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Preparation of a fluorous chiral BINAP and application to an asymmetric Heck reaction

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Abstract—Fluorous chiral BINAP ((*R*)-F_{13}BINAP) was prepared and was applied to an asymmetric Heck reaction. The enantioselectivity was similar in BTF homogeneous system (90% ee) to that of the original non-fluorous reaction and marginally higher in benzene and FC-72 biphasic system (93% ee) than that of the original non-fluorous one.

Chiral BINOL and BINAP are among the most useful and popular ligands for catalytic asymmetric reactions.[1] Several kinds of fluorous chiral BINOLs have been prepared and used as the ligands for catalytic asymmetric reactions.[2] If the molecules have enough fluorine content in the fluorous tags, the 'fluorous' molecules are recyclable in an organic-fluorous biphasic system and can be recovered easily by organic-fluorous biphasic extraction (liquid–liquid extraction) or by fluorous reverse-phase silica gel separation (solid–liquid extraction) for reuse.[3]

For example, the fluorous BINOLs, F_{13}BINOL and F_{17}BINOL that we have prepared were sufficiently fluorous to carry out the catalytic asymmetric addition of Et_2Zn to aldehydes in an organic/FC-72 (FC-72:$CF_3(CF_2)_4CF_3$) biphasic system and to be recovered with fluorous reverse-phase silica gel.[2a]

The important chiral ligand BINAP is usually prepared from the corresponding *O*,*O*′-bistriflate derivative of BINOL.[4] Very recently, Stuart and co-workers reported the preparation of (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-perfluoro-1-octyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and its application to asymmetric hydrogenation.[5] The ligand was prepared by the conventional procedure from the corresponding BINOL bistriflate precursor in good yield (85%). The derived ruthenium complex catalyzed the asymmetric hydrogenation of dimethyl itaconate in excellent enantioselectivity (95.7% ee), which is similar to that obtained in the original Ru–BINAP complex reaction (95.4% ee). We have recently prepared a more heavily fluorinated chiral BINAP (F_{13}BINAP) and we report herein the synthesis of the reagent and its use in a Heck reaction (Scheme 1).

When the bistriflate of (*R*)-F_{13}BINOL (**II**) was phosphinated with Ph_2PH by using $NiCl_2$(dppe) in benzotrifluoride (BTF) at 100°C for 3 days under argon, the desired product (**III**) was actually seen by TLC analysis in good yield. However, (*R*)-F_{13}BINOL and the starting material, bistriflate (**II**), had very close R_f values on TLC and it was very hard to separate them by flash column chromatography. During the workup and repeated attempts to purify the product with flash column chromatography, a significant amount of the desired product was oxidized to the corresponding dioxide ((*R*)-F_{13}BINAPO (**IV**)). Therefore, the crude product was oxidized with H_2O_2, and the oxidized product was easily purified by flash chromatography and recrystallization (87% yield based on **II**). That (*R*)-F_{13}BINAP (**III**) is very sensitive to oxygen in the air and is easily oxidized to (*R*)-F_{13}BINAPO apparently stems from its fluorous characteristics. It is well known that a long fluorous chain has strong affinity for oxygen.[6] Next, we examined reduction of (*R*)-F_{13}BINAPO by the silane reduction method,[7] which has been used as the standard reduction method of a chiral phosphine oxide such as BINAP oxide. However, (*R*)-F_{13}BINAP was not obtained by the reaction despite close scrutiny of the reaction conditions. We also attempted to carry out the reduction by using SmI_2–HMPA in the THF

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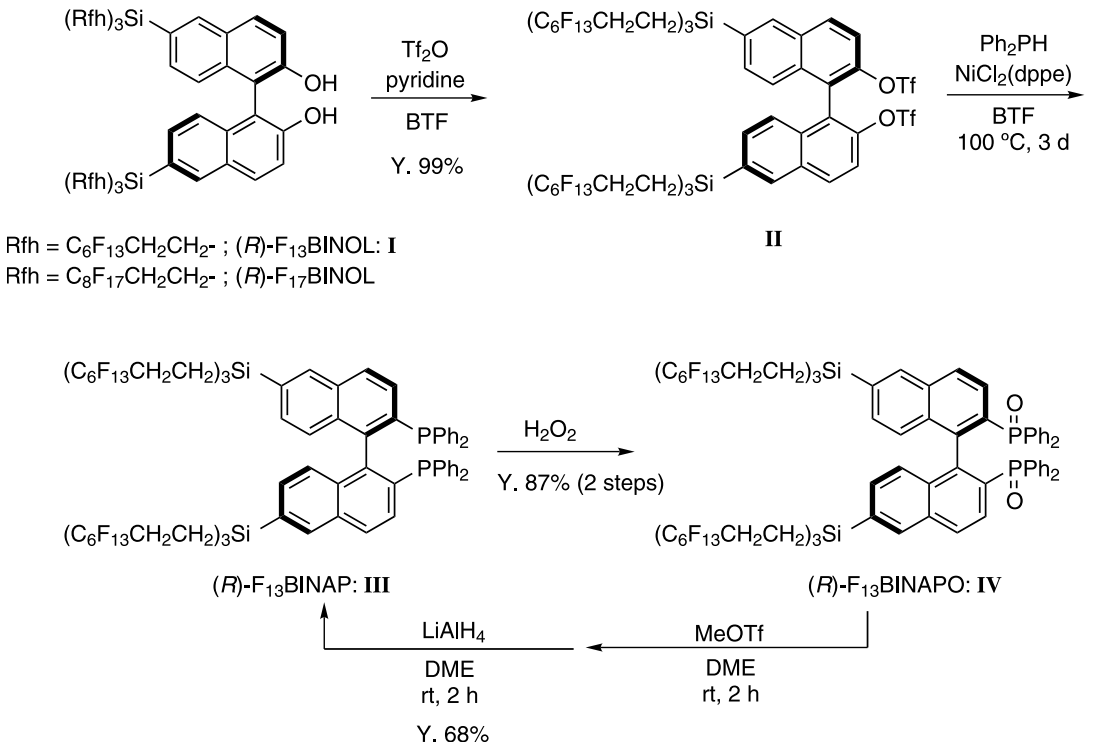


Scheme 1.

system,[8] but the yield was not high and it was practically impossible to separate (*R*)-F_{13}BINAP from the nonpolar by-products. Fortunately, we succeeded in obtaining high yields of (*R*)-F_{13}BINAP by employing Imamoto's method for reduction of chiral phosphine oxides.[9] The reaction was carried out as follows: (*R*)-F_{13}BINAPO was dissolved in DME and then MeOTf was added to the solution. The reaction mixture was stirred for 3 h at room temperature under argon. After cooling to 0°C, $LiAlH_4$ was added to the solution and then the reaction mixture was stirred at room temperature overnight. The color of the reaction mixture changed from light yellow to dark-red and then to yellow. After, the reaction was quenched by a small amount of a saturated Na_2SO_4 solution and then the reaction mixture was directly loaded on a short silica gel column and eluted by degassed solvent (hexane/Et_2O = 20/1) under argon. Careful workup, purification and solvent removal followed by flash column chromatography under argon afforded an oily residue which gradually transformed to white crystals (68%).

The ^{31}P NMR spectra of (*R*)-F_{13}BINAP and (*R*)-F_{13}BINAPO showed singlets at −14.1 and 28.7 ppm, respectively.[10] The enantiomeric purity of (*R*)- and (*S*)-F_{13}BINAPO was analyzed by HPLC by using DAICEL CHIRALCEL OD-H column to be higher than 99% ee.[11] Partition coefficients of (*R*)-F_{13}BINAPO and (*R*)-F_{13}BINAP are shown in Table 1.

In order to get preliminary information about (*R*)-F_{13}BINAP, we examined an asymmetric Heck reaction. Hayashi and co-workers have reported that $Pd(OAc)_2$–(*R*)-BINAP catalyzes the reaction between 2,3-dihydrofuran and 4-chlorophenyl triflate at 40°C for 22 h to give 2-(4-chlorophenyl)-2,3-dihydrofuran in 91% ee.[12]

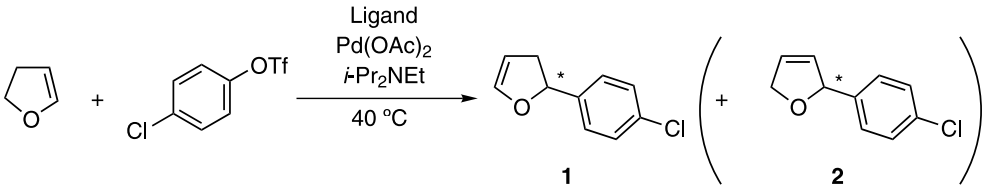
Table 1. Partition coefficients of (*R*)-F_{13}BINAPO and (*R*)-F_{13}BINAP in organic solvent and FC-72

	F (%)	Method	Organic solvent	FC-72/organic solvent
(*R*)-F_{13}BINAPO	53.09	A	CH_2Cl_2	76/24
		A	Benzene	90/10
(*R*)-F_{13}BINAP	53.70	A	Benzene	79/21
		B	Benzene	74/26
		B	CH_3CN	98/2
		B	DMF	98/2

Method A: A mixture of 100 mg of (*R*)-F_{13}BINAPO or (*R*)-F_{13}BINAP in FC-72 (2 mL) and organic solvent (2 mL) was stirred at room temperature for 10 min. Then the two phases were separated and the solvents were evaporated in vacuo. The contents of the fluorous compound in each phase were determined by weighing the residue.

Method B: A mixture of 20 mg of (*R*)-F_{13}BINAP in purified FC-72 (1 mL) and organic solvent (1 mL) was stirred at room temperature for 10 min under argon. The contents of the fluorous compound in each phase were determined by HPLC analysis.

Table 2. Asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate[a]



Entry	Ligand	Solvent	Reaction time (h)	Yield (%)[b]			% ee[c] (config.)[d]	
				1	**2**	**1/2**	**1**	**2**
1	(*R*)-BINAP	BTF	24	67	6	92/8	76 (*R*)	ND[e]
2	(*R*)-F_{13}BINAP	BTF	77	59	8	88/12	90 (*R*)	ND[e]
3	(*R*)-F_{13}BINAP	Benzene	62	59[f]	22[f]	72/28[f]	92 (*R*)	ND[e]
4	(*R*)-F_{13}BINAP	Benzene–FC-72 (1:1 v/v)	62	39	18	69/31	93 (*R*)	ND[e]
5[g]	(*R*)-F_{13}BINAP	Benzene–FC-72 (1:1 v/v)	50	2[f]	<1[f]	62/38[f]	93 (*R*)	ND[e]

[a] 4-Cl-C_6H_4OTf:2,3-dihydrofuran:*i*-Pr_2NEt:$Pd(OAc)_2$:ligand = 1.0:5.0:3.0:0.03:0.06 (molar ratio).
[b] Isolated yield.
[c] Determined by capillary GC analysis using SUPELCO β-DEX 120.
[d] Assigned by the sign of the optical rotation.
[e] Not determined.
[f] Determined by capillary GC analysis with SUPELCO β-DEX 120 by using mesitylene as an internal standard.
[g] The fluorous phase in entry 4 was reused as the catalyst solution.

We carried out reactions under the same reaction conditions except that BTF and (*R*)-F_{13}BINAP were used as the solvent and the chiral ligand,[13] and the results are summarized in Table 2 (entries 1–3). As seen in Table 2, the reaction rate is lower in the case of (*R*)-F_{13}BINAP than in that of (*R*)-BINAP. BTF is a good solvent for (*R*)-F_{13}BINAP (entry 2, 90% ee) but not for (*R*)-BINAP (entry 1, 76% ee). Benzene was also a good solvent for (*R*)-F_{13}BINAP (entry 3, 92% ee), although the chemical yield of **2** increased. The enantiomeric excess of product **1** was determined by GC analysis using a SUPELCO β-DEX120 chiral capillary column. (*R*)-F_{13}BINAP was recovered by using fluorous reverse-phase silica gel[3a,b,h] in about 70% yield. However, this percentage of recovery was not precise because the recovered material was a mixture of (*R*)-F_{13}BINAP and (*R*)-F_{13}BINAPO (mostly (*R*)-F_{13}BINAPO).

Finally, we carried out the Heck reaction in a benzene/FC-72 biphasic system (entries 4 and 5 in Table 2). The enantioselectivity was marginally higher (93% ee), although the chemical yield was much lower (39%) than in the original reaction (entry 4). After the first reaction, the benzene layer was changed for a fresh substrate benzene solution to test for recycling of the catalyst. However, the reaction did not proceed at all, probably because of inactivation of the catalyst by ligand oxidation (entry 5). (*R*)-F_{13}BINAP was demonstrated to have been oxidized in the FC-72 phase by monitoring with TLC. The color change of the FC-72 phase from wine-red to brown midway in the first reaction suggested the inactivation of the catalyst also.

In conclusion, we have prepared a fluorous BINAP, (*R*)-F_{13}BINAP, and examined an asymmetric Heck reaction. The preliminary results revealed that (*R*)-F_{13}BINAP had good solubility in fluorinated solvents and provided similar enantioselectivity in the BTF homogeneous system to that of the original reaction and higher enantiomeric excess in the benzene/FC-72 biphasic system than that of the original one. However, (*R*)-F_{13}BINAP is easily oxidized by a trace amount of oxygen in the fluorous phase during the reaction,[14] probably because of the strong affinity of the fluorous solvent and the tags of (*R*)-F_{13}BINAP for oxygen. Therefore, preventing (*R*)-F_{13}BINAP from oxidation throughout the reaction is the main problem to be solved to achieve more success.

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References

1. (a) *Catalytic Asymmetric Synthesis*, 2nd Edition; Ojima, I., Ed.; Wiley-VCH: New York, 2000; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994.

2. (a) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett*. **2000**, *41*, 57–61; (b) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y.; Curran, D. P. *Tetrahedron*, in press; (c) Chen, W.; Xu, L.; Xiao, J. *Tetrahedron Lett*. **2001**, *42*, 4275–4278; (d) Tian, Y.; Chan, K. S. *Tetrahedron Lett*. **2000**, *41*, 8813–8816.
3. Reviews: (a) Curran, D. P. *Synlett* **2001**, 1488–1496; (b) Curran, D. P.; Lee, Z. *Green Chem*. **2001**, G3–G7; (c) Kitazume, T. *J. Fluorine Chem*. **2000**, *105*, 265–278; (d) Fish, R. H. *Chem. Eur. J*. **1999**, *5*, 1677–1680; (e) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S. *J. Fluorine Chem*. **1999**, *94*, 183–193; (f) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev*. **1999**, *28*, 37–41; (g) Horváth, I. T. *Acc. Chem. Res*. **1998**, *31*, 641–650; (h) Curran, D. P. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 1174–1196.
4. Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem*. **1994**, *59*, 7180–7181.
5. Birdsall, D. J.; Hope, E. G.; Stuart, A. M.; Chen, W.; Hu, Y.; Xiao, J. *Tetrahedron Lett*. **2001**, *42*, 8551–8553.
6. Horváth, I. T.; Rávai, J. *Science* **1994**, *266*, 72–75.
7. (a) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett*. **1994**, *35*, 625–628; (b) Marsi, K. L. *J. Org. Chem*. **1974**, *39*, 265–267; (c) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc*. **1969**, *91*, 7012–7023; (d) Horner, L.; Balzer, W. D. *Tetrahedron Lett*. **1965**, *6*, 1157–1162.
8. Handa, Y.; Inanaga, J.; Yamaguchi, M. *J. Chem. Soc., Chem. Commun*. **1989**, 298–299.
9. Imamoto, T.; Kikuchi, S.; Miura, T.; Wada, Y. *Org. Lett*. **2001**, *3*, 87–90.
10. (*R*)-F_{13}BINAPO: White powder from hexane, mp 164–166°C; $[\alpha]_D^{20}$ +94.6 (*c* 1.02, BTF), $[\alpha]_{578}^{20}$ +99.2 (*c* 1.02, BTF), $[\alpha]_{546}^{20}$ +113.8 (*c* 1.016, BTF), $[\alpha]_{436}^{20}$ +206.6 (*c* 1.016, BTF), $[\alpha]_{365}^{20}$ +333.9 (*c* 1.016, BTF); ^{1}H NMR ($CDCl_3$) δ 1.10–1.18 (m, 6H, –CH_2C–), 1.95–2.11 (m, 6H, –CF_2CH_2–), 6.79 (d, 2H, Ar–*H*, *J*=8.4 Hz), 6.89 (d, 2H, Ar–*H*, *J*=8.4 Hz), 7.19–7.72 (m, 22H, Ar–*H*), 7.91 (dd, 2H, Ar–*H*, *J*=2.0 and 8.7 Hz), 7.94 (s, 2H, Ar–*H*); ^{31}P NMR ($CDCl_3$): δ 28.7; anal. calcd for $C_{92}H_{54}F_{78}O_2P_2Si_2$: C, 39.59; H, 1.95. Found: C, 39.45; H, 1.89.
(*R*)-F_{13}BINAP: ^{1}H NMR ($CDCl_3$) δ 1.08–1.18 (m, 6H, –CH_2C–), 1.95–2.11 (m, 6H, –CF_2CH_2–), 6.79 (d, 2H, Ar–*H*, *J*=9.0 Hz), 6.81 (d, 2H, Ar–*H*, *J*=9.0 Hz), 7.01–7.36 (m, 20H, Ar–*H*), 7.52 (d, 2H, Ar–*H*, *J*=8.5 Hz), 7.91 (s, 2H, Ar–*H*), 7.92 (d, 2H, Ar–*H*, *J*=8.5 Hz); ^{31}P NMR ($CDCl_3$): δ −14.1.
11. The optical purity was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane:2-propanol=100:1, flow rate=0.5 mL/min): t_R= 10.8 min for the (*R*)-enantiomer and t_R=15.2 min for the (*S*)-enantiomer.
12. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 1417–1419.
13. A typical procedure for entry 2 in Table 2: 4-Chlorophenyl trifrate (160.8 mg, 0.617 mmol), (*i*-Pr)$_2$NEt (252 mg, 1.95 mmol) and 2,3-dihydrofuran (230 mg, 3.28 mmol) were added to a solution of (*R*)-F_{13}BINAP (116 mg, 0.042 mmol) and $Pd(OAc)_2$ (4.2 mg, 0.0187 mmol) in BTF (2.2 mL) and the solution was stirred at 40°C for 77 h under argon. The reaction mixture was diluted with Et_2O (30 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was dissolved in Et_2O (2 mL). ((1*H*,1*H*,2*H*,2*H*)-perfluorooctyl)dimethylsilyl bound silica gel (1 g) was added to the solution, and then the solvent was evaporated to dryness. The powder obtained was loaded on a column of ((1*H*,1*H*,2*H*,2*H*)-perfluorooctyl)dimethylsilyl bound silica gel (3 g) and then eluted successively with acetonitrile (15 mL) and FC-72 (40 mL). The acetonitrile fraction was evaporated in vacuo and purified by silica gel column chromatography (pentane:Et_2O=20:1) to give (*R*)-**1** (66 mg, 59% yield) in 90% ee and **2** (9 mg, 8%). GC analysis using SUPELCO β-DEX chiral capillary column: (He= 1.0 mL/min, DET=250°C, INJ=240°C, OVEN=110°C (1 min) to 170°C, 2°C/min, Split=100:1): t_R=28.1 min for (*S*)-**1** and t_R=28.4 min for (*R*)-**1**. A (*R*)-F_{13}BINAP and (*R*)-F_{13}BINAPO mixture was obtained from the FC-72 fraction (86 mg).
14. Since no efficient method has been reported for removing oxygen from FC-72 and BTF, we just degassed under reduced pressure or bubbling argon gas into the solvents just before use. Therefore, the solvents might contain a trace amount of oxygen. Oxygen in the air could also enter the reaction vessel through the serum cap during the reaction.