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Asymmetric hydrosilylation of ketones catalyzed by ruthenium complexes with chiral tridentate ligands

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Abstract

A new chiral tridentate ligand containing two phosphines and one pyridine is effective for Ru-catalyzed asymmetric hydrosilylation of simple ketones (47–66% *ee*). Ruthenium complexes with either chiral tridentate nitrogen ligands or chiral bidentate phosphorus ligands are either inactive or non-selective for asymmetric hydrosilylation. This work has set a foundation for the asymmetric catalytic reactions based on chiral mixed P–N tridentate ligands. © 1997 Elsevier Science S.A.

1. Introduction

Asymmetric hydrosilylation of simple ketones to furnish silyl ethers, and subsequent hydrolysis of the silyl ethers provides efficient entry into the synthesis of secondary chiral alcohols (for reviews see Ref. [1]). Much prior work has utilized chiral bidentate ligands (for examples see Ref. [2]). Recently, chiral nitrogen ligands such as bidentate pythias [3] and tridentate pyboxes [4] have been successfully applied in the asymmetric hydrosilylation reaction. A number of other ligands containing nitrogen and/or phosphine atoms were also investigated for this catalytic reaction (for some recent examples see Ref. [5]). To date, only rhodium and iridium complexes have shown high enantioselectivities in asymmetric hydrosilylation of simple ketones [3–5]. Effective asymmetric catalysts using ruthenium compounds are more desirable because ruthenium metal is more readily available and less expensive than either rhodium or iridium. In an effort to develop efficient asymmetric catalysts, we have recently synthesized a chiral tridentate ligand containing two chiral phosphines in trans positions and a pyridine in the center (Fig. 1) [6]. Herein we report the results of preliminary studies on the ruthenium-catalyzed asymmetric hydrosilylation of simple ketones with this chiral tridentate ligand. We have also examined the enantioselectivities of the Ru-catalyzed reaction with several related ligands (Fig. 2).

2. Results

The syntheses of the chiral tridentate ligand **7** and bidentate ligand **8** used in this study are shown in Scheme 1. The chiral bidentate ligand **8** differs from the tridentate ligand **7** by the substitution of the pyridine ring with benzene. Optically pure phosphine **1** can be prepared on a gram-scale according to a literature procedure [7]. Deprotonation of **1** with *sec*-BuLi generates a Li compound **2**, which reacts with 2,6-bis(bromomethyl)pyridine **3** or the 2,6-bis(bromomethyl)benzene **4** to form **5** or **6** respectively in high yields. After removing the borane groups from **5** and **6**, tridentate ligand **7** and bidentate ligand **8** are obtained in high yield.

Table 1 summarizes the results of asymmetric hydrosilylation of acetophenone with diphenylsilane catalyzed by various ruthenium complexes. Asymmetric hydrosilylation catalyzed by $[RuCl_2(C_6H_6)]_2$ with chiral tridentate ligand **7** proceeds with low enantioselectivity (entry 1). Addition of AgOTf increases the enantioselectivity of hydrosilylation (entry 2). This increase is due to the removal of coordinated chlorides by Ag^+ salt which, in turn, generates coordination sites for binding of the ketone and activation of the Si–H bond [4]. We have investigated the enantioselectivity of the reaction with varying amounts of chiral ligand. For some chiral bidentate nitrogen ligands, it has been reported that more than a ten-fold excess of ligand is required to achieve high enantioselectivities in Rh-catalyzed systems [3]. Our results (entries 2 and 3) indicate

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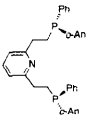


Fig. 1.

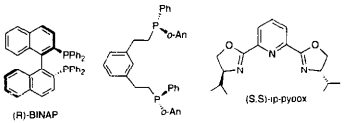


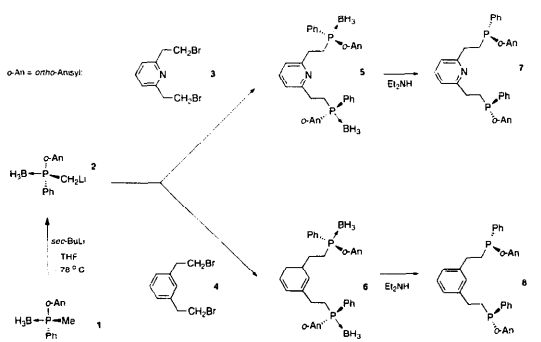
Fig. 2.

that 2 equiv. of ligand per ruthenium is sufficient to achieve maximum enantioselectivity.

While the hydrosilylation reaction can be carried out in neat diphenylsilane, we have studied the effect of several solvents on the enantioselectivity. Several rhodium-catalyzed asymmetric hydrosilylation systems which use CCl_4 as solvent are known to give high enantioselectivities [8]. However, the ruthenium compound is not an active catalyst in CCl_4 (entry 5) in the hydrosilylation reaction. We have also carried out the reaction in toluene, dioxane and THF (entries 6, 7 and 8) and found that THF is a good solvent for the asymmetric hydrosilylation reaction. Up to 54% *ee* has been obtained in the hydrosilylation of acetophenone in this solvent. Although the enantioselectivity here is much lower than that achieved with some rhodium-catalyzed hydrosilylation systems (e.g. 98% *ee* [3]), it is the best result yet observed in a ruthenium-catalyzed hydrosilylation reaction.

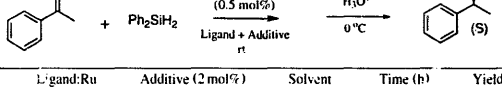
In order to understand the role that the chiral ligand **7** plays in this ruthenium-based asymmetric hydrosilylation, we performed the reaction with several other ligands (i.e. (*R*)-BINAP, chiral ligand **8** and (*S,S*)-ip-Pybox). The experimental results (entries 9 and 10) show that the enantioselectivity of the hydrosilylation reaction is much lower with the bidentate phosphine ligands (*R*)-BINAP and chiral ligand **8** than with tridentate ligand **7** (entry 3). Interestingly, the enantioselectivities in the hydrosilylation of acetophenone with ligand **7** (54% *ee*) and with ligand **8** (0% *ee*) are significantly different. This result contrasts with our previous study in symmetric alkylation reactions where the same enantioselectivities were observed with both ligands **7** and **8** [6]. This observation implies that the pyridine in the tridentate ligand **7** is crucial for achieving relatively high enantioselectivity in this hydrosilylation reaction. As the steric environment of the ruthenium complex with our tridentate ligand **7** is similar to the ruthenium complex with the chiral tridentate ligand Pybox, we were interested in comparing the electronic effect of these two ligand systems. Although rhodium complexes with tridentate (*S,S*)-ip-Pybox are excellent catalysts for asymmetric hydrosilylation [4], the ruthenium complex with the same ligand shows both low activity and enantioselectivity (entry 11). Replacement of the two oxazoline groups with electron-donating phosphines enhances both activity and selectivity in the ruthenium-catalyzed asymmetric hydrosilylation reaction.

We have performed asymmetric hydrosilylations of several aryl alkyl ketones under our optimum conditions (Table 2). Typically, 1 mol% of ruthenium catalyst was used with 2.2 mol% of the chiral tridentate ligand.



Scheme 1.

Table 1
Ruthenium-catalyzed asymmetric hydrosilylation of acetophenone



Entry	Ligand	Ligand:Ru	Additive (2 mol%)	Solvent	Time (h)	Yield (%)[a]	ee[c] (%)
1	**7**	2.2	—	—	24	93[b]	2
2	**7**	1.1	AgOTf	—	48	81	29
3	**7**	2.2	AgOTf	—	24	91	40
4	**7**	4.4	AgOTf	—	48	94[b]	38
5	**7**	2.2	AgOTf	CCl_4	24	0	—
6	**7**	2.2	AgOTf	$PhCH_3$	24	88	23
7	**7**	2.2	AgOTf	Dioxane	96	45	35
8	**7**	2.2	AgOTf	THF	24	97[b]	54
9	*R*-BINAP	2.2	AgOTf	—	24	95	5 (*R*)
10	**8**	2.2	AgOTf	—	21	43	0
11	(*S,S*)-ip-Pybox	4.4	AgOTf	—	72	16	0

[a] Yield determined by GC.
[b] Isolated yield.
[c] %*ee* was measured by GC using a β-Dex chiral column; the S absolute configuration was determined by comparing the optical rotation with literature values [3–5].

Table 2
Ruthenium-catalyzed asymmetric hydrosilylation of simple ketones

Entry	Ketone	Time (h)	Yield (%)[a]	ee[b] (%)
1		24	97	54
2		72	87	57
3		72	93	62
4		48	93	55
5		60	91	47[c]
6		30	85	48
7		24	98	66

[a] Isolated yield
[b] %*ee* was measured by GC using a β-Dex chiral column; S absolute configuration was determined by comparing the optical rotation with literature values [3–5].
[c] %*ee* was determined by HPLC (Chiracel OD column, hexane:^{i}PrOH = 98.5:1.5).

Enantioselectivities ranging from 47 to 66% were observed and the reactions occurred with excellent conversions (isolated yields from 85 to 98%). These values are the best results reported to date with ruthenium catalysts. Further studies will focus on the modification of the tridentate ligand structure to achieve higher enantioselectivities in this ruthenium-catalyzed hydrosilylation reaction.

3. Experimental section

3.1. General procedure

THF, benzene and toluene were distilled under nitrogen from a sodium–benzophenone ketyl. Methylene chloride was distilled under nitrogen from CaH_2. 2,6-Bis(bromomethyl)pyridine (**3**) [9], (R_P)-Ph(*o*-An)(Me)P–BH_3 (**1**) [7], were prepared according to published procedures.

3.2. (R,R)-2,6-Bis[(o-anisylboronatophenylphosphino)ethyl]pyridine (5)

(R_P)-Ph(*o*-An)(Me)P–BH_3 (**1**, 3.3 g, 13.5 mmol) was dissolved in freshly distilled THF (25 ml) and the resulting solution cooled to −78 °C. *sec*-BuLi (1.1 equiv., 14.8 mmol, 11.4 ml of a 1.3 M solution in cyclohexane) was then added dropwise over approximately 30 min, during which time a bright yellow color developed. The resulting solution (containing (R_P)-Ph(*o*-An)(CH_2Li)P–BH_3, **2**) was stirred for approximately 2 h while maintaining the temperature at approximately −78 °C. In a separate flask, 2,6-bis(bromomethyl)pyridine (**3**, 1.8 g, 6.7 mmol) was dissolved in freshly distilled THF (10 ml), and the resulting solution was transferred to an addition funnel via cannula, which was added dropwise to the yellow reaction mixture over approximately 20 min while maintaining the temperature at approximately −78 °C, during which time the solution became deep reddish brown. The reaction mixture was allowed to warm to room temperature over approximately 1.5 h and then distilled water (40 ml) was added. The organic layer was removed via cannula and the aqueous layer extracted with 1:1 ether–CH_2Cl_2 (2 × 20 ml). The combined organic extracts were dried over $MgSO_4$. The light yellow supernatant was removed by cannula and collected in a separate flask. The residual drying agent was washed with additional 1:1 ether–CH_2Cl_2 (2 × 20 ml), and the washings removed via cannula-filter and combined with the initial filtrate. Removal of the volatiles from the combined filtrates under reduced pressure afforded a viscous yellow oil which was redissolved in a minimal amount of 1:1 ether–CH_2Cl_2 and chromatographed on SiO_2 with hexane (50 ml), and then with 1:5 ether–hexane, to elute a small quantity of unreacted (R_P)-Ph(*o*-An)(Me)P–BH_3. Continued elution with 1:1 ether–hexane afforded **5** (2.7 g, 68% yield) as a flocculent solid: $[\alpha]_D^{20} = +16.7°$ ($c = 5.06$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.7–6.8 (m, 27 H), 3.6 (s, 6 H), 3.1–3.0 (br, 4 H), 2.9–2.6 (br, 4 H), 1.6–0.6 (br, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.2–110.9, 55.2 (s), 31.4 (s), 23.3 (d, $J_{PC} = 39.4$ Hz); ^{31}P NMR ($CDCl_3$) δ 16.3 (br); MS (FAB) m/z 592.5 (M^+); 576.4 ($M^+ - BH_3$); 562.5 ($M^+ - 2BH_3$). Anal. Calcd. for C, 71.10; H, 6.99; N, 2.37. Found: C, 70.83; H, 7.05; N, 2.32.

3.3. (R,R)-2,6-Bis[(o-anisylboronatophenylphosphino)ethyl]benzene (6)

(R_P)-Ph(*o*-An)(Me)P–BH_3 (**3**, 2.2 g, 9.0 mmol) was dissolved in freshly distilled THF (25 ml) and the resulting solution cooled to −78 °C. *sec*-BuLi (1.1 equiv., 9.9 mmol, 7.6 ml of a 1.3 M solution in cyclohexane) was then added dropwise over approximately 30 min, during which time a bright yellow color developed. The resulting solution (containing (R_P)-Ph(*o*-An)(CH_2Li)P–BH_3, **4**) was stirred for approximately 2 h while maintaining the temperature at approximately −78 °C. In a separate flask, 2,6-bis(bromomethyl)benzene (1.2 g, 4.5 mmol) was dissolved in freshly distilled THF (10 ml), and the resulting solution was transferred to an addition funnel via cannula. The solution was added dropwise to the yellow reaction mixture (**4**) over approximately 20 min while maintaining the temperature at approximately −78 °C, during which time the solution became deep reddish brown. The reaction mixture was allowed to warm to room temperature over approximately 1.5 h and then distilled water (40 ml) was added. The organic layer was removed via cannula and the aqueous layer extracted with 1:1 ether–CH_2Cl_2 (2 × 20 ml). The combined organic extracts were dried over $MgSO_4$. The light yellow supernatant was removed by cannula and collected in a separate flask. The residual drying agent was washed with additional 1:1 ether–CH_2Cl_2 (2 × 20 ml), and the washings removed via cannula-filter and combined with the initial filtrate. Removal of the volatiles from the combined filtrates under reduced pressure afforded a viscous yellow oil which was redissolved in a minimal amount of ether and chromatographed on SiO_2 eluting with hexane (50 ml), and then with 1:5 ether–hexane, to elute a small quantity of unreacted (R_P)-Ph(*o*-An)(Me)P–BH_3. Continued elution with 1:1 ether–hexane afforded **5** (2.2 g, 83% yield) as a flocculent solid: ^{1}H NMR ($CDCl_3$) δ 8.1–6.8 (m, 22 H), 3.7 (s, 6 H), 3.1–2.8 (br, 4 H), 2.5–2.7 (br, 4 H), 1.6–0.5 (br, 6 H); ^{13}C NMR ($CDCl_3$) δ 161.3, 141.8–111.1, 55.3 (s), 29.3 (s), 26.0 (d, $J_{PC} = 38.4$ Hz); ^{31}P NMR ($CDCl_3$) δ 16.0 (br); MS (EI) m/z 590 (M^+); 576 ($M^+ - BH_3$); 562 ($M^+ - 2BH_3$).

3.4. Deprotection of phosphine–boranes 5 and 6 to give chiral tridentate ligand 7 and bidentate ligand 8

Phosphine–borane **5** (3.4 g, 5.7 mmol) was dissolved in a minimal amount of dry, degassed CH_2Cl_2 and dry, degassed Et_2NH (approximately 20 ml) was added via cannula. The reaction mixture was then heated at reflux under N_2 overnight. The slightly yellow mixture was then allowed to cool to room temperature and the volatiles were removed under reduced pressure, affording a viscous yellow oily residue. This residue was taken up in dry, degassed ether (20 ml) and the solution was filtered through a 3" plug of degassed, basic Al_2O_3 via Schlenk frit. The slightly yellow filtrate was collected in a Schlenk flask under N_2, and removal of the volatiles under reduced pressure afforded pure **7** (2.2 g, 70% yield) as a viscous oil: ^{1}H NMR ($CDCl_3$) δ 7.6–6.8 (m, 27 H), 3.7 (s, 6H), 3.1–2.9 (br, m, 4H), 2.7–2.6 (br, m, 2H), 2.6–2.5 (br, m, 2H); ^{13}C NMR ($CDCl_3$) δ 161.0 (s), 160.7 (d, J_{PC} = 20 Hz), 137.4–109.9, 55.0 (s), 34.3 (d, J_{PC} = 18.3 Hz), 25.8 (d, J_{PC} = 12.4 Hz); ^{31}P NMR ($CDCl_3$) δ −24.8 (s).

Phosphine–borane **6** (1.0 g, 1.7 mmol) was dissolved in a minimal amount of dry, degassed CH_2Cl_2 and dry, degassed Et_2NH (approximately 10 ml) was added via cannula. The reaction mixture was then heated at reflux under N_2 overnight. The slightly yellow mixture was then allowed to cool to room temperature and concentrate to approximately 3 ml under reduced pressure, and diluted with 10 ml of ether. The solution was filtered through an alumina pipette filter. The colorless filtrate was collected in a Schlenk flask under N_2, and removal of the volatiles under reduced pressure afforded pure **8** (0.95 g, 100% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.6–6.8 (m, 22 H), 3.8 (s, 6H), 2.7–2.9 (br, m, 4H), 2.3–2.6 (ddt, J_{HH} = 12.2, 5.4 Hz; J_{PH} = 58.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 161.0 (d, J_{PC} = 12.9 Hz), 142.9 (d, J_{PC} = 12.2 Hz), 137.5–110.2, 55.3 (s), 32.1 (d, J_{PC} = 19.4 Hz), 28.1 (d, J_{PC} = 11.1 Hz); ^{31}P NMR ($CDCl_3$) δ −24.9 (s).

3.5. General procedure for hydrosilylation with the ruthenium complexes and diphenylsilane

In a Schlenk tube, a solution of $[RuCl_2(C_6H_6)]_2$ (4.3×10^{-3} mmol, 0.5 mol%) and ligand **7** (0.189 ml, 0.1 M in toluene, 2.2 mol%) in THF (1 ml) was stirred at room temperature for 10 min, and was treated with AgOTf (4.4 mg, 2 mol%) for 30 min. After the addition of ketone (0.86 mmol), the mixture was cooled to 0 °C and Ph_2SiH_2 (0.255 ml, 160 mol%) was added dropwise by a syringe. The temperature was gradually raised to room temperature. The reaction was monitored by TLC or GC. After the completion of the reaction, methanol (2 ml) was added carefully at 0 °C. After gas evolution ceased, the reaction mixture was poured into a solution of hydrochloric acid (1 N, 5 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h and extracted with CH_2Cl_2 (10 ml × 4). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography on silica gel. The optical purity of the alcohol products were determined by GC (β-Dex GC Column) or HPLC (Chiralcel OD Column).

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