



# Asymmetric alkylation of aromatic aldehydes with diethylzinc catalyzed by a fluorous BINOL–Ti complex in an organic and fluorous biphasic system

Yutaka Nakamura,<sup>a</sup> Seiji Takeuchi,<sup>a,\*</sup> Yoshiaki Ohgo<sup>a</sup> and Dennis P. Curran<sup>b,\*</sup>

<sup>a</sup>*Niigata College of Pharmacy, 5-13-2 Kamishin'ei cho, Niigata 950-2081, Japan*

<sup>b</sup>*Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, USA*

Received 13 September 1999; revised 14 October 1999; accepted 18 October 1999

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## Abstract

Fluorous chiral BINOL ((*R*)-FBINOL) was prepared by short reaction steps in good overall yield and was applied to the catalytic asymmetric alkylation in a toluene and FC-72 biphasic system. The (*R*)-FBINOL–Ti complex in the FC-72 phase was consecutively reused in the biphasic system and the enantioselectivity was still higher than 80% ee at the 5th reaction. © 1999 Elsevier Science Ltd. All rights reserved.

*Keywords:* fluorine; fluorine compounds; asymmetric; catalysis; alkylation.

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Transition metal catalysts in which fluorous ligands are coordinated to the metal ion can partition exclusively to a fluorous solvent such as FC-72 (F<sub>3</sub>C(CF<sub>2</sub>)<sub>4</sub>CF<sub>3</sub>) in an organic–fluorous biphasic system (FBS). The characteristic nature of the fluorous catalysts enables reactions to proceed consecutively in FBS. After the completion of a reaction, the organic phase in which the organic products are contained is removed and a new organic solution of the reactants is added to the fluorous phase to continue the reaction. The reaction can thus be repeated as long as the catalyst remains intact in the fluorous phase.<sup>1</sup> This is a liquid–liquid biphasic version of a catalytic reaction in a liquid–solid biphasic flow reactor system by metal complexes in which polymer-supported or polymeric ligands are coordinated to the metal ions and is expected to complement the drawbacks of the polymer catalysts.

Very recently, Gladysz and co-workers have reported hydroboration of alkenes and alkynes catalyzed by a fluorous rhodium complex in a toluene and CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub> biphasic system. The organoboron products were isolated or oxidized to the corresponding alcohols after separation from the catalyst in CF<sub>3</sub>C<sub>6</sub>F<sub>11</sub>. The yields were high and the overall TON values of the catalytic reaction turned out higher than 10000/cycle.<sup>2</sup>

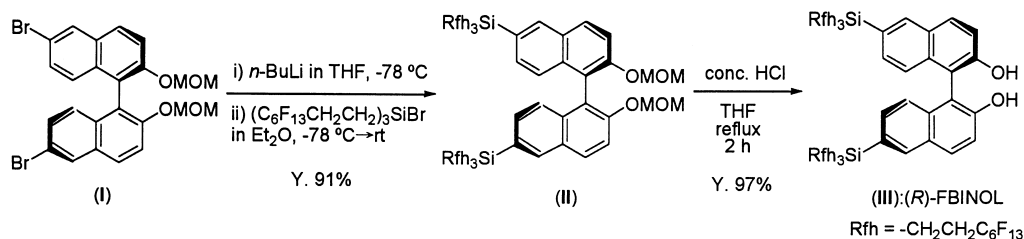
To our knowledge, however, only a few reports have been published on catalytic asymmetric reactions using the fluorous chiral catalysts<sup>3</sup> in spite of the successful attempts with chiral polymer catalysts.<sup>4</sup> This is simply attributable to the lack of useful fluorous analogues of popular chiral ligands such as BINOL or BINAP. Therefore, we have attempted to synthesize such fluorous ligands and succeeded in preparing

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\* Corresponding authors.

(*R*)-6,6'-bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-1,1'-binaphth-2,2'-diol ((*R*)-FBINOL) in good yield on a practical scale by the following route.

(*R*)-6,6'-Dibromo-2,2'-dimethoxymethoxy-1,1'-binaphthylene (**I**) was prepared from commercially available (*R*)-6,6'-dibromo-1,1'-binaphth-2,2'-diol by Pu's method.<sup>5</sup> (*R*)-6,6'-Bis[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]-2,2'-dimethoxymethoxy-1,1'-binaphthalene (**II**) was obtained in 91% yield via lithiation at the 6 and 6'-positions of (**I**) and then reaction with (C<sub>6</sub>F<sub>13</sub>CH<sub>2</sub>CH<sub>2</sub>)<sub>3</sub>SiBr<sup>6</sup> according to Curran's method (Scheme 1).<sup>7</sup> (*R*)-FBINOL (**III**) was isolated in 97% yield after removing the MOM groups.<sup>8</sup>



Scheme 1.

The approximate partition coefficients of **III** was determined by a simple method described in the footnote to Table 1, and the results are summarized in Table 1.

Table 1  
Partition coefficients of (*R*)-FBINOL in organic solvent and FC-72<sup>a</sup>

	Organic solvent	Organic solvent/FC-72
(R)-FBINOL ( <b>III</b> )	CHCl <sub>3</sub>	1/19
	THF	1/3
	toluene	1/49

<sup>a</sup> A mixture of 100 mg of (*R*)-FBINOL in FC-72 (2 mL) and an 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 fluoros compound in each phase were determined by weighing the residue.

Nakai and Chan have independently reported the asymmetric alkylation of aromatic aldehydes with diethylzinc catalyzed by a BINOL–Ti complex.<sup>9</sup> We chose the reaction for the toluene and FC-72 biphasic system to examine usefulness of (*R*)-FBINOL, because the reaction brought about a high percentage ee and yield by a simple procedure and with the use of commercially available reagents.<sup>10</sup>

When Ti(O-*i*Pr)<sub>4</sub> was added to the solution of (*R*)-FBINOL in FC-72, the reaction mixture became a light-red homogeneous solution, and then a colorless oily material was separated out on the surface of the FC-72 solution (Fig. 1). To the reaction mixture was added 1 M solution of Et<sub>2</sub>Zn in hexane. After cooling the reaction mixture to 0 °C, a benzaldehyde solution in toluene was added. The toluene phase (actually toluene and hexane phase; organic phase) 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 1.0 *N*-hydrochloric acid to ensure removal of (*R*)-FBINOL from the Ti complex. The product and (*R*)-FBINOL were simply and cleanly separated with 1*H*,1*H*,2*H*,2*H*-perfluorooctyldimethylsilyl binded silica gel (fluorous reverse phase silica gel; FRP silica gel)<sup>11</sup> by washing successively with acetonitrile and FC-72. The product alcohol from the acetonitrile eluate was purified by preparative TLC, and (*R*)-FBINOL was recovered from the FC-72 eluate in pure form. The enantioselectivity (83% ee) of the product was similar to that reported by Nakai and co-workers. To the fluoros layer new Ti(O-*i*Pr)<sub>4</sub>, the Et<sub>2</sub>Zn solution and benzaldehyde solution were

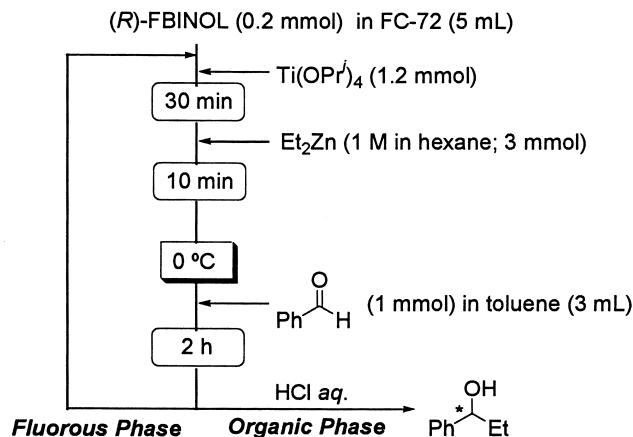


Figure 1.

Table 2

Asymmetric catalytic alkylation of benzaldehyde with diethylzinc using a (*R*)-FBINOL–Ti complex in FC-72/organic solvent biphasic system

Run	Yield (%) <sup>a</sup>	% ee <sup>b</sup>	Config. (Rotn.) <sup>c</sup>	Recovered ( <i>R</i> )-FBINOL (%) <sup>d</sup>
1	81	83	<i>R</i> (+)	10
2	89	82	<i>R</i> (+)	12
3	87	82	<i>R</i> (+)	12
4	87	81	<i>R</i> (+)	11
5	87	80	<i>R</i> (+)	10

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by HPLC analysis using DAICEL CHIRALCEL OD. <sup>c</sup> Assigned by the sign of the optical rotation. See Ref. 12. <sup>d</sup> Separation of organic and fluorous compounds by solid-phase extraction with FRP silica gel.

added, and the reaction was carried out in the same way. Thus, the reaction was repeated five times and the results are summarized in Table 2.

As seen in Table 2, the enantioselectivity was still higher than 80% at the 5th experiment (run 5). However, about 10% (0.02 mmol) of (*R*)-FBINOL was recovered from the organic phase in every experiment. Therefore, it was considered that the chiral catalyst was in the organic phase and asymmetric reaction occurred only in that phase. The fact that the organic phase had a pale brown color also led us to this conclusion. Thus, we carried out the reaction separately in the organic phase and in the toluene-FC-72 biphasic system. The procedure was the same until the reaction mixture was cooled to 0 °C after the addition of Et<sub>2</sub>Zn solution. Toluene was added to the reaction mixture and the two phases were separated. To the organic phase was added the benzaldehyde solution and the reaction was carried out as described above. To the FC-72 phase, the Et<sub>2</sub>Zn solution and the benzaldehyde solution were added and the reaction was carried out in the same way. From the organic phase the product was obtained in 73% ee (88% yield) and 10% of (*R*)-FBINOL was recovered. From the toluene-FC-72 biphasic system the product was obtained in 77% ee (81% yield) and 88% of (*R*)-FBINOL 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 an enantioselectivity higher than 83% ee. On the other hand, the enantioselectivity in the

toluene-FC-72 biphasic system was somewhat higher in spite of the lack of excess amount of  $\text{Ti}(\text{O}-i\text{Pr})_4$ . The presence of excess amount of  $\text{Ti}(\text{O}-i\text{Pr})_4$  is reported to be indispensable for the reaction to result in high enantioselectivity and yield.<sup>9a</sup>

When a similar experiment was carried out by using an  $\text{Et}_2\text{Zn}$  solution in toluene (1.1 M), the enantioselectivity was 78% ee in the biphasic system. However, the enantioselectivity in the separated toluene phase was dramatically reduced to 30% ee (49% yield) and the recovery of (*R*)-FBINOL from the phase was negligible.

Judging from the results, it is concluded that both phases are necessary to get enantioselectivity higher than 83% ee in the biphasic system, and hexane plays an important role to bring about the high enantiomeric excess.

## Acknowledgements

This work was partially supported by a grant-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

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8. The detailed preparation procedures will be published elsewhere. (*R*)-FBINOL (**III**) was a colorless syrup which gradually crystallized: mp 80–81°C,  $[\alpha]_D^{26}$  –16.9 (*c* 0.463, FC-72); IR (KBr) 3500, 2946, 1614, 1470, 1207, 1144, 1071, 1019, 900, 844, 746, 708,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz)  $\delta$  1.00–1.30 (m, 12H,  $-\text{SiCH}_2-$ ), 1.80–2.20 (m, 12H,  $-\text{CF}_2\text{CH}_2-$ ), 5.14 (s, 2H,  $-\text{OH}$ ), 7.22 (d, 2H, *ArH*, *J*=8.3 Hz), 7.31 (d, 2H, *ArH*, *J*=8.3 Hz), 7.47 (d, 2H, *ArH*, *J*=9.0 Hz), 7.99 (s, 2H, *ArH*), 8.04 (d, 2H, *ArH*, *J*=9.0 Hz); MS (EI) *m/z* (relative intensity) 2422 ( $\text{M}^+$ , 100). Anal. calcd for  $\text{C}_{68}\text{H}_{56}\text{F}_{78}\text{O}_2\text{Si}_2$ : C, 33.71; H, 1.50; F, 61.16. Found: C, 33.12; H, 1.25; F, 60.93. The enantiomeric excess (ee) of the product was determined to be >99% by HPLC analysis using a chiral column (DAICEL CHIRALCEL OD, hexane:2-propanol=95:5, flow rate=1.0 mL/min):  $t_R$ =8.9 min.
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10. At the outset, a uniphase reaction was carried out under the same conditions as those reported except that (*R*)-FBINOL and BTF ( $\text{CF}_3\text{C}_6\text{H}_5$ ) were used as the chiral ligand and the solvent. The work-up procedure was similar to that described in the text. The enantioselectivities and the yields for several aromatic aldehydes were as follows: benzaldehyde (84% ee, 92%); 3-methoxybenzaldehyde (85% ee, 95%), 4-methoxybenzaldehyde (80% ee, 97%), 1-naphthylaldehyde (91% ee, 98%), 2-naphthylaldehyde (78% ee, 93%). (*R*)-FBINOL was recovered quantitatively and was reusable.
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