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Asymmetric Catalytic Friedel–Crafts Reaction of Silyl Enol Ethers with Fluoral: A Possible Mechanism of the Mukaiyama-Aldol Reactions

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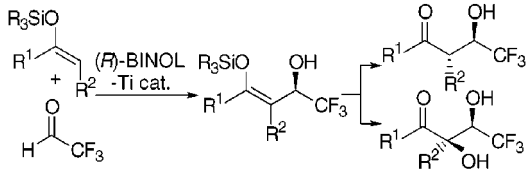
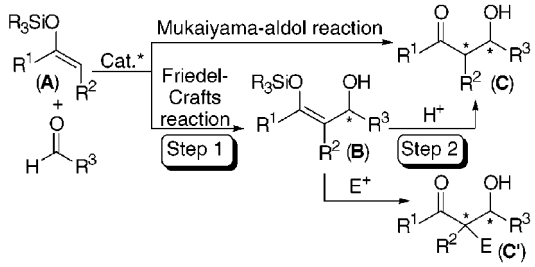
ABSTRACT



The catalytic asymmetric Friedel–Crafts reaction of silyl enol ethers with fluoral proceeds under Mukaiyama-aldol conditions to give silyl enol ether products. The sequential diastereoselective reactions of the resultant silyl enol ethers with electrophiles provide highly enantiopure functionalized organofluorine compounds of material and pharmaceutical interest.

The Mukaiyama-aldol reaction of silyl enol ethers (**A**) is one of the most important carbon−carbon bond-forming reactions in organic synthesis (Scheme 1).[1] Therefore, its application

Scheme 1



to the asymmetric catalytic synthesis of aldols (**C**) has been investigated in depth for the past decade.[2] An asymmetric catalytic Friedel−Crafts-type[3] (F−C) reaction might proceed under Mukaiyama-aldol conditions to give allylic alcohols (**B**) (step 1), in which case sequential reactions of the silyl enol ether products (**B**) with electrophiles (E^+) could yield more functionalized aldols (**C′**)[4] possessing adjacent stereogenic centers at both the α and β positions with high enantio- and diastereoselectivity (step 2). We report herein the asymmetric catalytic F−C reaction of silyl enol ethers, of which the mechanism may be involved in the Mukaiyama-

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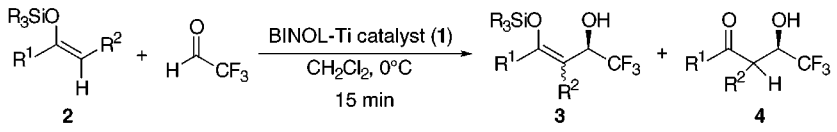
(3) Reviews: (a) Smith, M. B. *Organic Synthesis*; McGraw-Hill: New York, 1994; pp 1313. (b) Heaney, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 733. (c) Roberts, R. M.; Khalaf, A. A. In *Friedel−Crafts Alkylation Chemistry. A Century of Discovery*; Dekker: New York, 1984. (d) Olah, G. A. *Friedel−Crafts Chemistry*; Wiley-Interscience: New York, 1973.

(4) Chiral *syn*- or *anti*-α,β-dihydroxy thioesters as α-protected forms: (a) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc.* **1994**, *116*, 9805. (b) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708. Chiral α-amino-β-hydroxy esters: (c) Ito, Y.; Sawamura, M; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. (d) Ito, Y.; Sawamura, M; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253.

Table 1. Asymmetric Friedel−Crafts Reactions of Silyl Enol Ethers with Fluoral Catalyzed by BINOL-Ti Complex



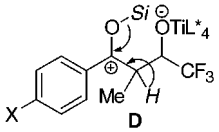
run	sub	SiR_3	R^1	R^2	cat. (mol%)	yield (%)[a] 3 (*E* : *Z*)	4 (*syn* : *anti*)	ee (%)[b]
1	**2a**	Si*t*-BuMe$_2$	Ph	H	5	**3a**: 67 (1 : 5)[c]	**4a**: 14	98 (*R*)
2	**2b**[d]	$SiMe_3$	4'-Me-Ph	Me	20	**3b**: 0	**4b**: 27[e]	-
3	**2c**	Si*i*-Pr$_3$	Ph	H	1	**3c**: 90 (1 : 5)[f]	**4a**: 4	96 (*R*)[g]
4	**2d**[d]	Si*t*-BuMe$_2$	4'-Me-Ph	Me	20	**3d**: 77 (1 : 6)[c]	**4d**: 10 (1 : 1)[h]	94 (*R*)[i]
5	**2e**[d]	Si*t*-BuMe$_2$	4'-MeO-Ph	Me	20	**3e**: 68 (1 : 5)[c]	**4e**: 22 (5 : 3)[h]	95 (*R*)
6	**2f**[d]	Si*t*-BuMe$_2$	4'-MeS-Ph	Me	20	**3f**: 72 (1 : 6)[c]	**4f**: 18 (2 : 1)[h]	95 (*R*)

[a] Isolated yield after silica gel column chromatography. [b] The enantiomeric excess of (*Z*)-**3**. Determined by chiral HPLC analysis of **4a** or *anti*-**4d**,**e**,**f** obtained by acidic hydrolysis of (*Z*)-**3**. In these hydrolyses, *anti*-isomer was obtained as the major diastereomer (*anti* / *syn* = ca. 3). [c] The geometry was determined on the basis of the chemical shifts of allylic protons in ^{1}H-NMR spectra. [d] >95% *Z*. [e] The usual aldol product (**4b**) was obtained as the trimethylsilyl ether. The diastereomeric ratio = 1 : 4. [f] The geometry was determined from similarities in the movement on TLC and chemical shifts of hydroxyl proton in ^{1}H-NMR. [g] The enantiomeric excess of **4a** was 43% ee (*R*). [h] The relative configuration was determined on the basis of the chemical shifts of α-methyl carbons in ^{13}C-NMR spectra. [i] The enantiomeric excess of (*E*)-**3d**, *syn*-**4d** and *anti*-**4d** were 66 (*R*), 22 (*R*) and 62% ee (*R*), respectively. The enantiomeric excess of (*E*)-**3d** was determined by the same chiral HPLC analysis as (*Z*)-**3d**. Also in this hydrolysis *anti*-**4d** was obtained as major diastereomer (*anti* / *syn* = ca. 4). *syn*-**4d**: Daicel, CHIRALPAK AS, *n*-hexane : *i*-PrOH = 98 : 2, 0.8 ml/min, 254 nm, t_R = 14 min (2*R*, 3*R*), 25 min (2*S*, 3*S*).

aldol reaction.[5] Sequentially, diastereoselective reactions of the F−C products with fluoral can thus produce highly functionalized organofluorine compounds[6] that are of material[7] and pharmaceutical[8] interest.

The F−C reaction of silyl enol ethers was investigated using a chiral binaphthol-derived titanium (BINOL-Ti) complex (**1**)[9] prepared from (*R*)-BINOL and $Cl_2Ti(OPr^i)_2$ in the presence of MS 4 Å (Table 1). Importantly, the F−C product (**3a**) rather than the usual aldol product (**4a**) was obtained in the catalytic reaction of *tert*-butyldimethylsilyl enol ether (**2a**) with fluoral (run 1). The F−C product (**3a**) was easily separated from the usual aldol product (**4a**) by simple flash chromatography. Notably, the enantiomeric excess of the major product (*Z*)-**3a** was found to be excellent (98% ee).[10] In contrast, the reaction of trimethylsilyl enol ether (**2b**) gave only the usual aldol-type product (**4b**) (run 2). The sterically bulky silyl and electron-withdrawing trifluoromethyl substituents might be important for preventing inter- or intramolecular nucleophilic attack on the silyl group in the zwitterion intermediate (**D**) where the aromatic substituent stabilizes the benzylic carbenium ion (Scheme 2).[11]

Scheme 2



Indeed, the use of sterically more demanding triisopropylsilyl enol ether (**2c**) led to the preferential (90% isolated

(5) The recent mechanistic works of this reaction: (a) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570. (b) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323. (c) Denmark, S. E.; Chen, C.-T. *Tetrahedron Lett.* **1994**, *35*, 4327. (d) Denmark, S. E.; Henke, R. B. *J. Am. Chem. Soc.* **1991**, *113*, 2177. (e) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (f) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077. (g) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576. (h) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481.

(6) In particular, asymmetric catalysis of carbon−carbon bond-forming reactions is the most attractive method. (a) Review: Iseki, K. *Tetrahedron* **1998**, *54*, 13887. (b) Mikami, K.; Yajima, T.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85. (c) Mikami, K.; Yajima, T.; Terada, M.; Uchimaru, T. *Tetrahedron Lett.* **1993**, *34*, 7591. (d) Soloshonok, V. A.; Hayashi, T. *Tetrahedron Lett.* **1994**, *35*, 2713 and references therein.

(7) Reviews: (a) Resnati, G.; Soloshonok, V. A., Eds. *Tetrahedron* **1996**, *52*, 1. (b) Olah, G. A.; Chambers, R. D.; Prakash, G. K. S. *Synthetic Fluorine Chemistry*; Wiley: New York, 1992.

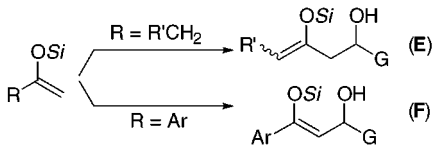
(8) Reviews: (a) Soloshonok, V. A., Ed. *Enantiocontrolled Synthesis of Fluoro-organic Compounds*; John Wiley & Sons: Chichester, 1999. (b) Ojima, I., McCarthy, J. R., Welch, J. T., Eds. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, D.C., 1996. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385.

(9) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.

(10) 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*-**4d**,**f**: 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*) for *anti*-**4d**, t_R = 28 min (2*R*,3*S*), 64 min (2*S*,3*R*) for *anti*-**4f**. *anti*-**4e**: Daicel, CHIRALPAK AS, *n*-hexane/*i*-PrOH 95:5, 0.8 mL/min, 254 nm, t_R = 19 min (2*R*,3*S*), 37 min (2*S*,3*R*).

yield) formation of the F−C product (**3c**) in excellent yields and enantioselectivity (run 3). Furthermore, the F−C product was also obtained in the reaction with glyoxylate esters. However, only the usual aldol product was detected in the reaction with benzaldehyde. The reaction of silyl enol ethers (**2d**,**e**,**f**)[12] bearing a methyl substituent at the α position also gave F−C products (**3d**,**e**,**f**) with similarly high enantioselectivity (runs 4−6).[10] Under Mukaiyama-aldol conditions catalyzed by the BINOL-Ti complex (Scheme 3), aliphatic

Scheme 3



ketone-derived silyl enol ethers (R = R′CH_2) yield the ene-type homoallylic alcohol products (**E**).[5e] In sharp contrast, the aromatic ketone-derived silyl enol ethers (R = Ar) now yielded the allylic (**F**) rather than homoallylic alcohol products.

The stereochemical assignment of the F−C products (**3a**,**d**,**e**,**f**) deserves special comment. On the basis of the chemical shifts of two types of allylic protons in the ^{1}H NMR spectra, the major isomers of the F−C products (**3**) were determined to be *Z* (Figure 1).[13] The major isomer of the

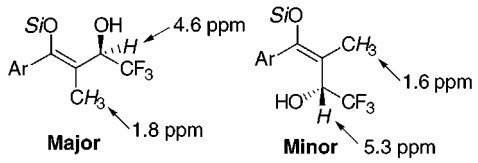
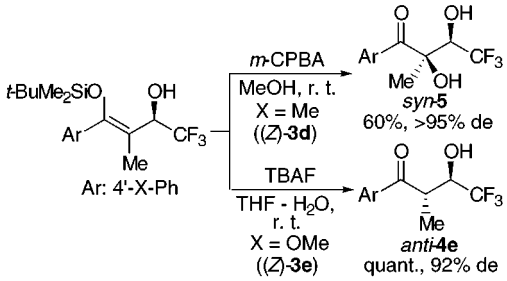


Figure 1. Chemical shifts in ^{1}H NMR spectra.

F−C product (**3c**) was also determined to be *Z* on the basis of similarities in their movement on TLC and the chemical shift of hydroxyl proton in the ^{1}H NMR spectra. The absolute configuration of (*Z*)-**3e** was determined to be *R* by Mosher's method.[14] Thus, the sense of asymmetric induction was the same as that observed in BINOL-Ti-catalyzed asymmetric reactions such as the carbonyl-ene[15] reaction; the (*R*)-BINOL-Ti catalyst produces an (*R*)-alcohol product.

The sequential diastereoselective reactions of the silyl enol ether products were then examined with electrophiles (Scheme 4). However, the epoxidation reactions of the

Scheme 4



tetrasubstituted silyl enol ethers (**3**) involve two conflicting allylic (A) strains ($A^{(1,3)}$ vs $A^{(1,2)}$) (Figure 2).[16,17] (*Z*)-Allylic

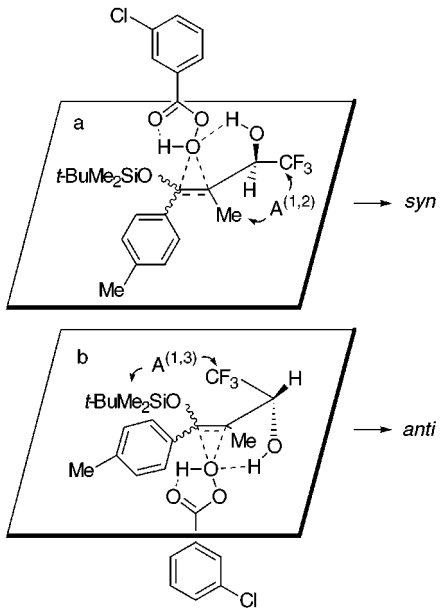


Figure 2. Transition state of epoxidation by *m*-CPBA.

alcohols are generally reported to be epoxidized with high *syn* (*threo*) selectivity due to the strong $A^{(1,3)}$ strain (Figure 2a). In cotrast, *anti* (*erythro*) selectivity is reported in the large $A^{(1,2)}$ strain (Figure 2b). The oxidation reaction of the F−C product by *m*-CPBA proceeded, however, highly diastereoselectively and yielded the *syn*-diastereomer in its unprotected form.[18]

(11) The F−C products were not obtained in the reaction of aliphatic ketone-derived silyl enol ethers without aromatic substituents such as 1-*tert*-butyldimethylsilyloxy-1-cyclohexene and 2-*tert*-butyldimethylsilyloxy-1-heptene.

(12) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. See ref 1b.

(13) Both vinylic proton and allylic proton of the major isomer are observed at upper field than the minor one in ^{1}H NMR spectra ($CDCl_3$) of **3a** (vinylic proton, 5.08 ppm (major), 5.15 ppm (minor); allylic proton, 4.46 ppm (major), 4.98 ppm (minor)): Rummens, F. H. A.; de Haan, J. W. *Org. Magn. Res.* **1970**, *2*, 351.

(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. The chemical shift of vinylic methyl proton in ^{1}H NMR spectra ($CDCl_3$) of MTPA ester of (*Z*)-**3e**: 1.79 ppm (*S*), 1.55 ppm (*R*); $\delta_S - \delta_R$ = positive.

(15) (a) Corey, E. J.; Barnes-Seeman, D.; Lee, T. W.; Goodman, S. N. *Tetrahedron Lett.* **1997**, *37*, 6513. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; **1989**, *111*, 1940.

(16) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

The relative configulation of the diol product **5** was determined to be *syn* by X-ray analysis of a single crystal (Figure 3).[19] The sterically highly demanding trifluoromethyl

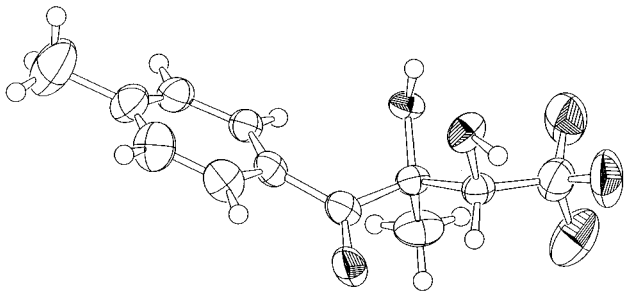


Figure 3. ORTEP drawing of *syn*-**5**.

substituent is located outside because of the larger $A^{(1,3)}$ strain with either the sterically demanding silyl or aromatic groups depending on the geometry. Likewise, the protodesilylation reaction of the F−C product ((*Z*)-**3e**) was also highly stereoselective to give the *anti*-diastereomer but in a similar stereoselective manner to that shown in *m*-CPBA oxidation (Scheme 4).[20,21]

In summary, we have reported the Friedel−Crafts-type reaction of silyl enol ethers as a possible mechanism in the Mukaiyama-aldol reaction. In addition, the sequential diastereoselective reactions of the resultant silyl enol ether products with electrophiles were shown to give highly functionalized trifluoro aldols with high enantio- and diastereoselectivity.

Supporting Information Available: Experimental details and spectral data for (*Z*)-**3a**,**c**−**f**, *syn*-**5** and *anti*-**4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Schwesinger, R.; Willaredt, J. In *Houben-Weyl E21*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 8. (b) Sharpless proposed the formation of hydrogen bond between hydroxy groups and *m*-CPBA: Sharpless, K. B.; Verhoeven, T. R. *Aldrichimca Acta* **1979**, *12*, 63. (c) Berti, G. In *Topics of Stereochemistry*; Allinger, N. L., Eliel, E. L., Eds.; Wiley: New York, L 1973; Vol. 7, pp 141, 147. (d) Vedejs, E.; Dent, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6861. (e) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1862. (f) Mihelich, E. D. *Tetrahedron Lett.* **1979**, *20*, 4729. (g) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733. (h) Chautemps, P.; Pierre, J.-L. *Tetrahedron* **1976**, *32*, 549. (i) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. B* **1970**, 1374.

(18) The diastereomeric excess of α,*β*-dihydroxy ketone (**5**) was determined to be >95% by ^{1}H and ^{19}F NMR analysis. The relative configuration was estimated to be *syn* on the basis of the chemical shifts of α-methyl carbons in ^{13}C NMR spectra ($CDCl_3$) of **5** (*syn* 23.4 ppm, *anti* 25.1 ppm): Heathcock, C. H.; Pirrung M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294.

(19) The single-crystal growth was carried out in a 1:1 *n*-hexane/dichloromethane mixed solvent at room temperature. X-ray crystallographic analysis was performed with a Rigaku AFC7R diffractometer (graphite monochromator, Mo Kα radiation, $\lambda = 0.71069$ Å). The structure was solved by direct method (SIR92), expanded using Fourier techniques (DIRDIF94), and full-matrix least-squares refinement (SHELXL-93). Crystal data for $C_{12}H_{13}F_3O_3$, colorless, crystal dimensions 0.30 × 0.20 × 0.10 mm, monoclinic, space group $P2_1$ (no. 4), $a = 10.345(2)$, $b = 10.538(3)$, $c = 11.747(2)$ Å, $\beta = 90.97(1)°$, $V = 1280.3(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.360$ g cm^{-3}, μ (Mo Kα) = 1.24 cm^{-1}, $T = 233$ K, 3112 reflections were independent and unique, and 1754 with $I > 2\sigma(I)$ ($2\theta_{max} = 55.0°$) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. $R = 0.042$, $Rw = 0.156$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-133938. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB@ 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). We are grateful to Dr. Masahiro Terada for his useful discussion and technical support on the X-ray analysis.

(20) The *anti*-diastereomer selectivity of α-methyl-*β*-hydroxy ketone (**4e**) was determined to be 96% by HPLC analysis (Daicel, CHIRALPAK AS, *n*-hexane/*i*-PrOH 95:5, 0.8 mL/min, 254 nm, $t_R = 16$ min (*syn*), 37 min (*anti*)).

(21) The relative configuration was determined to be *anti* on the basis of the chemical shifts of α-methyl carbon in ^{13}C NMR spectra ($CDCl_3$) of **4d** (*syn* 11.9 ppm, *anti* 16.3 ppm), **4e** (*anti* 16.5 ppm), respectively. See ref 18.