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Enantioselective carbon–carbon bond forming reactions using fluorous chiral catalysts

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Abstract

Fluorous chiral BINOLs and BINAP were prepared and used as the ligands for an asymmetric addition of Et_2Zn to aromatic aldehydes and an asymmetric Heck reaction, respectively. The enantioselectivities were similar in homogeneous system to those of the original non-fluorous reactions. Consecutive reactions were examined by utilizing fluorous–organic biphase and fluorous solid phase extraction techniques. Enantioselectivities in consecutive reactions were close to that attained in the non-fluorous system. The solid phase extraction method also enabled us to perform a simultaneous screening procedure.

Keywords: Addition reactions; Heck reactions; Asymmetric reactions; Fluorine and compounds; Perfluoroalkyl compounds

1. Introduction

Fluorous techniques are novel separation and immobilization techniques that are attracting great current interest in organic synthesis (see reviews in [1]). Fluorinated or highly fluorinated solvents such as perfluoroalkanes are called 'fluorous solvents'. They are immiscible with typical organic solvents and water at ambient temperature. However, these organic and fluorous two phases are miscible when the temperature is elevated. Compounds that have highly fluorinated carbon chains or perfluoroalkyl chains are dissolved in fluorous solvents. Fluorous techniques are based on these natures.

One of the techniques is called 'fluorous biphase catalysis'. Horváth and Ravái [2] introduced this innovative approach to catalysis in 1994. A metal complex bearing one or more highly fluorinated ligands is dissolved in a fluorous solvent, and this is mixed with substrates in an organic solvent. The catalytic reaction is then effected under biphasic conditions. In a significant variant, warming renders the organic and fluorous phases miscible and the reaction occurs under homogeneous conditions. In either case, the organic phase contains the pure products, and the fluorous phase contains the catalyst at room temperature. The fluorous phase can be separated and recycled. Fluorous biphasic catalytic methods have advanced rapidly, and a large number of fluorous catalysts have been reported (see recent examples for fluorous biphase catalysis in [3]).

Fluorous compounds can be separated from non-fluorous compounds by simple workup techniques of liquid–liquid extraction or solid phase extraction. For example, the liquid–liquid separation technique has demonstrated that fluorous tin hydrides have similar reactivity to the original tributyltin hydride but higher efficiency than the original one. The fluorous tin compounds are readily separable from organic compounds at the end of a reaction by the fluorous–organic biphase extraction with an organic solvent and FC-72 (a mixture of perfluorohexanes). The recovered tin compounds from FC-72 phase are recyclable without purification [4].

Fluorous solid phase extraction was introduced by Curran [1a]. The fluorous solid phase extraction is a very useful method to separate organic products from a fluorous catalyst or ligand, especially in cases where the fluorine content is not high enough to carry out the catalytic reaction in fluorous–organic biphase system successfully. Fluorous reverse phase (FRP) silica gel is polyfluoroalkylsilyl-bonded silica gel, which is easily prepared but now commercially available [5]. A crude reaction mixture is charged on the FRP silica gel and the silica gel is eluted first with a "fluorophobic" solvent such as acetonitrile to remove the organic compounds. Elution with a "fluorophilic" solvent such as FC-72 provides fluorous compounds.

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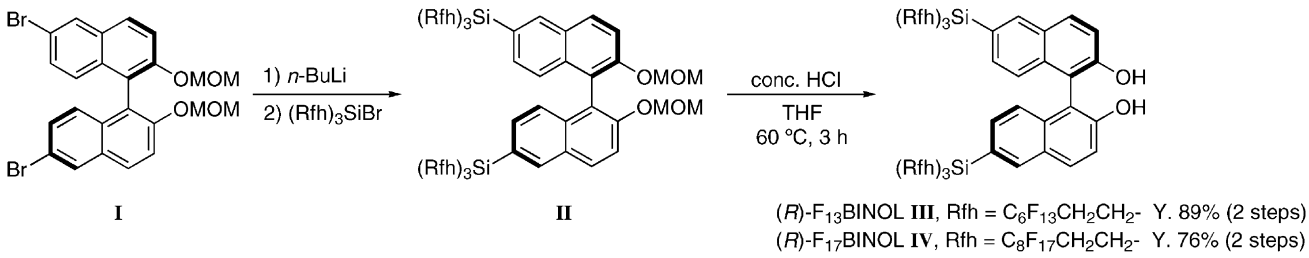


Scheme 1.

These fluorous techniques are very attractive techniques for researchers who are seeking practical and environmentally friendly catalytic systems of asymmetric reactions. Chiral ligands for metal catalysts are usually laborious to prepare and expensive. Therefore, fluorous chiral ligands that are reusable have a potential to afford catalytic systems that fit the needs of the researchers [6].

We have focused our attention on preparation of effective and recyclable fluorous chiral ligands and their application to catalytic asymmetric reactions [7]. Chiral BINOL and BINAP are among the most useful and popular ligands for catalytic asymmetric reactions [8]. If the molecules have enough fluorine content in the fluorous tag, the fluorous molecules are recyclable in an organic–fluorous biphasic system and can be recovered easily by fluorous separation techniques for reuse. We report here the usefulness of these techniques for creating practical and environmentally benign catalytic asymmetric reaction systems.

2. Results and discussion

2.1. Asymmetric addition of diethylzinc to aromatic aldehydes catalyzed by fluorous BINOL-Ti complexes

Fluorous chiral BINOLs, (*R*)-F_{13}BINOL and (*R*)-F_{17}-BINOL, were prepared by the following route shown in Scheme 1. The readily available tris(polyfluoroalkyl)silyl group were introduced to the 6 and 6′ positions as a fluorous tag of methoxymethyl (MOM) protected 6,6′-dibromo BINOL (**I**) [9]. The polyfluoroalkylsilylated BINOL derivative (**II**) was obtained in 91% yield via lithiation at the 6 and 6′ positions of **I** and then reaction with $(C_6F_{13}CH_2CH_2)_3SiBr$ according to Curran's method [10]. The MOM group of **II** was deprotected with hydrochloric acid in THF under reflux and vigorous stirring. (*R*)-6,6′-bis[tris(1*H*,1*H*,2*H*,2*H*-Perfluorooctyl)silyl]-1,1′-binaphth-2,2′-diol (**III**; (*R*)-F_{13}BINOL) was isolated in 97% yield. The enantiomeric excess (e.e.) of the (*R*)-F_{13}BINOL was determined to be higher than 99% by HPLC using a chiral column and the (*S*)-enentiomer of **III** as a standard. This was prepared by the same procedures as those of (*R*)-F_{13}BINOL from (*S*)-starting material.

(*R*)-bis[tris(1*H*,1*H*,2*H*,2*H*-Perfluorodecyl)silyl]-1,1′-binaphth-2,2′-diol (**IV**; (*R*)-F_{17}BINOL) was also synthesized from **I** and $(C_8F_{17}CH_2CH_2)_3SiBr$ in 76% overall yield by the same procedures described above. The approximate partition coefficients of FBINOLs were determined by the simple method described in the footnote of Table 1, and the results are summarized in the table.

The data in Table 1 show that (*R*)-F_{13}BINOL and (*R*)-F_{17}BINOL are highly fluorous and efficiently extracted to FC-72 phase.

We chose the asymmetric addition of diethylzinc to aromatic aldehydes catalyzed by a BINOL-Ti complex to examine usefulness of the FBINOLs. The reaction has been reported by Nakai and Chan independently [11]. It was selected for testing the FBINOLs by utilizing the fluorous–organic biphase and solid phase extraction techniques because the reaction occurs in high enantiomeric excess and yield by a simple procedure and with the use of commercially available reagents.

At the outset, a standard reaction was carried out under the same reaction conditions as those reported except that the FBINOLs and benzotrifluoride (BTF) were used as the chiral ligand and the solvent. The products and FBINOLs were simply and cleanly separated with 1*H*,1*H*,2*H*,2*H*-perfluorooctyldimethylsilyl-bonded silica gel (FRP silica gel) by washing successively with acetonitrile and FC-72 and the results for several aromatic aldehydes are summarized in Table 2.

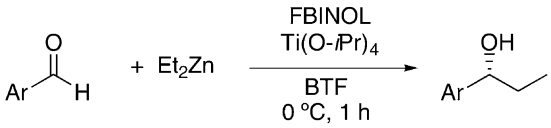
The chemical yields and the enantioselectivities are similar to those reported by Nakai (97 and 85% e.e. for benzaldehyde, respectively) [11a] and the recoveries of the FBINOLs were quantitative. 1-Naphthylaldehyde afforded higher enantioselectivity (91% e.e.) than that of 2-naphthy-

Table 1
Partition coefficients of (*R*)-FBINOLs in organic solvent and FC-72

FBINOL	Rfh	F (%)	Organic solvent	Organic solvent/FC-72
(*R*)-F_{13}BINOL	$C_6F_{13}CH_2CH_2$–	61.16	$CHCl_3$	5/95
			Toluene	2/98
(*R*)-F_{17}BINOL	$C_8F_{17}CH_2CH_2$–	64.10	CH_2Cl_2	1/99
			Toluene	1/99

A mixture of 100 mg of (*R*)-FBINOLs 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.

Table 2
Catalytic asymmetric addition of diethylzinc (1 M in hexane) to several aromatic aldehydes using FBINOL-Ti complexes [a]



Entry	Solvent	FBINOL	Ar	Yield (%)[b]	e.e. (%)[c]	Recovered FBINOL (%)[d]
1	BTF/hexane (1:1, v/v)	F_{13}BINOL	Ph	92	84	99
2	BTF/hexane (1:1, v/v)	F_{17}BINOL	Ph	86	83	100
3	BTF/hexane (1:1, v/v)	F_{13}BINOL	2-MeO–C_6H_4–	93	78	98
4	BTF/hexane (1:1, v/v)	F_{13}BINOL	3-MeO–C_6H_4–	95	85	100
5	BTF/hexane (1:1, v/v)	F_{13}BINOL	4-MeO–C_6H_4–	97	80	96
6	BTF/hexane (1:1, v/v)	F_{13}BINOL	4-Me–C_6H_4–	91	81[e]	100
7	BTF/hexane (1:1, v/v)	F_{13}BINOL	1-Naphthyl	98	91	98
8	BTF/hexane (1:1, v/v)	F_{13}BINOL	2-Naphthyl	93	78	98
9	BTF/hexane (1:1, v/v)	F_{13}BINOL	4-Cl–C_6H_4–	93	82[e]	100
10	BTF/hexane (1:1, v/v)	F_{13}BINOL	4-Br–C_6H_4–	93	86[e]	100

[a] Substrate/FBINOL/Ti(O-*i*Pr)$_4$/Et_2Zn = 1:0.2:1.2:3 (molar ratio).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL CHIRALCEL OD or OD-H. The (*R*)-configuration of the product in each case.
[d] Separated from the organic compounds by solid phase extraction with FRP silica gel.
[e] Determined by capillary GC analysis using SUPELCO β-DEX 120™.

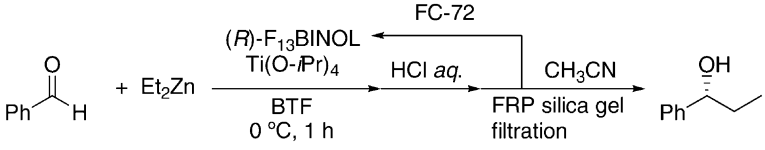
laldehyde (78% e.e.), which may be caused by the difference in steric hindrance around their aldehyde carbon atoms.

Subsequently, we examined a consecutive reaction by using the (*R*)-F_{13}BINOL recovered by the fluorous silica gel separation. The reaction was carried out in BTF at 0 °C for 1 h and the (*R*)-F_{13}BINOL was separated from the product with FRP silica gel. The recovered (*R*)-F_{13}BINOL was reused for the next reaction without further purification. The results of four consecutive reactions are summarized in Table 3.

As seen in Table 3, the enantioselectivities were the same as those reported by Nakai [10] and the recoveries of (*R*)-F_{13}BINOL were quantitative.

Liscamp and coworkers have reported a simultaneous substrate screening procedure for the ability to enantioselectively catalyze the Ti(O-*i*Pr)$_4$-mediated addition of Et_2Zn to aldehydes (see some examples of multisubstrate screening in asymmetric catalysis in [12a]). They used polymer-bound chiral ligand for the catalyst and gas chromatography with a chiral column for the analysis. The report and the successful results of consecutive reaction shown in Table 2 prompted us to apply Liscamp's methodology to our reaction system of fluorous solid extraction method. Thus, we carried out the reaction by using five different aldehydes as substrates. The product mixture was first separated on FRP silica gel, and then analyzed by gas chromatography with a SUPELCO β-DEX 120™ chiral capillary column. The enantiomer pairs of the corresponding products were well separated under the GC conditions and the results are summarized in Table 4 together with the data obtained by the separately performed experiments for each substrate.

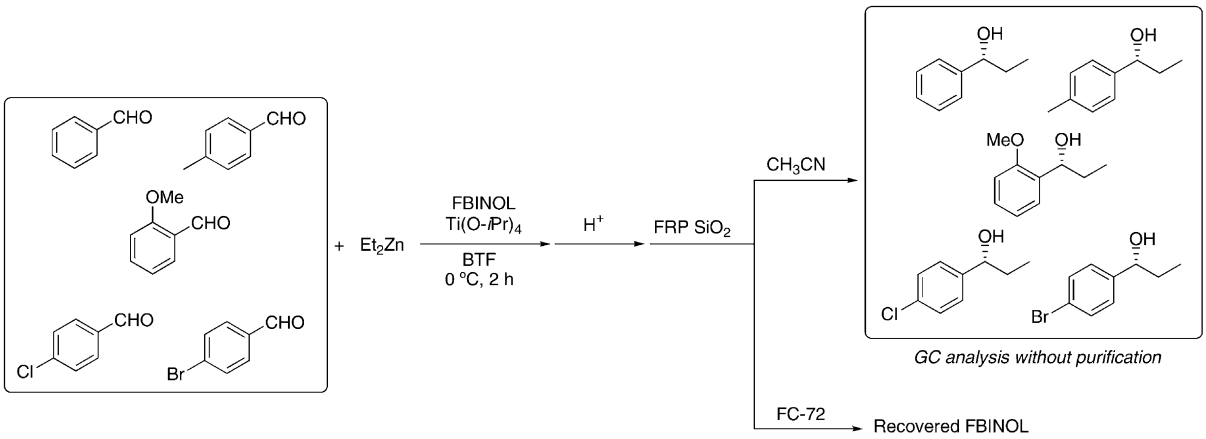
Table 3
Catalytic asymmetric addition of diethylzinc (1 M in hexane) to benzaldehyde reusing the same (*R*)-F_{13}BINOL [a]



Run	Solvent	FBINOL	Yield (%)[b]	e.e. (%)[c]	Recovered (*R*)-F_{13}BINOL (%)[d]
1	BTF/hexane (1:1, v/v)	F_{13}BINOL	92	84	99
2	BTF/hexane (1:1, v/v)	F_{13}BINOL	93	85	97
3	BTF/hexane (1:1, v/v)	F_{13}BINOL	96	84	99
4	BTF/hexane (1:1, v/v)	F_{13}BINOL	89	83	99

[a] Substrate/F_{13}BINOL/Ti(O-*i*Pr)$_4$/Et_2Zn = 1:0.2:1.2:3 (molar ratio).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL CHIRALCEL OD. The (*R*)-configuration of the product in each case.
[d] Separated from the organic compounds by solid phase extraction with FRP silica gel.

Table 4
Simultaneous catalytic asymmetric addition of diethylzinc (1 M in hexane) to various aromatic aldehydes [a]



Entry	Ar	(R)-F_{13}BINOL		(R)-F_{17}BINOL	
		Yield (%)[b,c]	e.e. (%)[b,c]	Yield (%)[b,c]	e.e. (%)[b,c]
1	Ph	97 (92)	82 (84[d])	91 (86)	83 (83)
2	4-Me–C_6H_4–	85 (93)	83 (81)	81	83
3	2-MeO–C_6H_4–	94 (91)	76 (78[d])	73	79
4	4-Cl–C_6H_4–	94 (93)	83 (82)	87	84
5	4-Br–C_6H_4–	96 (93)	84 (86)	83	85

[a] Substrate/FBINOL/Ti(O-iPr)$_4$/Et_2Zn = 1:0.2:1.2:3 (molar ratio).
[b] Numbers in parentheses are the data obtained by the separately performed experiments for each substrate.
[c] Determined by capillary GC analysis using SUPELCO β-DEX 120™.
[d] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H.

As seen in Table 4, the chemical yields and the enantioselectivities were very similar to those obtained by the reaction of each substrate.

The successful results in the uniphase reaction encouraged us to examine a toluene and FC-72 biphase system. Thus, the reaction was carried out repeatedly by using benzaldehyde and (R)-F_{13}BINOL as shown in Fig. 1.

When Ti(O-iPr)$_4$ was added to the solution of (R)-F_{13}BINOL in FC-72, the reaction mixture first became a light red and homogeneous and then a colorless oily material separated out on the surface of the FC-72 solution. A 1 M solution of Et_2Zn in hexane was then added. After cooling to 0 °C, a benzaldehyde solution in toluene was added. The organic phase (toluene and hexane) became pale yellow-brown and the FC-72 phase remained light red. The reaction mixture was stirred vigorously at 0 °C for 2 h, and then the organic phase was withdrawn with a syringe and was quenched with 1N hydrochloric acid to ensure removal of any residual (R)-F_{13}BINOL and to liberate the product alcohol from the Ti complex. The products and residual (R)-F_{13}BINOL were separated with FRP silica gel by washing successively with acetonitrile and FC-72. The product alcohol was obtained from the acetonitrile eluate. Fresh Ti(O-iPr)$_4$, the Et_2Zn and benzaldehyde solution were added to the fluorous phase, and the reaction was carried out in the same way. The reaction was repeated five times and the results are summarized in Table 5.

As seen in Table 5, the enantioselectivity remained at 80% or above throughout five runs. However, about 10% of (R)-F_{13}BINOL was recovered from the organic phase in every

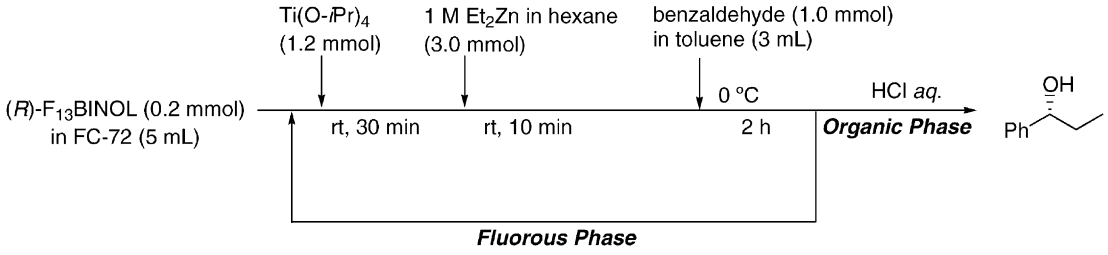


Fig. 1. Method for catalytic asymmetric addition of diethylzinc to benzaldehyde using a (R)-F_{13}BINOL-Ti complex in FC-72-organic solvent biphase system.

Table 5
Catalytic asymmetric addition of diethylzinc (1 M in hexane) to benzaldehyde using a (*R*)-F_{13}BINOL-Ti complex in FC-72-organic solvent biphase system

Run	Solvent	FBINOL	Yield (%)[a]	e.e. (%)[b]	Recovered (*R*)-F_{13}BINOL (%)[c]
1	Toluene/hexane/FC-72 (3:3:5, v/v/v)	F_{13}BINOL	81	83	10
2	Toluene/hexane/FC-72 (3:3:5, v/v/v)	F_{13}BINOL	89	82	12
3	Toluene/hexane/FC-72 (3:3:5, v/v/v)	F_{13}BINOL	87	82	12
4	Toluene/hexane/FC-72 (3:3:5, v/v/v)	F_{13}BINOL	87	81	11
5	Toluene/hexane/FC-72 (3:3:5, v/v/v)	F_{13}BINOL	87	80	10

[a] Isolated yield.
[b] Determined by HPLC analysis using DAICEL CHIRALCEL OD.
[c] Separated from the organic compounds by solid phase extraction with FRP silica gel.

experiment. Therefore, it seems likely that a significant amount of the chiral catalyst was in the organic phase and the asymmetric reaction took place only in that phase. That the organic phase had a pale brown color also supports this conclusion. To test this postulate, we carried out the reaction separately in the organic phase and in a toluene–FC-72 biphase system. The procedure was the same until the reaction mixture was cooled at 0 °C after the addition of Et_2Zn solution. Toluene was added to the reaction mixture and the two phases were separated. The benzaldehyde solution was added to the organic phase and the reaction was carried out as described above. The Et_2Zn solution and the benzaldehyde solution were added to the FC-72 phase and the reaction was carried out in the same way. From the organic phase the product was obtained in 73% e.e. (88% yield) and 10% of (*R*)-F_{13}BINOL was recovered. From the toluene–FC-72 biphase system the product was obtained in 77% e.e. (81% yield) and 88% of (*R*)-F_{13}BINOL was recovered. Therefore, it is clear that some of the chiral complex was actually in the organic phase but that the amount of the complex was too little to give the expected 83% e.e. On the other hand, the enantioselectivity in the toluene–FC-72 biphase system was somewhat higher in spite of the lack of excess amount of Ti(O-*i*Pr)$_4$. The presence of excess amount of Ti(O-*i*Pr)$_4$ was reported to be indispensable for the reaction to result in high enantioselectivity and yield [12a].

When a consecutive reaction was carried out by using Et_2Zn solution in toluene (1.1 M) instead of hexane solution in order to clarify a role of hexane in the biphase system, the enantioselectivities were lowered to 77–78% e.e., but the amount of (*R*)-F_{13}BINOL that leached into the toluene phase decreased to less than 1%, as shown in Table 6.

This reaction was also carried out in the toluene phase and in the toluene–FC-72 biphase system separately in the same way as described above. The enantioselectivity in the biphase system, 78% e.e. (85% yield), was similar to the values in Table 6. However, the enantioselectivity in the separated toluene phase was dramatically reduced to 30% e.e. (49% yield) and the recovery of (*R*)-F_{13}BINOL from the phase was negligible. Results (e.e., recovery of (*R*)-F_{13}BINOL from organic phase) seem to suggest that hexane dissolves the catalyst much better than toluene. Therefore, it is deduced that both phases are necessary to get the enantioselectivity higher than 83% e.e. in the biphase system and that hexane plays an important role to bring about the high enantiomeric excess.

When the reaction was carried out consecutively by using (*R*)-F_{17}BINOL and Et_2Zn solution in hexane as in Table 5, leaching of (*R*)-F_{17}BINOL into the organic phase was only about 1% in each experiment, while the enantioselectivities were consistently 78–79% e.e. as shown in Table 7.

Judging from all these results, it is concluded that a certain amount of FBINOLs are necessary to exist in the organic phase for getting enantioselectivity as high as 83% e.e. in the organic and FC-72 biphase system. However, it is also clear that the enantioselectivity was slightly improved and the immobilization of the F_{17}BINOL in FC-72 phase was much improved compared to the results of F_{13}BINOL in toluene–FC-72 and in organic (toluene and hexane)–FC-72 biphase systems, respectively, as a result of the increased fluorous content of the ligand.

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

The important chiral ligand BINAP is usually prepared from the corresponding *O*,*O*′-bistriflate derivative of BINOL [13]. Very recently, Stuart and coworkers [6d] reported the

Table 6
Catalytic asymmetric addition of diethylzinc (1.1 M in toluene) to benzaldehyde using a (*R*)-F_{13}BINOL-Ti complex in FC-72–organic solvent biphase system[a]

Run	Solvent	FBINOL	Yield (%)[b]	e.e. (%)[c]	Recovered (*R*)-F_{13}BINOL (%)[d]
1	Toluene/FC-72 (3:5, v/v)	F_{13}BINOL	85	78	<1
2	Toluene/FC-72 (3:5, v/v)	F_{13}BINOL	85	78	<1
3	Toluene/FC-72 (3:5, v/v)	F_{13}BINOL	80	77	<1

[a] Substrate/F_{13}BINOL/Ti(O-*i*Pr)$_4$/Et_2Zn = 1:0.2:1.2:3 (molar ratio).
[b] Isolated yield.
[c] Determined by HPLC analysis using DAICEL CHIRALCEL OD. The (*R*)-configuration of the product in each case.
[d] Separated from the organic compounds by solid phase extraction with FRP silica gel.

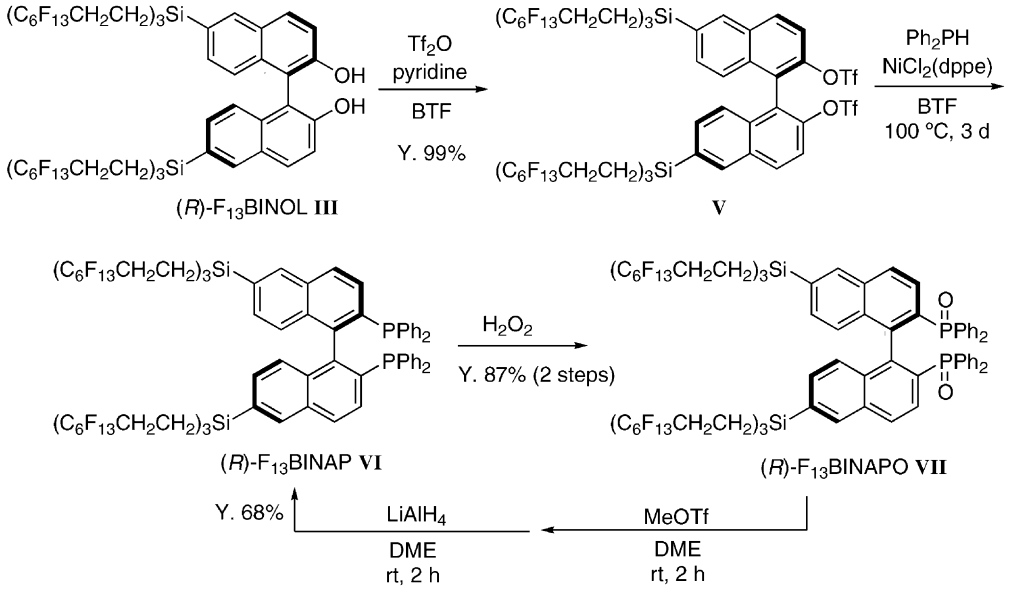
Table 7
Catalytic asymmetric addition of diethylzinc (1 M in hexane) to benzaldehyde using a (*R*)-F_{17}BINOL-Ti complex in FC-72–organic solvent biphase system[a]

Run	Solvent	FBINOL	Yield (%)[b]	e.e. (%)[c]	Recovered (*R*)-F_{17}BINOL (%)[d]
1	Toluene/hexane/FC-72 (1:1:2, v/v/v)	F_{17}BINOL	82	79	1
2	Toluene/hexane/FC-72 (1:1:2, v/v/v)	F_{17}BINOL	82	78	1
3	Toluene/hexane/FC-72 (1:1:2, v/v/v)	F_{17}BINOL	77	78	1

[a] Substrate/F_{17}BINOL/Ti(O-*i*Pr)$_4$/Et_2Zn = 1:0.2:1.2:3 (molar ratio).
[b] Isolated yield.
[c] Determined by capillary GC analysis using SIPELCO β-DEX 120™. The (*R*)-configuration of the product in each case.
[d] Separated from the organic compounds by solid phase extraction with FRP silica gel.

preparation of (*R*)-6,6′-bis(1*H*,1*H*,2*H*,2*H*-perfluorooctyl)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl and its application to asymmetric hydrogenation. 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% e.e.), which is similar to that obtained in the original Ru-BINAP complex reaction (95.4% e.e.). 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 2).

When the bistriflate of (*R*)-F_{13}BINOL (**V**) was phosphinated with Ph_2PH by using $NiCl_2$(dppe) in BTF at 100 °C for 3 days under argon, the desired product (**VI**) was actually seen by TLC analysis in good yield. However, (*R*)-F_{13}BINAP **IV** and the starting material, bistriflate **V**, had very close rf 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 (**VII**; (*R*)-F_{13}BINAPO). 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 **V**). That (*R*)-F_{13}BINAP 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 [2]. Next, we examined reduction of (*R*)-F_{13}BINAPO by the silane reduction method [14] 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 system [15], but the yield was not high and it was practically impossible to separate (*R*)-F_{13}BINAP from the non-polar by-products. Fortunately, we succeeded in getting high yield of (*R*)-F_{13}BINAP by employing Imamoto's method for reduction of chiral phosphine oxides [16]. The reaction was carried out as follows: (*R*)-F_{13}BINAPO was dissolved in 1,2-dimethoxyethane (DME) and then methyl triflate (MeOTf) was added to the solution. The reaction mixture was stirred for 2 h at room temperature under argon. After cooling to



Scheme 2.

Table 8
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.

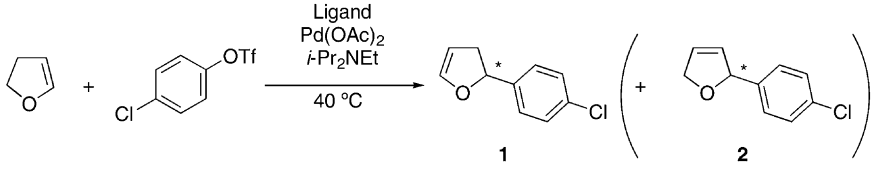
0 °C, $LiAlH_4$ was added to the solution and then the reaction mixture was stirred at room temperature for 2 h. The color of the reaction mixture changed from light yellow to dark red and then to yellow. The reaction was quenched by a small amount of saturated Na_2SO_4 solution and then the reaction mixture was directly loaded on a short silica gel column and eluted by a 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. 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% e.e. Partition coefficients of (*R*)-F_{13}BINAPO and (*R*)-F_{13}BINAP are shown in Table 8.

In order to get preliminary information about (*R*)-F_{13}BINAP, we examined an asymmetric Heck reaction. Hayashi and coworkers [17] 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 (**1**) in 91% e.e. 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, and the results are summarized in Table 9 (entries 1–3). As seen in Table 9, 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% e.e.) but not for (*R*)-BINAP (entry 1, 76% e.e.). Benzene was also a good solvent for (*R*)-F_{13}BINAP (entry 3, 92% e.e.), although the chemical yield of 2-(4-chlorophenyl)-2,5-dihydrofuran (**2**) increased. The enantiomeric excess of the product **1** was determined by GC analysis using SUPELCO *β*-DEX 120™ chiral capillary column. (*R*)-F_{13}BINAP was recovered by using fluorous reverse phase silica gel 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 9). The enantioselectivity was marginally higher (93% e.e.), 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

Table 9
Asymmetric Heck reaction of 2,3-dihydrofuran with 4-chlorophenyl triflate [a]



Entry	Ligand	Solvent	Reaction time (h)	Yield (%)[b]			e.e. (%)[c] (configuration)[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 (B)	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.

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 as well.

In conclusion, we have prepared highly fluorinated chiral BINOLs, (*R*)-F_{13}BINOL and (*R*)-F_{17}BINOL, and BINAP, (*R*)-F_{13}BINAP, and applied them to catalytic asymmetric C–C bond forming reactions. The FBINOLs were examined in the consecutive reactions by using fluorous–organic biphase and fluorous solid phase extraction techniques. In the biphase system, we obtained an enantioselectivity near maximum value that was attained in non-fluorous uniphase system and a good immobilization of the catalyst in the fluorous phase by tuning the fluorine atom content of the ligands. The FBINOLs were easily recovered by the solid phase extraction with FRP silica gel and reusable without further purification to give almost the same chemical yield and enantioselectivity as the first use. The solid phase extraction technique was applied successfully to a simultaneous screening procedure. On the other hand, (*R*)-F_{13}BINAP was examined to 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, 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 successful use of it.

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