

HETERO DIELS-ALDER REACTION CATALYZED BY NEW AXIALLY DISSYMMETRIC LIGANDS WITH FLUORINATED CHIRAL CENTERS

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This is dedicated to the 75th birthday of Professor Yuichi Kanaoka.

Abstract— We have reported a new type of axially dissymmetric ligand, (*R*)-bis{(*R*)-2,2,2-trifluorohydroxyethyl}biphenyl ((*R*)-(*R*)₂-**1**), which showed an excellent asymmetric induction in the reaction of Et₂Zn to benzaldehyde. Now, a pentafluoroethyl analog of this ligand ((*R*)-(*R*)₂-**6**) was synthesized. Both ligands were found to work as a ligand for an asymmetric hetero Diels-Alder reaction of benzaldehyde (**2**) with the Danishefsky's diene (**4**). Titanium or aluminum complexes of (*R*)-(*R*)₂-**1** or (*R*)-(*R*)₂-**6** catalyzed this asymmetric reaction moderately to give products of up to 54% ee.

An enantioselective reaction using a catalytic amount of transition metals or Lewis acids chelated with chiral ligands is one of the most important methods in asymmetric syntheses. One of the most widely used ligands is BINOL, an axially dissymmetric ligand with C₂ symmetry. BINOL can coordinate with various metals owing to the flexibility around C₂ axis and many kinds of metal-BINOL complex have been used successfully in asymmetric syntheses. We reported new dissymmetric ligands, (*R*)-(*R*)₂- and (*S*)-(*S*)₂-**1** (Fig. 1),¹ which had a chiral axis and two chiral centers.

Trifluoromethyl (CF₃) groups, placed on the chiral carbinol carbons, are of characteristics of **1**. The high electron-

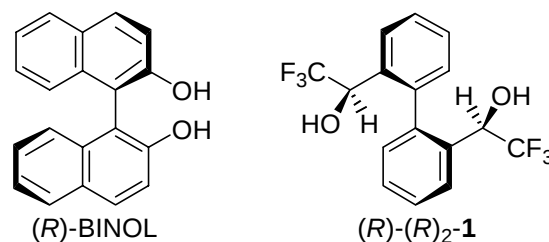


Figure1

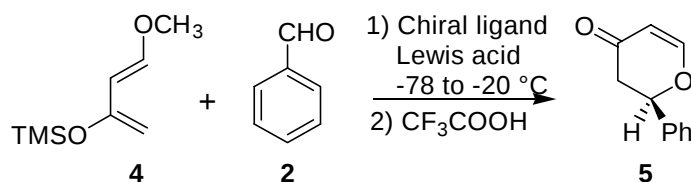
withdrawing effect of the CF₃ groups stabilizes the hydroxyl groups and inhibits racemization of the chiral centers. Further, the CF₃ groups make the acidity of the hydroxyl groups so high as that of phenol,

and this acidity makes **1** suitable as a ligand for Lewis acids or metals.¹

The effect of **1** for chiral synthesis was compared with that of BINOL. Nakai *et al.* reported that a complex prepared by simply mixing BINOL and an excess of titanium(IV) isopropoxide catalyzed an asymmetric reaction of benzaldehyde (**2**) and diethylzinc and that 1-phenyl-1-propanol (**3**) was obtained in 85% ee, when a 10 mol% of BINOL was used.² (*R*)-(*R*)₂-**1** was applied to the same reaction for evaluation of its asymmetric induction. Titanium complex of **1** prepared by the above method showed higher asymmetric induction than the Ti-BINOL complex: only a 5mol% of **1** gave **3** of 85% ee.³ These results suggest that our ligands form an asymmetric conformation in the titanium complex superior to that of BINOL. On the other hand, axial isomers, (*S*)-(*R*)₂- or (*R*)-(*S*)₂-**1** did not show any asymmetric induction. This is probably due to the fact that these could not work as a stable bidentate ligand due to the large steric repulsion between the CF₃ groups.

To investigate usefulness of our ligands to other asymmetric reactions, their application to a hetero Diels-Alder reaction of benzaldehyde (**2**) with the Danishefsky's diene (**4**) was examined.^{4,5} Chiral titanium and aluminum catalysts were prepared by mixing a toluene solution of the ligand and titanium(IV) isopropoxide or trialkylaluminum for 30 min at 50 °C. The reaction proceeded in moderate yields and ees. The catalyst prepared from (*R*)-(*R*)₂-**1** and more than three times of titanium(IV) isopropoxide showed better asymmetric induction than the aluminum catalysts to afford an adduct (**5**) of 40% ee (Table 1).

Our new ligand ((*R*)-(*R*)₂-**1**) was found to show moderate asymmetric induction. Now, we planned to synthesize a pentafluoroethyl analog of (*R*)-(*R*)₂-**1** ((*R*)-(*R*)₂-**6**), which had larger pentafluoroethyl groups and was expected to work as an better asymmetric inducer. For the synthesis of (*R*)-(*R*)₂-**6**, the same route for (*R*)-(*R*)₂-**1** was followed as shown in Scheme 1.¹ Thus, 1,2-dibromobenzene (**7**) was treated with butyllithium followed by ethyl pentafluoropropionate to give 2'-bromo-2,2,3,3,3-pentafluoropropiophenone (**8**). Asymmetric reduction of **8** with catecholborane in the presence of the (*S*)-oxazaborolidine catalyst gave 1-(2-bromophenyl)-2,2,3,3,3-pentafluoro-1-propanol (**9**) in a high yield and a high enantiomeric excess. After the hydroxyl groups of **9** were acetylated, the acetate (**10**) was treated with copper powder, followed by hydrolysis with LiOH to give (*R*)-(*R*)₂-**6** in 23% yield.⁶ This low yield must be due to the steric effect of the large 1-acetoxy-2,2,3,3,3-pentafluoropropyl groups on



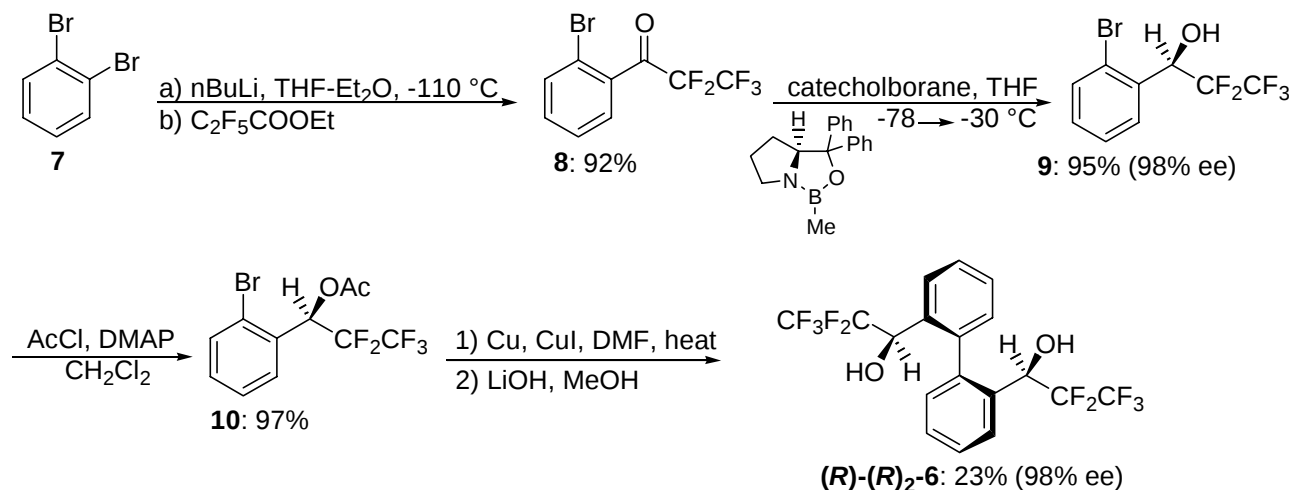
Ligand	Eq of ligand	L.A.(eq)	Yield(%)	ee(%)
(<i>R</i>)-(<i>R</i>) ₂ - 1	0.1	Ti(O ^{<i>i</i>} Pr) ₄ (0.1)	17	3.2
	0.1	Ti(O ^{<i>i</i>} Pr) ₄ (0.3)	51	40
	0.2	Ti(O ^{<i>i</i>} Pr) ₄ (0.6)	48	34
	1.0	Ti(O ^{<i>i</i>} Pr) ₄ (3.0)	45	39
	0.1	Al(C ₂ H ₅) ₃ (0.1)	20	7.2
	0.1	Al(C ₂ H ₅) ₃ (0.3)	26	15
	0.1	Al ^{<i>t</i>} Bu ₃ (0.3)	51	10

Table 1 Results of the Asymmetric Hetero Diels-Alder Reaction

Asymmetric reduction of **8** with catecholborane in the presence of the (*S*)-oxazaborolidine catalyst gave 1-(2-bromophenyl)-2,2,3,3,3-pentafluoro-1-propanol (**9**) in a high yield and a high enantiomeric excess. After the hydroxyl groups of **9** were acetylated, the acetate (**10**) was treated with copper powder, followed by hydrolysis with LiOH to give (*R*)-(*R*)₂-**6** in 23% yield.⁶ This low yield must be due to the steric effect of the large 1-acetoxy-2,2,3,3,3-pentafluoropropyl groups on

the adjacent carbons. In this synthesis, only one diastereo isomer was obtained. This means that the optical purity of the 1-acetoxy-2,2,3,3,3-pentafluoropropyl groups was not lost at all.

Scheme 1



The hetero Diels-Alder reaction of benzaldehyde (**2**) with the Danishefsky's diene (**4**) in the presence of (*R*)-(*R*)₂-**6** (0.1 eq.) and $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.3 eq.) gave the **5** in 20% yield and 54% ee. Although the yield was lower than that in the case of the (*R*)-(*R*)₂-**1**, the enantiomeric excess was improved.

In conclusion, our new axially chiral ligands with two chiral centers were found to show moderate asymmetric induction for hetero Diels-Alder reaction. The size of perfluoroalkyl groups on the chiral centers seems to play an important role for this induction. Now, syntheses of a series of ligands with various perfluoroalkyl substituents are under investigation.

REFERENCES AND NOTES

- 1) M. Omote, A. Kominato, M. Sugawara, K. Sato, A. Ando, and I. Kumadaki, *Tetrahedron Letters*, 1999, **40**, 5583.
- 2) M. Mori and T. Nakai, *Tetrahedron Letters*, 1997, **38**, 6233.
- 3) Enantiomeric excess of the product was determined using chiral capillary column (GAMMA DEXTM 225 Capillary Column, 30m x 0.25mm, SUPELCO Inc)
- 4) K. Maruoka, T. Itoh, T. Shirasaka, and H. Yamamoto, *J. Am. Chem. Soc.*, 1988, **110**, 310.
- 5) Typical procedure is as follows: To a solution of (*R*)-(*R*)₂-**1** (35 mg, 0.1 mmol) in toluene (4.0 mL), $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.089 mL, 0.3 mmol) was added at $0\text{ }^\circ\text{C}$, and the mixture was stirred for 30 min at $50\text{ }^\circ\text{C}$. Benzaldehyde (102 μL , 1.0 mmol) and 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (292 μL , 1.5mmol) were added at $-78\text{ }^\circ\text{C}$, and the mixture was allowed to warm up gradually to $-20\text{ }^\circ\text{C}$. After the mixture was stirred for 12 h, the reaction was quenched by 10% HCl. The mixture was extracted with ether. The organic layer was dried over MgSO_4 , and evaporated under vacuum.

After the residue was stirred with trifluoroacetic acid (116 μ L, 1.5 mmol) and CH_2Cl_2 (30 mL) at room temperature for 45 min, water was added to the mixture and extracted with CH_2Cl_2 . The organic layer was dried over MgSO_4 , and evaporated under vacuum. Purification by a column chromatography (SiO_2 , Et_2O :hexane = 1:4) afforded **5** (89 mg, 51%). Based on the sign of optical rotation,⁴ the stereochemistry of the major isomer was assigned as (*R*). Enantiomeric excess of the product was determined by chiral HPLC column (CHIRALCEL OD, DAICEL LTD, eluent: ethanol:n-hexane = 1:9)

- 6) (*R*)-(*R*)₂-**6**: Colorless crystals. mp 144.0 – 145.0 °C. MS *m/z*: 450 (M^+). HRMS Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{F}_6$ (M^+): 450.0678. Found: 450.0669. IR (KBr) cm^{-1} : 3428 (OH). ^1H -NMR (CDCl_3) δ : 7.76 (2H, dd, *J* = 7.4, 0.8 Hz), 7.46-7.56 (4H, m), 7.24 (2H, dd, *J* = 6.4, 0.8 Hz), 4.75 (2H, ddd, *J* = 17.6, 7.6, 7.6 Hz), 3.00 (2H, br d, *J* = 7.6 Hz). ^{19}F -NMR (CDCl_3) δ (from CFCl_3): - 82.78 (6 F, s), - 122.50 (2 F, dd, *J* = 275, 7.6 Hz), - 127.87 (2 F, ddd, *J* = 275, 17.6, 2.3 Hz).