Ruthenium-catalysed Oxidation of Secondary Amines to Imines using t-Butyl Hydroperoxide

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The ruthenium-catalysed oxidation of secondary amines with t-butyl hydroperoxide under mild conditions affords the corresponding imines in high yields.

Transition metal-catalysed reactions of amines are of biological and synthetic importance. Low-valent transition metals react with amines with and without N–H bonds to give imine[1] and iminium ion metal hydride intermediates,[2] respectively.

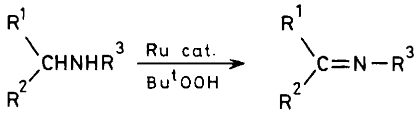
During our studies on the oxidation of metal hydrides, we found that ruthenium(II)-catalysed oxidation of secondary amines with t-butyl hydroperoxide gives the corresponding imines efficiently [equations (1) and (2)]. This is the first catalytic oxidative transformation of secondary amines to imines, although the stoicheiometric reactions have been well documented.[3] Ruthenium complexes are known to be good oxidising catalysts; however, the oxidation of amines with ruthenium catalysts is limited to a few reactions which involve transformation of the amines to either nitriles[4] or tertiary amine *N*-oxides.[5]

Table 1. Ruthenium-catalysed oxidation of amines.[a]

Amine[b]	Ratio Bu^tOOH: amine	Time/h	Isolated[c] yield/%
(**1a**)	2.0	2	80
(**1b**)	2.0	9[d]	79
(**1c**)	2.5	28	85
(**1d**)	1.6	4	74
(**1e**)	1.6	3	81
(**1f**)	1.6	4	80
(**2a**)	1.6	8	73
(**2b**)	1.6	6	56
(**2c**)	1.6	10	82
(**2d**)	1.6	9	98
Indoline	1.0	8	78

[a] The procedure is described in the text. [b] The products gave satisfactory i.r., n.m.r., and mass spectral data and elemental analyses. [c] The yields are of chromatographed samples, which are homogeneous by t.l.c. analysis. [d] At 60 °C.

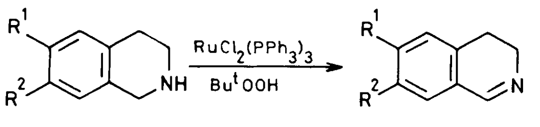
Secondary amines can be easily converted catalytically into the corresponding imines in high yields under mild reaction conditions. Table 1 summarizes the results for the formation of imines. The present reaction is particularly useful for the preparation of 1-azadienes and 3,4-dihydroisoquinolines [equation (2)], which are important precursors of nitrogen-containing natural products. Generally, thermodynamically stable imines are formed. Indoline was converted into indole in 78% yield.[6] Using excess of Bu^tOOH (5 mol equiv.) 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-



(1)

(**1**)

a; R^1 = Ph, R^2 = H, R^3 = CH_2Ph
b; R^1 = Ph, R^2 = H, R^3 = Ph
c; R^1 = Ph, R^2 = CN, R^3 = Ph
d; R^1 = PhCH=CH, R^2 = H, R^3 = Ph
e; R^1 = PhCH=CH, R^2 = H, R^3 = p-ClC_6H_4
f; R^1 = PhCH=CH, R^2 = H, R^3 = p-$MeOC_6H_4$



(2)

(**2**)

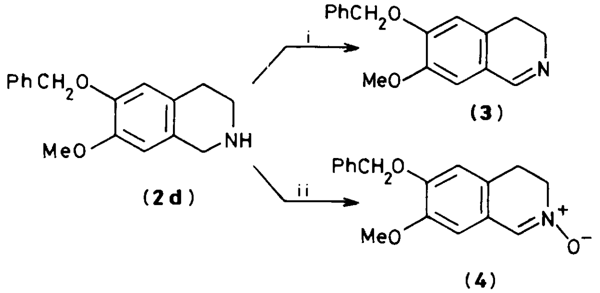
a; $R^1 = R^2 = H$
b; $R^1, R^2 = -OCH_2O-$
c; $R^1 = R^2 = OMe$
d; $R^1 = OCH_2Ph, R^2 = OMe$

quinoline can be converted into the corresponding isoquinoline and quinoline in 65% and 73% yields, respectively.

The catalytic activity of RuCl$_2$(PPh$_3$)$_3$ was the best among various metal complexes examined, but other catalysts such as RuCl$_3$·nH$_2$O, RuH$_2$(PPh$_3$)$_4$, RhCl(PPh$_3$)$_3$, and Rh$_6$(CO)$_{16}$ gave good results. Without a catalyst imines were formed in $<5\%$ yields on boiling. t-Butyl hydroperoxide in benzene was the best oxidant. *N*-Methylmorpholine *N*-oxide and hydrogen peroxide can also be utilized as oxidant. If necessary, molecular sieves may be added to retard the hydrolysis of the imines under the reaction conditions.

In a typical reaction, a solution of Bu^{t}OOH (3.2 mmol) in dry benzene (2 ml) was added dropwise to a mixture of amine (**2c**) (2.0 mmol), RuCl$_2$(PPh$_3$)$_3$ (0.04 mmol), and molecular sieves (Linde 4A; 0.6 g) in dry benzene (4.0 ml) at room temperature during 2 h. After complete addition the excess of Bu^{t}OOH was decomposed by treatment with palladium black.† Usual work-up followed by short column chromatography (Al$_2$O$_3$) gave 6,7-dimethoxy-3,4-dihydroisoquinoline (82%).

Recently we reported that the tungsten-catalysed oxidation of secondary amines with H$_2$O$_2$ gives nitrones highly efficiently.[7] Therefore, secondary amines can be transformed into either imines or nitrones depending on the catalytic system utilized. For example, the present ruthenium-catalysed reaction of dibenzylamine with Bu^{t}OOH gave *N*-benzylidenebenzylamine in 80% yield. In contrast, the tungsten-catalysed oxidation of the same amine with hydrogen peroxide gave *N*-benzylidenebenzylamine *N*-oxide in 85% yield. Similarly, amine (**2d**) can be converted into imine (**3**) in 93% yield by the ruthenium-catalysed reaction, while with the tungsten catalyst nitrone (**4**) was obtained in 86% yield (Scheme 1).



Scheme 1. *Reagents:* i, RuCl$_2$(PPh$_3$)$_3$–Bu^{t}OOH; ii, Na$_2$WO$_4$–H$_2$O$_2$.

The catalytic reaction can be extended to the oxidation of other types of nitrogen compounds. For example, the oxidation of diphenylmethylamine with Bu^{t}OOH gave benzophenone in 88% yield. Phenylhydroxylamine was converted into azoxybenzene efficiently.

The oxidation can be rationalized by the following mechanism. The initial step is the formation of ruthenium amide complexes (Ru–NR^{2}CH$_2$R^1) which undergo β-elimination to give imine–hydridoruthenium complexes.[1,8] Oxidation of the ruthenium hydride with Bu^{t}OOH gives imines along with Bu^{t}OH and H$_2$O to complete the catalytic cycle. The mechanism which involves oxygen transfer from metal-hydroperoxide to amines[7] appears not to be operative under the reaction conditions.

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† Aqueous Na$_2$SO$_3$ can be used to decompose excess of Bu^{t}OOH alternatively.