Amino alcohol effects on the ruthenium(II)-catalysed asymmetric transfer hydrogenation of ketones in propan-2-ol

Jun Takehara,[a] Shohei Hashiguchi,[a] Akio Fujii,[a] Shin-ichi Inoue,[b] Takao Ikariya[a] and Ryoji Noyori*†[a]

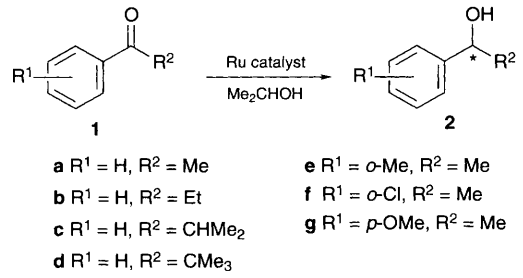
[a] *ERATO Molecular Catalysis Project, Research Development Corporation of Japan, 1247 Yachigusa, Yakusa-cho, Toyota 470-03, Japan*

[b] *Department of Applied Chemistry, Aichi Institute of Technology, 1247 Yachigusa, Yakusa-cho, Toyota 470-03, Japan*

A ruthenium(II) complex generated *in situ* from [{$RuCl_2(\eta^6$-$C_6Me_6)$}$_2$], (1*S*,2*S*)-2-methylamino-1,2-diphenylethanol and KOH serves as an efficient catalyst for asymmetric transfer hydrogenation of acetophenone derivatives in propan-2-ol to give (*S*)-enriched alcohols in up to 92% ee and in > 90% yield.

Excellent catalytic performance of ruthenium(II) complexes in transfer hydrogenation of ketones with propan-2-ol[1–3] prompted us to search for new organic ligands for asymmetric transformation. Most earlier works using transition-metal catalysts, except for our recent result with (1*S*,2*S*)-*N*-(toluene-*p*-sulfonyl)-1,2-diphenylethylenediamine,[1] utilised aza-aromatics[4] and imines[3] containing sp^2- hybridized nitrogen atoms together with diphosphine ligands[2] for modification of the metallic centre. We have now found that β-amino alcohols show a particularly high ligand-acceleration effect in the reduction of aromatic ketones in propan-2-ol which is catalysed by an arene–ruthenium(II) complex (Scheme 1) and that a highly enantioselective reaction is achievable when a chiral ancillary is used with suitable configuration and functionality.

We first examined the rate of reduction of acetophenone **1a** in propan-2-ol containing [{$RuCl_2(\eta^6$-$C_6Me_6)$}$_2$] and KOH in the presence of a simple bifunctional auxiliary {[**1a**] = 0.1 mol dm^{-3}; **1a** : Ru : auxiliary : KOH mole ratio = 200 : 1 : 2 : 5}. In the absence of any auxiliary, the reaction proceeded very slowly to give, after 1 h at 28 °C, **2a** in only 1% yield. The turnover frequency (TOF), defined as moles of product per mole of catalyst per hour (initial < 20 min period), was only 3. However, addition of ethanolamine (2 equiv. to Ru) under otherwise identical conditions gave TOF as high as 227 h^{-1}. The screening experiments with a range of functionalised compounds revealed that this simple β-amino alcohol displayed the highest rate enhancement, giving **2a** in 45% yield after 1 h at 28 °C or 93% yield after 5 h at the same temperature. Notably, ethylene glycol did not accelerate the reaction to any great extent (TOF 10 h^{-1}), while ethylenediamine almost completely suppressed the background transfer hydrogenation. Other tested auxiliaries and TOFs (h^{-1}) were: *N*-(toluene-*p*-sulfonyl)ethylenediamine,[1] 86; 3-aminopropanol, 23; trimethylene glycol, 9; 2,2′-bipyridyl, 18; 2,2′-methylenebis(5,5-dimethyl-4,5-dihydrooxazole), 3; butylamine, 7; diethylamine, 23; triethylamine, 10; and 1,2-bis(diphenylphosphino)ethane, 5. The highest TOF, 4700 h^{-1}, was obtained when the reaction was carried out in a 0.1 mol dm^{-3} solution of **1a** in propan-2-ol at 80 °C with a **1a** : Ru : ethanolamine : KOH mole ratio of 1000 : 1 : 2 : 5. Unlike the arene–ruthenium(II) complex, the diene complexes, [{$RuCl_2$(cod)}$_2$] and [{$RuCl_2$(nbd)}$_2$] (cod = cycloocta-1,5-diene, nbd = norbornadiene), and the phosphine complex, [$RuCl_2(PPh_3)_3$], appeared to be unsuitable for amino alcohol modification.



Scheme 1 *Reagents and conditions*: 0.25 mol % [{$RuCl_2(\eta^6$-arene)}$_2$]; 1 mol % β-amino alcohol; 2.5 mol % KOH. [ketone] = 0.1 mol dm^{-3} in propan-2-ol, 28 °C.

Encouraged by the marked acceleration with ethanolamine, we then tried the asymmetric reduction using a 0.1 mol dm^{-3} solution of **1a** containing KOH with a substrate/catalyst ratio (S/C) of 200, at 28 °C. The chiral catalyst was prepared *in situ* by heating a mixture of [{$RuCl_2(\eta^6$-arene)}$_2$][5] and a 2-amino-1,2-diphenylethanol derivative[6] with a *threo* or *erythro* configuration and various nitrogen-substitution patterns. The results, summarised in Fig. 1, revealed that the relative reactivities depend on the balance of the electronic and steric effects. Many factors affect the overall efficiency: (*i*) the presence of a primary or secondary amine end is crucially important for the acceleration, as has been observed in related Ru-catalysed reactions;[1,7] 2-dimethylamino alcohols were totally inactive. (*ii*) In the *erythro* series **3** and **4**, the *N*-methylation tends to significantly decrease the reactivity, while the amino and methylamino compounds in the *threo* series, **5** and **6**, showed comparable reactivities. (*iii*) The catalytic reactivity is decreased by increasing the bulkiness of the arene auxiliary and this effect is serious with the *erythro* series, **3** *vs.*

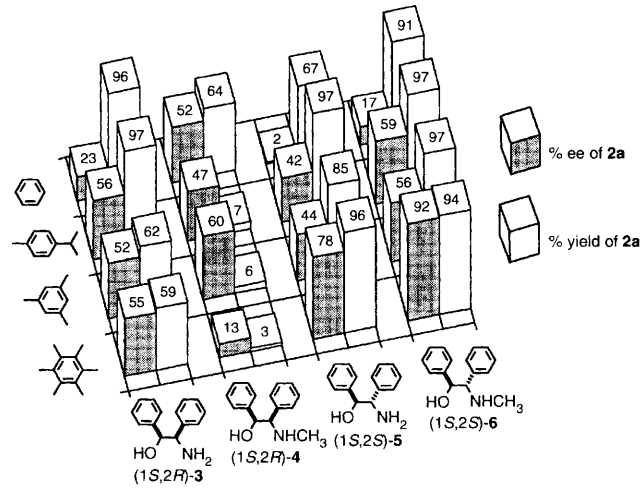
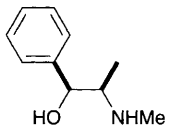


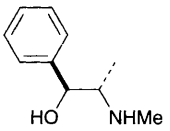
Fig. 1 Effects of arene and amino alcohol auxiliaries on the reactivity and stereoselectivity of the Ru-catalysed transfer hydrogenation of acetophenone **1a** in propan-2-ol. Reaction conditions: 0.25 mol% [{$RuCl_2(\eta^6$-arene)}$_2$]; 1 mol% β-amino alcohol; 2.5 mol% KOH. [**1a**] = 0.1 mol dm^{-3} in propan-2-ol, 28 °C, 1 h.

4. This effect is not significant in **5** and **6**. (*iv*) The sense of asymmetric induction is determined primarily by the configuration of the hydroxy-bearing carbon; the 1-(*S*) amino alcohols afford (*S*)-**2a** preferentially, whereas the 1-(*R*) auxiliary gives *R*-enriched **2a**. However, the amine-substituted asymmetric carbon also affects the extent of the enantioselection. (*v*) Both arene and amino alcohol ligands influence the enantioselectivity, but the tendency is not straightforward. High enantioselectivity is obtained only when an appropriate arene and chiral amino alcohol auxiliary are combined. Thus, the hexamethylbenzene–(1*S*,2*S*)-2-methylamino-1,2-diphenylethanol [(1*S*,2*S*)-**6**] combined system afforded the highest chiral efficiency, leading to (*S*)-**2a** in 92% ee and in 94% yield after 1 h of reaction at 28 °C. (*vi*) The reaction in most cases, though not always, is reversible.[8] Hence, prolonged exposure of the product to the catalyst tends to gradually deteriorate the enantiomeric purity. The β-amino alcohols acting as promotors proved stable under the reaction conditions, however.

This new catalyst system is characterised by high reactivity at room temperature. Reduction of **1a** catalysed by $[\{RuCl_2(\eta^6\text{-}C_6Me_6)\}_2]$ and **6** proceeded *ca.* five times faster than the reaction with the $[\{RuCl_2(\eta^6\text{-}C_6H_3Me_3\text{-}1,3,5)\}_2]$–(1*S*,2*S*)-*N*-(toluene-*p*-sulfonyl)-1,2-diphenylethylenediamine system[1] albeit with somewhat lower enantioselectivity. In addition, the reactivity and stereoselectivity are easily tunable by changing



(1*S*,2*R*)-**7**



(1*S*,2*S*)-**8**

Table 1 Asymmetric transfer hydrogenation of ketones in propan-2-ol catalysed by $[\{RuCl_2(\eta^6\text{-}C_6Me_6)\}_2]$–chiral amino alcohol systems[a]

Entry	Ketone	Amino alcohol	Alcohol *t*/h	% Yield[b]	% ee[c]	Confign.
1	**1a**	(1*S*, 2*S*)-**6**	1	94	92	*S*
2	**1a**	(1*S*, 2*R*)-**7**	1	95	91	*S*
3	**1a**[d]	(1*S*, 2*S*)-**6**	8	92(80)[e]	92	*S*
4	**1b**	(1*S*, 2*S*)-**6**	2	95	82	*S*
5	**1c**	(1*S*, 2*S*)-**6**	15	93	5[f]	*S*
6	**1d**	(1*S*, 2*S*)-**6**	20	22	40[f]	*R*
7	**1e**	(1*S*, 2*S*)-**6**	6	96	83[g]	*S*
8	**1f**	(1*S*, 2*S*)-**8**	1	99	89	*S*
9	**1g**	(1*S*, 2*S*)-**6**	4	73	79[g]	*S*
10	1′-acetonaphthone	(1*S*, 2*S*)-**6**	2	99	93[g]	*S*
11	α-tetralone	(1*S*, 2*S*)-**8**	4	62	94[g]	*S*
12	*c*-C_6H_{11}COMe	(1*S*, 2*S*)-**8**	3	93	75[h]	*S*

[a] The reaction was carried out at 28 °C using a 0.1 mol dm^{-3} solution (5.0 mmol) in propan-2-ol. Ketone : Ru : ligand : KOH = 200 : 1 : 2 : 5. [b] Yield was determined by GLC or 400 MHz ^1H NMR analysis. [c] Determined by capillary GLC analysis using a chiral CP-cyclodextrin-β-236-M-19 column unless otherwise specified. [d] Result of reaction with S/C = 1000 and Ru : ligand = 1 : 4.‡ [e] Isolated yield. [f] Determined by HPLC analysis using a Chiralpak AS column (eluent, 5 : 95 propan-2-ol–hexane; flow rate, 0.5 ml min^{-1}). [g] Chiralcel OB column (10 : 90 propan-2-ol–hexane). [h] Determined by the method of ref. 9.

the auxiliaries. Many chiral amino alcohols other than **3**–**6** can be used as chiral auxiliaries; ephedrine **7** and ψ-ephedrine **8** are obvious candidates. Table 1 lists some examples of the asymmetric reductions that were tried using this method. The reaction of aromatic ketones including 1′-acetonaphthone and α-tetralone gave the chiral alcoholic products in an acceptable chemical yield and enantiomeric purity. Reaction of alkyl phenyl ketones possessing a bulky alkyl substituent proceeded rather sluggishly. As the bulkiness of the alkyl group increases from methyl to ethyl to isopropyl, the extent of the enantioselectivity is lowered (entries 1, 4 and 5) and, with the *tert*-butyl analogue, the sense is reversed (entry 6). Cyclohexyl methyl ketone was reduced with a moderate enantioselectivity (entry 12).

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Footnotes

† *Permanent address*: Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-01, Japan.

‡ A preparative experiment using 20 mmol of acetophenone **1a** (S/C = 1000) was performed as follows: A suspension formed by mixing $[\{RuCl_2(\eta^6\text{-}C_6Me_6)\}_2]$[5] (6.6 mg, 0.010 mmol) and (1*S*,2*S*)-**6** (18.2 mg, 0.080 mmol) in propan-2-ol (5 ml) was heated at 80 °C for 20 min under an argon atmosphere. To the resulting orange solution, a degassed solution of **1a** (2.40 g, 20 mmol) in propan-2-ol (194 ml) and a solution of 0.1 mol dm^{-3} KOH in propan-2-ol (1.0 ml) were added. The mixture was stirred at 28 °C for 8 h, neutralised with dilute hydrochloric acid and concentrated *in vacuo*. The residue was diluted with ethyl acetate and the organic solution was washed with brine. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and distilled [108 °C (5.3×10^3 Pa)] to afford (*S*)-1-phenylethyl alcohol **2a**. Yield: 1.95 g (80%, 92% ee).

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