Pergamon

Tetrahedron 56 (2000) 351–356

TETRAHEDRON

Preparation of a Fluorous Chiral BINOL Derivative and Application to an Asymmetric Protonation Reaction

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Received 4 October 1999; accepted 12 November 1999

Abstract—Fluorous Chiral Proton Source (*R*,*S*)-FDHPEB resulted in a higher enantioselectivity (95% ee) than that of the original nonfluorous (*R*,*S*)-DHPEB (87% ee) in an enantioselective protonation of a samarium enolate. (*R*,*S*)-FDHPEB was easily recovered by a simple filtration through a fluorous reverse phase silica gel and was recyclable.

Compounds that have long perfluorinated carbon chains are "fluorous" and are easily separable from organic compounds by a simple partitioning procedure with a fluorous solvent such as FC-72 ($CF_3(CF_2)_4CF_3$) and a standard organic solvent. In an ideal case, after partitioning work-up, almost pure products are obtained from the organic phase, and fluorous product and reagent are recovered quantitatively from the fluorous phase. The organic products and the fluorous compounds can also be separated cleanly by a simple filtration through a fluorous reverse phase (FRP) silica gel column. Thus, fluorous chemistry is attracting the growing interest of organic chemists world-wide since it provides new options for solution phase combinatorial chemistry.[1c,2]

Another area of fluorous chemistry is a catalytic reaction in a fluorous and organic biphase system (FBS) using a fluorous catalyst.[1a,b,d,3] Homogeneous transition metal catalysts whose ligands are highly fluorous are dissolved only in the fluorous phase of FBS. Reactants in the organic phase can partition into the fluorous phase or the reaction can occur at the interface of FBS as well. The products are obtained from the organic phase by separating the phase from the fluorous phase after the reaction. The reaction can be repeated by adding a new organic solution containing the reactants, as long as the catalyst remains intact in the fluorous phase. Horváth and Gladysz have prepared a fluorous phosphine ligand $P(CH_2CH_2(CF_2)_5CF_3)_3$ and successfully applied this to hydroformylation and hydroboration in FBS catalyzed by rhodium complex.[3b,f]

In spite of the growing number of articles on fluorous chemistry, only a few reports have been published on asymmetric reactions using fluorous reagents or catalysts.[4] The main reason for this situation seems to be due to the lack of chiral fluorous ligands available. Therefore, we have attempted to synthesize such ligands and succeeded in preparing a chiral fluorous BINOL analogue via short steps and in good overall yield.

In this paper, we wish to report the preparation of the chiral fluorous BINOL and its derivative, and the application of the compound to an enantioselective protonation of a samarium enolate.

Results and Discussion

Preparation of chiral fluorous BINOL and its derivative

The chiral BINOL (**III**) and its derivative (**V**) were prepared by the route shown in Scheme 1.

(*R*)-6,6′-Dibromo-2,2′-dimethoxymethoxy-1,1′-binaphthalene (**I**) was prepared from commercially available (*R*)-6,6′-dibromo-1,1′-binaphth-2,2-diol by Pu's method.[5] (*R*)-6,6′-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2′-dimethoxymethoxy-1,1′-binaphthalene (**II**) was obtained in 91% yield via lithiation at the 6 and 6′-positions of **I** and then reaction with $(C_6F_{13}CH_2CH_2)_3SiBr$[2q] according to Curran's method.[2x] The MOM group of **II** was removed in hydrochloric acid and THF under reflux and vigorous stirring. (*R*)-6,6′-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-silyl]-1,1′-binaphth-2,2′-diol (**III**; (*R*)-FBINOL) was isolated in 97% yield. The enantiomeric excess (ee) of the fluorous (*R*)-FBINOL (**III**) was determined to be higher than 99% by HPLC using a chiral column, using the (*S*)-enantiomer of **III**

Keywords: fluorous chiral; enantioselective protonation; samarium enolate.
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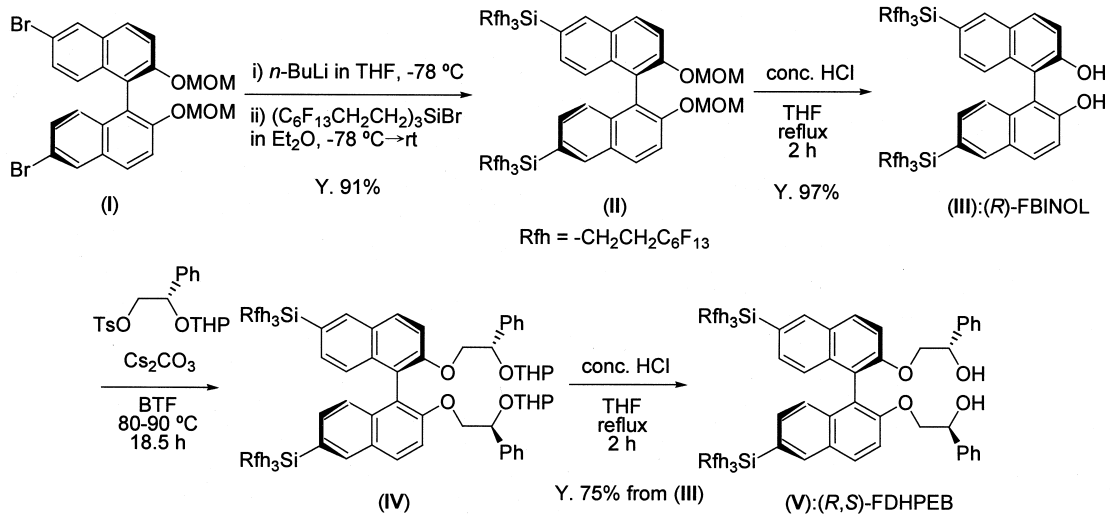
0040–4020/00/$ - see front matter
PII: S0040-4020(99)01004-2



Scheme 1.

Table 1. Partition coefficients of (*R*)-FBINOL and (*R,S*)-FDHPEB in organic solvent and FC-72

	Organic solvent	Organic solvent/FC-72
(*R*)-FBINOL (**III**)	$CHCl_3$	1/19
	THF	1/3
	Toluene	1/49
(*R,S*)-FDHPEB (**V**)	THF	19/1
	Benzene	1/32

A mixture of 100 mg of (*R*)-FBINOL or (*R,S*)-FDHPEB in FC-72 (2 mL) and organic solvent (2 mL) was stirred at room temperature for 10 min. Then the two phases were separated and the solvents were evaporated *in vacuo*. The contents of the fluorous compound in each phase were determined by weighing the residue.

as a standard. This was prepared by the same procedures as those of **III** from the (*S*)-starting material.

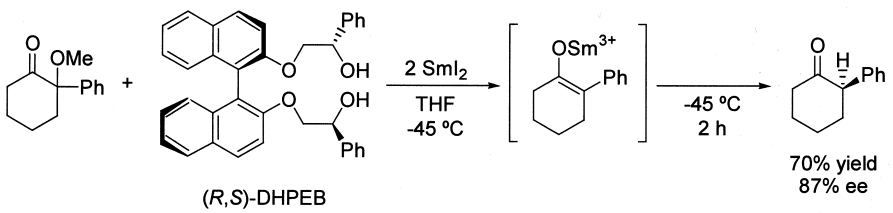
Next, we tried to synthesize (*R*)-2,2′-di[(*S*)-2-hydroxy-2-phenylethoxy]-6,6′-bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1′-binaphthyl (**V**; (*R,S*)-FDHPEB) by the procedures that we have already established for the preparation of the nonfluorous analogue.[6] However, **III** was very insoluble in DMF and the yield was very low. Thus, BTF ($CF_3C_6H_5$; benzotrifluoride) and Cs_2CO_3 were used as a solvent and a base respectively, and the reaction was carried out at 80–90°C for 18.5 h to give **IV**. The crude product of **IV** underwent deprotection to give the desired compounds **V** in 75% overall yield from **III**. In the procedures mentioned above, the fluorous products **II**–**V** were generally extracted with FC-72 ($CF_3(CH_2)_4CF_3$) and purified by silica gel column chromatography as described in the Experimental Section.

The approximate partition coefficients of **III** and **V** were determined by a simple method described in the footnote of Table 1, and the results are summarized in Table 1.

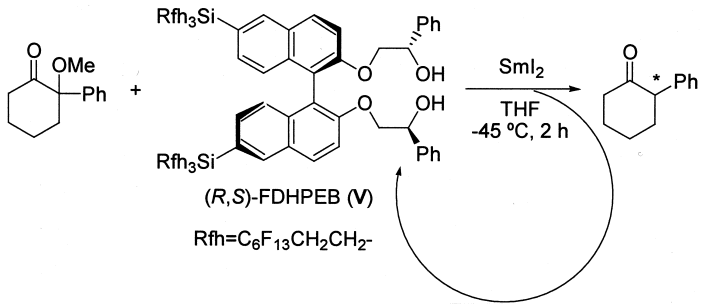
Recycling the fluorous chiral diol ((*R,S*)-FDHPEB; V) in the enantioselective protonation of the samarium enolate

We have reported in the previous paper that the methoxy group of 2-methoxy-2-phenylcyclohexanone was reductively cleaved by SmI_2 to give the corresponding samarium enolate. The enolate was protonated by (*R,S*)-DHPEB to afford the corresponding chiral ketone in 87% ee (Eq. (1)).[6]

Thus, we examined the reaction by using (*R,S*)-FDHPEB instead of (*R,S*)-DHPEB and tried to reuse the recovered (*R,S*)-FDHPEB for the next reaction without purification. (*R,S*)-FDHPEB is very insoluble in THF at −45°C and the reaction mixture seemed to be liquid–liquid biphase system, although (*R,S*)-FDHPEB is a glassy solid that is soluble in THF at room temperature. However, under the same reaction conditions as those shown in Equation (1), almost the same yield (76%) and enantioselectivity (85% ee) were obtained after purification of 2-phenylcyclohexanone by preparative TLC. (*R,S*)-FDHPEB was recovered quantitatively by extraction with FC-72 after quenching the reaction with 0.1N hydrochloric acid. However, the separation procedure was much simpler and more effective when the reaction mixture was filtered through the fluorous reverse phase silica gel (FRP silica gel).[2l,w] The product



(1)



Scheme 2.

Table 2. Enantioselective protonation of the samarium enolate derived from 2-methoxy-2-phenylcyclohexanone reusing the same chiral proton source without purification. (Reactions were carried out using 2.0 mol equiv. of (*R*,*S*)-FDHPEB and 2.4 mol equiv. of SmI_2)

Run	Yield (%)	% ee[a]	Config. (Rotn.)[b]	Recovered (*R*,*S*)-FDHPEB (%)
1	82	81	*R*(+)	98
2	81	85	*R*(+)	97
3	78	86	*R*(+)	98
4	74	89	*R*(+)	99
5	73	87	*R*(+)	99

[a] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H.
[b] Specific rotation was measured in benzene at 24°C.

and (*R*,*S*)-FDHPEB were cleanly separated simply by eluting first with CH_3CN and then FC-72 as described in the Experimental Section. The crude product obtained from the CH_3CN solution was purified by preparative TLC and (*R*,*S*)-FDHPEB recovered from FC-72 solution was used for the next reaction without further purification (Scheme 2). Thus, the reaction was repeated five times and the results are summarized in Table 2.

As seen from Table 2, it is clear that the enantioselectivities were higher than 85% ee on average even if the recovered (*R*,*S*)-FDHPEB was used for the reactions. The recovered (*R*,*S*)-FDHPEB after the fifth reaction in Table 2 showed the same NMR spectrum as that of a pure sample. Therefore, the results demonstrated that (*R*,*S*)-FDHPEB has almost the same ability to control the transition state of the enantioselective protonation as that of the original nonfluorous chiral proton source (*R*,*S*)-DHPEB but also has completely different characteristics from (*R*,*S*)-DHPEB which makes (*R*,*S*)-FDHPEB recyclable by the simple filtration with the FRP silica gel.

Finally, we tried to determine the enantiomeric excess of the product without purification by preparative TLC, because such a method can afford a high throughput assessment of the reaction. HPLC data analyzed by both UV and CD detectors are shown in Fig. 1.

As seen from Fig. 1, there was no peak due to products other than the desired product in the chromatograms with the CD detector although several additional peaks were recorded by the UV detector. The enantiomeric excesses obtained by the UV and CD detectors coincided with each other and the enantiomeric excess of the unpurified sample of the product reached 95% ee. However, after preparative TLC purification of the sample, the enantiomeric excess was reduced to 88% ee. Therefore, it is clear that the enantiomeric excess of the product before purification was much higher than that of the sample after preparative TLC purification. It is already known in our previous work that the product is rather easy to racemize.[6] The lower enantiomeric excess of the purified product must have been brought about by racemization during purification by preparative TLC. The wide range of enantiomeric excesses in Table 2 (81–89% ee) is considered to be due to racemization and the extent of racemization must depend upon the time taken for the purification procedures. Therefore, the separation method using FRP silica gel and the determination method using HPLC with both UV and CD detectors of the unpurified sample is a very useful method for a high throughput assessment of the enantioselective reaction, especially in the case of a product which is easily racemized during purification procedures.

The strategy of fluorous chemistry described so far is not only applicable to the other 2-alkyl or 2-aryl-2-heterosubstituted ketones which have brought about high enantiomeric excesses (83–94% ee) in asymmetric protonation by using (*R*,*S*)-DHPEB[6] but is also expected to be applicable to other asymmetric protonation reactions such as (*R*)-BINOL-$SnCl_4$ catalyzed protonation of silyl enol ethers and esters[7] or $LnNa_3$tris((*R*)-binaphthoxide) catalyzed Michael addition of thiol to α,β-unsaturated carbonyl compounds[8] reported by Yamamoto and Shibasaki, respectively.

Experimental

General

The melting point was determined by a Yanagimoto micro-melting point apparatus and was uncorrected. The IR spectra were recorded on a Perkin–Elmer 1720-X FT-IR spectrometer. The ^1H NMR spectra were obtained on a JEOL FX-200 and JEOL JNM-A400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The optical rotations were measured with a Perkin–Elmer 241 polarimeter. HPLC analysis was performed with Hitachi L-7100 flow system and L-7400 UV detector or JASCO CD-1595 CD detector using DAICEL CHIRALCEL OD or OD-H column. Preparative TLC was run on Wakogel B-5F and column chromatography was performed using Wakogel C-300. Tetrahydrofuran (THF) was distilled prior to use from sodium benzophenone ketyl under argon. FC-72 (commercially available from Sumitomo

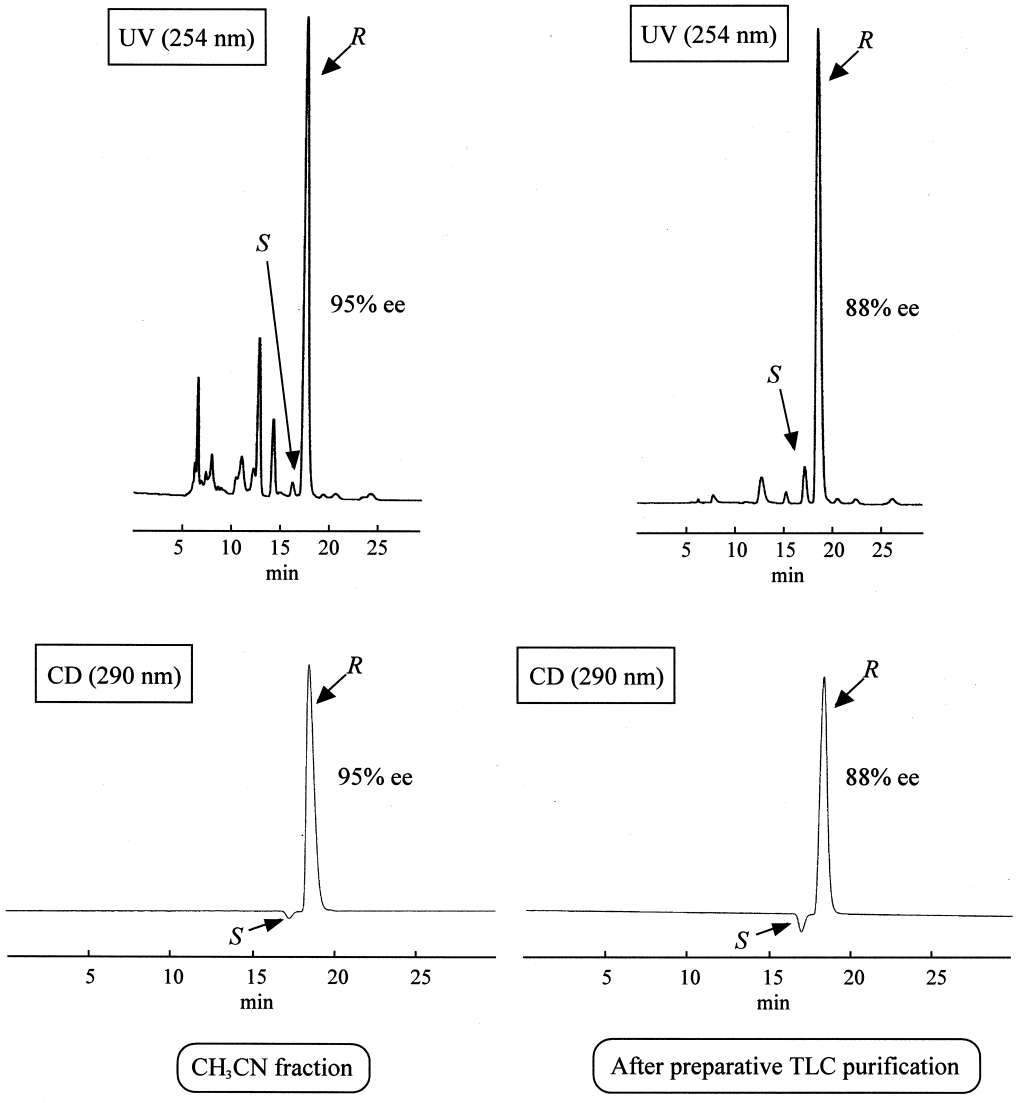


Figure 1. Chromatograms of 2-phenylcyclohexanone with UV and CD detectors.

3M) and benzotrifluoride were distilled from phosphorous pentoxide under argon. 0.1 M samarium iodide THF solution was prepared from samarium metal and diiodoethane by Kagan's method.[9] The fluorous reverse phase silica gel was prepared by Curran's method.[2w]

(*R*)-6,6′-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2′-dimethoxymethoxy-1,1′-binaphthalene (II). (*R*)-6,6′-dibromo-2,2′-dimethoxylmethoxy-1,1′-binaphthalene (**I**) (2.00 g, 3.76 mmol) was dissolved in THF (20 mL) and cooled to −78°C under argon. *n*-Butyl lithium (1.55 mol dm^{-3}, 5.4 mL, 8.3 mmol) was added dropwise, and the resulting yellow solution was stirred at that temperature for 50 min. A mixture of bromo tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silane (10.6 g, 9.22 mmol) in Et_2O (50 mL) was added to the reaction mixture. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (50 mL). The volatiles were removed in vacuo and CH_2Cl_2 (80 mL) was added. The mixture was washed with FC-72 (30 mL×5), the combined FC-72 layer was concentrated in vacuo. The resulting syrup was purified on a silica gel column (hexane:EtOAc=20:1) to afford the FBINOL diMOM ether (**II**) as a colorless syrup (8.6 g, 91% yield): $[\alpha]_D^{20}$ +17.5° (*c* 0.827, benzotrifluoride), $[\alpha]_{578}^{20}$ +18.4° (*c* 0.827, benzotrifluoride), $[\alpha]_{546}^{20}$ +21.5° (*c* 0.827, benzotrifluoride), $[\alpha]_{436}^{16}$ +50.3° (*c* 0.827, benzotrifluoride), $[\alpha]_{365}^{16}$ +167° (*c* 0.827, benzotrifluoride); IR (neat) 2947, 1617, 1473, 1443, 1362, 1240, 1070, 1023, 915, 845, 812, 737, 708 cm^{-1}; ^1H NMR (200 MHz) δ 1.10–1.30 (m, 12H, $-SiCH_2-$), 1.80–2.20 (m, 12H, $-CF_2CH_2-$), 3.16 (s, 6H, $-OCH_3$), 5.02 and 5.14 (d×2, 2H×2, $-CH_2O-$, *J*=6.8 Hz), 7.22 (s, 4H, Ar*H*), 7.67 (d, 2H, Ar*H*, *J*=9.0 Hz), 7.99 (s, 2H, Ar*H*), 8.01 (d, 2H, Ar*H*, *J*=9.0 Hz); MS (EI) *m*/*z* (relative intensity) 2511 (M^++1, 100), 2434 (96), 309 (10), 239 (18), 131 (18), 45 (90); Anal. calcd for $C_{72}H_{44}F_{78}O_4Si_2$: C, 34.44; H, 1.77; F, 59.01. Found C, 33.67; H, 1.57; F, 58.94.

(*R*)-6,6′-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1′-2-binaphthol (III). A mixture of FBINOL diMOM ether (**II**) (399 mg, 0.159 mmol), conc. HCl (4 mL)

and THF (8 mL) was stirred vigorously at 60°C for 3 h. After addition of CH_2Cl_2 (10 mL), the cloudy biphase was washed with FC-72 (10 mL×5). The combined FC-72 layer was concentrated in vacuo to give a syrup, which was purified on a silica gel column (hexane:EtOAc=10:1) to afford (*R*)-FBINOL as a colorless syrup which gradually crystallized (379 mg, 98% yield): mp 80–81°C, $[\alpha]_D^{26}$ −16.9° (*c* 0.463, FC-72), $[\alpha]_{578}^{26}$ −17.5° (*c* 0.463, FC-72), $[\alpha]_{546}^{26}$ −20.1° (*c* 0.463, FC-72), $[\alpha]_{436}^{26}$ −25.1° (*c* 0.463, FC-72), $[\alpha]_{365}^{26}$ +65.2° (*c* 0.463, FC-72); IR (KBr) 3500, 2946, 1614, 1470, 1207, 1144, 1071, 1019, 900, 844, 746, 708 cm^{-1}; ^1H NMR (200 MHz) δ 1.00–1.30 (m, 12H, $-SiCH_2-$), 1.80–2.20 (m, 12H, $-CF_2CH_2-$), 5.14 (s, 2H, –O*H*), 7.22 (d, 2H, Ar*H*, *J*=8.3 Hz), 7.31 (d, 2H, Ar*H*, *J*=8.3 Hz), 7.47 (d, 2H, Ar*H*, *J*=9.0 Hz), 7.99 (s, 2H, Ar*H*), 8.04 (d, 2H, Ar*H*, *J*=9.0 Hz); MS (EI) *m*/*z* (relative intensity) 2422 (M^+, 100); Anal. calcd for $C_{68}H_{36}F_{78}O_2Si_2$: C, 33.71; H, 1.50; F, 61.16. Found C, 33.12; H, 1.25; F, 60.93. The enantiomeric excess (ee) of the product was determined to be >99% ee by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD, hexane:2-propanol=95:5, flow rate=1.0 mL/min): t_R=8.9 min.

(*S*)-fluorous BINOL was prepared from (*S*)-6,6′-dibromo-2,2′-dimethoxylmethoxy-1,1′-binaphthalene by the procedure similar to that of (*R*)-FBINOL (54% overall yield): $[\alpha]_D^{26}$ +15.7° (*c* 0.594, FC-72), $[\alpha]_{578}^{26}$ +16.3° (*c* 0.594, FC-72), $[\alpha]_{546}^{26}$ +18.9° (*c* 0.594, FC-72), $[\alpha]_{436}^{26}$ +22.4° (*c* 0.594, FC-72), $[\alpha]_{365}^{26}$ −70.7° (*c* 0.594, FC-72). The ee of the product was determined to be >99% ee by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD, hexane:2-propanol=95:5, flow rate=1.0 mL/min): t_R=5.3 min.

(*R*)-2,2′-Bis[(*S*)-2-hydroxy-2-phenylethoxy]-6,6′-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-octyl)-silyl]-1,1′-binaphthyl (V). A suspension of (*R*)-FBINOL (500 mg, 0.206 mmol) and cesium carbonate (161 mg, 0.495 mmol) in benzotrifluoride (2 mL) was stirred vigorously at 80°C for 30 min. To the suspension was added (*S*)-2-phenyl-2-tetrahydropyranyloxy-1-*p*-toluenesulfonyloxyethane (186 mg, 0.495 mmol) and the reaction mixture was stirred at 80°C. After 6 h, the tosylate (186 mg, 0.495 mmol), cesium carbonate (161 mg, 0.495 mmol) and benzotrifluoride (2 mL) were added again to the reaction mixture, and then stirred at that temperature for 12 h. After cooling, the reaction mixture was diluted with Et_2O (50 mL) and the insoluble material was filtered off. The filtrate was concentrated in vacuo to give a syrup, which was purified on a silica gel column (hexane:EtOAc=20:1 then 10:1) to afford the diether derivative (**IV**) as a viscous syrup. A mixture of the syrup, conc. HCl (2 mL) and THF (4 mL) was stirred vigorously at 70°C for 2 h. The reaction mixture was extracted with Et_2O (15 mL×3), and washed with a saturated aqueous $NaHCO_3$ solution (10 mL) and then with brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and then concentrated *in vacuo*. The resulting oil was diluted with benzene (20 mL) and washed with FC-72 (10 mL×6). The combined FC-72 layer was concentrated in vacuo to give a syrup, which was purified on a silica gel column (hexane:EtOAc=5:1) to afford the (*R*,*S*)-FDHPEB (**V**) as a colorless viscous syrup (413 mg, 75% overall yield): $[\alpha]_D^{16}$ +7.94° (*c* 1.16, benzotrifluoride), $[\alpha]_{578}^{16}$ +8.29° (*c* 1.16, benzotrifluoride), $[\alpha]_{546}^{16}$ +9.59° (*c* 1.16, benzotrifluoride), $[\alpha]_{436}^{16}$ +24.8° (*c* 1.16, benzotrifluoride), $[\alpha]_{365}^{16}$ +132.6° (*c* 1.158, benzotrifluoride); IR (neat) 3445, 3065, 3034, 2943, 1736, 1616, 1474, 1240, 904, 845, 812, 707 cm^{-1}; ^1H NMR (400 MHz) δ 1.10–1.40 (m, 12H, $-SiCH_2-$), 2.00–2.20 (m, 12H, $-CF_2CH_2-$), 3.01 (d, 2H, –O*H*, *J*=2.9 Hz), 4.08 (dd, 2H, one proton of $-OCH_2-$, *J*=9.3 and 9.8 Hz), 4.20 (dd, 2H, another proton of $-OCH_2-$, *J*=2.9 and 9.8 Hz), 4.71 (ddd, 2H, –OC*H*–, *J*=2.9 and 9.3 Hz), 7.13–7.26 (m, 14H, Ar*H*), 7.51 (d, 2H, Ar*H*, *J*=9.0 Hz), 8.03 (s, 2H, Ar*H*), 8.06 (d, 2H, Ar*H*, *J*=9.3 Hz); MS (EI) *m*/*z* (relative intensity) 2662 (M^+, 60), 2525 (40), 2434 (22), 245 (20), 131 (32), 77 (100); Anal. calcd for $C_{84}H_{52}F_{78}O_4Si_2$: C, 37.88; H, 1.97; F, 55.64. Found C, 37.75; H, 1.77; F, 55.45.

Typical procedure for the enantioselective protonation of the samarium enolate derived from 2-methoxy-2-phenylcyclohexanone with (*R*,*S*)-FDHPEB. A SmI_2 solution (0.1 mol dm^{-3}, 6.2 mL, 0.62 mmol) was added to a suspension of 2-methoxy-2-phenylcyclohexanone (52.8 mg, 0.259 mmol) and (*R*,*S*)-FDHPEB (1.317 g, 0.495 mmol) in THF (5 mL) with stirring under argon at −45°C. After stirring 2 h at that temperature, the reaction mixture was quenched with 0.1N hydrochloric acid (6 mL). The mixture was washed with FC-72 (8 mL×6) and then the THF-H_2O layer was extracted with Et_2O (20 mL×3). The combined ether layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was purified by preparative TLC (hexane:EtOAc=4:1) to give 2-phenylcyclohexanone (34.1 mg, 76% yield) in 85% ee as a colorless solid: $[\alpha]_D^{24}$ +96.4° (*c* 0.276, benzene). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The enantioselectivity was determined by HPLC analysis using DAICEL CHIRALCEL OD-H, hexane:2-propanol=95:5, flow rate=0.5 mL/min). (*R*,*S*)-FDHPEB was recovered almost quantitatively from FC-72 washings without a loss of optical purity.

Solid phase extraction with fluorous reverse phase silica gel: The reaction was quenched with 0.1N hydrochloric acid (6 mL) and extracted with Et_2O (20 mL×4). The combined organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was dissolved in Et_2O (2 mL). To the solution was added (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dimethylsilyl bound silica gel (1 g), then the solvent was evaporated to dryness. The powder obtained was loaded on a column of (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)dimethylsilyl bound silica gel (4 g) and then eluted successively with acetonitrile (30 mL) and FC-72 (40 mL). The acetonitrile fraction was evaporated in vacuo to give crude 2-phenylcyclohexanone. (*R*,*S*)-FDHPEB was recovered almost quantitatively from FC-72 fraction without a loss of optical purity.

Acknowledgements

The authors wish to express their thanks to Professor Akira Kato and Professor Hidetoshi Fujiwara, Niigata College of Pharmacy, for the measurements of MS spectra, and to the Laboratory for Organic Elemental Microanalysis, Faculty of

Pharmaceutical Sciences, Kyoto University, for the elemental analysis. We also would like to thank to Miss Ayako Abe, Miss Takako Kazama, Miss Mayako Sato, and Miss Chiharu Suzuki for preparation of the fluorous compounds. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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