New Approach to a Novel Axially Chiral Ligand Showing Spontaneous Enrichment of Axial Chirality

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We have synthesized novel axially chiral ligand with two chiral centers, (*R*)-(*R*)$_2$- and (*S*)-(*S*)$_2$-2,2′-bis(2,2,2-trifluoro-1-hydroxyethyl)biphenyl (1), which showed a high asymmetric induction when used as ligand. Here, another new approach to 1 by kinetic and thermodynamic resolution is presented which gave these ligands in a much shorter steps, in a higher yield, and in a higher enantiomeric excess.

Key words chiral ligand; trifluorohydroxyethyl group; biphenyl; kinetic resolution; chirality enhancement

Nowadays, the importance of asymmetric synthesis has been increasing especially in biomedicinal fields to obtain bioactive stereoisomers of chiral compounds selectively. Axially chiral ligands, such as BINAP and BINOL, have been used for syntheses of a variety of chiral compounds.

In the course of our study of fluorine analogs of chiral hematoporphyrin, we found that a chiral 2,2,2-trifluoro-1-hydroxyethyl (TFHE) group was obtained in a high yield and a high enantiomeric excess by asymmetric reduction of a trifluoroacetyl group.[1)] The chiral TFHE group was found to be very stable to many reagents and its chirality was maintained through harsh reaction conditions. The hydroxyl group of the TFHE group is more acidic than common alcohols, and was expected to show a moderate chelating ability. We synthesized (*R*)-(*R*)$_2$-2,2′-bis(2,2,2-trifluoro-1-hydroxyethyl)biphenyl ((*R*)-(*R*)$_2$-**1**),[2)] where the first (*R*) shows the axial chirality and (*R*)$_2$ shows the chiralities of the TFHE groups. This is an axially chiral ligand with two chiral centers. This showed a little better asymmetric induction for the reaction of diethylzinc with benzaldehyde in the presence of titanium tetraisopropoxide than BINOL.[2)] The synthesis of **1** and its application for asymmetric reaction are summarized in Chart 1.

This synthesis needs five steps from dibromobenzene (**2**) and the yield of coupling reaction of **5** to **6** was unsatisfactory probably due to the large steric hindrance of the 1-acetoxy-2,2,2-trifluoroethyl group. We planned a new approach to (*R*)-(*R*)$_2$-**1**. Our working hypothesis is shown in Chart 2. Since a trifluoroacetyl group is much smaller than the 1-acetoxy-2,2,2-trifluoroethyl group, coupling of **3** would give a better yield of bis(trifluoroacetyl)biphenyl (**9**). Further, if the thermodynamic equilibrium between axial isomers of **9** was fast and (*R*)-**9** was reduced kinetically faster by asymmetric reduction using the (*S*)-oxazaborolidine catalyst than (*S*)-**9**, (*R*)-(*R*)$_2$-**1** would be formed selectively by kinetic resolution. As the biphenyl part of **9** is much larger than the phenyl group of **3**, we expected that the asymmetric reduction of **9** would give a higher enantiomeric excess than that of **3**.

The coupling of **3** in the presence of Cu powder and a catalytic amount of CuI gave the biphenyl compound **9** in 85% yield, much better than the coupling of **5**, as expected. The asymmetric reduction of **9** with catecholborane in the presence of (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine, which had been found to give (*R*)-TFHE compounds from trifluoroacetyl compounds,[1)] gave (*R*)-(*R*)$_2$-**1** (39%), (*S*)-(*R*)$_2$-**1** (27%), and (*R*,*S*)-**1** (27%), where (*R*,*S*) shows the chirality of the TFHE groups. This was a mixture of the axially chiral isomers. Optical purities of (*R*)-(*R*)$_2$-**1** and (*S*)-(*R*)$_2$-**1** were estimated to be more than 99% by the Mosher method, respectively. These optical purities are better than those obtained by the method shown in Chart 1.

In the above synthesis, (*R*)-(*R*)$_2$-**1** was obtained as a major product, but (*S*)-(*R*)$_2$-**1** was formed in a considerable amount. To clarify this point, we examined the conformations of **9** (see Fig. 1).

Between two conformers of the trifluoroacetyl groups of the (*R*)-**9** conformer, one that has two CF_3 groups in *exo* to each other must be more stable than the *endo* counterpart. To afford an (*R*)-TFHE group from a trifluoroacetyl group, a hydride ion must approach from *si*-face of the trifluoroacetyl group. This attack is unfavorable for the more stable CF_3-*exo* conformer of the (*R*)-**9** conformer, since this face is blocked by the other benzene ring. The *si*-face attack seems to be favorable for (*S*)-**9** CF_3-*exo* conformer. If so, (*S*)-(*R*)$_2$-**1** must be formed preferentially. Namely, our working hypothesis must be corrected as shown in Chart 3.

Analysis of the reaction mixture by TLC showed that only one isomer was formed primarily. This must be (*S*)-(*R*)$_2$-**1**. To clarify the reason why (*R*)-(*R*)$_2$-**1** was isolated preferentially, we examined the difference in the stabilities between (*R*)-(*R*)$_2$-**1** and (*S*)-(*R*)$_2$-**1**. A solution of (*S*)-(*R*)$_2$-**1** in toluene was heated, and the equilibrium was followed by TLC. The peak of (*S*)-(*R*)$_2$-**1** decreased gradually, and that of (*R*)-(*R*)$_2$-**1** increased. After 2 h, the mixture was separated by a column chromatography to give (*R*)-(*R*)$_2$-**1** and (*S*)-(*R*)$_2$-**1** (6.8 : 1).

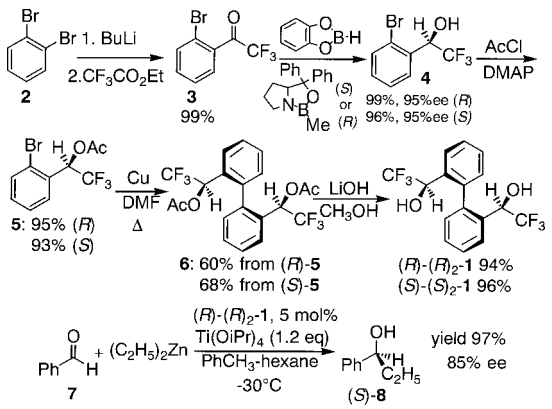

Chart 1

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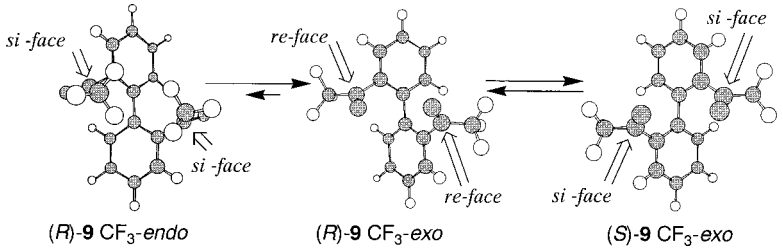

Fig. 1. Comparison of Conformers

This means that (*R*)-(*R*)$_2$-**1** is more stable than (*S*)-(*R*)$_2$-**1**, and suggests that the primary product, (*S*)-(*R*)$_2$-**1**, isomerized partly to (*R*)-(*R*)$_2$-**1** during workup. We name this spontaneous increase of active conformer as "spontaneous enrichment." After this separation, 62% of (*R*)-(*R*)$_2$-**1** was obtained in total.

In conclusion, both axially chiral isomers are stable enough to be separated by a collumn chromatography and recrystallized from hexane. Thus, by thermal equilibrium, separation, and recrystallization, (*R*)-(*R*)$_2$-**1** was obtained from **3** in a shorter steps, in a higher yield, and in higher enantiomeric excess than by our previous procedure. As shown above, (*R*)-(*R*)$_2$-**1** was found to be effective for asymmetric induction, while (*S*)-(*R*)$_2$-**1** was not. Thus, this new procedure gives the effective chiral ligands more efficiently.

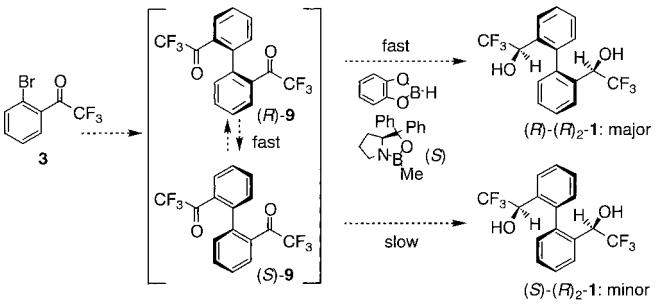

Chart 2

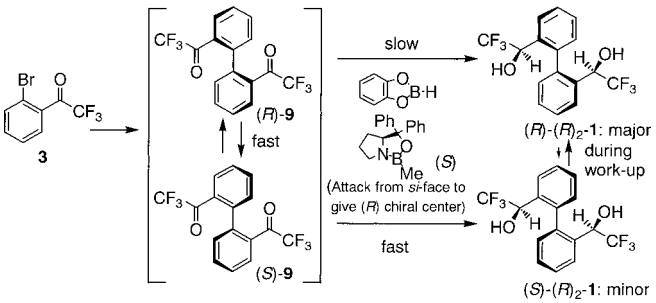

Chart 3

Experimental

2,2′-Bis(2,2,2-trifluoroacetyl)biphenyl (9) Copper powder,[3] formed according to literature, (7.4 g) and CuI (0.500 g, 2.63 mmol) was dried by heating in a Schlenk tube (20 ml) under vacuum. Ar was introduced to the tube and a solution of 2′-bromo-2,2,2-trifluoroacetophenone (**3**) (3.208 g, 12.7 mmol) in *N*,*N*-dimethylformamide (DMF) (3 ml) was added. The mixture was stirred at 180 °C for 47.5 h. After cooled to room temperature, the mixture was passed through a Celite layer, and the layer was washed with Et_2O. Combined organic layer was concentrated under vacuum, and the residue was separated by a column chromatography (SiO_2, hexane–CH_2Cl_2, 70 : 30). The effluent was recrystallized from hexane to give 2,2′-bis(2,2,2-trifluoroacetyl)biphenyl (**9**) (1.866 g, 85%).

9: Pale yellow crystals. mp 82.0—82.5 °C. MS *m*/*z*: 346 (M^+). High resolution (HR)-MS Calcd for $C_{16}H_8F_6O_2$ (M^+): 346.0429. Found: 346.0431. IR (KBr) cm^{-1}: 1724 (CO). ^{1}H-NMR ($CDCl_3$) δ: 7.99 (2H, ddd, *J*=8.0, 1.3, 0.5 Hz), 7.68 (2H, ddd, *J*=8.0, 7.2, 1.3 Hz), 7.57 (2H, ddd, *J*=7.6, 7.2, 1.3 Hz), 7.25 (2H, ddd, *J*=7.6, 1.3, 0.5 Hz). ^{19}F-NMR ($CDCl_3$) δ (from $CFCl_3$): −67.68 (s). ^{13}C-NMR ($CDCl_3$) δ: 181.34 (q, *J*=34.8 Hz), 142.97, 133.79, 131.00, 129.73 (q, *J*=3.6 Hz), 129.00, 127.82, 116.18 (q, *J*=290.7 Hz). *Anal.* Calcd for $C_{16}H_8F_6O_2$: C, 55.50; H, 2.33. Found: C, 55.73; H, 2.63.

Asymmetric Reduction of 2,2′-Bis(2,2,2-trifluoroacetyl)biphenyl (9) In an atmosphere of Ar, 2,2′-bis(2,2,2-trifluoroacetyl)biphenyl (**9**) (2.00 g, 5.78 mmol) and (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine (0.400 g, 1.75 mmol) were dissolved in tetrahydrofuran (THF) (20.0 ml). At −78 °C, a solution of catecholborane in THF (37.5 mmol in THF (44 ml), 22.0 ml: 17.2 mmol as catecholborane) was added to this solution in 1.5 h. The mixture was stirred at −78 °C for 12.5 h, then it was allowed to warm up to −30 °C in 6 h. After the mixture was stirred at this temperature for 26 h, it was treated with H_2O and 10% NaOH and stirred at room temperature for 6 h, then the mixture was extracted with Et_2O. The Et_2O layer was washed with 10% HCl, and dried over $MgSO_4$. After evaporation of the solvent under vacuum, the residue was separated by a column chromatography (SiO_2, CH_2Cl_2–Et_2O, 90 : 10—70 : 30) to afford three factions. Each fraction was purified by a column chromatography (SiO_2, CH_2Cl_2–Et_2O, 98 : 2—80 : 20) to give (*R*)-(*R*)$_2$-**1** (0.798 g, 39%), (*S*)-(*R*)$_2$-**1** (0.541 g, 27%), and (*R*,*S*)-**1** (0.549 g, 27%).

(*R*)-(*R*)$_2$-**1**: Colorless crystals (hexane). mp 130.6—131.0 °C. MS *m*/*z*: 350 (M^+). HR-MS Calcd for $C_{16}H_{12}F_6O_2$ (M^+): 350.0742. Found: 350.0746. IR (KBr) cm^{-1}: 3358 (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.72 (2H, dd, *J*=7.2, 1.2 Hz), 7.51 (2H, ddd, *J*=7.2, 7.2, 1.2 Hz), 7.47 (2H, ddd, *J*=7.2, 7.2, 1.2 Hz), 7.23 (2H, dd, *J*=7.2, 1.2 Hz), 4.66 (2H, q, *J*=7.3 Hz), 3.49 (2H, bs). ^{19}F-NMR ($CDCl_3$) δ: −72.01 (d, *J*=7.3 Hz). *Anal.* Calcd for $C_{16}H_{12}F_6O_2$: C, 54.87; H, 3.45. Found: C, 55.13; H, 3.61. $[\alpha]_D^{25}$=−8.35° (*c*=1.00, $CHCl_3$).

(*S*)-(*R*)$_2$-**1**: Colorless crystals (hexane). mp 119.9—120.2 °C. MS *m*/*z*: 350 (M^+). HR-MS Calcd for $C_{16}H_{12}F_6O_2$ (M^+): 350.0742. Found: 350.0746. IR (KBr) cm^{-1}: 3368 (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.81 (2H, dd, *J*=7.6, 1.6 Hz), 7.52 (2H, ddd, *J*=7.6, 7.6, 1.6 Hz), 7.46 (2H, ddd, *J*=7.6, 7.6, 1.6 Hz), 7.29 (2H, dd, *J*=7.6, 1.6 Hz), 4.89 (2H, m), 2.45 (2H, bd, *J*=6.0 Hz). ^{19}F-NMR ($CDCl_3$) δ: −71.61 (d, *J*=5.8 Hz). $[\alpha]_D^{25}$=5.83° (*c*=1.00, $CHCl_3$).

(*R*,*S*)-**1**: Colorless crystals (hexane–Et_2O). mp 123.0—123.2 °C. MS *m*/*z*: 350 (M^+). HR-MS Calcd for $C_{16}H_{12}F_6O_2$ (M^+): 350.0742. Found: 350.0747. IR (KBr) cm^{-1}: 3452 (OH). ^{1}H-NMR ($CDCl_3$) δ: 7.82 (1H, m), 7.77 (1H, m), 7.53 (2H, dddd, *J*=7.6, 7.6, 1.4, 1.6 Hz), 7.26 (2H, dddd, *J*=7.6, 7.6, 2.8, 1.6 Hz), 7.24 (1H, m), 7.20 (1H, m), 4.86 (1H, m), 4.74 (1H, m), 2.41 (1H, bd, *J*=4.8 Hz), 2.31 (1H, bd, *J*=4.8 Hz). ^{19}F-NMR ($CDCl_3$) δ: −72.34 (3F, d, *J*=5.9 Hz), −72.74 (3F, d, *J*=7.3 Hz).

Equilibrium between (*S*)-(*R*)$_2$-1 and (*R*)-(*R*)$_2$-1 A solution of (*S*)-(*R*)$_2$-**1** (0.040 g, 0.114 mmol) in toluene heated to its boiling point, and the equilibrium was followed by TLC. After 2 h, the area ratio of two spots became constant. After evaporation of the solvent, the residue was separated by a column chromatography (SiO_2, CH_2Cl_2–Et_2O, 95 : 5) to give (*R*)-(*R*)$_2$-**1** (0.034 g), (*S*)-(*R*)$_2$-**1** (0.005 g).

Mosher Ester from (*S*)-(*S*)$_2$-1 In an atmosphere of Ar, a mixture of (*S*)-(*S*)$_2$-**1** (0.020 g, 0.057 mmol), 4-dimethylaminopyridine (0.035 g, 0.29 mmol), CH_2Cl_2 (0.30 ml), (−)-2-methoxy-2-trifluoromethylphenylacetyl chloride[4] (0.035 ml, 0.19 mmol) was stirred at room temperature, then CH_2Cl_2 (0.10 ml) was added and stirred for further 1.5 h. After the mixture was treated with 10% HCl, it was extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$, and dried over $MgSO_4$. After evaporation of the solvent, NMR of the residue was examined. ^{1}H-NMR ($CDCl_3$) δ: 7.33—7.53 (14H, m), 7.17—7.24 (4H, m), 6.46 (2H, q, *J*=5.6 Hz), 3.51 (6H, s). ^{19}F-NMR ($CDCl_3$) δ: −67.55 (6F, s), 70.46 (6F, d, *J*=5.8 Hz). Peaks

ascribed to another diastereomer were not detected.

Mosher Ester from (*R*)-(*R*)$_2$-1 From (*R*)-(*R*)$_2$-**1**, the Mosher ester was derived similarly using (−)-2-methoxy-2-trifluoromethylphenylacetyl chloride. ^{1}H-NMR ($CDCl_3$) δ: 7.27—7.65 (18H, m), 6.11 (2H, q, J=5.6 Hz), 3.35 (6H, s). ^{19}F-NMR ($CDCl_3$) δ: −67.75 (6F, s), 70.03 (6F, d, J=4.4 Hz).

Refernces and Notes

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