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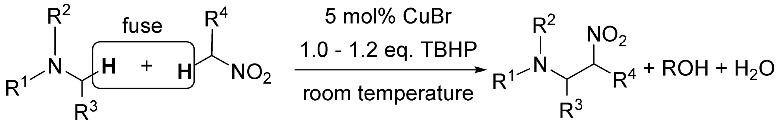

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Highly Efficient Copper-Catalyzed Nitro-Mannich Type Reaction: Cross-Dehydrogenative-Coupling between sp^3 C−H Bond and sp^3 C−H Bond

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C−C Bond formation reactions are among the most important processes in chemistry because they provide key steps in building more complex molecules from simple precursors. Transition metal-catalyzed C−H bond activations and subsequent C−C bond formations have attracted great interest in recent years.[1] On the other hand, transition metal-catalyzed cross-coupling reactions of various reactive functional groups are powerful methods for constructing C−C bonds (Scheme 1, path A).[2] From a practical point of view, a cross-dehydrogenative-coupling (CDC) reaction from two C−H bonds will avoid the preparation of functional groups and thus make synthetic schemes shorter and more efficient (Scheme 1, path B). Some excellent pioneering progress had been achieved on this subject.[3] To our best knowledge, there are no examples of efficient CDC reactions between sp^3 C−H and sp^3 C−H.[4] Herein, we report the first simple and efficient CDC reactions to construct β-nitroamine catalyzed by copper bromide in the presence of *tert*-BuOOH via combined reactions of sp^3 C−H and sp^3 C−H followed by C−C bond formations.

Vicinal diamines are important compounds in biologically active natural products in medicinal chemistry and more recently (as a core unit) in chiral auxiliaries and chiral ligands in asymmetric catalyses.[5] An efficient approach toward such compounds is via the nitro-Mannich (aza-Henry) reaction. The nucleophilic addition of nitroalkanes to imines gives β-nitroamine derivatives;[6] 1,2-diamines or α-amino carbonyl compounds are then readily obtained by the reduction of the nitro group[7] or the Nef reaction of β-nitroamine derivatives.[8]

Recently, we reported two new types of C−C bond formation: CuBr-catalyzed alkynylation of sp^3 C−H bonds adjacent to a nitrogen atom[3Aa, b] and $AuCl_3$/AgOTf-catalyzed addition of activated methylene compounds to alkene.[9] To address the even more challenging CDC reaction, our attentions are focused on sp^3 C−H and sp^3 C−H cross-coupling reaction to generate β-nitroamine derivatives.

To begin our study, we examined various copper salts, the reaction time, and the amount of catalysts for the desired CDC reaction (Table 1). Among the copper salts tested, CuBr and $CuBr_2$ were the most effective catalysts for this reaction (entries 2, 6, 9, and 10). Interestingly, CuOTf and $Cu(OTf)_2$ were less effective under the present conditions (entries 4 and 7). Although other copper salts are also effective, the reactions need a relatively longer time to reach reasonable yields (entries 1, 3, 5, and 8). The reaction also provided an excellent yield even when the amount of CuBr was reduced to 2 mol % (entry 10). No reaction was observed in the absence of the copper salts (entry 11).

Under the optimized conditions, various β-nitroamine derivatives were generated by this new methodology. Representative results obtained via the CDC reaction are summarized in Table 2. 1,2,3,4-Tetrahydroisoquinoline derivatives and 4-substituted *N,N*-dimethylaniline gave excellent yields of the desired products based on NMR analysis of the reaction mixture.[10] Moreover, when one equivalent of nitromethane was used, the desired products of **3a** and **3c** were obtained in 63% and 67% isolated yields respectively (Table 2). The use of nitroethane instead of nitromethane also gave the desired compounds with good isolated yields (the ratios of two diastereoisomers are 1.5−2:1). In the case of *N,N*-dimethylaniline, a low yield was obtained which was attributed to the formation of demethylated compound and other unidentified byproducts.

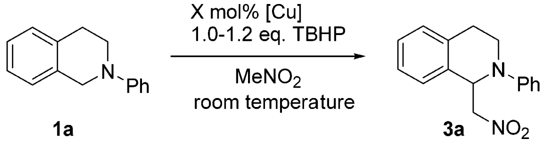
Scheme 1. Various Cross-Coupling Methods for the Formation of C−C Bonds

$$\text{C−X} + \text{Y−C} \xrightarrow[\textbf{\textit{Path A}}]{\textit{cat.}\text{ M}} \text{C−C}$$

X, Y = Br, OTf, SiR_3, SnR_3, BR_2, etc.

$$\text{C−H} + \text{H−C} \xrightarrow[\textbf{\textit{Path B}}]{\textit{cat.}\text{ M}} \text{C−C}$$

Table 1. Optimization of Reaction Conditions[a]



1a **3a**

entry	catalyst	X mol %	reaction time (NMR yield%)[b]
1	CuCl	10	3 h (70); 6 h (75)
2	CuBr	10	3 h (90)
3	CuI	10	3 h (60); 6 h (80)
4	CuOTf	10	3 h (20); 6 h (50)
5	$CuCl_2$	10	3 h (60); 6 h (80)
6	$CuBr_2$	10	3 h (40); 6 h (92)
7	$Cu(OTf)_2$	10	3 h (5); 6 h (35)
8	$Cu(OAc)_2{\cdot}H_2O$	10	3 h (50); 6 h (80)
9[c]	CuBr	5	6 h (92)
10[d]	CuBr	2	3 h (60); 6 h (90)
11	no	0	3 h (0)

[a] 0.1 mmol tetrahydroisoquinoline, 1.0 mL of nitromethane, and 0.02 mL of ^{t}BuOOH (5−6 M in decane). [b] Reported yields were based on tetrahydroisoquinoline and determined by NMR using an internal standard. [c] 0.2 mmol tetrahydroisoquinoline, 1.0 mL of nitromethane, and 0.04 mL of ^{t}BuOOH (5−6 M in decane). [d] 0.5 mmol tetrahydroisoquinoline, 2.0 mL of nitromethane, and 0.1 mL of ^{t}BuOOH (5−6 M in decane).

Other cyclic amines such as 1-phenyl-pyrrolidine also generated the desired product in good yield (Scheme 2). In this case, bis-CDC product is also formed in 4% isolated yield along with the mono-CDC product (53%).

The exact mechanism for the product formation is not clear at the present stage. However, on the basis of the results that we obtained in this paper and in the previous one,[3Aa,Ab] three types of intermediates are most likely involved in the reaction. (1) Copper catalyzed the formation of an imine-type intermediate **4** (coordinated to copper) through H-abstraction of sp^3 C−H adjacent to nitrogen.[11] (2) The copper catalyst also activated the nitroalkanes to form intermediate **5**,[12] and subsequent coupling of the two intermediates, **4** and **5**, resulted in the desired product (and regenerated the copper

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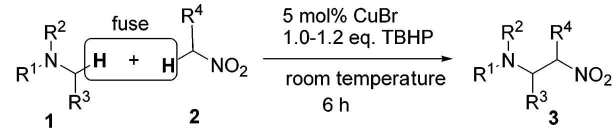
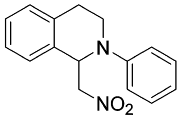
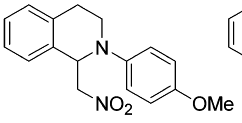
Table 2. CDC Reaction of Tertiary Amines with Nitroalkanes[a]



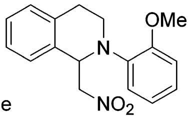
products (isolated yields %)[b]



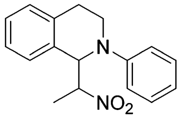
3a (75)
(63)[c]



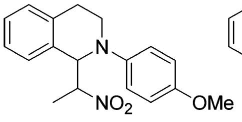
3b (54)



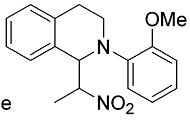
3c (71)
(67)[c]



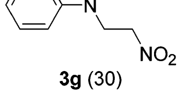
3d (53)



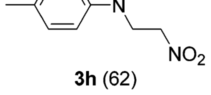
3e (51)



3f (32)



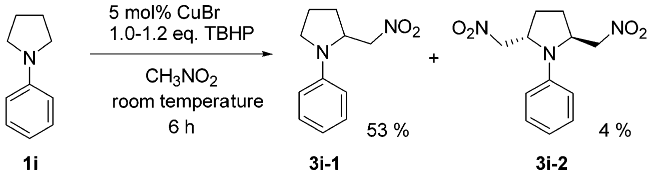
3g (30)



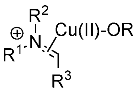
3h (62)

[a] 0.2 mmol amine, 1.0 mL of nitroalkane, and 0.04 mL of ^{t}BuOOH (5−6 M in decane). [b] Isolated yields were based on amines. [c] 1 equiv (0.2 mmol) of nitromethane was used.

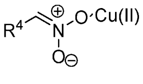
Scheme 2. Reaction of 1-Phenyl-pyrrolidine with Nitromethane



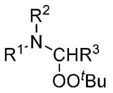
catalyst). (3) Alternatively, it is possible that *tert*-butylperoxide products **6** are involved as intermediates,[13] which were further converted into the corresponding cross-coupling products catalyzed by CuBr. [3Ab]



4



5



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In summary, CDC reaction represents a new chemical transformation. We report here the first highly efficient C−C bond formation via CDC reaction between sp^3 C−H bond and sp^3 C−H bond catalyzed by copper bromide. Because nitrogen-containing compounds are important structural features of natural products and pharmaceuticals, this catalytic reaction will be an efficient method for the synthesis of such compounds. The scope, mechanism, and synthetic application of this reaction are under investigation.

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Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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