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Dipole Interaction-Controlled Stereoselectivity in Aldol Reaction of α-CF_3 Enolate with Fluoral

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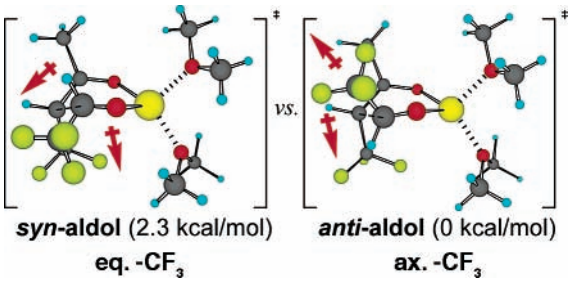
ABSTRACT



The stereoselectivity of a reaction is generally determined by minimizing steric repulsion. However, the aldol reaction of α-CF_3-ketone (*Z*)-enolate with fluoral anomalously gave an *anti*-aldol through a sterically demanding transition state, because of the strong dipole interaction of the two CF_3 groups. We have thus disclosed a paradigm shift from steric to electronic control of reaction stereoselectivity.

Development of stereoselective reactions is one of the most important topics in modern synthetic chemistry. Most of the stereoselective reactions reported so far have been designed on the basis of steric repulsion to attain large steric energy differences between two or more diastereomeric transition states.[1] In the preceding paper, we reported that the Baeyer−Villiger reaction of α-CF_3-ketone proceeds through a sterically demanding transition state with the bulky CF_3 group in axial orientation due to the stereoelectronic requirement (Figure 1).[2]

Therefore, we thought that strong dipole interaction could overcome the steric factor to determine not only the regioselectivity but also the stereoselectivity of a reaction via a sterically demanding transition state.

Aldol reaction is one of the most important carbon−carbon bond-forming reactions in organic synthesis. The chairlike six-membered transition state model proposed by Zimmerman and Traxler[3] is widely accepted with oxophilic metal enolates such as B and Ti. Syn and anti diastereoselectivity is often discussed on the basis of 1,3-diaxial repulsion between R and R′ groups, and the reaction proceeds through a less sterically demanding conformation (**TS1′**) with equatorial R (Figure 2). We considered that the aldol reaction of α-CF_3-carbonyl compounds with fluoral would be a good model for demonstrating the dipole interaction-controlled diastereoselective reaction, because the reaction might

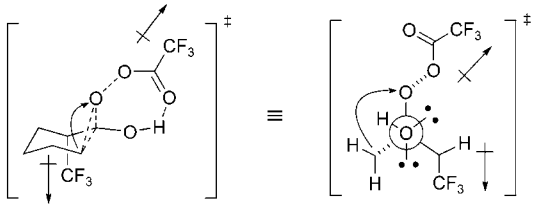


Figure 1. Baeyer−Villiger reaction of α-CF_3-ketone.

(1) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley: New York, 1994. (b) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*; Pergamon: London, 1996.

(2) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803−4806.

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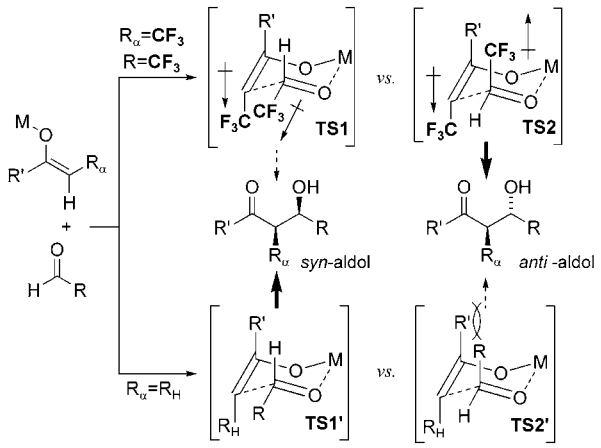


Figure 2. Diastereoselectivity of the aldol reaction.

proceed through a sterically demanding transition state due to the strong dipole interaction between the two CF_3 groups, which should be in diaxial conformation (**TS2**). We herein report an anomalous anti diastereoselectivity controlled by the dipole interaction of the two CF_3 groups in the aldol reaction of α-CF_3 (*Z*)-*O*-enolate with fluoral.

Ab initio molecular orbital calculation of the transition state (**TS**) of the aldol reaction of α-CF_3-acetone with fluoral was carried out at the MP2/6-31G*//HF/6-31G* level.[4,5] In addition, the aldol reaction of α-CH_3-acetone and acetaldehyde was also carried out as a reference. The enolate conformation was set to be (*Z*) to maximize the dipole interaction, which can control the diastereoselectivity. The optimized transition structures of aldol reaction have already been reported by the use of Li- or B-enolate.[6] Therefore, we employed Me_2O-coordinated Li-enolate as a chemical model to compare two diastereomeric **TS**s in the case of α-CH_3 and α-CF_3-enolate (Figure 3).[7]

Two diastereomeric transition structures optimized as stationary points were in the half-chair form, which were almost the same as in Houk's calculation (Figure 3).[6] In the case of the CF_3 substituent, however, **TS2** bearing sterically demanding *vic*-diaxial conformation of the CF_3 group leading to the anti diastereomer was 2.3 kcal/mol more stable than its diastereomeric **TS1**. The sterically demanding diaxial selectivity of CF_3 substituents could be attributed to the strong dipole interaction of the two CF_3 groups, as depicted in Figure 2. In sharp contrast, in the case of a sterically less

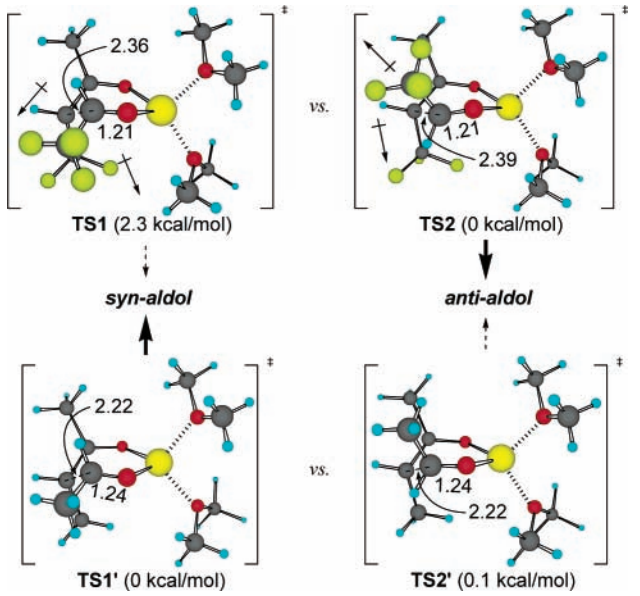
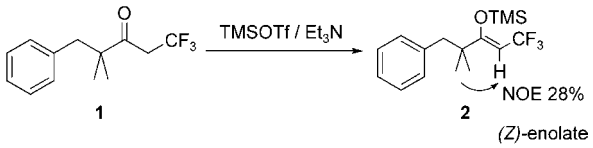


Figure 3. Transition state calculation of aldol reaction. The numbers are the distances in Å. The color of the atoms is as follows: black, carbon; blue, hydrogen; red, oxygen; green, fluorine; yellow, lithium.

demanding CH_3 substituent,[8] without strong dipole interaction, **TS1′** with CH_3 in an equatorial orientation is favorable, though only by 0.1 kcal/mol. Therefore, the strong dipole interaction would be effective in directing the sterically more demanding CF_3 group in axial orientation (**TS2**) to produce *anti*-aldol product.[9] On the basis of these calculations, we were encouraged to carry out the reaction to prove that the dipole interaction could lead to an anomalous *anti*-diastereoselectivity of (*Z*)-enolate.

1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**) was adopted as the substrate because the bulky substituent *s*-trans to the CF_3 group might prevent the formation of (*E*)-enolate and hence provide the desired (*Z*)-enolate. In fact, when the substrate was transformed to silyl enol ether, only (*Z*)-enolate was obtained on the basis of NMR experiment (Scheme 1).

Scheme 1. Formation of (*Z*)-Enolate



Ti-enolates, particularly derived from a Ti/amine system,[10,11] are known to force their aldol reactions to proceed

(3) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920−1923.

(4) All calculations were performed using the Gaussian 98 program package (Gaussian, Inc.: Pittsburgh, PA, 1998).

(5) Hehre, W. J.; Radom, L.; von Ragué Schleyer, P.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986; see also references therein.

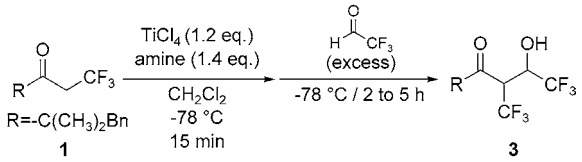
(6) (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3684−3686. (b) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493.

(7) Calculations with Ti-enolate of α-CF_3-acetaldehyde and fluoral were also carried out at the B3LYP/631LAN (LANL2DZ for Ti, 6-31G* for others) level. As expected, **TS1** was more stable (6.4 kcal/mol) than **TS2**.

(8) A-value: Me = 1.70, CF_3 = 2.4−2.5 (kcal/mol). Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139−195.

(9) We have carried out the single-point energy calculation with the self-consistent reaction field (SCRF) method based on the polarized continuum model (PCM, ϵ = 4.355 for ether) at the gas-phase geometry. The result was almost the same (**TS1** is 2.3 kcal/mol stable than **TS2**).

Table 1. Aldol Reaction of α-CF_3-Ketone and Fluoral

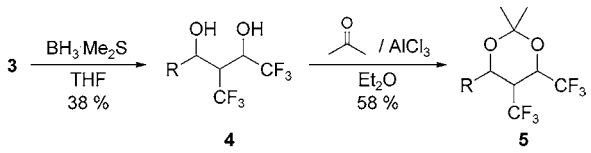


amine	yield [%]	de [%]
n-Bu_3N	83	81
Et_3N	61	79
EtN^iPr_2	41	83
pyridine	–	–

through a cyclic transition state. The Ti/amine system was found to be effective for the aldol reaction using the substrate **1** with fluoral (Table 1).[12] The product could be obtained in good to high yield along with high diastereoselectivity. The yields depend on the amine employed, probably due to the polymerization of the fluoral.[13]

Determination of the relative stereochemistry is the key to prove the dipole interaction-controlled anti diastereoselectivity.[14] Therefore, we converted the aldol product to acetonide by reduction (BH_3·Me_2S) and successive protection of the 1,3-diol (acetone/$AlCl_3$) to determine the relative stereochemistry.

Scheme 2. Conversion of the Aldol Product to Acetonide



First, relative stereochemistry of the 1,3-diol (**4**) could be determined by the difference of the NMR chemical shift of the acetonide carbon according to Rychnovsky's method.[15] In this case, the difference was 2.7 ppm, and hence the 1,3-diol (**4**) has an anti conformation. By considering the bulkiness of the substituent R (^{n}Bu), one CF_3 group (described as $^BCF_3$ in Figure 4) could be determined to be in axial orientation.

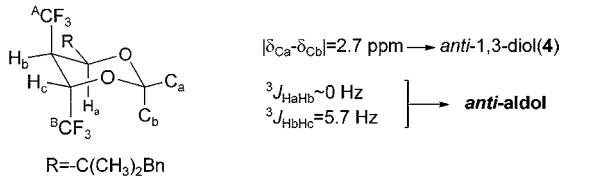


Figure 4. Determination of the relative stereochemistry.

Next, the orientation of $^ACF_3$ should be determined by analyzing the coupling constants of the acetonide. $^3J_{HaHb}$ (~0 Hz) and $^3J_{HbHc}$ (5.7 Hz) could be strong evidence for diaxial conformation of the two CF_3 groups, and thus the aldol product has anti stereochemistry (Figure 4).

In conclusion, we have demonstrated that a strong dipole interaction of the two CF_3 groups could overcome the steric repulsion to determine the stereochemistry of the aldol reaction of α-CF_3-ketone with fluoral.[16] Thus, we have disclosed a paradigm shift from steric to electronic control of reaction stereoselectivity; strong dipole interaction could overcome the steric effect to control not only the regioselectivity but also the stereoselectivity.

Acknowledgment. Generous allotment of computational time from the Institute for Molecular Science, Okazaki, Japan, is greatly acknowledged.

Supporting Information Available: NMR spectral data of the aldol product, a detailed experimental procedure, and Cartesian coordinates of the calculation model. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) With the Ti-amine system, there are many examples that support the formation of (*Z*)-enolate to give *syn*-aldol product via a cyclic TS. (a) Harrison. C. R. *Tetrahedron Lett.* **1987**, *28*, 4135−4138. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866−868. (c) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (d) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049. (d) Esteve, C.; Ferreró, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 5079−5082. (e) Tanabe, Y.; Matsumoto, N.; Higashi, T.; Misaki, T.; Itoh, T.; Yamamoto, M.; Mitarai, K.; Nishii, Y. *Tetrahedron* **2002**, *58*, 8269−8280. (f) Solsona, J. G.; Romea P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519−522.

(11) Characteristics of the $TiCl_3$-enolate and its aldol reaction: (a) Nakamura, E.; Shimada, J.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3341−3342. (b) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, *24*, 3343−3346.

(12) Typical experimental procedure. To a solution of 1,1,1-trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (**1**) (48.9 mg, 0.2 mmol) in dichloromethane (2 mL) was added titanium tetrachloride (26.3 μL, 0.24 mmol) at 0 °C, and the mixture was stirred for 10 min under an argon atmosphere. Then, the reaction mixture was cooled to −78 °C and added tributylamine (66.7 μL, 0.28 mmol) at this temperature. The reaction mixture was stirred for 15 min, and then an excess amount of freshly distilled fluoral was added. After stirring for 4 h at −78 °C, the reaction mixture was quenched by adding phosphorous buffer (pH = 7) at this temperature. The mixture was extracted three times with ether. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The crude mixture was purified by silica gel column chromatography (hexane/acetone = 10:1). 5-Hydroxy-2,2-dimethyl-1,5-diphenyl-4-trifluoromethyl-3-pentanone (**3**, 56.7 mg, 83%) was obtained.

(13) In the case of *n*-Bu_3N, fluoral could be introduced smoothly into the reaction mixture with moderate polymerization. But in the case of EtN^iPr_2, significant polymerization occurred and the reaction mixture was capped with gummy "polyfluoral" to avoid further introduction of the fluoral into the reaction mixture. In the case of Et_3N, polymerization also occurred but not as significantly as in the case of EtN^iPr_2. For pyridine, the reaction did not proceed at all probably due to the fact that it is able to make a complex with $TiCl_4$ to prevent deprotonation at the enolization step.

(14) Usual protocol for determining the relative stereochemistry by the ^{1}H-coupling constant (Jeffery, E. A.; Meisters, A.; Mole, T. J. *Organomet. Chem.* **1974**, *74*, 373−384) could not be used because of the small coupling constant of the aldol product (J = 2.8 Hz).

(15) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(16) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, in press.