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Asymmetric Hydrogenation of Ketones Using a Ruthenium(II) Catalyst Containing BINOL-Derived Monodonor Phosphorus-Donor Ligands

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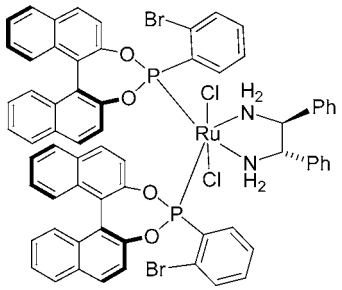
ABSTRACT



Catalyst for hydrogenation of ketones in up to 99% e.e.

A series of ruthenium(II) complexes containing BINOL-based monodonor phosphorus ligands have been prepared and applied to the asymmetric catalysis of the hydrogenation of aryl/alkyl ketones. The best ligands for this application are those which contain an aromatic groups with either a methoxide or bromide on the ortho position. Using these ligands, alcohols with ee's of up to 99% are formed.

The asymmetric reduction of ketones remains a pivotal method for the formation of enantiomerically pure alcohols.[1] Catalytic methods include transfer hydrogenation with Ru(II) and Rh(III) complexes[2] and pressure hydrogenation using organometallic complexes of Ru(II) and other metals.[3] Until recently, the latter process could only be successfully applied to substrates containing a nearby coordinating group.[4] However, a number of researchers[5] have now introduced hydrogenation systems that are capable of the highly enantioselective reduction of unfunctionalized ketones.[6,7] Perhaps the most notable of these is the Ru(II) system **1** reported by

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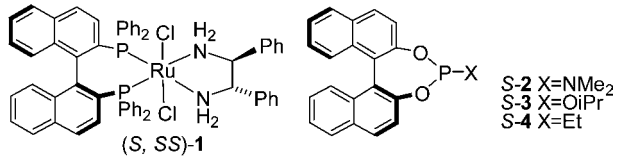
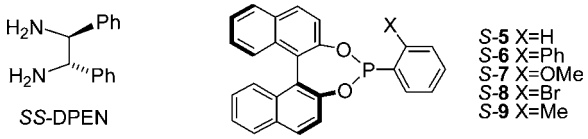
Noyori, which contains both a diphosphine and a diamine (typically DPEN) which cooperatively interact in an extremely active and enantioselective reduction catalyst.[5] This system works successfully for simple aryl/alkyl ketones, heterocyclic ketones, and enones. Many variants of this successful Ru(II)/diphosphine/diamine combination have been reported.[6]





A second significant development in asymmetric hydrogenation has been the introduction of monodonor chiral ligands, usually based on the BINOL backbone.[8] An example is Feringa's MONOPHOS **2**.[8−10] Rhodium complexes of **2**, typically containing two ligands per metal atom, are capable of the asymmetric reduction of C═C bonds in outstanding enantioselectivities. Best results are obtained with substrates containing coordinating functions, such as α-acylaminoacrylates and unsaturated carboxylic acids.[1,4] Given the excellent results obtained with BINOL-derived monodonor phosphorus ligands, we wished to establish whether such ligands could also replace diphosphines such as BINAP in **1**. If so, then this would have a significant advantage in terms of practicality, since the monodonor ligands are less expensive and more readily available than most chiral bidentate ligands. Toward this end, we prepared a series of BINOL-derived ligands. In addition to phosphoramidite **2**,[8] we prepared the known phosphite **3** and phosphonite **4**.[9,10] We also prepared a series of ligands **5**−**9** containing a substituted aromatic ring attached to the P atom. Ligands **5** and **7** have been reported previously;[9a,d,e,11] however, ligands **6**, **8**, and **9** are, to the best of our knowledge, new. The ligands were prepared by the reaction between *S*-BINOL and the appropriate bis(dimethylamino)phosphine precursors.

Each ligand was converted to the $[L_2RuCl_2(DPEN)]$ complex by reaction with $[RuCl_2(benzene)]_2$ followed by (*S*,*S*)-DPEN. The complexes were yellow-brown solids and, in their solid forms, stable to air and moisture. The structures of the complexes were confirmed by spectroscopic methods and by high-resolution mass spectrometry. An X-ray crystal structure of one of the complexes, that derived from *S*-**8**, was also obtained (Figure 1).

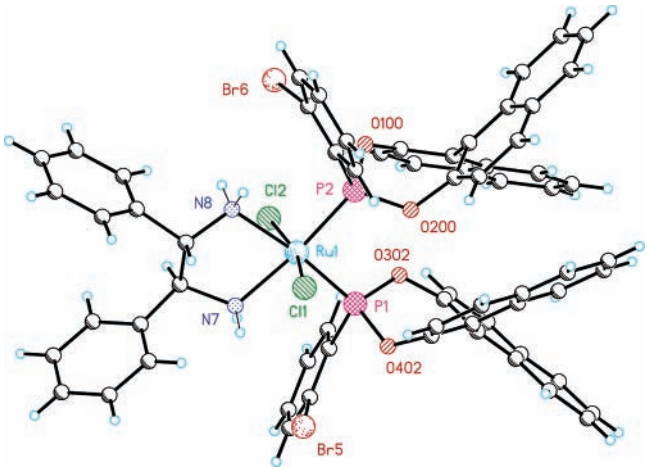
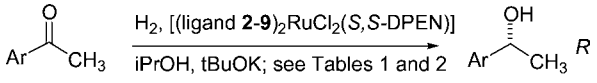


Figure 1. X-ray crystallographic structure of the (*S*,*S*,*SS*)-Ru(II)·DPEN complex derived from **8**.

An investigation into the applications of the new complexes to the asymmetric hydrogenation of simple ketones was undertaken (Scheme 1). In the first stage of the study,

Scheme 1



the (*S*,*S*,*SS*) complex derived from ligand **8** ('BrXuPHOS')[12] was selected for a short statistical experimental design study (MODDE 6).[13,14] A total of 17 experiments were carried out with variation of the substrate concentration, mol % of base, and the temperature. The substrate was acetophenone, S/C

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(12) The suggested trivial name for this ligand acknowledges the first researcher in the group to prepare and use it.

(13) The (*S*,*S*,*SS*) complex contains the matched combination of configurations. The corresponding complex of (*S*,*S*,*RR*) configuration gave a lower, reversed configuration of acetophenone reduction product (ca. 33% ee *S*).

(14) The MODDE optimised conditions for **8** may not correspond to those for other ligands.

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= 5000, solvent 2-propanol, run time = 20 h, and hydrogen pressure =10 bar. This, followed by a series of more focused studies, revealed that the best conditions with respect to ee were [ketone] = 0.3 M, 1 mol % base (with respect to substrate), and a temperature of 20 °C. Under these conditions, a product of 85% ee (*R*) was formed in 56% conversion after 40 h. Lowering the S/C to 2000 gave a 72% conversion in 86% ee after the same time (Table 1, entry 1). At S/C 1000 the conversion was complete in 15 h and the ee was 84% (entry 2).

Table 1. Asymmetric Hydrogenation of Ketones by Ruthenium(II) Complexes of Ligands **2**−**9**[a]

	ligand	Ar	S/C	[ketone] (M)	pressure (bar)	conv[b] (%)	ee[c] (%)
1[e]	**8**	C_6H_5	2000	0.30	10	72	86 (*R*)
2[h]	**8**	C_6H_5	1000	0.30	10	99	84 (*R*)
3[d]	**2**	C_6H_5	1000	0.30	10	100	54 (*R*)
4	**3**	C_6H_5	1000	0.30	10	11	43 (*R*)
5	**4**	C_6H_5	1000	0.30	10	2	17 (*R*)
6	**5**	C_6H_5	1000	0.30	10	7	37 (*R*)
7	**6**	C_6H_5	1000	0.30	10	5	35 (*R*)
8[e]	**7**	C_6H_5	1000	0.30	10	100	88 (*R*)
9	**9**	C_6H_5	1000	0.30	10	0	
10[f]	**8**	C_6H_5	2000	0.30	50	100	90 (*R*)
11[g]	**8**	C_6H_5	10000	0.30	50	80	90 (*R*)
12	**8**	*p*-$CF_3C_6H_4$	2000	0.15	10	100	75 (*R*)
13	**8**	*p*-BrC_6H_4	2000	0.30	10	100	80 (*R*)
14[e]	**8**	*o*-BrC_6H_4	2000	0.15	10	100	91 (*R*)
15	**8**	*m*-$CH_3C_6H_4$	2000	0.15	10	100	86 (*R*)
16	**8**	*p*-$CH_3C_6H_4$	2000	0.15	10	97	96 (*R*)
17	**8**	2′-naphthyl	2000	0.15	10	99	85 (*R*)
18	**8**	1′-naphthyl	2000	0.15	10	93	94 (*R*)
19	**8**	*p*-FC_6H_4	2000	0.30	10	98	94 (*R*)
20	**8**	*p*-$OCH_3C_6H_4$	2000	0.30	10	100	85 (*R*)
21	**7**	*p*-$CH_3C_6H_4$	1000	0.15	20	100	94 (*R*)
22	**7**	1′-naphthyl	1000	0.15	20	100	88 (*R*)
23	**7**	*p*-FC_6H_4	1000	0.15	20	100	89 (*R*)

[a] Reactions were conducted at 20−22 °C in 2-propanol for 20 h, 10 equiv of base wrt catalyst. [b] Determined by GC or ^{1}H NMR. [c] The eee's were determined by chiral GC or HPLC. The absolute configuration was determined by comparison of the sign of optical rotation or retention time with literature data. [d] Reaction time: 96 h. [e] Reaction time: 40 h. [f] Reaction time: <4 h. [g] Reaction time: 26 h. [h] Reaction time: 15 h.

Following these encouraging studies, a series of further investigations were completed using the other catalysts. Ligand **2**, excellent for C=C hydrogenation, gave a product in full conversion but only 54% ee. Phosphite ligand **3** and phosphonite **4** gave products in low conversion and moderate/low ee. Complexes derived from **5** and **6** were also poor; however, the result obtained from the complex derived from **7** (entry 8) was comparable to that obtained using **8**, while that using **9** was again poor.

Using ligand **8** at 50 bar and S/C of 2000, acetophenone was fully reduced with 90% ee in less than 4 h and at a S/C of 10 000 with the same ee but only 80% conversion over 26 h. A series of further ketones were reduced using the complex from **8**, under standard conditions (Table 1, entries 12−20). In all but two cases the reactions were essentially complete after 20 h at 10 bar, and the ee's generally high and in some cases better than that for acetophenone. The complex derived from **7** was also applied to three further ketones, giving enantioselectivities between 88% and 94% (entries 21−23).

A further improvement could be achieved at 0 °C. A higher pressure (50 bar) was required to counteract the rate reduction; however, products were obtained in up to 99% ee (Table 2).

Table 2. Asymmetric Hydrogenation of Ketones at 0 °C

entry	ligand	Ar	S/C	time (h)	conv[b] (%)	ee[c] (%)
1	**8**	C_6H_5	2000	4	95	93 (*R*)
2	**8**	1′-naphthyl	2000	8	92	99 (*R*)
3	**8**	o-BrC_6H_4	2000	8	93	99 (*R*)

[a] Reactions were conducted in 2-propanol, 0.5 mol % *t*-BuOK, and S/C = 2000 (autoclave placed in the ice bath) at 50 bar pressure with a 0.15 M solution of ketone. [b] Determined by GC or ^{1}H NMR. [c] ee's were determined by chiral GC or HPLC.

The reason for the high stereocontrol by ligands containing a modestly sized *ortho* substitutent is at present unclear. However, the X-ray structure reveals a tightly packed conformation of two ligands in a *cis* position. It is possible that the *ortho* substituent, which points away from the BINOL, is required to provide a "lock" into the structure which prevents ligand rotation and hence enforces a well-defined steric environment on the reaction. In conclusion, we have demonstrated that it is possible to use monodonor, BINOL-derived, ligands in Ru(II) complexes for asymmetric ketone hydrogenation. The ligand has an unexpected structural requirement for optimal results.

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Supporting Information Available: Experimental procedures, characterization data, NMR spectra, chiral chromatography analysis of reduction products, and results of the single-crystal X-ray analysis of the catalyst derived from **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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