beta$-lactams. Although several methods for construction of such units in water were reported,[3] some required expensive Au[3c] or Ag[3d] as catalyst, while some were limited to only one kind of aldehyde (the aromatic[3c] or aliphatic[3d]) or the aromatic

(1) (a) Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639. (b) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (c) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blacky Academic and Professional: London, 1998. (d) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (e) Chan, T. H.; Isaac, M. B. *Pure. Appl. Chem.* **1996**, *68*, 919. (f) Li, C.-J. *Acc. Chem. Res.* **2002**, *35*, 533.

(2) Shi, L.; Wang, M.; Fan, C.-A.; Zhang, F.-M.; Tu, Y.-Q. *Org. Lett.* **2003**, *5*, 3515.

(3) For the preparation of propargylamines in water, see: (a) Li, C.-J.; Wei, C. M. *Chem. Commun.* **2002**, 268. (b) Wei, C. M.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (c) Wei, C. M.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584. (d) Wei, C. M.; Li, Z. G.; Li, C.-J. *Org. Lett.* **2003**, *5*, 4473.

(4) For the preparation of propargylamines in other systems, see: (a) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970. (b) Brasseur, D.; Marek, I.; Normant, J.-F. *Tetrahedron* **1996**, *52*, 7235. (c) Aubrecht, K. B.; Winemiller, M. D.; Collum, D. B. *J. Am. Chem. Soc.* **2000**, *122*, 11084. (d) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319. (e) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244. (f) Koradin, C.; Gommermann, N.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2003**, *9*, 2797. (g) Jiang, Biao.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216.

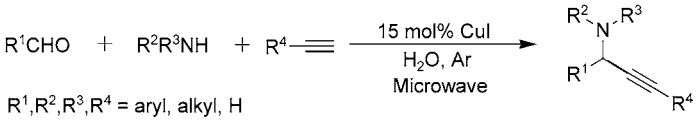
(5) For Cu-mediated addition of terminal acetylenes to *N*-alkyl imines at elevated temperatures, see: Rohm and Haas Co. U.S. Patent 2,665,311, 1950.

(6) (a) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (b) Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590. (c) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X.-M.; Paterson, I. A.; Yu, P. H. *Drug Dev. Res.* **1997**, *42*, 150.

(7) (a) Nilsson, B.; Vargas, H. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1992**, *35*, 285. (b) Hattori, K.; Miyata, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1151. (c) Jenmalm, A.; Berts, W.; Li, Y. L.; Luthman, K.; Csoregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139. (d) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

10.1021/ol049936t CCC: $27.50 
**Published on Web 02/24/2004**

**Table 1.** Coupling of Aldehyde, Alkyne, and Amine Catalyzed by CuI in Water[a]




| entry | $R^1$ | amine ($R^2$, $R^3$) | $R^4$ | product | time (min) | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | morpholine | Ph | **1a** | 20 | 90 |
| 2 | 2-$FC_6H_4$ | morpholine | Ph | **1b** | 20 | 89 |
| 3 | 2-$ClC_6H_4$ | morpholine | Ph | **1c** | 20 | 88 |
| 4 | 3-$ClC_6H_4$ | morpholine | Ph | **1d** | 20 | 90 |
| 5 | 4-$ClC_6H_4$ | morpholine | Ph | **1e** | 20 | 91 |
| 6 | 4-$BrC_6H_4$ | morpholine | Ph | **1f** | 20 | 90 |
| 7 | 4-$MeC_6H_4$ | morpholine | Ph | **1g** | 30 | 82 |
| 8 | 4-$MeOC_6H_4$ | morpholine | Ph | **1h** | 30 | 85 |
| 9 | 4-$NO_2C_6H_4$ | morpholine | Ph | **1i** | 5 | 41 |
| 10 | 2-furyl | morpholine | Ph | **1j** | 20 | 86 |
| 11 | 1-naphthyl | morpholine | Ph | **1k** | 20 | 88 |
| 12 | cyclohexyl | morpholine | Ph | **1l** | 20 | 90 |
| 13 | *n*-$C_3H_7$ | morpholine | Ph | **1m** | 20 | 78 |
| 14 | Ph | pyrrolidine | Ph | **2a** | 10 | 93 |
| 15 | Ph | piperidine | Ph | **2b** | 20 | 91 |
| 16 | Ph | $R^2 = R^3 =$ Et | Ph | **2c** | 20 | 90 |
| 17 | Ph | $R^2 = R^3 = (Me)_2CH$ | Ph | **2d** | 20 | 83 |
| 18 | Ph | $R^2 = R^3 =$ *c*-$C_6H_{11}$ | Ph | **2e** | 20 | 75 |
| 19 | Ph | $R^2 = R^3 =$ Ph | Ph | **2f** | 10 | 0[c] |
| 20 | Ph | $R^2 =$ Bn, $R^3 =$ Me | Ph | **2g** | 20 | 83 |
| 21 | Ph | $R^2 =$ Ph, $R^3 = H$ | Ph | **2h** | 10 | 85 |
| 22 | Ph | $R^2 = (Me)_3C$, $R^3 = H$ | Ph | **2i** | 10 | 76 |
| 23 | Ph | morpholine | *n*-$C_5H_{11}$ | **3a** | 20 | 83 |
| 24 | Ph | morpholine | TMS | **3b** | 20 | 80[d] |
| 25 | Ph | morpholine | $CH_2OTBS$ | **3c** | 20 | 86 |

[a] For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. [b] Isolated yields based on the aldehyde. [c] No desired product was obtained. [d] Under solvent-free conditions.

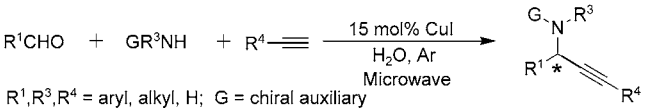
aldehyde and primary amine in the presence of $RuCl_3$ cocatalyst;[8] all of these reactions often proceeded slowly in water. In comparison to the methods above, our recently developed method showed particular advantages: (i) it required only the cheaper CuI as catalyst without Au, Ag, or other additives; (ii) it was applicable to a broader substrate scope (both aromatic and aliphatic aldehydes and secondary amines); and (iii) it proceeded faster and gave good to high yield, and its experimental process was simple and easy. In this paper, we present our experimental results.

The MW-promoted $A^3$ coupling experiment was performed (for the general procedure, see Supporting Information) by irradiation of the three-component/$H_2O$ system in the presence of 15 mol % CuI (it is necessary to freshly prepare CuI rather than using commercial CuI) in a sealed tube to afford the desired propargylamines within 30 min in good to excellent yields. The results are listed in Table 1. In each example we isolated mostly the propargylamine products, together with a small amount of oligomerization of the excessive alkynes in some cases (entries 1−8, 10−18, and 20−22). Additionally, a sealed tube was necessary for this reaction; otherwise, a low conversion and more byproducts were obtained.

At the beginning of the search for the aldehyde substrate scope, morpholine and phenylacetylene were used as model substrates (entries 1−13), and the results indicated that aromatic aldehydes bearing such functional groups as fluoro, chloro, bromo, methyl, or methoxy were able to effect the $A^3$ coupling. We have also observed delicate electronic effects:[3] that is, aryl aldehydes with electron-withdrawing groups (entries 2−6) reacted rapidly, while substitution of electron-rich groups (entries 7 and 8) on the benzene ring decreased the reactivity, requiring longer reaction times. Moreover, a very low yield for 4-nitrobenzaldehyde (entry 9), the substrate with a strong electron-withdrawing group, was observed because of the low conversion. When the reaction time was prolonged, a complicated mixture (not identified) was obtained. In addition, the 2-furaldehyde (entry 10) and 1-naphthaldehyde (entry 11) also gave good yields (86 and 88%, respectively) of products. On the other hand, the aliphatic aldehydes (entries 12 and 13) still displayed high reactivity and clean reactions under this standard condition. While unwanted trimerization of aliphatic alde-

(8) Some cocatalysts such as $RuCl_3$ or activations such as TMSOTf, $BF_3$·$Et_2O$ have been used; see: (a) Ref 4a. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c)Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

**Table 2.** Diastereoselective $A^3$ Coupling Induced with Chiral Amine Substrate[a]




R[1],R[3],R[4] = aryl, alkyl, H; G = chiral auxiliary

| entry | $R^1$ | amine (G, $R^3$) | $R^4$ | product | dr[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | Ph | (*S*)-proline methyl ester | Ph | **4a** | 95:5 | 88 |
| 2 | Ph | G = (*S*)-Ph($CH_3$)CH, $R^3$ = H | Ph | **4b** | 67:33 | 83 |
| 3 | Ph | G = (*S*)-Ph($CH_3$)CH, $R^3$ = Bn | Ph | **4c** | 67:33 | 81 |

[a] For a detailed experimental operation, see Supporting Information. All reactions were carried out on a 1 mmol scale with aldehyde/amine/alkyne = 1:1.3:1.6, 15 mol % CuI, and 1.5 mL of water. [b] Diastereomeric ratio (dr) was determined by $^1$H NMR; the absolute configuration has been not determined. [c] Isolated yields based on the aldehyde.

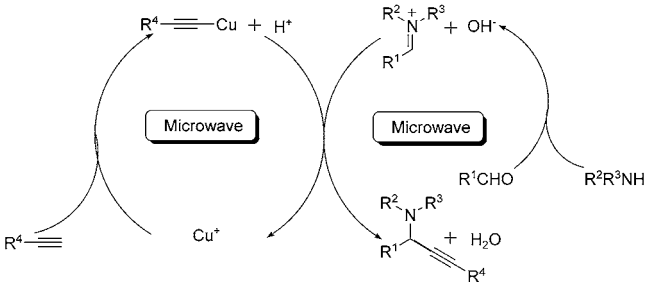
hydes was a major limitation of the $A^3$ coupling catalyzed by Au and Cu in water,[3] no trimer could be isolated in our experiments of entries 12 and 13.

To expand the scope of amine substrates, we used benzaldehyde and phenylacetylene as model substrates and examined various amines, including primary or secondary amines (entries 14−22). The coupling (except for entry 19) proceeded smoothly to afford the corresponding propargylamines in good yields under standard conditions. It was important to notice that N-substitution on amines could affect this reaction. Whereas dialkylamines reacted smoothly under these conditions, the bulky amines (entries 16−19) would lead to the lower yields of products. Particularly, when the two substituents were phenyls (entry 19), no expected product was observed.

Subsequently, a variety of other alkynes were also examined for the coupling using benzaldehyde and morpholine as model substrates (entries 23−25). In these cases, the reactions proceeded smoothly to give the corresponding propargylamines in a yield of 80−86%. It is worthwhile noting that this reaction under solvent-free conditions afforded a higher yield than that in water in entry 24, which may be due to the destabilization of TMS in microwave-assisted water.

Considering that chiral propargylamines are widely present in many important bioactive compounds, we subsequently tried to investigate a novel substrate-controlled asymmetric MW-promoted $A^3$ coupling in water using the same method as above. Therefore, three chiral amines sources, (*S*)-proline methyl ester, (*S*)-α-methylbenzylamine, and (*S*)-*N*-benzyl-1-phenylethylamine, were selected for examination using benzaldehyde and phenylacetylene as model substrates, and the results are summarized in Table 2. It was interesting to note that (*S*)-proline methyl ester exhibited high diastereoselectivity (95:5). This preliminary result implied that it was possible for the highly diastereoselective $A^3$ coupling to be achieved for additional substrates. It is also useful that the chiral imines in our experiment were not necessarily premade[9] but simply derived in situ from aldehydes and amines.

**Scheme 1**




To examine the reaction process of the MW-promoted $A^3$ coupling, further investigations were performed. Without MW irradiation, the $A^3$ coupling under heating required more than 5 days. In a stepwise experiment, the two-component coupling of phenylacetylene and the pre-made imine in the presence of 15 mol % CuI took one more day under conventional heating condition. These reactions proceeded very slowly, and only low conversions and yields were achieved. These facts indicated that MW irradiation was very necessary for speeding up both the $A^3$ coupling and the separate formation of alkynylcopper[10] and imine.[11] On the basis of the above experimental results, together with some literature reports,[3] a tentative mechanism was proposed as shown in Scheme 1. The MW irradiation first promoted CuI-catalyzed activation of the C−H bond of alkyne to give the copper acetylide as well as the formation of iminium ion. Then, the copper acetylide intermediate added to iminium ion to give the final propargylamine, with the Cu(I) catalyst being released for further cycle of reactions.

In summary, we have successfully developed a facile, economic, and green method for construction of propargylamines. In particular, the information that (*S*)-proline methyl ester could induce the high diastereoselectivity suggested that a general and useful method to the optically active propargylamines could be established. Investigations of the scope, absolute stereochemistry, and synthetic applications of this chiral reaction are now in progress in our laboratories.

**Acknowledgment.** We are grateful for the financial support of the NSFC (No. 29925205, 30271488, 20021001, and 203900501).

**Supporting Information Available:** Experimental details and data on the $A^3$ coupling reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049936T

(9) For diastereoselective additions to chiral C=N compounds, see: (a) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464. (b) Chang, Z. Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3475. (c) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103. (d) Ref 8b. (e) Fässler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3054. (f) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

(10) Alkynylcopper(I) is known to be stable in water and require a long time to be prepared; see: Olbrich, F.; Kopf, J.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1077.

(11) For MW-promoted synthesis of imines, see: Varma, R. S.; Dahiya, R.; Kumar, S. *Tetrahedron Lett.* **1997**, *38*, 2039.