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Pd-Catalyzed oxidative amidation of aldehydes with hydrogen peroxide

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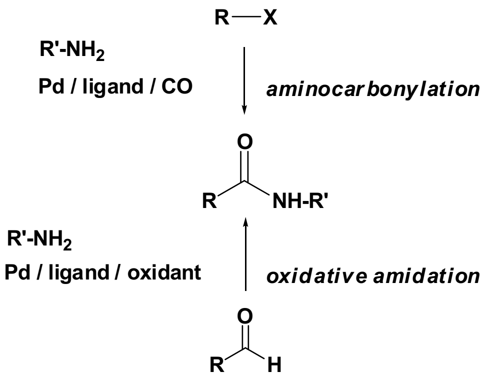
ABSTRACT

Using hydrogen peroxide as a key oxidant, catalytic oxidative amidation between aldehydes and amines was effectively carried out with $PdCl_2$–xantophos as a catalyst in methanol under acidic conditions. The new protocol is mechanistically different from the previous one through β-hydride elimination.

Amide bond linkage is ubiquitous and important core structure in pharmaceuticals, chemicals, as well as many natural products and hence, a variety of methods for the synthesis of this functionality have been developed to date.[1] Compared to the classical methods which often utilized stoichiometric amount of hazardous and/or toxic reagents, catalytic protocols with transition metal catalyst are of interests for an effective entry into a wide variety of derivatives. A safe and effective catalytic system is strongly desirable in view of the recent environmental concerns.

We have previously reported an effective Pd-catalyzed aminocarbonylation reaction (Scheme 1) with optimized solvent/base compositions, in which classic carbonylation reaction was improved by the additives to attain new scalable synthesis of Tolvaptan.[2] Our continuing efforts in development of a new catalytic system for amide synthesis have now focused on oxidative amidation, which can incorporate aldehydes and amines into amides in a single step without any hazardous reagents except oxidant.[3]



Scheme 1. Two catalytic amidation reactions.

In the literature precedent, Cu, Pd, Rh and Ru catalysts are claimed to be effective for the oxidative amidation of aldehydes,[4] whilst Cannizzaro-type amidation reactions (hydride transfer) were reported under basic conditions using LDA or lanthanide reagents.[5] Elegant alternative approaches to amides from alcohols via aldehydes were presented by Williams' and Milstein's group, respectively.[6]

Besides the metal catalyst, another important factor is an oxidant employed in stoichiometric amount. *t*-Butyl hydroperoxide (TBHP),[4a] aldehydes[5] and aryl bromide[4d] were reported to be effective terminal oxidants for the transition metal catalyzed amidation. Wolf's and Wang's group recently reported metal-free oxidative amidation using TBHP or oxone (potassium peroxomonosulphate) as an oxidant, respectively.[7]

Hydrogen peroxide (H_2O_2) is also an attractive and inexpensive oxidant widely used in laboratory and industry synthesis. From the view point of green chemistry, H_2O_2 has become more and more popular with regard to the formation of water as a sole byproduct. However, no example for catalytic amidation from aldehydes has been reported with H_2O_2.[8] Described herein is our preliminary study on H_2O_2-mediated amidation of aldehyde using a new Pd–ligand composition, with some interesting mechanistic consideration.

At the very beginning of our survey, we found oxidative amidation of benzaldehyde using aq H_2O_2 did proceed in moderate yield under acidic conditions without a catalyst (Table 1, entry 1). Initial screening of metal salts led to the finding that $Pd(OAc)_2$ was a promising catalyst (Table 1, entry 2). Other Pd salts such as $PdCl_2$, $PdSO_4$ and $Pd(NO_3)_2$ were less effective at this stage as a catalyst (entries 3 and 4), whilst other transition metals such as Co, Ni, Cu (entries 5–7) and transition metal oxides such as RuO_2 and WO_3 retarded the reaction (not shown in the Table). Under the conditions examined, the major byproduct was benzoic acid that was formed by direct oxidation of benzaldehyde itself. We hypothesized water in aq H_2O_2 prevented the formation of imine, which was key intermediate of this reaction. As expected, the use of H_2O_2–urea, instead of aq H_2O_2 significantly reduced the formation of benzoic acid (12%, entry 8). Interestingly, other oxidants such as

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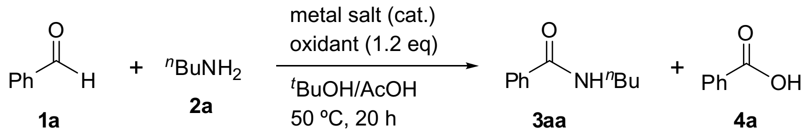
Table 1
Initial survey for metal salt and oxidant[a]



Entry	Metal salt (mol %)	Oxidant	Yield (%)[b,c]	**3aa**/**4a**
1	None	H_2O_2 aq	26 (48)	0.54
2	$Pd(OAc)_2$ (2.5)	H_2O_2 aq	47 (26)	1.8
3	$PdCl_2$ (2.5)	H_2O_2 aq	32 (33)	0.97
4	$PdS0_4$ (2.5)	H_2O_2 aq	34 (28)	1.2
5	$Ni(OAc)_2$ (5.0)	H_2O_2 aq	Trace (N.D.)	—
6	$Cu(OAc)_2$ (5.0)	H_2O_2 aq	Trace (N.D.)	—
7	$Zn(OAc)_2$ (5.0)	H_2O_2 aq	11 (N.D.)	—
8	$Pd(OAc)_2$ (2.5)	H_2O_2–urea	37 (12)	3.1
9	$Pd(OAc)_2$ (2.5)	TBHP	8 (N.D.)	—
10	$Pd(OAc)_2$ (2.5)	Oxone	Trace (N.D.)	—
11	$Pd(OAc)_2$ (2.5)	*m*-CPBA	Trace (N.D.)	—

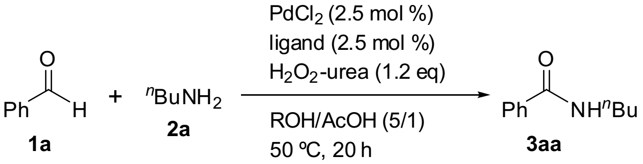
[a] Conditions: aldehyde 1.0 mmol, amine 1.2 mmol, ^{t}BuOH/AcOH 500/100 (μL).
[b] Determined by ^{1}H NMR of the crude mixture.
[c] Yield of benzoic acid is shown in parentheses.

TBHP, oxone and *m*-CPBA were not effective for this reaction. Additionally, some *N*-oxide oxidants (pyridine *N*-oxide and NMMO) were also ineffective (not shown in the Table). In the absence of H_2O_2 the reaction did not proceed at all even using 10–20 mol % of $Pd(OAc)_2$. Thus, H_2O_2 proved to be a key oxidant in the oxidative amidation for the first time.[8]

For further optimization, phosphine and amine ligands were then screened (Table 2). Ligand screening with $Pd(OAc)_2$ did not show any promising results. With $PdCl_2$ as a Pd salt, however, xantphos,[9] a ligand for its capability in a *trans*-chelation, showed superior results compared to other monodentate and bidentate phosphine ligands (Table 2, entries 1–4). Pyridine ligands did not retard the reaction but yields were lower than the case of xantphos.

Very interestingly, by changing the solvent from ^{t}BuOH to ^{i}PrOH, higher yield was obtained (entry 7). We further attempted the reaction in MeOH. To our delight, the reaction in MeOH reached to 78% yield and further optimization of solvent ratio slightly improved the yields. Finally, the best result was obtained in MeOH/AcOH = 500/150 (μL, 1 mmol scale) using 1.4 equiv of H_2O_2–urea and 2.5 mol % of $PdCl_2$–xantphos as a catalyst; the product was obtained in 82% yield. For $Pd(OAc)_2$, MeOH was ineffective and the product was obtained only in 5% yield.

Table 2
Ligand effect on the oxidative amidation of aldehydes[a]



Entry	Ligand	ROH	Yield (%)[b]
1	PPh3	^{t}BuOH	29
2	dppe	^{t}BuOH	26
3	(R)-BINAP	^{t}BuOH	28
4	Xantphos	^{t}BuOH	42
5	2,2′-bipyridine	^{t}BuOH	25
6	1,10-Phenanthroline	^{t}BuOH	15
7	Xantphos	^{i}PrOH	61
8	Xantphos	MeOH	78
9[c]	Xantphos	MeOH	5
10[d]	Xantphos	MeOH	82[e]
11	None	MeOH	30

[a] Conditions: aldehyde 1.0 mmol, amine 1.2 mmol, ^{t}BuOH/AcOH 500/100 (μL).
[b] Determined by ^{1}H NMR of the crude mixture.
[c] $Pd(OAc)_2$ was used instead of $PdCl_2$.
[d] 1.4 equiv of H_2O_2 urea was used. MeOH/AcOH 500/150 (μL).
[e] Isolated yield.

With our improved protocol in hand, substrate generality was investigated under the optimized reaction conditions[10] as shown in Table 3. Aromatic aldehydes with electron-withdrawing substituents gave good yields and ester and nitrile functionalities survived intact under these conditions. This amidation protocol was highly influenced by electric and steric factors and for electron-rich aldehydes and aliphatic aldehydes less satisfactory results were obtained. Using amine **2b** and amino alcohol **2c** the reaction smoothly proceeded (entries 12 and 13), although sterically demanding amines afforded less satisfactory results (entry 14).

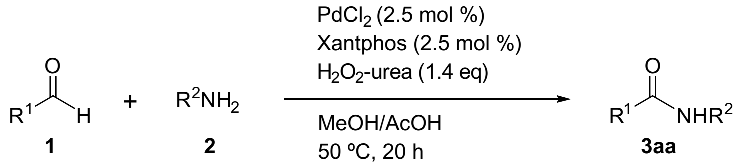
Unfortunately, these reaction conditions were not applicable to such aldehydes with high coordinating functionality and secondary amines (entries 11 and 15).

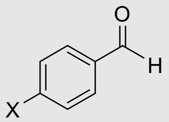
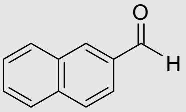
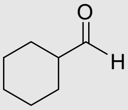
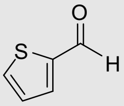
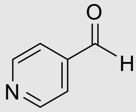
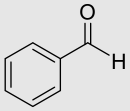
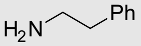
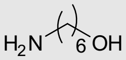
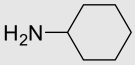
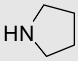
Additional experiments showed that reactions with aromatic amine such as aniline gave low yield of amidation product. Other reactions with aliphatic aldehydes also resulted in moderate conversion.

For further improvement, several experiments were performed next, particularly to gain insight into the reaction mechanism. If the reaction mechanism involves a Pd(II)-mediated β-hydride elimination as mentioned in Ru, Rh and Pd-catalyzed oxidative amidation of aldehydes,[4b,c] $PdCl_2$–xantphos complex could afford stoichiometric amount of product without any oxidant. However, without H_2O_2–urea the reaction did not proceed at all even using 20 mol % of $PdCl_2$–xantphos complex. This result suggests that the reaction does not proceed through the β-hydride elimination in our catalytic amidation, instead, an intermediate with a peroxide functionality might be involved.

We next carried out the reaction using the oxaziridine **5**[11] as a substrate, which was previously proposed to be a key intermediate in the oxidative amidation of aldimines by *m*-CPBA and $BF_3{\cdot}OEt_2$.[12] As shown in Scheme 2, the reaction was carried out under similar conditions as in Table 3. Without H_2O_2 oxidant, the amide **3aa** was obtained in 30% yield concomitant with a formation of the α,β-unsaturated aldehyde **6**[13] (35% yield, a cross-aldol product presumably from the oxidation of the amine and/or oxaziridine), which was not observed at all in the standard conditions with

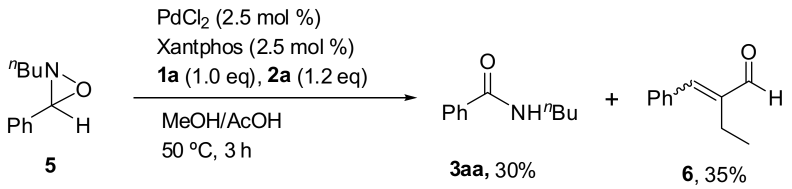
Table 3
Scope and limitations of the oxidative amidation



Entry	Aldehyde			Amine	Yield[a] (%)
1		**1a**: X	H	**2a**	81
2		**1b**: X	Cl	**2a**	83
3		**1c**: X	NO_2	**2a**	79
4		**1d**: X	CO_2Me	**2a**	86
5		**1e**: X	CN	**2a**	82
6		**1f**: X	Me	**2a**	74
7		**1g**: X	OMe	**2a**	62
8	 **1h**			**2a**	83
9	 **1j**			**2a**	49
10	 **1i**			**2a**	50
11	 **1j**			**2a**	13
12	 **1a**			 **2b**	72
13	**1a**			 **2c**	72
14	**1a**			 **2d**	53
15	**1a**			 **2e**	Trace

Conditions: aldehyde 1.0 mmol, amine 1.2 mmol, MeOH/AcOH 500/150 (μL).

[a] Isolated yield.

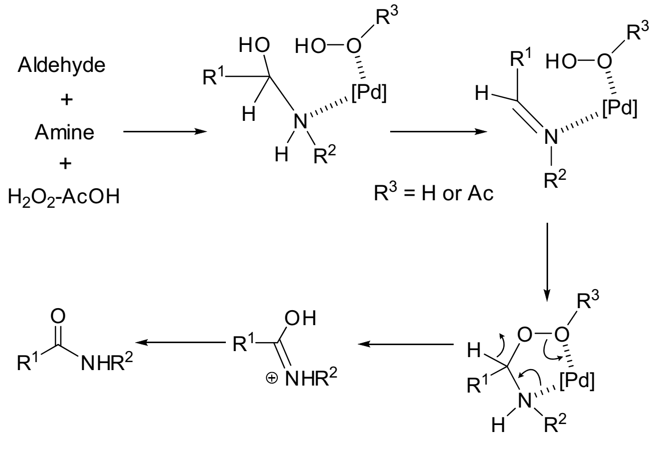


Scheme 2. Reaction with oxaziridine.

H_2O_2–urea. Byproduct **6** was also obtained in the absence of benzaldehyde and butylamine. Although the exact mechanism to afford **6** is still unclear, these results indicate that the H_2O_2–urea mediated oxidative amidation does not proceed through oxiaziridine as a pivotal intermediate.

One of the most possible reaction mechanisms is oxidation and/or rearrangement through a hydroperoxide intermediate generated from hemiaminal and/or imine intermediate as shown in Scheme 3. There are ample literature precedents, which indicated the formation of a peroxide intermediate in the related oxidative transformations.[3,14]

Particularly, Mimoun proposed formation of a palladium hydroperoxide species (XPd–OOH) in the reaction of aq H_2O_2 (large excess) and Pd(II) catalyst for the Wacker type oxidation of



Scheme 3. Mechanistic speculation.

olefins.[14] Thus, Pd-catalyst can transfer OOH moiety to the coordinated imine intermediate to form the key peroxide intermediate as shown.

Even though we are not quite sure how the peroxide intermediate can be transformed into the final amide product, a Baeyer–Villiger type degradation shown in Scheme 3 might be most plausible. Further mechanistic studies to gain deeper insight into the key intermediate are in progress and the result will be reported in due course.[15]

In summary, we have developed a new catalytic oxidative amidation of aldehydes with amines, in which $PdCl_2/H_2O_2$–urea was a preferable reagent combination with xantphos as a key supporting ligand under mild acidic conditions (MeOH/AcOH). Further optimization of the reagents should be necessary, particularly based on the careful mechanistic insights into the intermediate involved. Progress along these lines is under active investigation in our laboratory for the development of new Pd-mediated synthetic avenues as well as metal-free conversion.[16]

Acknowledgments

We are grateful to Drs. F. Sato and D. Tanaka at Dainippon Sumitomo Pharmaceutical Co., Ltd. for critical literature survey. Thanks are due to Prof. V. K. Yadav of IIT at Kanpur, for his kind suggestion in manuscript preparation. We also thank to Dr. M. Yamashita in our University for his helpful discussions.

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10. *General procedure*: A solution of $PdCl_2$ (4.4 mg, 0.025 mmol) and xantphos (14.9 mg, 0.025 mmol) in MeOH (500 μL) was stirred at 50 °C for 1 h. To the resulting mixture, AcOH (150 μL, ca. 2 equiv to amine), butylamine (120 μL, 1.2 mmol), 4-chlroro benzaldehyde (141 mg, 1.0 mmol) and H_2O_2–urea (136 mg, 1.4 mmol) were added successively. The mixture was stirred at 50 °C for 20 h. After addition of ca. 20 mL of AcOEt, the organic layer was washed with saturated $NaHCO_3$ aq two times and NaCl aq and dried over Na_2SO_4. Volatiles were removed by evaporation and purification with silica-gel column chromatography afforded *N*-butyl-4-chlorobenzamide in 82% yield (176 mg).
11. *Compound* **5** *was prepared by the reported procedure:* Lin, Y.-M.; Miller, M. J. *J. Org. Chem.* **1997**, *64*, 7451. Compound **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.41–7.36 (m, 3H), 4.49 (s, 1H), 2.97 (dt, *J* = 12.0, 7.5 Hz, 1H), 2.78 (dt, *J* = 12.0, 6.5 Hz, 1H), 1.75–1.68 (m, 2H), 1.51–1.42 (m, 2H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 Hz, $CDCl_3$) δ 135.0, 130.1, 128.6, 127.7, 80.7, 62.1, 30.1, 20.7, 14.1; IR (neat) 2959, 2936, 2872, 1460, 1406, 758, 696 cm^{-1}; ESIMS *m*/*z* 178 (M+H$^+$).
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13. Spectral data of compound 6 are consistent with the reported one: Duhamel, L.; Tombret, F. *J. Organomet. Chem.* **1985**, *280*, 1.
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15. In place of $PdCl_2$, similar reactions with $CuCl_2$, $NiCl_2$ and $FeCl_3$ as an alternative metal salt were examined in the optimized conditions, however, resulting in very low yields of the amide product, presumably because of facile decomposition of H_2O_2. These results indicated $PdCl_2$–xantphos catalyst did not participate in a decomposition reaction of H_2O_2. Instead, $PdCl_2$–xantphos system was interacting with peroxide intermediate and facilitating the formation of the key peroxide intermediate as shown in Scheme 3.
16. Very recently, Reddy has disclosed a new oxidative amidation reaction with KI-TBHP as a key oxidant Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Kantam, M. L. *Eur. J. Org. Chem.* **2008**.