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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente No. 06-127.752

Solicitud de patente de invención titulada: "PREPARACIÓN ENANTIOSELECTIVA
DE UN DERIVADO DE QUINOLINA".

Solicitante: NOVARTIS AG

Nuestra Ref.: P2006/000245

RESPUESTA AL OFICIO No. 05323, NOTIFICADO POR FIJACIÓN EN LISTA No. 140,
DE FECHA 23 DE ABRIL 2010
(REQUERIMIENTO ARTÍCULO 46)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa de los siguientes documentos exigidos por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

1)

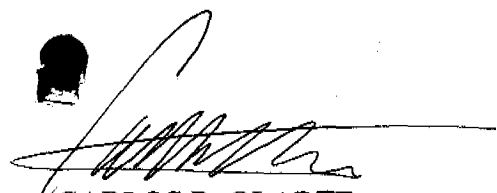
K. PÜNTENER ET. AL.: "New Efficient
Catalysts for Enantioselective Transfer
Hydrogenations."
TETRAHEDRON LETTERS,
vol. 37, no. 45, 1996, pages 8165-8168,
XP002367502

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2)

KERL-JOSEF HAACK ET. AL.: "The Catalyst Precursor, Catalyst, and Intermediate in the Ru(II) Promoted Asymmetric Hydrogen Transfer Between Alcohols and Ketones."
ANGEWANDTE CHEMIE, INTERNATIONAL EDITION
IN ENGLISH,
vol. 36, no. 3, 1997, pages 285-288,
XP002367503

Atentamente,



CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Artículos mencionados.



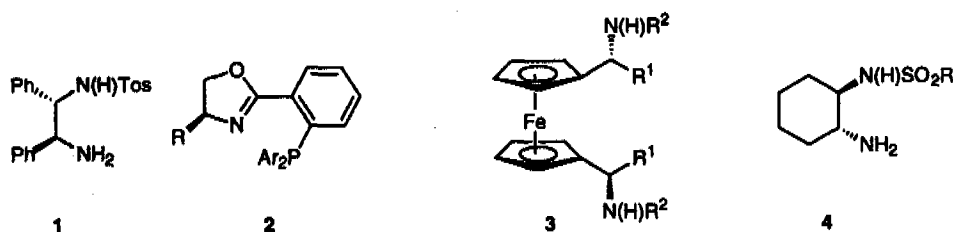
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New Efficient Catalysts for Enantioselective Transfer Hydrogenations

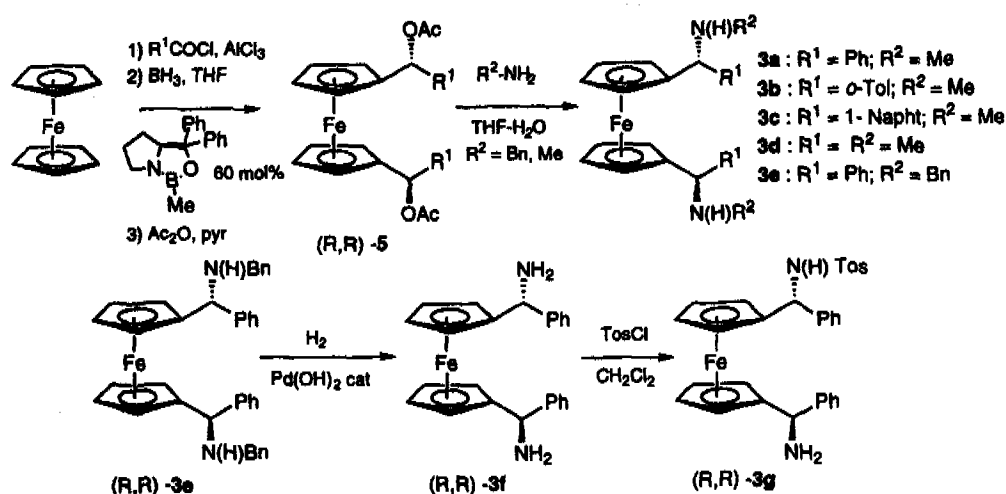
Kurt Püntener, Lothar Schwink and Paul Knochel*
 Fachbereich Chemie der Philipps-Universität Marburg
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Summary: New C_2 -symmetrical diaminoferrocenyl derivatives **3** and 2-amino(sulfonamido)cyclohexanes **4** were found to be highly active ligands for the ruthenium catalyzed asymmetric transfer hydrogenation of ketones. Contrary to many existing catalytic systems, the ligands **3** show a high activity at 25 °C and operate even at -30 °C (up to 90 % ee). On the other hand, the slightly less active ligands **4** are very easily prepared and are highly enantioselective at 30 °C in $HCOOH/Et_3N$ (up to 96 % ee).
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The catalytic enantioselective reduction of ketones has been extensively studied during the last decade.¹ A especially useful method is the catalytic transfer hydrogenation² using i -PrOH³ or a $HCOOH/Et_3N$ mixture⁴ as hydride source and a chiral ruthenium catalyst bearing ligands such as **1** or **2**. In the course of our work on the preparation of new chiral C_2 -symmetrical ferrocenyl derivatives for asymmetric catalysis,⁵ we have now discovered that the ruthenium complexes of the diaminoferrocenyl derivatives of type **3** are a new class of highly efficient transfer hydrogenation catalysts operating even at -30 °C with high conversion and good enantioselectivity.

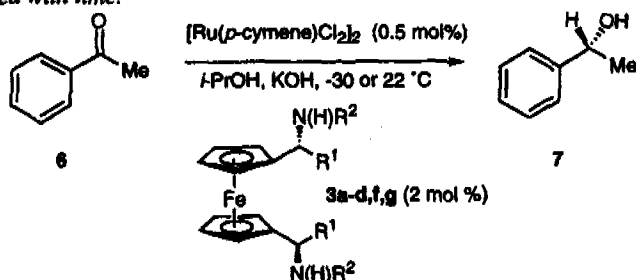


Herein we report our preliminary results with the new chiral ligand system as well as a highly enantioselective transfer hydrogenation using N -monosulfonylated 1,2-diaminocyclohexane derivatives of type **4**. The ferrocenes **3** were prepared from ferrocene in four steps (Scheme 1). Acylation of ferrocene (R^1COCl , CH_2Cl_2 , $AlCl_3$, 0 °C to 25 °C, 4 h) provides ferrocenyldiketones (71 - 92 %) which were reduced enantioselectively with an oxazaborolidine catalyst (CBS-reduction) providing 1,1'-ferrocenyl diols in 90 % - 96 % yield and > 99 % ee.⁵ Acetylation of these diols (Ac_2O , pyridine, 25 °C, 12 h) gives quantitatively the corresponding diacetates **5** which undergo a substitution with an excess of primary amines ($THF-H_2O$, 25 °C, 12 h) furnishing the diaminoferrocenes **3a-e** (56 % - 93 %) with retention of configuration.⁶ Hydrogenolysis of **3e** (H_2 , $Pd(OH)_2$ cat) leads to the unprotected diaminoferrocene derivative **3f** (96 %).⁷ Monotosylation of **3f** ($TosCl$ (1 equiv), CH_2Cl_2 , 0 °C, 1 h) affords the aminosulfonamide **3g** in 36 % yield.⁸ The aminoferrocenes **3a-d,f,g** were tested in the catalytic reduction of acetophenone (**6**). Thus, a i -PrOH solution of the catalytic system prepared from the ferrocene derivatives **3a-d,f,g** (2 mol %) and



Scheme 1

$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (0.5 mol %) was treated at temperatures between $-30\text{ }^\circ\text{C}$ and $22\text{ }^\circ\text{C}$ with a *i*-PrOH solution of acetophenone (6) in the presence of KOH (5 mol %) affording (*R*)-1-phenylethanol (7) with excellent conversions and enantioselectivities up to 80 % *ee* (Scheme 2 and Table 1).⁹ No decrease of the enantioselectivity is observed with time.



Scheme 2

Similarly 1-acetylnaphthalene (8) is reduced to (*R*)-1-naphthyl-1-ethanol (9) with an enantioselectivity up to 90 % *ee*. Entries 1-6 of Table 1 compare the results of the different ligands 3a-d,f,g at $22\text{ }^\circ\text{C}$. All except the monosulfonamido derivative 3g are highly effective and high conversions are reached within a few minutes to a few hours at rt. The best enantioselectivities are obtained with 3a and 3b, both bearing an aryl substituent ($R^1 = \text{Ph}$ or *o*-Tol) and a *N*-methylamino substituent. The free diaminoferrocene derivative 3f shows a good catalytic activity but leads to a moderate enantioselectivity (52 % *ee*, see entry 5). The increase of the size of the aryl substituent R^1 (phenyl to 1-naphthyl) doubles the catalytic activity but lowers the enantioselectivity (71 % *ee* to 60 % *ee*, compare entries 1 and 3). Remarkably, the high activity of our catalytic system allows us to lower further the reaction temperature. Carrying out the acetophenone reduction at $-14\text{ }^\circ\text{C}$ with the ligand 3a increases the enantioselectivity from 71 % *ee* to 79 % *ee*. Lowering the temperature further to $-30\text{ }^\circ\text{C}$ (120 h) furnishes the alcohol 7 with 80 % *ee* (compare entries 1, 7 and 8). A similar temperature effect is observed with 1-acetylnaphthalene (8). By using the most selective ligands 3a and 3b, enantioselectivities of 78 % *ee* and 85 % *ee* were obtained at rt. Lowering the reaction

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Table 1. Enantioselective transfer hydrogenation of ketones **6** and **8** in *i*-PrOH in the presence of 0.5 mol % of [Ru(*p*-cymene)Cl₂]₂ and 2 mol % of the aminoferrocenes **3a-d**, **f**, **g**.

entry	ketone	ligand	T (°C)	reaction time (h)	conversion (%) ^[a]	ee (%) ^[a]
1	6	3a	22	0.5	98	71
2	6	3b	22	1.5	97	80
3	6	3c	22	0.25	98	60
4	6	3d	22	3	94	62
5	6	3f	22	1	98	52
6	6	3g	22	24	97	56
7	6	3a	-14	41	96	79
8	6	3a	-30	120	95	80
9	6	3g	30	120	42	83 ^[b]
10	8	3a	22	1	99	78
11	8	3a	-30	120	91	90
12	8	3b	22	1	97	85
13	8	3b	0	12	96	88

[a] Determined by GC analysis (Chirasil-DEX CB) [b] A HCOOH/Et₃N mixture was used.

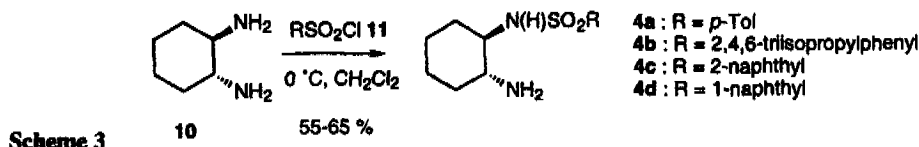
Table 2. Enantioselective transfer hydrogenation of ketones **6**, **8** and **12** in *i*-PrOH or HCOOH/Et₃N in the presence of 0.5 mol % of [Ru(*p*-cymene)Cl₂]₂ and 2 mol % of the aminosulfonamides **4a-d**.

entry	ketone	ligand	T (°C)	reaction time (h)	conversion (%) ^[a]	ee (%) ^[a]
1	6	4a	22 (30)	24	97 (>99)	89 (94)
2	6	4b	22 (30)	24	96 (>99)	90 (89)
3	6	4c	22 (30)	24	97 (>99)	90 (95)
4	6	4d	22 (30)	24	96 (>99)	92 (96)
5	8	4d	22 (30)	36	99 (>99)	92 (96)
6	12	4d	22 (30)	65	60 (54)	23 (67)

[a] Determined by GC analysis (Chirasil-DEX CB). Conversions and % ee in HCOOH-Et₃N are indicated in parenthesis.

temperature with the ligand **3a** to -30 °C and for **3b** to 0 °C allows to increase the enantioselectivity respectively to 90 % ee and 88 % ee (compare entries 10 to 13). The high catalytic activity observed using the ligand **3a**, even allows the reduction of sterically hindered ketones. Thus *t*-butylphenylketone was reduced with high conversion (> 93 %) within 17 h at 22 °C leading to (*S*)-2,2-dimethyl-1-phenyl-1-propanol with 38 % ee. Interestingly, the less active transfer hydrogenation ligand the monosulfonamide **3g** reacts with high enantioselectivity by replacing the *i*-PrOH/KOH reaction medium by the solvent mixture HCOOH/Et₃N (5:2). Under these conditions, a moderate conversion is obtained (42 %, 120 h) but the enantioselectivity increases from 56 % ee to 83 % ee (compare entries 6 and 9). This enantioselectivity increase

led us to prepare several monosulfonamides derived from the readily available (*1R,2R*)-1,2-diaminocyclohexane (**10**). Thus, treatment of commercially available **10** with various arylsulfonyl chlorides **11** (1 equiv, 0 °C, CH₂Cl₂) furnishes highly enantioselective transfer hydrogenation ligands **4a-d** (Scheme 3 and Table 2).¹⁰



The reduction of acetophenone (**6**) proceeds smoothly with the aminosulfonamides **4a-d**. High enantioselectivities (90-92 % *ee*) are obtained with **4a-d** in *i*-PrOH. Switching to the HCOOH/Et₃N solvent system leads to a further increase of the enantioselectivity (94-96 % *ee*) and to almost quantitative conversions (see entries 1-4 of Table 2).¹¹ 1-Acetylnaphthalene (**8**) behaves as expected in the same way and furnishes the alcohol **9** in 96 % *ee* (see entry 5 of Table 2). Interestingly, the sterically hindered isopropylphenylketone **12** is reduced in 23 % *ee* using the *i*-PrOH/KOH system, whereas an enantioselectivity of 67 % *ee* is obtained with the HCOOH/Et₃N system.

In summary, we have reported two new classes of highly active transfer hydrogenation catalysts derived from C₂-symmetrical diaminoferrocene derivatives or readily available 2-(sulfonamido)cyclohexanes. Extension of this work is currently underway.

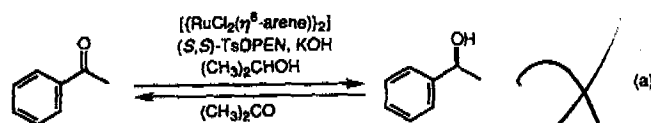
Acknowledgment: We thank the DFG (SFB 260), Fonds der Chemischen Industrie, BASF AG, Witco AG, Chemetall, Sipsy, Bayer AG and Chiroscience for generous financial support and gift of chemicals.

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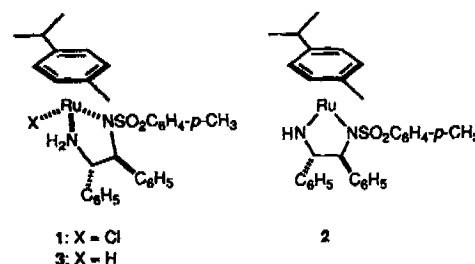
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- (8) **3a**: ¹H NMR (CDCl₃, 300 MHz): δ 7.30-7.15 (m, 10H), 4.33-4.30 (m, 2H), 4.28 (s, 2H), 4.08-4.05 (m, 4H), 4.00-3.99 (m, 2H), 2.36 (s, 6H), 2.0 (s, br, 2H). [α]_D²⁵ +56 (c 0.55, CHCl₃). **3b**: [α]_D²⁵ -34 (c 2.00, CHCl₃). **3c**: [α]_D²⁵ -5 (c 2.33, CHCl₃). **3d**: [α]_D²⁵ -6 (c 1.73, CHCl₃). **3e**: [α]_D²⁵ -98 (c 0.71, CHCl₃). **3f**: [α]_D²⁵ +30 (c 2.39, CHCl₃). **3g**: [α]_D²⁵ -32 (c 2.52, CHCl₃).
- (9) The experiments were carried out according to Noyori's procedure (ref. 2 h) using a 0.05 M solution of the ketone.
- (10) Compounds **4a-d** were isolated as hydrochlorides. **4a**: [α]_D²⁵ +57 (c 3.50, MeOH). **4b**: [α]_D²⁵ +54 (c 0.98, MeOH). **4c**: [α]_D²⁵ +31 (c 1.26, MeOH). **4d**: [α]_D²⁵ +164 (c 0.98, MeOH).
- (11) A mixture of [Ru(*p*-cymene)Cl₂]₂ (4.5 mg, 7.3 μmol) and **4a** (7.9 mg, 29 μmol) was heated in MeOH at 80 °C for 30 min under an argon atmosphere. After the solvent had been removed, **6** (0.17 mL, 1.5 mmol) and HCOOH/Et₃N (5:2) (0.73 mL) were added and the mixture stirred at 30 °C for 24 h.

(Received in Germany 30 August 1996; accepted 17 September 1996)

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- [10] The formation of a chromacyclobutane followed by rearrangement to a η^3 -complex and reductive elimination was postulated.
- [11] For considerations of α,β -unsaturated carbene complexes as chromabutadiene derivatives see: R. Aumann, P. Hinterding, *Chem. Ber.* **1990**, *123*, 2047–2051; R. Aumann, H. Heinen, P. Hinterding, N. Sträter, B. Krebs, *ibid.* **1991**, *124*, 1229–1236.
- [12] As for all Diels–Alder reactions of two 1,3-dienes, an exchange of diene and dienophile in our example also leads to identical products if the [4 + 2] cycloaddition is followed by a [3,3] sigmatropic rearrangement. We see no reason to discuss this more complicated alternative for our case.
- [13] Postulated Diels–Alder reactions of metalladienes: with palladium: B. M. Trost, A. S. K. Hashmi, *J. Am. Chem. Soc.* **1994**, *116*, 2183–2184; with rhodium: J. Schnaubelt, E. Marks, H.-U. Reissig, *Chem. Ber.* **1996**, *129*, 73–75.
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molecular structures of a preformed catalyst precursor **1**, the true catalyst **2**, and the reactive intermediate **3** for this asymmetric transfer hydrogenation using 2-propanol. The functions of the added KOH and the NH moiety in the TsDPEN auxiliary



have also been clarified. Here we describe a very rare catalytic system in asymmetric transformations for which both the true catalyst and the reactive species have been isolated in a pure state.^[4] The success can be attributed to the reversible reactions with different but comparable energy profiles.

First, the catalyst precursor **1** was prepared as orange crystals in >90% yield by reacting $[(RuCl_2(\eta^6\text{-p-cymene}))_2]$, (*S,S*)-TsDPEN, and KOH (Ru:diamine:KOH = 1:1:1 molar ratio in CH_2Cl_2 at room temperature) or, more effectively, triethylamine (Ru:diamine:NEt₃ = 1:1:2 in 2-propanol at 80 °C). The single-crystal X-ray analysis illustrated in Figure 1 indicates

The Catalyst Precursor, Catalyst, and Intermediate in the Ru^{II}-Promoted Asymmetric Hydrogen Transfer between Alcohols and Ketones**

Karl-Josef Haack, Shohei Hashiguchi, Akio Fujii, Takao Ikariya, and Ryoji Noyori*

Well-designed chiral Ru^{II}-arene complexes catalyze the asymmetric transfer hydrogenation of ketones or imines with stable organic hydrogen donors such as 2-propanol^[1,2] and formic acid.^[3] In these reactions certain derivatives of 1,2-diamines and β -amino alcohols can serve as excellent chiral modifiers and lead to high reactivity and enantioselectivity. For example, when a 0.1 M solution of acetophenone in 2-propanol containing $[(RuCl_2(\eta^6\text{-arene}))_2]$, (1*S*,2*S*)-*N*-*p*-toluenesulfonyl-2-diphenylethylenediamine ((*S,S*)-TsDPEN), and KOH (ketone:Ru:diamine:KOH = 200:1:1:2 molar ratio) was allowed to stand at 28 °C for 10 h, (*S*)-1-phenylethanol was obtained in up to 97% ee and in 98% yield [Eq. (a)].^[1a] We here disclose the

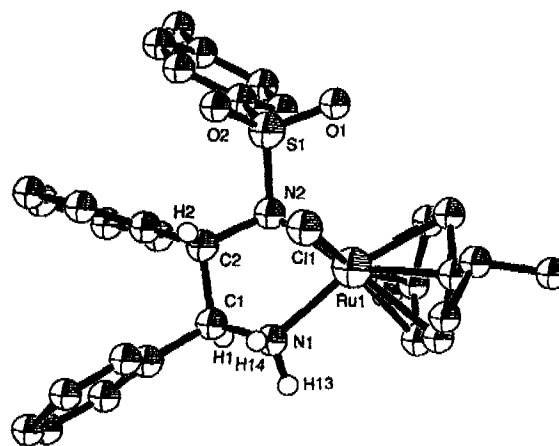


Figure 1. Molecular structure of **1** in the crystal. All hydrogen atoms except for the proton of the amine ligand and those at the carbon atoms in the chelate backbone and one crystal water molecule have been omitted for the sake of clarity. Selected distances [Å] and angles [°]: Ru–Cl 2.435(4), Ru–N1 2.117(9), Ru–N2 2.144(8), RuCl $\cdots$ HN 2.57; N1–Ru–N2 79.4(3), Ru–N1–C1 112.8(7), Ru–N2–C2 111.6(6).

that this 18-electron Ru^{II} complex has a distorted octahedral coordination environment with η^6 -arene, amino, sulfonamido, and chloro ligands.^[3] The chirality of (*S,S*)-TsDPEN forming a δ -configured five-membered ring determines the (*R*) configuration at the Ru center.^[6] Noteworthy is the very short Cl $\cdots$ HN distance of 2.57 Å (expected van der Waals separation, 3.0 Å), which is ascribed to an intramolecular hydrogen bond.^[7] The ¹H NMR spectrum confirmed that **1** exists as a single diastereomer in $CDCl_3$ solution.

The Ru complex **1**, which catalyzes the asymmetric transfer hydrogenation of acetophenone in 2-propanol containing

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[**] The authors are grateful to Professor Masashi Yamakawa of Kinjo Gakuin University, Dr. Philip Jessop, and Kazuhiko Matsumura for valuable discussions. Thanks are also due to Miesko Kunieda of the Research Development Corporation of Japan for skillful analytical assistance.

KOH, is merely a catalyst precursor. This complex has acidic NH_2 protons as confirmed by rapid H/D exchange with CH_3OD . Complex 1 undergoes facile elimination of HCl probably by a D_{el} mechanism^[8] on treatment with one equivalent of KOH in a CH_2Cl_2 – water two-phase system at room temperature to afford the true catalyst 2 as deep purple crystals in 87% yield. This complex reverts back to 1 upon reaction with triethylammonium chloride. The X-ray crystallographic analysis (Figure 2) reveals that 2 is a monomeric, formally 16-electron neu-

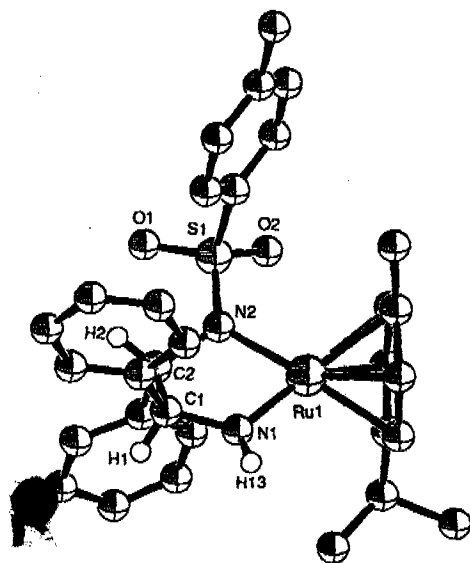
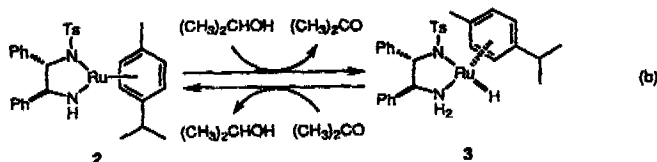


Figure 2. Molecular structure of 2 in the crystal. All hydrogen atoms except for the proton of the amide ligand and those at the carbon atoms in the chelate backbone have been omitted for the sake of clarity. Selected distances [Å] and angles [°]: Ru–N1 1.897(6), Ru–N2 2.065(6), N1–H13 0.88(6); N1–Ru–N2 78.9(2), Ru–N1–C1 121.2(5), Ru–N2–C2 114.9(4).

tral Ru^{II} complex with a square-planar geometry;^[5,9] the metal center is coordinated to two anionic nitrogen atoms and to *p*-cymene, which acts as a bis(three-electron) donor (neutral formalism). The basic skeleton (substituents on the nitrogens and arene neglected) has a mirror plane and the face of the arene ligand is perpendicular to the N1–Ru–N2 plane. Both N1 and N2 have planar geometry. Most notably, the N1–Ru bond (1.897 Å) is shorter than the N–Ru single bond in a Ru^{II} -anilide (2.01–2.16 Å)^[10] but longer than the distance in a Ru^{II} -imide complex (1.75 Å) for which an N–Ru triple bond may be assumed.^[11] This finding implies significant double bond character for the N1–Ru bond in 2.^[12] The N2–Ru bond in 2 (2.065 Å) is shorter than that in 1 (2.144 Å) but substantially longer than the N1–Ru bond in 2 owing to the electronegative tosyl substituent.

Because of the unique nature of the Ru–N1 bond, 2 shows distinct dehydrogenative activity for methanol, ethanol, and 2-propanol. For instance, when the purple complex 2 was treated with 2-propanol at room temperature in the absence of base, rapid elimination of acetone took place to produce the yellow ruthenium hydride species 3, which gives rise to a ^1H NMR signal at $\delta = -5.47$ in $[\text{D}_8]\text{toluene}$ [Eq. (b)]. The kinetically



controlled reaction was highly stereoselective giving the (*R*)-configured, octahedral Ru^{II} complex,^[6] whereas its diastereomer was formed in <1% yield according to ^1H NMR spectroscopy. The major stereoisomer 3 was isolated as the hydrate in 70% yield as yellow needles by recrystallization from wet CH_3OH . When the purple complex 2 was mixed with *tert*-butyl alcohol neither the color nor the ^1H NMR spectrum changed. The Ru complex 3 was also obtained by reaction of 2 and molecular hydrogen in toluene at room temperature, but only at 80 atm. The single-crystal X-ray analysis indicates that this ruthenium hydride is structurally similar to the chloride complex 1 except for the orientation of the tosyl substituent (Figure 3).^[5] The distorted octahedral complex possesses a δ -configured, five-membered chelate ring (N1–Ru 2.110 Å,

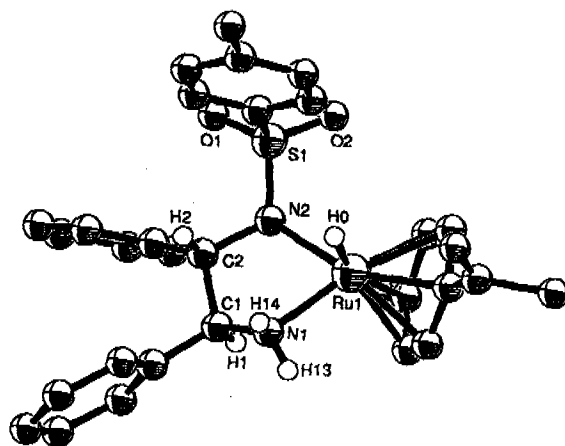


Figure 3. Molecular structure of 3 in the crystal. All hydrogen atoms except for the hydride at ruthenium, the two protons of the amine ligand, and those at the carbon atoms in the chelate backbone, as well as two water molecules in the lattice have been omitted for the sake of clarity. Selected distances [Å] and bond angles [°]: Ru–H0 1.40(1), Ru–N1 2.110(1), Ru–N2 2.139(9), N1–H13 0.90(1), N1–H14 0.7(1), RuH0...H14N1 2.29; N1–Ru–N2 78.3(4), Ru–N1–C1 108.7(7), Ru–N2–C2 113.0(7).

N2–Ru 2.139 Å), an η^6 -arene ligand, and a hydrido ligand (Ru–H 1.40 Å). The distance between H0 on Ru and H14 on N1 is short (2.29 Å; van der Waals separation 2.4 Å), indicating a possible hydrogen bonding interaction.^[13] One water molecule is hydrogen bonded to H14 on N1, while the second water molecule within the lattice is disordered. Treatment of 3 with a tenfold excess of acetone led instantaneously to the 16-electron species 2 and 2-propanol [Eq. (b)].

The purple complex 2 indeed catalyzes the asymmetric reduction of acetophenone in 2-propanol without KOH to afford (*S*)-1-phenylethanol in up to 95% *ee*. The yellow hydride 3 behaves in the same manner under catalytic conditions. The catalytic activity and stereoselectivity are identical to those observed with the complex formed in situ.^[14] Thus, under the conditions of Equation (a), KOH is necessary only for the generation of the catalyst 2 via the precursor 1. The isolation of 3 confirms that the Ru-catalyzed transfer hydrogenation takes place by way of a metal hydride rather than the metal alkoxides presumed for the Meerwein–Ponndorf–Verley type reaction.^[14] The extent of the enantioselectivity in the acetophenone reduction is independent of the bulkiness or chirality of the hydrogen donors. Methanol, ethanol, 2-propanol, and (*R,S*)-, (*R*)-, and (*S*)-2-butanol all gave (*S*)-1-phenylethanol in the same enantiomeric purity, $95 \pm 0.5\%$ *ee*, indicating that 3 is the common intermediate. Reduction of acetophenone with $(\text{CH}_3)_2\text{CDOH}$ (0.996 D at C2) catalyzed by 2 gave (*S*)- $\text{C}_6\text{H}_5\text{CD}(\text{OH})\text{CH}_3$ (0.936 D at

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C1) in 95% ee as expected. Experiments using mixtures of $(\text{CH}_3)_2\text{CHOH}$ and $(\text{CH}_3)_2\text{CDOH}$ revealed a k_H/k_D value of 1.5 ± 0.1 (^1H NMR and GCMS). Because of microscopic reversibility, the (S,S)-TsDPEN-based complex **2** dehydrogenates (S)-1-phenylethanol in acetone more readily than the (R) enantiomer, allowing efficient kinetic resolution of the racemate.^[2] Notably, the reductive formation of **3** from **2** is consistently diastereoselective, regardless of the structure of the hydrogen-donating alcohol.

Preliminary kinetic investigations proved the isolated complexes **2** and **3** to be the true catalyst and intermediate, respectively, in the hydrogen transfer reaction following Equation (b). The reaction of $(\text{CD}_3)_2\text{CO}$ with $(\text{CH}_3)_2\text{CHOH}$ (0.37 to 1.9 M) and **2** (0.45×10^{-2} to 4.0×10^{-2} M) at 23 °C was monitored by following the disappearance of the methyl resonance of $(\text{CH}_3)_2\text{CHOH}$ in the ^1H NMR spectra. We found that the rate of acetone reduction is first order in $[(\text{CH}_3)_2\text{CHOH}]$ and first order in **2**. By reversing the deuteration of the acetone dependence could be measured. The reduction of $(\text{CH}_3)_2\text{CO}$ with $(\text{CD}_3)_2\text{CHOH}$ catalyzed by **3** (or **2**) was found to be zero order in $[(\text{CH}_3)_2\text{CO}]$ (saturation kinetics) at high concentration (> 0.4 M), thus, $-d[2\text{-propanol}]/dt = k[2][2\text{-propanol}]$, where $k = 2.5 \times 10^{-3} \text{ M}^{-1} \text{ s}^{-1}$, whereas at low concentrations of acetone (0.19 to 0.39 M) the rate is first order with respect to $[(\text{CH}_3)_2\text{CO}]$. These results demonstrate that the reaction of **2** with 2-propanol is the turnover-limiting step in the steady-state hydrogen transfer [Eq. (b)] and that the reverse reaction of **3** with acetone is more facile.

In summary, the Ru-catalyzed hydrogen transfer between alcohols and ketones occurs reversibly and is promoted by the bifunctional metal/ligand catalysts **2** and **3** possibly via a six-membered cyclic transition state.^[1d] The interconversion between these 16- and 18-electron Ru complexes takes place by the action of an alcohol or ketone either directly or via a very short-lived intermediate. No other complexes that limit the rates are involved.

Experimental Section

All operations were conducted under an atmosphere of dry argon and standard Schlenk-type glassware was used.

1: A mixture of $[\{\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})\}_2]$ [**15**] (1.53 g, 2.5 mmol), (S,S)-TsDPEN [**16**] (1.83 g, 5.0 mmol), and triethylamine (1.4 mL, 10 mmol) in 2-propanol was heated at 80 °C for 1 h. The orange solution was concentrated and the resulting solid was collected by filtration. The crude compound was washed with a small amount of water and dried under reduced pressure to give complex **1**. Yield 2.99 g (94%). Recrystallization from 99% methanol afforded orange crystals. Decomp > 100 °C; IR (KBr): $\tilde{\nu} [\text{cm}^{-1}]$: 3272, 3219, 3142 (H–N), 3063, 3030 (H–C_{arom}), 2963, 2874 (H–C_{alk}); ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 1.32, 1.34 (each d, $^3J(\text{H,H})$ = 7 Hz, 3H; $\text{CH}(\text{CH}_3)_2$), 2.19 (s, 3H; CH_3 in *p*-cymene), 2.28 (s, 3H; CH_3 in *p*-Ts), 3.07 (m, 1H; $\text{CH}(\text{CH}_3)_2$), 3.26 (m, 1H; NHH), 3.54 (m, 1H; HCNH), 3.66 (d, $^3J(\text{H,H})$ = 11 Hz, 1H; $\text{HCN-}p\text{-Ts}$), 5.68, 5.70, 5.72, 5.86 (each d, 1H; CH_{arom} in *p*-cymene), 6.61 (m, 1H; NHH), 6.29–7.02 (14H; *p*- $\text{CH}_3\text{C}_6\text{H}_4\text{-SO}_2\text{NCH}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_6\text{H}_5)\text{NH}_2$). Anal. calcd. for $\text{C}_{31}\text{H}_{35}\text{ClN}_2\text{O}_2\text{RuS}$: C 58.53, H 5.54, N 4.40, Cl 5.57, Ru 15.89; found: C 58.37, H 5.44, N 4.36, Cl 5.75, Ru 15.83.

2: A mixture of $[\{\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})\}_2]$ [**15**] (306.2 mg, 0.5 mmol), (S,S)-TsDPEN [**16**] (366.4 mg, 1.0 mmol), and KOH (400 mg, 7.1 mmol) in CH_2Cl_2 (7 mL) was stirred at room temperature for 5 min. On addition of water (7 mL) to the reaction mixture, the color changed from orange to deep purple. The purple organic layer was washed with water (7 mL), dried over CaH_2 , and concentrated to dryness to afford deep purple **2** (522 mg, 87% yield). The same complex was prepared by treatment of **1** with one equivalent of KOH in CH_2Cl_2 at room temperature. Decomp > 80 °C; IR (KBr): $\tilde{\nu} [\text{cm}^{-1}]$: 3289 (H–N), 3070, 3017 (H–C_{arom}), 2968, 2920, 2859 (H–C_{alk}); ^1H NMR (400 MHz, CDCl_3 , 25 °C, TMS): δ = 1.20, 1.25 (each d, $^3J(\text{H,H})$ = 7 Hz, 3H; $\text{CH}(\text{CH}_3)_2$), 2.05 (s, 3H; CH_3 in *p*-cymene), 2.22 (s, 3H; CH_3 in *p*-Ts), 2.53 (m, 1H; $\text{CH}(\text{CH}_3)_2$), 4.08 (d, 1H, $^3J(\text{H,H})$ = 4.4 Hz, HCNH), 4.89 (s, 1H; $\text{HCN-}p\text{-Ts}$), 5.11, 5.27, 5.28, 5.39 (each d, $^3J(\text{H,H})$ = 6 Hz, 1H; CH_{arom} in *p*-cymene), 6.64 (br. d, 1H; NH), 6.87, 7.67 (each d, $^3J(\text{H,H})$ = 8 Hz, 2H; CH_{arom} in *p*-Ts), 7.2–7.7 (m, 10H; *p*- $\text{TsNCH}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_6\text{H}_5)\text{NH}_2$). Anal. calcd. for

$\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2\text{RuS}$: C 62.09, H 5.71, N 4.67, Ru 16.85; found: C 62.06, H 5.77, N 4.66, Ru 16.47.

3: The purple complex **2** (600 mg, 1.0 mmol) was dissolved in 2-propanol (10 mL), and the resulting red solution was stirred at room temperature for 15 min. The solvent was then removed under reduced pressure at room temperature to give a brownish yellow compound, which was washed with cold pentane and recrystallized from methanol to provide orange needles (420 mg, 70% yield). Under vacuum at room temperature the needles turned brown. The same compound **3** was obtained by stirring a toluene solution of **2** (600 mg, 1.0 mmol) under 80 atm H_2 in an autoclave at room temperature for 18 h. Decomp > 60 °C; IR (KBr): $\tilde{\nu} [\text{cm}^{-1}]$: 3335, 3317, 3228, 3153 (H–N), 3060, 3025 (H–C_{arom}), 2960, 2917, 2867 (H–C_{alk}), 1911 (broad, H–Ru); ^1H NMR (400 MHz, D_2O , 25 °C, TMS): δ = –5.47 (s, 1H; RuH), 1.53, 1.59 (each d, $^3J(\text{H,H})$ = 6 Hz, 3H; $\text{CH}(\text{CH}_3)_2$), 2.29 (s, 3H; CH_3 in *p*-cymene), 2.45 (s, 3H; CH_3 in *p*-Ts), 2.79 (m, 1H; NHH), 2.93 (m, 1H; $\text{CH}(\text{CH}_3)_2$), 3.80 (d, $^3J(\text{H,H})$ = 8 Hz, 1H; $\text{HCN-}p\text{-Ts}$), 4.02 (m, 1H; HCNH), 5.15, 5.19, 5.43, 5.58 (each d, $^3J(\text{H,H})$ = 6 Hz, 1H; CH_{arom} in *p*-cymene), 5.29 (m, 1H; NHH), 6.49, 7.59 (each d, $^3J(\text{H,H})$ = 8 Hz, 2H; CH_{arom} in *p*-Ts), 6.9–7.3 (m, 10H; *p*- $\text{TsNCH}(\text{C}_6\text{H}_5)\text{CH}(\text{C}_6\text{H}_5)\text{NH}_2$). Anal. calcd. for $\text{C}_{31}\text{H}_{34}\text{N}_2\text{O}_2\text{RuS}$: C 61.88, H 5.62, N 4.66, Ru 16.80; found: C 61.79, H 5.94, N 4.70, Ru 16.56.

Kinetic study: The reaction was initiated by adding 2-propanol to a mixture of acetone and **2** at 23 °C. The total volume was maintained at 0.7 mL. When a small amount of acetone was employed, 2-min sonication was necessary to dissolve **2**. The reaction was monitored at 5-min intervals by measuring the integrals of the methyl proton signals in the ^1H NMR spectrum [δ = 1.06 (2-propanol) and 2.04 (acetone)].

The reaction of $(\text{CD}_3)_2\text{CO}$ and 2-propanol (0.37–1.9 M) with **2** (2.3×10^{-2} M) was monitored over a period of 60 min with 2-propanol conversion in the range of 11 to 20%. The plot of $\lg(\text{initial rate})$ versus $\lg[2\text{-propanol}]_0$ showed a linear dependence, giving $n = 1.2$ (assumed to be 1, within experimental error). Thus, $-d[2\text{-propanol}]/dt = k_{\text{obsd}}[2\text{-propanol}]$, where $k_{\text{obsd}} = 5.4 \times 10^{-5} \text{ s}^{-1}$ at 23 °C. The reaction of $(\text{CD}_3)_2\text{CO}$ and 2-propanol (1.87 M) with **2** (0.45×10^{-2} to 4.0×10^{-2} M) was monitored over a period of 60 min with 2-propanol conversion in the range of 6.7 to 28%. The plot of $\lg(\text{initial rate})$ versus $\lg[2]_0$ gave $n = 0.8$ (assumed to be 1, within experimental error). Thus, $-d[2\text{-propanol}]/dt = k_{\text{obsd}}[2]$, where $k_{\text{obsd}} = 4.7 \times 10^{-3} \text{ s}^{-1}$ at 23 °C.

The reaction of acetone (0.19–0.39 M) with **2** (1.3×10^{-2} M) in $(\text{CD}_3)_2\text{CHOH}$ was monitored over a period of 5 min with 2-propanol conversions of up to 40%. The plot of $\lg(\text{initial rate})$ versus $\lg[\text{acetone}]_0$ gave $n = 1.0$. Thus, $-d[\text{acetone}]/dt = k_{\text{obsd}}[\text{acetone}]$, where $k_{\text{obsd}} = 1.4 \times 10^{-3} \text{ s}^{-1}$ at 23 °C. The initial rate became zero order for acetone concentration > 0.4 M. Thus, $-d[\text{acetone}]/dt = k_{\text{obsd}}$, where $k_{\text{obsd}} = 7.8 \times 10^{-4} \text{ M s}^{-1}$.

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- 243 K. 4282 Reflections were independent and unique, and 2162 with $I > 3.00 \sigma(I)$ ($2\theta_{\max} = 55^\circ$) were used for the structure solution. The hydrogen atoms at Ni and at Ru could be localized and were refined isotropically, and the remaining hydrogen atoms were calculated from ideal geometries, fixed, and included in the calculation of the structural factor. $R = 0.050$, $R_w = 0.067$, $w = (\sigma^2(F) + 0.0025 F^2)^{-1}$. Rigaku AFC7R diffractometer (graphite monochromator, $\text{MoK}\alpha$). The structures were solved with PATTY and DIRDIF94 [5b]. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-149. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code + (1223) 336-033; e-mail: deposit@chemcrs.cam.ac.uk), on quoting the full journal citation; P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel, J. M. M. Smits, C. Smykalla, *The DIRDIF Program System, Technical Report of the Crystallographic Laboratory, University of Nijmegen, The Netherlands*, 1994.
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Kinetic Resolution of Racemic Secondary Alcohols by Ru^{II} -Catalyzed Hydrogen Transfer**

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The recent discovery of highly reactive, chiral metal complexes led to rapid advances in catalytic asymmetric transfer hydrogenation.^[1–7] Chiral diamine-based Ru^{II} complexes are particularly efficient catalysts for the enantioselective reduction of prochiral ketones under mild conditions using 2-propanol as

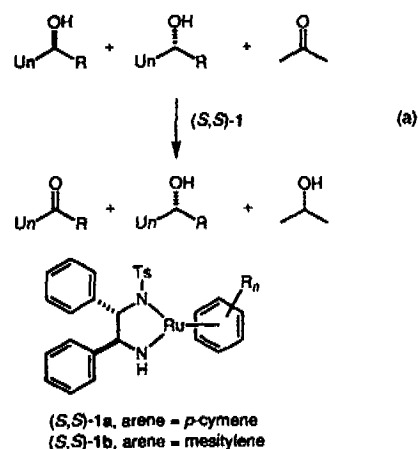
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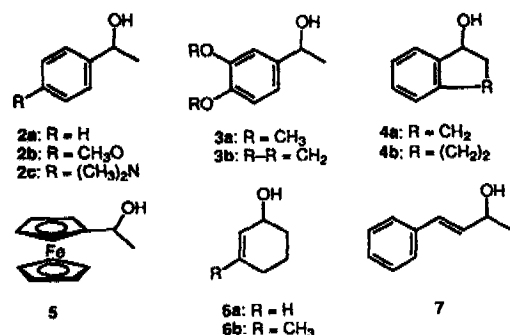
a hydrogen source.^[1,3,4] Since this asymmetric reaction is reversible, the efficiency is highly dependent on the redox properties of the alcohols formed^[8] in addition to the chiral recognition capabilities of the catalyst. Therefore, high enantioselectivity is not possible in the preparation of alcohols having a high reduction potential such as 2,3-benzo-2-cyclohexenols and 1-phenylethanols with an electron-donating group on the aromatic ring.^[1] Although this is the greatest flaw of this otherwise attractive asymmetric catalysis, the same tendency provides an opportunity for kinetic resolution of such secondary alcohols. However, this is possible only with a suitable catalyst and under suitable reaction conditions. Here, we report on an example of the direct resolution, without derivatization,^[9] of simple racemic alcohols by a purely chemical method,^[5c, 10–12] which is a useful complement to the asymmetric reduction of achiral ketones.^[1–7]

Excellent kinetic differentiation of enantiomeric alcohols is achieved with the novel purple-colored Ru^{II} complexes (*S,S*)-1 (Ts = *p*-toluenesulfonyl, see Scheme 1).^[3] The kinetic resolu-



Scheme 1. Un = unsaturated group.

tion in acetone occurs with the general sense of Equation (a). Thus, when a 2 M solution of racemic 1-phenylethanol (2a) in acetone containing (*S,S*)-1b (substrate/catalyst molar ratio (S/C) = 500) was left at 28 °C for 30 h, a 97:3 mixture of (*R*)- and (*S*)-2a (94% ee) was recovered in 51% yield in addition to the



acetophenone product in 49% yield. The use of (*S,S*)-1, which has a unique 16-electron configuration, is a key reason for the success when the reaction is conducted under nearly neutral conditions. Although treatment of the HCl adduct of 1, which has an 18-electron configuration,^[2] with KOH generates the catalytically active species (*S,S*)-1 in situ,^[1a, 2, 3] excess base