



Metal-free multicomponent coupling reaction of aliphatic amines, formaldehyde, organoboronic acids, and propiolic acids for the synthesis of diverse propargylamines



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ABSTRACT

A metal-free multicomponent coupling reaction of aliphatic amines, formaldehyde, organoboronic acids, and propiolic acids has been reported for the synthesis of diverse propargylamines. This transformation involves a MCR² of PBM and decarboxylative three-component coupling reactions.

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Propargylamines are important intermediates and skeletons for the preparation of diverse heterocyclic compounds, such as pyrroles,¹ pyrrolidines,² pyrrolophanes,³ aminoindolizines,⁴ isoindoline,⁵ imidazolidinones,⁶ 2-aminoimidazoles,⁷ and oxazolidinones.⁸ Among variety strategies for the synthesis of propargylamines, the three-component coupling reaction of an aldehyde, an amine, and an alkyne (A³-coupling) has been recognized as the most efficient and powerful method.^{9,10} However, transition metal catalysts are necessary in A³-coupling to generate metal acetylde intermediate to fulfill the reaction. Lee and co-workers¹¹ reported the synthesis of propargylamines via a metal-free decarboxylative three-component reaction of propiolic acids,¹² paraformaldehyde, and secondary amines. The replacement of alkynes with propiolic acids in their reported reaction can lead to easy generation of carbon nucleophile for further attacking the iminium salt, avoiding the use of metal catalysts. However, only secondary amines were adoptable in this reaction restricting its application. Therefore, it is of high demand to develop a more applicable metal-free strategy for the synthesis of propargylamines.

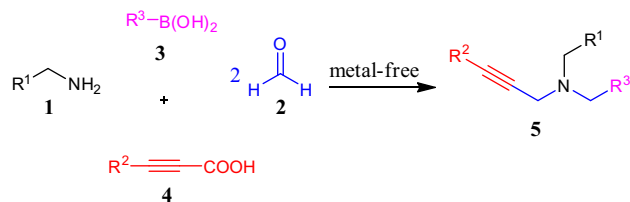
The combination of multicomponent reactions (MCR²),¹³ which combines different types of MCRs in one pot process inheriting the high selectivity, efficiency, and atom economy of MCR, has gained more and more attention, since Dömling and Ugi reported the first

MCR² of a modified Asinger four-component reaction (4CR) and the Ugi 4CR.¹⁴ However, most of the reported MCR² cases are limited in isonitrile based multicomponent reactions.¹⁵ Recently, we developed a combination of Petasis borono-Mannich (PBM)^{16,17} and A³-coupling reactions, where the secondary amines produced from PBM reaction participated in further A³-coupling affording the final propargylamines.¹⁸ However, a catalytic amount of Cu(OAc)₂ was needed. As our interest in the development of novel MCR² and metal-free MCR,¹⁹ we reported herein a metal-free multicomponent reaction of amines, formaldehyde, organoboronic acids, and propiolic acids for the direct synthesis of diverse propargylamines (Scheme 1).

The optimization of reaction conditions was initially performed on the model reaction of phenylmethanamine (**1a**), formaldehyde (**2**), phenylboronic acid (**3a**), and phenylpropiolic acid (**4a**) with a ratio of 1.0:2.5:1.2:1.2. Toluene was found to be the most suitable solvent for the multicomponent reaction with a desired product yield of 81% (Table 1, entry 1), while xylene and 1,2-dichloroethane (DCE) were less effective and afforded the product in 61% and 64% yields, respectively (Table 1, entries 2 and 3). Replacement of toluene with other solvents, such as tetrahydrofuran (THF), dioxane, acetonitrile, water, ethanol, *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), either delivered quite low yields (Table 1, entries 4–7) or gave no products (Table 1, entries 8–10). Investigation on the ratio of reactants indicated that a 1.0:2.5:1.5:1.3 ratio of **1a/2/3a/4a** gave the best result with an isolated yield of 87% (Table 1, entries 11–19). Further screening

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Scheme 1. Metal-free synthesis of propargylamines.

of the reaction conditions revealed that decreasing the temperature down to 60 or 25 °C (Table 1, entries 20 and 21) or elevating up to 100 °C (Table 1, entry 22) or increasing the reaction time to 30 h (Table 1, entry 23) did not promote the reaction yields. While the reaction was conducted under air atmosphere, less than 5% yield of desired product was detected, and 45% yield of *N*-benzyl-*N*-methyl-3-phenylpropargylamine was obtained as the main byproduct (Table 1, entry 24).²⁰

With the reaction conditions in entry 16 of Table 1, we began to explore the scope of the multicomponent reaction. First, various primary amines were subjected to the reaction with 2, 3a, and 4a (Table 2). In general, phenylmethanamine bearing *para*-, *ortho*-, and *meta*-substituents such as fluoro, chloro, bromo, bromo, trifluoromethyl, methyl, and methoxyl groups on the benzene ring participated in the reaction to afford the desired products 5aaa–5iaa in moderate to good yields. Naphthalen-1-ylmethanamine and 2-phenylethanamine also produced their corresponding

Table 1
Optimization of conditions for the synthesis of propargylamine^a

Entry	1a/2/3a/4a (ratio)	T (°C)	Time (h)	Solvent	Yield ^b (%)
1	1.0/2.5/1.2/1.2	80	20	Toluene	81
2	1.0/2.5/1.2/1.2	80	20	Xylene	61
3	1.0/2.5/1.2/1.2	80	20	DCE	64
4	1.0/2.5/1.2/1.2	80	20	THF	6
5	1.0/2.5/1.2/1.2	80	20	Dioxane	<5
6	1.0/2.5/1.2/1.2	80	20	MeCN	<5
7	1.0/2.5/1.2/1.2	80	20	Water	<5
8	1.0/2.5/1.2/1.2	80	20	EtOH	nd
9	1.0/2.5/1.2/1.2	80	20	DMF	nd
10	1.0/2.5/1.2/1.2	80	20	DMSO	nd
11	1.0/2.5/1.1/1.2	80	20	Toluene	68
12	1.0/2.5/1.4/1.2	80	20	Toluene	84
13	1.0/2.5/1.5/1.2	80	20	Toluene	89
14	1.0/2.5/1.6/1.2	80	20	Toluene	88
15	1.0/2.5/1.5/1.1	80	20	Toluene	85
16	1.0/2.5/1.5/1.3	80	20	Toluene	94 (87)
17	1.0/2.5/1.5/1.4	80	20	Toluene	87
18	1.0/2.5/1.5/1.3	80	20	Toluene	78
19	1.0/2.5/1.5/1.3	80	20	Toluene	82
20	1.0/2.5/1.5/1.3	25	20	Toluene	75
21	1.0/2.5/1.5/1.3	60	20	Toluene	78
22	1.0/2.5/1.5/1.3	100	20	Toluene	82
23	1.0/2.5/1.5/1.3	80	20	Toluene	84
24	1.0/2.5/1.5/1.3	80	20	Toluene	<5 ^c + 45 ^{c,d}

The bold values are the most effective conditions for the model reaction.

^a All reactions were performed on a 1.0 mmol-scale with 2.5 mL solvent under a nitrogen atmosphere. Formaldehyde aqueous solution (40%) was used. nd = not detected.

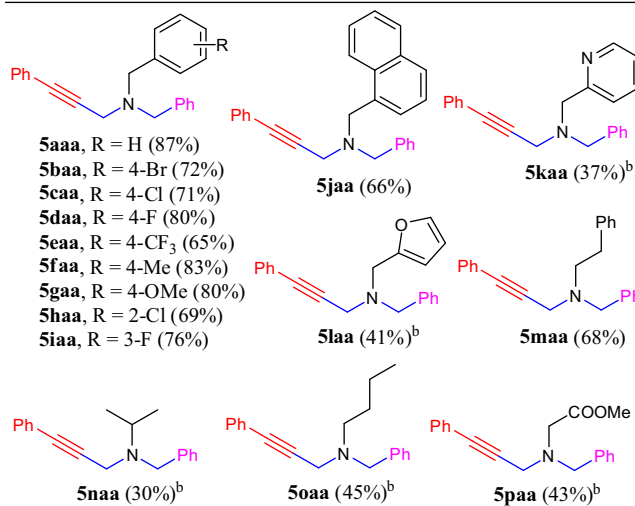
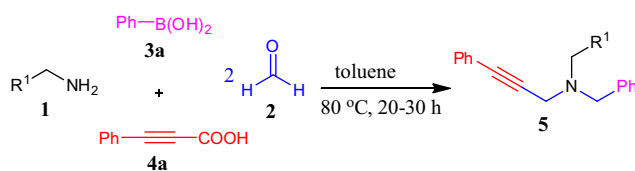
^b Yields were determined by GC using an internal standard. Isolated yield was given in parentheses.

^c Under air atmosphere.

^d Isolated yield of *N*-benzyl-*N*-methyl-3-phenylpropargylamine.

Table 2

Reaction of various primary amines with formaldehyde, phenylboronic acid, and phenylpropionic acid^a



^a The reaction conditions were the same as entry 16 in Table 1. Isolated yields were given in parentheses.

^b The reaction time is 30 h.

products 5jaa and 5maa in 66% and 68% yields, respectively. Derivation from the phenyl substituent to aromatic heterocycles such as pyridinyl and furanyl decreased the yield (5kaa and 5laa). Other simple aliphatic amines such as propan-2-amine, butan-1-amine, and methyl 2-aminoacetate, were also applicable with lower yields (5naa, 5oaa, and 5paa).

Next, the reaction of phenylmethanamine (1a), formaldehyde (2), phenylpropionic acid (4a), and various organoboronic acids was examined (Table 3). Generally, electron-donating substituents (–OMe and –Me) on the phenyl ring of arylboronic acids resulted in higher yields than electron-withdrawing groups (–Cl and –F) (see 5aba–5aga). While a highly electron withdrawing group on the phenyl ring led to a dramatic decrease in product yield (see 5aha). Furthermore, the use of (*E*)-styrylboronic acid delivered corresponding 1,6-enyne product (5aia) with 70% yield. Unfortunately, aromatic heterocycle and aliphatic boronic acids shut down the reaction (see 5aja and 5aka).

Subsequently, the scope of propiolic acids was then investigated (Table 4). A nitro group on the phenyl ring or an aliphatic propiolic acid delivered the desired products (5aae and 5aaf) with lower yields. However, both arylpropionic acids and aliphatic propiolic acid were applicable in the multicomponent reaction in satisfactory yields (5aab–5aaf). Finally, the multicomponent coupling reaction of amines, formaldehyde, organoboronic acids, and propiolic acids was applied for the synthesis of diverse propargylamines (Table 5).

A tentative mechanism for the metal-free, five-component reaction is proposed in Scheme 2. The reaction of primary amine 1, formaldehyde 2, and organoboronic acid 3 afforded a secondary amine 6 via the PBM reaction,¹⁶ which could undergo a second PBM reaction with formaldehyde 2 and organoboronic acid 3 to produce the byproduct 7 as detected by GC–MS.^{19a} The reaction of the secondary amine 6 and formaldehyde 2 generated hemiaminal B. The proton from propiolic acid 4 accelerated the formation of iminium salt C, which was further attacked by the

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