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Tetrahedron Letters 47 (2006) 8293–8297
Tetrahedron Letters

Palladium-catalyzed aerobic oxidation of amines

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Received 26 July 2006; revised 18 September 2006; accepted 19 September 2006
Available online 10 October 2006

Abstract—Pd-Catalyzed aerobic oxidation of different amines was systematically examined for the first time. A $PdCl_2/PPh_3$ system was successfully developed to catalyze the aerobic oxidation of several types of amines including Ar–CH_2NHPh, Ar–CH_2NHOMe, and Ar–CH_2NHMs with high yields. Theoretical studies showed a remarkable difference in the energy barriers of β-hydride elimination between an alcohol and various amines.

Selective oxidation of organic compounds with O_2 as a sole oxidant is valuable from both environmental and economic points of view.[1] For this reason, considerable efforts have been devoted in recent years to develop transition metal-catalyzed aerobic oxidation reactions. Among the transition metals used, Pd is the most attractive because one Pd-catalyzed aerobic oxidation reaction (i.e., the Wacker process) has already received an industrial success.[2] Many recent studies have also shown that Pd^{2+} can catalyze other oxidative transformations including alcohol oxidation, dehydrosilylation of sily enol ethers, and oxidative C–O, C–N, and C–C coupling reactions with olefins.[3] Despite these successes, there remain some important oxidative transformations for which it has been extremely difficult to find an effective Pd catalyst system. One such example is the aerobic oxidation of amines to yield nitriles or imines.

The importance of the aerobic amine oxidation is at least twofold: (1) the products of the reaction, that is, imines or nitriles, are valuable intermediates in organic synthesis; (2) on the basis of catalytic amine oxidation it is possible to develop kinetic resolution methods to access enantiomerically enriched secondary amines. Previously James and Bailey reported a Ru–porphyrin catalyzed aerobic procedure for the oxidation of amines to imines.[4] Mizuno and Yamaguchi reported a Ru-catalyzed heterogeneous aerobic oxidation of primary amines to nitriles.[5] More recently, Bäckvall and co-workers reported biomimetic aerobic oxidation of secondary amines to imines catalyzed by Ru and hydroquinone.[6] Some Cu salts have also been reported to be able to mediate aerobic oxidation of amines.[7] Nonetheless, no Pd catalyst system has ever been reported for the aerobic oxidation of amines.

Herein we report our recent success in finding some Pd catalyst systems that can catalyze aerobic oxidation of amines. Initially, we examined the oxidation of benzyl alcohol and a number of substituted benzyl amines with Uemura's ($Pd(OAc)_2$/pyridine/MS3 Å/O_2) catalyst system (Table 1).[8] Although benzyl alcohol (entry 1) was smoothly oxidized to benzaldehyde, benzylamine, and *N*-methyl benzyl amine (entries 2 and 3) were unreactive. Gratefully, *N*-phenyl benzylamine could be oxidized to the corresponding imine by the procedure, although the yield (43%) was only modest (entry 4). Next, we examined *N*-benzylacetamide but found it completely unreactive (entry 5). *N*-Benzylmethanesulfonamide and *N*-benzyl-toluenesulfonamide, on the other hand, were found to be oxidized to sulfoximines by the procedure (entries 6 and 7). It was also found that *N*-methoxylbenzylamine could be successfully oxidized to the corresponding oxime (entry 8) with a satisfactory yield (89%).

The above results indicated that Pd-catalyzed aerobic oxidation of amines was not something forbidden by nature. However, it was also found that the chemical structures of the amines exerted significant effects on the efficiency of oxidation. To improve the yields and thereby the practicability of the transformation, we next examined a number of reaction conditions as shown in Table 2. Briefly, by extending the reaction time from 2 h to 14 h, the yield increased dramatically from 43% to 70% (entry 1). Using pyridine as the ligand we tried

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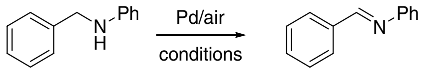
doi:10.1016/j.tetlet.2006.09.088

Table 1. Aerobic oxidation of benzyl alcohol and benzylic amines catalyzed by the Pd(II)/pyridine catalyst system[a]

Entry	Reactant	Product	GC yield (%)
1	$PhCH_2OH$	PhCHO	99
2	$PhCH_2NH_2$	No reaction	0
3	$PhCH_2NHCH_3$	No reaction	0
4	$PhCH_2NHPh$	$PhCH{=}NPh$	43
5	$PhCH_2NHAc$	No reaction	0
6	$PhCH_2NHMs$	$PhCH{=}NMs$	23
7	$PhCH_2NHTs$	$PhCH{=}NTs$	16
8	$PhCH_2NHOMe$	$PhCH{=}NOMe$	89

[a] Conditions: reactant = 0.5 mmol, $Pd(OAc)_2$ = 5 mol %, pyridine = 20 mol %, toluene = 5 mL, MS3 Å = 0.25 g, O_2 = 1 atm, 80 °C, 2 h.

Table 2. Aerobic oxidation of *N*-phenyl benzylamine[a]



Entry	Catalyst	Ligand	Base	Solvent	GC yield (%)
1	$Pd(OAc)_2$	Pyridine	—	Toluene	70
2	$PdCl_2$	Pyridine	—	Toluene	0
3	$Pd(OAc)_2$	Pyridine	—	DMSO	25
4	$Pd(OAc)_2$	Pyridine	—	DMF	65
5	$Pd(OAc)_2$	—	$NaHCO_3$	DMSO	68
6	$Pd(OAc)_2$	NEt_3	—	CH_2Cl_2	3
7	$Pd(OAc)_2$	NEt_3	—	DMF	15
8	$Pd(OAc)_2$	NEt_3	NaOAc	DMF	74
9	$Pd(OAc)_2$	Phen	NaOAc	DMF	0
10	$Pd(OAc)_2$	Bipyridine	NaOAc	DMF	1
11	$Pd(OAc)_2$	*i*-Pr_2NEt	—	DMF	10
12	$Pd(OAc)_2$	TMEDA	—	DMF	2
13	$PdCl_2$	PPh_3	NaOAc	DMF	96
14	$PdCl_2$	PPh_3	NaOAc	Toluene	10
15	$PdCl_2$	PPh_3	NaOAc	DMSO	98
16	$PdCl_2$	PPh_3	NaOAc	DMA	97
17	$PdCl_2$	PPh_3	NaOAc	NMP	97
18	$PdCl_2$	PPh_3	—	DMF	7
19	$Pd(OAc)_2$	PPh_3	NaOAc	DMF	88
20	$PdCl_2$	PPh_3	*t*-BuOK	DMF	29
21	$PdCl_2$	PPh_3	K_2CO_3	DMF	64
22	$PdCl_2$	PPh_3	NaOH	DMF	50
23	$PdCl_2$	PPh_3	*i*-Pr_2NEt	DMF	0
24	$PdCl_2(PPh_3)_2$	—	NaOAc	DMF	99
25	$PdCl_2$	PPh_3	NaOAc	DMF	95 (in air)

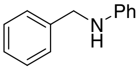
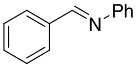
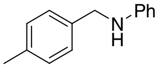
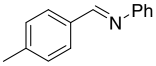
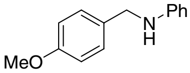
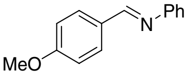
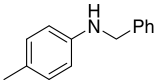
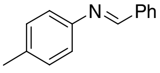
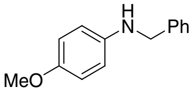
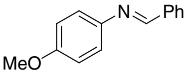
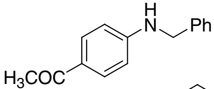
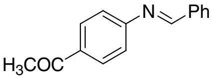
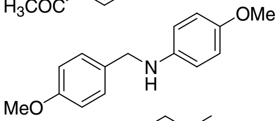
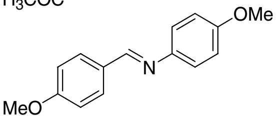
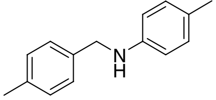
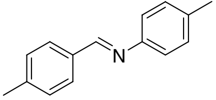
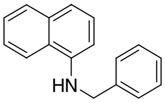
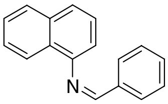
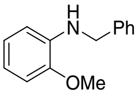
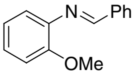
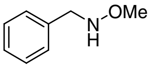
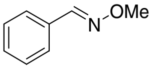
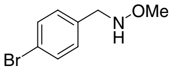
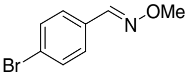
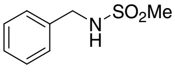
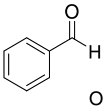
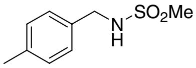
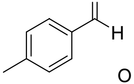
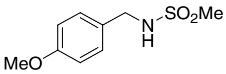
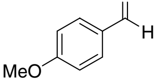
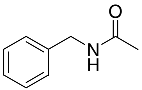
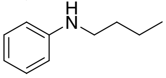
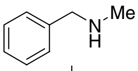
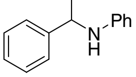
[a] Conditions: reactant = 0.5 mmol, Pd salt = 5 mol %, ligand = 10 (for PPh_3) or 20 mol % (for others), solvent = 5 mL, MS3 Å = 0.25 g, O_2 = 1 atm (except for entry 25), base = 0.5 mmol, 80 °C, 14 h.

several solvent systems such as DMSO and DMF which were previously reported to be favorable for Pd-catalyzed aerobic oxidations[9] (entries 2–4). The results revealed that toluene provided the highest yield. Next, we tried some other ligands including no ligand,[10] triethylamine,[11] bipyridine, diisopropylethylamine, 1,10-phenanthroline (Phen), and tetramethylethylene-diamine (TMEDA) (entries 5–12). Triethylamine was found to provide the highest yield (74%) when NaOAc was present (entry 8).[12]

An interesting breakthrough was then made when we used triphenylphosphine as the ligand (entry 13). This finding was quite counterintuitive because phosphines are oxygen sensitive and therefore, not expected to be useful in oxidation reactions.[13] Nonetheless, the yields of the phosphine-mediated amine oxidation reaction were always high (96–98%) in a few different solvents (DMF, DMSO, DMA, and NMP) except for toluene (entries 13–17). NaOAc was found to be essential to the reaction (entry 18) when $PdCl_2$ was used as the catalyst. However, $Pd(OAc)_2$ was less effective than the combination of $PdCl_2$ and NaOAc (entry 19). Compared to NaOAc, other bases including *t*-BuOK, K_2CO_3, NaOH, and *i*-Pr_2NEt gave much lower yields (entries 20–23). It was also found that the commercially available $PdCl_2(PPh_3)_2$ complex was as effective as the combination of $PdCl_2$ and PPh_3 (entry 24). Furthermore, we were pleased to find that the aerobic oxidation could also be performed with a high yield (95%) in air (entry 25).

Having confirmed that $PdCl_2$/PPh_3/NaOAc/DMF provided excellent conditions for the aerobic oxidation of

Table 3. Aerobic oxidation of different amines or amides catalyzed by the $PdCl_2/PPh_3$/NaOAc/DMF procedure[a]

Entry	Reactant	Product	Isolated yield (%)
1			95
2			48[b]
3			58[b]
4			95
5			98
6			63
7			95
8			56[b]
9			56
10			25[b]
11			91
12			92
13			76
14			82
15			95
16		No reaction	0
17		No reaction	0
18		No reaction	0
19		No reaction	0

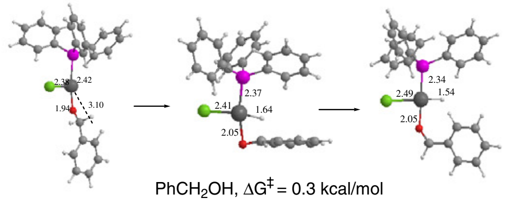
[a] Conditions: reactant = 1 mmol, $PdCl_2$ = 5 mol %, PPh_3 = 10 mol %, DMF = 10 mL, MS3 Å = 0.5 g, O_2 = 1 atm, NaOAc = 1 mmol, 80 °C, 14 h.

[b] Determined by ^1H NMR.

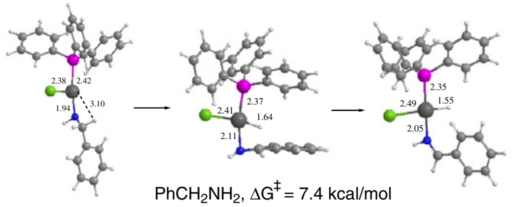
N-phenyl benzylamine, we next examined whether the same procedure could be used to oxidize other amines. Instead of determining the GC yields, herein we focused on the isolated yields to ensure the practicability of the newly developed reaction (Table 3). Firstly we changed the aromatic groups at both the *N*-phenyl site and the benzylamine site. It was found that both electron-rich and poor aromatic groups could be tolerated (entries 1–9). Nonetheless, it was found that an aryl group with an *ortho*-substituent (entry 10) would dramatically decrease the yield. This indicated that the reaction was sensitive to steric crowding of the substrate. As to *N*-methoxylamines, it was found that the PPh_3 procedure was superior to the pyridine procedure because the yields were relatively higher (entries 11 and 12). The PPh_3 procedure also provided much higher yields in the cases of *N*-methanesulfonamides, although the major products were the corresponding aldehydes (entries 13–15). A proposed explanation for this observation was that the sulfoximine products were rapidly hydrolyzed under the reaction conditions (where H_2O was produced as a by-product unavoidably).

Amides, *N*-phenylalkylamines, and *N*-alkyl benzylamines (entries 16–19) were not oxidized by the PPh_3 procedure. Evidently both the electronic and steric effects played vital roles in the reaction. Before the aerobic oxidation of more challenging amines, we decided to utilize theoretical tools to obtain some physical insights into the reaction. Thus we calculated the free energy barrier of the β-hydride elimination step for various substrates using standard B3PW91/LANL2DZ + p//B3PW91/LANL2DZ methods.[14,15] It is worth noting that in many previous studies β-hydride elimination was proposed to be the rate-determining step.[16,17]

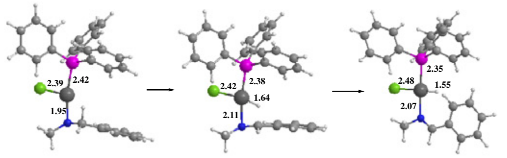
From the theoretical results (Fig. 1), it was evident that the energy barrier of β-hydride elimination for $PhCH_2NH_2$ was about 7 kcal/mol higher than that for $PhCH_2OH$ (which could be translated to ca. 10^5-fold difference in reactivity). The addition of a methyl group in the case of $PhCH_2NHCH_3$ only decreased the energy barrier by 0.1 kcal/mol. By contrast, a phenyl group in $PhCH_2NHPh$ dramatically reduced the energy barrier to 1.7 kcal/mol, so that the reactivity between $PhCH_2OH$ and $PhCH_2NHPh$ differed only by about 10-fold. This explained why $PhCH_2NHPh$ could be oxidized relatively easily. Furthermore, the energy barriers for $PhCH_2NHAc$ and $PhCH_2NHMs$ were 6.7 and 3.6 kcal/mol, respectively. This explained why $PhCH_2NHMs$ could be oxidized but $PhCH_2NHAc$ could not. Finally, the energy barrier for $PhCH_2NHOMe$ was 1.9 kcal/mol. Thus, $PhCH_2NHOMe$ was also a good substrate for Pd-catalyzed aerobic oxidation. The energy barrier for PhCH- $(CH_3)NHPh$ was 7.6 kcal/mol, which was about 6 kcal/mol higher than that for $PhCH_2NHPh$. Accordingly, a secondary amine was much more difficult to oxidize than a primary amine because of the steric problems.



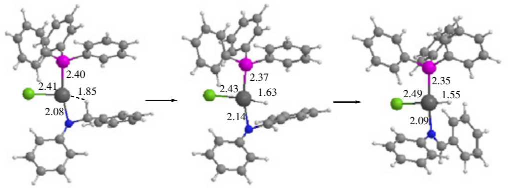
$PhCH_2OH$, $\Delta G^{\ddagger} = 0.3$ kcal/mol



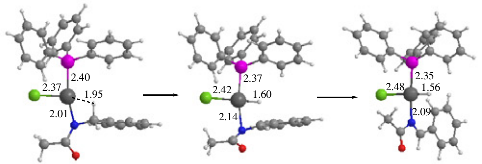
$PhCH_2NH_2$, $\Delta G^{\ddagger} = 7.4$ kcal/mol



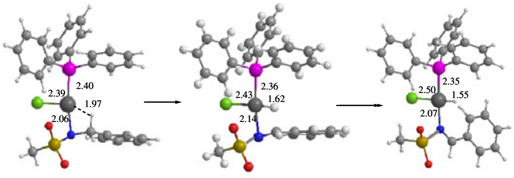
$PhCH_2NHCH_3$, $\Delta G^{\ddagger} = 7.3$ kcal/mol



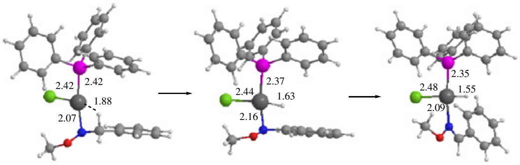
$PhCH_2NHPh$, $\Delta G^{\ddagger} = 1.7$ kcal/mol



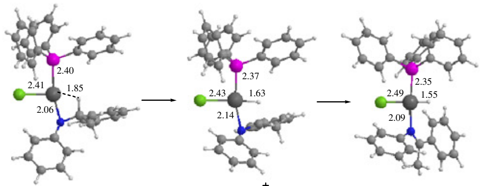
$PhCH_2NHCOCH_3$, $\Delta G^{\ddagger} = 6.7$ kcal/mol



$PhCH_2NHSO_2CH_3$, $\Delta G^{\ddagger} = 3.6$ kcal/mol



$PhCH_2NHOMe$, $\Delta G^{\ddagger} = 1.9$ kcal/mol



$PhCHCH_3NHPh$, $\Delta G^{\ddagger} = 7.6$ kcal/mol

Figure 1. Structures of the starting material (left), transition state (middle), and product of β-hydride elimination (right).

To conclude, in the present study we reported the first examples of Pd-catalyzed aerobic oxidation of amines. An interesting $PdCl_2/PPh_3$ procedure was developed and it was successfully utilized to catalyze the aerobic oxidations of several different types of amines including

Ar–CH_2NHAr, Ar–CH_2NHOMe, and Ar–CH_2NHMs with high yields. Further theoretical studies showed a remarkable difference in the free energy barrier of the β-hydride elimination step for different amines. Thus, in order to oxidize those 'more difficult' amines we need to find more powerful solutions to reduce their energy barriers for β-hydride elimination. Given the fact that many phosphine ligands are available and many of them have been known to exhibit extraordinary effects in Pd catalysis, we are optimistic that some Pd/phosphine system could be developed in the near future to catalyze the aerobic oxidations of more general amines under milder conditions.

Acknowledgment

This research was supported by the NSFC (No. 20332020 and 20472079).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.088.

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