Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 319–322

Synthesis of new axially dissymmetric ligand with large perfluoroalkyl groups

Masaaki Omote, Yuji Nishimura, Kazuyuki Sato, Akira Ando and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata 573-0101, Japan

Received 17 September 2004; revised 1 November 2004; accepted 5 November 2004
Available online 25 November 2004

Abstract—A new axially dissymmetric ligand with large perfluoroalkyl groups, 2,2′-bis(1-hydroxy-1*H*-perfluorooctyl)biphenyl (**1c**), which could not be obtained by the coupling reaction of the aryl bromide using copper powder, was synthesized successfully by the coupling reaction using $Ni(COD)_2$. This ligand showed much higher asymmetric induction in the reaction of diethylzinc with benzaldehyde than the trifluoromethyl (**1a**) or pentafluoroethyl (**1b**) analogues.

An asymmetric reaction to provide enantiomerically enriched product is of great importance to recent organic reaction. A number of chiral ligands for the asymmetric synthesis have been synthesized, and new methodologies using them have been developed. Among the chiral ligands, 1,1′-bi-2-naphthol (BINOL) is one of the most widely used and well-studied chiral ligands with C_2 symmetry.[1] Many outstanding reports on the asymmetric reactions with BINOL and its derivatives have been published.[2]

We have already reported the synthesis of new axially dissymmetric ligands of C_2 symmetry with two chiral centers, (*R*)-(*R*)$_2$- and (*S*)-(*S*)$_2$-**1a** and **1b**, as chiral ligands for Lewis metals (Fig. 1).[3] Concerning the representation of stereochemistry, the first (*R*) indicates axial chirality and the second (*R*) the chirality of side chains. Perfluoroalkyl (R_f) groups, composing the chiral centers, are characteristic of our ligands. The electron withdrawing and hard R_f groups inhibit racemization of the chiral centers on the side chains. Further, the R_f groups increase the acidity of the hydroxyl groups near to that of phenols. This makes the hydroxyl groups favorable as a ligand for Lewis metals. The ligands, **1a** or **1b**, catalyzed asymmetric addition reaction of diethylzinc to benzaldehyde, and **1b** showed higher asymmetric induction than **1a**. This suggested that the larger perfluoroalkyl groups would give the larger asymmetric induction. Thus, we designed a perfluoroheptyl analogue of **1a** (**1c**) expecting much higher asymmetric induction. However, the coupling reaction with copper powder used for the synthesis of **1a** or **1b** did not work for the synthesis of **1c**. In this paper, we would like to report the synthesis of **1c** using nickel complex and its application to asymmetric synthesis.

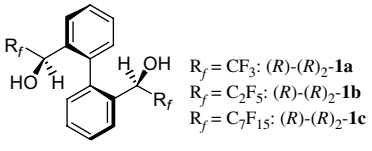
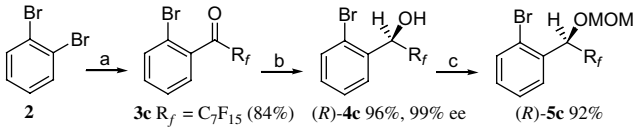


Figure 1. Structure of (*R*)-(*R*)$_2$-**1a**–**c**.

The key step for the synthesis of the ligands (**1a** or **1b**) was the Ullmann type coupling reaction of corresponding aryl bromides using copper powder. The chiral substrate (**5c**) for the same coupling reaction was prepared according to the previous route as shown in Scheme 1. Thus, enantioselective reduction of **3c**[4] with catecholborane in the presence of CBS catalyst[5] gave **4c**[6] quantitatively in a high ee. Interestingly, while (*S*)-**4a** was obtained with (*R*)-CBS catalyst, (*R*)-**4c** was obtained with the (*R*) catalyst.[7] This suggested that the order of steric bulkiness is $C_7F_{15} \gg C_6H_5 \gg C_2F_5 > CF_3$. The reduction of heptafluoropropyl analogue with the (*R*) catalyst gave the (*S*)-product only in 60% ee, which means that the bulkiness of C_3F_7 is slightly smaller than

Keywords: Fluorine; Chiral; Axial dissymmetry; Ligand; Coupling reaction; Asymmetric synthesis.
* Corresponding author. Tel.: +81 72 866 3140; fax: +81 72 850 7020; e-mail: kumadaki@pharm.setsunan.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.11.038



Scheme 1. Reagents and conditions: (a) (i) BuLi, THF–Et_2O, −110 °C, (ii) R_fCOOEt, (b) catecholborane, THF, (*R* or *S*)-5,5-diphenyl-2-methyl-3,4-propano-1,2,3-oxazaborolidine, −78 to −30 °C, (c) NaH, MOMCl, THF.

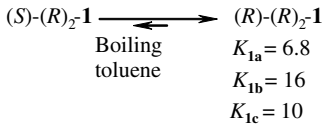


Figure 2. Thermal equilibrium of **1**.

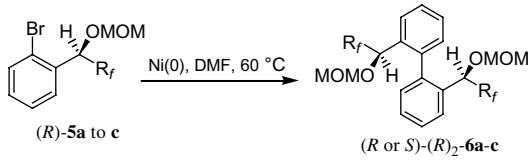
C_6H_5. After protection of the hydroxyl groups, (*R*)-**5c**[8] was used for the next coupling reaction.

Coupling reaction of **5c** using copper powder was extremely difficult probably due to the strong repulsion between the large C_7F_{15} groups. To solve this problem, tetrakis(triphenylphosphine)nickel(0), $Ni(PPh_3)_4$, or bis(1,5-cyclooctadiene)nickel(0), $Ni(COD)_2$, were examined in the place of active copper powder, since they were reported to have high activity on oxidative addition to aryl bromides.[9] Results of the coupling reaction are summarized in Table 1. The coupling reaction of (*R*)-**5c** with $Ni(COD)_2$ in DMF at 60 °C gave **6c** in total 71% yield, 59% of (*R*)-(*R*)$_2$-**6c** and 12% of the axial isomer (*S*)-(*R*)$_2$-**6c**[10] after separation by a column chromatography (entry 1). The latter was easily converted to (*R*)-(*R*)$_2$-**1c** after hydrolysis as mentioned later. When NMP was used as a solvent, the total yield was decreased to 30% (entry 2). Raising the reaction temperature did not improve the yield of the coupling reaction (entry 3). When $Ni(PPh_3)_4$ was used, the total yield of **6c** was decreased to 6%, and a fairly large amount of **5c** was recovered. This suggested that the low reactivity might be due to a low oxidative additivity of this nickel complex to aryl bromide. This coupling reaction using $Ni(COD)_2$ in DMF gave much higher yields of **6a** or **6b** than the former method[3] (entry 5 and 6).

Deprotection of (*R*)-(*R*)$_2$-**6a–c** with TFA gave the desired ligands (*R*)-(*R*)$_2$-**1a–c** quantitatively. The axial isomers (*S*)-(*R*)$_2$-**6a–c** were also deprotected quantitatively to (*S*)-(*R*)$_2$-**1a–c**. The (*S*)-(*R*)$_2$-ligands could be converted to the corresponding (*R*)-(*R*)$_2$-ligands by thermal equilibration followed by separation. Namely, refluxing a solution of each (*S*)-(*R*)$_2$-ligand in toluene gave an equilibrium mixture, where the corresponding (*R*)-(*R*)$_2$-ligand predominated. The efficiency of the conversion depended on each equilibrium constant (*K*) shown in Figure 2. The equilibrium mixture was separated by silica-gel column chromatography to a major amount of the desired (*R*)-(*R*)$_2$-ligand and a minor amount of (*S*)-(*R*)$_2$-ligand. The large *K* values of **1b** and **1c** facilitated the conversion of (*S*)-(*R*)$_2$-**1b** or **1c** to the corresponding (*R*)-(*R*)$_2$-isomers over 90%[11] in only once equilibration followed by separation. (*S*)-(*R*)$_2$-**1a** was also converted into (*R*)-(*R*)$_2$-**1a** in 93% yield by twice equilibration and separation. (*S*)-(*S*)$_2$-**1c** was obtained similarly.

Activities on asymmetric induction of **1c** were evaluated by the reaction of diethylzinc with benzaldehyde in the presence of a stoichiometric amount of Ti(O*i*-Pr)$_4$.[12] The results are summarized with the previous results of **1a** and **1b** in Table 2. The trifluoromethyl analogue **1a** showed a good asymmetric induction, as reported before: The product was obtained in 85% ee using 5 mol% of **1a**.[13] The pentafluoroethyl analogue **1b** with bulkier pentafluoroethyl groups showed higher asymmetric induction: Ee of the product increased to 91% with the same amount of **1b** as **1a**. The highest asymmetric induction was achieved by the perfluoroheptyl analogue **1c**. A 5 mol% of **1c** catalyzed the reaction efficiently to give the product of 97% ee. Increasing the amount of **1c** to 8 mol% resulted in a further improvement of the ee. Only 1 mol% of (*S*)-(*S*)$_2$-**1c** gave the (*R*)-product in 88% ee. These results suggest that the asymmetric induction depends significantly on the size of perfluoroalkyl moieties of the ligands. The larger perfluoroalkyl groups give better asymmetric induction.

Table 1. Ni mediated homo-coupling reaction



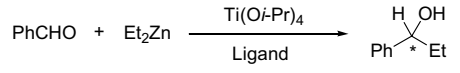
(*R*)-**5a** to **c**

(*R* or *S*)-(*R*)$_2$-**6a-c**

Entry	Substrate	Catalyst		Product	Yield[a] (%)	
1	(*R*)-**5c**	$Ni(COD)_2$	(*R*)-(*R*)$_2$-**6c**	59	(*S*)-(*R*)$_2$-**6c**	12
2[b]		$Ni(COD)_2$		25		5
3[c]		$Ni(COD)_2$		55		10
4		$Ni(PPh_3)_4$		5		1
5	(*R*)-**5a**	$Ni(COD)_2$	(*R*)-(*R*)$_2$-**6a**	56	(*S*)-(*R*)$_2$-**6a**	36
6	(*R*)-**5b**	$Ni(COD)_2$	(*R*)-(*R*)$_2$-**6b**	69	(*S*)-(*R*)$_2$-**6b**	11

[a] Isolated yield.
[b] NMP was employed as a solvent.
[c] Reaction was carried out at 120 °C.

Table 2. Asymmetric reaction of benzaldehyde with Et_2Zn



Ligand	Mol%	Yield[a] (%)	Ee[b] (%)	Config.[c]
(*S*)-(*S*)$_2$-**1a**	2	95	81	*R*
(*R*)-(*R*)$_2$-**1a**	2	97	82	*S*
	3	92	81	*S*
	5	94	85	*S*
	10	97	85	*S*
(*R*)-(*R*)$_2$-**1b**	1	97	63	*S*
	2.5	99	90	*S*
	5	96	91	*S*
	10	99	93	*S*
(*S*)-(*S*)$_2$-**1c**	1	92	88	*R*
	3	93	94	*R*
	5	97	96	*R*
(*R*)-(*R*)$_2$-**1c**	5	96	97	*S*
	8	91	98	*S*

[a] Isolated yield.
[b] Ee was determined by chiral GLC analysis.
[c] Determined by sign of optical rotation.

Another characteristic of **1c** is that the perfluoroalkyl groups are comprised in the active center of the ligand, while almost all of the catalysts designed so far for fluorous extraction have perfluoroalkyl groups far from the active center. In the latter cases, activity of the ligands is hardly increased.

In conclusion, we have succeeded in the synthesis of new axially dissymmetric ligands, (*R*)-(*R*)$_2$- and (*S*)-(*S*)$_2$-**1c** by coupling reaction of **5c** using $Ni(COD)_2$ in DMF. The undesired axial diastereomer, (*S*)-(*R*)$_2$-**1c**, was converted efficiently into the desired ligand (*R*)-(*R*)$_2$-**1c** by the thermal equilibration and separation. This methodology could be used for less bulky analogue to give better results than the conventional Ullmann reaction using copper powder. (*R*)-(*R*)$_2$- or (*S*)-(*S*)$_2$-**1c** showed very high asymmetric induction in the reaction of diethylzinc with benzaldehyde to give up to 98% ee of the product. Furthermore, the high fluorine content of **1c** was expected to allow it to be recoverable by a fluorous solvent. The detailed study on the recovery of the ligand is under investigation.

References and notes

1. (a) Pummerer, R.; Prell, E.; Rieche, A. *Chem. Ber.* **1926**, *59*, 2159; (b) Noyori, R.; Tomino, I.; Tanimoto, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3129–3131.
2. Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*(8), 3155–3211.
3. (a) Omote, M.; Kominato, A.; Sugawara, M.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **1999**, *40*, 5583–5585; (b) Omote, M.; Hasegawa, T.; Sato, K.; Ando, A.; Kumadaki, I. *Heterocycles* **2003**, *59*, 501–504; (c) Hasegawa, T.; Omote, M.; Sato, K.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **2003**, *51*, 265–267.
4. Compound **3c** was prepared according to Ref. 3a. Compound **3c**: a colorless oil. ^1H NMR ($CDCl_3$): δ 7.76–7.70 (1H, m), 7.56–7.50 (1H, m), 7.49–7.41 (2H, m). LRMS (EI) *m/z*: 552 (M^+), 533 (M^+-F), 183 ($M^+-C_7F_{15}$, base peak). HRMS calcd for $C_{14}H_4O_{79}BrF_{15}$ (M^+): 551.921. Found: 551.921.
5. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611; (b) Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I.; Shiro, M. *Heterocycles* **1998**, *47*, 65–68.
6. Compound (*R*)-**4c** was prepared according to the Ref. 3a. Compound (*R*)-**4c**: colorless crystals. Mp 43.5–44.5 °C. $[\alpha]_D^{24}$ +15.2 (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.62 (1H, d, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 7.36 (1H, dd, *J* = 7.8, 7.8 Hz), 7.24 (1H, ddd, *J* = 7.8, 7.8, 1.4 Hz), 5.89 (1H, ddd, *J* = 19.8, 5.3 Hz, 2.5 Hz), 2.78 (1H, d, *J* = 5.3 Hz). LRMS (EI) *m/z*: 554 (M^+), 185 ($M^+-C_7F_{15}$, base peak). HRMS (EI) calcd for $C_{14}H_6O_{79}BrF_{15}$ (M^+): 553.936. Found 553.937.
7. Absolute configurations of **4c** were determined by converting them to (*S*)-methoxyphenyl(trifluoromethyl)acetic acid esters. The α-proton of the ester from (*R*)-**4c** was observed at 6.98 ppm, while that of the ester from (*S*)-isomer at 7.07 ppm. Structure optimization by MOPAC calculation suggested that **4c** has large substituents and the Mosher rule could not be simply applied. By this optimization, the former proton is near the benzene ring of MTP acid, while the latter is far from it. These results support the configurations shown in the text. The results of asymmetric synthesis using these ligands are comparable to the results of **1a**, the structure of which was determined by X-ray analysis.[3a]
8. Compound (*R*)-**5c** was prepared according to the usual procedure. Compound (*R*)-**5c**: a colorless oil. $[\alpha]_D^{24}$ +54.5 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.65 (1H, ddd, *J* = 7.8, 1.8, 1.8 Hz), 7.60 (1H, dd, *J* = 8.1, 1.2 Hz), 7.39 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 7.25 (1H, ddd, *J* = 8.1, 7.8, 1.8 Hz), 5.90 (1H, dd, *J* = 20.3, 1.5 Hz), 4.64 (1H, dd, *J* = 7.2, 1.5 Hz), 4.52 (1H, d, *J* = 7.2 Hz), 3.34 (3H, s). LRMS (EI) *m/z*: 598 (M^+), 537 ($M^+-CH_3OCH_2O$), 229 ($M^+-C_7F_{15}$, base peak). HRMS calcd for $C_{16}H_{10}O_{79}BrF_{15}$ (M^+): 597.963. Found 597.962.
9. Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*(22), 5908–5910.
10. A typical procedure is as follows. To a suspension of $Ni(COD)_2$ (633 mg, 2.3 mmol) in anhydrous DMF (4 mL) was added (*R*)-**5c** (2.00 g, 3.3 mmol) at room temperature and the mixture was stirred for 24 h at 60 °C. The reaction was quenched by adding aqueous HCl (5%) and extracted with ether. The organic layer was evaporated after dehydration, and the residue was separated by silica-gel chromatography (Et_2O–hexane = 5:95–20:80) to give (*R*)-(*R*)$_2$-**6c** (1.01 g, 59%) and (*S*)-(*R*)$_2$-**6c** (0.21 g, 12%). Compound (*R*)-(*R*)$_2$-**6c**: colorless crystals. Mp 108.5–111.0 °C. $[\alpha]_D^{25}$ +1.8 (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.84 (1H, d, *J* = 7.6 Hz), 7.44 (1H, dd, *J* = 7.6, 7.6 Hz), 7.34 (1H, d, *J* = 7.6, 7.6 Hz), 7.12 (1H, dd, *J* = 7.6, 6.1 Hz), 5.25 (1H, d, *J* = 20.9 Hz), 5.08 (1H, d, *J* = 7.0 Hz), 4.57 (1H, d, *J* = 7.0 Hz), 3.11 (3H, s). LRMS (EI) *m/z*: 1038 (M^+), 669 ($M^+-C_7F_{15}$), 563 (base peak). HRMS calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088. Found 1038.088. Compound (*S*)-(*R*)$_2$-**6c**: colorless crystals. Mp 57.0–58.0 °C. $[\alpha]_D^{25}$ −41.2 (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.8 (2H, m), 7.51–7.42 (6H, m), 5.36 (2H, d, *J* = 21.1 Hz), 4.73 (4H, d, *J* = 1.9 Hz), 3.30 (6H, s). LRMS (EI) *m/z*: 1038 (M^+), 669 ($M^+-C_7F_{15}$), 563 (base peak). HRMS calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088. Found 1038.088.
11. Deprotection of (*R*)-(*R*)$_2$-**6c** (1.01 g) by TFA (5 mL) and water (0.5 mL) gave (*R*)-(*R*)$_2$-**1c** (894 mg, 96%). Treatment of (*S*)-(*R*)$_2$-**6c** (210 mg) with TFA (1 mL) and water (0.1 mL) gave its axial diastereomer (*S*)-(*R*)$_2$-**1c** (183 mg, 95%). (*S*)-(*R*)$_2$-**1c** (183 mg) was converted to (*R*)-(*R*)$_2$-**1c** by refluxing in toluene for 4 h. The equilibrium mixture was

separated by silica-gel chromatography (Et_2O–hexane = 1:9–3:7) to give (*R*)-(*R*)$_2$-**1c** (166 mg) in 91% conversion. For further purification, (*R*)-(*R*)$_2$-**1c** was recrystallized by toluene, dissolving the crystal under 60 °C so as to avoid the axial isomerization. (*R*)-(*R*)$_2$-**1c**: colorless crystals. Mp 82.0–83.0 °C. $[\alpha]_D^{25}$ +13.6 (*c* 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.76 (2H, d, J = 7.5 Hz), 7.53 (2H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.48 (2H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.24 (2H, d, J = 7.5 Hz), 4.88 (2H, dd, J = 19.1, 7.0, 7.0 Hz), 3.34 (2H, d, J = 7.0 Hz). ^{19}F NMR ($CDCl_3$, BTF): δ −18.0 (6F, t, J = 10.8 Hz), −54.9 (2F, d, J = 286.6 Hz), −58.4 (2F, d, J = 285.3 Hz), −59.3 (8F, s), −59.6 (2F, d, J = 295.3 Hz), −60.0 (2F, d, J = 303.9 Hz), −59.9 (2F, d, J = 303.9 Hz), −61.8 (2F, d, J = 286.6 Hz), −63.5 (2F, d, J = 303.9 Hz), −63.7 (2F, d, J = 303.9 Hz). LRMS (EI) *m*/*z*: 950 (M^+), 669 ($M^+-C_7F_{15}$), 563 (base peak). HRMS calcd for $C_{28}H_{12}O_2F_{30}$ (M^+): 950.036. Found 950.036.

12. (a) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*(35), 6233–6236; (b) Balsells, J.; Davis, T. J.; Carroll, P.; Patrick, J. W. *J. Am. Chem. Soc.* **2002**, *124*(35), 10336–10348.
13. Ee was determined by GLC analysis using GAMMA DEX capillary column.