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Zinc(II)-Catalyzed Redox Cross-Dehydrogenative Coupling of Propargylic Amines and Terminal Alkynes for Synthesis of *N*-Tethered 1,6-Enynes

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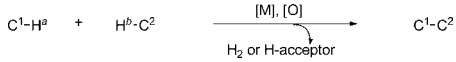
Supporting Information

ABSTRACT: The zinc(II)-catalyzed redox cross-dehydrogenative coupling (CDC) of propargylic amines and terminal alkynes proceeds to afford *N*-tethered 1,6-enynes. In the current CDC reaction, a C(sp)−C(sp^3) bond is formed between the carbon adjacent to the nitrogen atom in the propargylic amine and the terminal carbon of the alkyne with reduction of the C−C triple bond of the propargylic amine, which acts as an internal oxidant.

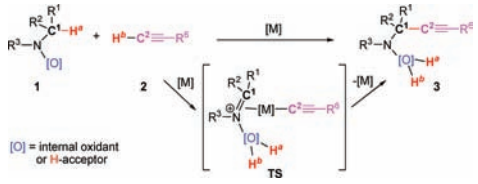
The 1,6-enyne skeleton is highly versatile because it undergoes transition-metal-catalyzed reactions, including cycloaddition reactions,[1] cycloisomerizations,[2] and cascade isomerizations.[3] *N*-Tethered 1,6-enynes, in particular, are important synthetic precursors for the construction of bioactive ring systems.[4] In general, *N*-tethered 1,6-enynes with substituents at the propargylic position are synthesized by the addition of alkynylides to *N*-allyliminium intermediates in situ.[5] Li et al. developed a copper-catalyzed cross-dehydrogenative coupling (CDC) method that uses terminal alkynes, tertiary amines, and stoichiometric oxidants, such as *tert*-butyl hydroperoxide, for the synthesis of propargylic amines.[6c] CDC is one of the most efficient atom-economic strategies for C−C bond formation as it does not require a substrate prefunctionalization step (Scheme 1).[6]

Scheme 1. CDC Methodology



We envisaged a novel synthetic approach toward *N*-tethered 1,6-enynes through the CDC pathway, which utilizes tertiary amines **1** with an internal oxidant[6o,p] in their structures (Scheme 2). After deprotonation of terminal alkyne **2** and reduction of the internal oxidant, catalytic oxidation of the $C^1(sp^3)$−H^a bond adjacent to the nitrogen atom of tertiary amine **1** could provide a reactive iminium intermediate that might be alkynylized (TS) to afford propargylic amine **3** (Scheme 2). By treatment of tertiary amine **1** containing a C−C triple bond, which plays the role of an oxidant, CDC would proceed without the addition of an external oxidant and the C−C triple bond would be reduced.[7] Indeed, propargylic amines acted as oxidative tertiary amines **1** in the presence of zinc(II) salts to give *N*-tethered 1,6-enynes **3**.

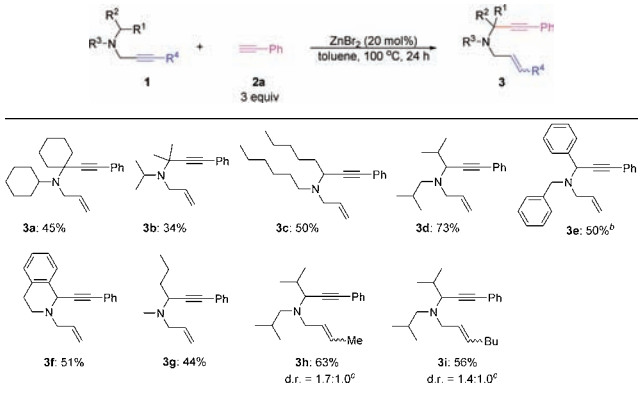
Scheme 2. Plausible CDC Pathway with Oxidative Amine 1



We recently reported the copper(I)-catalyzed alkyne substitution reaction of propargylic amines with terminal alkynes.[8] Aside from our report, other transition-metal-catalyzed cross-coupling reactions of propargylic amines with terminal alkynes have been published.[9] Herein we describe the zinc(II)-catalyzed redox[10] CDC of propargylic amines **1** and terminal alkynes **2** to afford *N*-tethered 1,6-enynes **3**.

The screening results for propargylic amines **1** are summarized in Table 1. Treatment of propargylic amines **1** with 3 equiv of ethynyl benzene **2a** under our optimized conditions,[11] namely, in the presence of 20 mol % of zinc(II) bromide in toluene at 100 °C for 24 h, provided corresponding *N*-tethered 1,6-enynes **3a**−**3i**. Tertiary or secondary C(sp^3)−H

Table 1. $ZnBr_2$-Catalyzed CDC of Various Propargylic Amines and Ethynyl Benzene 2a[a]



[a]Isolated yields. Propargyl amine **1** (0.3 mmol), ethynyl benzene **2a** (0.9 mmol), and $ZnBr_2$ (0.06 mmol) were heated in toluene in a closed vial tube under N_2 at 100 °C for 24 h. [b]50 mol % of $ZnBr_2$ were loaded. [c]Determined by ^{1}H NMR spectroscopy of the *E*/*Z* mixture.

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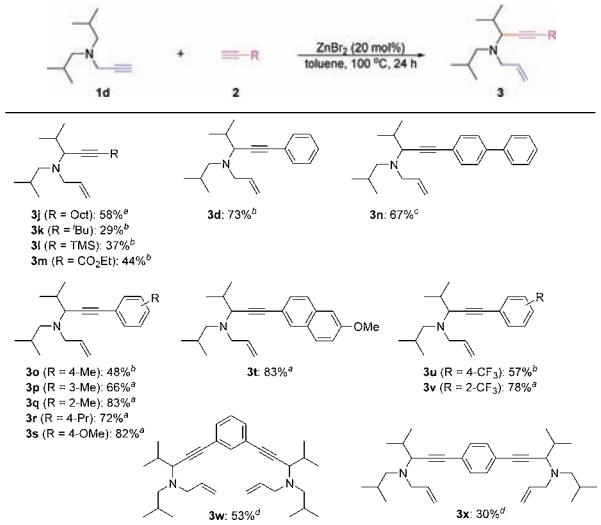
bonds adjacent to nitrogens were activated (**3a**−**3d**). The *N*,*N*-dibenzyl amino group in propargylic amines **1** required the loading of 50 mol % of zinc bromide to furnish corresponding 1,6-enyne **3e** in 50% yield, undergoing zinc-mediated redox CDC. In order to investigate regioselectivity in the current CDC reaction, we employed a 1,2,3,4-tetrahydroisoquinoline derivative and *N*-methylbutylamine derivative as propargylic amines **1** and obtained major products **3f** and **3g**, respectively. With respect to the generation of 1,6-enyne **3f**, the alkynylation took place at the C1 position preferentially and no isomer of 1,6-enyne **3f** was observed. The formation of **3g** indicates that the secondary C−H bond preferentially undergoes the alkynylation rather than the primary C−H bond. Moreover, even in the case in which an alkyl group was introduced to the terminal position of propargylic amine **1** (R^4 = Me or Bu), the corresponding 1,6-enyne **3h** or **3i** was obtained in moderate yield (1.7:1 d.r. and 1.4:1 d.r., respectively).[12]

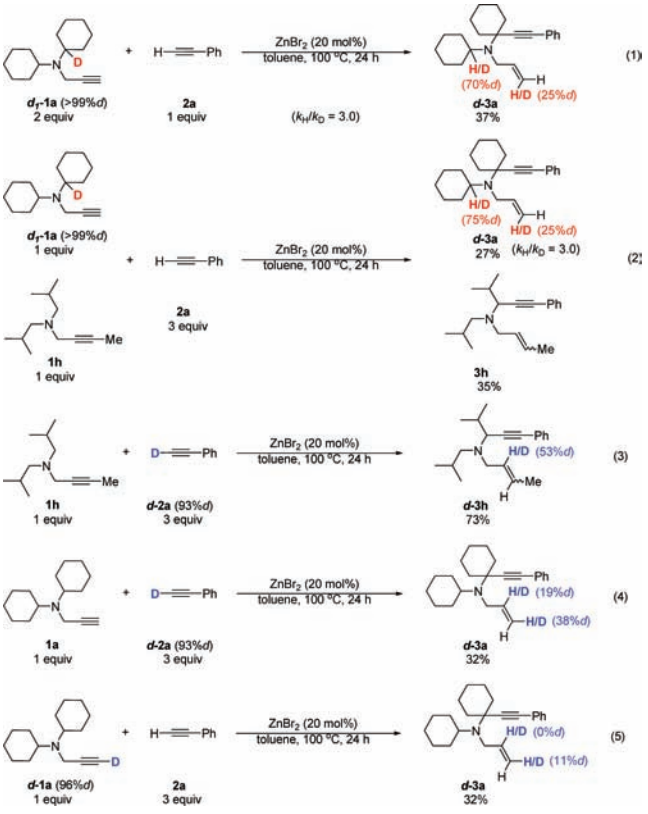
Table 2 depicts the scope of terminal alkyne **2** in the reaction with *N*,*N*-diisobutyl amine derivative **1d**. The generation of desired compounds **3** dramatically increased in some cases by changing the ratios of propargyl amine **1d** to terminal alkynes **2** from the optimized reaction conditions for the synthesis of 1,6-enyne **3a**. The ratio of the substrates was optimized for each synthesis due to the higher yield of the corresponding 1,6-enyne **3**. Decyne (R = Oct), 4-methyl-1-pentyne (R = ^{i}Bu), and ethynyl(trimethyl)silane (R = TMS) were applied to the current CDC (**3j**−**3l**); however more bulky alkyl-substituted terminal alkynes **2** did not work. Treatment of ethyl propionate (R = CO_2Et) with propargyl amine **1d** afforded the corresponding 1,6-enyne **3m** in 44% yield. Aryl-substituted terminal alkynes **2** were tolerated for this reaction, and corresponding 1,6-enynes **3d** and **3n**−**3v** were obtained in moderate to high yields. The reaction proceeded regardless of whether the aromatic group has an electron-donating group (**3o**−**3t**) or an electron-withdrawing group (**3u** and **3v**), and whether the aromatic group is substituted at the *para* (**3o**, **3r**, **3s**, and **3u**), *meta* (**3p**), or *ortho* (**3q** and **3v**) position. Diynes were employed in particular, and **3w** and **3x** were synthesized.[13]

Table 2. $ZnBr_2$-Catalyzed CDC of *N*,*N*-Diisobutyl Propargyl Amine 1d and Various Terminal Alkynes 2



[a]Isolated yields. *N*,*N*-Diisobutyl propargyl amine **1d** (0.45 mmol), alkyne **2** (0.3 mmol), and $ZnBr_2$ (0.06 mmol) were heated in toluene in a closed vial tube under N_2 at 100 °C for 24 h. [b]*N*,*N*-Diisobutyl propargyl amine **1d** (0.3 mmol) and alkyne **2** (0.9 mmol) were used. [c]*N*,*N*-Diisobutyl propargyl amine **1d** (0.3 mmol) and alkyne **2** (0.3 mmol) were used. [d]*N*,*N*-Diisobutyl propargyl amine **1d** (0.9 mmol) and diyne **2** (0.3 mmol) were used.

To gain further insight into the reaction mechanism, the reaction of deuterated substrates ***d*$_1$-1a**, ***d*-1a**, or ***d*-2a** was carried out, as shown in eqs 1 −5. The deuterium at the carbon adjacent to the nitrogen atom shifted to the position *cis* to the amino methyl group in 1,6-enyne ***d*-3a** (eq 1). The kinetic isotope effect (k_H/k_D) was 3.0, suggesting that the activation of the C−H bond adjacent to the nitrogen atom is a kinetically relevant process in this reaction (eq 1). H/D scrambling between ***d*$_1$-1a** and **1h** did not occur. The results indicate that the current CDC proceeds with the intramolecular hydride shift of propargylic amine **1** (eq 2). The deuterium of ***d*-2a** was incorporated at the position geminal to the amino methyl group of ***d*-3 h** (eq 3). Similarly, the deuterium of ***d*-2a** was added to the multiple bond of **1a** (eq 4). In eq 4, the deuterium atoms incorporated in the alkene positions of ***d*-3a** were situated *cis* and located on the terminal carbon of the alkene position preferentially rather than on the substituted carbon. The deuterium at the terminal alkyne position of ***d*-1a** might have been eliminated and exchanged with a proton (eq 5).



Finally, we propose the reaction mechanism on the basis of the isotopic labeling experiments, as shown in Scheme 3. Initially, the zinc alkynylide species would be generated from terminal alkyne **2**.[14] There might be equilibrium between **5** and **6** in the case in which propargylic amine **1** bears a terminal alkyne (R^4 = H). Next, the multiple bond of propargylic amine **1** would be coordinated by zinc(II) to give complex **7**,[15] which, in turn, would afford iminium intermediate **8** via a 1,5-hydride shift.[16] There would be the avoidance of the methylene group and the zinc atom in the case in which propargylic amine **1** is an

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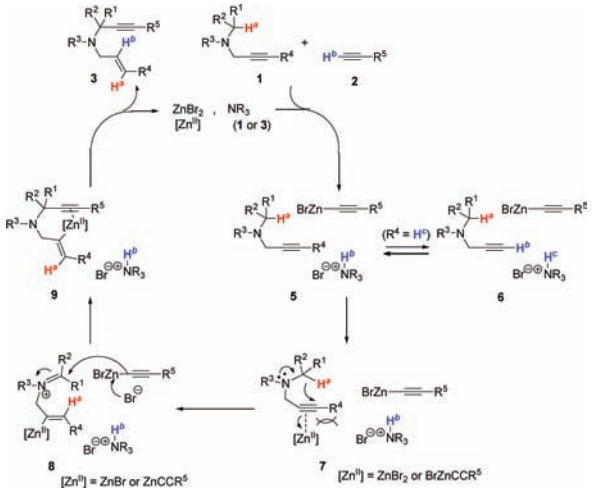
Scheme 3. Proposed Mechanism for $ZnBr_2$-Catalyzed CDC of Propargylic Amines 1 and Terminal Alkynes 2



internal alkyne (R^4 = Me or Bu). The attack of the zinc alkynylide to the iminium ion followed by the protonation of σ-vinylzinc complex **9** furnishes 1,6-enyne **3**. Thus, alkynes **2** are substituted at the carbon adjacent to the nitrogen atom of propargylic amine **1**, with the generation of an allyl group.

In conclusion, we have demonstrated the synthesis of *N*-tethered 1,6-enynes from propargylic amines **1** and terminal alkynes **2** by the zinc(II)-catalyzed redox cross-dehydrogenative coupling reaction. This cross-coupling reaction should attract attention from an atom economic point of view. The current CDC offers a novel approach to the synthesis of useful structures with an internal oxidant in the molecule of the starting materials and without generation of waste.

■ ASSOCIATED CONTENT

Supporting Information

Details of synthesis and characterization. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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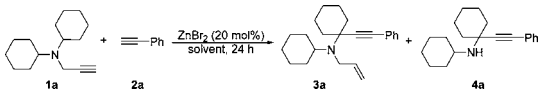
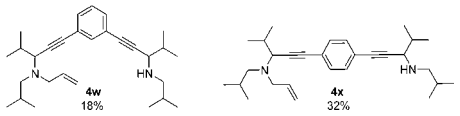
(11) We selected *N,N*-dicyclohexylamine derivatives **1a** as a model substrate in order to optimize the reaction conditions. In the synthesis of 1,6-enyne **3a**, secondary amine **4a** was also obtained, which is considered to be a product of the addition of alkyne **2a** to the imine generated by transformation from propargylic amine **1a** to the allene. See Table S1 in the Supporting Information.



(12) The diastereomeric ratios were determined by ^{1}H NMR spectroscopy. See Supporting Information for details about the analysis.

(13) We observed byproducts **4**, the structures of which were the ones that the allyl groups eliminated from enynes **3**.



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(15) *N,N*-Diisobutylbut-3-yn-1-amine **10** and *N*-allyl-*N*-cyclohexylcyclohexanamine **11** did not work under the optimized conditions of the current redox CDC reaction. It is indicated that the 1,5-hydride shift of propargylic amines **1** is the driving force of the reaction.

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