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Copper-Catalyzed Cross Dehydrogenative Coupling Reactions of Tertiary Amines with Ketones or Indoles

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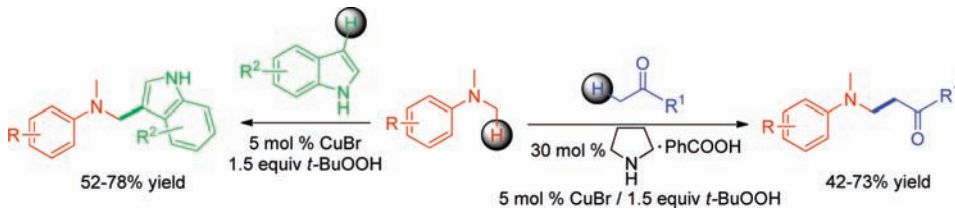
ABSTRACT



A novel cross dehydrogenative coupling (CDC) reaction of *N*,*N*-dimethylanilines with methyl ketones by cooperative copper and aminocatalysis has been developed, which leads to the formation of *β*-arylamino ketones in 42−73% yields. Moreover, the copper-catalyzed alkylation of free (NH) indoles with *N*,*N*-dimethylanilines via CDC reaction is also presented, affording alkylated indoles in 52−78% yields.

It is known that transition-metal-catalyzed cross-coupling reactions are among the most important methods for C−C bond formation. However, these cross-coupling reactions generally need functionalized substrates.[1] Recently, much attention has been focused on C−H bond activation and subsequent C−C bond formation.[2] Nevertheless, most of them still require another functionalized substrate.[1] Due to direct use of C−H bonds, cross dehydrogenative coupling (CDC) is a very promising method for the formation of a C−C bond, which avoids the use of functionalized substrates and is a more atom-economic and environmentally friendly method.[3] In recent years, several groups, especially Li's research group, have done excellent work on CDC reactions of various sp^3 C−H bonds, such as benzylic or allylic C−H, α-C−H bonds of tertiary amines, α-C−H bonds of ethers, or C−H bonds of alkanes with other C−H bonds. Among them, great interest was paid to C−H activations of tertiary amines and subsequent C−C formations with nucleophiles.[1,4]

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(1) Li, Z.-P.; Bohle, D.-S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

(2) For a book and representative reviews on C−H activation and subsequent C−C bond-forming reactions, see: (a) Dyker, G. *Handbook of C-H Transformations*; Wiley-VCH: Weinheim, 2005. (b) Jia, C.-G.; Piao, D.-G.; Oyamada, J.; Lu, W.-J.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (c) Chen, X.; Engle, K.-M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082.

(3) For reviews on CDC reactions: (a) Li, C.-J.; Li, Z.-P. *Pure Appl. Chem.* **2006**, *78*, 935. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Scheuermann, C.-J. *Chem. Asian J.* **2010**, *5*, 436.

(4) For representative papers on CDC reactions of tertiary amines, see: (a) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672. (c) Li, Z.-P.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (d) Murahashi, S.-I.; Komiya, N.; Terai, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 6931. (e) Catino, A.-J.; Nichols, J.-M.; Nettles, B.-J.; Doyle, M.-P. *J. Am. Chem. Soc.* **2006**, *128*, 5648. (f) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc.* **2008**, *130*, 11005. (g) Condie, A.-G.; Gonzalez-Gomez, J.-C.; Stephenson, C.-R.-J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (h) Sud, D.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (i) Shen, Y.-M.; Li, M.; Wang, S.-Z.; Zhan, T.-G.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (j) Liu, P.; Zhou, C.-Y.; Xiang, S.; Che, C.-M. *Chem. Commun.* **2010**, 2739. (k) Shu, X.-Z.; Yang, Y.-F.; Xia, X.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2010**, *8*, 4077. (l) Wang, M.-Z.; Zhou, C.-Y.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2010**, *16*, 5723.

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At the same time, enamines as elegant nucleophiles have become crucial reactive intermediates in organocatalysis for C−C formations.[5] However, there are only a few reports on the application of aminocatalysis in the C−C bond formation after C−H activation of tertiary amines by transition-metal catalysis.[4g,k] In 2009, Klussmann's research group revealed a CDC reaction of tertiary amines with methyl ketones by dual catalysis of the vanadium complex and proline, and almost all tertiary amines employed efficiently in the CDC reaction are limited to tetrahydroisoquinoline derivatives.[4g] The investigation on the CDC reactions of tertiary amines with ketones by cooperative metal and aminocatalysis, including the use of common tertiary amines and cheap metals, is a challenging subject. In this paper, we report a CDC reaction of *N*,*N*-dimethylanilines with methyl ketones by cooperative CuBr and pyrrolidine catalysis.

Initially, various aminocatalysts **1**−**5** (Figure 1) were tested for the CDC reaction of *N*,*N*-dimethylaniline **6a** with acetone

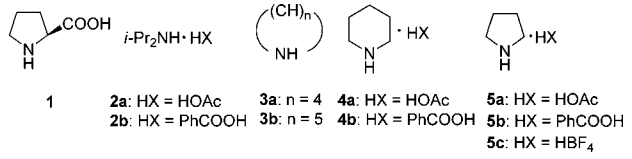
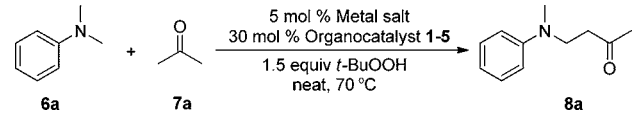


Figure 1. Organocatalysts **1**−**5**.

7a in the presence of 5 mol % CuI and 1.5 equiv of *tert*-butyl hydroperoxide (TBHP) as an oxidant (entries 1−6, Table 1). When L-proline was employed as an organocatalyst, no desired coupling product **8a** was obtained (entry 1, Table 1). Gratifyingly, using diisopropylamine acetic salt **2a** led to the desired **8a** in a 12% yield (entry 2, Table 1). After screening of secondary amines and their salts **3**−**5**, pyrrolidine benzoate **5b** was found to be optimal with a 36% yield of **8a** (entry 5, Table 1, also see Supporting Information (SI)). Then various metal salts, such as CuCl, $CuCl_2$, CuBr, $Cu(acac)_2$, $FeCl_2$, $FeCl_3$, and $Fe(acac)_3$, were examined. The experiment indicated that CuBr was most effective among the metal catalysts, which resulted in a 53% yield of **8a** (entries 7−13, Table 1). Oxidants including *tert*-butyl peroxide (TBP), *tert*-butyl hydroperoxide, 70 wt % in water (T-HYDRO), H_2O_2, and oxygen were also probed in the reaction, which led to **8a** in the lower yields of 0−48% as compared to that of TBHP (for details, see SI). Finally, various solvents were examined in the reactions, and the yield of **8a** was further improved to 64% by adding a small amount of MeOH (entry 14, Table 1; also see SI). It is noteworthy that only a trace amount of coupling product **8a** was obtained in the absence of pyrrolidine salt **5b** (entry 15, Table 1). This result demonstrates that the organocatalyst **5b** is crucial for the CDC reaction.

(5) For representative books and reviews on aminocatalysis, see: (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis - From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (b) Dalko, P.-I. *Enantionselective Organocatalysis*; Wiley-VCH: Weinheim, 2007. (c) Mukherjee, S.; Yang, J.-W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

Table 1. Screening for the CDC Reaction of *N*,*N*-Dimethylaniline with Ketone by Cooperative Transition-Metal and Aminocatalysis[a]



6a **7a** **8a**

entry	metal salt	organocatalyst	*t* (h)	yield (%)[b]
1	CuI	**1**	8	0[c]
2	CuI	**2a**	8	12
3	CuI	**2b**−**4**	8	trace−17
4	CuI	**5a**	4	23
5	CuI	**5b**	4	36
6	CuI	**5c**	4	18
7	CuCl	**5b**	4	42
8	$CuCl_2$	**5b**	4	35
9	CuBr	**5b**	4	53
10	$Cu(acac)_2$	**5b**	8	27
11	$FeCl_2$	**5b**	4	28
12	$FeCl_3$	**5b**	4	23
13	$Fe(acac)_3$	**5b**	8	18
14	CuBr	**5b**	4	64[d]
15	CuBr	-	4	trace

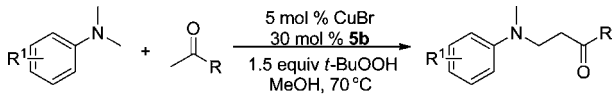
[a] Reaction conditions: amine (0.5 mmol), acetone (5.0 mmol), metal salt (0.025 mmol), organocatalyst **1**−**5** (0.15 mmol), and TBHP-decane (0.75 mmol) at 70 °C. [b] Isolated yields. [c] MeOH (1.0 mL) as a solvent. [d] A small amount of MeOH (0.2 mL) was added.

After screening of various organocatalysts, metal catalysts, solvents, and oxidants, it can be concluded that the optimized reaction should be performed under the cooperative catalysis of 5 mol % CuBr and 30 mol % pyrrolidine salt **5b** using 1.5 equiv of TBHP as an oxidant and methanol as a solvent. Under the optimal reaction conditions, a set of *N*,*N*-dimethylanilines were probed in the CDC reaction. It was found that *N*,*N*-dimethylanilines bearing either electron-donating or electron-withdrawing groups on the benzene rings **6a**−**g** could perform the CDC reaction with methyl ketones **7a**−**c** to give the desired β-arylamino ketones **8a**−**k** in satisfactory yields (42−73%). The coupling always occurs at the nonsubstituted α-position of the ketones **7**, and no coupling product was obtained using 3-pentanone or cyclohexanone probably because the CDC reaction was sensitive to steric hindrance.

Additionally, indole derivatives are also good nucleophiles and have many important biological and pharmaceutical activities.[6] Recently, Li's[1] and Che's[4j] research group successively developed the CDC reaction of tetrahydroisoquinolines with indoles under the catalysis of copper(I) bromide or silica-supported iron complex (Table 2), respectively. In 2009, Che et al. found that *N*,*N*-dimethylanilines could undergo a CDC reaction with *N*-aryl indoles by ruthenium catalysts.[4l] However, the CDC reaction of *N*,*N*-dimethylanilines with *N*-alkyl- or *N*-H-indoles did not

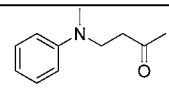
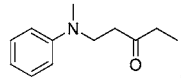
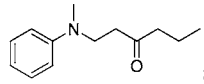
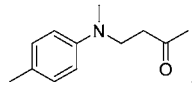
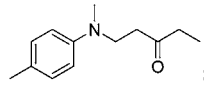
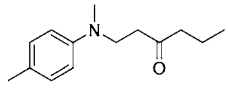
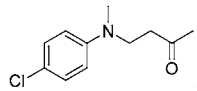
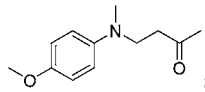
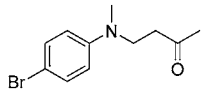
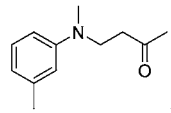
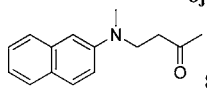
(6) (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (b) Kochanowska-Karamyan, A.-J.; Hamann, M.-T. *Chem. Rev.* **2010**, *110*, 4489.

Table 2. CDC Reaction of *N*,*N*-Dimethylanilines **6** with Methyl Ketone **7** under the Cooperative Catalysis of CuBr and Pyrrolidine Salt **5b**[a]



6a-g **7a-c** **8a-k**

6a: R^1 = H
6b: R^1 = 4-Me
6c: R^1 = 4-Cl
6d; R^1 = 4-OMe
6e: R^1 = 4-Br
6f : R^1 = 3-Me
6g: *N*,*N*-dimetyl-2-naphthylamine
7a: R^2 = Me
7b: R^2 = Et
7c: R^2 = n-Pr

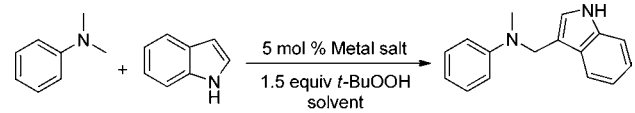
entry	amine	ketone	*t* (h)	product	yield (%)[b]
1	**6a**	**7a**	4	 **8a**	64
2	**6a**	**7b**	8	 **8b**	53
3	**6a**	**7c**	8	 **8c**	42
4	**6b**	**7a**	4	 **8d**	73
5	**6b**	**7b**	8	 **8e**	56
6	**6b**	**7c**	8	 **8f**	44
7	**6c**	**7a**	8	 **8g**	57
8	**6d**	**7a**	8	 **8h**	58[c]
9	**6e**	**7a**	8	 **8i**	52
10	**6f**	**7a**	4	 **8j**	68
11	**6g**	**7a**	8	 **8k**	55[c]

[a] Reaction conditions: amine (0.5 mmol), ketone (5.0 mmol), CuBr (0.025 mmol), organocatalyst **5b** (0.15 mmol), TBHP-decane (0.75 mmol), MeOH (0.20 mL), 70 °C. [b] Isolated yields. [c] The reaction was performed at 50 °C.

perform smoothly. At the same reaction conditions, using *N*-H- or *N*-alkyl-indoles efficiently resulted in dimethylaminobenzyl indoles rather than the expected CDC products with *N*,*N*-dimethylanilines.[4l] To the best of our knowledge, no literature was disclosed on the CDC reaction of *N*,*N*-dimethylanilines with free (NH)-indole derivatives. Herein, we wish to present our recent results on this CDC reaction catalyzed by CuBr.

Considering that some CDC reactions of tetrahydroisoquinolines with indoles or ketones proceed smoothly under neat conditions,[1,4i] the reaction of *N*,*N*-dimethylaniline **6a** with indole **9a** was initially tested in the presence of 5 mol % CuBr and 1.0 equiv of TBHP at 40 °C under neat conditions. To our delight, the desired product **10a** was formed in 38% yield (entry 1, Table 3). Then, other copper

Table 3. Screening of Reaction Conditions for the CDC Reaction of *N*,*N*-Dimethylaniline with Indole[a]



6a **9a** **10a**

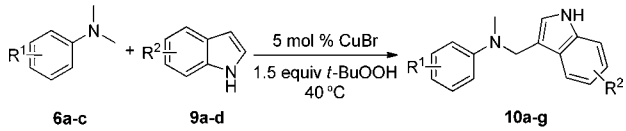
entry	metal salt	TBHP (equiv)	*t* (h)	solvent	yield (%)[b]
1	CuBr	1.0	3	neat	38
2	CuCl	1.0	3	neat	26
3	$CuCl_2$	1.0	3	neat	16
4	CuI	1.0	3	neat	25
5	$Cu(OAc)_2$	1.0	3	neat	18
6	CuBr	1.5	3	neat	52
7	CuBr	1.5	12	neat	17[c]
8	CuBr	1.5	3	neat	22[d]
9	CuBr	1.5	12	CH_3CN	9
10	CuBr	1.5	12	hexane	18
11	CuBr	1.5	12	toluene	25

[a] Reaction conditions: *N*,*N*-dimethylaniline (1.0 mmol), indoles (0.5 mmol), metal catalyst (0.025 mmol), 40 °C. [b] Isolated yields. [c] The reaction was performed at rt. [d] The reaction was performed at 50 °C.

salts, such as CuCl, $CuCl_2$, CuI, and $Cu(OAc)_2$, were examined, and it was found that CuBr was the most effective metal catalyst (entries 2−5, Table 3). The optimizing experiment also indicated that increasing the amount of TBHP from 1.0 to 1.5 equiv improved the yield of **10a** (compare entry 1 with 6, Table 3). Among the reaction temperatures tested, 40 °C was the most suitable temperature (entries 6−8, Table 3). After further screening of solvents such as toluene, hexane, and CH_3CN, the neat conditions were still optimal for the CDC reaction.

On the basis of screening the above CDC reaction conditions, it can be concluded that the optimized reaction should be performed in the presence of 5 mol % CuBr and 1.5 equiv of TBHP at 40 °C under neat conditions. Under the optimal conditions, it was found that different *N*,*N*-dimethylanilines **6a**−**c** and free (NH)-indoles **9a**−**d** could undergo the CDC reaction smoothly to afford the corresponding alkylated indoles, *N*-indolylmethyl-*N*-methylbenzenamine **10a**−**g** in 52−78% yields (entries 1−7, Table 4). The 4-substituted *N*,*N*-dimethylanilines **6b**,**c** led to higher yields of **10b**−**d** than those resulting from **6a** probabaly because **6a** with indole **9a** could form 4-indolylmethyl *N*,*N*-dimethylbenzenamine as a byproduct

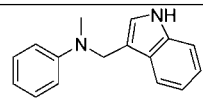
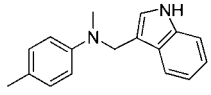
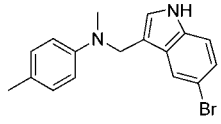
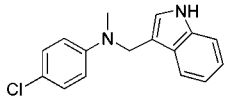
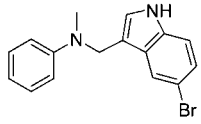
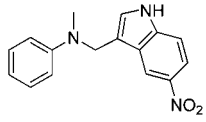
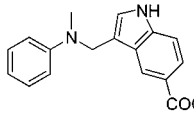
Table 4. CDC Reaction of *N*,*N*-Dimethylanilines **6** with Indoles **9** Catalyzed by CuBr[a]



6a-c **9a-d** **10a-g**

6a: R^1 = H
6b: R^1 = 4-Me
6c: R^1 = 4-Cl

9a: R^2 = H
9b: R^2 = 5-Br
9c: R^2 = 5-NO_2
9d: R^2 = 6-$COOCH_3$

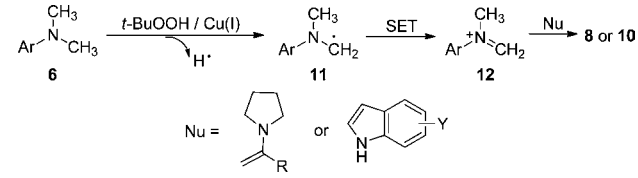
entry	amine	indole	product	yield (%)[b]
1	**6a**	**9a**	 **10a**	52
2	**6b**	**9a**	 **10b**	72
3	**6b**	**9b**	 **10c**	76
4	**6c**	**9a**	 **10d**	67
5	**6a**	**9b**	 **10e**	69
6	**6a**	**9c**	 **10f**	78[c]
7	**6a**	**9d**	 **10g**	64[c]

[a] Reaction conditions: amine (1.0 mmol), indole (0.5 mmol), CuBr (0.025 mmol), TBHP-decane (0.75 mmol), 40 °C, 3 h. [b] Isolated yields. [c] The reaction time is 12 h.

(compare entries 2−4 with 1, Table 4).[4l,7] When 5-methylindole was employed, we could not isolate the pure coupling product due to its instability, and using other 5-electron-donating group substituted indoles led to no coupling product.

Furthermore, it was found that when 2,6-di-*tert*-butyl-4-methyl phenol (BHT), a radical inhibitor, was added into the above CDC reaction systems of *N*,*N*-dimethylaniline **6a** with acetone **7a** or indole **9a** the yield of the coupling product **8a** was decreased dramatically to 18%, or no coupling product **10a** was observed under the optimal conditions. Therefore, the mechanism of the two CDC reactions may undergo radical pathways. As shown in Scheme 1, a *tert*-butoxyl radical generateded by copper-catalyzed decomposition of TBHP initially abstracts an α-hydrogen to form radical **11**, followed by a single electron transfer (SET) to generate imine cation **12**.[1] Then, **12** may undergo a nucleophilic attack by an enamine formed from ketone and pyrrolidine in situ or by an indole derivative, affording the coupling product **8** after hydrolysis or **10**, respectively.

Scheme 1. Depiction of Plausible Mechanism



In conclusion, we have developed a novel CDC reaction of *N*,*N*-dimethylanilines **6** with methyl ketones **7** by the cooperative catalysis of 5 mol % CuBr and 30 mol % pyrrolidine benzoate **5b** in the presence of TBHP, affording *β*-arylamino ketones **8a**−**k** in 42−73% yields. Moreover, we also found that under the catalysis of 5 mol % CuBr and in the presence of TBHP *N*,*N*-dimethylanilines **6** could undergo CDC reaction with free (NH)-indoles **9** smoothly to afford the alkylated indoles **10** in 52−78% yields. Further investigations on the extension of substrate scopes are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures, spectroscopic data, and spectra of ^{1}H NMR, ^{13}C NMR, and MS for coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) We also isolated 4-indolymethyl *N*,*N*-dimethylbenzenamine as a byproduct.