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A novel axially dissymmetric ligand with chiral 2,2,2-trifluoro-1-hydroxyethyl groups

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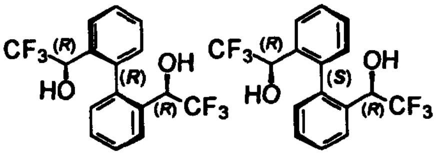
Abstract

Novel axially dissymmetric ligands (**1**) with two more chiral carbons were synthesized through homo-coupling of *o*-bromo-(*R* or *S*)-(2,2,2-trifluoro-1-acetoxyethyl)benzene. A high asymmetric induction was accomplished using 5 mol% of the Ti complex of this ligand for the reaction of benzaldehyde with Et_2Zn giving 85% ee of 1-phenylpropanol in 97% isolation yield. © 1999 Elsevier Science Ltd. All rights reserved.

An enantioselective synthesis using a transition metal or Lewis acid catalyst chelated with chiral ligands is one of the most important fields in recent organic chemistry. One of the most important ligands widely used is BINOL, an axially dissymmetric ligand with C_2 symmetry. Now, we would like to report the synthesis and use of another axially dissymmetric ligand with two more chiral carbons and C_2 symmetry.

We expected that the biphenyl with two chiral 2,2,2-trifluoro-1-hydroxyethyl (TFHE) groups (**1**) shown in Fig. 1 would be highly effective as a ligand, since these are axially dissymmetric and have two more chiral carbons. Like BINOL these also have C_2 symmetry. Trifluoromethyl groups are fairly large and highly electronegative, giving the hydroxyl groups comparable acidity to the hydroxyl group of phenol. These characteristics of compound **1** provide a more effective asymmetric space as a ligand than BINOL.



(R)-$(R)_2$-1 **(S)-$(R)_2$-1**
and their enantiomers

Figure 1.

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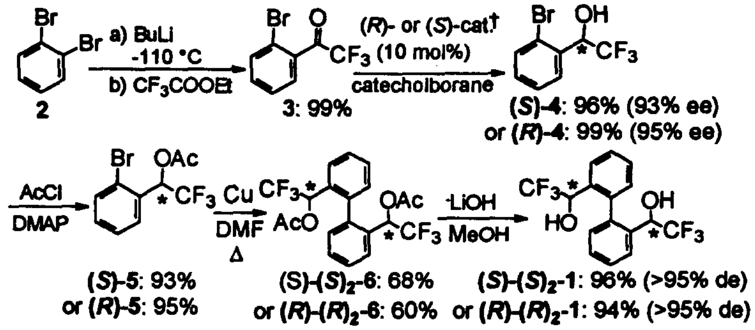
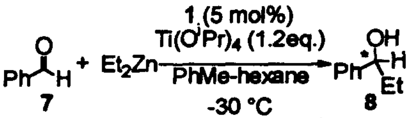
With these expectations, we started synthesis of **1**. *o*-Dibromobenzene (**2**) was lithiated with butyllithium,[1] followed by treatment with ethyl trifluoroacetate, to give 2′-bromo-2,2,2-trifluoroacetophenone (**3**) in 99% yield. Enantioselective reduction of **3** with catecholborane in the presence of (*R*)- or (*S*)-2-methyl-5,5-diphenyl-3,4-propano-1,2,3-oxazaborolidine,[2] gave (*S*)- or (*R*)-2,2,2-trifluoro-1-(2-bromophenyl)ethanol (**4**),[3] respectively. After protection of the hydroxyl groups of **4**, the bromo compound (**5**) was subjected to a homo-coupling reaction using activated copper.[4] The reactions from each chiral **4** proceeded successfully to give a single diastereoisomer (**6**) without loss of enantiomeric excesses[5] of the chiral centers. The formation of one diastereomer means that the coupling reaction occurred in high diastereoselectivity. This selectivity might be due to a strong repulsive effect between CF_3 groups. Finally, the acetyl groups of **6** were removed by LiOH in MeOH to give both the novel axially dissymmetric ligands (*R*)-(*R*)$_2$- and (*S*)-(*S*)$_2$-**1**[6] in >95% diastereomeric excess. The absolute configuration around the dissymmetric axis of (*S*)-(*S*)$_2$-**1** was determined by X-ray analysis. All of the results are shown in Scheme 1.



† cat.= (*R*)- or (*S*)-2-Methyl-5,5-diphenyl-3,4-propano-1,2,3-oxazaborolidine

Scheme 1.

To evaluate the efficiency of **1** as a chiral ligand, the reaction of benzaldehyde with diethylzinc in the presence of titanium tetraisopropoxide was carried out. Our results are shown in Scheme 2.



cat.(1)	*config.* of 8[a]	yield (%)[b]	ee (%)[a]
(*R*)-(*R*)$_2$-	*S*	97	85
(*S*)-(*S*)$_2$-	*R*	96	82

[a] Determined by the sign of the optical rotation.
[b] Isolated yields

Scheme 2.

The reactions proceeded within 3 hours at −30°C quantitatively to give either enantiomer of **8** with high ee.[7] Namely, (*R*)-(*R*)$_2$-**1** gave (*S*)-**8**, and (*S*)-(*S*)$_2$-**1** gave (*R*)-**8**. Only 5 mol% amounts of **1** gave 85% ee. Nakai et al.[8] have reported that **8** of 85% ee was obtained using 10 to 20 mol% of Ti-BINOL. These facts suggest that **1** could work as a better ligand in some reactions than BINOL. Seebach et al.[9] have reported that the same reaction in the presence of TADDOL gave **8** with a much higher ee than our results. However, our experiment is a preliminary one using the reagent of 95% ee. Our total yields are better than those reported by Seebach et al. We anticipate that use of enantiometrically pure **1** would improve the ee of our reaction, and purification of **1** is now in progress.

References

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2. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Reduction of CF_3COR: Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I.; Shiro, M. *Heterocycles* **1998**, *47*, 65–68.
3. The absolute configurations of the THFE groups were determined by Mosher's method.
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5. Estimated by NMR spectra of the Mosher ester.
6. (*R*)-(*R*)$_2$-**1**: colorless crystal. $[\alpha]_D^{20}$=−3.48 (c=1.00, $CHCl_3$). Mp: 130.0–130.5°C. MS *m/z*: 350 (M^+). HRMS calcd for $C_{16}H_{12}F_6O_2$ 350.0742, found 350.0739. ^1H NMR ($CDCl_3$) δ: 7.73 (2H, dd, *J*=7.4, 1.7 Hz), 7.51 (2H, ddd, *J*=7.8, 7.4, 1.7 Hz), 7.47 (2H, ddd, *J*=7.8, 7.4, 1.7 Hz), 7.23 (2H, dd, *J*=7.4, 1.7 Hz), 4.67 (2H, q, *J*=6.9 Hz), 3.42 (2H, bs). ^{19}F NMR ($CDCl_3$) δ: −76.80 (6F, d, *J*=6.9 Hz). (*S*)-(*S*)$_2$-**1**: $[\alpha]_D^{20}$=3.35.
7. A typical procedure. $Ti(O^iPr)_4$ (0.886 mL, 3.0 mmol) was added to a solution of (*R*)-(*R*)$_2$-**1** (44 mg, 0.125 mmol) in toluene (1.0 mL) at room temperature. After the mixture was stirred for 30 min at 50°C, Et_2Zn (in hexane, 3.0 mL, 3.0 mmol) was added at −78°C, and the whole mixture was stirred for 30 min. After a solution of benzaldehyde (0.254 mL, 2.5 mmol) in anhydrous toluene (2.0 mL) was added at −78°C, the mixture was allowed to warm up gradually to −30°C and stirred for 2 h at that temperature. The reaction was quenched by adding 10% HCl and worked up as usual, followed by silica gel column chromatography which afforded an excellent yield of (*S*)-**8**. (*S*)-(*S*)$_2$-**1** gave a comparable yield of (*R*)-**8**.
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