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Mechanism of ruthenium-catalyzed hydrogen transfer reactions. Evidence for a stepwise transfer of CH and NH hydrogens from an amine to a (cyclopentadienone)ruthenium complex†

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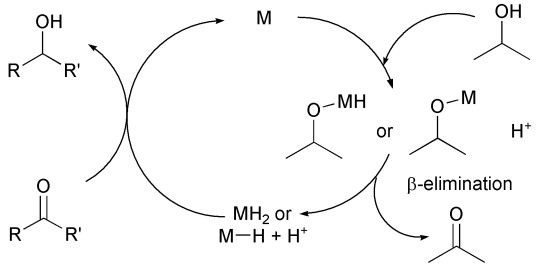
Kinetic deuterium isotope effects and racemization studies indicate that dehydrogenation of an amine by a (cyclopentadienone)ruthenium complex occurs *via* a slow β-hydride elimination of coordinated amine followed by a proton transfer from nitrogen to carbonyl oxygen.

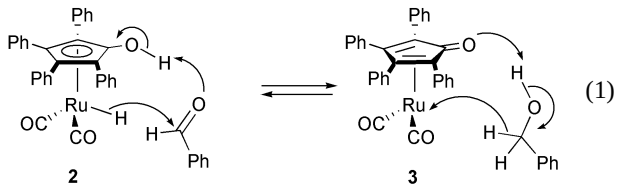
Transition metal-catalyzed hydrogen transfer reactions have attracted considerable attention recently, in particular the enantioselective version of the reaction.[1–3] Many metal complexes of ruthenium, rhodium and iridium have been found to be active catalysts in hydrogen transfer reactions and some of these catalysts have been applied to asymmetric transfer hydrogenation.[2,3] The metal-catalyzed hydrogen transfer reaction is typically used for reductions of ketones[4] and imines[5] with a hydrogen donor but it can also be used for oxidation of alcohols[6] and amines[7] employing a hydrogen acceptor and for racemization of alcohols in combination with enzymes for dynamic kinetic resolution (DKR).[8]

In the original mechanism for transition metal-catalyzed hydrogen transfer, *e.g.* from an alcohol to a ketone, it was suggested that formation of metal alkoxide followed by β-hydride elimination occurs.[1] The metal hydride formed would then add to the ketone *via* a pathway which is the microscopic reverse of the first step (Scheme 1).



Scheme 1 Mechanism of transition metal catalyzed hydrogen transfer.

More recently, however, it was proposed that with certain ruthenium complexes hydrogen transfer proceeds *via* a six-membered transition state in a concerted reaction without coordination of either the alcohol or ketone to the metal.[9] Also, a concerted pathway was proposed for hydrogen transfer from the hydroxycyclopentadienyl ruthenium hydride **2** to an aldehyde to give **3** and the alcohol (eqn. 1).[10] Experimental support for this mechanism was obtained from the kinetic deuterium isotope effects of **2**(OD), **2**(RuD) and **2**(OD, RuD).



(1)

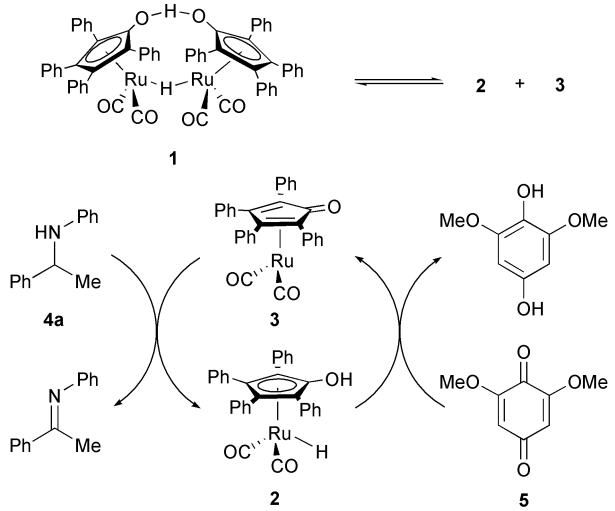
The monodeuterated complexes **2**(OD) and **2**(RuD) gave isotope effects of 2.2 and 1.5, respectively and dideuterated complex **2**(OD, RuD) afforded an isotope effect of 3.6 close to the product of the isotope effect of **2**(OD) and **2**(RuD).

We have recently studied ruthenium-catalyzed transfer hydrogenation of imines and transfer dehydrogenation of amines employing the dimeric Shvo catalyst (**1**), which dissociates under thermal conditions to an 18-electron species **2** and a 16-electron complex **3**.[5,7] In the present communication we have studied the deuterium isotope effect for hydrogen transfer from an amine using **1** as the catalyst and found that the two hydrogens are transferred to **3** in separate steps with the C–H bond cleavage being the slow step. Our results indicate that the reaction proceeds *via* coordination of the amine followed by β-hydride elimination.

One of the objectives of the present study was to measure the deuterium isotope effect for the two hydrogens in the hydrogen transfer from an amine to ruthenium complex **3**. This is difficult to do in a stoichiometric reaction since complex **3** cannot be isolated, and also because the reaction is reversible with the equilibrium shifted towards the amine. One way to circumvent this problem is to study the corresponding catalytic dehydrogenation of the amine involving ruthenium complex **3**. By using 2,6-dimethoxybenzoquinone (**5**) as hydrogen acceptor, the reaction can be studied in a catalytic fashion, as the 18e⁻ complex formed, **2**, is quickly recycled back to **3** after delivery of the hydride and proton to quinone **5** (Scheme 2). The reaction chosen for this purpose is shown in Scheme 2 and involves a ruthenium-catalyzed hydrogen transfer from amine **4a** to quinone **5**.

We have recently shown that the rate limiting step of this process is the dehydrogenation of the amine, which is an irreversible step when an excess of quinone **5** is employed.[7] The kinetic deuterium isotope effect of the hydrogen transfer from amine **4a** to ruthenium complex **3** can therefore be obtained from the overall isotope effect of the catalytic reaction.

The deuterated amines **4b**, **4c** and **4d** were used for the different kinetic isotope effect studies. Amine **4b** was prepared from the corresponding imine by reduction with $LiAlD_4$. To



Scheme 2 Coupled catalytic system for dehydrogenation of amines.

† Electronic supplementary information (ESI) available: general kinetic procedures used. See http://www.rsc.org/suppdata/cc/b3/b303258b/

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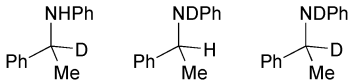
obtain deuterated amines **4c** and **4d** NH was exchanged to ND by shaking a solution of **4a** and **4b**, respectively, with a mixture of D_2O/MeOD.



4b **4c** **4d**

The dehydrogenation reaction of amines **4** was studied by ^{1}H NMR spectroscopy in toluene-d_8 at 100 °C using > 2.5 equiv. of quinone **5** as the hydrogen acceptor. The overall reaction proceeds with a first order dependence on amine concentration, as determined by observing the disappearance of the amine that followed pseudo-first-order kinetics to over 90% conversion. The rate of the overall hydrogen transfer from amine to quinone was measured. As discussed above the rate limiting step in the overall reaction is the hydrogen transfer from amine **4** to complex **3**. Therefore the rate of this step should be equal to that of the overall process. Determination of the observed rate was done by plotting the formation of the imine *versus* time and fitting the curve to a non-linear least squares fit. The observed rate constants for non-deuterated **4** and deuterated species **4b**, **4c** and **4d** are given in Table 1 with the different kinetic isotope effects in Table 2.

It is interesting to note that there is a large isotope effect for the cleavage of the C–H bond of the amine with k_{CHNH}/k_{CDNH} = 3.24. This individual isotope effect is equal (within experimental error) to the combined isotope effect k_{CHNH}/k_{CDND} = 3.26, obtained from simultaneous deuteration at both positions of the amine (**4d**). This clearly shows that the rate-limiting step is the cleavage of the C–H bond and that the transfer of the hydrogens from the amine to the ruthenium catalyst is not a concerted reaction. The kinetic isotope effect for the transfer of the hydrogen from the nitrogen to the oxygen is dependent on whether the α-carbon of the amine is deuterated or not. Thus, with α-deuterated amine k_{CDNH}/k_{CDND} = 1.01 whereas with non-deuterated amine k_{CHNH}/k_{CHND} = 1.39. An explanation for this discrepancy is that although transfer of hydrogen from carbon to ruthenium is significantly slower than that from nitrogen to oxygen, the difference is not large. For the C–D derivative, in which the cleavage of the carbon–hydrogen bond is retarded by the isotope effect, the difference is large enough so that no kinetic isotope effect for the N–H transfer to oxygen is observed. However, for the C–H derivative the difference has become small enough to give a small observable isotope effect for the N–H transfer to oxygen.

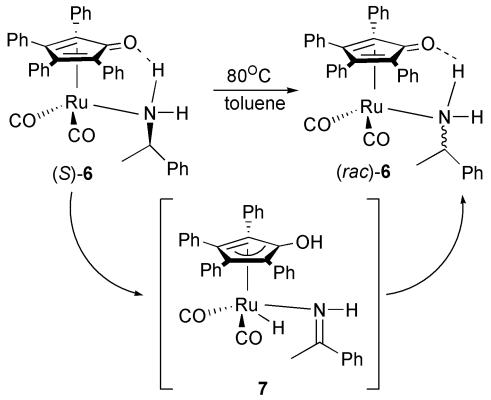
To obtain further support for the proposed mechanism we studied the enantiomerically pure chiral amine complex (*S*)-**6** and its tendency to racemize. If the complex can undergo racemization in the absence of free amine it would be good support for a β-elimination. A solution of (*S*)-**6** (> 98% ee) in toluene was stirred under argon at 80 °C and after 3 hours partial racemization had occurred and **6** was found to be 70% ee. After another 21 hours of stirring at 80 °C the recovered complex was almost racemic (4% ee).[11] The proposed mechanism for the racemization is given in Scheme 3. Slow β-hydride elimination *via* η^2-coordinated cyclopentadiene followed by proton transfer

Table 1 Observed rate constants at 100 °C for dehydrogenation of *N*-phenyl-*N*-(1-phenylethylamine)

k_{CHNH}	$(9.85 \pm 0.03) \times 10^{-4}$ s^{-1}
k_{CDNH}	$(3.04 \pm 0.14) \times 10^{-4}$ s^{-1}
k_{CHND}	$(7.05 \pm 0.64) \times 10^{-4}$ s^{-1}
k_{CDND}	$(3.02 \pm 0.22) \times 10^{-4}$ s^{-1}

Table 2 Kinetic deuterium isotope effects for the dehydrogenation of *N*-phenyl-*N*-(1-phenylethylamine)

k_{CHNH}/k_{CDNH}	3.24 ± 0.16
k_{CHNH}/k_{CHND}	1.39 ± 0.13
k_{CHNH}/k_{CDND}	3.26 ± 0.25
k_{CDNH}/k_{CDND}	1.01 ± 0.12
k_{CHND}/k_{CDND}	2.33 ± 0.38



Scheme 3 Racemization of amine complex (*S*)-**6**.

would give imine complex **7** with an η^3-coordinated cyclopentadienyl ring. This imine complex may also be in equilibrium with η^2-coordinated imine. Insertion of the imine into the Ru-H bond will give (*rac*)-**6**. It is likely that the imine complex **7** is in equilibrium with free imine and complex **2**.

In conclusion, we have shown that hydrogen transfer from an amine **4** to ruthenium complex **3** occurs in two discrete steps most likely *via* a slow β-hydride elimination followed by a proton transfer from the imine to the oxygen of the cylcopentadienone ligand. The racemization of complex (*S*)-**6** supports this mechanism.

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