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A Catalyst for Efficient and Highly Enantioselective Hydrogenation of Aromatic, Heteroaromatic, and α,β-Unsaturated Ketones

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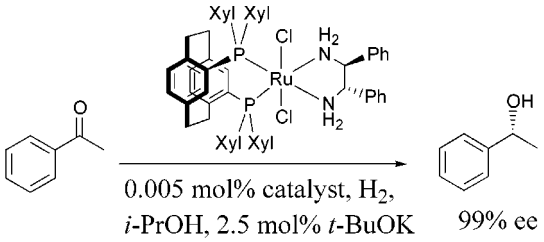
ABSTRACT



PhanePhos–ruthenium–diamine complexes catalyze the asymmetric hydrogenation of a wide range of aromatic, heteroaromatic, and α,β-unsaturated ketones with high activity and excellent enantioselectivity.

The quest for economic methods to prepare enantiomerically pure alcohols continues as a result of the important role these intermediates serve in drug design. A direct route to single enantiomer alcohols through catalytic reduction of ketones appears most attractive, and various strategies have been introduced.[1−3] Recently, a groundbreaking discovery was disclosed by Noyori and co-workers, who found that diphosphine−ruthenium−diamine complexes are very effective catalysts for selective hydrogenation of aldehydes and ketones.[4] Significantly, use of the chiral diphosphines BINAP and xylyl-BINAP, along with certain chiral diamines, allowed development of very efficient catalysts for highly enantioselective hydrogenation of a wide range of prochiral ketones.[4a,5] To date, no other asymmetric diphosphine ligand has been reported to approach the utility of xylyl-BINAP in this

(1) Hydroboration: (a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Singh, V. K. *Synthesis* **1991**, 605. (d) Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3426. (e) Brown, J. M.; Hulmes, D. I.; Layzell, T. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1673.

(2) Hydrosilylation: (a) Brunner, H.; Nishiyama, H.; Itoh, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; Chapter 6. (b) Sun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640.

(3) Hydrogen transfer: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97 and references therein. (b) Jiang, Y.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1998**, *120*, 3817. (c) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186. (d) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291.

(4) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872.

(5) (a) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (b) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (c) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749.

(6) (a) Noyori, R.; Ohkuma, T. *Pure Appl. Chem.* **1999**, *71*, 1493. (b) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495. (c) Cao, P.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 2127. (d) Ikariya, T.; Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Seido, N.; Noyori, R. European Pat. Appl. EP 95308891, 1995.

(7) For a recent example of a rhodium catalyst for enantioselective ketone hydrogenations, see: Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100.

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important reaction.[6,7] We now have found that ruthenium complexes based upon the novel PhanePhos series[8] of ligands **1** (Figure 1) serve as efficient catalyst precursors for highly

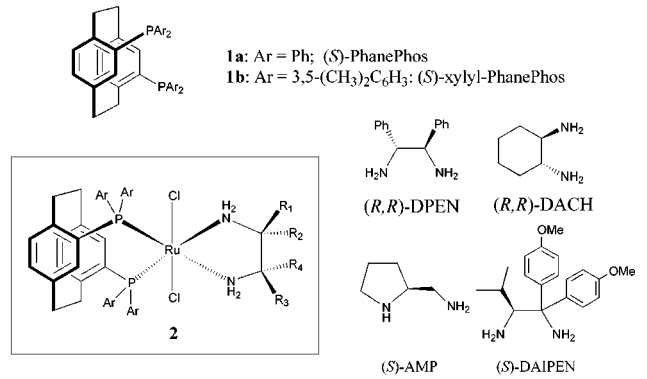


Figure 1.

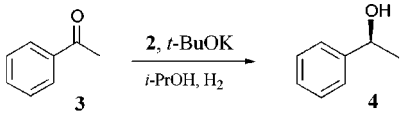
enantioselective hydrogenation of a wide array of ketones, including heteroaromatic and α,β-unsaturated derivatives. The rates, catalytic efficiencies, and enantioselectivities achieved with these catalysts are comparable to those reported for the single best system based upon xylyl-BINAP and the diamine DIAPEN.[5,9]

Our initial efforts were aimed at assessing the utility of different asymmetric diphosphine/diamine combinations in the Noyori reduction system. These experiments were conducted using the catalyst precursors obtained by reacting diphosphine ligands with $[(C_6H_6)RuCl_2]_2$ in DMF, or preferably a toluene/DMF mixture, followed by treatment with an appropriate diamine.[9] The complexes thus obtained either were isolated and purified, or were used directly in the catalytic reactions illustrated below. Spectroscopic data indicated that these adducts possess a *trans*-dichloro geometry and may be assigned the general structure **2**, analogous to that of the structurally characterized Tol-BINAP−Ru−diamine derivatives.[10] Preliminary catalytic results revealed that complexes of type **2**, derived from the PhanePhos ligands (**1**), displayed both high catalytic activity and high enantioselectivity in hydrogenation of the model substrate acetophenone **3**. Results of our screening studies involving catalysts **2** are listed in Table 1.

Under a standard set of reaction conditions (18−20 °C, 8 bar H_2, 2.0−2.5 M solutions, *i*-PrOH solvent, *t*-BuOK/Ru = 50/1) we assessed a range of precatalysts **2** composed of different PhanePhos and diamine ligands. Catalysts **2** displayed considerable effects of matching/mismatching between stereochemical elements of the chiral diphosphine and diamine ligands in the hydrogenation of **3**. With the parent PhanePhos ligand (**1a**), the highest enantioselectivity (98% ee) was attained using the precatalyst [((*S*)-**1a**)Ru((*R*,*R*)-DPEN)Cl_2]. Introduction of 3,5-dimethyl groups on the *P*-phenyl rings of xylyl−PhanePhos ligand **1b** was found to increase enantioselectivity slightly; the matched precatalyst [((*R*)-**1b**)Ru((*S*,*S*)-DPEN)Cl_2] provided 1-phenylethyl alcohol (**4**) in 99% ee over 30 min at S/C = 3000 (entry 4).[11] Examination of other basic cocatalysts revealed that KOH is as effective as *t*-BuOK, while much lower catalytic rates were observed with K_2CO_3. We surveyed other diamine ligands and found that readily available *trans*-1,2-diaminocyclohexane (DACH) was as useful as DPEN in most cases, whereas 2-aminomethylpyrrolidine (AMP) was somewhat inferior (Table 1, entries 5−8). Surprisingly, the unique diamine DAIPEN, which was so effective when used in combination with BINAP-type ligands,[5] proved less availing in the present system (Table 1, entry 9; the analogous mismatched DAIPEN-based catalyst afforded **4** with only 25% ee and 50% conversion). High catalytic efficiency was demonstrated by performing the reaction at S/C = 20,000, whereby complete conversion was observed over 1.5 h and with no diminution of enantioselectivity (entry 11).

In a preparative scale experiment, 96 g of acetophenone was hydrogenated smoothly over 4 h at S/C = 40,000 to

Table 1. Hydrogenation of Acetophenone *3* Using PhanePhos−Ru Precatalysts 2[a]



entry	phosphine	diamine	S/C[b]	time[c]	% ee[d,e]
1	(*S*)-**1a**	(*S*,*S*)-DPEN	3 000	1.25	43 (*S*)
2	(*S*)-**1a**	(*R*,*R*)-DPEN	3 000	0.5	98 (*S*)
3	(*S*)-**1b**	(*S*,*S*)-DPEN	3 000	1	41 (*R*)
4	(*R*)-**1b**	(*S*,*S*)-DPEN	3 000	0.5	99 (*R*)
5	(*S*)-**1b**	(*S*,*S*)-DACH	3 000	2	8 (*R*)
6	(*S*)-**1b**	(*R*,*R*)-DACH	3 000	0.5	98 (*S*)
7	(*S*)-**1b**	(*S*)-AMP	3 000	2	53 (*S*)
8	(*R*)-**1b**	(*S*)-AMP	3 000	2.5	92 (*R*)
9	(*R*)-**1b**	(*S*)-DAIPEN	3 000	2	80 (*R*)
10	(*R*)-**1b**	(*S*,*S*)-DPEN	10 000[f]	1	99 (*R*)
11	(*R*)-**1b**	(*S*,*S*)-DPEN	20 000[g]	1.5	99 (*R*)
12	(*R*)-**1b**	(*S*,*S*)-DPEN	40 000[h]	4	98.5 (*R*)

[a] Reactions were performed with 2−2.5 M solutions of acetophenone in *i*-PrOH with added *t*-BuOK (base/Ru = 50/1) at 18−20 °C and 8 bar initial hydrogen pressure. [b] Substrate-to-catalyst molar ratio. [c] Time in hours allowed for reaction to proceed. In all cases complete (100%) conversion to **4** was observed. [d] Enantiomeric excess was determined by chiral GC or chiral HPLC. [e] Configuration of major enantiomer determined by comparison of GC retention time and sign of optical rotation with authentic material. [f] Base/Ru = 250/1. [g] Base/Ru = 500/1. [h] Experiment performed in thermostated 600 mL vessel at 25 °C using 96 g of acetophenone substrate and base/Ru = 1000.

(8) PhanePhos = 4,12-bis(diphenylphosphino)-[2.2]paracyclophane. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207. (b) Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441.

(9) DAIPEN = 1,1-dianisyl-2-isopropyl-1,2-ethylenediamine; see: Wey, S.-J.; O'Conner, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, *34*, 1905. DPEN = 1,2-diphenylethylenediamine. DACH = *trans*-1,2-diaminocyclohexane. AMP = 2-aminomethylpyrrolidine.

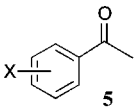
(10) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703

(11) Xylyl−PhanePhos = 4,12-bis(di-3,5-xylylphosphino)-[2.2]paracyclophane (xylyl refers to the 3,5-dimethylphenyl group). Pye, P. J.; Rossen, K.; Volante, R. P. Merck & Co., PCT Appl. WO 97/47632, 1997.

afford **4** in 98.5% ee and 97% isolated yield (Table 1, entry 12). At high S/C ratios (>10,000), it was necessary for consistent results to purify the substrate by stirring over solid K_2CO_3, followed by distillation. In agreement with Noyori's results, the stereochemistry of the phosphine ligand in [(**1b**)-Ru(DPEN)Cl_2] dictates the configuration of product alcohol **4**.

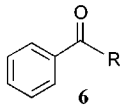
We next sought to investigate the scope of ketone substrates that may be effectively reduced with the xylyl−PhanePhos−Ru precatalyst [((*S*)-**1b**)Ru((*R*,*R*)-DPEN)Cl_2]. (Table 2). As can be discerned from the data in Table 2, a range of substituted acetophenone derivatives were hydrogenated with very high enantioselectivities. Increasing the size of the nonaromatic group in **6** shows that branching at the α-position of the *R*-substituent imposes intolerable steric restrictions for the xylyl−PhanePhos catalyst (e.g., 31% ee for **6d**). Use of the parent PhanePhos precatalyst [((*S*)-**1a**)-Ru((*R*,*R*)-DPEN)Cl_2] in this case led to an increase in enantioselectivity to 71% ee in the hydrogenation of **6d** (entry 12). With many substrates essentially identical results were achieved with the analogous PhanePhos−Ru catalyst systems derived from the diamine DACH.[12]

Table 2. Hydrogenation of Ketones **5**−**7** Using Precatalyst [((*S*)-**1b**)Ru((*R*,*R*)-DPEN)Cl_2][a]



5

a: X = *p*-CF_3 **e**: X = *o*-CF_3
b: X = *p*-Br **f**: X = *o*-CH_3
c: X = *p*-OMe **g**: X = *o*-Br
d: X = *m*-CF_3 **h**: X = *o*-OMe



6

a: R = Et
b: R = *n*-Bu
c: R = CH_2Ph
d: R = *i*-Pr

7

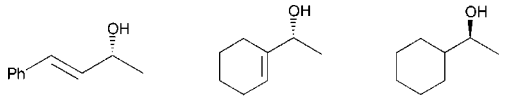
a: Ar = 1'-naphthyl **f**: Ar = 3-thienyl
b: Ar = 2'-naphthyl **g**: Ar = 2-pyridyl
c: Ar = ferrocenyl **h**: Ar = 3-pyridyl
d: Ar = 2-furyl **i**: Ar = 4-pyridyl
e: Ar = 2-thienyl **j**: Ar = 2-benzofuryl

entry	ketone	% ee[b]	entry	ketone	% ee[b]
1	**5a**	97	12	**6d**	71[d]
2	**5b**	99	13	**7a**	98
3	**5c**	97	14	**7b**	99
4	**5d**	99	15	**7c**	92
5	**5e**	98	16	**7d**	96
6	**5f**	97	17	**7e**	96
7	**5g**	99	18	**7f**	98
8	**5h**	94[c]	19	**7g**	78[e]
9	**6a**	98	20	**7h**	99[e]
10	**6b**	96	21	**7i**	96[f]
11	**6c**	98	22	**7j**	97

[a] Reactions were performed with 1.0−2.0 M solutions of ketone in *i*-PrOH at S/C 3000/1 unless otherwise noted, with added *t*-BuOK (base/Ru = 50/1) at 18−20 °C and 5.5−8.0 atm initial hydrogen pressure. Reactions were allowed to proceed for 0.5−2.5 h, giving complete conversion, unless otherwise noted. The absolute configuration was determined by comparison of the sign of optical rotation with literature data. [b] Enantiomeric excess was determined by chiral GC or chiral HPLC. [c] Reaction time was 2.5 h at S/C = 500. [d] Reaction conducted with parent PhanePhos−Ru−DPEN catalyst [((*S*)-**1a**)Ru((*R*,*R*)-DPEN)Cl_2]. [e] Reaction conducted at S/C = 1500 over 18 h. [f] Reaction conducted at S/C = 1000 over 16 h. See Supporting Information for analytical details.

Importantly, the catalysts **2** were found to be very effective for hydrogenation of a range of other aromatic and heteroaromatic ketones **7** (Table 2, entries 13−22). Despite the versatility of these catalysts, some limitations were noted. For example, 2-acetylpyridine (**7g**) was reduced slowly with catalyst [((*S*)-**1b**)Ru((*R*,*R*)-DPEN)Cl_2] (18 h, S/C = 1500), and the corresponding alcohol was obtained with only 78% ee. It is likely that the pyridyl group proximal to the ketone functionality in **7g** perturbs the catalytic process through coordination to ruthenium, leading to diminished selectivity.

To further explore substrate scope, we examined the efficacy of catalysts **2** for chemoselective hydrogenation of the carbonyl group of two representative α,β-unsaturated ketones. Both substrates were reduced smoothly with precatalyst [((*R*)-**1b**)Ru((*S*,*S*)-DPEN)Cl_2], to afford the corresponding allylic alcohols **8** and **9** with 97% and 94% ee, respectively. Precatalyst [((*S*)-**1b**)Ru((*R*,*R*)-DACH)Cl_2] produced the alcohol **8** with very similar enantioselectivity (96% ee, *S* enantiomer). No over-reduction of the alkene functionality was observed in these reactions. Dialkyl ketones still represent a challenge for the present catalysts; hydrogenation of acetylcyclohexane with [((*R*)-**1b**)Ru((*S*,*S*)-DPEN)-Cl_2] furnished **10** with a modest 49% ee (Figure 2).



8; 97% ee **9**; 94% ee **10**; 49% ee

Figure 2.

The unique structural features (e.g., very large P−P distance and P−M−P bite angle)[13] and chemical behavior of the PhanePhos series of ligands[8] have allowed development of a useful class of catalysts for highly efficient and highly enantioselective hydrogenation of a diverse range of simple aromatic, heteroaromatic, and α,β-unsaturated ketones. The results reported above are equivalent to those achieved with the best system yet described, the xylyl−BINAP−Ru−DAIPEN catalyst for asymmetric ketone hydrogenation. In contrast to the latter catalyst, which requires the unique diamine DIAPEN[9] for optimum results, the current systems employ significantly less expensive diamine ligands such as DPEN and DACH.[14] This feature, combined with the broad substrate scope, high catalytic activity, and

(12) Additional catalytic results are included in the Supplementary Information section.

(13) Dyer, P. W.; Dyson, P. J.; James, S. L.; Martin, C. M.; Suman, P. *Organometallics* **1998**, *17*, 4344.

(14) Strem Chemical Company provides research quantities of all three diamines. For comparison: DIAPEN ($1200/g), DPEN ($80/g), DACH ($27/g).

high level of absolute stereocontrol that these catalysts exhibit, suggests that they will find wide application in the cost-effective production of many valuable enantiomerically pure alcohols.

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Supporting Information Available: Experimental procedures for the synthesis of PhanePhos−diamine−ruthenium complexes, ^{1}H and ^{31}P NMR spectra, procedures for the hydrogenation of acetophenone and other ketones, GC and HPLC data, and summary table of all hydrogenation experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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