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Aerobic cross-dehydrogenative coupling of terminal alkynes and tertiary amines by a combined catalyst of Zn^{2+} and OMS-2†

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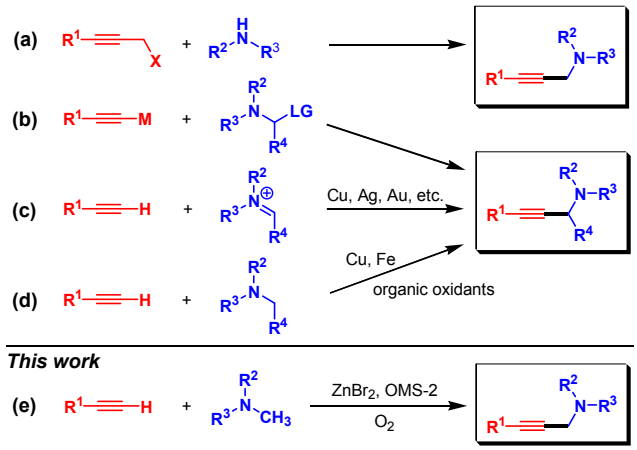
In the presence of $ZnBr_2$ and a manganese oxide-based octahedral molecular sieve (OMS-2), cross-dehydrogenative coupling of a wide range of terminal alkynes and tertiary amines to propargylamines efficiently proceeded using molecular oxygen as the terminal oxidant.

Propargylamines are key structural motifs in various bioactive compounds[1] and have widely been utilized as synthetic intermediates for nitrogen-containing compounds such as pyrazines, oxazoles, and pyrroles.[2] To date, various synthetic procedures for propargylamines have been developed, and the following four procedures have mostly been utilized; i) nucleophilic substitution of propargyl halides with amines (Scheme 1 (a)),[3] ii) nucleophilic substitution of α-functionalized tertiary amines with metal acetylide reagents (Scheme 1 (b)),[4] iii) metal-catalyzed nucleophilic addition of terminal alkynes to iminium species formed by dehydrative condensation of aldehydes and amines (Scheme 1 (c)),[5] and iv) oxidative cross-dehydrogenative coupling (CDC)[6] of terminal alkynes and tertiary amines (Scheme 1 (d)).[7] Although the procedures (a)–(c) provide excellent approaches to propargylamines, the procedure (d) which proceeds through C–H bond activation and subsequent C–C bond formation has become a promising alternative for synthesis of propargylamines due to its high synthetic efficiency and environmentally benign nature.

With regard to the CDC pathways for propargylamines, copper-[7a–i], iron-,[7j,k] or silver-catalyzed[7l] reactions have been developed in the last decade. However, these catalytic systems have employed at least stoichiometric amounts of organic oxidants such as *t*-BuOOH, $(t\text{-BuO})_2$, *N*-bromosuccinimide, and diethyl azodicarboxylate, resulting in generation of vast amounts of wastes. The photoredox systems in the presence of transition metal catalysts have also been applied to the CDC reactions for synthesis of propargylamines.[7m–o] Although these systems show high catalytic performance, the scope of amine coupling partners is typically limited to only tetrahydroisoquinoline derivatives.[7m–o] Therefore, the development of new CDC pathways for propargylamines with wide substrate applicabilities that utilize naturally abundant molecular oxygen as the terminal oxidant would be of great significance. Recently, we have developed several catalytic CDC-type reactions including C–N,[8a,b] P–N,[8c] Si–N,[8d,e] and Si–C[8f] bond forming reactions. In line with our research interest, we devoted to develop a novel catalyst system for synthesis of propargylamines by employing the CDC strategy using molecular oxygen as the terminal oxidant. Quite



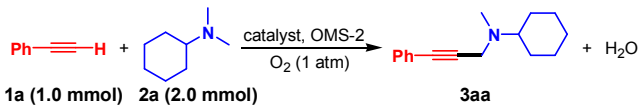
Scheme 1 Synthetic procedures for propargylamines (X = Cl, Br; M = Li, Mg; LG = leaving group).

recently, we have successfully developed the OMS-2-promoted aerobic oxidative α-cyanation of tertiary amines.[9,10] This reaction possibly proceeds through the formation of iminium intermediates by the step-by-step two-electron oxidation of tertiary amines by OMS-2.[10] Thus, we envisioned that an appropriate metal source, which can generate metal acetylide species, in combination with OMS-2 would promote CDC of terminal alkynes and tertiary amines through nucleophilic addition of the metal acetylide species to the iminium intermediates.

Herein, we disclose for the first time aerobic CDC of terminal alkynes and tertiary amines to produce propargylamines in the presence of a combined catalyst of Zn^{2+} (typically $ZnBr_2$) and OMS-2 (Scheme 1 (e)).[11] Various kinds of propargylamines could successfully be synthesized by the present CDC. In this reaction, molecular oxygen could be used as the terminal oxidant, and OMS-2 could be reused several times.

Initialy, the CDC reaction of phenylacetylene (**1a**) and *N,N*-dimethylcyclohexylamine (**2a**) to *N*-methyl-*N*-(3-phenylprop-2-yn-1-yl)cyclohexylamine (**3aa**) was carried out in the presence of various kinds of metal catalysts and OMS-2 under 1 atm of O_2.‡ Among various zinc catalysts examined such as $ZnCl_2$, $Zn(OTf)_2$ (OTf = triflate), ZnF_2, ZnI_2, and $ZnBr_2$ in toluene (Table 1, entries 1–5), $ZnBr_2$ showed the best performance, giving **3aa** in 59 % yield (Table 1, entry 5). In this case, the alkynylation exclusively took place at the methyl position without methine alkynylation. Other metal catalysts such as $InCl_3$, $NiCl_2{\cdot}6H_2O$, $FeCl_3$, $CuCl_2{\cdot}2H_2O$, $CoCl_2$, and $MgCl_2$ gave lower yields of **3aa** in comparison with $ZnBr_2$ (Table 1, entries 6–11). When

Table 1 The CDC of phenylacetylene (**1a**) and *N,N*-dimethylcyclohexylamine (**2a**) with various metal catalysts[a]



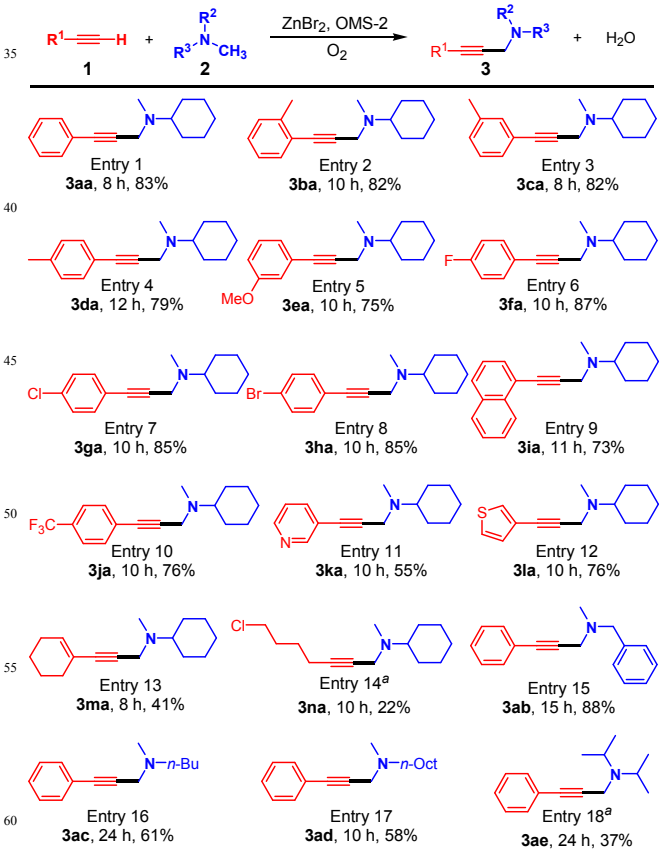
1a (1.0 mmol) **2a (2.0 mmol)** **3aa**

Entry	Catalyst	Conv. (%)		Yield of
		1a	**2a**	**3aa** (%)
1	$ZnCl_2$	61	36	51
2	$Zn(OTf)_2$	24	32	8
3	ZnF_2	12	23	1
4	ZnI_2	29	29	4
5	$ZnBr_2$	72	43	59
6	$InCl_3$	37	29	24
7	$NiCl_2·6H_2O$	21	22	7
8	$FeCl_3$	23	28	8
9[b]	$CuCl_2·2H_2O$	98	41	37
10	$CoCl_2$	58	37	43
11	$MgCl_2$	23	28	7
12[c]	$ZnBr_2$	95	56	85
13[c,d]	$ZnBr_2$	28	8	16
14[c,e]	$ZnBr_2$	8	2	1
15[c,f]	$ZnBr_2$	68	11	14
16[c]	None	10	23	<1

[a] Reaction conditions: Catalyst (metal: 5 mol%), OMS-2 (100 mg), **1a** (1.0 mmol), **2a** (2.0 mmol), toluene (2 mL), 100 ºC, O_2 (1 atm), 4.5 h. Conversion and yield were determined by GC analysis. [b] 1,4-Diphenylbutadiyne was formed in 43 % yield. [c] CPME (2 mL), 8 h. [d] Ar (1 atm). [e] Without OMS-2. [f] BHT (2.0 mmol).

$CuCl_2·2H_2O$ was employed, a significant amount of 1,4-diphenylbutadiyne derived from the copper-catalyzed Glaser–Hay homocoupling of **1a** was formed as the byproduct (Table 1, entry 9). A remarkable improvement of the yield was observed when using cyclopentylmethylether (CPME) as the solvent instead of toluene, and **3aa** was obtained in 85 % yield (Table 1, entry 12, Table S2). Other solvents such as trifluorotoluene, *N*-methylpyrrolidone, dimethylformamide, dimethylacetamide, 1,4-dioxane, dimethylsulfoxide, and diethylcarbonate gave lower yields of **3aa** than CPME (Table S2). Only 16 % yield of **3aa** was obtained when the CDC reaction was carried out under 1 atm of Ar, indicating that molecular oxygen is the terminal oxidant (Table 1, entry 13). Both $ZnBr_2$ and OMS-2 were the indispensable components, and the reaction hardly proceeded in the absence of $ZnBr_2$ or OMS-2 (Table 1, entries 14 and 16). OMS-2 showed higher performance than the commercially available activated MnO_2 and β-MnO_2. *t*-BuOOH was not the effective oxidant. The present CDC reaction was significantly suppressed by the presence of a radical scavenger of dibutylhydroxytoluene (BHT) (Table 1, entry 15), suggesting that radical intermediates are included in the present CDC.

After the CDC reaction of **1a** and **2a**, OMS-2 could easily be retrieved from the reaction mixture by simple filtration with >97 % recovery. The retrieved OMS-2 could be reused several times for the same reaction though its performance gradually decreased (fresh: 85 % yield of **3aa** for 8 h, the 1st reuse: 87 %, the 2nd reuse: 75 %, and the 3rd reuse: 72 %, see Fig. S1).



Scheme 2 Scope of the present CDC of terminal alkynes and tertiary amines. Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $ZnBr_2$ (5 mol%), OMS-2 (100 mg), CPME (2 mL), 100 ºC, under O_2 (1 atm). Yields (based on **1**) of isolated products are shown. [a] $ZnBr_2$ (20 mol%).

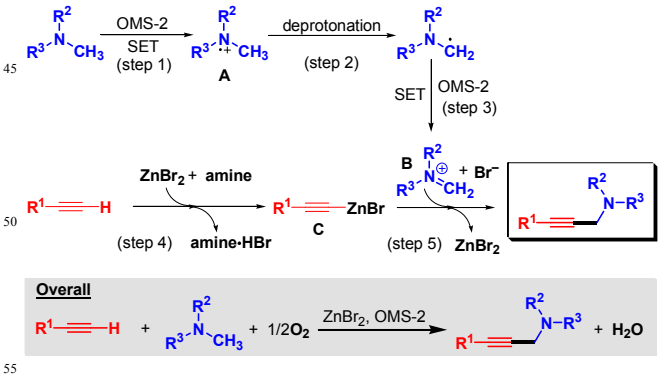
Next, the substrate scope of the present Zn^{2+}-OMS-2-mediated CDC of terminal alkynes and tertiary amines was investigated. Under the optimized reaction conditions, various kinds of structurally diverse propargylamines could be synthesized from terminal alkynes and tertiary amines (Scheme 2 and Fig. S2). All products could readily be isolated (see the ESI for detailed procedures and compound data†), and the yields of isolated products are shown in Scheme 2.

Aromatic alkynes with electron-donating as well as electron-withdrawing substituents were all efficiently reacted with **2a** to give the corresponding propargylamines (Scheme 2, entries 1–10). In the present system, the steric effect of substituents on aromatic rings is likely negligible because the CDC reactions of 2-, 3-, and 4-ethynyltoluenes were almost equally effective (Scheme 2, entries 2–4). In the case of halo-substituted aromatic alkynes, the reaction smoothly proceeded without dehalogenation (Scheme 2, entries 6–8). Thus, it would be possible to utilize these halo-functionalities for further derivatization of these propargylamines. Heteroaromatic alkynes such as 3-ethynylthiophene and 3-ethynylpyridine were also applicable to the present CDC (Scheme 2, entries 11 and 12). In addition, the reaction of an enyne and **2a** efficiently proceeded to give the corresponding propargylamines (Scheme 2, entry 13). Not only

aromatic alkynes but also an aliphatic one could act as the coupling partner while the yield of the desired product was low (Scheme 2, entry 14). As for the amine coupling partners, various aliphatic tertiary amines could be applied to the present CDC reaction, and in all these cases the alkynylation exclusively occurred at the methyl positions even in the presence of methylene and methine positions (Scheme 2, entries 15–18). This methyl selectivity is possibly due to the stereoelectronically controlled deprotonation of amine cation radicals (step 2 in Scheme 3).[12] As for the stereoelectronically controlled deprotonation, the overlap between the half-vacant nitrogen p orbital and the generating carbon radical p orbital is required, resulting in selective deprotonation of the less substituted α-C–H bond (methyl > methylene > methine).[12]

An aniline derivative, *N,N*-dimethylaniline, did not react with **1a** under the conditions described in Scheme 2. In the presence of a stoichiometric amount of triethylamine as a base for the CDC of *N,N*-dimethylaniline and **1a**, the corresponding coupling product could be obtained though the yield was only 6 % for 24 h. In this case, no product derived from the alkynylation of triethylamine was produced. These results indicates that the basicity of amines (for deprotonation of terminal alkynes) and steric effect of substituents of amines (stereoelectronic effect) are very significant for the present CDC reaction.

The plausible reaction mechanism for the present Zn^{2+}-OMS-2-mediated CDC is shown in Scheme 3. Firstly, the single-electron transfer (SET) from a tertiary amine to OMS-2 generates an amine cation radical species **A** (step 1). Then, the successive deprotonation of the cation radical species **A** (step 2) and the second SET give an iminium intermediate **B** (step 3). In the previous work, we have successfully detected the iminium intermediate by NMR analysis during the reaction of a tertiary amine in the presence of OMS-2 and $LiBF_4$.[10] The above-mentioned stereoelectronic effect also supports this mechanism. Meanwhile, a zinc acetylide species **C** can be formed from a terminal alkyne, and the tertiary amine likely act as a base to promote the deprotonation of the terminal alkyne (step 4).[13] Finally, the nucleophilic attack of the acetylide species **C** to the iminium intermediate **B** gives the corresponding propargylamines as the final product (step 5). The reduced OMS-2 can be reoxidized by molecular oxygen.[9]



Scheme 3 A plausible reaction mechanism for the present CDC of terminal alkynes and tertiary amines.

In summary, we have successfully developed the Zn^{2+}-OMS-2-mediated CDC reaction of terminal alkynes and tertiary amines to propargylamines. Various kinds of structurally diverse propargylamines could be synthesized. The present CDC reaction could employ molecular oxygen as the terminal oxidant which provides a green synthetic route to propargylamines.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, data of propargylamines, Tables S1 and S2 and Figs. S1 and S2, See DOI: 10.1039/b000000x/

‡ A typical procedure for CDC of terminal alkynes and tertiary amines: Into a Pyrex glass reactor (volume: ca. 20 mL) were successively placed $ZnBr_2$ (11.3 mg, 0.05 mmol), OMS-2 (100 mg), **1** (1 mmol), **2** (2 mmol), CPME (2 mL), and a Teflon-coated magnetic stir bar, and the reaction mixture was purged with oxygen gas, and then vigorously stirred at 100 °C. After the reaction was completed, an internal standard (diphenyl) was added to the reaction mixture, and the conversions of **1** and **2** and the product yield were determined by GC analysis. As for isolation of propargylamine products, an internal standard was not added. After the reaction, OMS-2 was filtered off (>97 % recovery), and then the filtrate was concentrated by evaporation of CPME. The crude product was subjected to column chromatography on silica gel (typically using n-hexane/diethylether as the eluent), giving the pure propargylamines. The products were identified by GC-MS and NMR (^{1}H and ^{13}C) analyses.

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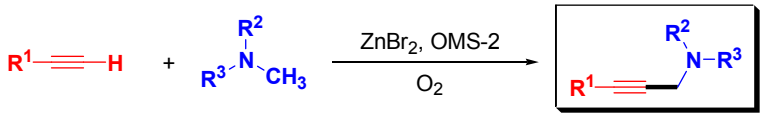
Graphical abstract



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