A Dehydrogenative Homocoupling Reaction for the Direct Synthesis of Hydrazines from *N*-Alkylanilines in Air

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Abstract: A copper-catalyzed N–N bond-forming reaction was performed by a dehydrogenative homocoupling of *N*-alkylanilines, affording *N*,*N*′-dialkyl-*N*,*N*′-diphenylhydrazines in 72–88% yields. This new strategy has the advantages of direct synthesis from *N*-alkylanilines, using air as the oxidant, convenient manipulations, mild reaction conditions and moderate to good yields. A possible mechanism by coordination and reductive elimination has been proposed.

Key words: homocoupling, oxidative dehydrogenation, copper catalyst, direct synthesis, hydrazine

Recently, oxidative dehydrogenative couplings are becoming an important strategy for modern organic synthesis due to high efficiency, atom economy and minimal environment impact.[1] By dehydrogenative homocoupling, various symmetric C–C bonds can be formed directly.[2] Many studies on the dehydrogenative homocoupling of thiols to form S–S bond have been carried out for the synthesis of disulfides.[3] A few literatures disclosed the formation of Si–Si[4a] and Sn–Sn[4b] bonds by the direct homocoupling of hydrostannanes and secondary silanes, respectively. Different from the investigations on the formations of S–S bonds and Sn–Sn bonds, the direct formation of N–N bond by dehydrogenative coupling was rarely reported.[5] As a main class of compounds containing N–N bonds, hydrazine derivatives are important building blocks in organic synthesis,[6] and usually show significant biological activities.[7] Most synthesis of them are based on the compounds containing N–N or N=N bonds.[6,8] Besides, N-protected oxaziridines, ureas, and nitroarene can also be used as starting materials for the synthesis of hydrazines.[9–11] Tsuji revealed a protocol for the direct synthesis of hydrazines from amines by copper-catalyzed oxidative coupling.[5a] However, it seems that for *N*-alkylanilines as starting materials, only one example, *N*-methylaniline is suitable for this protocol to give *N*,*N*′-dimethyl-*N*,*N*′-diphenylhydrazine in 52% yield. Herein, we wish to report our recent work on the direct dehydrogenative homocoupling of *N*-alkylanilines to afford tetrasubstituted hydrazines in satisfactory yields.

Initially, we examined the oxidative homocoupling of *N*-methylaniline (**1a**), using CuBr (20 mol%) as a metal catalyst and 4 Å molecular sieves (MS) as an additive at 95 °C in DMF under air for 24 hours. A trace amount of the desired product **2a** was obtained [Table 1, entry 1; for other copper catalysts see Supporting Information (SI)]. Gratifyingly, when *N*,*N*,*N*′′*N*′-tetramethylethylenediamine (TMEDA) was employed as a ligand, the yield was increased to 49% (Table 1, entry 2). After the survey of other ligands, such as *N*′,*N*′-dimethylpropane-1,3-diamine (DMAPA), and ethane-1,2-diamine (EDA), TMEDA proved to be the best (Table 1, entries 3 and 4; also see SI). When metal oxides, such as CuO, SnO_2, SeO_2, and Fe_2O_3 were employed as co-catalysts, the yield of **2a** increased remarkably, among which CuO was the most effective (Table 1, entries 5–8; also see SI).[12] In the presence of CuO, other copper catalysts, such as CuCl, CuI, $CuCl_2\cdot 2H_2O$, and $CuSO_4\cdot 5H_2O$ also gave the desired product in moderate to good yields (Table 1, entries 9–12), but $CuBr_2$ and $Cu(OAc)_2\cdot H_2O$ led to poor yields. It is noteworthy that the oxidative homocoupling did not occur in the absence of copper catalyst (Table 1, entry 15). Using oxygen instead of air resulted in a similar yield. When the reaction was conducted under nitrogen, only trace hydrazine **2a** was obtained, indicating that oxygen is crucial for this reaction. Other oxidants, such as *t*-BuOOH, *t*-BuOO*t*-Bu, and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) led to poor yields (Table 1, entries 18–20). Polar solvents, such as DMF, DMSO, and MeCN were suitable, and DMF is an optimal solvent for the reaction (see SI). Addition of 4 Å MS was favorable to the reaction.[12,13] The optimal reaction temperature was found to be 95 °C.

After screening of various copper catalysts, ligands, metal oxides, oxidants, bases, reaction temperatures and solvents, we concluded that the optimized reaction should be performed by the catalysis of CuBr (20 mol%) at 95 °C in DMF using CuO (20 mol%) as a co-catalyst, TMEDA (2.0 equiv) as a ligand and air as an oxidant. Under the optimized conditions, the scope of the reaction substrates was investigated (Scheme 1).[14] The experiments demonstrated that various *N*-alkylanilines **1a**–**d** performed the homocoupling reaction smoothly to give the desired *N*,*N*′-dialkyl-*N*,*N*′-diphenylhydrazines **2a**–**d** in good yields. The *N*-alkylanilines, **1e**–**j**, bearing electron-donating

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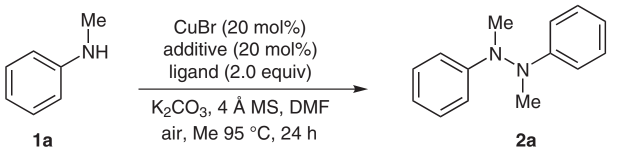
Table 1 Optimization of the Dehydrogenative Homocoupling Conditions[a]



Entry	Cu catalyst	Additive	Ligand	Yield (%)[b]
1	CuBr	–	–	trace
2	CuBr	–	TMEDA	49
3	CuBr	–	DMAPA	25
4	CuBr	–	EDA	0
5	CuBr	CuO	TMEDA	84
6	CuBr	SnO$_2$	TMEDA	82
7	CuBr	SeO$_2$	TMEDA	78
8	CuBr	Fe$_2$O$_3$	TMEDA	75
9	CuCl	CuO	TMEDA	70
10	CuI	CuO	TMEDA	78
11	CuCl$_2$·2H$_2$O	CuO	TMEDA	81
12	CuSO$_4$·5H$_2$O	CuO	TMEDA	80
13	CuBr$_2$	CuO	TMEDA	58
14	Cu(OAc)$_2$·H$_2$O	CuO	TMEDA	32
15	–	CuO	TMEDA	0
16[c]	CuBr	CuO	TMEDA	82
17[d]	CuBr	CuO	TMEDA	trace
18[e]	CuBr	CuO	TMEDA	30
19[f]	CuBr	CuO	TMEDA	35
20[g]	CuBr	CuO	TMEDA	trace

[a] The mixture of **1a** (1.0 mmol), Cu catalyst (20 mol%), metal oxide (20 mol%), ligand (2.0 equiv), K$_2$CO$_3$ (2.0 equiv), 4 Å MS (0.1 g) in DMF (2 mL) was stirred at 95 °C under air for 24–48 h.

[b] Isolated yields.

[c] O$_2$ (1 atm) was used as an oxidant.

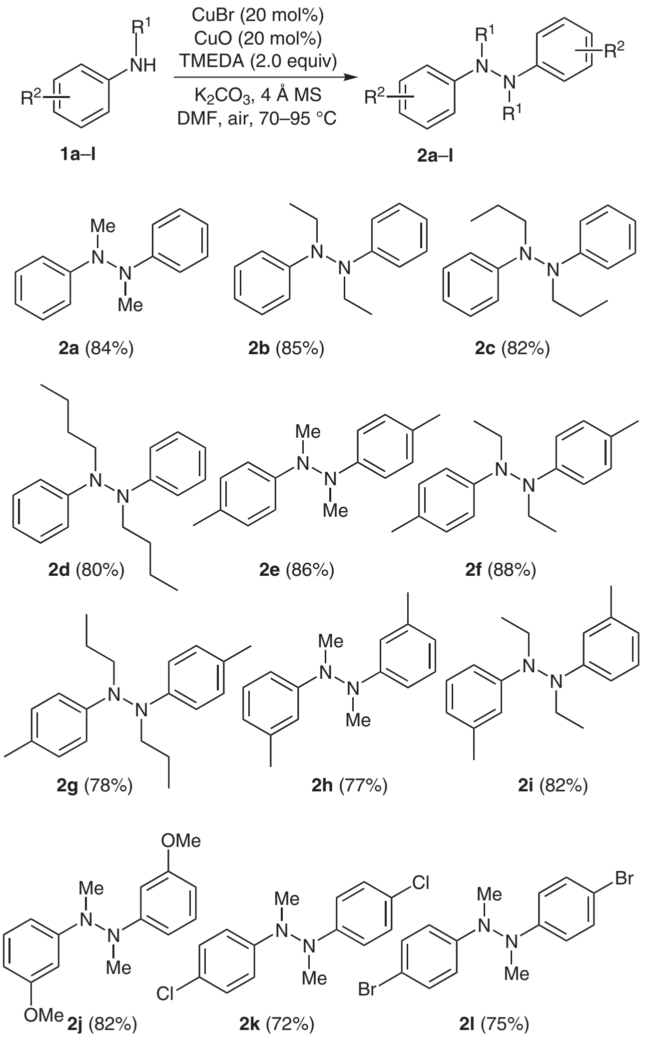
[d] The reaction was carried out under N$_2$ (1 atm) for 48 h.

[e] *t*-BuOOH was used as oxidant.

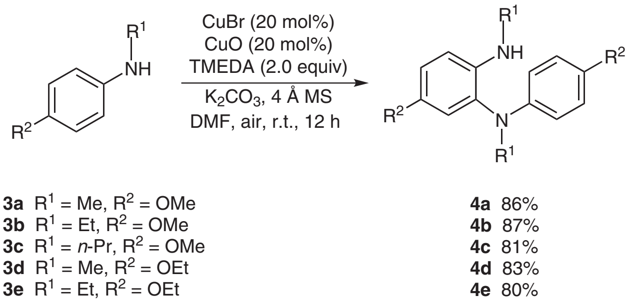
[f] *t*-BuOO*t*-Bu was used as oxidant.

[g] DDQ was used as oxidant.

groups on benzene ring resulted in better yields, shorter reaction time and lower reaction temperature as compared to those bearing electron-withdrawing groups on benzene ring (**1k**–**l**), and 4-nitro-*N*-alkylaniline did not undergo the homocoupling reaction. 2-Methyl- or 2-methoxy-*N*-methylanilines and *N*-isopropylaniline were proved unreactive probably due to steric hindrance. Interestingly, when 4-methoxy- or 4-ethoxy alkylanilines **3a**–**e** were employed, no desired homocoupling product of hydrazine was observed under the above optimal conditions. When the reaction temperature was lowered to room temperature, it was found that *o*-semidines **4a**–**e** were isolated in good yields (Scheme 2).

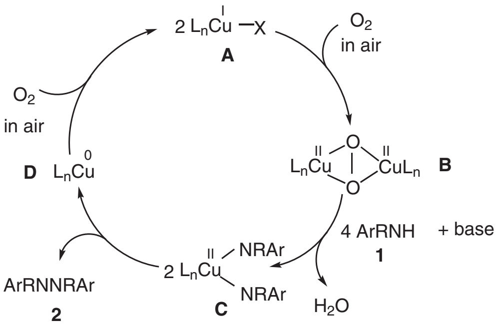


Scheme 1 Dehydrogenative homocoupling for the direct synthesis of hydrazines. The mixture of *N*-alkylaniline **1** (1.0 mmol), CuBr (20 mol%), CuO (20 mol%), TMEDA (2.0 equiv), K$_2$CO$_3$ (2.0 equiv) and 4 Å MS (0.1 g) in DMF (2.0 mL) was stirred at 70 °C or 95 °C for 8–24 h under air. Compounds **1a**–**d** or **1k**–**l** were reacted at 95 °C for 12–24 h and **1e**–**j** were reacted at 70 °C for 8–12 h. Isolated yields are reported.



Scheme 2 Dehydrogenative homocoupling for the direct synthesis of *o*-semidines. General conditions: alkylaniline (1.0 mmol), CuBr (20 mol%), K$_2$CO$_3$ (2.0 equiv), DMF (2.0 mL), TMEDA (2.0 equiv), CuO (20 mol%) and 4 Å MS (0.1 g) under air at r.t. for 12 h. Isolated yields are reported.

A possible mechanism for the direct synthesis of hydrazine **2** from *N*-alkylaniline **1** is depicted in Scheme 3. Initially, Cu(I) complex **A** is oxidized to peroxo-dicopper(II) complex **B** by air.[15] Then, the dicopper(II) complex **B** is subjected to nucleophilic attack by *N*-alkylaniline **1** to generate diamino complex **C**, followed by reductive elimination to give the hydrazine **2**. A successive oxidation of copper(0) complex **D** to copper(I) complex **A** completes a catalytic cycle. The presence of CuO in the reaction system may promote the decomposition of dicopper(II) complex **B**, facilitating the attack of *N*-alkylaniline **1**.[12]



Scheme 3 Proposed mechanism for the copper-catalyzed oxidative dehydrogenative homocoupling of *N*-alkylanilines

In summary, we have developed a copper-catalyzed N–N bond-forming reaction by the direct dehydrogenative homocoupling of *N*-alkylanilines, furnishing *N*,*N′*-dialkyl-*N*,*N′*-diphenylhydrazines **2a**–**l** in 72–88% yields. This new strategy has the advantages of using air as oxidant, direct synthesis from *N*-alkylanilines, convenient manipulations, mild reaction conditions and good yields. A possible mechanism by coordination and reductive elimination has also been proposed. Further studies on the mechanism and extension of the copper-catalyzed oxidative dehydrogenative homocoupling are currently underway.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) For recent reviews on oxidative cross-dehydrogenative-coupling, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Scheuermann, C. J. *Chem. Asian J.* **2010**, *5*, 436. (c) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243.

(2) For representative papers on oxidative dehydrogenative homocouplings for the formation of C–C bonds, see: (a) Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200. (b) Chen, Q.-A.; Dong, X.; Chen, M.-W.; Wang, D.-S.; Zhou, Y.-G.; Li, Y.-X. *Org. Lett.* **2010**, *12*, 1928. (c) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082. (d) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (e) Matsushita, M.; Kamata, K.; Yamaguchi, K.; Mizuno, N. *J. Am. Chem. Soc.* **2005**, *127*, 6632. (f) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (g) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (h) Kamata, K.; Yamaguchi, S.; Kotani, M.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2407. (i) Oi, S.; Sato, H.; Sugawara, S.; Inoue, Y. *Org. Lett.* **2008**, *10*, 1823. (j) Oishi, T.; Katayama, T.; Yamaguchi, K.; Mizuno, N. *Chem. Eur. J.* **2009**, *15*, 7539.

(3) For representative papers on the synthesis of disulfides by dehydrogenative homocoupling reactions, see: (a) Arterburn, J. B.; Perry, M. C.; Nelson, S. L.; Dible, B. R.; Holguin, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 9309. (b) Singh, D.; Galetto, F. Z.; Soares, L. C.; Rodrigues, O. E. D.; Braga, A. L. *Eur. J. Org. Chem.* **2010**, *14*, 2661. (c) Banfield, S. C.; Omori, A. T.; Leisch, H.; Hudlicky, T. *J. Org. Chem.* **2007**, *72*, 4989. (d) Choi, J.; Yoon, N. M. *J. Org. Chem.* **1995**, *60*, 3266. (e) Ramesha, A. R.; Chamedarsekran, S. *J. Org. Chem.* **1994**, *59*, 1354.

(4) (a) Rosenberg, L.; Davis, C. W.; Yao, J.-Z. *J. Am. Chem. Soc.* **2001**, *123*, 5120. (b) Braunstein, P.; Morise, X. *Chem. Rev.* **2000**, *100*, 3541.

(5) (a) Kajimoto, T.; Takahashi, H.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3673. (b) For an excellent report on copper-catalyzed dehydrogenative coupling of anilines leading to azo compounds, see: Zhang, C.; Jiao, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 6174.

(6) (a) *Hydrazine and Its Derivatives,* In *Kirk-Othmer Encyclopedia of Chemical Technology*, Vol. 13, 4th ed.; Wiley: New York, **1995**. (b) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, **1995**. (c) Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205.

(7) (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 2539. (b) Zhang, R.; Durkin, J. P.; Windsor, W. T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1005. (c) Lee, T.-W.; Cherney, M. M.; Huitema, C.; Liu, J.; James, K. E.; Powers, J. C.; Eltis, L. D.; James, M. N. G. *J. Mol. Biol.* **2005**, *353*, 1137.

(8) For representative papers for the synthesis of hydrazines from the compounds containing N–N or N=N bonds, see: (a) Bredihhin, A.; Groth, U. M.; Maeorg, U. *Org. Lett.* **2007**, *9*, 1097. (b) Kisseljova, K.; Tsubrik, O. *Org. Lett.* **2006**, *8*, 43. (c) Bredihhin, A.; Maeorg, U. *Org. Lett.* **2007**, *9*, 4975. (d) Maeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem. Int. Ed.* **1996**, *35*, 2626. (e) Rosamilia, A. E.; Aricò, F.; Tundo, P. *J. Org. Chem.* **2008**, *73*, 1559. (f) Tsubrik, O.; Maeorg, U. *Org. Lett.* **2001**, *3*, 2297. (g) Alberti, A.; Canè, F.; Dembech, P.; Lazzari, D.; Ricci, A.; Seconi, G. *J. Org. Chem.* **1996**, *61*, 1677. (h) Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Gregoire, B. *J. Org. Chem.* **2001**, *66*, 2869. (i) Grehn, L.; Lohn, H.; Ragnarsson, U. *Chem. Commun.* **1997**, *15*, 1381. (j) Brosse, N.; Pinto, M.-F.; Jamart-Gregoire, B. *J. Org. Chem.* **2000**, *65*, 4370. (k) Maeorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, *39*, 681. (l) Maeorg, U.; Pehk, T.; Ragnarsson, U. *Acta Chem. Scand.* **1999**, *53*, 1127. (m) Bredihhin, A.; Maeorg, U. *Tetrahedron* **2008**, *64*, 6788. (n) Tsubrik, O.; Maeorg, U.; Sillard, R.; Ragnarsson, U. *Tetrahedron* **2004**, *60*, 8363.

(9) Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.* **1998**, *39*, 8845.

(10) Huddleston, P. R.; Coutts, G. C. *Comprehensive Organic Functional Group Transformations*, Vol. 2; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W., Eds.; Pergamon/Elsevier: Oxford, **1995**, 371–383.

(11) Furst, A.; Moore, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 5492.

(12) Similarly, inorganic metal oxide MnO_2 promoted an oxygen-mediated oxidation: Joyce, L. L.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2792.

(13) (a) Steinhoff, B. A.; King, A. E.; Stahl, S. S. *J. Org. Chem.* **2006**, *71*, 1861. (b) Schultz, M. J.; Hamilton, S. S.; Jensen, D. R.; Sigman, M. S. *J. Org. Chem.* **2005**, *70*, 3343.

(14) **General Experimental Procedure**: To a solution of *N*-alkylaniline **1** (0.107 g, 1.0 mmol) in DMF (2 mL) were added CuBr (0.029 g, 0.2 mmol), TMEDA (0.232 g, 2.0 mmol), CuO (0.016 g, 0.2 mmol), K_2CO_3 (0.276 g, 2.0 equiv) and 4 Å MS (0.1 g) successively, and the reaction mixture was stirred at 70 °C or 95 °C for 12–24 h in air. After the reaction was completed, the mixture was filtered, and the residue was washed with EtOAc (3 × 5 mL). Then, the combined filtrates were concentrated in vacuum, and the residue was purified by column chromatography (silica gel, PE–EtOAc as eluent) to afford the desired hydrazine **2**.

(15) (a) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (b) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013. (c) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892.