Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 4061–4066

Novel fluorous prolinol as a pre-catalyst for catalytic asymmetric borane reduction of various ketones

Sakiko Goushi, Kazumasa Funabiki,* Masaya Ohta, Keisuke Hatano and Masaki Matsui

Department of Materials Science and Technology, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-1193, Japan

Received 15 January 2007; revised 26 February 2007; accepted 28 February 2007
Available online 2 March 2007

Abstract—Novel prolinol carrying two perfluorohexylethyl groups at the α-position was prepared from L-proline as a starting chiral substrate. Catalytic asymmetric reduction of various ketones, including mono-, di-, and trifluoromethylated acetophenones, using fluorous oxazaborolidines derived from fluorous prolinol afforded the corresponding alcohols in good to excellent yields and with high enantioselectivities (up to 93.2% ee). The fluorous prolinol was recovered without any fluorous solvents or silica gel by simply cooling the organic phase and filtration.

1. Introduction

Since the first report of a catalytic reaction using a organic/fluorous liquid/liquid biphasic system (FBS) as an environmentally benign recyclable system by Horváth and Rábai,[1] there have been many successful examples of catalytic asymmetric reactions using a catalyst with fluorous ponytails as well as the recovery of fluorous catalyst under a liquid/liquid FBS system.[2] However, this system has a serious drawback, in that fluorous solvents, which are more expensive than ordinary organic solvents, are needed in the liquid/liquid biphasic system. Gladysz et al.,[3] Ishihara et al.,[4] and Mikami et al.[5] have independently reported the use of fluorous achiral catalysts in a 1,4-addition reaction, direct amide condensation, and Friedel–Crafts reaction as well as in the recovery of the catalysts *without the use of fluorous solvents* (Fig. 1).

These reactions involve a new concept, i.e., *temperature-dependent organic/fluorous liquid/solid phase separation*, which has some advantages, such as the ability to use

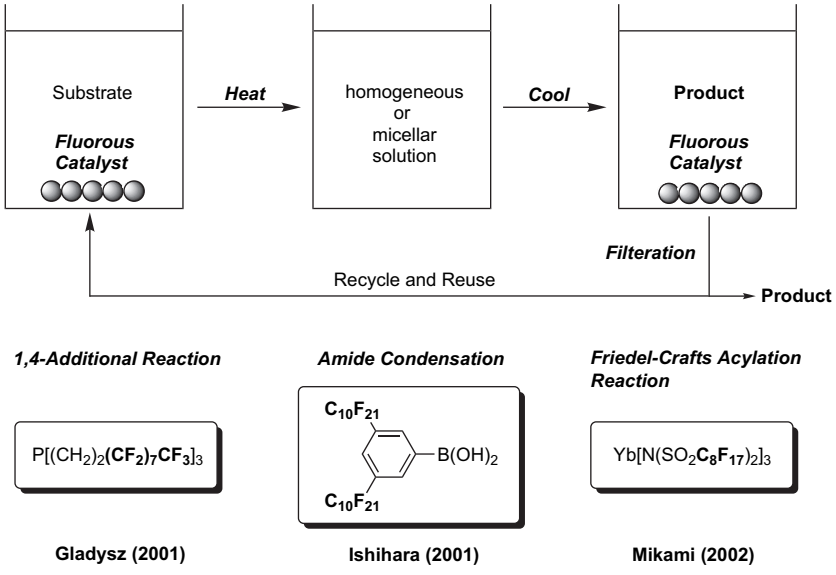


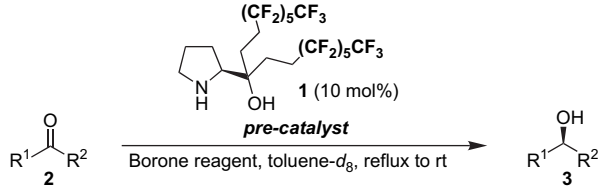
Figure 1. Reported examples of synthesis using a liquid/solid biphasic system without fluorous solvent or silica gel.

* Corresponding author. E-mail: funabiki@gifu-u.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.02.117

ordinary organic solvents, no need for expensive fluorous solvents or silica gel,[6] and a significant decrease in the number of steps. In particular, after the reaction with fluorous catalyst is carried out under homogeneous or micellar conditions at an elevated reaction temperature, the fluorous catalyst can be recovered by simple cooling and filtration of the precipitate. However, no report of a catalytic *asymmetric reaction* using fluorous asymmetric catalyst based on this concept has appeared in the literature.

We describe here the synthesis of a novel fluorous solid prolinol[7,8] carrying two perfluorohexylethyl groups at the α-position, the asymmetric borane reduction[9] of a variety of ketones including mono-, di-, and trifluoromethylated acetophenones using this fluorous prolinol as a pre-catalyst, and the recovery of fluorous pre-catalyst **1** *without any fluorous solvents or silica gel* (Scheme 1).

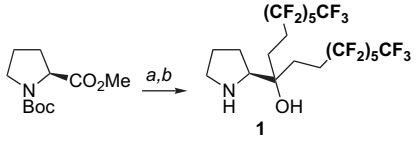


Scheme 1. Asymmetric reduction of ketone using novel fluorous prolinol **1**.

2. Results and discussion

2.1. Synthesis of fluorous prolinol

Fluorous prolinol **1** was synthesized as follows (Scheme 2). Treatment of *N*-(*tert*-butoxycarbonyl)proline methyl ester with perfluorohexylethyllithium, prepared by reacting commercially available perfluorohexylethyl iodide (8,8,8,7,7,6,6,5,5,4,4,3,3-tridecafluorooctyl iodide) and *t*-BuLi, produced *N*-Boc fluorous prolinol in 57% yield and subsequent deprotection of *N*-Boc fluorous prolinol with trifluoroacetic acid (TFA) led to the fluorous prolinol **1** in quantitative yield.

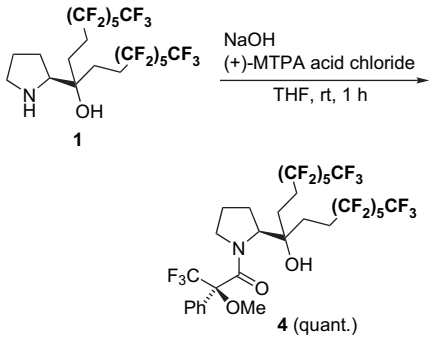


Reagents and conditions: (a) *t*-BuLi, $CF_3(CF_2)_5CH_2CH_2I$, Et_2O, -78 to 0 °C, 2 h, 57%; (b) CH_2Cl_2-CF_3CO_2H (v/v = 1/1), 0 °C to rt, 1.5 h, quant.

Scheme 2. Preparation of fluorous prolinol **1**.

As shown in Scheme 3, the enantiomeric purity of fluorous prolinol **1** was determined to be >99% ee by ^1H, ^{19}F NMR, and GC analyses of the crude reaction mixture of (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((+)-MTPA) amide derivative **4**, prepared by reacting fluorous prolinol **1** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in the presence of sodium hydroxide.

The content of the fluorine atoms in fluorous prolinol **1** is 62.27% and prolinol **1** can be classified as a heavy fluorous compound. Fluorous prolinol **1** was a white solid that was insoluble in a small amount of ordinary organic solvent and FC-72.



Scheme 3. Transformation of fluorous prolinol **1** to Mosher amide.

2.2. Optimization of reaction conditions

We initially investigated the effects of boron reagents for preparing oxazaborolidine as well as a stoichiometric reducing agent on the enantioselectivity and yield in the reduction of acetophenone **2a** using fluorous prolinol **1** as a pre-catalyst. The results are summarized in Table 1.

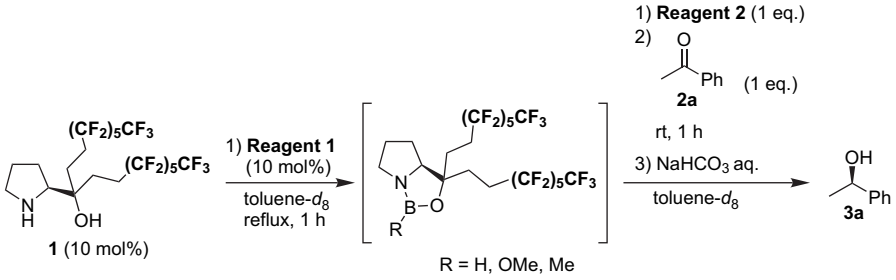
When borane–tetrahydrofuran ($BH_3\cdot THF$) complex was used not only as a reagent to prepare the fluorous oxazaborolidine but also as a reducing agent, the corresponding alcohol **3a** was obtained in 85% yield with 73.0% ee (entry 1). Among other boron reagents examined, such as trimethoxyborane ($B(OMe)_3$)[10] and trimethylboroxine, in place of $BH_3\cdot THF$ as a reagent to prepare the oxazaborolidine, $B(OMe)_3$ gave the best enantioselectivity (93.2% ee, entry 2). Borane–dimethyl sulfide ($BH_3\cdot SMe_2$) complex and catecholborane[11] as a reducing agent were not effective compared to $BH_3\cdot THF$ complex (entries 4 and 5).

2.3. Catalytic asymmetric reduction of various ketones

Next, various ketones were investigated under the reaction conditions using $BH_3\cdot THF$ or $B(OMe)_3$ as reagents to prepare the oxazaborolidine and to reduce the ketones. The results are summarized in Table 2.

Chiral oxazaborolidine (R=H), derived from $BH_3\cdot THF$ complex, was not an effective catalyst in the enantioselective reduction of some acetophenones carrying electron-donating or electron-withdrawing groups at the 4-position of the phenyl group and gave the corresponding alcohols **3a–e** with lower enantioselectivities (71.0–74.4% ee, entries 1–4). On the other hand, as shown in Table 2, reduction using $B(OMe)_3$ as a reagent to prepare the oxazaborolidine (R=OMe) gave much better enantioselectivities. Reduction of acetophenone **2a** proceeded smoothly to give the best enantioselectivity (93.2% ee, entry 6). Other acetophenones **2b–e** carrying methyl, methoxy, chloro, and trifluoromethyl groups at the 4-position on the phenyl group gave the products **3b–e** with good to high enantioselectivities (entries 2–5). The reduction of 4-acetylpyridine **2f** also proceeded smoothly to give the corresponding alcohols **3f** with 90.2% ee (entry 11). α-Tetralone **2h** also participated in the reduction to produce the alcohol **3h** in 95% yield with high enantioselectivity (entry 13). Unfortunately, however, pinacoline

Table 1. Screening of reagents for asymmetric reduction[a]



Entry	Reagent **1**	Reagent **2**	Yield[b] (%)	Isomer ratio[c] (*R*/*S*)	ee[c] (%)	Conversion[b] (%)	Recovery of **1**[d] (%)
1	$BH_3\cdot THF$[e]	$BH_3\cdot THF$[e]	85	86.5:13.5	73.0	>99	59
2	$B(OMe)_3$	$BH_3\cdot THF$[e]	78	96.6:3.4	93.2	>99	43
3	Trimethylboroxine[e]	$BH_3\cdot THF$[e]	83	81.6:18.4	63.2	>99	63
4	$BH_3\cdot THF$[e]	$BH_3\cdot SMe_2$[e]	83	81.9:18.1	63.8	95	86
5	$BH_3\cdot THF$[e]	Catecholborane[e]	51	69.3:30.7	38.6	66	40

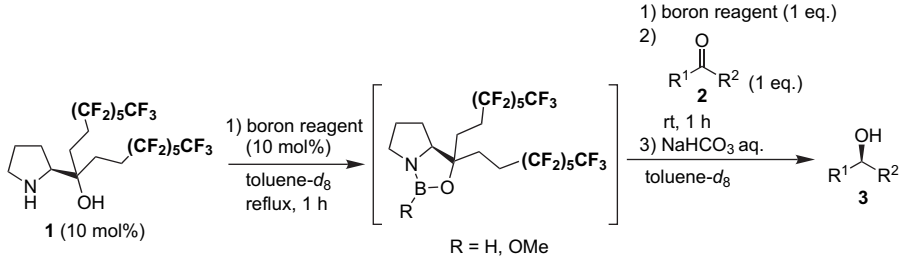
[a] The reaction was carried out with fluorous ligand **1** (0.1 mmol) and acetophenone **2a** (1 mmol).
[b] Determined by ^1H NMR.
[c] Determined by HPLC analysis with DAICEL Chiralcel OD-H column.
[d] After quenching of the reaction, removal of the aqueous phase, and storage at −30 °C for 40 h, the supernatant was removed via syringe and the fluorous ligand was determined by weighing the residue.
[e] THF solution (1.0 M) was used.

2g gave the product **3g** with much lower enantioselectivity (30.4% ee, entry 12).

Significantly, the enantioselectivities of the alcohols **3** using the fluorous oxazaborolidine derived from $B(OMe)_3$ are much better than those using $BH_3\cdot THF$. These results can be explained by an increase in the Lewis acidity of the boron atom of the oxazaborolidine in the transition state.[12] In all cases, ligand **1** was recovered by filtration from the suspension in good yield (up to 84%).

To further expand the utility of this fluorous oxazaborolidine-catalyzed asymmetric reduction, three fluoromethylated ketones **5** were examined, as shown in Table 3. α-Monofluorinated and difluorinated acetophenones **5a**,**b** participated in the reaction to give the corresponding

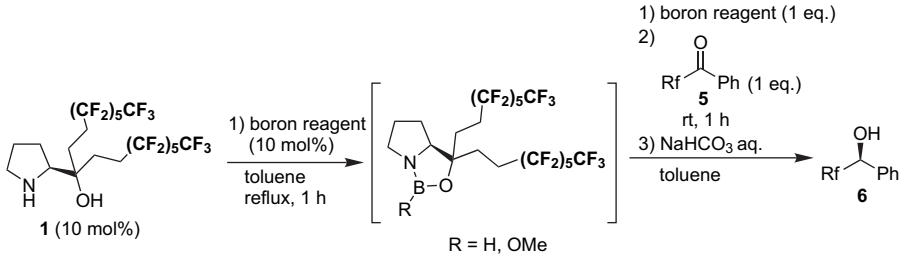
Table 2. Asymmetric reduction of various ketones[a]



Entry	Boron reagents	Ketones **2**	R^1, R^2	Yield[b] (%)	Isomer ratio (*R*/*S*)	ee (%)	Recovery of **1**[c] (%)
1	$BH_3\cdot THF$[d]	**2a**	Me, Ph	85	86.5:13.5[e]	73.0[e]	59
2	$BH_3\cdot THF$[d]	**2b**	Me, 4-MeC_6H_4	82	87.2:12.8[e]	74.4[e]	63
3	$BH_3\cdot THF$[d]	**2c**	Me, 4-$MeOC_6H_4$	>99	86.2:13.8[e]	72.4[e]	84
4	$BH_3\cdot THF$[d]	**2d**	Me, 4-ClC_6H_4	69	85.5:14.5[e]	71.0[e]	58
5	$BH_3\cdot THF$[d]	**2e**	Me, 4-$CF_3C_6H_4$	71	86.0:14.0[e]	72.0[e]	74
6	$B(OMe)_3$	**2a**	Me, Ph	78	96.6:3.4[e]	93.2[e]	43
7	$B(OMe)_3$	**2b**	Me, 4-MeC_6H_4	76	96.1:3.9[e]	92.2[e]	32
8	$B(OMe)_3$	**2c**	Me, 4-$MeOC_6H_4$	83	94.4:5.6[e]	88.8[e]	66
9	$B(OMe)_3$	**2d**	Me, 4-ClC_6H_4	88	96.0:4.0[e]	92.0[e]	43
10	$B(OMe)_3$	**2e**	Me, 4-$CF_3C_6H_4$	91	93.0:7.0[e]	86.0[e]	54
11	$B(OMe)_3$	**2f**	Me, 4-Pyridyl	50	95.1:4.9[f]	90.2[f]	72
12	$B(OMe)_3$	**2g**	Me, *t*-Bu	>99[g]	65.2:34.8[f]	30.4[f]	38
13	$B(OMe)_3$	**2h**	α-Tetralone	95	94.4:5.6[f]	88.8[f]	41

[a] The reaction was carried out with fluorous ligand **1** (0.1 mmol) and ketones **2** (1 mmol) in toluene-d_8.
[b] Determined by ^1H NMR.
[c] After quenching of the reaction, removal of the aqueous phase, and storage at −30 °C for 40 h, the supernatant was removed via syringe and the fluorous ligand was determined by weighing the residue.
[d] THF solution (1.0 M) was used.
[e] Determined by HPLC analysis.
[f] Determined by GC analysis using InertCap CHIRAMIX (GL Sciences).
[g] Determined by GC.

Table 3. Asymmetric reduction of various α-fluorinated ketones[a]



Entry	Boron reagents	Ketones **5**	Rf	Yield[b] (%)	Isomer ratio (*R*/*S*)	ee (%)	Recovery of **1**[c] (%)
1	$B(OMe)_3$	**5a**	CH_2F	56	8.3:91.7[d]	83.4[d]	38
2	$B(OMe)_3$	**5b**	CHF_2	80	11.8:88.2[d]	76.4[d]	31
3	$B(OMe)_3$	**5c**	CF_3	85	50.6:49.4[e]	0.8[e]	40
4	$BH_3\cdot THF$[f]	**5c**	CF_3	54	51.6:48.6[e]	3.2[e]	58

[a] The reaction was carried out with fluorous ligand **1** (0.1 mmol) and ketones **5** (1 mmol).
[b] Determined by ^1H or ^{19}F NMR.
[c] After quenching of the reaction, removal of the aqueous phase, and storage at −30 °C for 40 h, the supernatant was removed via syringe and the fluorous ligand was determined by weighing the residue.
[d] Determined by HPLC analysis.
[e] Determined by GC analysis.
[f] THF solution (1.0 M) was used.

alcohols **6a**,**b** in good yields with high enantioselectivities (entries 1 and 2). However, the reduction of trifluoroacetophenone **5c** resulted in a significant decrease in the enantioselectivity (entries 3 and 4). There are two possible explanations for these results: (1) the carbonyl group of trifluoroacetophenone **5c** cannot coordinate to the boron atom of the oxazaborolidine, since the oxygen atom in trifluoroacetophenone **5c** is much less basic than those of other acetophenone derivatives. (2) Uncatalyzed reduction with $BH_3\cdot THF$ could occur in the case of trifluoroacetophenone **5c**, since the LUMO of ketone **5c** is much lower than those of other acetophenones.[13] Fluorous prolinol **1** could be recovered in fair to moderate yields.

Finally, the reusability of the recovered fluorous prolinol **1** was investigated. After work-up in this reaction using $B(OMe)_3$ to prepare the oxazaborolidine, the fluorous ligand **1** was recovered from the suspension with a glass filter and washed with a small amount of cold aq sodium hydrogen carbonate as well as cold hexane, and dried under vacuum at room temperature. Unfortunately, the second reduction using the obtained fluorous ligand **1** gave a similar yield (78%) of the product **3a** but with lower enantioselectivity (*R*/*S*=68.4:31.6). Epimerization of the recovered fluorous prolinol **1** did not occur in this reaction, because the enantiomeric purity of the recovered fluorous prolinol **1** was also determined to be >99% ee by ^1H and ^{19}F NMR analyses of the crude reaction mixture of (+)-MTPA amide derivative **4**, prepared by reacting the recovered fluorous prolinol **1** with (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride. While the exact reason for the decrease in enantioselectivity is not yet clear, it may be due to the presence of a small amount of water[14] or boric acid derivatives along with the recovered fluorous prolinol **1**.

3. Conclusions

Catalytic asymmetric reduction of a variety of ketones using fluorous oxazaborolidines derived from a novel fluorous prolinol with two perfluorohexylethyl groups at the α-position afforded the corresponding alcohols in good yields and good to high enantioselectivities (up to 93.2% ee). Moreover, up to 86% of the fluorous ligand **1** could be recovered by filtration without the use of any fluorous solvents or silica gel.

4. Experimental

4.1. General methods

^1H (500 MHz) and ^{13}C (126 MHz) NMR spectra were measured with a JEOL ECA-500 FTNMR spectrometer in deuterochloroform ($CDCl_3$) solutions with tetramethylsilane (Me_4Si) as an internal standard. ^{19}F NMR (471 MHz) spectra were recorded on a JEOL ECA-500 FT NMR in $CDCl_3$ solutions using trichlorofluoromethane ($CFCl_3$) as an external standard. Anhydrous tetrahydrofuran (THF) and diethyl ether were purchased from Kanto Chemical Co., Inc. and used directly without any treatment. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride under argon. Toluene-d_8 was purchased from Cambridge Isotope Laboratories, Inc. and used without any treatment. The ee values of the products were determined by chiral HPLC or GC analyses.

4.2. *N*-*tert*-Butoxycarbonyl-(2*S*)-bis(3,3,4,4,5,5,6,6,7,7,-8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol

A solution of 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl iodide (4.181 g, 8.82 mmol) in dry Et_2O (24 ml) was cooled to −78 °C and *t*-BuLi (5.8 ml, 8.58 mmol) was added slowly. The mixture was stirred for 20 min at −78 °C. After *N*-(*tert*-butoxycarbonyl)-(L)-proline methyl ester (0.338 g, 1.47 mmol) in dry Et_2O (10 ml) was added slowly, the solution was stirred for 1 h at −78 °C and then slowly warmed to 0 °C with stirring. The mixture was poured into an ice solution of satd aq NH_4Cl/10% aq HCl=3:1 (80 ml), the organic

layer was separated, and the aqueous layer was extracted with Et_2O (2×50 ml). The combined organic layers were washed with brine (50 ml) and dried over Na_2SO_4. After Et_2O was evaporated, the residue was purified by column chromatography on silica gel (eluant: hexane/Et_2O=30:1) to give *N*-*tert*-butoxycarbonyl-(2*S*)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (0.758 g, 0.849 mmol). R_f 0.13 (Hexane/Et_2O=30:1); $[\alpha]_D^{23}$ −22.4 (*c* 1.00, $CHCl_3$); IR (KBr): 3292 (OH), 1662 (C=O) cm^{-1}; mp 89.5 °C; ^1H NMR ($CDCl_3$): δ 1.47 (s, 9H), 1.52–1.89 (m, 8H), 2.05–2.22 (m, 3H), 2.30–2.54 (m, 1H), 3.13–3.20 (m, 1H), 3.71–3.76 (m, 1H), 3.99 (t, *J*=7.81 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.16 (s), 25.16 (s), 25.23 (t, *J*=21.92 Hz), 25.29 (t, *J*=21.09 Hz), 28.11 (s), 28.24 (s), 28.32 (s), 48.56 (s), 65.24 (s), 74.36 (s), 81.64 (s), 105.33–121.92 (m, 12C), 158.37 (s); ^{19}F NMR ($CDCl_3$): δ −48.49 to −48.41 (m, 4F), −45.68 (br s, 4F), −45.16 (br s, 4F), −44.17 (br s, 4F), −37.80 to −36.11 (m, 4F), 3.12 (t, *J*=9.92 Hz, 6F); HRMS (FAB^+) found: *m*/*z* 894.1496, calcd for $C_{26}H_{26}F_{26}NO_3$: M+H, 894.1498.

4.3. (2*S*)-Bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (1)

A solution of *N*-*tert*-butoxycarbonyl-(L)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (0.953 g, 1.07 mmol) in CH_2Cl_2 (6.3 ml) was cooled to 0 °C and TFA (6.3 ml) was added. The mixture was stirred for 1.5 h at room temperature. After the mixture was poured into a satd aq Na_2CO_3 solution (60 ml), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×60 ml). The combined organic layers were washed with brine and dried over Na_2SO_4. CH_2Cl_2 was evaporated to give (2*S*)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (0.814 g, 1.21 mmol). $[\alpha]_D^{23.5}$ −5.34 (*c* 0.374, $CHCl_3$ and AK-225G); IR (KBr): 3101 (OH) cm^{-1}; mp 50.0–52.0 °C; ^1H NMR ($CDCl_3$ and AK-225G): δ 1.64–1.94 (m, 8H), 1.98–2.33 (m, 6H), 2.84–2.93 (m, 1H), 3.02–3.12 (m, 1H), 3.14–3.22 (m, 1H); ^{13}C NMR ($CDCl_3$ and AK-225G): δ 24.98 (s), 25.76 (t, *J*=22.33 Hz), 25.89 (s), 27.61 (s), 46.96 (s), 63.98 (s), 72.13 (s), 107.14–125.80 (m, 12C); ^{19}F NMR ($CDCl_3$ and AK-225G): δ −126.55 to −126.30 (m, 4F), −123.52 (s, 4F), −123.06 (s, 4F), −122.09 (s, 4F), −115.07 to −114.42 (m, 4F), −81.21 (t, *J*=10.22 Hz, 6F); HRMS (FAB^+) found: *m*/*z* 794.0790, calcd for $C_{21}H_{18}F_{26}NO$: M+H, 794.0973.

4.4. *N*-α-Methoxy-α-(trifluoromethyl)phenylacetyl-(2*S*)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-(pyrrolidin-2-yl)methanol (4)

To a solution of (L)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (0.158 g, 0.199 mmol) in THF (4 ml) was added 1.0 M aq NaOH (1.0 M, 0.2 ml, 0.200 mmol). The mixture was stirred, (+)-MTPA acid chloride (0.101 g, 0.400 mmol) was added, and the mixture was stirred for 1 h at room temperature. After the mixture was poured into brine (50 ml), the organic layer was separated, and the aqueous layer was extracted with Et_2O (2×50 ml). The combined organic layers were dried over Na_2SO_4. After the solution was evaporated, the residue was purified by column chromatography on silica gel (hexane/ethyl acetate=4:1) to give *N*-α-methoxy-α-(trifluoromethyl)phenylacetyl-(2*S*)-bis(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)(pyrrolidin-2-yl)methanol (0.157 g, 0.198 mmol). R_f 0.6 (hexane/EtOAc=4:1); $[\alpha]_D^{23.0}$ +24.36 (*c* 0.67, $CHCl_3$); IR (NaCl): 3304 (OH), 1628 (C=O) cm^{-1}; mp 98.0–102.0 °C; ^1H NMR ($CDCl_3$): δ 1.40–1.66 (m, 5H), 1.77–1.89 (m, 2H), 2.04–2.18 (m, 4H), 2.45–2.62 (m, 2H), 3.66 (s, 3H), 4.04–4.08 (m, 1H), 4.39 (t, *J*=8.31 Hz, 1H), 6.37 (d, *J*=1.72 Hz, 1H), 7.35–7.41 (m, 3H), 7.50–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 24.65–25.44 (m, 4C), 25.18 (s, 2C), 27.12 (s, 2C), 48.43 (s, 1C), 55.98 (s, 1C), 75.17 (s, 1C), 85.18 (q, *J*=25.99 Hz, 1C), 108.13–124.70 (m, 12C), 126.67 (s, 2C), 128.56 (s, 2C), 129.64 (s, 1C), 133.38 (s, 1C), 168.63 (s, 1C); ^{19}F NMR ($CDCl_3$): δ −126.12 (d, *J*=14.09 Hz, 4F), −123.39 to −123.19 (m, 4F), −122.84 (s, 4F), −121.82 (d, *J*=7.59 Hz, 4F), −115.45 to −113.72 (m, 4F), −80.81 (t, *J*=9.75 Hz, 3F), −80.83 (t, *J*=10.12 Hz, 3F), −71.22 (s, 3F); HRMS (FAB^+) found: *m*/*z* 1010.1364, calcd for $C_{31}H_{25}F_{29}NO_3$: M+H, 1010.1371.

4.5. Typical procedure for the asymmetric reduction of ketones with fluorous prolinol 1 (Table 1, entry 2)

To a toluene-d_8 (1 ml) solution of fluorous prolinol **1** (0.079 g, 0.100 mmol), was added trimethoxyborane ($B(OMe)_3$) (0.1 mmol, 0.01 ml) at room temperature under an argon atmosphere. After being refluxed for 1 h, the reaction mixture was cooled to room temperature. After the successive addition of a THF solution of $BH_3\cdot THF$ complex (1.0 M tetrahydrofuran solution, 1.0 mmol, 1.0 ml) and a toluene-d_8 (8 ml) solution of acetophenone **2a** (0.120 g, 1 mmol) over 3 h at room temperature, the reaction mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was then quenched with MeOH (1 ml) and satd aq $NaHCO_3$ (3 ml), the aqueous phase was removed and the mixture was held at −30 °C for 40 h, the supernatant was removed via syringe, and the fluorous ligand was determined by weighing the residue (0.034 g, 43%). Measurement of the organic phase by ^1H NMR using anisole (0.104 g, 0.962 mmol) as an internal standard gave the corresponding alcohol **3a** in 78% yield (0.779 mmol).

4.5.1. 1-Phenylethanol (3a).[15,16] ^1H NMR ($CDCl_3$): δ 1.44 (d, *J*=6.52 Hz, 3H), 3.89 (s, 1H), 4.52–4.85 (m, 1H), 7.26–7.38 (m, 5H). Enantiomer separation of **3a**: HPLC (Daicel Chiralcel OD-H column, 0.4 ml/min, 254 nm, hexane/*i*-PrOH=95:5, t_1 (*R*-isomer)=16.6 min, t_2 (*S*-isomer)=20.3 min).

4.5.2. 1-(4-Methylphenyl)ethanol (3b).[15,16] ^1H NMR ($CDCl_3$): δ 1.33 (d, *J*=6.34 Hz, 3H), 2.23 (s, 3H), 2.39 (s, 1H), 4.69 (q, *J*=6.34 Hz, 1H), 7.03 (d, *J*=7.81 Hz, 2H), 7.12 (d, *J*=7.81 Hz, 2H). Enantiomer separation of **3b**: GC (InertCap CHIRAMIX (GL Sciences), 40–180 °C, programming rate=2.0, t_1 (*R*-isomer)=54.7 min, t_2 (*S*-isomer)=56.2 min).

4.5.3. 1-(4-Methoxyphenyl)ethanol (3c).[15,16] ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H), 1.83 (s, 1H), 3.80 (s, 3H), 4.86 (s, 1H), 6.88–7.31 (m, 4H). Enantiomer separation of **3c**: GC (InertCap CHIRAMIX (GL Sciences), 40–180 °C, programming rate=2.0, t_1 (*R*-isomer)=66.2 min, t_2 (*S*-isomer)=67.0 min); HPLC (Daicel Chiralcel OD column, 0.3 ml/min,

hexane/*i*-PrOH=95:5, t_1 (*R*-isomer)=36.8 min, t_2 (*S*-isomer)=41.8 min).

4.5.4. 1-(4-Chlorophenyl)ethanol (3d).[15,16] ^{1}H NMR ($CDCl_3$): δ 1.43 (d, J=6.34 Hz, 3H), 2.34 (s, 1H), 4.82 (q, J=6.34 Hz, 1H), 7.25–7.30 (m, 4H). Enantiomer separation of **3d**: HPLC (Daicel Chiralcel OD column, 0.4 ml/min, 254 nm, hexane/*i*-PrOH=95:5, t_1 (*R*-isomer)=30.0 min, t_2 (*S*-isomer)=28.9 min).

4.5.5. 1-(4-Trifluoromethylphenyl)ethanol (3e).[16] ^{1}H NMR ($CDCl_3$): δ 1.51 (d, J=6.10 Hz, 3H), 1.97 (s, 1H), 4.97 (q, J=6.10 Hz, 1H), 7.49 (d, J=8.06 Hz, 2H), 7.61 (d, J=8.06 Hz, 2H). Enantiomer separation of **3e**: GC (InertCap CHIRAMIX (GL Sciences), 40–180 °C, programming rate=2.0, t_1 (*R*-isomer)=54.7 min, t_2 (*S*-isomer)=56.7 min).

4.5.6. 1-(4-Pyridyl)ethanol (3f).[17] ^{1}H NMR ($CDCl_3$): δ 1.41–1.45 (m, 3H), 2.69 (s, 1H), 4.80–4.94 (m, 1H), 7.21–7.44 (m, 2H), 8.35–8.43 (m, 2H). Enantiomer separation of **3f**: HPLC (Daicel Chiralcel AS-H column, hexane/*i*-PrOH=95:5, 254 nm, 0.5 ml/min, t_1 (*S*-isomer)=71.4 min, t_2 (*R*-isomer)=83.9 min).

4.5.7. 3,3-Dimethyl-2-butanol (3g).[18] ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 9H), 1.04 (d, J=6.52 Hz, 3H), 2.52 (s, 1H), 3.62 (q, J=6.52 Hz, 1H). Enantiomer separation of **3g**: GC (CP-Chirasil-Dex CB (VARIAN), 40–225 °C, programming rate=2.0, t_1 (*R*-isomer)=18.7 min, t_2 (*S*-isomer)=20.3 min).

4.5.8. 1,2,3,4-Tetrahydronaphthalen-1-ol (3h).[18] ^{1}H NMR ($CDCl_3$): δ 1.79–2.00 (m, 5H), 2.68–2.86 (m, 2H), 4.77 (t, J=4.83 Hz, 1H), 7.09–7.11 (m, 1H), 7.17–7.22 (m, 2H), 7.40–7.43 (m, 1H). Enantiomer separation of **3h**: HPLC (Daicel Chiralcel AS-H column, hexane/*i*-PrOH=95:5, 254 nm, 0.2 ml/min, t_1 (*R*-isomer)=42.7 min, t_2 (*S*-isomer)=34.9 min).

4.5.9. 2-Fluoro-1-phenylethanol (6a).[19] ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 1H), 4.59–4.34 (m, 2H), 5.05–4.99 (m, 1H), 7.38–7.42 (m, 5H). Enantiomer separation of **6a**: HPLC (Daicel Chiralcel OD column, 0.8 ml/min, 254 nm, hexane/*i*-PrOH=95:5, t_1 (*S*-isomer)=15.1 min, t_2 (*R*-isomer)=18.9 min).

4.5.10. 2,2-Difluoro-1-phenylethanol (6b).[19] ^{1}H NMR ($CDCl_3$): δ 2.43 (s, 1H), 4.83 (dt, J=10.08, 4.75 Hz, 1H), 5.77 (dt, J=56.02, 4.75 Hz, 1H), 7.42–7.36 (m, 5H). Enantiomer separation of **6b**: HPLC (Daicel CHIRALPAK AS-H, hexane/*i*-PrOH=95:5, 0.8 ml/min, 254 nm, t_1 (*S*-isomer)=12.0 min, t_2 (*R*-isomer)=12.7 min).

4.5.11. 2,2,2-Trifluoro-1-phenylethanol (6c).[19] ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 1H), 5.02 (q, J=6.68 Hz, 1H), 7.47–7.41 (m, 5H). Enantiomer separation of **6c**: GC (CP-Chirasil-Dex CB (VARIAN), 50–160 °C, programming rate=2.0, t_1 (*S*-isomer)=43.5 min, t_2 (*R*-isomer)=44.2 min).

Acknowledgements

We thank Professors and T. Ishihara, T. Konno and H. Yamanaka of the Kyoto Institute of Technology for the HRMS measurements. K.F. also gratefully acknowledges the AZINOMOTO Award in Synthetic Organic Chemistry, Japan.

References and notes

1. Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72.
2. (a) Gladysz, J. A.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3823 and the following articles in this special issue entitled 'Fluorous Chemistry'; (b) *The Handbook on Fluorous Chemistry*; Gladysz, J. A., Horváth, I. T., Curran, D. P., Eds.; Wiley-VCH: New York, NY, 2004.
3. (a) Wende, M.; Meier, R.; Gladysz, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 11490; (b) Wende, M.; Gladysz, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5861.
4. Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371.
5. Mikami, K.; Mikami, Y.; Matsuzawa, H.; Matsumoto, Y.; Nishikido, J.; Yamamoto, F.; Nakajima, H. *Tetrahedron* **2002**, *58*, 4015.
6. For a recent review, see: Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, *62*, 11837.
7. For α,α-diphenylprolinols carrying the perfluoroalkyl group on the phenyl group, see: (a) Dalicsek, Z.; Pollreisz, F.; Gömöry, Á.; Soós, T. *Org. Lett.* **2005**, *7*, 3243; (b) Park, J. K.; Lee, H. G.; Bolm, C.; Kim, B. M. *Chem.—Eur. J.* **2005**, *11*, 945.
8. For a α,α-diphenylprolinol tetramethylsilyl ether carrying the perfluoroalkyl group on the phenyl group, see: Zu, L.; Li, H.; Wang, J.; Yu, X.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 5131.
9. For reviews, see: (a) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475; (b) Singh, V. K. *Synthesis* **1992**, 605; (c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.
10. Masui, M.; Shioiri, T. *Synlett* **1997**, 273.
11. Gilmore, N. J.; Jones, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2115.
12. Farfan, N.; Contreras, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, 771.
13. Asao, N.; Asano, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3206.
14. For the effect of water on the enantioselectivities, see: (a) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763; For the effect of anions on the the enantioselectivities, see: (b) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6860.
15. Kobayashi, Y.; Kodama, K.; Saigo, K. *Org. Lett.* **2004**, *6*, 2941.
16. Hedberg, C.; Källström, K.; Arvidsson, P.; Andersson, P. G.; Brandt, P. *J. Am. Chem. Soc.* **2005**, *127*, 15083.
17. Schmitzer, A. R.; Franceschi, S.; Perez, E.; Rico-Lattes, I.; Lattes, A.; Thion, L. *J. Am. Chem. Soc.* **2001**, *123*, 5956.
18. Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902.
19. Nakamura, K.; Yamanaka, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2529.