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Peroxide-Mediated Transition-Metal-Free Direct Amidation of Alcohols with Nitroarenes

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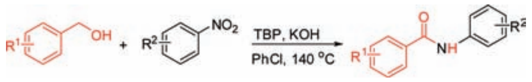
ABSTRACT



An unusual direct amidation of alcohols with nitroarenes mediated by peroxides has been discovered. The reaction tolerated a wide range of functionalities, and various aromatic amides were obtained in moderate to good yields in the absence of transition-metal catalyst. The peroxides and solvents had a significant impact on the reaction yield.

Amide motifs are present in many natural products, pharmaceuticals, polymers, and biological systems.[1] Amides are also of great importance as intermediates for the preparation of various useful organic compounds.[2] Amide formation reaction is one of the key cornerstone reactions in organic chemistry.[3] The amide bonds are typically synthesized from the corresponding carboxylic acids and amines mediated by stoichiometric amount of coupling reagents or by prior conversion of carboxylic acids to activated derivatives such as acid chlorides or anhydrides (Scheme 1, eq 1).[4] In the past few years, great efforts have been made to develop environmentally friendly processes toward amide synthesis.[5] Recently, Li et al. reported a transition-metal-catalyzed oxidative amidation of aldehydes with primary amines, and various aliphatic amides have been achieved in high yields.[6]

Very recently, an important breakthrough for amide formation has been made by Milstein et al. The direct coupling between amine and alcohol leading to amide was realized using ruthenium pincer complex as catalyst by the extrusion of dihydrogen (Scheme 1, eq 2). In this unique transformation, alcohol was oxidized into aldehyde in situ by the extrusion of dihydrogen (dehydrogenation),[7] and no external oxidant was used as the hydrogen acceptor. The intermediate aldehyde reacted with amine to give a hemiaminal that was subsequently dehydrogenated to the

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(1) (a) Humphrey, J. M.; Chamberlin, A. R. *Chem. Rev.* **1997**, *97*, 2243. (b) Larock, R. C. *Comprehensive Organic Transformation*; VCH: New York, 1999.

(2) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 6th ed.; Wiley: Weinheim, Germany, 2007.

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(4) Smith, M. B. *Compendium of Organic Synthetic Methods*; Wiley: New York, 2001.

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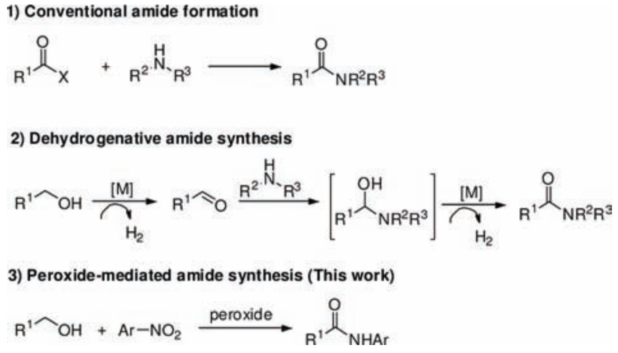
(6) (a) Yoo, W. J.; Li., C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 13064. For other examples on amide synthesis from aldehydes and amines, see: (a) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798. (b) Saidi, O.; Bamford, M. J.; Blacker, A. J.; Lynch, J.; Marsden, S. P.; Plucinski, P.; Watson, R. J.; Williams, J. M. J. *Tetrahedron Lett.* **2010**, *51*, 5804.

(7) For reviews on dehydrogenation, see: (a) Dobereiner, G. E.; Grabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (b) Gunanathan, C.; Milstein, D. *Acc. Chem. Res.* **2011**, *44*, 588.

10.1021/ol203211k

Scheme 1. Different Pathways for the Amide Bond Formation



amide.[8] This direct catalytic conversion of alcohols and amines into amides is a particularly desirable reaction because of its high atom efficiency and has inspired several other research groups to further develop the reactions using transition-metal catalysts with[9] or without hydrogen acceptors.[10] However, special handling of expensive metal complexes and ligands is required in many cases.[11] Kobayashi et al. developed a heterogeneous catalytic system for amide synthesis. Gold or even very cheap iron, nickel, and cobalt nanoparticles were used as catalysts, and the catalysts could be recovered and reused several times without loss of activity.[12,13] However, in most cases, aliphatic or benzylic amines were used as starting materials. Amide formation from aromatic amines (or even nitroarenes) in the absence of transition-metal catalyst is rare.[14]

Aromatic amines are in general synthesized from the corresponding nitroarenes by using reducing reagents.[15] The direct use of stable, cheap and easily handled nitroarenes with alcohols instead of aromatic amines is an attractive approach for C–N bond formation. However, external reducing reagents such as hydrogen and transition-metals are necessary in most cases.[16] Recently, we and others developed various catalytic systems for amine and imine formation between alcohols and nitroarenes.[17] The nitroarenes were reduced to amines in situ using the borrowing hydrogen strategy (or hydrogen transfer method),[18] and no external oxidants or reducing reagents were added to the reaction mixture. We also discovered an unusual transition-metal-free direct amination of simple cycloalkanes with nitroarenes, and secondary amines were formed under oxidative conditions.[19] As a continuing effort to construct C–N bonds using nitroarenes directly, herein, we wish to report a transition-metal-free direct amidation of alcohols with aromatic nitroarenes (Scheme 1, eq 3).

Our initial investigations were focused on the amidation of benzyl alcohol (**1a**) with nitrobenzene (**2a**), and the results are summarized in Table 1. When nitrobenzene was reacted with benzyl alcohol in chlorobenzene in the absence of peroxide, no *N*-phenylbenzamide (**3a**) was formed as determined by GC–MS and ^{1}H NMR methods (Table 1, entry 1). Instead, azoxybenzene (PhN═NOPh) was obtained in 48% yield together with large amount of benzaldehyde.[20] The choice of peroxides was crucial for this reaction. Various peroxides were investigated under an atmosphere of air.[21] *tert*-Butyl hydroperoxide (TBHP), cumene hydroperoxide, *p*-benzoquinone, and benzoyl peroxide were inefficient for this kind of transformation (Table 1, entries 2–5). When dicumyl peroxide was used, the desired product was formed in 63% yield (Table 1, entry 6). Among the various peroxides

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(13) For other supported catalytic systems, see: (a) Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem.—Eur. J.* **2009**, *15*, 9977.

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(16) For amination of nitroarenes with alcohols or aldehydes using molecular hydrogen as reductant, see: (a) Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5162. (b) Sreedhar, B.; Reddy, P.; Devi, D. *J. Org. Chem.* **2009**, *74*, 8806. (c) Gelman, F.; Blum, J.; Avnir, D. *New J. Chem.* **2003**, *27*, 205. (d) Hu, L.; Cao, X. Q.; Ge, D. H.; Hong, H. Y.; Guo, Z. Q.; Chen, L.; Sun, X. H.; Tang, J. X.; Zheng, J. W.; Lu, T. M.; Gu, H. W. *Chem.—Eur. J.* **2011**, *17*, 14283.

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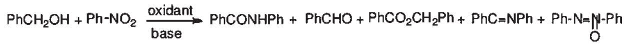
(20) The reduction of nitrobenzene in acidic media affords phenylhydroxylamine, whereas reduction in basic media affords azoxy compound. See: Patai, S. In *The Chemistry of Amines, Nitroso, Nitro and Related Groups*; John Wiley & Sons: Chichester, U. K., 1996.

(21) ***Caution!*** *Be careful when using TBP at these temperatures.*

examined, *tert*-butyl peroxide (TBP) was the most effective, and its use resulted in the formation of **3a** in 87% yield (Table 1, entry 7). Replacement of the peroxide with oxygen did not lead to the desired product **3a** (Table 1, entry 8). Solvents also played an important role, and the reactions in other solvents led to much lower yield (Table 1, entries 9−13).[22] The choice of bases was crucial for this reaction. Other bases were less effective (Table 1, entries 14−19). The amount of TBP is another important factor for the yield of the product. The use of 2 equiv of TBP led to a lower yield of **3a** (Table 1, entry 20). The yield did not change when the reaction was carried out under argon (Table 1, entry 21), whereas a slightly lower yield was obtained when the reaction was carried out in oxygen (Table 1, entry 22). Under the optimized reaction conditions, the reaction showed good selectivity, and the overall stoichiometry of the amide reaction was given in Scheme 2.

Table 1. Optimization of the Reaction Conditions[a]

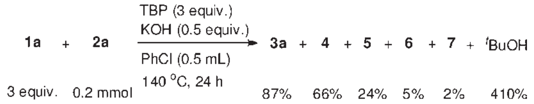


$$\text{PhCH}_2\text{OH} + \text{Ph-NO}_2 \xrightarrow[\text{base}]{\text{oxidant}} \text{PhCONHPh} + \text{PhCHO} + \text{PhCO}_2\text{CH}_2\text{Ph} + \text{PhC=NPh} + \text{Ph-N=}\underset{\text{O}}{\text{N}}\text{-Ph}$$

					yield (%)[b]				
entry	oxidant	solvent	base	conv 2a (%)	3a	4	5	6	7
1		PhCl	KOH	98	0	45	0	0	48
2	TBHP	PhCl	KOH	0	0	42	4	0	0
3	$\text{PhC(CH}_3)_2\text{OOH}$	PhCl	KOH	0	0	35	0	0	0
4	*p*-benzoquinone	PhCl	KOH	0	0	12	0	0	0
5	$(\text{PhCOO})_2$	PhCl	KOH	0	0	0	78	0	0
6	dicumyl peroxide	PhCl	KOH	93	63	63	11	11	8
7	**TBP**	**PhCl**	**KOH**	**98**	**87**	**66**	**24**	**5**	**2**
8	O_2	PhCl	KOH	70	0	81	0	9	29
9	TBP	DMF	KOH	100	0	21	16	12	0
10	TBP	diglyme	KOH	100	0	32	0	12	0
11	TBP	NMP	KOH	100	0	19	0	0	0
12	TBP	anisole	KOH	100	56	56	56	29	5
13	TBP	*p*-xylene	KOH	81	53	6	3	10	3
14	TBP	PhCl	none	85	63	51	10	14	0
15	TBP	PhCl	KF	75	52	33	52	11	3
16	TBP	PhCl	NaOH	100	78	30	15	11	3
17	TBP	PhCl	K_2CO_3	72	39	39	39	39	9
18	TBP	PhCl	K_3PO_4	70	29	30	16	15	11
19	TBP	PhCl	Cs_2CO_3	66	0	23	22	59	0
20[c]	TBP	PhCl	KOH	100	58	32	13	2	17
21[d]	TBP	PhCl	KOH	100	86	86	86	0	5
22[e]	TBP	PhCl	KOH	100	74	23	18	5	9

[a] Conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), oxidant (3.0 equiv), base (0.1 mmol), solvent (0.5 mL), 140 °C, 24 h in air unless otherwise noted. [b] GC yield based on **2a**. [c] 2.0 equiv of TBP was used. [d] Under argon. [e] Under oxygen.

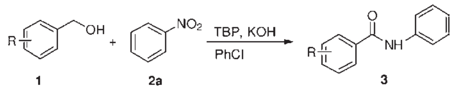
Scheme 2. Overall Stoichiometry of the Amide Reaction

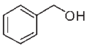
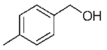
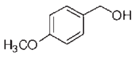
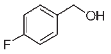
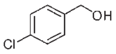
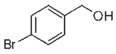
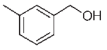
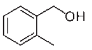
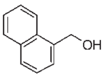


$$\underset{3\text{ equiv.}}{\mathbf{1a}} + \underset{0.2\text{ mmol}}{\mathbf{2a}} \xrightarrow[\text{PhCl (0.5 mL)},\ 140\ ^\circ\text{C, 24 h}]{\text{TBP (3 equiv.), KOH (0.5 equiv.)}} \underset{87\%}{\mathbf{3a}} + \underset{66\%}{\mathbf{4}} + \underset{24\%}{\mathbf{5}} + \underset{5\%}{\mathbf{6}} + \underset{2\%}{\mathbf{7}} + \underset{410\%}{{}^t\text{BuOH}}$$

With the optimized reaction conditions established, the scope of the reaction with respect to nitrobenzene and various benzylic alcohols was investigated (Table 2). The reactions with benzylic alcohols bearing electron-donating groups (Table 2, entries 2 and 3) and electron-withdrawing substituents at the aromatic ring (Table 2, entries 4 and 5) proceeded smoothly to give the desired products in good yields. A slightly lower yield was obtained when 4-bromobenzyl alcohol was used, and the desired product was achieved in 55% yield (Table 2, entry 6). The position of the substituents on the phenyl ring of benzyl alcohols affected the reaction yield slightly. Moderate yields were obtained when (2-methylphenyl)methanol (**1g**), (3-methylphenyl)methanol (**1h**), and 1-naphthalenemethanol (**1i**) were used as starting materials (Table 2, entries 7−9). It should be noted that about 20−30% imine byproducts formed when **1h** and **1i** were used as the starting materials, and only trace amount of imines formed in other cases. No significant difference was observed when 99.99% and ACS reagent purity potassium hydroxide was used.

Table 2. Reaction of Nitrobenzene with Benzylic Alcohols[a]



entry	alcohol		product	yield (%)[b]
1		1a	3a	70
2		1b	3b	68
3		1c	3c	64
4		1d	3d	72
5		1e	3e	67
6		1f	3f	55
7		1g	3g	46
8		1h	3h	51
9		1i	3i	61

[a] Conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), oxidant (3.0 equiv), KOH (0.1 mmol, 99.99%), solvent (0.5 mL), 140 °C, 24 h under air. [b] Isolated yield.

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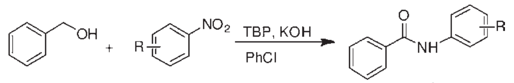
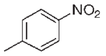
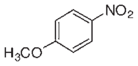
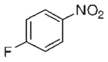
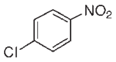
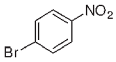
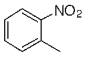
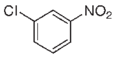
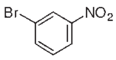
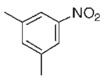
[22] For Table 1, entry 7, the conversion of **1a** and **2a** was 72 and 100%, respectively. For Table 1, entries 9−11, the using of these solvents resulted other side reactions and no desired product, and imine and azoxybenzene were observed. For other nitroarene substrates, the conversion of **2** was above 95%.

Table 3. Reaction of Benzyl Alcohol with Nitroarenes[a]

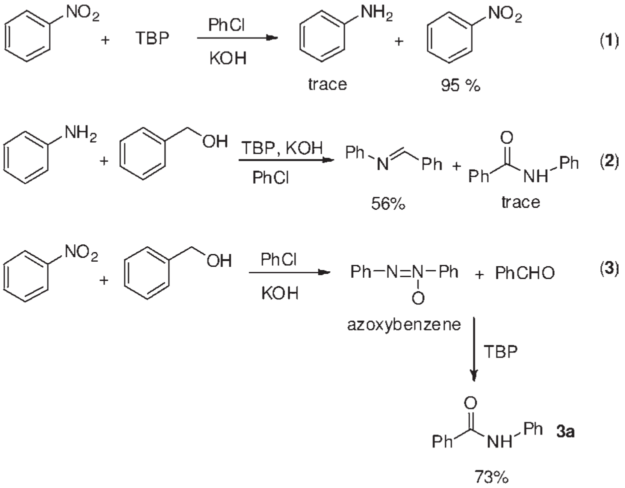


1a + **2** → **3**

entry	nitroarene		product	yield (%)[b]
1		2b	3j	66
2		2c	3k	76
3		2d	3l	51
4		2e	3m	72
5		2f	3n	70
6		2g	3o	51
7		2h	3p	65
8		2i	3q	63
9		2j	3r	52

[a] Conditions: **1a** (0.6 mmol), **2a** (0.2 mmol), oxidant (3.0 equiv), KOH (0.1 mmol, 99.99%), solvent (0.5 mL), 140 °C, 24 h under air. [b] Isolated yield.

Scheme 3. Control Experiments under Various Conditions[a]



[a] Yields are determined by ^{1}H NMR using an internal standard.

To further explore the scope of the reaction, various nitroarenes **2b**–**j** were employed to react with **1a** under the optimized conditions (Table 3). A series of functional groups including methyl, methoxy, chloro, bromo, and fluoro were well tolerated under the optimal reaction conditions, and the desired products were obtained in moderate to good yields (Table 3, entries 1–5). The position of the substituents on the phenyl ring of nitrobenzene slightly affected the reaction yield. Unfortunately, aliphatic nitro compounds and aliphatic alcohols are not suitable substrates for this kind of reactions under the optimal conditions.

To gather more information, some control experiments were set up under various reaction conditions (Scheme 3). Under standard reaction conditions, more than 95% nitrobenzene survived in the absence of benzyl alcohol, and only trace amount of aniline was observed (Scheme 3, eq 1). The reaction between benzyl alcohol and aniline mainly afforded an imine adduct (Scheme 3, eq 2). As we previously indicated, azoxybenzene was observed as the major adduct in the absence of TBP. However, the desired product **3a** could be obtained in 73% yield when azoxybenzene was further treated with TBP under the standard reaction conditions (Scheme 3, eq 3).[23] Although the mechanism for the present transition-metal-free amidation of alcohols with nitroarenes is not completely clear for now, our preliminary experiments revealed that the amidation should start from aldehydes (in situ oxidized from alcohols) and azoxyarenes (in situ reduced from nitroarenes under basic media).[20] The hydrogen generated from alcohols acted as the reducing reagent for nitro group.

In summary, we have developed a novel direct amidation of alcohols with nitroarenes mediated by peroxide. Aromatic amides were formed in moderate to good yields in the absence of transition-metal catalyst. The reaction showed very good selectivity, amides were formed as the major products, and only trace amounts of imine byproducts were observed in most cases. Hydrogen generated from alcohol oxidation acted as the nitro reducing reagent. The nitro reduction, alcohol oxidation, and amide formation were realized in a cascade. Further investigation including the scope and mechanism of this reaction are in progress in our laboratory.

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Supporting Information Available. General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] A similar yield was obtained when pure azoxybenzene reacted with benzaldehyde under standard reaction conditions.

The authors declare no competing financial interest.