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Mechanistic studies on ruthenium-catalyzed hydrogen transfer reactions

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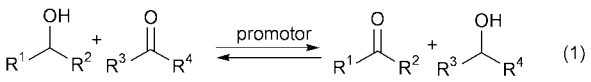
Ruthenium-catalyzed hydrogen transfer from (*S*)-α-deuterio-α-phenylethanol [(*S*)-1] to acetophenone with catalyst 3 occurs with retention of deuterium at the α-carbon of the alcohol product whereas H/D scrambling occurs with catalyst 2.

Hydrogen transfer reactions in which hydrogen is transferred from one organic molecule to another is of great importance in organic synthesis since one can avoid the use of molecular hydrogen.[1,2] In particular the reaction in which one equivalent of hydrogen is transferred from an alcohol to a ketone [eqn. (1)]



(1)

has become useful. This transformation has been known since 1925[3,4] and in the original version an aluminium alkoxide was employed as promotor [Meerwein–Ponndorf–Verley (MPV) reduction and Oppenauer oxidation].[1] In these reactions a direct transfer of a hydride is supposed to take place (Fig. 1, A).[5]

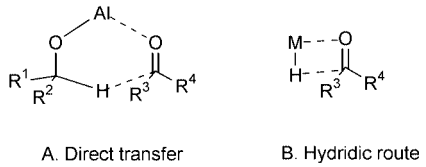
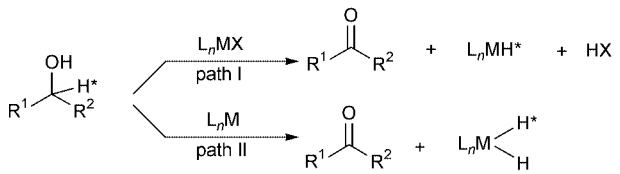


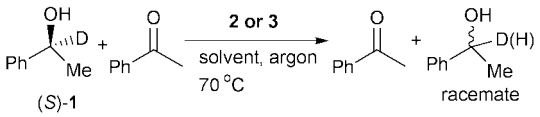
Fig. 1

More recently, transition metal-catalyzed versions of these reactions have been developed.[6,7] The latter reactions are supposed to involve metal hydride intermediates[7,8] (Fig. 1, B) and recently hydride intermediates were isolated from ruthenium–catalyzed hydrogen transfer reactions.[9,10] An interesting question is whether the metal hydride arises purely from the α-hydrogen of the secondary alcohol (path I, Scheme 1) or if hydride on the metal also originates from the OH group (path II, Scheme 1).



Scheme 1

To answer this question and to gain further insight into the mechanism of hydrogen transfer reactions we have studied the ruthenium-catalyzed hydrogen transfer from (*S*)-α-deuterated α-phenylethanol [(*S*)-**1**)] to acetophenone [eqn. (2)].

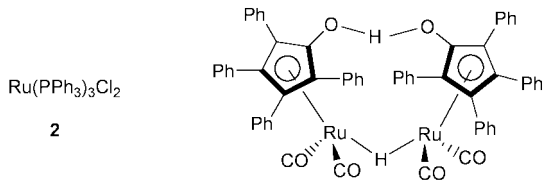


(2)

(*S*)-**1**

The use of enantiomerically pure α-deuterated alcohol (*S*)-**1** makes it possible to monitor the progress of the reaction since the hydrogen transfer catalyzed by the achiral catalyst should lead to racemization. The alcohol (*S*)-**1** is readily obtained from the enzymatic resolution of the corresponding racemic alcohol.[11] The latter was in turn obtained from $LiAlD_4$ reduction of acetophenone.

Ruthenium-catalyzed reaction of (*S*)-**1** with acetophenone resulted in moderate to slow racemization of the alcohol. Two different catalysts **2** and **3** were used in the present study. The



2

3

important question is to what extent deuterium is retained in the racemized alcohol. The racemization of (*S*)-**1** with both catalysts was carried out in aprotic as well as in protic solvents (Table 1). The reaction of (*S*)-**1** with **2** as the catalyst in THF in the presence of base and 0.5% of water resulted in complete racemization within 4 h (Table 1, entry 1). ^{1}H NMR and MS analyses showed that a significant loss of the deuterium had occurred and the deuterium content in the α-position was only 37%. In contrast, when **3** was employed as catalyst in the racemization of (*S*)-**1**, which took 24 h, essentially all of the deuterium was maintained in the α-position of the alcohol (entry 2). When the racemization experiment was carried out in a protic solvent (Bu^{t}OH) catalyst **2** gave a dramatic drop in the deuterium content to 15% (entry 3), whereas with catalyst **3** a high α-deuterium content was still maintained (91% D, entry 4). Interestingly, when catalyst **3** was employed in toluene, (*S*)-**1** gave a racemized product with 82% deuterium in the α-position. This suggests that slow aromatic activation of toluene by the active catalyst takes place leading to some H/D exchange.

The results from the racemization of (*S*)-**1**† suggest that catalysts **2** and **3** operate by two different mechanisms. With catalyst **2** it is evident that the hydride on the metal arises both from the α-position and the OH group of the alcohol (path II, Scheme 1), whereas with catalyst **3** the hydride arises only from the α-position (path I, Scheme 1). The former mechanism (path

Table 1 Racemization of (*S*)-**1** *via* Ru-catalyzed hydrogen transfer[a]

Entry	Catalyst	Base	Solvent	Water (%)	*t*/h	Result[b]
1	**2**	NaOH	THF	0.5	4	37% D
2	**3**	—	THF	—	24	95% D
3	**3**	—	Bu^{t}OH	0.5	72	91% D
4	**2**	NaOH	Bu^{t}OH	0.5	4	15% D
5	**3**	—	Toluene	—	24	82% D

[a] 2 mol% of the catalyst was employed together with 1 equiv. of acetophenone at 70 °C. [b] The deuterium content was determined by ^{1}H NMR and also by mass spectrometry and refers to the amount in the α-position.

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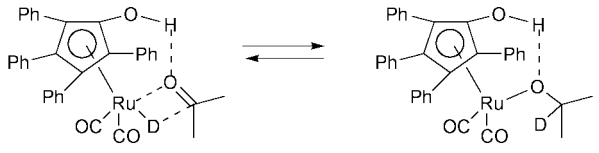
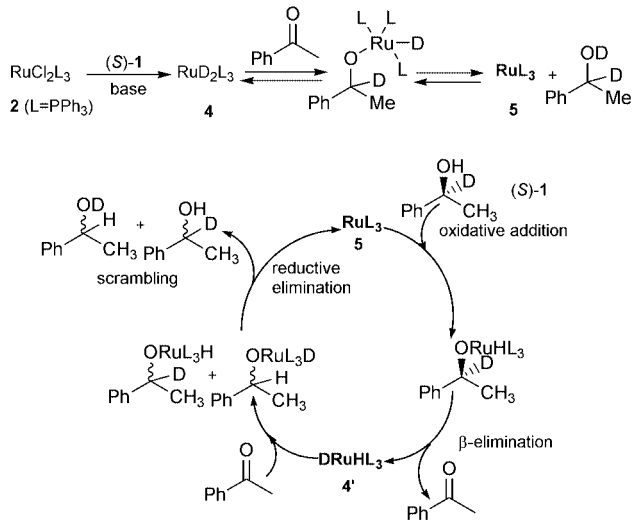


Fig. 2

II) is expected to give a H/D ratio of 50/50 in the α-position of the racemized alcohol from (*S*)-**1**. With path I (Scheme 1), (*S*)-**1** would give only ruthenium deuteride and as a result the α-position would be 100% deuterated in the racemized product.

The mechanism for catalyst **3**, which follows path 1, probably involves an intermediate in which the hydrogen transferred to the carbonyl carbon comes from the metal and the hydrogen transferred to the ketone oxygen arises from the OH group of the catalyst (Fig. 2). This may involve insertion of the ketone into a Ru–D bond followed by protonation of the ruthenium alkoxide by the OH group. In the reversed reaction a β-elimination from the alkoxide gives the ruthenium deuteride. This is in line with the mechanism proposed in our previous studies on ruthenium-catalyzed hydrogen transfer reactions with catalyst **3**.[12]

In the hydrogen transfer reaction with catalyst **2** it is known that the chlorides are eliminated under the formation of a ruthenium dihydride species.[9] With substrate (*S*)-**1** a di-deuterated complex **4** would be formed, which can react with the ketone to give a ruthenium(0) complex RuL_3 **5** after reductive elimination (Scheme 2). The latter complex should be in equilibrium with **4**.



Scheme 2 Hydrogen transfer with catalyst **2**.

In the catalytic cycle (Scheme 2) oxidative addition of (*S*)-**1** to **5** would give a ruthenium alkoxide, which on β-elimination produces acetophenone and $DRuHL_3$ **4′**. The mixed hydride-deuteride species **4′** can now add to acetophenone, and after reductive elimination, the alcohol obtained would have deuterium scrambled between the α- and oxygen-positions. Any exchange with protons in the medium (*e.g.* a protic solvent) at this stage will lower the deuterium content of **1** by exchange of deuterium in the oxygen-position (*cf.* entry 4, Table 1). This is in contrast to catalyst **3** for which there will be no such H/D exchange since the hydride on the metal only arises from the α-position of the alcohol.

In conclusion, the results presented here show that quite different mechanisms may operate in ruthenium-catalyzed hydrogen transfer. Evidence is provided that catalyst **2** does not distinguish between the α-hydrogen and the OH hydrogen in hydrogen transfer from an alcohol to a ketone. In contrast, catalyst **3** selectively transfers the α-hydrogen to the carbonyl group and the OH hydrogen to the keto oxygen in the corresponding hydrogen transfer.

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Notes and references

† *Typical procedure* for racemization of (*S*)-**1**: the ruthenium catalyst (2 mol%) and the base (10 mol%) were placed in a Schlenk tube, which was evacuated and filled with argon. Argon was bubbled through a solution of (*S*)-**1** (123 mg, 1 mmol) and acetophenone (120 mg, 1 mmol) in 1.25 ml of the appropriate solvent and transferred *via* a canula to the Schlenk tube containing the catalyst. The reaction mixture was heated to 70 °C (when THF was used as the solvent, the Schlenk tube was sealed with the help of a stopcock). The reaction was followed by chiral GC, worked up by filtration through a bed of Celite and purified by column chromatography. The racemized alcohol obtained was analyzed by ^{1}H NMR and MS for the deuterium content in the α-position.

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11 (*a*) To α-deuterated α-phenylethanol (0.625 g, 5 mmol) in toluene was added *p*-chlorophenyl acetate (0.844 g, 10 mmol) and enzyme N-435 (0.4 g) and the mixture stirred at 70 °C for 48 h.[11b] Workup followed by chromatography gave (*S*)-**1** (0.257 g, > 99% ee) and (*R*)-*O*-acetyl-α-deuterated α-phenylethanol (0.249 g, > 99% ee). (*b*) B. A. Persson, A. L. E. Larsson, M. L. Ray and J. E. Bäckvall, *J. Am. Chem. Soc.*, 1999, **121**, 1645.

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