ORGANIC LETTERS

2007
Vol. 9, No. 17
3429−3432

Metal-Free One-Pot Oxidative Amination of Aldehydes to Amides

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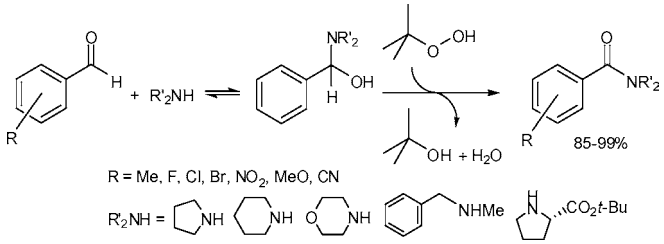
Received June 20, 2007

ABSTRACT



Metal-free oxidative amination of aromatic aldehydes in the presence of TBHP provides convenient access to amides in 85–99% under mild reaction conditions within 5 h. This method avoids free carboxylic acid intermediates and integrates aldehyde oxidation and amide bond formation, which are usually accomplished separately, into a single operation. Proline-derived amides can be prepared in excellent yields without noticeable racemization.

The formation of amide bonds is one of the most important organic reactions due to the abundance of this functional group in natural products, polymers, and pharmaceuticals. Routine amide synthesis from amines and free carboxylic acids generally relies on the use of coupling agents such as carbodiimides and 1-hydroxybenzotriazoles.[1] Alternatively, amides are often prepared from activated carboxylic acid derivatives.[2] Few methods that utilize other starting materials have been developed. Among the most prominent examples are variations of the Staudinger reaction by using thioacids or thioesters in the presence of azides,[3] and the acid-promoted Schmidt reaction that forms an amide from a ketone and an alkyl azide or a hydrazoic acid analogue, for example, trimethylsilylazide.[4] Several procedures exploiting hydrative amidation of alkynes,[5] transfer of a carbamoyl ligand from nickel to alkyl halides,[6] and transition metal-catalyzed aminocarbonylation of aryl halides,[7] alkenes,[8] and alkynes[9] have been reported.

Nakagawa and co-workers discovered that aromatic aldehydes can be directly converted to amides in the presence of ammonia and stoichiometric amounts of nickel peroxide.[10] An important advantage of this approach is that C−N bond formation and oxidation are integrated into a single operation while the generation of a free carboxylic acid intermediate,

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(3) (a) Nilson, B. L.; Kiessling, L. L.; Raines, R. T. *Org. Lett.* **2000**, *2*, 1939−1940. (b) Damakaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408−4409. (c) Shangguan, N.; Katukojvala, S.; Greenberg, R.; Williams, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 7754−7755. (d) Merkx, R.; Brouwer, A. J.; Rijkers, D. T. S.; Liskamp, R. M. J. *Org. Lett.* **2005**, *7*, 1125−1128.

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(6) Fukuoka, S.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1971**, *36*, 2721−2723.

(7) (a) Lin, Y.-S.; Alper, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 779−781. (b) Uozumi, Y.; Arii, T.; Watanabe, T. *J. Org. Chem.* **2001**, *66*, 5272−5274. (c) Namayakkara, P.; Alper, H. *Chem. Commun.* **2003**, 2384−2385.

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(9) (a) Knapton, D.; Meyer, T. Y. *Org. Lett.* **2004**, *6*, 687−689. (b) Uenoyama, Y.; Fukuyama, T.; Nobuta, O.; Matsubara, H.; Ryu, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 1075−1078.

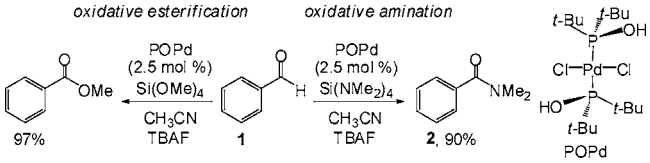
(10) Nakagawa, K.; Onoue, H.; Minami, K. *J. Chem. Soc., Chem. Commun.* **1966**, 17−18.

10.1021/ol7014626 CCC: $37.00
Published on Web 07/27/2007

which may not be compatible with other functional groups, is avoided. Although direct oxidative amination of aldehydes utilizes readily available starting materials and is considered an economically attractive alternative to routine amide formation, only a few examples have been reported to date. Yoshida et al. found that palladium-catalyzed oxidative transformation of aldehydes affords morpholine-derived amides when bromobenzene is used as the oxidant.[11] Murahashi's and Beller's groups employed ruthenium catalysts in oxidative aminations of aromatic aldehydes with secondary amines.[12] Recently, Li described an elegant copper-catalyzed procedure that allows oxidative amination of aldehydes in the presence of silver iodate.[13] A common shortcoming of these methods is that expensive transition metal catalysts are required and amides are obtained in only moderate yields in some cases. We wish to report the first metal-free oxidative amination of aldehydes. Our procedure eliminates the need for transition metal catalysts, base, and other additives that are commonly employed in oxidative aminations of aldehydes.

On the basis of our previous reports that palladium-phosphinous acids such as POPd effectively catalyze oxidative esterifications of aldehydes to esters in the presence of tetraalkyl orthosilicates,[14] we attempted to exploit the same conditions for direct oxidative amination using tetrakis(dimethylamino)silane as the amine source (Scheme 1).

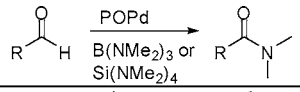
Scheme 1. Palladium-Catalyzed Oxidative Esterification and Amination of Benzaldehyde

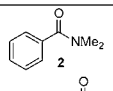
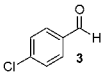
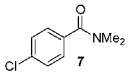
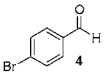
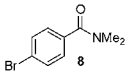
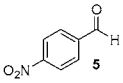
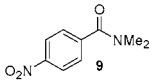
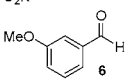
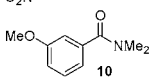
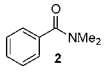
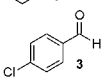
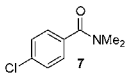
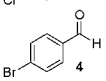
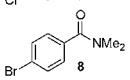
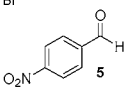
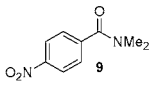
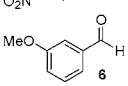
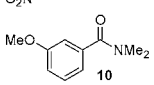


Employing 2.5 mol % of POPd and stoichiometric amounts of $Si(NMe_2)_4$ in acetonitrile at room temperature, we found that benzaldehyde, **1**, is converted in a single step to *N*,*N*-dimethylbenzamide, **2**, in 90% yield (Table 1, entry 1). Unfortunately, oxidative amination of aldehydes **3**−**6** gave the corresponding *N*,*N*-dimethylbenzamides **7**−**10** in only 50−55% (entries 2−5). We found that the POPd-catalyzed reaction also proceeds in the presence of tris(dimethylamino)-borane, providing benzamide **2** in 88% yield (entry 6). Again, unsatisfactory yields were obtained when this procedure was applied to other aromatic aldehydes (entries 7−10), and screening of other palladium catalysts, additives, and solvents did not improve results. The decreased yields were generally due to low conversion and substantial amounts of starting materials were recovered in these cases.

According to the mechanism of the POPd-catalyzed oxidative esterification, tetrakis(dimethylamino)silane and tris(dimethylamino)borane probably serve as both the dimethylamino donor and the hydride acceptor (Figure 1).[14]

Table 1. POPd-Catalyzed Oxidative Amination of Aromatic Aldehydes



entry	aldehyde	amine source	product	yield (%)
1	 1	$Si(NMe_2)_4$	 2	90[a]
2	 3	$Si(NMe_2)_4$	 7	55[b]
3	 4	$Si(NMe_2)_4$	 8	50[b]
4	 5	$Si(NMe_2)_4$	 9	50[b]
5	 6	$Si(NMe_2)_4$	 10	50[b]
6	 1	$B(NMe_2)_3$	 2	88[c]
7	 3	$B(NMe_2)_3$	 7	65[d]
8	 4	$B(NMe_2)_3$	 8	60[d]
9	 5	$B(NMe_2)_3$	 9	87[d]
10	 6	$B(NMe_2)_3$	 10	70[d]

[a] 100 mg of aldehyde, $Si(NMe_2)_4$ (1.3 equiv), POPd (2.5 mol %), acetonitrile (2 mL), 25 °C, 24 h. [b] 50 °C. [c] 100 mg of aldehyde, $B(NMe_2)_3$ (1.3 equiv), POPd (2.5 mol %), acetonitrile (2 mL), 25 °C, 24 h. [d] 80 °C.

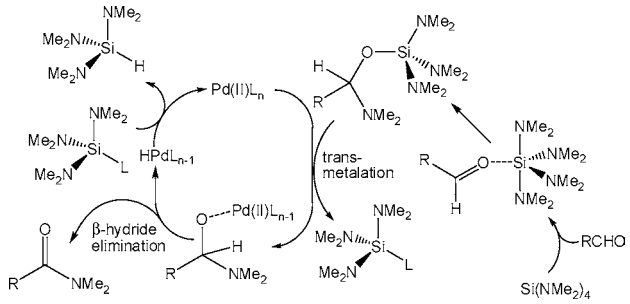


Figure 1. Pd(II)-catalyzed oxidative amination of aldehydes.

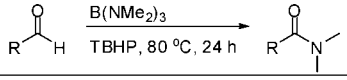
We anticipated that the conversion of the oxidative amination could be increased in the presence of a stronger oxidizing agent. As expected, we observed that yields improve when *tert*-butyl hydroperoxide, TBHP, is used in addition to the palladium catalyst. While the POPd-catalyzed oxidative

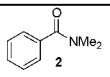
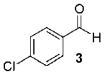
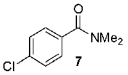
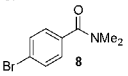
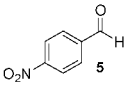
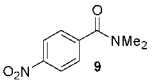
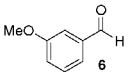
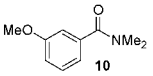
(11) Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* **1983**, 474−476.
(12) (a) Noata, T.; Murahashi, S. I. *Synlett* **1991**, 693−695. (b) Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* **2001**, 523−528.
(13) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13065−13066.
(14) Lerebours, R.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13052−13053.

esterification of aldehydes is significantly enhanced by tetraalkylammonium fluorides due to formation of hypervalent silicates that promote alkoxy transfer to the aldehyde, we found that poor results are obtained when fluorides are employed in the oxidative amination reaction. This is likely due to an increase in the concentration of free dimethylamine, which strongly coordinates to POPd and thus decreases the activity of the palladium catalyst.[15]

To avoid problems with catalyst poisoning and low conversion, we decided to explore the feasibility of metal-free transformation of aldehydes to amides. In fact, oxidative amination in the presence of tris(dimethylamino)borane and TBHP gave *N*,*N*-dimethylbenzamides **2** and **7**−**10** in excellent yields even in the absence of POPd (Table 2).

Table 2. Metal-Free Oxidative Amination of Aromatic Aldehydes[a]



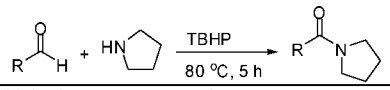
entry	aldehyde	amine source	product	yield (%)
1		$B(NMe_2)_3$		99
2		$B(NMe_2)_3$		93
3		$B(NMe_2)_3$		98
4		$B(NMe_2)_3$		97
5		$B(NMe_2)_3$		95

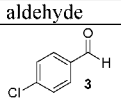
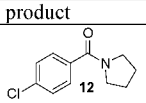
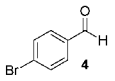
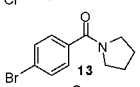
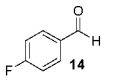
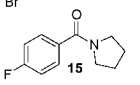
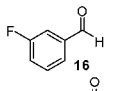
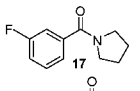
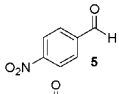
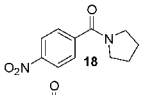
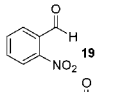
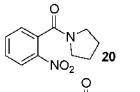
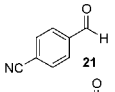
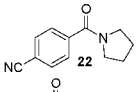
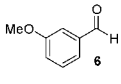
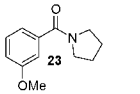
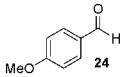
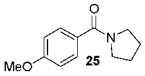
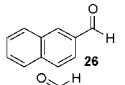
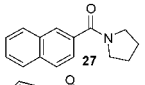
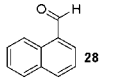
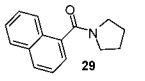
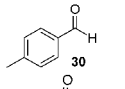
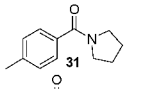
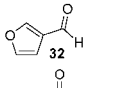
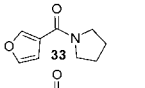
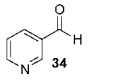
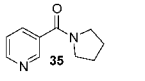
[a] Reagents and conditions: 100 mg of aldehyde, $B(NMe_2)_3$ (1.2 equiv), TBHP (1.2 equiv), acetonitrile (3 mL), 80 °C, 24 h.

Further screening revealed that our metal-free oxidative amination procedure tolerates a wide range of aromatic aldehydes and free amines, thus rendering the use of expensive triaminoborane or tetraaminosilane reagents unnecessary. The formation of several benzamides derived from pyrrolidine, piperidine, morpholine, and *N*-methylbenzylamine occurred with excellent yields and was completed within 5 h. For example, 4-chlorobenzaldehyde, **3**, was almost quantitatively converted to *N*-(4-chlorobenzoyl)-pyrrolidine, **12** (Table 3, entry 1). The TBHP-promoted oxidative amination provides convenient access to both electron-deficient and electron-rich arylamides (entries 2−9). Similarly, naphthaldehydes **26** and **28**, 4-methylbenzaldehyde, **30**, and heterocyclic aldehydes **32** and **34** gave the corresponding benzoylpyrrolidines in 85−97% yield (entries 10−14). Importantly, proline-derived amides can be prepared in excellent yields at 60 °C and without noticeable racemization (Scheme 2).

(15) The POPd-catalyzed oxidative amination did not occur when tetrakis(dimethylamino)silane and tris(dimethylamino)borane were replaced by free amines.

Table 3. Oxidative Amination of Aldehydes with Pyrrolidine, **11**, and TBHP[a]



entry	aldehyde	product	yield (%)
1			98
2			94
3			86
4			96
5			97
6			95
7			90
8			92
9			94
10			85
11			89
12			86
13			90
14			97

[a] Reagents and conditions: aldehyde (100 mg), pyrrolidine (1.2 equiv), TBHP (1.2 equiv) in 3 mL of refluxing acetonitrile for 5 h.

We were pleased to find that our method affords benzoylpiperidines **39**−**41** and benzoylmorpholines **42**−**45** in 92−99% yield (Figure 2). However, only low yields (less than 30%) were obtained when diethylamine was used. In contrast to our method, rhodium-catalyzed amination of aldehydes with piperidine or morpholine requires the use of

Scheme 2. Formation of Proline-Derived Amides

21: R = CN
34: R = Me

36
91% ee

37: R = CN: 92%
38: R = Me: 86%

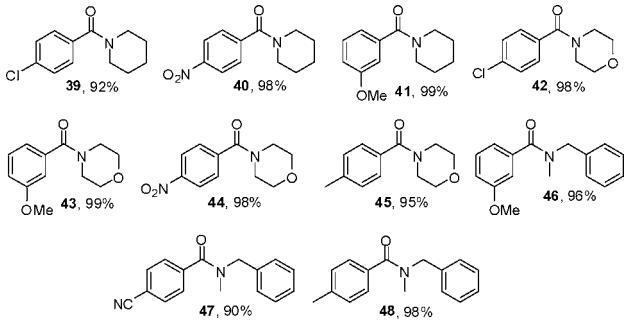
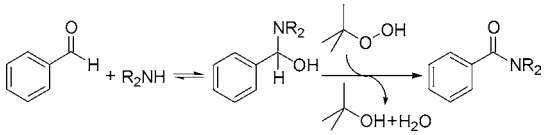


Figure 2. Synthesis of amides derived from piperidine, morpholine, and *N*-methylbenzylamine.

either substrate in excess and affords the corresponding benzamides in lower yields despite the use of harsh reaction conditions.[12] Acyclic amines such as *N*-methylbenzylamine, **49**, are also suitable for TBHP-promoted oxidative amination, providing *N*-benzyl-*N*-methylbenzamides **46**−**48** in 90−98% yield (Figure 2).

One could imagine that the aldehyde is first oxidized to the corresponding carboxylic acid, which then reacts with the amine to form an amide. However, no sign of amide formation was observed when the reaction was carried out with benzoic acids such as 4-chlorobenzaldehyde, **3**, under the same conditions. We therefore assume that the oxidative amination does not proceed via an intermediate carboxylic acid. It is most likely that the reaction pathway involves a carbinolamine that is subsequently oxidized to the amide by TBHP (Scheme 3).

Scheme 3. Proposed Mechanism of the Oxidative Amination of Aldehydes with TBHP



In summary, we have presented the first metal-free oxidative amination of a range of aromatic aldehydes. We believe that this method combines several attractive features: it affords amides in 85−99% yield with use of readily available TBHP and it is completed within 5 h; it integrates two reactions that are usually accomplished separately into a single operation; and in contrast to previously reported procedures, it does not require the use of an expensive transition metal catalyst, base, or other additives, or an excess of either the amine or aldehyde, and it avoids harsh reaction conditions.

Supporting Information Available: Synthetic procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7014626