Oxidation of secondary amines catalyzed by dirhodium caprolactamate†

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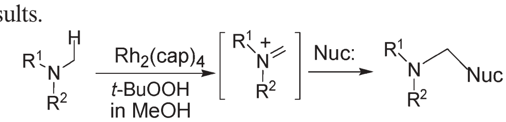
The dirhodium caprolactamate [$Rh_2(cap)_4$] catalyzed oxidation of secondary amines to imines by *tert*-butyl hydroperoxide (TBHP) occurs with high chemo- and regioselectivity.

The dehydrogenation of secondary amines to imines is of current and intense interest.[1] Stoichiometric methods in synthetic applications using hypervalent iodine reagents,[2] phenylselenic anhydride,[3] and *N*-*tert*-butylphenylsulfinimidoyl chloride[4] have generally replaced older methods using metal salts. Catalytic processes that employ *tert*-butyl hydroperoxide (TBHP) have been reported with ruthenium(II) chloride[5] and with a cobalt Schiff base complex,[6] but these early examples were optimally performed in benzene or DMSO and were limited in scope. Other metal–oxidant combinations have been described with mixed results,[7] but the developing successes with ruthenium-catalyzed aerobic oxidations of Bäckvall and coworkers are worthy of note.[8] We have recently reported highly efficient hydrocarbon oxidations by *tert*-butyl hydroperoxide catalyzed by rhodium(II) caprolactamate.[9] When extended to oxidations of selected tertiary amines,[10] this oxidation provided a means for functionalization on the carbon adjacent to nitrogen, presumably through an iminium ion intermediate (eqn. 1). The potential of this mild methodology that uses low catalyst loading to oxidize secondary amines generally (eqn. 2) was suggested by these results.



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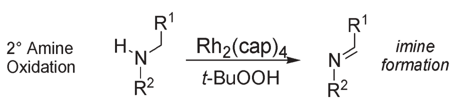
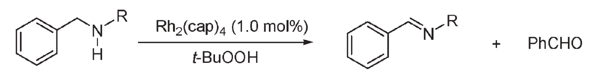


(2)

N-Phenylbenzylamine (**1**) was selected to determine suitable conditions for oxidation with TBHP catalyzed by $Rh_2(cap)_4$ at 1.0 mol % catalyst loading (Table 1). Previously described conditions for benzylic oxidation (entry 1)[9b] gave complete conversion of **1**, but benzylideneaniline (**2**) was accompanied by its hydrolysis product benzaldehyde (**3**). Benzaldehyde formation with complete substrate conversion was diminished in the absence of $NaHCO_3$ (entry 2). Attempts to decrease the extent of hydrolysis even further using molecular sieves or anhydrous $MgSO_4$ were unsuccessful (entries 3 and 4) because they significantly limited the oxidation of **1**. Methanol, the solvent of choice for the oxidation of *N*-aryl tertiary amines,[10] was found be effective (entry 5); however, when *N*-cyclohexylbenzylamine was submitted to reaction under the same conditions, *no* imine product was obtained at room temperature (entry 6), and only trace amounts were obtained at temperatures up to 60 °C. However, the use of acetonitrile as the solvent gave optimal results for both *N*-phenyl- and *N*-cyclohexylbenzylamine substrates (entries 7 and 8) with quantitative conversion, chromatographically pure product in high yield, and the absence of hydrolysis. We assume that steric effects in the two solvents are responsible for the difference in reaction outcomes (entries 6 and 8).

Table 1 Optimization of the conditions for the oxidation of benzylphenylamine[a]



1 2 3

Entry	R	Conditions	Conv. (%)[b]	2 : 3[b]
1	Ph	CH_2Cl_2, $NaHCO_3$ (50 mol %)	> 95	48 : 52
2	Ph	CH_2Cl_2	> 95	80 : 20
3	Ph	CH_2Cl_2, 4 Å MS (50 wt %)	28	90 : 10
4	Ph	CH_2Cl_2, $MgSO_4$ (1 equiv)	56	90 : 10
5	Ph	MeOH	> 95	> 95 : 5
6	Cy	MeOH	0	—
7	Ph	CH_3CN	> 95 (94)[c]	> 95 : 5
8	Cy	CH_3CN	> 95 (90)[c]	> 95 : 5

[a] Reactions were performed using $Rh_2(cap)_4$ (1.0 mol %), amine (1.0 equiv), *t*-BuOOH (6.5 M in decane, 2.0 equiv), and solvent at room temperature for 16 hours. [b] Determined by ^{1}H NMR. [c] Isolated yield of analytically pure compound.

Results from the oxidation of representative secondary amines under conditions optimized for **1** are reported in Table 2. In contrast to the ruthenium-catalyzed oxidation process of Bäckvall and coworkers,[8] the dirhodium-catalyzed oxidation of *N*-phenylbenzylamines with electronically diverse substituents at the *para* position (entries 1–3) gives the corresponding imines in nearly quantitative yield. The reaction conditions employed allow the same transformation to occur with the furanyl analog (entry 4). *N*-Phenylcinnamylamine is oxidized to the α,β-unsaturated imine in high yield despite the potential for allylic oxidative amidation (entry 6). Regioselective oxidation is observed for *N*-benzyl-*N*-1-phenethylamine which yielded aldimine to the exclusion of ketimine (entry 7). In addition, the presence of a pendant alcohol does not interfere with amine oxidation, indicating a high degree of functional group tolerance (entries 8 and 9). Moreover, complete retention of configuration at the benzylic position adjacent to nitrogen is observed for the oxidation of (*R*)-*N*-benzyl-phenylglycinol (entry 9).[11] *N*-Alkylbenzylamines (entries 10 and

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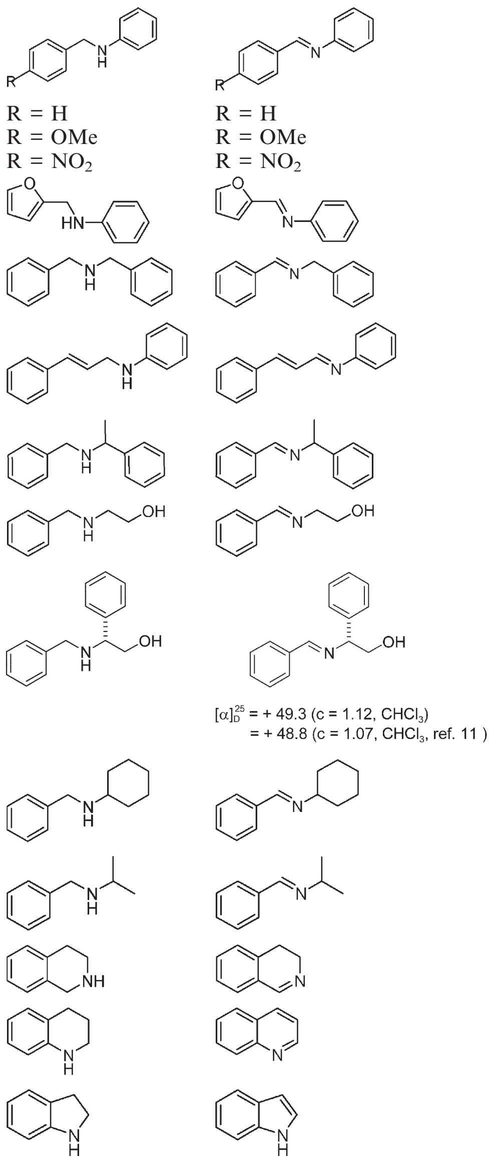
† Electronic supplementary information (ESI) available: Experimental details and NMR data for **7**. See DOI: 10.1039/b615805f

Table 2 Oxidation of secondary amines with $Rh_2(cap)_4$[a]



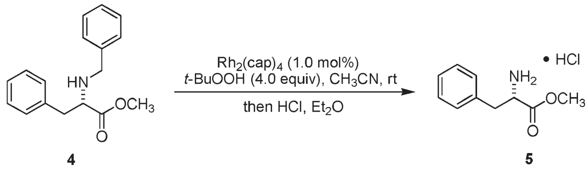
Entry	Amine	Imine	yield[b]
1	R = H	R = H	94
2	R = OMe	R = OMe	92
3	R = NO_2	R = NO_2	93
4			84
5			95
6			87
7			81
8			74
9		$[\alpha]_D^{25}$ = + 49.3 (c = 1.12, $CHCl_3$) = + 48.8 (c = 1.07, $CHCl_3$, ref. 11)	90
10			90
11			85
12			85
13			82[c]
14			87

[a] Reactions were performed at room temperature for 16 h using $Rh_2(cap)_4$ (1.0 mol %), substrate (1.0 equiv), and *t*-BuOOH (2.0 equiv) in CH_3CN (0.27 M/[substrate]). [b] Isolated yield after filtration. [c] Using 4.0 equiv of *t*-BuOOH.

11) and heterocyclic amines (entries 12–14) are oxidized to the corresponding imines and includes overoxidation resulting in quinoline formation (entry 13) and tautomerization to aromatic indole (entry 14). Conversion of tetrahydroquinoline to quinoline has been observed previously,[5,7,12] but rarely as cleanly as is observed with dirhodium catalysis.

Since this oxidative methodology exhibited significant preference for the benzylic position, its potential for oxidative deprotection was examined. As an example, benzyl protected phenylalanine methyl ester **4** was transformed to amino acid ester hydrochloride **5** in 78% yield without epimerization using 4.0 equiv TBHP (eqn. 3).

Pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD)-based compounds have received considerable attention as potential antitumor and gene targeted drugs.[13] A member of this class, DC-81 analog **7** (62%) was obtained *via* amine oxidation of **6** using stoichiometric PIFA ($PhI(O_2CCF_3)_2$) in CF_3CH_2OH or $(CF_3)_2CHOH$.[14] Catalysis with $Rh_2(cap)_4$ and *t*-BuOOH in CH_3CN gave rapid conversion to the desired eneamine tautomer exclusively (not shown). We surmised that tautomerization was likely the result of using a polar solvent and mildly acidic *t*-BuOOH. Therefore, using CH_2Cl_2 sufficiently buffered with K_2CO_3 as a mild base, imine **7** was obtained exclusively in 80% yield (eqn. 4).



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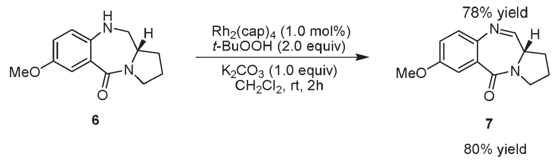

(4)

In summary, we have developed a mild, efficient, and selective oxidation of 2° amines catalyzed by $Rh_2(cap)_4$. Further investigations are currently underway to develop new transformations as well and to gain insight into the mechanism of dirhodium catalyzed oxidations.

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