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COMMUNICATION

Synthesis of tertiary propargylamines via a rationally designed multicomponent reaction of primary amines, formaldehyde, arylboronic acids and alkynes

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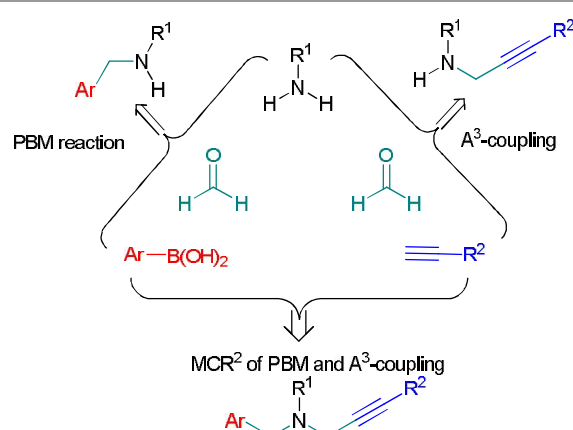
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Jiayi Wang,^{a,b} Qiaoying Shen,^a Pinzhen Li,^a Yanqing Peng^a and Gonghua Song^{*a}

A novel approach for the synthesis of tertiary propargylamines is achieved through a Cu(OAc)₂-catalyzed multicomponent reaction of primary amines, formaldehyde, arylboronic acids and alkynes, where a combination of PBM and A³-coupling reactions is involved in this new multicomponent reaction.

Multicomponent reactions (MCR), generally with high selectivity, flexibility and atom economy, are one of the most powerful synthetic strategies to access diverse complex structures from small molecular compounds.¹ And a variety of new MCRs have been developed.²⁻³ Among them, the combination of MCR (MCR²), which combines two different types of MCRs in a single process, has gained considerable attentions.⁴ However, the Ugi reaction, as well as isonitriles are indispensably involved in most of MCR² cases.^{2a,2c,4} Therefore, the development of novel MCR² without Ugi reaction is highly valuable.

The three-component reaction of aldehydes, amines and alkynes (A³-coupling) provides an efficient strategy to the synthesis of propargylamines, which are often useful key intermediates and building blocks for the preparation of many biologically active compounds.⁵⁻⁶ A number of metal catalysts, such as Au salts,^{7a} Ag salts,^{7b} FeCl₃/Fe₂O₃/Fe₃O₄,^{7c-7d} InCl₃,^{7e} Cu salts,^{7f-7i} and so on,^{5,6b} have been applied for this reaction *via* C-H activation of terminal alkynes. Meanwhile, the Petasis-borono Mannich (PBM) reaction of aldehydes, amines and boronic acids, developed by Petasis in 1993,⁸ has attracted considerable attention in the synthesis of diverse α -hydroxyl amines, α -amino acids and nitrogen-containing heterocycles.⁹⁻¹⁰ Realizing both amines and aldehydes are involved in A³-coupling and PBM reactions, and a second amine is generally preferable to primary one in A³ reaction,^{5,7} it is possible to develop a novel multicomponent reaction in which the secondary amines produced from PBM reaction could serve as the amine component in further A³-coupling to construct the final propargylamines. Thus, a novel five-component MCR² of PBM and A³-coupling reactions has been accomplished and reported herein (Scheme 1).

Scheme 1 A combination of PBM and A³-coupling reactions

At the outset, CuI was chosen as the catalyst to screen the effect of solvents on the model reaction of aniline, formaldehyde, phenylboronic acid and phenylacetylene at 80 °C for 24 h. The nature of solvent significantly affected the reaction (Table 1). Among the solvents screened, 1,2-dichloroethane (DCE) was found to be the most suitable solvent for this combination of PBM and A³-coupling reactions with a desired product yield of 86% (Table 1, entry 1). Toluene was inferior and generated the corresponding product in 72% yield (Table 1, entry 2), whereas acetonitrile and 1,4-dioxane afforded lower yields of the desired products (Table 1, entries 3-4). Tetrahydrofuran (THF), ethanol and water delivered less than 5% yield (Table 1, entries 5-7), and no desired product was determined when the reactions were performed in *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (Table 1, entries 8-9). When the reaction was performed in the absence of solvent, a lower yield of 22% was obtained (Table 1, entry 10). And no desired product was detected without the catalyst (Table 1, entry 11).

Table 1 Effect of solvent for the five-component reaction^a

entry	solvent	yield ^b (%)
1	DCE	86
2	toluene	72
3	1,4-dioxane	12
4	MeCN	32
5	THF	<5
6	EtOH	<5
7	H ₂ O	<5
8	DMF	0
9	DMSO	0
10	neat	22
11	DCE	0 ^c

^a Reaction conditions: aniline (1 mmol), formaldehyde (40% aqueous solution) (2.2 mmol), phenylboronic acid (1.05 mmol), phenylacetylene (1.2 mmol), CuI (10 mol %), solvent (3 mL), 80 °C, 24 h. ^b Yields were determined by GC using an internal standard. ^c Without catalyst.

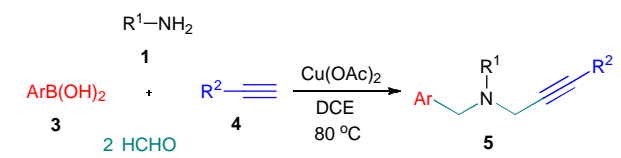
We next investigated the catalytic activity of various copper salts (Table 2). Cu(OAc)₂ was found to be the most effective catalyst with a high yield of 96% (Table 2, entry 6). Interestingly, except for CuOAc/Cu(OAc)₂, Cu(I) catalysts showed better catalytic activities than Cu(II) catalysts (Table 2, entries 1-12). Cu(OAc)₂ was therefore adopted for the optimization of other reaction conditions. As to the temperature, 80 °C was found to be optimal. The reactions at lower temperatures generated less product (Table 2, entry 13-14). Lowering catalyst loading amount to 5 mol %, or reducing the reaction time to 12 h also resulted in decrease of yield (Table 2, entries 15-16).

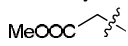
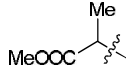

Table 2 Catalyst and conditions screening for the five-component reaction^a

entry	catalyst	temp. (°C)	time (h)	yield ^b (%)
1	CuI	80	24	86
2	CuBr	80	24	89
3	CuCl	80	24	71
4	CuOAc	80	24	89
5	Cu ₂ O	80	24	68
6	Cu(OAc)₂	80	24	96
7	CuBr ₂	80	24	46
8	CuCl ₂	80	24	51
9	CuSO ₄	80	24	68
10	CuO	80	24	54
11	Cu	80	24	65
12	Cu(CF ₃ SO ₃) ₂	80	24	32
13	Cu(OAc) ₂	25	24	<5
14	Cu(OAc) ₂	60	24	72
15	Cu(OAc) ₂	80	24	62 ^c
16	Cu(OAc) ₂	80	12	71

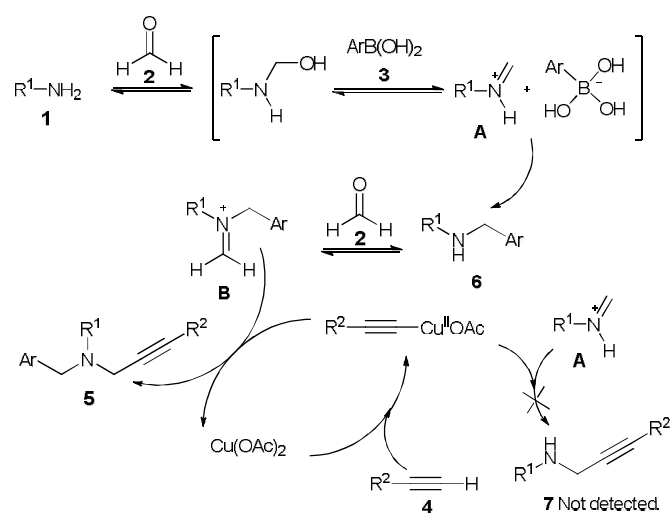
^a Reaction conditions: aniline (1 mmol), formaldehyde (40% aqueous solution) (2.2 mmol), phenylboronic acid (1.05 mmol), phenylacetylene (1.2 mmol), catalyst (10 mol %), DCE (3 mL) at a temperature indicated in Table 2, 12-24 h. ^b Yields were determined by GC using an internal standard. ^c 5 mol % of Cu(OAc)₂ was used.

On the basis of the optimized reaction conditions (Table 2, entry 6), the scope of this five-component reaction was evaluated (Table 3). In general, for all components in this reaction, electron-donating substituents (-MeO and -Me) on the phenyl ring lead to higher yields than electron-withdrawing groups (-Cl and -F) (Table 3, entries 1-7, 13-17 and 19-23). The reaction was almost ceased when a reactant with highly electron deficient substituent, such as 4-nitroaniline or 4-(trifluoromethyl)phenylboronic acid was adopted (Table 3, entries 8 and 18). For the amine component, substituted anilines delivered corresponding products in 60-92% yields (Table 3, entries 1-7). Aliphatic amines, such as phenylmethanamine and butan-1-amine, also delivered desired products in satisfactory yields (Table 3, entries 9-10). Furthermore, the successful application of methyl 2-aminoacetate and methyl 2-aminopropanoate in this MCR² (Table 3, entries 11-12) might provide a complementary approach to the functionalization of NH₂-terminal amino acid esters or peptides.^{7h-i} As for the alkyne component, in addition to the success of phenylacetylenes (Table 3, entries 1-7, 9-17 and 19-23), aliphatic alkynes also worked smoothly and desired products were obtained in moderate yields with prolonged reaction time of 48 h (Table 3, entries 24-26).

Table 3 Substrate scope and limitations^a


entry	R ¹	Ar	R ²	yield ^b (%)
1	Ph	Ph	Ph	92
2	<i>p</i> -(MeO)-Ph	Ph	Ph	91
3	<i>p</i> -Me-Ph	Ph	Ph	78
4	<i>p</i> -Cl-Ph	Ph	Ph	60
5	<i>p</i> -F-Ph	Ph	Ph	66
6	<i>o</i> -Me-Ph	Ph	Ph	74
7	<i>m</i> -Me-Ph	Ph	Ph	86
8	<i>p</i> -NO ₂ -Ph	Ph	Ph	0
9	Bn	Ph	Ph	90
10	<i>n</i> -Butyl	Ph	Ph	71 ^c
11		Ph	Ph	64 ^c
12		Ph	Ph	60 ^c
13	Ph	<i>p</i> -(MeO)-Ph	Ph	95
14	Ph	<i>p</i> -Me-Ph	Ph	87
15	Ph	<i>p</i> -Cl-Ph	Ph	61
16	Ph	<i>p</i> -F-Ph	Ph	60
17	Ph	<i>o</i> -(MeO)-Ph	Ph	79
18	Ph	<i>p</i> -CF ₃ -Ph	Ph	0
19	<i>p</i> -(MeO)-Ph	<i>p</i> -(MeO)-Ph	Ph	86 ^c
20	Ph	Ph	<i>p</i> -Me-Ph	82
21	Ph	<i>p</i> -Cl-Ph	<i>p</i> -Me-Ph	61 ^c
22	<i>p</i> -(MeO)-Ph	<i>p</i> -(MeO)-Ph	<i>p</i> -Me-Ph	82
23	Ph	Ph	<i>p</i> -Cl-Ph	70
24	Ph	Ph	<i>n</i> -Butyl	82 ^c
25	Ph	Ph	<i>n</i> -Pentyl	78 ^c
26	Ph	Ph	MeOOC- 	40 ^c

^a A mixture of aniline **1** (1 mmol), formaldehyde **2** (40% aqueous solution) (2.2 mmol), arylboronic acid **3** (1.05 mmol), alkyne **4** (1.2 mmol), Cu(OAc)₂ (10 mol %) and DCE (3 mL) was stirred at 80 °C for 24 h. ^b Isolated yields. ^c The reaction time is 48h.

**Scheme 2** Proposed reaction mechanism

A tentative mechanism for this five-component reaction is proposed in Scheme 2. The reaction of primary amine **1**, formaldehyde **2**, and arylboronic acid **3** afforded a secondary amine **6** via PBM reaction,^{8-9,11} which was detected by GC-MS throughout the reaction. The secondary amine **6** might further react with formaldehyde **2** to produce iminium intermediate **B**. The copper acetylide intermediate, generated from alkyne **4** and Cu(OAc)₂, reacted with iminium **B** to give the corresponding propargylamine **5** and regenerated the copper catalyst for further reactions.^{5,7} Thus, this five-component reaction involved a MCR² of PBM and A³-coupling reactions.

In conclusion, we have developed a novel approach to the synthesis of tertiary propargylamines via a rationally designed Cu-catalyzed multicomponent reaction of primary amines, formaldehyde, arylboronic acids and alkynes. The combination of PBM and A³-coupling reactions provides an efficient and fast one-pot approach to the tertiary propargylamines. Both aromatic and aliphatic amines and alkynes are applicable. Furthermore, the MCR² also provided a complementary pathway to the functionalization of NH₂-terminal amino acid esters and peptides.

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^aShanghai Key Laboratory of Chemical Biology, School of Pharmacy, East China University of Science and Technology, Shanghai, 200237, P.R. China. Email: ghsong@ecust.edu.cn; Tel: +86-21-64253140; Fax: +86-21-64252603.

^bShanghai Key Laboratory of Catalysis Technology for Polyolefins, Shanghai Research Institute of Chemical Industry, Shanghai, 200062, P. R. China.

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: Experimental section, spectroscopic data. See DOI: 10.1039/c000000x/

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