# Asymmetric Catalysis of the Friedel−Crafts Reaction with Fluoral by Chiral Binaphthol-Derived Titanium Catalysts through Asymmetric Activation

Akihiro Ishii,† Vadim A. Soloshonok, and Koichi Mikami*

*Department of Chemical Technology, Tokyo Institute of Technology, Ookayama, Meguro-ku, Tokyo 152-8552, Japan*

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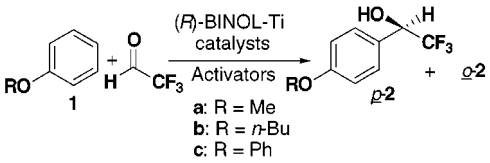
## Introduction

Asymmetric synthesis of organofluorine compounds is an important issue in pharmaceutical chemistry[1] and optoelectronic material science.[2] In particular, asymmetric catalysis of carbon−carbon bond forming reactions is the most attractive method, because the carbon skeleton of chiral organofluorine molecules can be constructed at the time of asymmetric induction.[3] The Friedel−Crafts (F−C) reaction is one of the most fundamental carbon−carbon bond forming reactions in organic synthesis.[4] However, its application to catalytic asymmetric synthesis has been quite limited.[5,6,7] Herein, we report a practical synthetic route to chiral 1-aryl-2,2,2-trifluoroethanol derivatives of synthetic importance[8] through the F−C reaction with fluoral using chiral binaphthol-derived titanium (BINOL-Ti) catalysts[9] via *asymmetric activation*.[10] In combination with chiral activators, the catalytic activity and enantioselectivity of BINOL-Ti catalysts can be enhanced (Scheme 1).

**Scheme 1**




## Result and Discussion

In the F−C reaction, the catalytic activity and enantioselectivity of BINOL-Ti catalysts[11] were found to be critically influenced by the substituents of BINOL derivatives (Table 1). (1) (*R*)-6,6′-$Br_2$-BINOL-Ti catalyst was the most effective catalyst. This F−C reaction did not proceed easily as compared with the carbonyl-ene reaction[3d,e] or the Mukaiyama-aldol reaction[3d] with fluoral. Therefore, the role of the electron-withdrawing group at the 6,6′-position of BINOL was found to be very important for increasing the Lewis acidity (runs 1−3). Relatively high enantioselectivity was obtained even when using 1 mol % of (*R*)-6,6′-$Br_2$-BINOL-Ti catalyst (run 4). (2) Polar solvent was more effective for producing higher *para* regioselectivity (run 5). When toluene was used as a solvent, the enantio-enriched adducts of fluoral to toluene were also obtained, along with the expected F−C product with anisole. (3) Interestingly, a lower reaction temperature leads to a decrease in the enantioselectivity of *para*-isomer, presumably because of the oligomeric nature of the BINOL-Ti catalysts at lower temperature (run 6). (4) The steric bulkiness of the alkyl ether portion of the aromatic substrates was essential for producing higher *para* regioselectivity (run 7). Interestingly, the bis-adduct with fluoral was not obtained even when using a large excess of fluoral in the reaction of diphenyl ether (run 8).

The sense of asymmetric induction was the same as observed in BINOL-Ti-catalyzed asymmetric reactions such as the carbonyl-ene reaction[11,13] and the Mu-

* To whom correspondence should be addressed.
† On leave from Chemical Research Center, Central Glass Co. Ltd., Kawagoe, Saitama 350-1151.

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**Table 1. The F-C Reactions with Fluoral Catalyzed by (*R*)-BINOLs/$Cl_2Ti(OPr^i)_2$/MS 4A[a]**

| run | **1** | chiral ligand | cat. (mol%) | solvent | temp (°C) | yield (%)[c] | *p*-**2**:*o*-**2**[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|---|
| 1 | **a** | (*R*)-BINOL | 30 | $CH_2Cl_2$ | 0 | 82 | 4:1 | 73 (*R*) |
| 2 | **a** | (*R*)-$H_8$-BINOL[b] | 5 | $CH_2Cl_2$ | 0 | 11 | 4:1 | 22 (*R*) |
| 3 | **a** | (*R*)-6,6′-$Br_2$-BINOL | 5 | $CH_2Cl_2$ | 0 | 94 | 4:1 | 84 (*R*) |
| 4 | **a** | (*R*)-6,6′-$Br_2$-BINOL | 1 | $CH_2Cl_2$ | 0 | 99 | 4:1 | 72 (*R*) |
| 5 | **a** | (*R*)-6,6′-$Br_2$-BINOL | 30 | toluene | 0 | 99 | 2:1 | 83 (*R*) |
| 6 | **a** | (*R*)-6,6′-$Br_2$-BINOL | 5 | $CH_2Cl_2$ | −30 | 94 | 4:1 | 79 (*R*) |
| 7 | **b** | (*R*)-6,6′-$Br_2$-BINOL | 15 | $CH_2Cl_2$ | 0 | 85 | 8:1 | 83 (*R*[e]) |
| 8 | **c** | (*R*)-6,6′-$Br_2$-BINOL | 10 | $CH_2Cl_2$ | 0 | 90 | 3:1 | 54 (*R*[e]) |

[a] BINOL-Ti catalysts were prepared as previously reported (ref 11). An excess of fluoral was used in all runs, because of the self-polymerization. [b] (*R*)-Octahydrobinaphthol. [c] Isolated yield after silica gel column chromatography. [d] The enantiomeric excess of *p*-**2**. Determined by chiral HPLC. *p*-**2a**: Daicel, CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 98:2, 0.8 mL/min, 254 nm, $t_R$ = 43 min (*S*), 49 min (*R*). *p*-**2b**: Daicel, CHIRALPAK AS, *n*-hexane:*i*-PrOH = 99:1, 0.8 mL/min, 254 nm, $t_R$ = 40 min (*S*), 42 min (*R*). *p*-**2c**: Daicel, CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 98:2, 0.8 mL/min, 254 nm, $t_R$ = 34 min (*R*), 44 min (*S*). The absolute configuration of *p*-**2a** was determined by the comparison of optical rotation with the literature values (ref 12). [e] The absolute configurations of *p*-**2b** and *p*-**2c** were assumed to be *R* from a similarity.

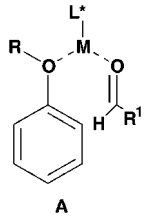
**Table 2. The F−C Reactions with Fluoral Catalyzed by BINOL-Ti Complex through Asymmetric Activation[a]**

| run | **1** | cat. (mol%) | additive | temp (°C) | yield (%)[c] | *p*-**2**:*o*-**2**[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | **a** | 10 | − | 0 | 66 | 4:1 | 70 (*R*) |
| 2 | **a** | 10 | pentafluorophenol | 0 | 94 | 3:1 | 68 (*R*) |
| 3 | **a** | 10 | (*R*)-BINOL | 0 | 97 | 3:1 | 64 (*R*) |
| 4 | **a** | 10 | (*R*)-5-Cl-BIPOL[b] | 0 | 88 | 4:1 | 78 (*R*) |
| 5 | **a** | 10 | (*R*)-6,6′-$Br_2$-BINOL | 0 | 89 | 4:1 | 90 (*R*) |
| 6 | **b** | 10 | (*R*)-6,6′-$Br_2$-BINOL | 0 | 90 | 8:1 | 90 (*R*) |

[a] (*R*)-6,6′-$Br_2$-BINOL-Ti($OPr^i$)$_2$ was activated by the additive in a molar ratio of 1:1 in dichloromethane (2 mL) at room temperature under an argon atomosphere for 1 h. The F−C reaction was carried out in situ by the addition of anisole (1 mmol) in dichloromethane (1 ml) and then passing an excess amount of fluoral. [b] 5,5′-Dichloro-4,4′,6,6′-tetramethyl-2,2′-biphenol. [c] Isolated yield after silica gel chromatography. [d] Refers to that of *p*-**2**.

kaiyama-aldol reaction[14] regardless of the preparative procedure of the catalysts; (*R*)-BINOL-Ti catalyst produces an (*R*)-alcohol product.

This F−C reaction cannot proceed through a six-membered transition state (**A**) involving a chiral Lewis acid, which has been reported to preferentially produce an *ortho*-F−C-product in the reaction of phenol[5e,6b] or 1-naphthol.[6a] In our case, however, the *para*-isomer is the major product.




**A**

The catalyst efficiency and enantioselectivity of BINOL-Ti complexes can be further increased through *asymmetric activation*.[10] Thus, the (*R*)-6,6′-$Br_2$-BINOL-Ti-($OPr^i$)$_2$, prepared from Ti($OPr^i$)$_4$ and (*R*)-6,6′-$Br_2$-BINOL, is activated by the addition of acidic activators such as (*R*)-5-Cl-BIPOL and (*R*)-6,6′-$Br_2$-BINOL (Table 2). In all runs, chemical yields are obviously improved by the addition of acidic activators, in sharp contrast to a similar reaction catalyzed by Yb($OTf$)$_3$, in which the addition of (*R*)-6,6′-$Br_2$-BINOL obviously decreases the catalytic activity.[15] The highly acidic catalyst was prepared by the coordination of the acidic 6,6′-$Br_2$-BINOL with the (*R*)-6,6′-$Br_2$-BINOL-Ti($OPr^i$)$_2$, in particular.[10a,b] In combination with the matched chiral activator, the enantioselectivity can be improved up to 90% ee as well as producing a high chemical yield (runs 5, 6).

We have thus reported the first example of asymmetric catalysis of the Friedel−Crafts reaction with fluoral. Chiral 1-aryl-2,2,2-trifluoroethanol derivatives of synthetic importance are obtained by the catalysis of chiral binaphthol-derived titanium complexes through asymmetric activation.

## Experimental Section

**General.** Melting point is uncorrected. $^1$H NMR spectra were recorded at 300 MHz;$^{13}$C NMR spectra were recorded at 75 MHz. Tetramethylsilane ($\delta$ = 0 ppm) was used as an internal standard, and $CDCl_3$ was used as the solvent. Analytical thin-layer chromatography (TLC) were performed on a glass plates precoated with silica gel (Merck Kieselgel 60 $F_{254}$, layer thickness 0.25 mm). Visualization was accomplished by UV light (254 nm) and phosphomolybdic acid. Column chromatography was performed on Silica Gel 60 (70−230 mesh) purchased from Kanto Chemical Co., Inc. Molecular sieves (MS) 4A (activated powder) was purchased from Aldrich Chemical Co., Inc. Dehydrated dichloromethane and toluene were purchased from Kanto Chemical Co., Inc. Fluoral was generated by the addition of fluoral hydrate to concentrated $H_2SO_4$ at 100 °C.

**General Procedure for the Friedel−Crafts Reactions with Fluoral Catalyzed by BINOL-Ti Complexes through Asymmetric Activation**. To a solution of Ti($OPr^i$)$_4$ (28.4 mg, 0.1 mmol) in dehydrated dichloromethane (1 mL) was added (*R*)-6,6′-$Br_2$-BINOL (44.4 mg, 0.1 mmol) at room temperature under an argon atomosphere. After stirring for 1 h, the additive (0.1 mmol) in dehydrated dichloromethane (1 mL) was added to the mixture. After stirring for additional 1 h, aromatic substrate (1 mmol) in dehydrated dichloromethane (1 mL) was added, and then an excess amount of freshly dehydrated and distilled fluoral was passed to the catalyst solution at 0 °C. The reaction mixture was stirred for 12 h at the same temperature. Dichloromethane (5 mL) and $H_2O$ (3 mL) were added to the mixture. Insoluble material was filtered off through a pad of Celite, and the filtrate was extracted three times with dichloromethane. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatographic separation by silica gel (dichloromethane:*n*-hexane = 3:2) gave the product.

*p*-**2a**: colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 2.73 (d, $J$ = 4.5 Hz, 1H), 3.81 (s, 3H), 4.93 (dq, $J$ = 4.5, 6.6 Hz, 1H), 6.91 (d, $J$ = 9.0

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(15) The same reaction in the presence of Yb($OTf$)$_3$ (10 mol %) gave the F−C products in 78% yield (*para*/*ortho* = 7). The addition of (*R*)-6,6′-$Br_2$-BINOL (1 or 2 equiv) decreased the chemical yields (42% (*para*/*ortho* = 13) or 45% (*para*/*ortho* = 16), respectively).

Hz, 2H), 7.38 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 55.4, 72.5 (q, $J$ = 32 Hz), 114.1, 124.4 (q, $J$ = 282 Hz), 126.2, 128.9, 160.5. IR (neat) 3440, 1170 cm$^{-1}$. MS (EI) $m/z$ 206 [M$^+$], 137. $[\alpha]^{29}_D$ -23.0° ($c$ 1.62, EtOH) (61% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK OD-H, $n$-hexane:$i$-PrOH = 98:2, 0.8 mL/min, 254 nm) $t_R$ = 43 min ($S$), 49 min ($R$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane:$n$-hexane = 3:2) 0.24.

*o*-**2a**: colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 3.66 (d, $J$ = 7.8 Hz, 1H), 3.88 (s, 3H), 5.27 (quin, $J$ = 7.8 Hz, 1H), 6.95 (d, $J$ = 7.8 Hz, 1H), 7.02 (t, $J$ = 7.8 Hz, 1H), 7.37 (t, $J$ = 7.8 Hz, 1H), 7.39 (d, $J$ = 7.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 55.8, 69.8 (q, $J$ = 33 Hz), 111.4, 121.1, 122.2, 124.7 (q, $J$ = 283 Hz), 129.3, 130.6, 157.6. IR (neat) 3450, 1174 cm$^{-1}$. MS (EI) $m/z$ 206 [M$^+$], 137. $[\alpha]^{31}_D$ −11.8° ($c$ 2.05, EtOH) (50% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK OD-H, $n$-hexane:$i$-PrOH = 98:2, 0.8 mL/min, 254 nm) $t_R$ = 20 min ($R$), 27 min ($S$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane:$n$-hexane = 3:2) 0.33.

*p*-**2b**: colorless needles. mp 65 °C ($n$-hexane). $^1$H NMR ($CDCl_3$) $\delta$ 0.98 (t, $J$ = 7.5 Hz, 3H), 1.49 (sex., $J$ = 7.5 Hz, 2H), 1.77 (quin, $J$ = 7.5 Hz, 2H), 2.43 (d, $J$ = 4.5 Hz, 1H), 3.97 (t, $J$ = 7.5 Hz, 2H), 4.96 (dq, $J$ = 4.5, 6.6 Hz, 1H), 6.92 (d, $J$ = 9.0 Hz, 2H), 7.38 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 13.9, 19.3, 31.3, 67.9, 72.6 (q, $J$ = 32 Hz), 114.7, 124.4 (q, $J$ = 282 Hz), 126.0, 128.8, 160.2. IR (neat) 3400, 1174 cm$^{-1}$. MS (EI) $m/z$ 248 [M$^+$], 179. $[\alpha]^{29}_D$ −34.1° ($c$ 1.08, EtOH) (100% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK AS, $n$-hexane:$i$-PrOH = 99:1, 0.8 mL/min, 254 nm) $t_R$ = 40 min ($S$), 42 min ($R$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane:$n$-hexane = 3:2) 0.27.

*o*-**2b**: colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (t, $J$ = 7.5 Hz, 3H), 1.50 (sex., $J$ = 7.5 Hz, 2H), 1.81 (m, 2H), 3.83 (d, $J$ = 7.5 Hz, 1H), 4.05 (m, 2H), 5.24 (quin, $J$ = 7.5 Hz, 1H), 6.94 (d, $J$ = 7.5 Hz, 1H), 6.99 (t, $J$ = 7.5 Hz, 1H), 7.35 (t, $J$ = 7.5 Hz, 1H), 7.36 (d, $J$ = 7.5 Hz, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 13.6, 19.1, 31.1, 68.3, 70.6 (q, $J$ = 33 Hz), 112.2, 121.1, 122.2, 125.0 (q, $J$ = 284 Hz), 129.8, 130.8, 157.5. IR (neat) 3440, 1172 cm$^{-1}$. MS (EI) $m/z$ 248 [M$^+$]. $[\alpha]^{30}_D$ −0.8° ($c$ 0.51, EtOH) (6% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK OD-H, $n$-hexane:$i$-PrOH = 98:2, 0.8 mL/min, 254 nm) $t_R$ = 26 min ($S$), 34 min ($R$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane:$n$-hexane = 3:2) 0.48.

*p*-**2c**: colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 2.53 (d, $J$ = 4.2 Hz, 1H), 5.01 (dq, $J$ = 4.2, 6.7 Hz, 1H), 7.02 (d, $J$ = 9.0 Hz, 2H), 7.04 (d, $J$ = 7.5 Hz, 2H), 7.15 (t, $J$ = 7.5 Hz, 1H), 7.37 (t, $J$ = 7.5 Hz, 2H), 7.44 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR ($CDCl_3$) $\delta$ 72.5 (q, $J$ = 32 Hz), 118.5, 119.5, 124.0, 124.3 (q, $J$ = 282 Hz), 128.5, 129.1, 130.0, 156.5, 158.7. IR (neat) 3440, 1170 cm$^{-1}$. MS (EI) $m/z$ 268 [M$^+$], 199. $[\alpha]^{29}_D$ −21.6° ($c$ 0.90, EtOH) (77% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK OD-H, $n$-hexane:$i$-PrOH = 98:2, 0.8 mL/min, 254 nm) $t_R$ = 34 min ($R$), 44 min ($S$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane: $n$-hexane = 3:2) 0.27.

*o*-**2c**: colorless oil. $^1$H NMR ($CDCl_3$) $\delta$ 3.16 (d, $J$ = 6.9 Hz, 1H), 5.48 (quin, $J$ = 6.9 Hz, 1H), 6.83 (d, $J$ = 8.3 Hz, 1H), 7.03 (d, $J$ = 8.3 Hz, 2H), 7.16 (t, $J$ = 8.3 Hz, 2H), 7.31 (t, $J$ = 8.3 Hz, 1H), 7.37 (t, $J$ = 8.4 Hz, 2H), 7.58 (d, $J$ = 8.3 Hz, 1H). $^{13}$C NMR ($CDCl_3$) $\delta$ 68.4 (q, $J$ = 33 Hz), 117.9, 119.6, 123.6, 124.3, 124.7, 124.7 (q, $J$ = 283 Hz), 129.4, 130.2, 130.8, 155.9, 156.4. IR (neat) 3440, 1176 cm$^{-1}$. MS (EI) $m/z$ 268 [M$^+$]. $[\alpha]^{29}_D$ −15.1° ($c$ 1.59, EtOH) (63% ee of $R$ isomer). Chiral HPLC (Daicel, CHIRALPAK OD-H, $n$-hexane:$i$-PrOH = 99:1, 0.8 mL/min, 254 nm) $t_R$ = 23 min ($R$), 28 min ($S$). $R_f$ (Merck Kieselgel 60 $F_{254}$/dichloromethane: $n$-hexane = 3:2) 0.36.

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**Supporting Information Available:** $^1$H NMR spectra of compounds *p*- or *o*-**2a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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