Pergamon

Tetrahedron, Vol. 53, No. 48, pp. 16503-16510, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)01031-4

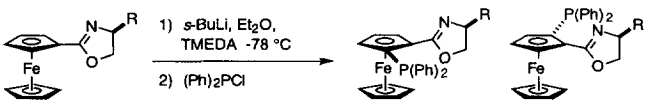
New Chiral Ligands for the Asymmetric Copper Catalyzed Conjugate Addition of Grignard Reagents to Enones

Eric L. Stangeland and Tarek Sammakia*

Department of Chemistry and Biochemistry, University of Colorado
Boulder, Colorado 80309-0215

Abstract: The copper catalyzed conjugate addition of *n*-butyl Grignard to enones in the presence of chiral ferrocenyl phosphine oxazoline ligands has been studied and found to provide useful levels of asymmetric induction. A comparison of the ferrocene derived ligands **3** and **6** with the corresponding phenyl derived ligands **8** and **9** reveals that the ferrocene template plays an essential role in the reaction.
© 1997 Elsevier Science Ltd.

As part of a broader program in asymmetric catalysis, we recently developed a highly diastereoselective method for the preparation of chiral ferrocene derivatives via the diastereoselective metalation and trapping of chiral ferrocenyl oxazolines (eq. 1).[1] One of the goals of this program is to systematically explore the use chiral



(1)

> 300 : 1

R = *i*-Pr(**3**), Me(**4**), Bn(**5**), Ph(**6**), *t*-Bu(**7**)

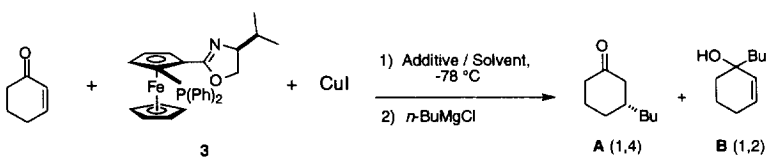
ferrocene derivatives as ligands for transition metal catalyzed reactions, and when feasible, to assess the influence of the "complexation induced chirality" imparted by the ferrocene system on the enantioselectivity of these reaction.[2,3] We describe in this article our studies on the use of chiral ferrocenyl oxazoline phosphine derivatives (**1**, Figure 1) as ligands for copper in the copper catalyzed conjugate addition of Grignards to enones.[4] We also briefly describe the use of chiral phenyl oxazoline phosphine derivatives (**2**, Figure 1) and compare the results obtained using these ligands to those obtained with our ferrocene ligands.

Figure 1 **1** **2**

The ligands required for this study were prepared as described in eq 1 by the metalation of the parent ferrocene oxazoline derivatives using *s*-BuLi in ether containing one equiv of TMEDA followed by trapping with chlorodiphenylphosphine. Ligands prepared by this procedure consist of a greater than 300:1 mixture of diastereomers. In most cases, any traces of the minor diastereomer can be removed by chromatography or by recrystallization.

Our initial goal in this study was to assess the influence of our ligands on the rate and enantioselectivity of the reaction. We therefore examined conjugate addition reactions in which we employed between 12 and 15 mol% of the valine derived ferrocenyl oxazoline phosphine (**3**) with 10 mol% copper iodide. As our substrates, we used cyclohexenone and *n*-BuMgCl, and assayed the enantioselectivity of the products by converting the ketone to the ketal derived from (2*R*,4*R*)-(-)-pentanediol and measuring the diastereomeric excess by capillary gas chromatography.[5] In our initial experiments, we had trouble obtaining consistent results, and after some experimentation, found that this was due to incomplete dissolution of the copper iodide. We, therefore, routinely stir the copper iodide-ligand solution at room temperature for 2 hours before adding the remainder of the reagents. With this modification of the reaction procedure, the reaction is completely reproducible. With a consistent procedure in hand, we measured the effects of solvent and additives on yield and enantioselectivity of the reaction and found that changes in these parameters can cause significant changes in the selectivity of the reaction. The most notable result is that THF is a poor choice of solvent for achieving high enantioselectivity. Thus, reactions run in ether or toluene (with no additives) provide enantiomeric excesses of 82% and 71%, while those run in THF provide an enantiomeric excess of only 12% (Table 1, entries 1, 5, and 6). We then examined the influence of TMSCl, MeI, and HMPA as additives on reactions run in ether (Table 1, entries 2-4). We found that these species either had no beneficial effect on the enantioselectivity of the reaction, or caused a decrease in the enantioselectivity, and did not consider their use further. We also performed a control experiment in which CuI was omitted and, not surprisingly, observed no conjugate addition (Table 1, entry 7).

Table 1: Survey of Reaction Conditions for the Conjugate Addition of Butyl Grignard to Cyclohexenone



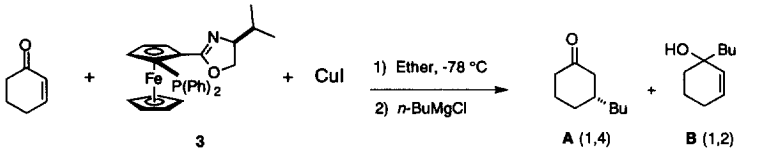
3 **A** (1,4) **B** (1,2)

Entry	%**3**	%CuI	Solvent	Additive[a]	A:B[b]	%ee	%Yield **A**[7]
1	15	10	Et_2O	None	15:1	82	80
2	15	10	Et_2O	TMSCl	12:1	82	74
3	15	10	Et_2O	CH_3I	7:1	83	77
4	15	10	Et_2O	HMPA	>100:1	56	80
5	12	10	Toluene	None	1.4:1	71	39
6	12	10	THF	None	126:1	12	87
7	15	0	Et_2O	None	<1:100	–	0

(a) 2 equivalents of additive were used. (b) As determined by GC of crude reaction mixture.

We also examined the effects of stoichiometry in the preparation of the catalyst and found that only a slight excess of the ligand relative to copper is necessary to achieve the best enantioselectivities (Table 2). The effect of catalyst loading on the reaction was then examined and we found that although the extent of conjugate addition is slightly improved at loadings higher than 10%, the enantioselectivity is unchanged within experimental error (Table 2, entries 1-3). However, if the catalyst loading is decreased below 10%, the extent of conjugate addition is slightly diminished (Table 2, entry 5).

Table 2: Effects of Stoichiometry of Catalyst Preparation and Catalyst Loading



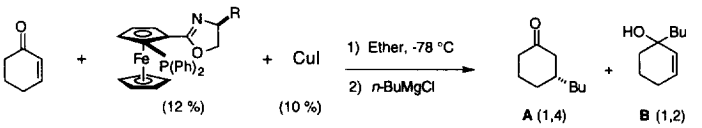
3 A (1,4) B (1,2)

Entry	%3	%CuI	A:B[a]	%ee	%Yield A[7]
1	120	100	19:1	84	84
2	30	10	11:1	84	91
3	15	10	15:1	82	80
4	12	10	10:1	83	80
5	7.5	5	7:1	81	61

(a) As determined by GC of crude reaction mixture.

We then set out to study the effects of varying the alkyl group of the oxazoline ring (Table 3). We found that the size of the alkyl group had little influence on the enantioselectivity of the reaction, with the exception of the *tert*-butyl substituted oxazoline. In this case, lower enantioselectivity and less conjugate addition was observed (Table 3, entry 5). This could be attributed to several factors, the most likely of which are a combination of steric inhibition to the formation of the copper-ligand complex, and a decreased reactivity of this complex such that conjugate addition catalyzed by free Cu salts in solution competes with the ligand bound copper species. Interestingly, the phenyl and benzyl substituted oxazoline ligands provide a dramatic increase in the preference for conjugate addition (Table 3, entries 3 and 4). We therefore chose to use the phenyl substituted oxazoline ligand for the remainder of our studies.[6]

Table 3: Effect of Variations of the Alkyl Group of the Oxazoline



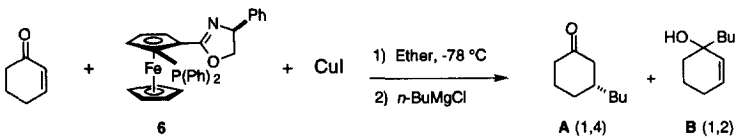
(12 %) (10 %) A (1,4) B (1,2)

Entry	R	A:B[a]	%ee	%Yield A[7]
1	*i*-Pr (**3**)	10:1	83	80
2	CH_3 (**4**)	5:1	81	68
3	Bn (**5**)	>100:1	82	97
4	Ph (**6**)	>100:1	83	97
5	*t*-Bu (**7**)	87:1	46	87

(a) As determined by GC of crude reaction mixture.

Given the greater efficacy of ligand **6** for conjugate addition and for enantioselectivity, we wished to examine the effects of catalyst loading using this ligand. We therefore compared catalyst loadings of 10%, 5% and 1%, and found that as the catalyst loadings decreased, both the enantioselectivity and extent of conjugate addition decreased. However, we note that with a catalyst loading of only 1%, we still observe 77% enantiomeric excess and an isolated yield of 74% .[7]

Table 4: Effects of Catalyst Loading on Yield and Selectivity



6 A (1,4) B (1,2)

Entry	%CuI	%6	A:B[a]	%ee	%Yield A[7]
1	10	12	>100:1	83	97
2	5	6	70:1	79	90
3	1	1.2	8:1	77	74

(a) As determined by GC of the crude reaction mixture.

We briefly explored the scope of this reaction and examined the addition of *n*-butyl Grignard to the enones shown in Table 5. We found that for cyclic enones, enantioselectivites increased as the ring size increased from cyclopentenone to cyclohexenone and cycloheptenone (Table 5, entries 1-3). Interestingly, the sense of asymmetric induction observed in the addition to cyclopentenone is tentatively assigned as the opposite of that observed in additions to cyclohexenone and cycloheptenone.[8] The origin of this effect is not clear and an explanation must await further mechanistic studies. We also examined the addition of *n*-butyl Grignard to the acyclic enone benzalacetone, and observed similar levels of asymmetric induction (Table 5, entry 4).

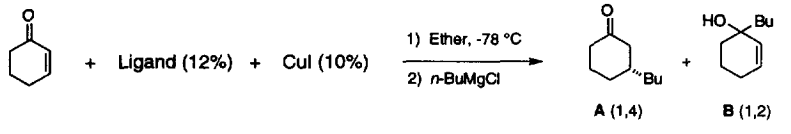
Table 5: Selectivity of Conjugate Additions to Various Enones using 12 % Ligand 6 and 10% CuI in Ether at -78°C

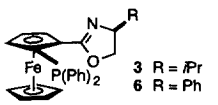
Entry	Enone	Product	1,4 : 1,2	%ee	%Yield[7]
1			>100:1	65	82
2			>100:1	83	97
3			>100:1	92	82
4			80:1	81	61

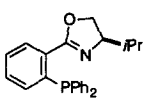
(a) The stereochemistry of this substrate has not been determined.

In order to study the importance of the planar chirality of the ferrocene template on the asymmetric induction of the reaction, we examine the use of an analogous ligand in which the ferrocene unit is replaced by a phenyl group (**8** and **9**, Table 6). We found that the ferrocene plays an essential role in determining the level of asymmetric induction and conjugate addition in this reaction. Thus, using the ferrocenyl derived ligand **3** or **6** for the addition of *n*-butyl Grignard to cyclohexenone we observe an enantiomeric excess of 83%. The corresponding phenyl derived ligands **8** and **9** (R=*i*-Pr, Ph) provide enantiomeric excesses of 26% and 0%, respectively. Furthermore, phenyl derived ligand **9** provides only a 6% yield of the conjugate addition product, and therefore suffers from poor chemical yields as well. Clearly the ferrocenyl template plays a major role in the

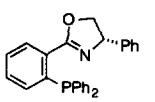
Table 6: Comparison of Ferrocenyl Derived Ligands with Phenyl Derived Ligands







8



9

Entry	Ligand	A:B[a]	%ee	%Yield A[7]
1	**3**	10:1	83	80
2	**6**	>100:1	82	97
3	**8**	60:1	-26[b]	77
4	**9**	1:10	0	6

(a) As determined by GC of crude reaction mixture. (b) The enantiomer of **A** is observed in this reaction, however the sense of asymmetric induction is the same as observed with the ferrocenyl ligands since the opposite enantiomer of the catalyst was used.

efficacy of this reaction.

In conclusion, we have found that catalysts derived from the ferrocenyl oxazoline phosphine ligands described in this article and CuI are effective for inducing asymmetry in the conjugate addition of Grignards to enones. Furthermore, we have found that the additional planar chirality imparted by the ferrocenyl template is essential for producing high levels of asymmetric induction. Our current efforts are focused on gaining a better understanding of the mechanism of these reaction and at using ligands **3** - **6** in other asymmetric catalytic processes.

Experimental Section:

General: All moisture sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glassware using solvents purified according to standard procedures. ^1H NMR spectra were obtained at 400 MHz and ^{13}C NMR spectra at 100 MHz in chloroform-*d*, with chemical shifts reported in PPM referenced to residual chloroform (7.24 PPM for ^1H and 77.0 PPM for ^{13}C). Infrared spectra were recorded as thin films on NaCl plates. Melting points are uncorrected. Gas chromatography was accomplished using a Supelco β-dex™ 120 column (β-cyclodextrin chiral phase) or Hewlett Packard HP-5 (crosslinked 5% Ph-Me-siloxane stationary phase) with H_2 as the carrier gas. Optical rotations were obtained at 589 nm on a Jasco DIP 370 polarimeter. Concentrations for optical rotations are reported in grams / mL.

Typical experimental procedure: 3-Butylcyclohexanone. Ligand **6** (62 mg, 1.2 x 10^{-3} mol, 0.12 equiv) and CuI (14 mg, 1.0 x 10^{-3} mol, 0.1 equiv) were placed in a 100 ml round bottom flask which was flushed with N_2. Diethyl ether (50 ml) was then transferred to the reaction flask via cannula and the solution was allowed to stir at room temperature until all the salts dissolved (at least 2 h). Cyclohexenone (97 µl, 1.0 x 10^{-3} mol, 1 equiv) was added via syringe and the reaction mixture was cooled to -78 °C. *n*-BuMgCl (1.2 ml of a 1.1M soln in Et_2O, 1.3 equiv) was added via syringe pump over 5 minutes. The reaction was allowed to stir for 30 min at -78 °C then was quenched with methanol (2 ml). After warming to room temperature, the reaction mixture was washed with 1M HCl, $NaHCO_3$, and brine, dried over $MgSO_4$ and concentrated at reduced

pressure. Flash chromatography (10:1 hexanes/ethyl acetate) provided 149 mg (97 %) of (*R*)-3-Butylcyclohexanone (83% ee). Enantiomeric excess was determined by formation of the ketal with (*R,R*)-2,4-pentanediol in refluxing toluene with catalytic PTSA and 4A MS for 30 min. The crude reaction mixture of the conjugate addition was analyzed for 1,2- vs 1,4-addition by GC (phenyl-methyl siloxane stationary phase), and the crude reaction mixture of the ketal formation reaction was analyzed by GC (either phenyl-methyl siloxane or β-cyclodextrin stationary phase).

Characterization of Ligands: Ligands were prepared according to the procedure provided in reference 1c.

Ligand **3**: R_f 0.6 (3:1 Hexanes/Ethyl Acetate); $[\alpha]^{23}_D$ = +25.6° (*c* 0.0067 g/ml, $CHCl_3$); IR ($CHCl_3$): 1645, 1477, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.65 (d, *J* = 6.69 Hz, 3H), 0.80 (d, *J* = 6.69 Hz, 3H), 1.63 (m, 1H), 3.58 (m, 1H), 3.65 (t, *J* = 8.2 Hz, 1H), 3.83 (m, 1H), 4.20 (s, 5H), 4.24 (t, *J* = 8.6 Hz, 1H), 4.34 (m, 1H), 4.96 (m, 1H), 7.16 - 7.50 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.5, 18.7, 32.0, 69.5, 70.7, 71.2, 72.0, 72.1 (d, *J* = 2.1 Hz), 73.8 (d, *J* = 3.6 Hz), 75.3 (d, *J* = 16.0 Hz), 78.5 (d, *J* = 14.5 Hz), 127.8, 128.0 (d, *J* = 6.5 Hz), 128.1 (d, *J* = 7.3 Hz), 128.9, 132.3 (d, *J* = 19.6 Hz), 134.8 (d, *J* = 21.1 Hz), 138.1 (d, *J* = 13.1 Hz), 139.4 (d, *J* = 13.1 Hz), 165.1; Anal. Calcd for $C_{28}H_{28}NOPFe$: C, 69.87; H, 5.86. Found: C, 69.83; H, 5.97.

Ligand **4**: R_f 0.5 (1:1 Hexanes/Ethyl Acetate); $[\alpha]^{23}_D$ = +95.2° (*c* 0.005 g/ml, $CHCl_3$); IR ($CHCl_3$): 1641, 1476, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.09 (d, *J* = 6.4 Hz, 3H), 3.34 (t, *J* = 8.2 Hz, 1H), 3.60 (m, 1H), 4.08 (m, 1H), 4.20 (s, 5H), 4.36 (m, 1H), 4.38 (t, *J* = 7.75 Hz, 1H), 4.97 (m, 1H), 7.16 - 7.49 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 61.6, 70.8, 71.0, 72.1 (d, *J* = 1.8 Hz), 73.9 (d, *J* = 4.0 Hz), 74.0, 74.9 (d, *J* = 15.6 Hz), 78.4 (d, *J* = 14.1 Hz), 127.9, 128.0 (d, *J* = 6.5 Hz), 128.2 (d, *J* = 7.3 Hz), 129.1, 132.3 (d, *J* = 19.3 Hz), 134.9 (d, *J* = 21.1 Hz), 138.0 (d, *J* = 12.4 Hz), 139.4 (d, *J* = 12.4 Hz), 170.3; Anal. Calcd for $C_{26}H_{24}NOPFe$: C, 68.89; H, 5.34; N, 3.09. Found: C, 68.62; H, 5.28; N, 3.23.

Ligand **5**: R_f 0.7 (3:1 Hexanes/Ethyl Acetate); $[\alpha]^{23}_D$ = +54.3° (*c* 0.0065 g/ml, $CHCl_3$); IR ($CHCl_3$): 1646, 1495, 1476, 1453, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.30 (dd, *J* = 9.4 and 13.6 Hz, 1H), 3.08 (dd, *J* = 4.6 and 13.6 Hz, 1H), 3.61 (t, *J* = 7.7 Hz, 1H), 3.64 (m, 1H), 4.17 (m, 1H), 4.18 (s, 5H), 4.26 (m, 1H), 4.37 (m, 1H), 4.97 (m, 1H), 7.11 - 7.50 (m, 15H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.7, 67.6, 70.8, 70.9, 71.7, 72.2, 74.0 (d, *J* = 4.0 Hz), 74.9 (d, *J* = 16.4 Hz), 77.2, 78.5 (d, *J* = 15.3 Hz), 126.3, 127.9, 128.1 (d, *J* = 6.6 Hz), 128.3 (d, *J* = 7.2 Hz), 128.4, 129.0, 132.4 (d, *J* = 18.5 Hz), 134.9 (d, *J* = 21.8 Hz), 138.0 (d, *J* = 13.0 Hz), 138.1, 139.6 (d, *J* = 12.7 Hz), 166.1; Anal. Calcd for $C_{32}H_{28}NOPFe$: C, 72.60; H, 5.33; N, 2.65. Found: C, 71.90; H, 5.51; N, 3.21.

Ligand **6**: R_f 0.5 (5:1 Hexanes/Ethyl Acetate); $[\alpha]^{23}_D$ = +36.8° (*c* 0.005 g/ml, $CHCl_3$); IR ($CHCl_3$): 1438, 1279, 1186 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.65 (m, 1H), 3.79 (t, *J* = 8.9 Hz, 1H), 4.26 (s, 5H), 4.40 (m, 1H), 4.66 (dd, *J* = 1.5, 9.9 Hz, 1H), 5.018 (m, 1H), 5.06 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.92 (m, 2H, ArH), 7.18 - 7.52 (m, 13H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 69.90, 70.80, 70.82, 70.97, 72.33 (d, *J* = 1.4 Hz), 73.97 (d, *J* = 3.6 Hz), 74.57 (d, *J* = 16.0 Hz), 74.9, 79.0 (d, *J* = 14.5 Hz), 126.8, 127.3, 128.2 (d, *J* = 6.5 Hz), 128.20, 128.25 (d, *J* = 7.3 Hz), 128.5, 129.0, 132. (d, *J* = 19.6 Hz), 134.7 (d, *J* = 19.6 Hz), 137.8 (d, *J* = 13.2 Hz), 139.6 (d, *J* = 13.1 Hz), 142.3; 166.9 Anal. Calcd for $C_{31}H_{26}NOPFe$: C, 72.25; H, 5.09, N, 2.72. Found: C, 72.05; H, 5.22, N, 2.87.

Ligand **7**: R_f 0.7 (3:1 Hexanes/Ethyl Acetate); $[\alpha]^{23}_D$ -74.1° (*c* 0.0049 g/ml, $CHCl_3$); IR ($CHCl_3$): 1644, 1479, 1434 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.75 (s, 9H), 3.58 (m, 1H), 3.71 (dd, *J* = 7.8 and 9.9 Hz, 1H), 3.83 (t, *J* = 8.3, 1H), 4.17 (dd, *J* = 8.6 and 9.7 Hz, 1H), 4.19 (s, 5H), 4.33 (m, 1H), 4.92 (m, 1H), 7.17 - 7.48 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.7, 33.5, 68.4, 70.6, 70.7, 72.1, 73.8 (d, *J* = 4.0 Hz), 75.5 (d, *J* = 16.7 Hz), 75.9, 78.6 (d, *J* = 14.5 Hz), 127.8, 127.9 (d, *J* = 6.9 Hz), 128.1 (d, *J* = 6.9 Hz), 128.8, 132.4 (d, *J* = 19.6 Hz), 134.9 (d, *J* = 21.4 Hz), 138.3 (d, *J* = 13.4 Hz), 139.6 (d, *J* = 12.4 Hz), 164.7; Anal. Calcd for $C_{29}H_{30}NOPFe$: C, 70.31; H, 6.10; N, 2.83. Found: C, 69.92; H, 6.12; N, 3.16.

Ligand **8**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (d, J = 6.7 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 1.44 - 1.52 (m, 1H), 3.81 - 3.89 (m, 2H), 4.10 - 4.165 (m, 1H), 6.85 - 6.88 (m, 1H, ArH), 7.26 - 7.35 (m, 12H, ArH), 7.88 - 7.91 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.3, 18.6, 32.7, 70.0, 73.1, 127.9, 128.18, 128.26, 128.30, 128.4, 128.5, 129.75, 129.78, 130.3, 131.9, 132.1, 133.59, 133.80, 133.81, 133.83, 134.15, 134.36, 138.05, 138.15, 138.27, 138.39, 138.70, 138.95, 162.9; ^{31}P NMR ($CDCl_3$) δ - 5.65.

o-Cyanophenyl(diphenyl)phosphine.[9] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 - 7.04 (m, 1H), 7.27 - 7.48 (m, 12H, ArH), 7.68 - 7.71 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 117.5, 117.81, 118.13, 128.77, 128.83, 128.85, 129.4, 132.3, 133.4, 133.70, 133.75, 133.92, 134.12, 134.64, 134.7, 142.97, 143.17; ^{31}P NMR ($CDCl_3$) δ - 8.65.

Ligand **9**. *o*-Cyanophenyl(diphenyl)phosphine (0.93 g, 3.2 mmol), (*S*)-phenylglycinol (0.48 g, 3.5 mmol), and $ZnCl_2$ (anh) (44 mg, 0.32 mmol) were place in a 10 ml round bottom flask attached to a condenser and then flushed with nitrogen. The reaction mixture was heated to 180 °C for 2h and allowed to cool. The reaction mixture was then diluted with diethyl ether (30 ml) and washed with water, dried over $MgSO_4$ and concentrated at reduced pressure. Flash chromatography (9:1 hexanes/ethyl acetate) gave 0.30 g (23%) ligand **9**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92 (t, J = 8.3 Hz, 1H), 4.54 (dd, J = 8.3, 9.5 Hz, 1H), 5.21 (t, J = 9.5 Hz, 1H), 6.88 - 6.90 (m, 3H, ArH), 7.13 - 7.39 (m, 16H, ArH), 7.97 - 8.00 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 70.10, 74.37, 126.64, 127.12, 128.05, 128.40, 128.51, 128.58, 128.71, 130.69, 131.34, 131.52, 133.78, 133.99, 134. 24, 134.46, 137.95, 138.98, 142.00; ^{31}P NMR ($CDCl_3$) δ - 6.51. In addition, *o*-Cyanophenyl-(diphenyl)phosphine (0.4 g, 37%) and (*S*)-phenylglycinol (0.16 g, 33%) was recovered from the reaction.

Characterization of Reaction Products:

(*S*)-3-Butylcyclopentanone: Enantiomeric excess = 65%; $[\alpha]^{23}_D$ - 86.58° (*c* 1.20, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 - 0.91 (m, 3H), 1.23 - 1.57 (m, 8H), 1.73 - 1.80 (m, 1H), 2.06 - 2.17 (m, 3H), 2.24 - 2.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.02, 22.74, 29.54, 30.05, 35.37, 37.19, 38.54, 45.33, 219.87. Enantiomeric excess was determined by ^{13}C analysis of the ketal derived from (2*R*,3*R*)-(-)-butanediol and integration of the diastereomeric resonances at δ = 44.91 (minor diastereomer) and 44.61 (major diastereomer) ; 38.01 (minor diastereomer) and 37.42 (major diastereomer) ; 37.95 (minor diastereomer) and 37.58 (major diastereomer) ; 30.51 (minor diastereomer) and 30.38 (major diastereomer) .

(*R*)-3-Butylcyclohexanone: Enantiomeric excess = 83%; $[\alpha]^{23}_D$ + 7.2° (*c* 1.14, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 - 0.87 (m, 3H), 1.24 - 1.34 (m, 7H), 1.52 - 1.76 (m, 2H), 1.83 - 1.93 (m, 1H), 1.96 - 2.04 (m, 2H), 2.18 - 2.41 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.00, 22.71, 25.30, 28.83, 31.32, 36.28, 35.06, 41.52, 48.24, 212.19. Enantiomeric excess was determined by GC analysis (phenyl-methyl siloxane or β-cyclodextrin stationary phase) of the ketal derived from (2*R*,4*R*)-(-)-pentanediol and integration of the GC signals (the major isomer is the faster eluting isomer).

(*R*)-3-Butylcycloheptanone: Enantiomeric excess = 92%; $[\alpha]^{23}_D$ + 31.4° (*c* 1.18, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.84 - 0.88 (m, 3H), 1.20 - 1.42 (m, 8H), 1.55 - 1.65 (m, 2H), 1.81 - 1.90 (m, 3H), 2.32 - 2.47 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.03, 22.74, 24.41, 28.54, 29.13, 36.02, 36.90, 43.90, 49.98, 214.76. Enantiomeric excess was determined by GC analysis of the conjugate addition product directly by GC using β-cyclodextrin as the stationary phase (the major isomer is the slower eluting isomer).

4-Phenyloctan-2-one: Enantiomeric excess = 81%; $[\alpha]^{23}_D$ + 36.3° (*c* 1.23, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (t, J = 7.2 Hz, 3H), 1.01 - 1.31 (m, 4H), 1.48 - 1.64 (m, 2H), 1.99 (s, 3H), 2.64 - 2.74 (m, 2H), 3.05 - 3.12 (m, 1H), 7.14 - 7.28 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.93, 22.58, 29.55, 30.64, 36.17, 41.27, 50.95, 126.28, 127.45, 128.43, 144.60, 208.04. Enantiomeric excess was determined by GC analysis (phenyl-methyl siloxane stationary phase) of the corresponding imine derived from *S*-(-)-α-methylbenzylamine (the major isomer is the slower eluting isomer).

Acknowledgments. We thank the National Institutes of Health (GM48498), Novartis Pharmaceuticals Corporation, and Pfizer for financial support of this research. T.S. is a recipient of an American Cancer Society Junior Faculty Research Award and is an Alfred P. Sloan Research Fellow.

1 (a) Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10; (b) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1995**, *60*, 6002; (c) Sammakia, T.; Latham, H. A. *J. Org. Chem.* **1996**, *61*, 1629. For related work on the metalation of ferrocene oxazolines, see: (d) Richards, C. J.; Damalidis, T.; Hibbs, D. E.; Hursthouse, M. B. *Synlett* **1995**, 74; (e) Nishibayashi, Y.; Uemura, S. *Synlett* **1995**, 79; Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3748; (f) Park, J.; Lee, S.; Ahn, K. H.; Cho, C.-W. *Tetrahedron Lett.* **1995**, *36*, 7263; (g) Richards, C. J.; Mulvaney, W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419; (h) Zhang, W.; Hirao, I.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545; (i) Zhang, W.; Adachi, Y.; Ikeda, I. *Tetrahedron: Asymmetry* **1996**, *7*, 451; (j) Ahn, K. H.; Cho, C-W.; Baek, H-H.; Park, J.; Lee, S. *J. Org. Chem.* **1996**, *61*, 4937.

2 Abbenhuis, H. C. L.; Burckhardt, U.; Gramlich, V.; Martelletti, A.; Spencer, J.; Steiner, I.; Togni, A. *Organometallics* **1996**, *15*, 1614.

3 For examples of the use of related ligands in asymmetric catalysis, see: Nishibayashi, Y.; Segawa, K.; Ohe, K.; Uemura, S. *Organometallics* **1995**, *14*, 5486; Richards, C. J.; Hibbs, D. E.; Hursthouse, M. B. *Tetrahedron Lett.* **1995**, *36*, 3745; Zhang, W.; Hirao, T.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 4545; Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419; Zhang, W. B.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Tetrahedron Lett.* **1996**, *37*, 7995.

4 (a) For a recent review, see: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. For more recent work, see (b) Tomioka, K.; Kanai, M. Koga, K. *Tetrahedron Lett.* **1992**, *33*, 7193; (c) Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, E. F.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965; (d) Tanaka, K.; Matsui, J.; Suzuki, H. *J. Chem. Soc. Perkin Trans 1* **1993**, 153; (e) Pfaltz, A.; Zhou, Q. *Tetrahedron Lett.* **1993**, *34*, 7725; (f) Tanaka, K.; Matsui, J.; Somemiya, K.; Suzuki, H. *SynLett* **1994**, 351; (g) Pfaltz, A.; Zhou, Q. *Tetrahedron* **1994**, *50*, 4467; (h) Rossiter, B. E.; Swingle, N. M.; Reddy, K. V. *Tetrahedron* **1994**, *50*, 4455; (i) Alexakis, A.; Frutos, J.; Mangeny, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427; (j) Tomioka, K.; Kanai, M. *Tetrahedron Lett.* **1994**, *35*, 895; (k) van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G. V. *Tetrahedron Lett.* **1994**, *35*, 6135; (l) Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455; (m) Tomioka, K.; Kanai, M. *Tetrahedron Lett.* **1995**, *36*, 4273; (n) Tomioka, K.; Kanai, M. *Tetrahedron Lett.* **1995**, *36*, 4275; (o) Miao, G.; Rossiter, B. *J. Org. Chem.* **1995**, *60*, 8424; (p) Cran, G. A.; Gibson, C. L.; Handa, S.; Kennedy, A. R. *Tetrahedron: Asymmetry* **1996**, *7*, 2511.

5 The best separation of the diastereomers was observed using a chiral stationary phase (β-cyclodextrin). The absolute configuration of the product was determined by comparison of the optical rotation of our product with that reported by Seebach See: Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710.

6 We examined two other solvents with this ligand, methyl-*tert*-butyl ether (MTBE) and *iso*-propyl ether and found both to be inferior to ethyl ether. In the case of MTBE, the enantioselectivity was slightly dimished (72% ee) whereas with *iso*-propyl ether the CuI-ligand complex did not dissolve, and we observed 13% conjugate addition and no enantioselectivity.

7 All yields refer isolated yields of homogenous products purified by flash chroatography.

8 Other workers have prepared this substrate and assigned the stereochemistry as we have. However, we consider this assignment as tentative since we could find no definitive stereochemical assignment of 3-*n*-butyl-cyclopentanone. Pfaltz has assigned the (+) isomer the (*R*)-configuration based on the observed Cotton effect.

9 Prepared according to the procedure reported by Storhoff, B. N.; Harper, D. P.; Saval, I. H.; Worstell, J. H. *J. Organomet. Chem.* **1981**, *205*, 161.

(*Received* 6 *January* 1997; *accepted* 9 *March* 1997)