Highly Enantioselective Hydrogenation of Simple Ketones Catalyzed by a Rh–PennPhos Complex**

Qiongzhong Jiang, Yutong Jiang, Dengming Xiao, Ping Cao, and Xumu Zhang*

The development of new chiral ligands plays a crucial role in expanding the utility of transition metal catalyzed asymmetric reactions.[1] A major research goal in asymmetric catalysis is to impart high enantioselectivity and activity to important reactions by the invention of new chiral ligands and the optimization of reaction conditions for use of these ligands. Many effective chiral bisphosphanes contain a diarylphosphane as the key steric group that defines the electronic properties.[1] Recently, we designed conformationally rigid *endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptanes as new chiral scaffolds, and demonstrated that these monophosphane species can be more effective for some asymmetric reactions[2] than the conformationally flexible 2,5-disubstituted phospholanes characteristic of the DuPhos and BPE ligands[3] (Figure 1). Herein we report the synthesis of a novel class of conformationally rigid chiral bisphosphanes, *P,P′*-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptanes (PennPhos, **5** and **6**).[4] Although PennPhos shares some features with DuPhos, such as electron-donating properties and a modular structure, it is bulkier, more rigid, and does not form C_2-symmetric compounds with many transition metals. In addition, PennPhos can be made in large quantities from inexpensive starting materials and is an air-stable solid.

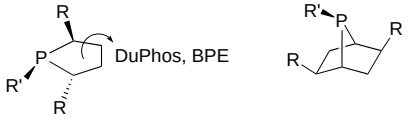
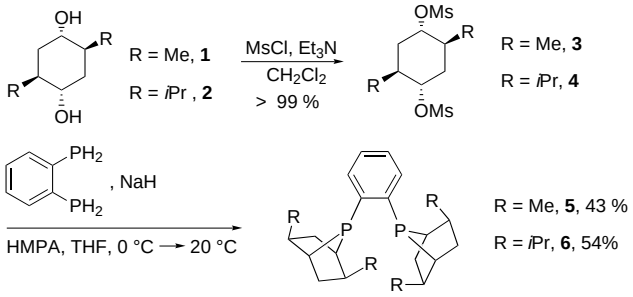


Figure 1. Structural motifs of chiral 1,2-bis(phospholano)benzene (DuPhos) and 1,2-bis(phospholano)ethane (BPE) as well as rigid dialkyl-7-phosphabicyclo[2.2.1]heptane.

We have directed much attention toward enantioselective hydrogenation of simple ketones as a showcase for enantioselective transition metal catalyzed reactions with PennPhos. Asymmetric hydrogenation is one of the most efficient methods of making chiral alcohols, because transition metal hydrogenation catalysts have potentially high catalytic activity compared to stoichiometric[5] and other catalytic reduction systems.[6] While systems for efficient transition metal catalyzed asymmetric hydrogenation of functionalized ketones have been realized,[7] highly enantioselective hydrogenation of simple ketones that lack anchoring heteroatoms has not been fully developed. Among the direct hydrogenation catalytic systems,[8] promising results were achieved for asymmetric hydrogenation of alkyl aryl ketones with a mixture of a Ru^{II}–BINAP complex (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-dinaphthyl), a chiral diamine, and KOH.[8d] In this catalytic system, the chelating chiral diamine is as important a stereochemistry-controlling element as the chiral BINAP ligand. To date, simple metal complexes with chiral bisphosphane ligands are ineffective for highly enantioselective hydrogenation of simple ketones. Furthermore, asymmetric reduction of simple dialkyl ketones generally proceeds with low enantioselectivity in all reduction systems with few exceptions.[5b, 5c] With a Rh–PennPhos catalyst, we have achieved unprecedented high enantioselectivity in hydrogenation of both aryl alkyl and dialkyl ketones. This success is based on the important finding that a weak base can facilitate Rh-catalyzed hydrogenation of simple ketones; the discovery itself may have fundamental significance for organometallic chemistry.

The synthesis of PennPhos is illustrated in Scheme 1. Enantiomerically pure cyclic 1,4-diols **1** and **2**, which are easily prepared by Halterman's procedure,[9] are converted



Scheme 1. Synthesis of the PennPhos ligands. HMPA = hexamethyl phosphoramide, Ms = methanesulfonyl.

into the corresponding mesylates **3** and **4** in high yields. Nucleophilic substitution of the methanesulfonate groups by 1,2-phenylenediphosphane[10] in the presence of NaH generates the desired products *P,P′*-1,2-phenylenebis{(1*R*,2*S*,4*R*,5*S*)-2,5-dimethyl-7-phosphabicyclo[2.2.1]heptane} (**5**, (*R,S,R,S*)-Me-PennPhos) and *P,P′*-1,2-phenylenebis[(1*R*,2*R*,4*R*,5*R*)-2,5-diisopropyl-7-phosphabicyclo[2.2.1]-heptane} (**6**, (*R,R,R,R*)-*i*Pr-PennPhos), respectively.

Effective asymmetric hydrogenation of simple ketones requires high intrinsic activity in the nonchiral form of the reaction. Since simple ketones are typically poorer ligands than are olefins, many Rh–phosphane complexes show no activity for the hydrogenation of simple ketones. An important finding by Osborn and Schrock is that $[RhH_2L_2X_2]^+$ (L = electron-donating phosphanes such as PPh_2Me or PMe_3, X = solvent) is a reasonable catalyst for the hydrogenation of simple ketones in the presence of a small amount of water.[11] Since PennPhos ligands are more electron rich

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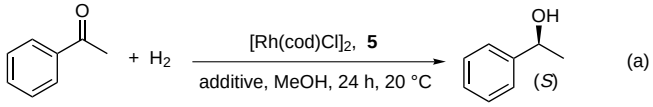
than triarylphosphanes, we anticipated that they might show good activity towards asymmetric hydrogenation of simple ketones.

Table 1 outlines the results of asymmetric hydrogenation according to Equation (a) with acetophenone as a typical



(a)

Table 1. Rh-catalyzed asymmetric hydrogenation of acetophenone according to Equation (a).[a]

Entry	Additive	Conversion [%] (*ee* [%]) for the following ratios of additive:Rh catalyst					
		0.0	0.1	0.15	0.2	0.3	1.0
1	NaOMe	45 (57)	56 (70)	69 (83)	71 (88)	41 (80)	25 (15 *R*)
2	LiO*t*Bu			80 (91)	58 (89)	19 (78)	20 (23 *R*)
3	LiCl		49 (66)		46 (70)	47 (72)	44 (67)
4	**KBr**		**74 (80)**		**82 (88)**	**85 (89)**	**89 (92)**
5	Et_3N			89 (90)	78 (92)	28 (82)	18 (4 *R*)
6	2-Me-imidazole		86 (87)		94 (94)	79 (92)	12 (1)
7	**2,6-lutidine**		**72 (83)**	**84 (90)**	**94 (94)**	**97 (95)**	**93 (95)**

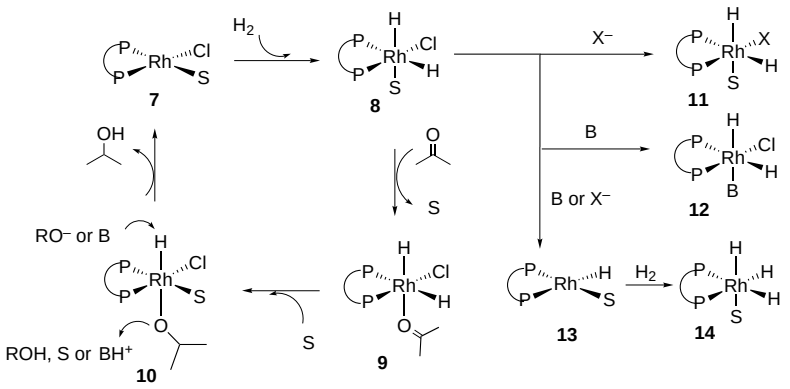
[a] Reaction conditions: room temperature, 30 atm of H_2, 24 h, 1.0 mmol of substrate, 0.1 M, substrate:[Rh(cod)Cl]$_2$:**5** = 1:0.005:0.01. See Experimental Section for further details.

substrate and the Rh complex of **5** as the catalyst. Initially, extensive screening of catalytic conditions showed that the asymmetric hydrogenation gave good enantioselectivity and activity when [Rh(cod)Cl]$_2$ was used as the precursor under 30 atm of H_2 in MeOH. The Rh complex of **6** is a less effective catalyst than the Rh complex of **5**. Unlike the hydrogenation system of Osborn and Schrock, addition of a small amount of water had no effect on the catalytic activity. However, we found a dramatic effect with other additives. Not only does the enantioselectivity strongly depend on the additive used, but catalytic activity also varies to a great extent.

Three classes of additives were screened in the catalytic system: ionic bases (Table 1, entries 1, 2), halides (entries 3, 4), and neutral bases (entries 5–7). In the absence of additives, asymmetric hydrogenation of acetophenone catalyzed by the Rh complex of **5** was sluggish and gave the secondary alcohol with only 57% *ee* (entry 1). In the presence of catalytic amounts of additives (0.1–0.2 equiv based on Rh), both reactivity and enantioselectivity were increased.

Different effects were observed depending on the type and amount of additives used. For the ionic bases (entries 1, 2), addition of one equivalent of base slowed down the reaction and surprisingly gave the chiral alcohol with the opposite configuration. The halide effect was studied with two different salts. The presence of excess chloride showed little effect on the catalyst activity and selectivity (entry 3). However, the addition of bromide could enhance both the enantioselectivity and the rate of the reaction over the entire concentration range (0.1–1 equiv, entry 4). With Et_3N as the additive (entry 5), higher conversion and better enantioselectivity were observed when less than 0.2 equivalents of base were present in the catalytic system. Use of more than 0.3 equivalents of Et_3N caused a decrease in reactivity and enantioselectivity. The reaction gave the opposite configuration with low conversion when one equivalent of Et_3N was used. Hydrogenation in the presence of 2-methylimidazole (entry 6) also showed initial enhancement and then erosion of both the reactivity and selectivity. In contrast, both enantioselectivity and conversion were increased when 0.1 to 1 equivalent of 2,6-lutidine was used (entry 7). Up to 95% *ee* was observed for the hydrogenation of acetophenone. This is the highest enantioselectivity achieved with a direct hydrogenation catalyst of a Group 8 transition metal (87% *ee* was obtained with Noyori's Ru system[8d]). Therefore, bromide and 2,6-lutidine are useful promoters for the Rh-catalyzed enantioselective hydrogenation of acetophenone.

The mechanism of this Rh-catalyzed asymmetric hydrogenation is not well understood at present. Based on the commonly accepted mechanism,[12] we offer the following rationale to explain our observations (Scheme 2): Addition of **5** to [Rh(cod)Cl]$_2$ in MeOH generates [Rh(cod)(**5**)]Cl.[13] This catalytic precursor can be hydrogenated to give the Rh^I intermediate **7**. Oxidative addition of hydrogen to **7** produces the six-coordinate Rh^{III} species **8**, which is converted into **9** by ligand substitution. Insertion of the ketone into the Rh–H bond forms the Rh^{III}–alkoxyl complex **10**, in which the remaining hydride is located *trans* relative to the alkoxide group. Therefore, the reductive elimination of **10** to regenerate **7** is difficult under normal conditions. The major function of the added bases may be to deprotonate **10**, while the conjugate acid can protonate the alkoxide ligand. A similar push–pull mechanism was suggested by Osborn and Schrock for the Rh-catalyzed hydrogenation of simple ketones promoted by small quantities of water.[11] With a 1:1 ratio of Rh:additives, a variety of Rh derivatives can be generated. For example, halide and alkoxide may displace the chloride in **8** to form **11**, which can lead to a Rh dimer or other unproductive species. With strongly coordinating ligands such as an imidazole, irreversible formation of coordinately

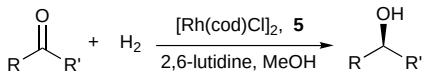


Scheme 2. Proposed mechanism for Rh-catalyzed asymmetric hydrogenation. S = MeOH, B = neutral base, X = halogen, OR.

saturated species **12** is possible. Replacing these ligands by simple ketones is difficult, and low catalytic activity is expected. In the presence of strong bases such as alkoxide or Et_3N, reductive elimination of HCl from **8** will form the Rh^I–hydrido species **13**, which may lead to the opposite enantiomer by a competitive pathway.[11] Clearly, the enantioselectivity of the reaction is a useful probe for understanding the reaction mechanism of the Rh-catalyzed hydrogenation. Oxidative addition of H_2 to **13** is likely to be slow, as **14** has two hydrido ligands located *trans* to phosphane ligands. On the other hand, substitution of chloride by bromide changes the electronic nature of the Rh complex, and may generate more active catalysts for the hydrogenation of ketones. Use of noncoordinating and weaker bases such as 2,6-lutidine could accelerate the reductive elimination of **10** without unwanted formation of **12** and **13**.

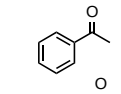
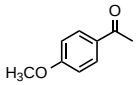
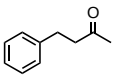
Based on the observation that bromide and 2, 6-lutidine are important promoters for the hydrogenation of simple ketones, we examined the asymmetric hydrogenation of various simple ketones with the Rh complex of **5** as the catalyst [Eq. (b), Table 2]. Two sets of reaction conditions were applied to achieve high enantioselectivity: 1) use of 0.4 equivalents of 2,6-lutidine (based on Rh) or 2) use of 0.8 equivalents of 2,6-lutidine and 1 equivalent of KBr (based on Rh). For most aryl methyl ketones (Table 2, entries 1–8), high enantioselectivities (93–96% *ee*) were observed. The presence of both 2,6-lutidine and KBr accelerated the reaction and enhanced the enantioselectivity (entries 4/3 and 6/5). These conditions were then used for the hydrogenation of other ketones. Increasing the bulk of the alkyl group by going from methyl to ethyl or isopropryl in the alkyl aryl ketone dramatically decreased the reactivity and enantioselectivity (entries 1/5 and 6/7). This clearly indicates that the chiral environment around the Rh complex of **5** can effectively discriminate between methyl and other alkyl groups. To test this speculation, we carried out asymmetric hydrogenations of several alkyl methyl ketones—the toughest problem for asymmetric reduction (entries 9–14). Enantiomeric excesses of up to 94% *ee* for *tert*-butyl methyl ketone (entry 14) and 92% *ee* for cyclohexyl methyl ketone (entry 13) were observed. The enantioselectivity decreased with smaller alkyl groups. With isopropyl methyl ketone and isobutyl methyl ketone, 84% *ee* (entry 12) and 85% *ee* (entry 11) were achieved respectively. However, even with unbranched alkyl groups, good enantioselectivities of 73% *ee* (entry 9) and 75% *ee* (entry 10) were still achieved. To the best of our knowledge, our results of asymmetric hydrogenation of alkyl aryl ketones by the Rh complex of **5** are comparable to or better than those with other hydrogenation catalysts, and our hydrogenation results of alkyl methyl ketones with this system gives the highest enantioselectivity reported to date.

In summary, we have synthesized new conformationally rigid bisphosphanes, the PennPhos ligands. For the asymmetric hydrogenation of ketones catalyzed by Rh complexes of these ligands, remarkable additive effects and high enantioselectivies for both alkyl aryl and alkyl methyl ketones are found. Continuing research will focus on understanding the reaction mechanism and enhancing the reaction rate. Fine-tuning the steric and electronic environment of the PennPhos ligand should lead to practical asymmetric hydrogenation catalysts for simple ketones.



(b)

Table 2. Asymmetric hydrogenation of simple ketones catalyzed by a Rh–PennPhos complex according to Equation (b).[a]

Entry	Ketone	Equiv of lutidine[b]	Equiv of KBr	Time [h]	Yield [%]	*ee* [%]
1		0.4	–	24	97	95
2		0.4	–	53	94	95
3		0.8	–	108	56	91
4		0.8	1.0	48	83	94
5		0.8	–	108	71	89
6		0.8	1.0	88	95	93
7		0.8	1.0	94	20	72
8		0.8	1.0	100	99	96
9		0.8	1.0	56	99	73
10		0.8	1.0	48	96	75
11		0.8	1.0	75	66	85
12		0.8	1.0	94	99	84
13		0.8	1.0	106	90	92
14		0.8	1.0	96	51	94

[a] Reaction conditions: room temperature, 30 atm of H_2, 0.5 mmol of substrate, 0.125 M, substrate:[Rh(cod)Cl]$_2$:**5** = 1:0.005:0.01]. See Experimental Section for further details. Long reaction time was used to achieve the maxium conversion; for many substrates the reaction may be complete within a much shorter time. [b] Based on Rh.

Experimental Section

Compounds **1**–**4**[9] and 1,2-phenylenediphosphane[10] were made according to literature procedures. MeOH was distilled from Mg/Na over a long column under N_2. All the operations were carried out under a N_2 atmosphere.

5: ^{1}H NMR ($CDCl_3$): δ = 7.25–7.10 (m, 2H, aromatic), 7.08–6.95 (m, 2H, aromatic), 3.21 (br d, 2H, ^2J(P,H) = 14.5 Hz, PCH), 2.58 (br d, 2H, ^2J(P,H) = 13.4 Hz, PCH), 1.90–1.60 (m, 12H), 1.55–1.35 (m, 2H), 1.17 (d, 6H, ^3J(H,H) = 6.3 Hz, CH_3), 0.60 (d, 6H, ^3J(H,H) = 6.3 Hz, CH_3); ^{13}C

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NMR ($CDCl_3$): $\delta = 143.94$, 143.66, 143.48, 143.20, 131.05, 131.00, 130.93, 126.33, 46.24, 46.20, 46.17, 46.13, 45.92, 45.69, 45.61, 45.38, 40.17, 40.05, 39.89, 39.73, 39.61, 39.52, 39.33, 39.29, 39.26, 34.76, 34.61. 34.51, 34.41, 34.26, 22.69, 22.65, 22.61, 20.82; ^{31}P NMR ($CDCl_3$): $\delta = -7.3$; $[\alpha]_D = +221.8^\circ$ ($c = 1.01$, $CHCl_3$); HR-MS calcd for $C_{22}H_{32}P_2$: 358.1975; found: 358.1982.

6: ^1H NMR ($CDCl_3$): $\delta = 7.20-7.10$ (m, 2H, aromatic), 7.05–6.90 (m, 2H, aromatic), 3.38 (br d, 2H, $^2J(P,H) = 14.2$ Hz, PCH), 2.85 (br d, 2H, $^2J(P,H) = 13.5$ Hz, PCH), 1.85–1.45 (m, 12H), 1.30–1.08 (m, 4H), 1.03 (d, 6H, $^3J(H,H) = 6.4$ Hz, CH_3), 0.96 (d, 6H, $^3J(H,H) = 5.6$ Hz, CH_3), 0.86 (d, 6H, $^3J(H,H) = 6.5$ Hz, CH_3), 0.47 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 143.97$, 143.62, 143.56, 143.50, 143.45, 143.09, 130.96, 130.90, 130.86, 126.11, 54.10, 54.06, 54.03, 48.65, 48.56, 48.46, 42.02, 41.96, 41.24, 41.20, 41.18, 41.14, 37.94, 37.77, 37.60, 37.46, 33.29, 33.27, 33.24, 31.69, 23,45, 23.40, 23.35, 22.22. 20.97, 20.54; ^{31}P NMR ($CDCl_3$): $\delta = -8.7$; $[\alpha]_D = +226.7$ ($c = 1.03$, $CHCl_3$); HR-MS calcd for $C_{30}H_{48}P_2$: 470.3231; found: 470.3229.

General procedure for asymmetric hydrogenation: To a solution of $[Rh(cod)Cl]_2$ (2.5 mg, 0.005 mmol) in MeOH (10 mL) was added **5** (3.7 mg, 0.01 mmol). After the reaction mixture was stirred at room temperature for 10 min, acetophenone (1.0 mmol) was added. The orange-yellow solution was stirred for 2 min, and the desired amount of the additive (as a solution in MeOH) was then added. This mixture was stirred for about 5 min, and hydrogen was introduced. The hydrogenation was performed in a Parr autoclave at room temperature under 30 atm of hydrogen for 24 h. The residue was passed through a short silica gel column to remove the catalyst, and eluted with diethyl ether. The enantiomeric excesses and reaction conversion were measured by gas chromatography on a Supelco β-DEX 120 column. The absolute configuration of the product was determined by comparing the observed rotation with the reported value.[5c,8d]

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[13] ^{31}P NMR data for [Rh(cod)**5**]Cl (prepared in situ, CD_3OD): ABX system, $\delta = 50.7$ (dd, $^1J(Rh,P) = 140.6$ Hz), $^2J(P,P) = 23.6$ Hz), 37.1 (dd, $^1J(Rh,P) = 141.6$ Hz, $^2J(P,P) = 23.6$ Hz)). It is noteworthy that the ligand **5** in [Rh(cod)(**5**)]Cl does not have C_2 symmetry. A possible explanation is that the phosphabicyclo[2.2.1]heptane is too bulkly to allow the PennPhos to exist in a C_2-symmetrical fashion.

Amine Additives Greatly Expand the Scope of Asymmetric Hydrosilylation of Imines**

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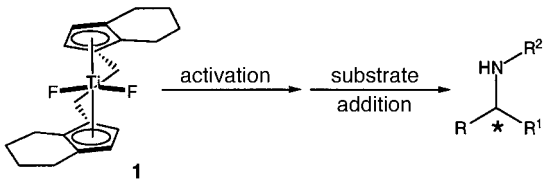
Dedicated to Professor Satoru Masamune

The demand for enantiomerically pure secondary amines has prompted considerable effort[1] in the development of catalytic processes for asymmetric hydrogenation[2] and hydrosilylation[3] of imines. We recently reported a highly enantioselective titanium-catalyzed hydrosilylation of imines.[4] This method involves treatment of (*S,S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)titanium difluoride[5] (**1**) with phenylsilane,[4, 6] which yields a very active catalytic system for the hydrosilylation of *N*-methyl and cyclic imines [Eq. (1)]. For example, *N*-methylimine **2** undergoes complete hydrosilylation within 12 h at room temperature (Table 1, entry 1). Although high turnover numbers (up to 5000) and



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