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Dehydrogenation of aromatic amines to imines *via* ruthenium-catalyzed hydrogen transfer

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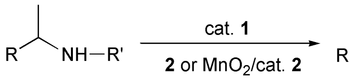
An efficient ruthenium-catalyzed transfer dehydrogenation of amines to imines was achieved under mild conditions using 2,6-dimethoxy benzoquinone (2) or cat. 2/MnO$_2$ as oxidant.

We have recently studied ruthenium-catalyzed hydrogen transfer reactions involving reduction of ketones to alcohols,[1] oxidation of alcohols to aldehydes[2] and ketones[3] as well as racemization of alcohols.[4] The latter reaction was successfully combined with enzyme catalysis to obtain dynamic kinetic resolution (DKR).[5] We[6] and others[7] have also studied the corresponding transfer hydrogenation of imines but to our knowledge no hydrogen transfer-based procedure for oxidation of amines to imines has been reported.[8,9] The latter process is of general synthetic interest and also important for racemization of amines[10] under transfer hydrogen conditions involving dehydrogenation of amine to imine and readdition of hydrogen.

In this manuscript we report on a novel procedure for the oxidation of amines to imines *via* a ruthenium-catalyzed hydrogen transfer. The reaction proceeds in refluxing toluene with **1**[11] as catalyst and quinone **2** as hydrogen acceptor. It is also demonstrated that the quinone can be used as electron transfer mediator (ETM) in catalytic amounts employing an external oxidant for recycling of the hydroquinone to quinone **2**.



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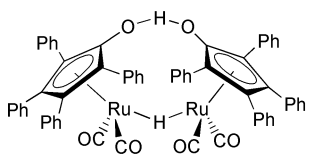

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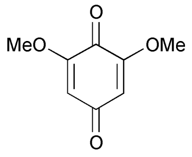

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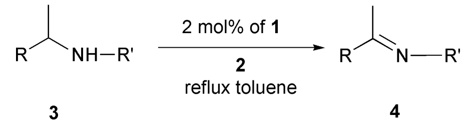
Oxidation of *N*-phenyl-*N*-(1-phenylethyl)amine (**3a**) was studied under various reaction conditions employing **1** as catalyst and quinone **2** as hydrogen acceptor. From a survey of solvents, toluene was found to be the most efficient. Thus, oxidation of **3a** in toluene employing 2 mol% of **1** and 1.5 equiv. of quinone **2** afforded **4a** in 70% yield after 5 hours (Table 1).

When the amount of **1** was lowered to 1 mol%, the rate of the reaction slightly decreased. In the absence of **1** no imine formation was observed. A number of different secondary amines were oxidized by quinone **2** employing this catalytic system (Table 1). We found that electronic variation of the amine substrate has an effect on the efficiency of the dehydrogenation reaction. As can be seen from Table 1, amines **3c**–**3g** having electron-donating substituents (entries 3–7) on any of the aromatic rings reacted faster than **3a**, and gave a high yield of imine. On the other hand, an electron-withdrawing substituent has a negative influence on the outcome of the oxidation (entry 2), and led to a lower reaction rate.

This new catalytic oxidation *via* low-valent ruthenium-catalyzed hydrogen transfer gives remarkably clean reactions and the selectivity for the corresponding imines was >99% in all cases. Unfortunately, this system failed to catalyze the oxidation of nonaromatic amines. This is probably due to the lower thermal stability of the corresponding nonaromatic imine. When compared to ruthenium-catalyzed dehydrogenation of alcohols, the reaction rate of amines is much slower and harsher conditions are required in order to achieve high conversions.[13]

Table 1 Ruthenium-catalyzed oxidation of secondary amines by 2,6-dimethoxybenzoquinone[a]

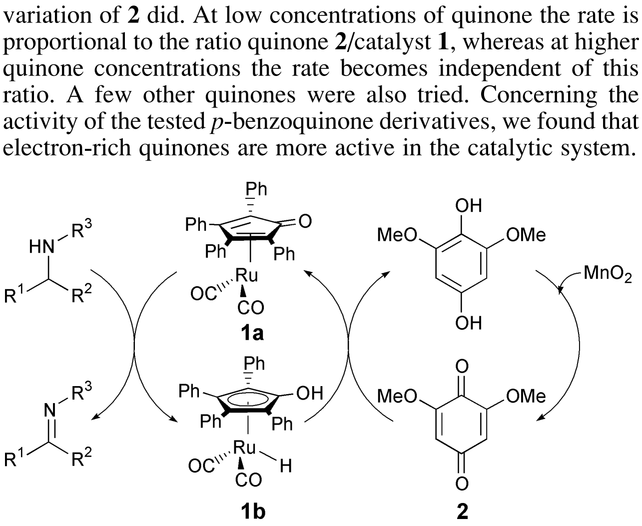


Entry	Substrate	R	R'	Time (h)	Yield[b] (%)
1	**3a**	Ph	Ph	5	70
2	**3b**	*p*-F-C$_6$H$_4$	Ph	6	71
3	**3c**	*p*-Me-C$_6$H$_4$	Ph	2	95
4	**3d**	*p*-MeO-C$_6$H$_4$	Ph	2	93
5	**3e**	Ph	*p*-MeO-C$_6$H$_4$	2	95
6	**3f**	Ph	*o*-Me-C$_6$H$_4$	2	90
7	**3g**	*p*-MeO-C$_6$H$_4$	*p*-MeO-C$_6$H$_4$	1.5	93

[a] The reaction was performed on a 0.5 mmol scale in refluxing toluene (4 mL) with 2 mol% of **1** and 1.5 equiv. of **2**. [b] Determined by ^{1}H NMR spectroscopy.

The use of the system MnO$_2$/catalytic amount of quinone **2** (Scheme 1) was also successfully applied to the oxidation of a number of substituted aromatic amines **3** (Table 2).

It was demonstrated in a control experiment that the process with manganese dioxide (Scheme 1) requires the presence of quinone **2**. Without **2** the conversion of **3** to **4** was <9% after 24 hours. The amount of MnO$_2$ did not effect the rate but the variation of **2** did. At low concentrations of quinone the rate is proportional to the ratio quinone **2**/catalyst **1**, whereas at higher quinone concentrations the rate becomes independent of this ratio. A few other quinones were also tried. Concerning the activity of the tested *p*-benzoquinone derivatives, we found that electron-rich quinones are more active in the catalytic system.



Scheme 1 A coupled catalytic system for dehydrogenation of secondary amines.

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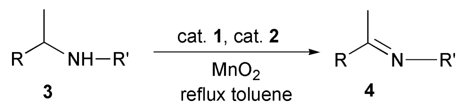
Table 2 Ruthenium-catalyzed oxidation of secondary amines by MnO_2[a]

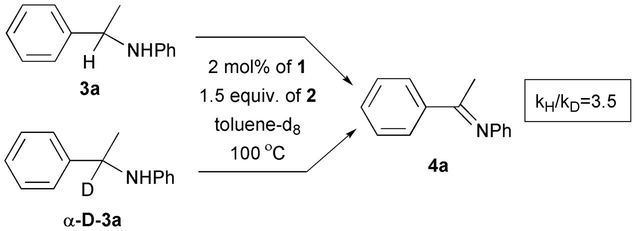


Entry	Substrate	R	R'	Time (h)	Yield[b] (%)
1	**3a**	Ph	Ph	5	76
2	**3b**	p-F-C_6H_4	Ph	5	70
3	**3c**	p-Me-C_6H_4	Ph	5	83
4	**3d**	p-MeO-C_6H_4	Ph	5	94
5	**3e**	Ph	p-MeO-C_6H_4	5	91
6	**3f**	Ph	o-Me-C_6H_4	5	90
7	**3g**	p-MeO-C_6H_4	p-MeO-C_6H_4	4	94
8	**3h**	Ph	2,4,6-triMe-C_6H_4	4	90

[a] The reaction was performed on a 0.5 mmol scale in refluxing toluene (0.5 mL) with 2 mol% of **1**, 20 mol% of **2** and 1.5 equiv. of MnO_2 [b] Determined by ^1H NMR spectroscopy.

It is interesting to note that in all cases the reaction proceeds significantly faster with quinone **2** as terminal oxidant compared to the coupled catalytic system with cat. **2**/MnO_2 (Scheme 1), even though the reaction mixture is four times more diluted because of the low solubility of **2**.

The deuterium isotope effect for the amine to imine oxidation was determined by comparing the rates for dehydrogenation of α-deuterio-**3a** and **3a** (Scheme 2). The reaction was run with 1.5 equiv. of **2** to amine and without MnO_2. The ratio of the rates for the reaction was determined at low conversions (initial rate method). An isotope effect of $k_H/k_D = 3.5$ was obtained.[12] In principle this isotope effect may originate from the dehydrogenation step (**3a** → **4a**) or from addition of hydrogen to quinone **2**.



Scheme 2 Observed deuterium isotope effect for the amine to imine oxidation.

The following equations [eqns. (2) and (3)] are involved where Q is quinone **2**, HQ the corresponding hydroquinone and **1a** and **1b** are the two halves of catalyst **1** shown in Scheme 1.

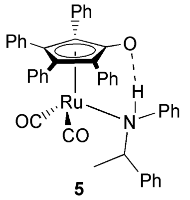
$$\mathbf{3a} + \mathbf{1a} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathbf{4a} + \mathbf{1b} \qquad (2)$$

$$\mathbf{1b} + \mathrm{Q} \xrightarrow{k_2} \mathbf{1a} + \mathrm{HQ} \qquad (3)$$

There is no doubt that $k_2 >> k_1$. This follows from the fact that the turnover frequency (TOF) for recycling benzoquinone **2** to its hydroquinone is $>4000\ h^{-1}$.[13] In the present system the overall TOF is $50\ h^{-1}$, which requires that the dehydrogenation is the slow step. Now if $k_2[Q] > k_{-1}$ [**4a**] we will have an irreversible rate-determining dehydrogenation of **3a** to **4a** and the isotope effect will originate from that step. In this case the overall rate will be independent of the quinone concentration. However, if $k_2[Q] < k_1$ [**4a**] there will be a pre-equilibrium and the isotope effect would have to originate from the addition of ruthenium hydride to quinone and also from the equilibrium of eqn. (2).[14] In the latter case the rate of the reaction will depend on the concentration of quinone.

One way to distinguish between the two different possibilities is to determine if there is a dependence or not of the quinone **2** on the rate. We found that the rate of dehydrogenation of **3a** is independent of quinone for **2**/**1** > 40, *i.e.* with more than 0.8 equiv. of **2**. Since our experiments were carried out with 1.5 equiv. of **2** we conclude that there is no pre-equilibrium under these conditions and the isotope effect should originate from the dehydrogenation.

A likely intermediate in the dehydrogenation of **3a** is the amine complex **5**, which after β-hydride abstraction by the metal would give the imine. Attempts to isolate **5** have so far been unsuccessful. However, the primary amine complex **6**[15] was prepared and it was demonstrated that it acts as a catalyst in the amine dehydrogenation reaction according to eqn. (1).[16]



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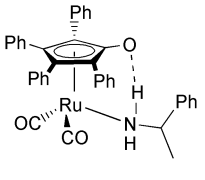

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Our novel coupled catalytic system *via* ruthenium-catalyzed hydrogen transfer provides a new method for selective oxidation of secondary amines to the corresponding imines. The amine is dehydrogenated by a ruthenium catalyst and the Ru-hydride produced reacts with p-benzoquinone to give hydroquinone. At present the recycling of the hydroquinone is demonstrated by the use of MnO_2, and in this way the quinone becomes an electron transfer mediator (ETM). The use of air or molecular oxygen for this recycling is currently being studied.

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Notes and references

1 R. L. Chowdhury and J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1991, 1063.
2 J.-E. Bäckvall, R. L. Chowdhury and U. Karlsson, *J. Chem. Soc., Chem. Commun.*, 1991, 473.
3 (*a*) G.-Z. Wang, U. Andreasson and J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1994, 1037; (*b*) M. L. S. Almeida, M. Beller, G.-Z. Wang and J.-E. Bäckvall, *Chem. Eur. J.*, 1996, **2**, 1533.
4 F. F. Huerta, A. B. E. Minidis and J.-E. Bäckvall, *Chem. Soc. Rev.*, 2001, **30**, 321.
5 B. A. Persson, A. L. E. Larsson, M. LeRay and J.-E. Bäckvall, *J. Am. Chem. Soc.*, 1999, **121**, 1645.
6 G.-Z. Wang and J.-E. Bäckvall, *J. Chem. Soc., Chem. Commun.*, 1992, 980.
7 (*a*) E. Mizushima, M. Yamaguchi and T. Yamagishi, *Chem. Lett.*, 1997, 237; (*b*) N. Uematsu, A. Fujii, S. Hashiguchi, T. Ikariya and R. Noyori, *J. Am. Chem. Soc.*, 1996, **118**, 4916; (*c*) J. Mao and D. C. Baker, *Org. Lett.*, 1999, **1**, 841.
8 Oxidation of amines by high valent ruthenium has been reported: (*a*) A. J. Bailey and B. R. James, *J. Chem. Soc., Chem. Commun.*, 1996, 2343; (*b*) S.-I. Murahashi, *Angew. Chem. Int. Ed. Engl.*, 1995, **34**, 2443; (*c*) S.-I. Murahashi, T. Naota and H. Taki, *J. Chem. Soc., Chem. Commun.*, 1985, 613; (*d*) P. Müller and D. M. Gilabert, *Tetrahedron Lett.*, 1988, **44**, 7171.
9 For other methods for oxidation of amines to imines see: (*a*) J. P. Marino and R. D. Larsen, *J. Am. Chem. Soc.*, 1981, **103**, 4642; (*b*) J. J. Cornejo, K. D. Larson and G. D. Mendenhall, *J. Org. Chem.*, 1985, **50**, 5382.
10 (*a*) M. T. Reetz and K. Schimmosek, *Chimia*, 1996, **50**, 668; (*b*) M. J. Hateley, D. A. Schichl, H.-J. Kreuzfeld and M. Beller, *Tetrahedron Lett.*, 2000, **41**, 3821; (*c*) Y. K. Choi, M. J. Kim, Y. Ahn and M.-J. Kim, *Org. Lett.*, 2001, **3**, 4099.
11 Y. Blum and Y. Shvo, *J. Organomet. Chem.*, 1985, C7.
12 The reported isoptope effect k_H/k_D for addition of **1b** (Ru_H/Ru_D) to benzaldehyde is 1.5: C. P. Casey, S. W. Singer, D. R. Powell, R. K. Hayashi and M. Kavana, *J. Am. Chem. Soc.*, 2001, **123**, 1090.
13 G. Csjernyik, A. H. Éll, L. Fadini, B. Pugin and J.-E. Bäckvall, *J. Org. Chem.*, 2002, **67**, 1657.
14 Equilibrium isotope effects are usually much smaller than kinetic isotope effects.
15 M. Abed, I. Goldberg, Z. Stein and Y. Shvo, *Organometallics*, 1988, **7**, 2054.
16 β-Hydride abstraction from **6** gives the active catalyst.