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Journal of Fluorine Chemistry 97 (1999) 51–55

JOURNAL OF FLUORINE CHEMISTRY

Short communication

Asymmetric Friedel–Crafts reactions of vinyl ethers with fluoral catalyzed by chiral binaphthol-derived titanium catalysts

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Received 27 November 1998; received in revised form 8 January 1999; accepted 8 January 1999

Dedicated to Professor Yoshiro Kobayashi on the occasion of his 75th birthday

Abstract

Asymmetric Friedel–Crafts reactions of vinyl ethers with fluoral catalyzed by chiral binaphthol-derived titanium catalysts gave reactive vinyl ether products. Sequential diastereoselective reactions of resultant vinyl ethers with *m*-CPBA provided highly functionalized organofluorine compounds in high enantiomeric purity.

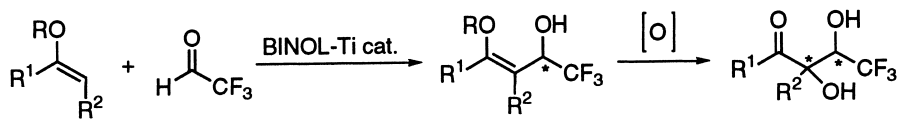
Keywords: Friedel–Crafts reaction; Asymmetric catalysis; Fluoral; Vinyl ether

1. Introduction

Asymmetric synthesis of organofluorine compounds is an important issue in pharmaceutical chemistry [1,2] and optoelectronic material science [3,4]. 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 [5–7]. The Friedel–Crafts (F–C) reaction is one of the most fundamental carbon–carbon bond-forming reactions in organic synthesis [8–11]. However, its application to catalytic asymmetric synthesis has been quite limited [12–20]. Recently, we reported the asymmetric F–C reactions of aromatic compounds with fluoral catalyzed by chiral binaphthol-derived titanium (BINOL-Ti) catalysts [21]. Herein, we disclose the catalytic asymmetric F–C reaction of alkyl vinyl ethers instead of aromatic compounds as a nucleophile and sequential diastereoselective oxidation reactions of the F–C products (Scheme 1).

2. Results and discussion

The catalyst (**1a**) prepared from 6,6′-Br_2-BINOL-Ti(O-Pr^i)$_2$/6,6′-Br_2-BINOL [22], which was the most effective catalyst in the F–C reaction of aromatic compounds, was first employed in this reaction (Table 1, run 1). However, only the aldol product (**4a**) was obtained with high enantioselectivity. We supposed that the F–C product would be hydrolyzed by the acidic protons of the 6,6′-Br_2-BINOL-Ti(OPr^i)$_2$/6,6′-Br_2-BINOL complex. Accordingly, the catalysts without proton sources were expected to be effective to this F–C reaction. These catalysts were prepared in isolated form by the previously reported procedure [23]. Thus, the same reaction was examined using the isolated catalyst (**1b**)



Scheme 1.

prepared from (*R*)-6,6′-Br_2-BINOL and $Cl_2Ti(OPr^i)_2$ in the presence of MS 4A without addition of Br_2-BINOL (run 2). The F–C product (**3a**) was obtained together with a small amount of the aldol product (**4a**). The enantiomeric excess

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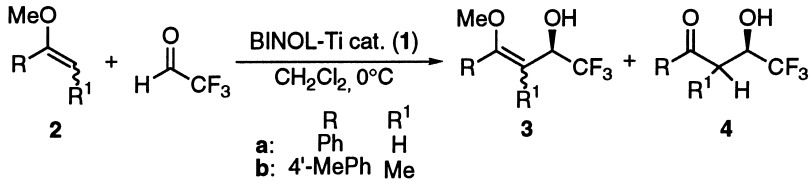
0022-1139/99/$ – see front matter
PII: S0022-1139(99)00025-1

Table 1
Asymmetric Friedel–Crafts reactions of methyl vinyl ethers with fluoral catalyzed by BINOL-Ti catalysts



Run	Ether (**2**)	Catalyst (**1**)	mol%	Yield (%)[a]		Enantiomeric excess (%)[b]
				3(*E*:*Z*)	**4**	
1	**a**	(*R*)-6,6′-Br_2-BINOL-Ti(OPr^i)$_2$/(*R*)-6,6′-Br_2-BINOL (**a**)	20	0	53	70 (*R*)[c]
2	**a**	(*R*)-6,6′-Br_2-BINOL/Cl_2Ti(OPr^i)$_2$/MS 4A (**b**)	20	48 (1:2)	7	58 (*R*)[d]
3	**a**	(*R*)-BINOL/Cl_2Ti(OPr^i)$_2$/MS 4A (**c**)	10	54 (1:2)	–	72 (*R*)[e]
4	**b**[f]	(*R*)-BINOL/Cl_2Ti(OPr^i)$_2$/MS 4A (**c**)	20	64 (5:1)	–	85 (*R*)[g]

[a] Isolated yield after silica gel column chromatography.
[b] The enantiomeric excess of **3a** or **3b**. Determined by chiral HPLC analysis of **4a** or *anti*-**4b** obtained by acidic hydrolysis of **3a** or **3b**. In the hydrolysis of (*E*)-**3b**, *anti*-isomer was obtained as the major diastereomer (*anti*/*syn*=ca. 2) (The relative configuration of the major diastereomer was determined to be *anti* on the basis of the chemical shifts of α-methyl carbon in ^{13}C-NMR spectra ($CDCl_3$) of **4b** (*syn*: 11.9 ppm, *anti*: 16.3 ppm), see [26]). Chiral HPLC conditions, **4a**: Daicel, CHIRALPAK OD-H, *n*-hexane:*i*-PrOH=95:5, 0.8 ml/min, 254 nm, t_R=10 min (3*S*), 12 min (3*R*). *anti*-**4b**: Daicel, CHIRALPAK AS, *n*-hexane:*i*-PrOH=98:2, 0.8 ml/min, 254 nm, t_R=11 min (2*R*, 3*S*), 38 min (2*S*, 3*R*).
[c] The enantiomeric excess of **4a**.
[d] The enantiomeric excess of *E*,*Z*-mixture (2:3) of **3a**.
[e] The enantiomeric excess of *E*,*Z*-mixture (1:2) of **3a**.
[f] *E*:*Z*=1:1.
[g] The enantiomeric excess of (*E*)-**3b**.

of the F–C product was moderate. The product ratio of **3** vs. **4** was found to be critically influenced by the preparative procedure and the ligands of the catalysts. The isolated catalyst (**1c**) derived from (*R*)-BINOL, which is less acidic than the corresponding 6-Br-analogue, proved to be more effective in terms of both chemical yield and enantioselectivity (run 3). The aldol product was essentially not obtained in this case. Thus, the BINOL-Ti catalyst was superior in this reaction to the 6,6′-Br_2-BINOL-Ti catalyst in sharp contrast to the F–C reaction of aromatic compounds. The higher enantioselectivity was obtained in the reaction of methyl vinyl ether (**2b**) possessing β-methyl substituent irrespective of the geometry (run 4). This F–C reaction with alkyl vinyl ethers was found to more easily proceed as compared with that of aromatic compounds. Therefore, a large excess of fluoral was not necessary because of the high nucleophilicity of alkyl vinyl ethers.

The stereochemical assignments deserve special comments. The geometries of products (**3**) were determined on the basis of the chemical shifts in ^{1}H-NMR spectra (Fig. 1). In a similar manner to β-methylstyrene [24], (*Z*)-**3a** shows the vinylic proton at higher field (4.8 ppm). Likewise, (*E*)-**3b** shows the vinylic methyl group at higher field (1.7 ppm). The absolute configuration of (*E*)-**3b** was determined to be *R* by Mosher's method [25].[2]

Then we focused our attention to sequential diastereoselective oxidation reactions of the F–C products by *m*-CPBA (Scheme 2). Regardless of the geometry of the F–C products, single diastereomer of α,β-dihydroxy ketone (**7**) having a chiral quarternary carbon was obtained in high chemical yield and high diastereoselectivity through the acidic hydrolysis of intermediates (**5** and **6**). The other diastereomer was not observed in the reaction mixture as determined by ^{1}H-NMR.

The relative stereochemistry was determined to be *syn* on the bases of the chemical shifts of α-methyl carbons in ^{13}C-NMR spectra of **7** [26].[3] Therefore, the diastereoselectivity can be explained as follows, the trifluoromethyl substituent is located outside because of a 1,3-allylic strain [27], and then *m*-CPBA should attack from the direction of the hydroxy substituent perpendicular to the olefin π-face through hydrogen bonding (Fig. 2) [28,29].[4] These products are of synthetic importance because of similar skeletal features to Merck L-784512 [30] with cyclooxygenase-2 selective inhibitory activity.

In summary, we have reported the asymmetric Friedel–Crafts reactions of alkyl vinyl ethers with fluoral catalyzed by chiral binaphthol-derived titanium catalysts and sequential diastereoselective oxidation reactions of the Friedel–Crafts products.

[2]The chemical shift of vinylic methyl proton in ^{1}H-NMR spectra ($CDCl_3$) of MTPA ester of (*E*)-**3b**: 1.60 ppm (*S*), 1.36 ppm (*R*); $\delta_S-\delta_R$=positive.

[3]*syn*: 23.4 ppm, *anti*: 25.1 ppm ($CDCl_3$).

[4]Sharpless proposed the formation of hydrogen bond between hydroxy groups and *m*-CPBA.

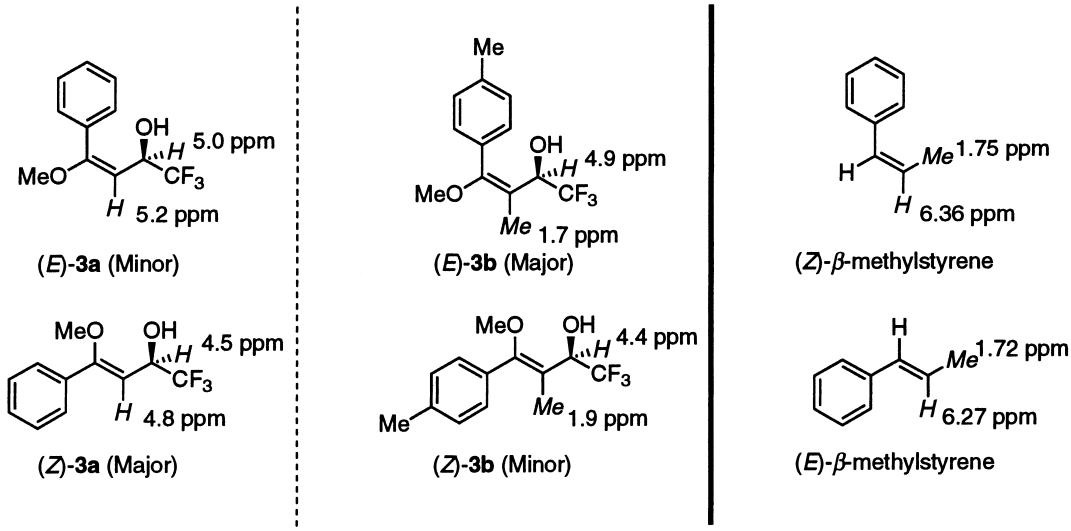
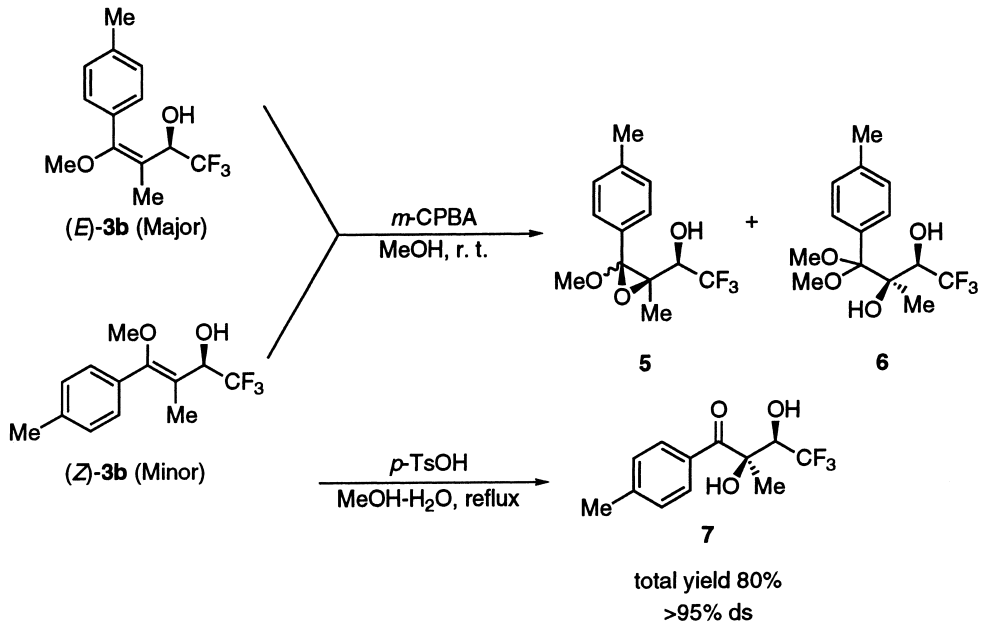


Fig. 1.

3. Experimental

General. ^{1}H NMR and ^{13}C NMR were measured on a Varian Gemini 300 (300 MHz) spectrometers. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard (0 ppm) in $CDCl_3$. Significant ^{1}H NMR date were tabulated in the following order: multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; quin: quintet; sex: sextet; sep: septet, m: multiplet). Chemical shifts of ^{13}C NMR were expressed in parts per million in $CDCl_3$ as an internal standard (77.1 ppm). Liquid chromatographic analyses were conducted on a JASCO PU-980 instrument equipped with model UV-975 spectrometers as an ultra violet light (254 nm) and chiral column (Daicel CHIRALCEL OD-H or AS). Peak area was calculated by a Shimadzu model C-R6A as an automatic integrator. Analytical thin layer chromatography (TLC) were performed on glass plates pre-coated 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. Molecular sieve (MS) 4A (activated powder) was purchased from Aldrich. Dehydrated dichloromethane and toluene were purchased from Kanto. Fluoral was generated by the addition of fluoral hydrate to conc. H_2SO_4 at 100°C.



Scheme 2.

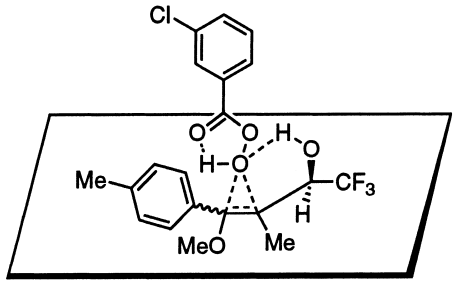


Fig. 2.

3.1. Preparation of catalysts

1a: To a solution of $Ti(OPr^i)_4$ (0.05 mmol) in dehydrated dichloromethane (0.75 ml) was added (*R*)-6,6′-Br_2-BINOL (0.05 mmol) at room temperature under an argon atmosphere. After stirring for 1 h, (*R*)-6,6′-Br_2-BINOL (0.05 mmol) in dehydrated dichloromethane (0.75 ml) was added to the mixture again. Catalyst solution was prepared by stirring for additional 30 min.

1b, **c**: The mixture containing (*R*)-6,6′-Br_2-BINOL or (*R*)-BINOL (1 mmol), $Cl_2Ti(OPr^i)_2$ (1 mmol), MS 4A (5 g) and dehydrated dichloromethane (10 ml) was stirred at room temperature under an argon atmosphere. After 1 h, dehydrated toluene (20 ml) was added to the mixture. Clear catalyst solution was recovered by centrifugal separator followed by Celite filtration. Isolated catalyst was obtained as a reddish brown solid by evaporating under reduced pressure at room temperature.

3.2. General procedure for asymmetric Friedel–Crafts reactions

To a solution of catalyst (**1**, 0.025 or 0.05 mmol) in dehydrated dichloromethane (1.5 ml) was added vinyl ether (**2**, 0.25 mmol) at 0°C under an argon atmosphere, and then freshly dehydrated and distilled fluoral (ca. 0.75 mmol) was passed to the solution. After stirring for 30 min at the same temperature, dichloromethane and sat. $NaHCO_3$ were added to the reaction mixture. Insoluble material was filtered off through a pad of Celite and the aqueous layer 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 (**3**).

(*E*)-**3a** pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.92 (d, *J*=6.9 Hz, 1H), 3.57 (s, 3H), 5.02 (sex, *J*=6.9 Hz, 1H), 5.20 (d, *J*=6.9 Hz, 1H), 7.36–7.48 (m, 5H).

(*Z*)-**3a** pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.05 (d, *J*=5.9 Hz, 1H), 3.76 (s, 3H), 4.46 (dquin, *J*=9.9, 5.9 Hz, 1H), 4.83 (d, *J*=9.9 Hz, 1H), 7.36–7.48 (m, 5H).

(*E*)-**3b** pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H), 2.39 (s, 3H), 3.30 (s, 3H), 3.78 (d, *J*=7.8 Hz, 1H), 4.93 (quin, *J*=7.8 Hz, 1H), 7.21 (m, 4H).

(*Z*)-**3b** pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.07 (d, *J*=6.4 Hz, 1H), 2.39 (s, 3H), 3.30 (s, 3H), 4.44 (quin, *J*=6.4 Hz, 1H), 7.12–7.24 (m, 4H).

3.3. Sequential diastereoselective oxidation reactions

To a solution of (*E*) or (*Z*)-**3b** (0.1 mmol) in methanol (1 ml) was added *m*-CPBA (0.25 mmol) at room temperature. After stirring for 12 h, solvent was evaporated under reduced pressure. The residue was diluted with dichloromethane and the organic layer was washed with sat. $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of solvent under reduced pressure gave the mixture of **5** and **6**. To a solution of **5** and **6** in methanol–H_2O (3:1, 3 ml) was added *p*-TsOH·H_2O (0.5 mmol). After the mixture was stirred for 30 min under reflux condition, solvent was evaporated under reduced pressure. The residue was diluted with dichloromethane and the organic layer was washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and evaporated under reduced pressure. Chromatographic separation by silica gel (ethyl acetate:*n*-hexane=1:4) gave **7** in 80% yield.

7 colorless needle. ^{1}H NMR ($CDCl_3$) δ 1.74 (q, *J*=1.8 Hz, 3H), 2.44 (s, 3H), 3.21 (d, *J*=10.5 Hz, 1H), 4.53 (s, 1H), 4.57 (dq, *J*=10.5, 6.9 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 2H), 7.95 (d, *J*=8.1 Hz, 2H).

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