Mechanistic investigation on the hydrogenation of imines by [*p*-(Me₂CH)C₆H₄Me]RuH(NH₂CHPhCHPhNSO₂C₆H₄-*p*-CH₃). Experimental support for an ionic pathway

Jenny B. Åberg, Joseph S. M. Samec and Jan-E. Bäckvall*

The need for acidic activation in the stoichiometric hydrogenation of benzyl-[1-phenyl-ethylidene]-amine (**6a**) or [1-(4-methoxy-phenyl)-ethylidene]-methyl-amine (**6b**) by Noyori's catalyst [*p*-(Me₂CH)C₆H₄Me]RuH(NH₂CHPhCHPhNSO₂-C₆H₄-*p*-CH₃) (**2**) is inconsistent with the proposed concerted mechanism and supports an ionic mechanism.

Optically active compounds are important in the fine-chemical, pharmaceutical, and agrochemical industries.[1] Chiral amines can be prepared by catalytic reduction of imines, and transfer hydrogenation has been used successfully for both imines and ketones.[2,3] In transfer hydrogenation, an alcohol, *e.g.* 2-propanol, or a formate is used as hydrogen source. After our report of Ru-catalysed transfer hydrogenation of imines by 2-propanol,[4] the first asymmetric transfer hydrogenation of imines was reported by Noyori *et al.*[5] In the latter reaction HCOOH was employed as the hydrogen donor. Chiral Ru(II)–TsDPEN complex **1** (Fig. 1) was used as catalyst in transfer hydrogenation of both ketones and imines to give quantitative yields and high enantioselectivities (ee's up to 97% for imines).[3,5–7]

Some additional recent contributions of transfer hydrogenation of imines include Ru(II)-,[8] Rh(III)-,[9] Ir(III)-,[10] and Ni(0)-[11] catalysts. No asymmetric transfer hydrogenation of imines using 2-propanol as hydrogen donor has been reported.

The proposed mechanism for transfer hydrogenation of ketones and imines by **2**, formed from **1**, involves a cyclic transition state (**A**) where the hydride and the proton are transferred from the catalyst to the substrate in a concerted reaction without coordination of the substrate (Fig. 2).[6,7]

The mechanism has been studied by several groups. Noyori and co-workers have isolated **2** and **3** and proven that they are the active species in catalysis involving ketones (aldehydes) and
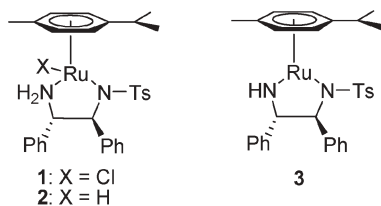

Fig. 1 Noyori's Ru–TsDPEN catalyst precursor **1**, true catalyst **2** and reactive intermediate **3**.

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden. E-mail: jeb@organ.su.se; Fax: +46-8-154908; Tel: +46-8-674 7178
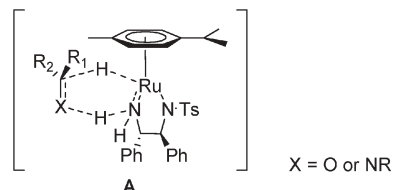

Fig. 2 Proposed cyclic transition state for hydrogenation of ketones and imines.

alcohols.[5] The concerted pathway is supported by kinetic isotope measurements carried out by Casey *et al.*[12] and calculations performed by the groups of Noyori,[13] Andersson,[14] and van Leeuwen.[15] While mechanistic studies have been extensive for ketones/alcohols, the studies on the corresponding reaction involving imines/amines are limited. It has merely been assumed that both classes of compounds follow the same mechanistic pathway.[7,13]

We[16] and Casey *et al.*[17] have recently shown that for the related metal ligand bifunctional catalyst **4**, transfer hydrogenation of imines (Scheme 1) occurs *via* a different mechanism to that of ketones.

Here we report that the concerted mechanism proposed for addition of hydride **2** to ketones (aldehydes) and imines (Fig. 2) is not operating for imines. The hydride species **2**, which reacts fast with ketones (aldehydes), does not react with imines. However, when an acid is added in the latter case a fast reduction occurs. These results support an ionic mechanism for the reduction of imines by **1**, where the substrate is pre-activated by protonation prior to hydrogen transfer. Recently, an ionic mechanism has been proposed by Norton and Bullock for the hydrogenation of ketones (aldehydes) and imines by different transition metal catalysts.[18]

2-Propanol alone cannot be used as the terminal reductant in the transfer hydrogenation of imines catalyzed by **1**.[5] Instead a mixture of formic acid and triethylamine is used. We argued that this may be due to product inhibition where the amine produced
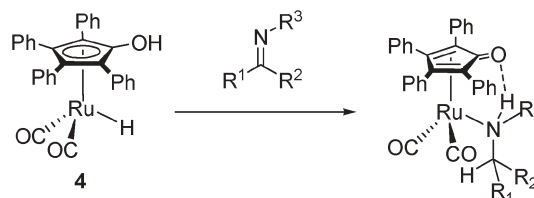
Scheme 1 Studied reaction between Shvo's catalyst **4** and imines.
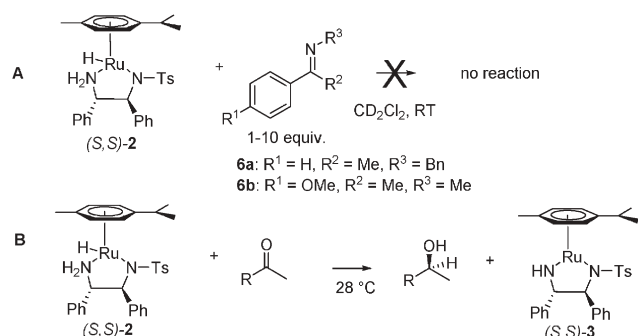
Scheme 2 Stoichiometric reaction between **2** and imine **6** does neither form any complex, nor reduce the substrate.

coordinates to **3**, formed from **2**, to give a stable Ru–amine complex.† To investigate this complexation we mixed stoichiometric amounts of **2** with an imine. To our surprise, neither a Ru–amine complex, nor free amine was observed (Scheme 2, Path A).

Both the chemical shifts and the integrals (400 MHz, CD_2Cl_2) of the hydride signal of **2** at δ −5.87 (s, 1 H) and the benzyl hydrogens at δ 4.66 (s, 2 H) and methyl group at δ 2.29 (s, 3 H) of imine **6a** remained unchanged. In a similar experiment with imine **6b** the signals of the methyl groups of the imine at δ 3.83 (s, 3 H), δ 3.29 (s, 3 H) and δ 2.19 (s, 3H) also remained unchanged. The singlet of ferrocene at δ 4.12 was used as an internal standard.

Even with a large excess of imine (10 equiv.) no reaction between hydride **2** and the imine occurred after 12 hours (Scheme 2, path A).‡,§ This is in sharp contrast to the reaction of ketones, where treatment of **2** with a tenfold excess of acetone (R = Me Scheme 2, path B) instantaneously gave the 16 electron species **3** and 2-propanol.[6] Since formic acid/triethylamine is used for catalytic transfer hydrogenation of imines we argued that the activation barrier is too high to overcome without acidic activation of the imine by protonation. This was supported by the fact that addition of one equivalent of formic acid to the reaction mixture afforded the corresponding amine (Table 1, entry 1).

To confirm that the formic acid was not working as hydrogen donor we performed the hydrogenation of imines **6** by **2** with different Brønsted acids and one Lewis acid. Interestingly, most of these acids worked well to promote the hydrogenation. The use of tetrafluoroboric acid afforded the amine in excellent yield (Table 1, entry 3). Trifluoroacetic as well as acetic acid gave high yields after prolonged reaction times (Table 1, entries 6 and 8). Scandium triflate, which has been used for activation of imines in reductive amination,[20] also gave an excellent yield in the reaction between imine **6a** and catalyst **2** (Table 1, entry 9). This further supports the proposal that the role of the acid is to activate the imine. Only the sterically hindered benzoic and pivalic acid gave moderate yields in this transformation (Table 1, entries 11 and 12). The striking difference when using no acid is still evident, since no amine is formed, even after 31 hours (Table 1, entry 13). All yields and ee values are comparable to those of the catalytic version (*cf.* 72% yield and 77% ee after 36 h).[5]

Based on our studies, we conclude that the concerted pathway previously reported[7,13] (Fig. 2) does not operate for imines. Acidic activation of the imine is required and further studies on how the protonated imine is hydrogenated by hydride **2** are currently underway.

Table 1 Addition of acid is necessary for reduction of imine **6a** by **2**[a].

Entry	Acid	pK_a[b]	Time/h	Conversion[c] (%)	Ee[d] (%)
1	HCOOH	3.75	1	96	91
2	HCOOH	3.75	23	96	85
3	HBF_4	0.5	1	> 99	78
4	HBF_4	0.5	23	> 99	75
5	CF_3COOH	0.52	1	39	69
6	CF_3COOH	0.52	23	73	84
7	CH_3COOH	4.76	1	39	94
8	CH_3COOH	4.76	23	78	89
9	$Sc(OTf)_3$		1	> 99	80
10	$Sc(OTf)_3$		23	> 99	78
11	PhCOOH	4.2	23	26	82
12	Me_3COOH	5.03	23	29	80
13	—	—	31[e]	—	—

[a] Unless otherwise noted, 35 μmol of imine was mixed with acid 1 equiv. followed by **2** 2 equiv. in CH_2Cl_2 under argon. The reaction mixture was worked up with 2 M NaOH, extracted with CH_2Cl_2, dried (Na_2SO_4) and purified by bulb-to-bulb distillation. [b] pK_a values apply to dilute aqueous solutions and are taken from ref. 19. [c] Conversion determined by NMR. [d] (S)-configuration, ee determined by GC analysis. [e] 4 equiv. of **2** were used.

Notes and references

† The corresponding Ru–amine complexes of bifunctional catalyst **4** have recently been reported by us and Casey, see refs. 16 and 17.
‡ Slow decomposition of the hydride was detected, but this also occurred in the absence of imine.
§ To prove that this was not due to unfavorable thermodynamics, attempts were made to study the reverse reaction by mixing the coordinatively unsaturated 16 electron species **3** and amine **7a** in CD_2Cl_2. A tenfold excess of amine did not produce any detectable amounts (by ^{1}H NMR) of dehydrogenation products.

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