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Catalytic asymmetric hydrogenation of β-ketoesters using new BINAP complexes of ruthenium

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Abstract

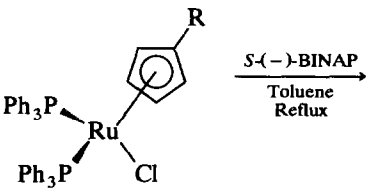
Two new, air-stable BINAP complexes of ruthenium(II), (RCp)Ru(*S*-(−)-BINAP)Cl (R = H, CH_3) have been prepared in good yield from the reaction of (RCp)Ru(PPh_3)$_2$Cl with *S*-(−)-BINAP in refluxing toluene. The structure of the methylcyclopentadienyl analog has been determined by X-ray crystallography. Both complexes have been found to be effective homogeneous catalysts for the enantioselective hydrogenation of β-ketoesters.

1. Introduction

In recent years the development of chiral ruthenium-BINAP catalysts for the asymmetric hydrogenation of functionalized ketones has sparked tremendous interest. The success of these catalysts derives from the chiral diphosphine ligand BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), which appears uniquely suited for imparting high activity and selectivity to a variety of catalytic reductions. To date relatively few ruthenium catalysts (or catalyst precursors) containing the BINAP ligand have been synthesized. These include (BINAP)Ru(O_2CR)$_2$ [1], [(BINAP)RuCl_2]$_2$ · Et_3N [2], (arene)Ru(BINAP)X_2 [3] and (BINAP)$_2$-RuHCl [4]. In this communication we describe the synthesis and reactivity of two new ruthenium(II) BINAP complexes, (RCp)Ru(BINAP)Cl (R = H or CH_3), which are effective catalysts for the asymmetric hydrogenation of β-ketoesters in high enantiomeric yields.

2. Results and discussion

Reaction of *S*-(−)-BINAP with (RCp)Ru(PPh_3)$_2$Cl, **1**, (R = H or CH_3) in refluxing toluene gave the expected chiral products (RCp)Ru(*S*-(−)-BINAP)Cl, **2**, in good yields (eqn. (1)) [5*]. (The analogous *S,S*-(+)-DIOP complex, (MeCp)Ru(*S,S*-(+)-DIOP)Cl, **3**, was obtained similarly in 90% yield.) Recrystallization from acetone/CH_2Cl_2 afforded air-stable solids which were characterized by elemental analysis and ^1H, ^{13}C, and ^{31}P NMR spectroscopy [6*]. Although complex **2a** was isolated as an acetone solvate, the more sterically crowded methylcyclopentadienyl (MeCp) analog, **2b**, was not. The dissymmetry of the molecules was best exemplified in the ^{31}P NMR spectra which showed



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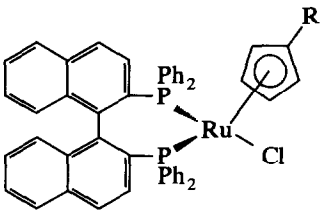

(1)

2a, (R = H), 72%
2b, (R = CH_3), 73%

characteristic doublets for each of the diastereotopic phosphorus atoms of the chiral BINAP ligand. Re-

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* References with asterisk indicate a note in the list of references.

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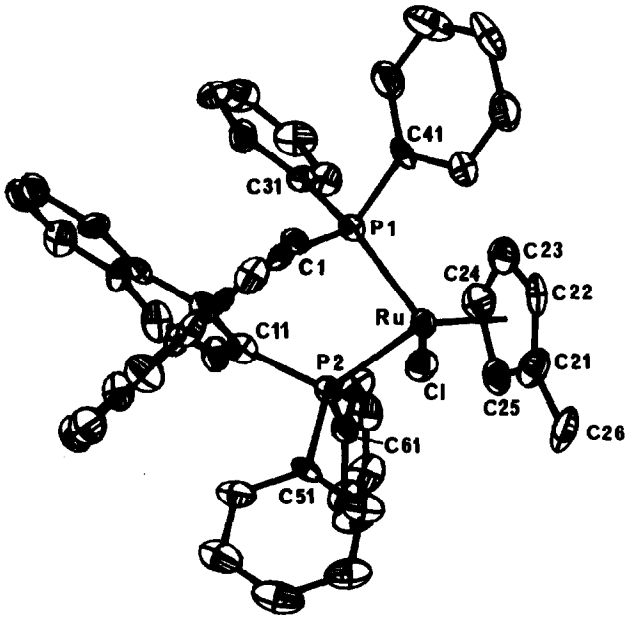

Fig. 1. ORTEP diagram of **2b** showing the 30% probability thermal ellipsoids and the atom labelling scheme. Hydrogen atoms have been omitted. Selected bond lengths (in Å) are: Ru–Cl = 2.437(3), Ru–P1 = 2.292(3), and Ru–P2 = 2.304(3); Selected bond angles (in °) are: P1–Ru–P2 = 91.6(1), P1–Ru–Cl = 87.8(1), and P2–Ru–Cl = 94.4(1).

moval of the chloride in **2a** via reaction with one equivalent of $AgPF_6$ in CH_2Cl_2 gave the corresponding cationic complex, [(Cp)Ru(*S*-(−)-BINAP)] [PF_6], **4**, in 92% yield. Analytical and spectroscopic data was consistent with loss of chloride and retention of the organic ligands [7*].

The structure of **2b** has been confirmed by X-ray crystallography (Fig. 1) [8*]. Overall, the ruthenium atom has a distorted octahedral geometry defined by chloride, the two phosphorus atoms of BINAP, and the tridentate methylcyclopentadienyl ligand. The Ru–P bond distances (2.292(3) and 2.304(3) Å) are nearly identical and fall within the range reported for related ruthenium-phosphine complexes (2.20–2.45 Å) [1a,9]. Likewise, the P1–Ru–P2 angle of 91.6(1)° which defines the bite of the BINAP ligand is within the range reported for related Ru–BINAP complexes (86.3–93.2°) [1a,3a,4a,9]. The dissymmetric *S*-(−)-BINAP ligand coordinates to ruthenium and forms a skewed, seven membered chelate ring which is fixed in the δ conformation. This causes orientation of the four phenyl substituents on the two phosphorus atoms to be arranged in an alternating edge-face manner [4a,10]. The dihedral angle of 78.0° between the two planes defined by the naphthalene rings is also similar to that found in related ruthenium BINAP complexes [1a,3a,4a,9]. While the methyl–Cp ligand was found to be planar (mean deviation of 0.015°), the geometry of the five membered ring was found to contain one long (C22–C23 = 1.54(2) Å) and one short (C23–C24 = 1.37(2) Å) bond length. Careful examination of the electron density map in the region containing the MeCp ring showed diffuse electron density (~ 1.2 e $Å^{-3}$) between atoms C23 and C24 and no obvious ring disorder. The anomalous electron density in this region was found to contract the C23–C24 bond length in the unrestricted refinement of atoms in the ring.

Complexes **2a** and **2b** have been found to catalyze the enantioselective reduction of β-ketoesters in good enantiomeric yields (Table 1). Catalytic hydrogenation using 7 ml (~ 60 mmol) of β-ketoester were accomplished in the presence of 0.11–0.18 mol% of the chiral ruthenium complex at 1000 psi H_2 in a 100 ml stainless steel autoclave. Aqueous (3.5%) methanol or ethanol was used as the reaction solvent, the choice depending on the particular ester substituent (methyl or ethyl, respectively) of the substrate. Use of the aqueous solvent eliminated alcoholysis of the substrate [3a] and control experiments using methyl acetoacetate as substrate and **2b** as catalyst showed that ee was unchanged when either methanol or 3% aqueous methanol was used. Elevated temperatures (≥ 60°C) were normally required to achieve reduction at an acceptable rate. Product yields were determined by gas chromatography. Alcohols were isolated by distillation, and enantiomeric purity was determined by polarimetry and/or ^1H NMR spectroscopy using the chiral shift reagent tris(heptafluoropropylcamphorato)europium-(III), Eu-$(hfc)_3$.

Initially, methyl acetoacetate (MAA) was used as the substrate to investigate the effect of catalyst, tem-

TABLE 1. Enantioselective hydrogenation results for β-ketoesters [a]

Substrate	Catalyst	Temp. (°C)	Time (h)	Yield (%)	ee (%)
MAA [b]	**2b**	100	4.5	≥ 99	78
MAA	**2a**	100	18	≥ 99	76
MAA	**2b**	60	40	≥ 99	76
MAA	**2a**	60	90	≥ 99	94
MAA [c]	**2b**	100	16	≥ 99	62
MAA	**4**	100	16	≥ 99	0
MAA [d]	**4**	100	24	≥ 99	8
EAA [e,f]	**2b**	100	18	≥ 99	58
EAA [f]	**2b**	60	63	≥ 99	91
EDMAA [g,f]	**2b**	60	96	≥ 99	80
MTMAA [h]	**2b**	100	22	≥ 99	15
MAA	**3**	100	37	≥ 99	3

[a] Unless otherwise specified, all reactions were accomplished at 1000 psi H_2 using 97% aqueous methanol and 0.11–0.18 mole% catalyst. [b] MAA = methyl acetoacetate. [c] 400 psi H_2. [d] Methanol only. [e] EAA = ethyl acetoacetate. [f] 97% aqueous ethanol. [g] EDMAA = ethyldimethyl acetoacetate. [h] MTMAA = methyltrimethyl acetoacetate.

perature, and pressure on hydrogenation. At 100°C both (Cp)Ru(*S*-(−)-BINAP)Cl, **2a**, and (MeCp)Ru(*S*-(−)-BINAP)Cl, **2b**, gave (+)-methyl 3-hydroxybutyrate ((+)-MHB) in ≥ 99% yield and ~ 77% ee. The reaction time using **2a** was considerably longer than for **2b**, and an induction period of approximately two hours was also observed for this slower reaction. Although ee (76%) and yield (≥ 99%) were unchanged at 60°C using **2b**, ee improved to 94% using **2a**. (Others have observed similar substrate specific variations in ee with temperature as well [11].) Again, the reaction time using **2a** (90 h) was considerably longer than using **2b** (40 h), and induction periods of several hours were observed in both reactions. For **2b**, lowering the reaction pressure from 1000 to 400 psi (reaction temperature of 100°C) reduced ee to 62%. This is an unusual result since enantiomeric yields in asymmetric hydrogenation of ketones are typically unaffected by pressure [11]. When (Cp)Ru(S,S-(+)-DIOP)Cl, **3**, was used as the catalyst, (−)-MHB was obtained in ≥ 99% yield but only 3% ee. Consistent with other published work, this clearly illustrates the unique ability of the BINAP ligand to direct high enantioselectivity in catalytic hydrogenations [1–4].

Unexpectedly, when the cationic complex [(Cp)Ru(*S*-(−)-BINAP)] [PF_6], **4**, was used as the catalyst, only racemic methyl 3-hydroxybutyrate was obtained (≥ 99% yield). If 100% methanol was used as the reaction solvent, enantioselectivity slightly improved (8%), but the configuration of the dominant enantiomer was opposite to that produced by **2a** or **2b**. These results suggest that the chloride ligand in the neutral catalysts (**2a** or **2b**) is essential for promoting a reaction mechanism which directs high enantioselectivity. Presumably, initial catalyst activation occurs by liberation of cyclopentadiene or methylcyclopentadiene with corresponding formation of a catalytic intermediate. Retention of the chloride ligand in this intermediate apparently provides the necessary molecular template to promote a reaction mechanism which generates product of high enantiomeric purity. In the absence of chloride this template is lost, hydrogenation of either face of the prochiral carbonyl group becomes equally facile, and racemic product is formed.

In comparison to other ruthenium–BINAP complexes [1–4], **2a** and **2b** are stable for months in air at room temperature. Presumably, the source of this stability is the strongly coordinated Cp and MeCp ligands. This stability, however, also appears to reduce catalytic efficiency as reflected in the higher temperatures (≥ 60°C) required for hydrogenation. The significant induction periods observed with the slower reactions of **2a** and **2b** are consistent with the cyclopentadienyl ligand being a poor leaving group and catalyst activation being a slow step. In addition, we have found that catalyst activation in the absence of methyl acetoacetate followed by subsequent hydrogenation results in a significant improvement in reaction rate. After activation of **2a** at 100°C and 1000 psi H_2 for 24 h, MAA could be quantitatively hydrogenated (≥ 99% yield) in 24 h at 60°C. As described previously, without the separate catalyst activation step hydrogenation of MAA at 60°C with **2a** required 90 h for complete hydrogenation. Despite this improvement in rate, however, enantioselectivity was reduced from 94 to 82%.

In addition to methyl acetoacetate, several other β-ketoesters were subjected to catalytic hydrogenation using the neutral MeCp complex, **2b** (Table 1). Like the hydrogenation of MAA with **2a**, hydrogenation of ethyl acetoacetate (EAA) with **2b** was found to show a marked variation of enantioselectivity with reaction temperature. At 100°C and 1000 psi H_2, (+)-ethyl 3-hydroxybutyrate was produced in ≥ 99% yield and 58% ee. However, enantioselectivity increased to 91% when the temperature was decreased to 60°C. As mentioned previously, others have observed similar substrate specific variations of ee with temperature as well [11a]. At 60°C ethyldimethyl acetoacetate (EDMAA) could be hydrogenated to 3-hydroxy-4-methyl pentanoate in ≥ 99% yield and 80% ee. Although methyltrimethyl acetoacetate (MTMAA) was unreactive under these conditions, hydrogenation could be accomplished at 100°C. Conversion to 3-hydroxy-4,4-dimethyl pentanoate was quantitative, but enantioselectivity was only 15%. Ethyl 2-methylacetoacetate was likewise unreactive at 60°C. Although both possible diastereomers of ethyl 3-hydroxy-2-methyl butyrate were formed quantitatively at 120°C (diastereomeric ratio ~ 1.3 : 1), each was racemic. Clearly, enantioselectivity in the asymmetric hydrogenation of β-ketoesters using the new cyclopentadienyl–BINAP complexes of ruthenium is very sensitive to the structure of the specific β-ketoester substrate utilized. Further work aimed at investigating the scope of this new catalytic system is continuing.

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5 Compounds **2–3** were prepared according to the general metathetical procedure reported for achiral diphosphines [5a]. In a typical experiment, a 40 ml toluene solution containing 0.866 g (1.17 mmol) of $(MeCp)Ru(PPh_3)_2Cl$, **1b** [5b,5c] and 0.733 g (1.18 mmol) of *S*-(−)-BINAP was refluxed under argon for 6 d, cooled to room temperature, and then concentrated in vacuo to *ca.* 20 ml. Addition of 80 ml of hexane gave a yellow-orange precipitate which was filtered under argon (PPh_3 remained in solution) and dried *in vacuo*. Recrystallization from acetone/CH_2Cl_2 (3/2 v/v) gave 0.72 g (0.85 mmol, 73%) of (MeCp)Ru(*S*-(−)-BINAP)Cl, **2b**, as a red, air stable solid, mp (sealed capillary): > 260°C.

$(Cp)Ru(PPh_3)_2Cl$, **1a**, was more resistant to BINAP substitution. To ensure complete conversion, the crude hexane precipitate (containing unreacted BINAP and **1a**) was re-dissolved in 40 ml of toluene and refluxed a further 3 d. Concentration *in vacuo*, precipitation with hexane, and recrystallization from acetone/CH_2Cl_2 as described for **2b** gave (Cp)Ru(S-(−)-BINAP)Cl·acetone, **2a** (72%), as an air-stable, orange solid, mp (sealed capillary): > 200°C (slow dec.).

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6 For **2a**: ^{31}P NMR ($CDCl_3$, 80.98 MHz): δ 41.90 (d, J = 52.6 Hz), 53.66 (d, J = 53.4 Hz); ^1H NMR (CD_2Cl_2, 200 MHz): δ 2.12 (s, 6H, acetone), 4.21 (s, 5H, Cp), 6.2–8.0 (complex m, 32H, BINAP); ^{13}C {^1H} NMR ($CDCl_3$, 50.31 MHz): δ 82.12 (s, Cp), 124.8–134.8 (complex m, BINAP); Anal. Calcd. for $C_{52}H_{43}ClOP_2Ru$: C, 70.78; H, 4.91%. Found: C, 70.59; H, 4.98%.

For **2b**: ^{31}P NMR ($CDCl_3$, 80.98 MHz): δ 44.61 (d, J = 53.5 Hz), 54.22 (d, J = 53.4 Hz); ^1H NMR (CD_2Cl_2, 200 MHz): δ 1.75 (d, J = 2.1 Hz, 3H, Cp–CH_3), 3.65 & 4.15 (m, 4H, Cp–H), 6.2–8.0 (complex m, 32H, BINAP); ^{13}C {^1H} NMR (CD_2Cl_2, 50.31 MHz): δ 12.72 (s, Cp–CH_3), 74.00 (s, Cp–H), 78.70 (s, Cp–H), 81.16 (s, Cp–H), 84.80 (s, Cp–H), 105.60 (s, *ipso* Cp–H), 125.0–143.9 (complex m, BINAP); Anal. Calcd. for $C_{50}H_{39}ClP_2Ru$: C, 71.64; H, 4.69%. Found: C, 71.68; H, 4.54%.

For **3**: ^{31}P NMR ($CDCl_3$, 80.98 MHz): δ 35.70 (d, J = 42.9 Hz), 38.68 (d, J = 43.7 Hz); ^1H NMR (CD_2Cl_2, 200 MHz): δ 1.20 (s, 3H, DIOP CH_3), 1.24 (s, 3H, DIOP CH_3), 1.73 (d, J = 1.1 Hz, 3H, Cp–CH_3), 2.2 (m, 1H, DIOP CH_2), 2.7 (m, 1H, Cp–H), 2.8 (m, 1H, DIOP CH_2), 3.1 (m, 1H, DIOP CH_2), 3.1 (m, 1H, Cp–H), 3.6 (m, 2H, DIOP CH&CH_2), 3.8 (broad s, 1H, Cp–H), 4.3 (m, 1H, DIOP CH), 4.6 (broad s, 1H, Cp–H), 6.9–8.1 (complex m, 20H, Ph); ^{13}C {^1H} NMR ($CDCl_3$, 50.31 MHz): δ 12.15 (s, Cp–CH_3), 26.87 (s, DIOP CH_3), 27.18 (s, DIOP CH_3), 27.68 (d, J = 21.7 Hz, DIOP CH_2), 33.21 (d, J = 23.7 Hz, DIOP CH_2), 73.33 (s, Cp–CH), 74.49 (s, Cp–CH), 74.76 (s, Cp–CH), 77.98 (s, Cp–CH), 79.46 (d, J = 8.8 Hz, DIOP CH), 79.93 (d, J = 9.2 Hz, DIOP CH), 108.00 (s, *ispo* Cp), 108.62 (s, DIOP $C(CH_3)_2$), 127.7–135.4 (complex m, Ph), 133.91 (d, J = 38.9 Hz, *ipso* Ph), 142.55 (d, J = 44.4 Hz, *ipso* Ph), 144.45 (d, J = 46.2 Hz, *ipso* Ph); Anal. Calcd. for $C_{37}H_{39}ClO_2P_2Ru$: C, 62.22; H, 5.50%. Found: C, 62.14; H, 5.60%; mp (sealed capillary): > 250°C.

7 To a 20 ml CH_2Cl_2 solution containing 0.75 g (0.91 mmol) of (Cp)Ru(*S*-(−)-BINAP)Cl, **2a**, was added dropwise by cannula under argon a 10 ml solution of CH_2Cl_2 containing 0.23 g (0.91 mmol) of $AgPF_6$. A white precipitate formed immediately. After stirring at room temperature for 20 h, the reaction mixture was filtered under argon through a thin pad of Celite. Removal of the solvent *in vacuo* gave 0.78 g (0.84 mmol, 92%) of [(Cp)Ru(*S*-(−)-BINAP)] [PF_6], **4**, as a bright yellow solid, mp (sealed capillary): > 250°C. ^{31}P NMR (CD_2Cl_2, 80.98 MHz): δ 14.65 (d, J = 43.7 Hz), 74.59 (d, J = 43.7 Hz); ^1H NMR (CD_2Cl_2, 200 MHz): δ 4.39 (s, 5H, Cp), 5.9–8.2 (complex m, 32H, BINAP); ^{13}C {^1H} NMR (CD_2Cl_2, 50.3 MHz) δ 88.23 (s, Cp), 125.9–136.5 (complex m, BINAP); Anal. Calcd. for $C_{49}H_{37}F_6P_3Ru$: C, 63.02; H, 3.99%. Found: C, 62.71; H, 4.24%.

8 Single crystal X-ray diffraction studies of **2b** were conducted on an Enraf Nonius CAD-4F diffractometer using Mo–Kα radiation and a graphite monochromator. Compound **2b** crystallizes in the orthorhombic space group $P2_12_12_1$ (as determined from systematic absences and axial photographs) with the following unit cell parameters: a = 10.825(2), b = 15.774(5), c = 23.012(4) Å; V = 3922(1) Å^3; Z = 4. The structure was solved by means of standard Patterson and Fourier methods using 3862 unique reflections ($2\theta \leq 50°$). Neutral atom scattering factors, anomalous dispersion corrections, and hydrogen atom scattering factors were used in conjunction with SHELX-76 for the structure refinement. Anisotropic thermal parameters were used for all non-hydrogen atoms, and hydrogen atoms on the phenyl and naphthalene rings were placed in calculated positions and were constrained with fixed geometry during refinement. Full-matrix least squares refinement using 493 parameters converged at R_F = 6.07 and R_{WF} = 5.82. Complete details of the data collection and refinement including a complete listing of atomic positional and thermal parameters, interatomic bond lengths and angles, and observed and calculated structure factors are presented as supplementary material (Tables S1–S4).

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