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Highly enantioselective hydrosilylation of simple ketones catalyzed by rhodium complexes of P-chiral diphosphine ligands bearing *tert*-butylmethylphosphino groups

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Abstract—P-Chiral diphosphine ligands, (*S*,*S*)-1,2-bis(*tert*-butylmethylphosphino)ethane [(*S*,*S*)-*t*-Bu-BisP*], (*R*,*R*)-bis(*tert*-butylmethylphosphino)methane [(*R*,*R*)-*t*-Bu-MiniPHOS], and (*R*,*R*)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline [(*R*,*R*)-QuinoxP*], were applied to the rhodium-catalyzed enantioselective hydrosilylation of simple ketones. The corresponding secondary alcohols were obtained in high yields with good to excellent enantiomeric excesses of up to 99%.

1. Introduction

The asymmetric reduction of ketones to produce optically active secondary alcohols constitutes a most fundamental and synthetically important organic transformation, and extensive investigations have been carried out over the last two decades to develop practically useful methodologies. The ruthenium-catalyzed asymmetric hydrogenation of simple ketones is a landmark discovery in this area along with the asymmetric hydrogen-transfer reaction.[1] The enantioselective hydrosilylation of prochiral ketones is also an attractive reaction.[2] Since the pioneering work by Nishiyama and Itoh using rhodium complexes of tridentate pyridine–bisoxazoline ligands (Pybox), this area has seen significant development.[3] The most successful results are based on the use of chiral bidentate ligands containing nitrogen, oxygen, sulfur, or carbon donor atoms. In particular, P,N-,[4] P,S-,[5] P,C-,[6] N,C-[7] mixed or N,N-,[3,8] C,C-[9] homo bidentate ligands afford high to excellent enantioselectivities.[10] In contrast, most of the diphosphine ligands give rise to low enantioselectivities in the rhodium-catalyzed asymmetric hydrosilylation of ketones, except for *trans*-chelating diphosphine ligands that are quite effective in achieving exceedingly high enantioselectivities of up to 99%.[11]

We previously synthesized a new P-chiral diphosphine ligand, (*S*,*S*)-1,1′-bis(*tert*-butylmethylphosphino)ferrocene **1**, and tested its asymmetric induction ability in the rhodium-catalyzed hydrosilylation of ketones.[12] The good to high enantioselectivities observed of up to 92% are an indication of its potential utility as a chiral ligand in this type of asymmetric reaction. On the other hand, we prepared structurally similar P-chiral ligands, (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethane (BisP*),[13] (*R*,*R*)-bis(alkylmethylphosphino)methane (MiniPHOS),[14] and (*R*,*R*)-2,3-bis(*tert*-butylmethylphosphino)quinoxaline (QuinoxP*),[15] and observed very high to almost perfect enantioselectivities when these were employed in the rhodium-catalyzed asymmetric hydrogenations of enamides and related substrates. These experimental findings prompted us to examine the enantioinduction abilities of these *cis*-chelating diphosphine ligands in the rhodium-catalyzed asymmetric hydrosilylation of ketones. Herein, we report the hydrosilylation results and discuss the enantioselection mechanism induced by these P-chiral diphosphine ligands.[16]

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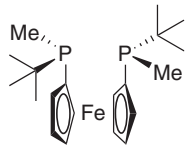

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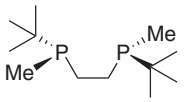
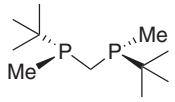
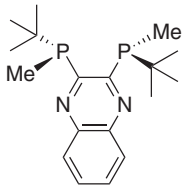


(*S,S*)-*t*-Bu-BisP*



(*R,R*)-*t*-Bu-MiniPHOS



(*R,R*)-QuinoxP*

2. Results and discussion

2.1. Scope of asymmetric hydrogenation catalyzed by rhodium complexes of BisP*, MiniPHOS, and QuinoxP*

Our initial trials for the rhodium-catalyzed asymmetric hydrosilylation using BisP*, MiniPHOS, and QuinoxP* as chiral ligands were carried out using acetophenone as the model substrate. We tested and compared various reaction conditions by changing silane reagents, and the results are summarized in Table 1.

It was noted that in the BisP* ligands, the enantioselectivity was increased with increasing size of the substituent at the phosphorus atoms (entries 1, 3, and 4). Thus, (*S,S*)-1-Ad-BisP* gave the highest selectivity (91%) when diphenylsilane was used. It is also noteworthy that the level of enantioselectivity was highly dependent on the choice of silane reagents; the bulkiest reagent, α-naphthylphenylsilane, afforded higher enantioselectivities than less bulky diphenylsilane and phenylsilane.

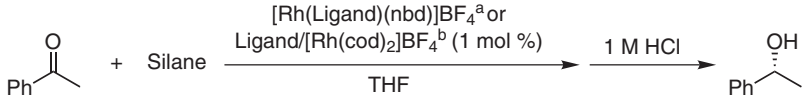
Based on the optimization study described in Table 1, various ketones, including aliphatic ones were subjected to hydrosilylation with α-naphthylphenylsilane by using (*S,S*)-*t*-Bu-BisP*, (*R,R*)-*t*-Bu-MiniPHOS, and (*R,R*)-QuinoxP* as chiral ligands. All reactions were carried out in THF with a catalyst loading of 1%. The results are listed in Table 2.

In the series of aryl methyl ketones, considerably high enantioselectivities were observed and the highest selectivity (99%) was achieved for the reduction of 2-methoxyphenyl methyl ketone by the use of *t*-Bu-BisP* (entry 15). When alkyl phenyl ketones, which had a larger alkyl group than the methyl group were used, the reactions proceeded rather slowly and afforded decreased enantioselectivities (entries 4–7). In particular, the reaction of *tert*-butyl phenyl ketone was extremely sluggish, giving only trace amounts of the corresponding product (entry 7).

Cyclic aromatic ketones were reduced in good enantioselectivities (70–82% ee) (entries 22–24). However, the results are inferior compared with the previously reported excellent results (84–98% ee) obtained by the use of P,S- and P,N-mixed ligands[4c,5] and *trans*-chelating diphosphine ligands.[11c]

The reduction of dialkyl ketones proceeded in moderate selectivities, except for the reaction of 1-adamantyl methyl ketone. The latter reaction, which used *t*-Bu-MiniPHOS as the chiral ligand resulted in 99% enantioselectivity (entry 34). This excellent asymmetric

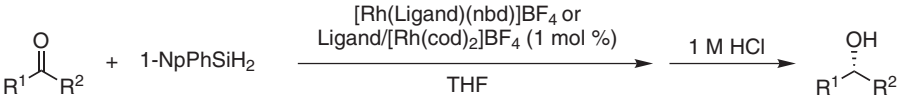
Table 1. Asymmetric hydrosilylation of acetophenone



Entry	Ligand	Silane	Temp.	Time (h)	Yield (%)[c]	ee (%)[d]
1	(*S,S*)-*t*-Bu-BisP*	Ph_2SiH_2	−20 °C	30	89	82
2	(*S,S*)-*t*-Bu-BisP*	1-NpPhSiH$_2$	−20 °C	30	99	93
3	(*S,S*)-Cy-BisP*[e]	Ph_2SiH_2	−20 °C	30	80	75
4	(*S,S*)-1-Ad-BisP*[f]	Ph_2SiH_2	−20 °C	30	99	91
5	(*S,S*)-1-Ad-BisP*[f]	1-NpPhSiH$_2$	−20 °C	30	86	95
6[g]	(*R,R*)-*t*-Bu-MiniPHOS	1-NpPhSiH$_2$	−40 °C	30	86	91
7	(*R,R*)-QuinoxP*	$PhSiH_3$	rt	2	11[h]	10
8	(*R,R*)-QuinoxP*	Ph_2SiH_2	rt	2	22[h]	71
9	(*R,R*)-QuinoxP*	1-NpPhSiH$_2$	rt	2	>98[h]	88
10	(*R,R*)-QuinoxP*	1-NpPhSiH$_2$	0 °C	2	98	89
11	(*R,R*)-QuinoxP*	*n*-Hex$_3$SiH	rt	2	Trace	n.d.

[a] Entries 1–5.
[b] Entries 7–11.
[c] Isolated yield.
[d] Enantiomeric excesses were determined by HPLC analysis using a chiral column.
[e] (*S,S*)-1,2-Bis(cyclohexylmethylphosphino)ethane.
[f] (*S,S*)-1,2-Bis(1-adamantylmethylphosphino)ethane.
[g] [Rh((*R,R*)-*t*-Bu-MiniPHOS)$_2$]BF$_4$ was used as the precursor catalyst.
[h] Determined by NMR relative to unreacted acetophenone.

Table 2. Asymmetric hydrosilylation of ketones



Entry	R^1	R^2	Ligand	Temp. (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	Ph	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	99	93 (*R*)
2[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	30	86	91 (*R*)
3			(*R*,*R*)-QuinoxP*	0	2	98	89 (*R*)
4	Ph	Et	(*S*,*S*)-*t*-Bu-BisP*	−20	30	87	86 (*R*)
5[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−20	72	81	83 (*R*)
6	Ph	iPr	(*S*,*S*)-*t*-Bu-BisP*	−20	30	41	rac.
7	Ph	*t*-Bu	(*S*,*S*)-*t*-Bu-BisP*	−20	30	Trace	n.d.
8	2-MeC_6H_4	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	83	90 (*R*)
9[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	96	95 (*R*)
10			(*R*,*R*)-QuinoxP*	0	4	94	86 (*R*)
11	3-MeC_6H_4	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	94	89 (*R*)
12[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	0	72	83	89 (*R*)
13	4-MeC_6H_4	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	99	91 (*R*)
14			(*R*,*R*)-QuinoxP*	0	3	91	82 (*R*)
15	2-$MeOC_6H_4$	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	99	99 (*R*)
16[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−15	72	88	90 (*R*)
17			(*R*,*R*)-QuinoxP*	0	2	72	56 (*R*)
18	1-Np	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	99	89 (*R*)
19[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	90	97 (*R*)
20	2-Np	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	95	94 (*R*)
21[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	99	94 (*R*)
22	1-Indanone		(*R*,*R*)-QuinoxP*	0	2	77	79 (*R*)
23	1-Tetralone		(*S*,*S*)-*t*-Bu-BisP*	−20	30	78	82 (*R*)
24			(*R*,*R*)-QuinoxP*	0	2	99	70 (*R*)
25	$PhCH_2CH_2$	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	99	79 (*R*)
26[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−20	72	93	80 (*R*)
27	$Ph(CH_2)_2CH_2$	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	93	77 (*R*)
28[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	94	71 (*R*)
29	*n*-Hex	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	81	72 (*R*)
30[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	83	77 (*R*)
31	Cy	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	82	87 (*R*)
32[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	76	58 (*R*)
33	1-Ad	Me	(*S*,*S*)-*t*-Bu-BisP*	−20	30	63	70 (*R*)
34[c]			(*R*,*R*)-*t*-Bu-MiniPHOS	−40	72	94	99 (*R*)
35	Ethyl 2,2-dimethyl-3-oxobutanoate		(*R*,*R*)-QuinoxP*	0	2	75	97 (*R*)
36	2,4-$Cl_2C_6H_3$	CH_2Cl	(*S*,*S*)-*t*-Bu-BisP*	−10	72	82	99 (*S*)
37			(RJJ)-QuinoxP*	0	2	95	94 (*S*)

[a] Isolated yield.
[b] Enantiomeric excesses were determined by HPLC analysis or GC analysis by using chiral columns.
[c] [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]BF_4 was used as the precursor catalyst.

induction is probably a consequence of the large difference in bulkiness between 1-adamantyl and methyl groups and the asymmetric environment imposed by the four-membered rhodium complex.

Finally, we examined the asymmetric hydrosilylation of 2,2′,4′-trichloroacetophenone to obtain the corresponding optically active alcohol that is used as a precursor for the synthesis of (*R*)-(−)-(*E*)-[4-(2,4-dichlorophenyl)-1,3-dithiolan-2-ylidene]-1-imidazoleacetonitrile (NND-502, Luliconazole), an antifungal agent.[17] The reaction that used (*S*,*S*)-*t*-Bu-BisP* as the ligand afforded the product in 82% yield with 99% ee (entry 36), although it required a long reaction time at −10 °C. The use of (*R*,*R*)-QuinoxP* at 0 °C shortened the reaction time to give the product in 95% yield with 94% ee (entry 37).

The results shown in Table 2 suggest the potential utility of the *cis*-chelating P-chiral diphosphine ligands in the rhodium-catalyzed asymmetric hydrosilylation of prochiral ketones to prepare optically active secondary alcohols.

2.2. Mechanistic aspect

It was interesting to consider the enantioinduction mechanism of the asymmetric hydrosilylation catalyzed by the rhodium complexes of the P-chiral diphosphine ligands. The rhodium complexes of (*S*,*S*)-*t*-Bu-BisP*, (*R*,*R*)-*t*-Bu-MiniPHOS, and (*R*,*R*)-QuinoxP* used in this study are C_2-symmetric and possess the same structural motif in their quadrant diagrams, as illustrated in Figure 1. Thus, the two bulky *tert*-butyl groups occupy the upper left and lower right quadrants and the two

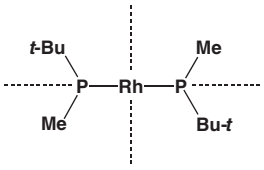
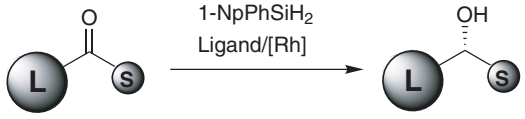


Figure 1. Quadrant diagram of the rhodium complexes of (*S*,*S*)-*t*-Bu-BisP*, (*R*,*R*)-*t*-Bu-MiniPHOS, and (*R*,*R*)-QuinoxP*.

smallest alkyl groups (two methyl groups) are located at the upper right and lower left quadrants. It should be noted that all asymmetric hydrosilylations catalyzed by these rhodium complexes provided the same sense of enantioselection, based on predictions of the relative size of the two ketone substituents, as depicted in Scheme 1.

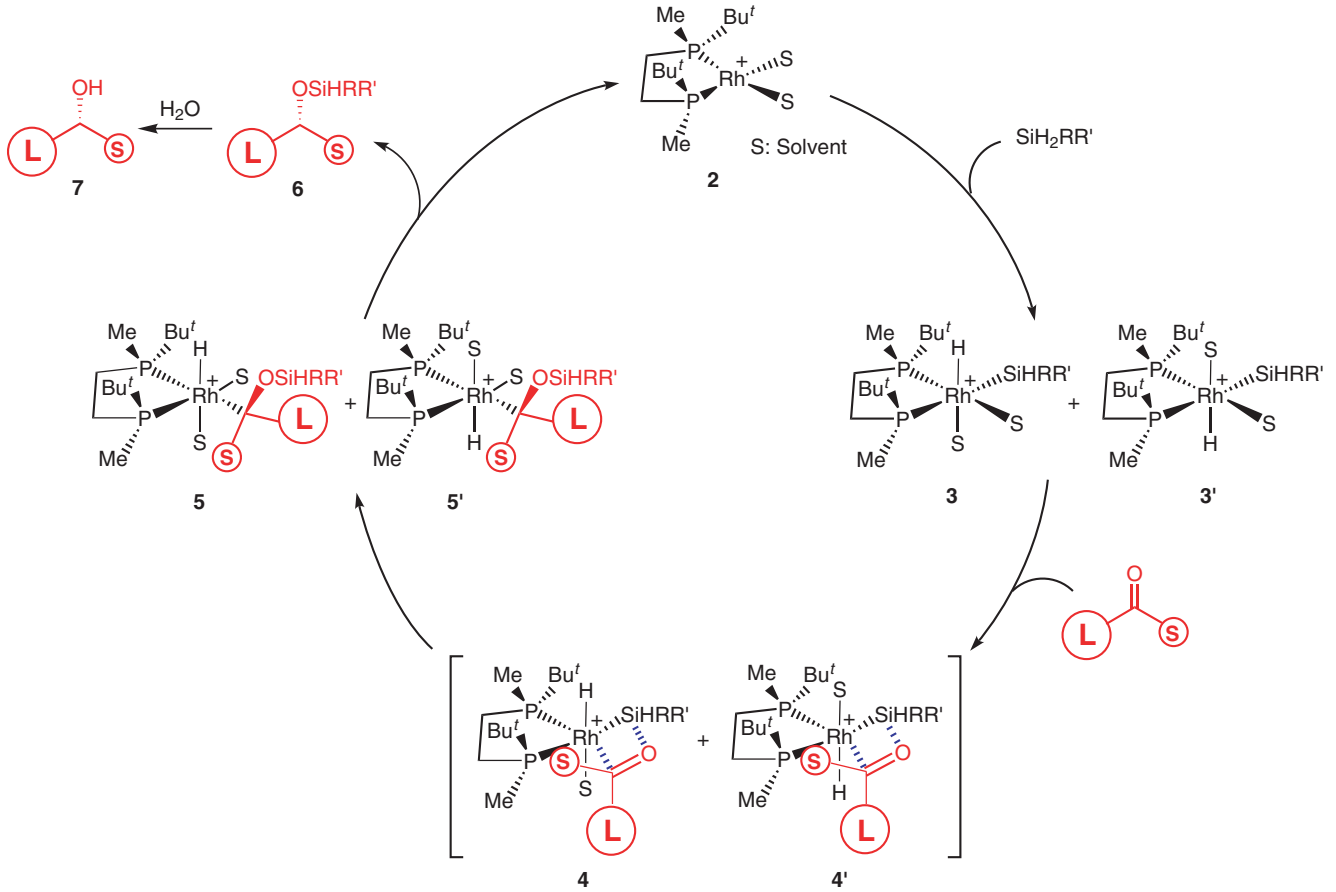


Scheme 1.

Based on these results together with previously reported mechanistic studies,[2,11c,18] we propose that the reaction proceeds through the catalytic cycle shown in Scheme 2. The reaction could be initiated by the generation of a reactive Rh(I) solvate complex **2**, which would be subjected to oxidative addition of the bulky silane reagent to produce two hydrido(silyl)rhodium(III) complexes **3** and **3′**. These species are a pair of diastereomers, both of which have the Rh–Si bond *trans* to the Rh–P bond and the Rh–H bond *cis* to the Rh–P bonds. These species would react with the ketone to liberate the coordinated solvent and to give monohydride species **5** and **5′**. This step plays a key role in the enantioselection of the asymmetric hydrosilylation. It is reasonable to consider that the ketone approaches rhodium complexes **3** and **3′** while avoiding the steric repulsion between the *tert*-butyl group on the phosphorus atom and the larger ketone substituent. The subsequent insertion of the carbon–oxygen double bond into the rhodium–silicon bond probably takes place via four-membered transition states **4** and **4′** to result in the formation of Rh(III) monohydride complexes **5** and **5′**, respectively.[19] The final reductive elimination with regeneration of Rh(I) solvate complex **2** affords optically active silyl ether **6** that is hydrolyzed to secondary alcohol **7**.[20]

3. Conclusion

In summary, we have applied *cis*-chelating P-chiral diphosphine ligands to the rhodium-catalyzed asymmetric hydrosilylation of simple ketones and obtained the



Scheme 2. Plausible mechanism of the asymmetric hydrosilylation of ketones catalyzed by rhodium complexes of (*S*,*S*)-*t*-Bu-BisP*, (*R*,*R*)-*t*-Bu-MiniPHOS, and (*R*,*R*)-QuinoxP*.

corresponding secondary alcohols in high yields with good to high enantiomeric excesses. The sense of the stereoselection has been rationalized by considering that the enantioselection occurs at the migratory insertion step.

4. Experimental

4.1. Materials: catalyst precursors

Catalyst precursor rhodium complexes, [Rh((*S*,*S*)-R-BisP*)(nbd)]BF_4 (R = *tert*-butyl, cyclohexyl, 1-adamantyl) and [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]BF_4, were prepared according to the literature procedures.[13,14] A chiral diphosphine ligand (*R*,*R*)-QuinoxP* was prepared by the method described in the literature[15] and its rhodium complex prepared in situ by the reaction with [Rh(cod)$_2$]BF_4 in THF.

4.2. General procedure for asymmetric hydrosilylation of ketones

The catalyst precursor [Rh((*S*,*S*)-*t*-Bu-BisP*)(nbd)]BF_4 (0.005 mmol) or [Rh((*R*,*R*)-*t*-Bu-MiniPHOS)$_2$]BF_4 (0.005 mmol) was placed in a 10 mL Schlenk flask that was evacuated and backfilled with nitrogen four times. Dry THF (1 mL) was added and the flask immersed in a constant temperature bath. To the solution was added a mixture of ketone (0.5 mmol) and 1-naphthylphenylsilane (0.75 mmol) in THF (1 mL) with stirring. After the reaction was complete, 1 M HCl (1 mL) was added and the mixture allowed to warm to room temperature overnight. This was neutralized with 1 M $NaHCO_3$ and extracted with Et_2O, washed with brine, and then dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography or Kügelrohr distillation to provide the desired alcohol. The chiral secondary alcohols prepared were pure and fully characterized by spectroscopic methods. The enantiomeric excesses of the products were determined by HPLC analysis or GC analysis using chiral columns.

Hydrosilylation by the use of (*R*,*R*)-QuinoxP* was carried out as follows: Ligand ((*R*,*R*)-QuinoxP*) (1.8 mg, 0.0055 mmol) and [Rh(cod)$_2$]BF_4 (2.0 mg, 0.0050 mmol) were placed in a Schlenk flask that was evacuated and backfilled with nitrogen four times. Dry THF (2.5 mL) was added to the flask and the mixture was stirred at room temperature. After 10 min, ketone (0.50 mmol) and 1-naphthylphenylsilane (176 mg, 0.75 mmol) were added at 0 °C and the mixture was stirred at the same temperature. After the reaction was completed, the mixture was worked up in a similar manner as described above. The enantiomeric excesses of the products were determined by HPLC analysis or GC analysis using chiral columns.

4.3. Conditions for the determination of the enantiomeric excesses of chiral secondary alcohols

1-Phenyl-1-ethanol: HPLC, Chiralcel OD-H, hexane/2-propanol = 95:5, 0.5 mL/min, 254 nm, (*R*)t_1 = 16.0 min, (*S*)t_2 = 19.2 min; *1-Phenyl-1-propanol:* Capillary GC, Lipodex A (25 m), 90 °C, isothermal, flow rate, 33 cm/s, (*S*)t_1 = 31.9 min, (*R*)t_2 = 33.0 min; *2-Methyl-1-phenyl-1-propanol:* HPLC, Chiralcel OB, hexane/2-propanol = 199:1, 0.5 mL/min, 254 nm, t_1 = 20.9 min, t_2 = 24.4 min; *1-(2-Methylphenyl)-1-ethanol:* Capillary GC, DexCB, 80 °C (20 min), 1 °C/min ramp, 100 °C (60 min), 155 kPa, (*R*)t_1 = 47.0 min, (*S*)t_2 = 58.8 min; *1-(3-Methylphenyl)-1-ethanol:* HPLC, Chiralcel OJ, hexane/2-propanol = 30:1, 0.5 mL/min, 254 nm, (*S*)t_1 = 28.6 min, (*R*)t_2 = 33.9 min; *1-(4-Methylphenyl)-1-ethanol:* Capillary GC, DexCB, 80 °C (20 min), 1 °C/min ramp, 100 °C (30 min), 172 kPa, (*R*)t_1 = 36.2 min, (*S*)t_2 = 40.6 min; *1-(2-Methoxyphenyl)-1-ethanol:* HPLC, Chiralcel OB, hexane/2-propanol = 95:5, 0.5 mL/min, 254 nm, (*S*)t_1 = 17.0 min, (*R*)t_2 = 32.9 min; *1-(1-Naphthyl)-1-ethanol:* HPLC, Chiralcel OJ, hexane/2-propanol = 9:1, 1.0 mL/min, 254 nm, (*S*)t_1 = 12.6 min, (*R*)t_2 = 16.8 min; *1-(2-Naphthyl)-1-ethanol:* HPLC, Chiralcel OJ, hexane/2-propanol = 9:1, 1.0 mL/min, 254 nm, (*S*)t_1 = 12.7 min, (*R*)t_2 = 16.0 min; *1-Indanol:* HPLC, Chiralcel OB, hexane/2-propanol = 95:5, 0.5 mL/min, (*R*)t_1 = 15.0 min, (*S*)t_2 = 26.9 min; *1,2,3,4-Tetrahydro-1-naphthol:* HPLC, Chiralcel OB, hexane/2-propanol = 95:5, 0.5 mL/min, 254 nm, (*R*)t_1 = 6.1 min, (*S*)t_2 = 10.0 min; *4-Phenyl-2-butanol:* HPLC, Chiralcel OD-H, hexane/2-propanol = 30:1, 1.0 mL/min, 254 nm, (*S*)t_1 = 21.4 min, (*R*)t_2 = 24.0 min; *5-Phenyl-2-pentanol:* HPLC, Chiralcel OJ, hexane/2-propanol = 95:5, 0.5 mL/min, 254 nm, (*S*)t_1 = 17.5 min, (*R*)t_2 = 20.1 min; *2-Octanol:* 2-naphthoate, Chiralcel OD-H, hexane/2-propanol = 199:1, 0.5 mL/min, 254 nm, (*S*)t_1 = 20.2 min, (*R*)t_2 = 31.0 min; *1-Cyclohexyl-1-ethanol:* 2-naphthoate, HPLC, Chiralcel OD-H, hexane/2-propanol = 199:1, 0.5 mL/min, 254 nm, (*R*)t_1 = 19.0 min, (*S*)t_2 = 23.8 min; *1-Adamantyl-1-ethanol:* 2-naphthoate, HPLC, Chiralcel OD-H, hexane/2-propanol = 199:1, 0.5 mL/min, (*R*)t_1 = 17.7 min, (*S*)t_2 = 18.7 min; *Ethyl 3-hydroxy-2,2-dimethylbutanoate:* HPLC, Chiralpak AS, hexane/2-propanol = 99:1, 1.0 mL/min, 220 nm, (*S*)t_1 = 10.4 min, (*R*)t_2 = 12.7 min; *2-Chloro-1-(2,4-dichlorophenyl)ethanol:* HPLC, Chiralcel OB, hexane/2-propanol = 99:1, 0.5 mL/min, 254 nm, (*R*)t_1 = 29.1 min, (*S*)t_2 = 38.1 min.

Acknowledgement

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