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

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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 novel multicomponent reaction.

Multicomponent reactions (MCR), generally with high selectivity, flexibility and atom economy, are among the most powerful, synthetic strategies to access diverse complex structures from small molecular compounds, and a variety of new MCRs have been developed. Among them, the combination of MCR (MCR2), which combines two different types of MCRs in a single process, has gained considerable attention. However, the Ugi reaction as well as isonitriles are indispensably involved in most of the MCR2 cases. Therefore, the development of novel MCR2 without the 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. A number of metal catalysts, such as Au salts, Ag salts, FeCl3/Fe2O3/Fe3O4, InCl3, Cu salts, and so on, 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, has attracted considerable attention in the synthesis of diverse o-hydroxyl amines, o-amino acids and nitrogen-containing heterocycles. Realizing both amines and alkynes are involved in A3-coupling and PBM reactions, and a secondary amine is generally preferable to a primary one in A3 reaction; 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).

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 the solvent significantly affected the reaction (Table 1). Among the solvents screened, 1,2-dichloroethane (DCE) was found to be the most suitable solvent for the 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 and 4). Tetrahydrofuran (THF), ethanol and water delivered less than 5% yield (Table 1, entries 5–7), and no desired product was achieved when the reactions were performed in N,N-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) (Table 1, entries 8 and 9). When the reaction was performed in the absence of a solvent, a lower yield of 22% was obtained.
in the table, 12). Without catalyst, 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, entries 13 and 14). Lowering the catalyst load amount to 5 mol%, or reducing the reaction time to 12 h also resulted in decrease of yield (Table 2, entries 13 and 14). The reaction time is 48 h.

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, entries 13 and 14). Lowering the catalyst load amount to 5 mol%, or reducing the reaction time to 12 h also resulted in decrease of yield (Table 2, entries 15 and 16).

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 almost ceased when a reactant with a 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 aldehydes delivered the 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 and 10). Furthermore, the successful application of methyl 2-aminoacetate and methyl 2-amino propanoate in this MCR3 (Table 3, entries 11 and 12) might provide a complementary approach to the functionalization of NH2-terminal amino acid esters or peptides.7,8 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).

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 the PBM reaction, which was detected by GC-MS throughout the reaction. The secondary amine 6 might further react with formaldehyde 2 to produce an 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, formaldehydes, 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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