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Synthesis of a Trans-Chelating Chiral Diphosphine Ligand with Only Planar Chirality and its Application to Asymmetric Hydrosilylation of Ketones

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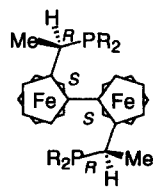
Abstract

Optically active diphosphine (*S*,*S*)-2,2"-bis[(diethylphosphino)methyl]-1,1"-biferrocene (abbreviated to (*S*,*S*)-EtTRAP-H) was synthesized from ferrocenyloxazoline derived from L-valinol in 47% overall yield. The new chiral ligand, (*S*,*S*)-EtTRAP-H, which coordinates to a rhodium atom in a trans-chelating manner, was effective for asymmetric hydrosilylation of ketones to give optically active secondary alcohols with up to 94% ee.

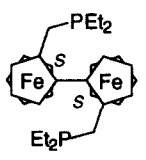
Key Words: Asymmetric reactions; Catalysts; Ferrocenes; Reduction

As reported in the preceding papers, chiral diphosphine ligands, TRAP (**1**), which coordinate to transition metals with trans-chelation [1–3], have been utilized as efficient catalysts for some enantioselective reactions.[4–16] The chiral diphosphines **1**, which possess the central chirality at the α-position of the phosphorus atoms as well as planar chirality due to the unsymmetrical disubstitution on the cyclopentadienes, provided high enantioselectivities, depending on the choice of *P*-substituents of TRAP. Herein, we wish to describe preparation of a new trans-chelating chiral diphosphine, (*S*,*S*)-2,2"-bis[(diethylphosphino)methyl]-1,1"-biferrocene (**2**) (abbreviated to EtTRAP-H), which has only planar chirality, and its application to catalytic asymmetric reduction of simple ketones with hydrosilane (hydrosilylation).[4–6,17–26]

Trans-chelating chiral diphosphine (*S*,*S*)-EtTRAP-H was synthesized from optically active ferrocenyloxazoline (*S*)-**3** derived from L-valinol as shown in Scheme 1. Diastereoselective ortholithiation of (*S*)-**3** according to Sammakia's procedure [27] followed by treatment with 1,2-diiodoethane gave iodoferrocene (*S*)-(*S*)-**4**, in which *S*-planar chirality was newly induced [(*S*)-



(*R*,*R*)-(*S*,*S*)-TRAP (**1**)



(*S*,*S*)-EtTRAP-H (**2**)

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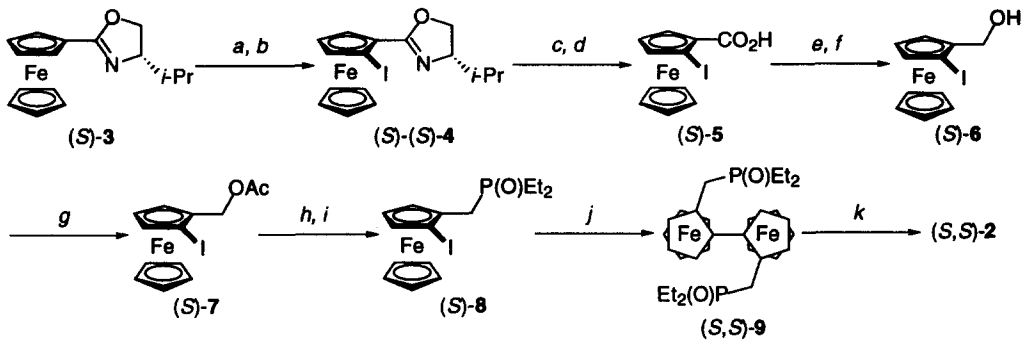


Scheme 1. *Reagents and conditions:* [a] *sec*-BuLi, TMEDA, hexane, –78 °C, 2 h; [b] $I(CH_2)_2I$, hexane–THF, –78 °C to rt (91% from **3**); [c] MeOTf, CH_2Cl_2, 0 °C, 30 min; [d] 10% KOH aq., EtOH, reflux, 17 h (93% from **4**); [e] $(COCl)_2$, CH_2Cl_2, rt, 1 h; [f] $NaBH_4$, THF, rt, 10 h (85% from **5**); [g] Ac_2O, Et_3N, DMAP *cat.*, THF, rt, 1 h (100%); [h] $HPEt_2$, AcOH, 80 °C, 30 min; [i] 30% H_2O_2 aq., acetone, 0 °C, 5 min (90% from **7**); [j] Cu (neat), 80 °C, 24 h (74%); [k] $HSiCl_3$, Et_3N, C_6H_6, 100 °C, 10 h (99%).

(*S*)-**4**/(*S*)-(*R*)-**4** = 99:1]. The oxazolinium ion of (*S*)-(*S*)-**4** prepared by treatment with MeOTf was hydrolyzed with KOH to give planar chiral (*S*)-**5**. The carboxylic acid was converted into alcohol (*S*)-**6** by reduction with $NaBH_4$ of the corresponding acyl chloride.[28] After acetylation of **6**, substitution reaction of **7** with diethylphosphine in acetic acid followed by oxidation with H_2O_2 gave phosphine oxide (*S*)-**8**. A homocoupling of (*S*)-**8** was performed with activated copper powder, and the phosphine oxide (*S*,*S*)-**9** isolated was reduced with $HSiCl_3$–Et_3N to give (*S*,*S*)-EtTRAP-H (**2**).[29] The overall yield of (*S*,*S*)-**2** was 47% from (*S*)-**3**.

The chiral diphosphine **2** reacted with 0.5 molar equivalent of $[RhCl(CO)_2]_2$ in CD_2Cl_2 to give a single rhodium complex, RhCl(CO)[(*S*,*S*)-EtTRAP-H], whose ^{31}P NMR exhibited a pair of double doublet peaks at δ 20.84 and 26.48 ppm with J_{P-P} = 340 Hz (J_{P-Rh} = 119 and 120 Hz, respectively) (Figure 1). The large P–P spin coupling constant is characteristic of a *trans*-bis(phosphine)–metal complex. This observation may indicate that α-alkyl branching on the phosphorus atoms of **1** is not indispensable for the trans-chelating structure of TRAP ligands.

EtTRAP-H (**2**) thus obtained was applied to rhodium-catalyzed asymmetric hydrosilylation of simple ketones. After stirring a solution of (*S*,*S*)-**2** (3.2 mg, 5.6 μmol) and $[Rh(COD)_2]BF_4$ (2.0 mg, 4.9 μmol) in THF (0.5 ml) for 10 min, ketone **10** (0.5 mmol) and dihydrosilane **11** (0.75 mmol) were added to the solution at the indicated reaction temperature and stirred. The reaction

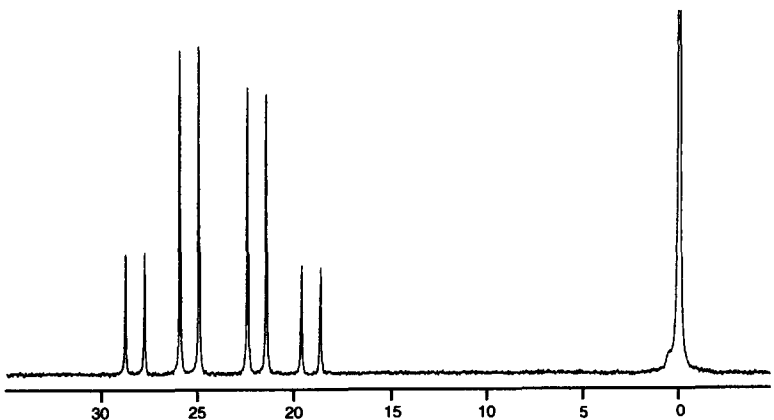
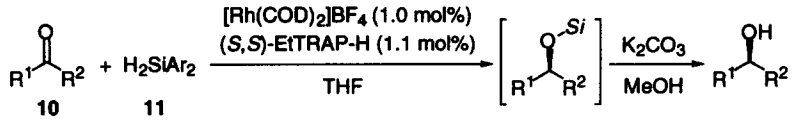


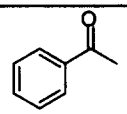
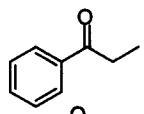
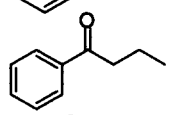
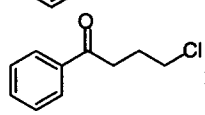
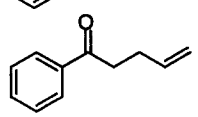
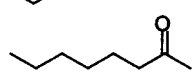
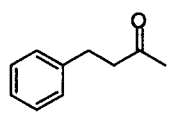
Figure 1. $^{31}P\{^1H\}$ NMR Spectrum (121.5 MHz, CD_2Cl_2, 85% H_3PO_4 aq) of *trans*-RhCl(CO)[(*S*,*S*)-EtTRAP-H].

Table 1. Asymmetric Hydrosilylation of Ketones Catalyzed by (*S*,*S*)-TRAP-H–Rhodium Complex.[a]



10 11

Ar = Ph (**11a**), *m*-FC_6H_4 (**11b**)

entry	ketone (**10**)	**11**	temp, °C	time, h	yield, %[b]	ee, %	config[c]
1	 **10a**	**11a**	–40	4	89	94[d]	*S*
2	 **10b**	**11a**	–30	24	96	80[e]	*S*
3		**11b**	–40	24	99	88[e]	*S*
4	 **10c**	**11b**	–40	24	93	89[e]	*S*
5	 **10d**	**11b**	–40	24	99	88[f]	—
6	 **10e**	**11b**	–40	24	90	89[e]	—
7	 **10f**	**11a**	–50	48	82[g]	77[h]	*S*
8	 **10g**	**11a**	–50	48	94	81[e]	*S*

[a] All reactions were carried out in THF (1.0 M). The ratio of **10**:**11**:[$Rh(COD)_2$]BF_4:(*S*,*S*)-TRAP-H was 100:150:1:1.1. [b] Isolated yield by PTLC unless otherwise noted. [c] Assigned by specific rotation. [d] Determined by chiral GLC analysis with Chiraldex G-TA. [e] Determined by chiral HPLC analysis with Chiralcel OB-H. [f] Determined by chiral HPLC analysis with Chiralcel OD-H. [g] Isolated yield by MPLC. [h] Determined by chiral HPLC analysis of the *N*-(3,5-dinitrophenyl)carbamate derivative with Sumichiral OA-4500.

mixture was quenched with 0.1% K_2CO_3 solution in MeOH (1.0 ml), stirred at room temperature over 4 h, and evaporated under reduced pressure. The residue was subjected to purification with PTLC or MPLC to give the corresponding optically active alcohol.

The results are summarized in Table 1. In general, EtTRAP-H was more effective for the asymmetric hydrosilylation than other TRAP ligands (**1**). The reaction of acetophenone (**10a**) with diphenylsilane (**11a**) using (*S*,*S*)-EtTRAP-H yielded (*S*)-1-phenylethanol with 94% ee (entry 1) (cf. EtTRAP: 85% ee, BuTRAP: 92% ee).[4] The results indicate that the planar chirality of **1** would be more important for the enantiofaceselection of ketone than the central chirality. Remarkable improvement of the enantioselectivities by EtTRAP-H was observed in the reduction of phenyl alkyl ketones **10b–e**. Although the reaction of **10b** proceeded sluggishly with 62% ee by a BuTRAP–rhodium catalyst, the EtTRAP-H–rhodium catalyst gave 80% ee of (*S*)-1-phenylpropanol in high yield (entry 2). Use of **11b** as a reducing agent brought about increase in

the enantioselectivity, giving 88% ee of the product (entry 3). Other ketones **10c–e** were also converted into the corresponding alcohols in 88–89% ee (entry 4–6). Functional groups such as chloro and olefin on the ketonic substrates were tolerable in the asymmetric hydrosilylation using the EtTRAP-H–rhodium catalyst.

Asymmetric reduction of linear 2-alkanone is a challenging goal in modern organic chemistry. Of note is that the EtTRAP-H–rhodium catalyst was effective for the hydrosilylation of 2-octanone (**10f**) to give (*S*)-2-octanol with 77% ee (entry 7). To the best of our knowledge, the enantioselectivity is the highest attained in catalytic asymmetric reduction of linear 2-alkanones.[30] Primary alkyl methyl ketone **10g** having a phenyl group at the β-position was also reduced with high enantioselectivity (entry 8).[31]

In summary, we have succeeded in the synthesis of a new trans-chelating diphosphine EtTRAP-H with only planar chirality, and demonstrated that the chiral diphosphine coordinates to a rhodium atom in a trans-chelating manner. EtTRAP-H thus obtained was more effective for asymmetric hydrosilylation of ketones than other TRAP ligands reported previously. Further development of the related TRAP-Hs bearing other *P*-substituents and their application to catalytic asymmetric reactions are now in progress.

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[28] Enantiomeric excess of (*S*)-**6** was determined by chiral HPLC analysis of Chiralcel OJ to be 99% ee.
[29] (*S,S*)-**2**: Orange oil; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 0.88 (dt, *J* = 14.1, 7.2 Hz, 6H), 0.97 (dt, *J* = 14.4, 7.5 Hz, 6H), 1.12–1.32 (m, 8H), 2.28 (dd, *J* = 15.0, 2.3 Hz, 1H), 4.20 (d, *J* = 1.8 Hz, 2H), 4.27 (s, 5H), 4.40 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.32 (d, *J* = 12.7 Hz), 9.67 (d, *J* = 13.9 Hz), 18.97 (d, *J* = 12.7 Hz), 19.09 (d, *J* = 11.6 Hz), 25.2 (d, *J* = 14.9 Hz), 65.98, 68.46 (d, *J* = 6.9 Hz), 69.68, 70.47, 84.62, 86.76 (d, *J* = 11.5 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ –17.67.
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