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Pd-Catalyzed Oxidation of Aldimines to Amides

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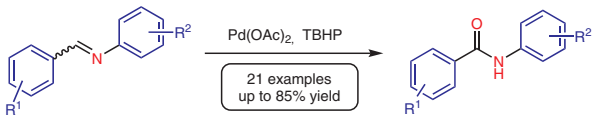

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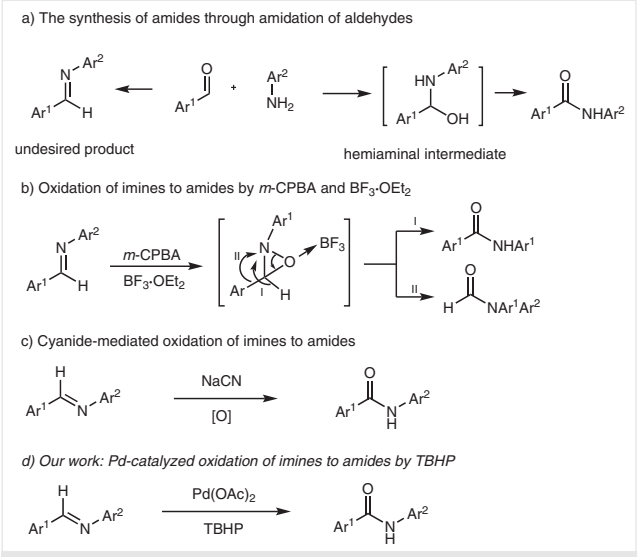
Abstract Methods for the synthesis of amides *via* the direct oxidation of imines are rarely reported. Here we report an efficient method for Pd-catalyzed oxidation of imines to amide derivatives by the use of cheap aqueous *tert*-butyl hydroperoxide as an oxidant through a Wacker-type reaction. This method is practically convenient and displays high functional group tolerance, allowing a variety of imines to transform into the corresponding amide derivatives in moderate to good yields.

Key words Pd-catalyzed, amides, imines, oxidation, *tert*-butyl hydroperoxide

The amide motif is one of the most important architectures in organic chemistry; they represent the building blocks of peptides and some polymer materials, and are frequently found in natural products and drug molecules.[1] Amides are generally synthesized by the coupling of carboxylic acids with amines, however, these methods require the use of coupling agents such as carbodiimides and 1-hydroxybenzotriazoles,[2]or activated carboxylic acid derivatives.[3] Methods that focus on the amination of nonactivated carboxylic acids have also been developed.[4] On the other hand, the Schmidt reaction[5] and the Beckmann rearrangement[6] represent classical methods for the preparation of amides. More recently, transition-metal-mediated procedures have allowed for the preparation of amides from a variety of reagents.[7]

A range of transition-metal-catalyzed and transition-metal-free procedures for the oxidative amination of amines with aldehydes have also been reported.[8] In these cases it is possible that the reaction proceeds though an imine intermediate, however, investigations so far have dismissed the formation of imines and instead propose a pathway proceeding through a hemiaminal intermediate (Scheme 1, a). For example, Song, Yang and co-workers have reported a copper-catalyzed amidation of aldehydes with primary amines in which they propose hemiaminal formation, rather than imine formation.[8a] This hypothesis was based on the fact that imine reagents displayed poor reactivity under the standard reaction conditions. Indeed, the imines formation is irreversible in the oxidative amidation of aldehydes or alcohols.[9] The formation of hemiaminal was also suggested in the transition-metal-free procedures for TBHP-mediated oxidative amidation of aldehyde.[8f] Thus, reports that describe the oxidative amination of imines remains scarce. Imines are easy to access synthetic building blocks, therefore, investigating their reactivity towards oxidative amidation may reveal useful synthetic pathways and unique reactivities.



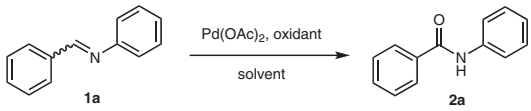
Scheme 1 Strategies for oxidation of imines to amides

Despite these significant developments of methods for the synthesis of amides through transition-metal-catalyzed direct oxidation of imines has yet to be realized. Imines, often referred to as Schiff bases, are an important class of synthetic reagents that are easily accessed *via* substitution of carbonyl compounds. Rhee and co-workers reported an efficient method for the synthesis of amides by oxidation of aldimines in the presence of *meta*-chloroperoxybenzoic acid (*m*-CPBA) and $BF_3{\cdot}OEt_2$.[10] This procedure performed well for the preparation of formamide derivatives, however, the reaction was very sensitive to the electronics of the aryl substituents and the preparation of benzamide products proved more difficult (Scheme 1, b). A selective and more general procedure has been developed by Cheon and co-workers who reported a cyanide-mediated aerobic oxidation of imines (Scheme 1, c).[11] However, the use of highly toxic NaCN limits the application of this methodology. Other methods for the oxidation of imines to amides by the use of potassium permanganate[12] and sodium chlorite[13] were also reported. The development of selective, efficient, and scalable methods for the oxidation of imines to amides are therefore warranted.

Herein, we provide a new transformation of imines to amide derivatives through a Pd-catalyzed Wacker-type oxidation using cheap aqueous TBHP as an oxidant (Scheme 1, d). This protocol is practical, convenient, displays high functional group tolerance, and can be performed under air without the requirement of any extra additive or ligand. A variety of substituted aldimines have been examined and found to be oxidized to the corresponding amides in moderate to good yields.

N,1-Diphenylmethanimine (**1a**) was chosen as a model substrate, treated with $Pd(OAc)_2$ (2 mol%) in the presence of H_2O_2 (3.0 equiv) in MeCN, heating at 120 °C for 5 h to provide the *N*-phenylbenzamide product (**2a**) in 5% yield (Table 1, entry 1). Other oxidants potassium persulfate ($K_2S_2O_8$), Oxone, and TBHP were then tested, and TBHP was found to be the most efficient oxidant, leading to the desired product *N*-phenylbenzamide (**2a**) in 20% yield (Table 1, entry 4). Solvent screen showed that DCE was the most suitable solvent among those tested (Table 1, entries 5–8). Different catalyst loadings were also tested and it was found that 5 mol% of $Pd(OAc)_2$was the most suitable catalyst loading (Table 1, entries 9 and 10). Finally, the yield could be significantly improved by increasing the amount of TBHP to 6.0 equivalents (Table 1, entry 11). The control reaction in the absence of $Pd(OAc)_2$ was also tested and found that 18% of amide product was obtained (Table 1, entry 13). This is probably due to the decomposition of imine to aldehyde and aniline, which could then undergo oxidative amination of aldehyde process in the presence of TBHP.[8f] However, no product was observed when the reaction was performed without TBHP (Table 1, entry 14).

Table 1 Optimization of Oxidation of Aldimine to Amide[a]



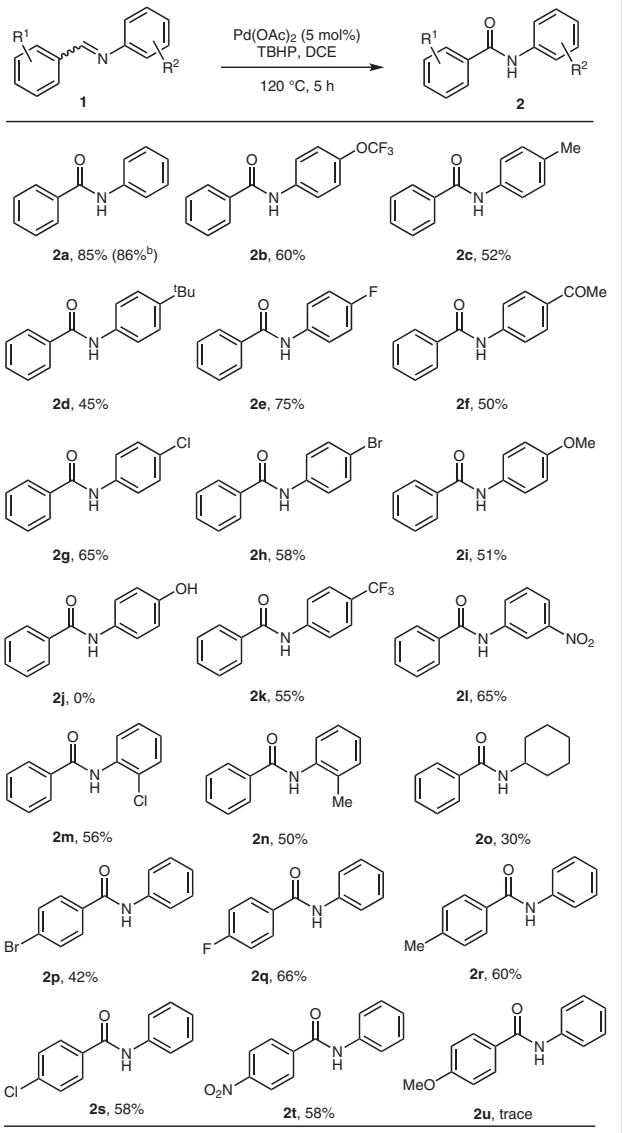
1a 2a

Entry	$Pd(OAc)_2$	Oxidant (equiv)	Solvent	Yield (%)
1	2	H_2O_2 (3.0)[b]	CH_3CN	5
2	2	Oxone (3.0)	CH_3CN	NR
3	2	$K_2S_2O_8$(3.0)	CH_3CN	NR
4	2	TBHP (3.0)[c]	CH_3CN	20
5	2	TBHP (3.0)[c]	DMSO	NR
6	2	TBHP (3.0)[c]	H_2O	8
7	2	TBHP (3.0)[c]	$PhCH_3$	13
8	2	TBHP (3.0)[c]	DCE	25
9	5	TBHP (3.0)[c]	DCE	32
10	10	TBHP (3.0)[c]	DCE	33
11	5	TBHP (6.0)[c]	DCE	85
12	5	TBHP (8.0)[c]	DCE	84
13	–	TBHP (6.0)[c]	DCE	18
14	5	–	DCE	NR

[a] Yields are of pure isolated products; the reactions were performed by using 0.2 mmol of **1a**, in 1.5 mL of solvent at 120 °C for 5 h.
[b] 30% wt H_2O_2 in water.
[c] 70% wt of TBHP in water.

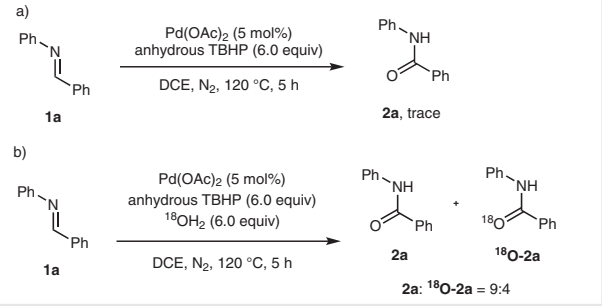
With suitable conditions in hand, we then turned our attention to the scope of the reaction. A variety of functional substituents, such as OCF_3, Me, *t*-Bu, F, COMe, on the aniline aromatic ring were tested and found to be compatible, giving place to the corresponding amide products in moderate to good yields (Scheme 2, 2b–f). Halogen substituents, Cl and Br on aniline ring were also tested, leading to the corresponding amides **2g** and **2h** in 65% and 58%, respectively. These provide convenient handles for further functionalizations. Satisfyingly, imine with the strong electron-donating methoxy group on the aniline ring underwent this oxidation process smoothly to furnish the amide product **2i** in 51% yield. However, the substrates with a hydroxyl group provided only the recovered starting material and aldehyde and aniline by the hydrolysis of imine (Scheme 2, 2j) Substrates with strong electron-withdrawing trifluoromethyl and nitro groups on the aniline ring gave the corresponding amides **2k** and **2l** in 55% and 65% yields, respectively. Imine with a chlorine atom or a methyl group at the *ortho* position of aniline ring could still underwent oxidation process, leading to amide product **2m** and **2n** in 56% and 50% yield, respectively. The oxidation of *N*-cyclohexyl-1-phenylmethanimine was also tested, and the corresponding amide product **2o** was obtained in a synthetic useful yield. We were then attempted to oxidize different functional substituents on the aldehyde aromatic ring, and found that the substrates with F, Cl, Br, Me, and NO_2 groups could be

oxidized to the corresponding amides in moderate yields (Scheme 2, 2p–t). However, the strong methoxy group substituted on the aldehyde ring did not provide the amide **2s**, with only starting material and hydrolyzed products were obtained. This methodology is easily scalable. 86% isolated yield of amide product **2a** could be obtained by the treatment of **1a** (6.0 mmol, 1.09 g) under our standard conditions without any modification.



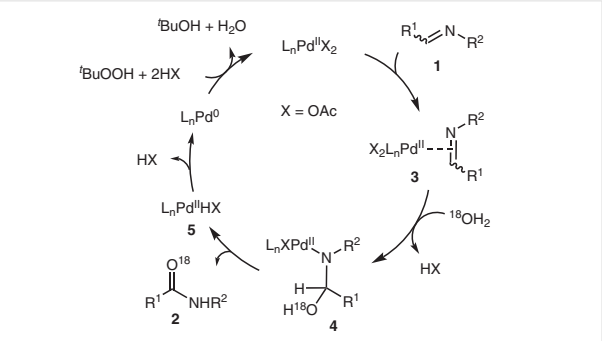
Scheme 2 Scope of the oxidation of imines to amides.[a] Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (0.01 mmol), TBHP (70% wt in H_2O, 6.0 equiv) in DCE (1.5 mL), heated at 120 °C for 5 h; Yields are of pure isolated products; [b] 6.0 mmol of **1a** was used.

A primary mechanism for this transformation was investigated. The oxidation reaction was performed under anhydrous conditions, and only trace of amide product was obtained, which suggests water is necessary for the reaction (Scheme 3, a). We also ran the reaction under a nitrogen atmosphere employing TBHP with $^{18}OH_2$, and we saw some incorporation of ^{18}O into the product. This suggests that this oxygen may originate from water in the reaction.



Scheme 3 Primary mechanism studies

On the basis of the above observation, the catalytic cycle may undergo the coordination of the Pd catalyst with C=N double bond, which followed by the reaction with water to form the Pd complex **4**. β-Hydride elimination of **4** gives the amide product, with the concomitant expulsion of Pd species **5**. Pd(0) species could be generated from **5** by the loss of acetic acid.[14] The catalytic cycle can be completed by the oxidation of Pd(0) to Pd(II) catalyst in the presence of TBHP (Scheme 4). Alternatively, the formation of the hemiaminal intermediate through the reaction between H_2O and imine could also be possible. The intermediate would then coordinate to Pd(II) species, which is followed by β-hydride elimination to give the amide product.[12,15]



Scheme 4 Proposed mechanism for Pd-catalyzed oxidation of imines

To be noted, if this classical Wacker-type mechanism were in operation then the product should form from the reaction of the substrate with stoichiometric palladium in the presence of water. However, when trying this experiment none of the desired product was formed. In addition, the observation of unlabeled amide product **2a** in the reaction in the presence of $^{18}OH_2$ indicates that the oxygen may also originate from TBHP (Scheme 3, b). These results may suggest a more complex mechanism is in operation and that there are still plenty of other possible mechanisms.

In conclusion, we report a method for Pd-catalyzed oxidation of aldimines to amides by the use of cheap aqueous TBHP as an oxidant.[16] This protocol provides an alternative for the synthesis of amide derivatives from imines through a Wacker–Tsuji oxidation process. The method is practically convenient and display high functional group tolerance, and it enriches the rarely reported methods for the transformation of imines to amides.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610653.

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(16) **Typical Procedure for the Preparation of *N*-Phenylbenzamide (2a)**

$Pd(OAc)_2$ (0.01 mmol), *N*,1-diphenylmethanimine (**1a**, 0.2 mmol), TBHP (70 % solution in H_2O, 6.0 equiv, 1.2 mmol), and DCE (1.5 mL) were added to a vial. The reaction mixture was stirred under 120 °C for 5 h. After that time, the reaction mixture was quenched with saturated Na_2SO_3 solution (consumption of residual TBHP) and extracted with EtOAc. The organic layer was separated and dried with Na_2SO_4. Removal of solvent followed by flash column chromatographic purification (EtOAc/PE) afforded *N*-phenylbenzamide (**2a**) as a white solid (33.5 mg, yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (br s, 1 H), 7.86 (d, *J* = 7.3 Hz, 2 H), 7.65 (d, *J* = 7.9 Hz, 2 H), 7.54 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 7.36 (t, *J* = 7.8 Hz, 2 H), 7.15 (t, *J* = 7.4 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.7, 137.9, 135.0, 131.9, 129.1, 128.8, 127.0, 124.6, 120.2 ppm.