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Conformational Fixation of Enolates by Intramolecular Metal···Fluorine Interaction

Takashi Yamazaki,*,† Makoto Ando,† Tomoya Kitazume,† Toshio Kubota,‡ and Masao Omura‡

Department of Bioengineering, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226−8501, Japan, and Department of Materials Science, Ibaraki University, Nakanarusawa 4-12-1, Hitachi, Ibaraki 316-8511, Japan

tyamazak@bio.titech.ac.jp

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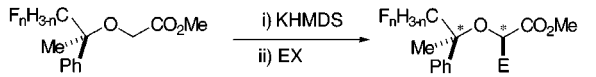
ABSTRACT



MeI: 82-90% de (n=1-3), 56% de (n=0)
BnBr: 80-84% de (n=1-3), 48% de (n=0)
Allyll: 62-72% de (n=1-3), 28% de (n=0)

Methyl acetates with fluorine-containing auxiliaries at their 2 position were demonstrated to react smoothly with various electrophiles in a *re* face preferential manner (up to 90% de). This was interpreted as the result of an intermediary enolate constructing a bicyclo[3.3.0] system by the concomitant intramolecular chelation of a metal with α-oxygen and fluorine, resulting in the auxiliary effectively blocking attack from the opposite *si* face.

Stereoselective introduction of electrophiles α to a carbonyl moiety has been extensively investigated.[1] For instance, esters or amides possessing stereogenic center(s) at the corresponding alcohol or amine, respectively, sometimes demonstrate excellent diastereoselectivities by successful formation of conformationally rigid enolates leading to ready discrimination of two enolate π faces. On the other hand, while it seems to be an intriguing and promising route to stereoselectively construct a new carbon−carbon bond with the aid of an auxiliary directly connected to the reaction site, only a small number of examples have appeared in the literature thus far.[2]

This led us to investigate the diastereoinducing ability of tertiary alkoxy auxiliaries at the 2 position of methyl acetate. Our present plan is based on the expectation that fluorine in **1** (R═$CH_{3-n}F_n$, $n = 1-3$) would successfully participate in fixation of enolate conformations[3] by intramolecular F···metal interaction.[4,5] If this is really the case, the environment around two enolate π faces becomes more or less different, which consequently results in diastereofacially discriminating reactions with appropriate electrophiles. To inspect such ability in detail, three types of fluorinated substrates **1a**, **1b**, and

† Tokyo Institute of Technology.
‡ Ibaraki University.

(1) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 1. (b) *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Seyden-Penne, J., Ed.; John Wiley & Sons: New York, 1995; p 157.

(2) α-R*$_2$N substrates: (a) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1998**, *63*, 2382. (b) Blaser, D.; Ko, S.-Y.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 6230. (c) Tabcheh, M.; El Achqar, A.; Pappalardo, L.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4611. (d) Chaari, M.; Jenhi, A.; Lavergne, J.-P.; Viallefont, P. *Tetrahedron* **1991**, *47*, 4619. (e) McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chadha, R. *J. Org. Chem.* **1988**, *53*, 1947. α-R*O substrates: (a) Fujita, M.; Lainé, D. Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1647. (b) d'Angelo, J.; Pagès, O.; Maddaluno, J.; Sumas, F.; Revial, G. *Tetrahedron Lett.* **1983**, *24*, 3951. See also Touzin, A. M. *Tetrahedron Lett.* **1975**, 1477.

(3) (a) Ooi, T.; Kagoshima, N.; Uraguchi, D.; Maruoka, K. *Tetrahedron Lett.* **1998**, *39*, 7105. (b) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754. (c) Ooi, T.; Kondo, Y.; Miura, T.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 3951.

(4) (a) Yamazaki, T.; Kitazume, T. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A., Ed.; John Wiley & Sons: New York, 1999; Chapter 19. (b) Murphy, E. F.; Murugavel, R.; Roesky, H. W. *Chem. Rev.* **1997**, *97*, 7, 3425. (c) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363.

(5) Although such interaction has been computationally expected, very little experimental evidence has been reported on the metal···fluorine interaction. See ref 4 for details.

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1c, were prepared as their racemic forms along with nonfluorinated **1d** with an isopropyl group, sometimes referred to as a steric equivalent to a CF_3 moiety,[6] as a reference.

First, trifluoromethyl-containing ester **1a** was subjected to conditions under various combinations of bases and solvents, and the resultant enolate solution was then treated with benzyl bromide as a representative electrophile (Scheme 1,

Scheme 1

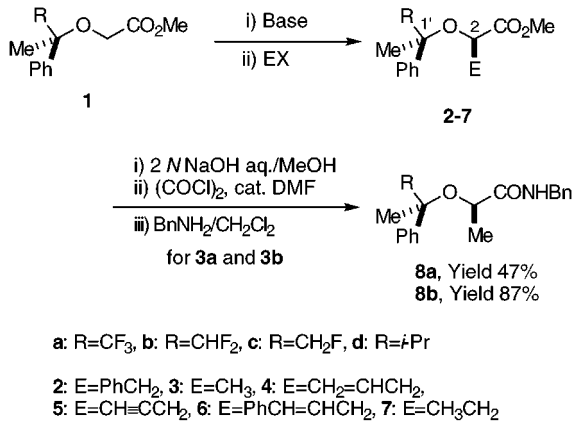


Table 1). Although bases with lithium as a countercation provide low yields of product **2a** (entries 1 and 2), KHMDS proved to work quite efficiently to form **2a** in 79% isolated yield with 80% diastereomeric excess (entry 4). Use of Et_2O instead of THF resulted in a decrease of enolate reactivity (entry 5). Further study allowed us to conclude that the best condition would be employment of 1.2 equiv of KHMDS as a base[7] in THF at −78 °C along with the addition of 1.2 equiv of an appropriate electrophile to the resultant potassium enolate.

Reactions of the trifluorinated substrate **1a** were carried out with various active electrophiles under the conditions depicted above (entries 7−13),[8,9] and it was observed as the general trend that alkylation furnished the products **2a** to **6a** in good to excellent yields with diastereoselectivities (DS) in the range of 68−90% de. Addition of HMPA affected DS values of products only slightly (entries 8 and 9), and sufficiently increased the enolate reactivity to form the adduct **7a** with ethyl iodide which could not be obtained at all without this additive (entry 14).

Table 2 describes the results (yields and steric factors[8,10]) when esters **1a** to **1d** are independently reacted with such typical electrophiles as methyl iodide, benzyl bromide, and allyl iodide. A stepwise decrease of the number of fluorine atoms resulted in lower alkylation yields while the DS values of the products did not seem to be remarkably influenced as long as substrates contained at least one fluorine atom. In quite a sharp contrast, the nonfluorinated counterpart **1d** was found to be the less potent nucleophile especially in terms of diastereoselectivity, 30−40% lower than the others. Relative stereochemistries of **3a** and **3b** were unambiguously clarified as 1′*S**,2*R** by X-ray crystallographic analyses after their derivatization into the corresponding benzyl amides **8a** and **8b**,[8,11,12] respectively, with complete retention of the original DS values (Scheme 1).

Table 1. Reaction of **1a** with Various Electrophiles[a]

entry	EX	time (h)		yield[b] (%)	DS (% de)
1[c]	$PhCH_2Br$	2.0		(12)	86
2[c]	$PhCH_2Br$	1.0		(trace)	
3[c]	$PhCH_2Br$	2.0		(41)	76
4	$PhCH_2Br$	2.0	79	(85)	80
5[d]	$PhCH_2Br$	14.0		(9)	83
6[e]	$PhCH_2Br$	1.5		(37)	75
7	MeI	1.0	67	(80)	90
8[f]	MeI	1.0		(69)	80
9[f]	MeI	1.0		(40)	76
10	CH_2=$CHCH_2I$	1.5	82	(85)	68
11	CH_2=$CHCH_2Br$	2.0	32	(58)	70
12	CH≡CCH_2Br	0.5	60	(68)	80
13	(*E*)-PhCH=$CHCH_2I$	2.0	58	(61)	76
14[f]	EtI	2.0	37	(37)	76

[a] Unless otherwise noted, 1.2 equiv of KHMDS was added to **1a** in THF at −78 °C, and after 0.5 h, an appropriate electrophile (1.2 equiv) was added. [b] The yield determined by ^{19}F NMR is shown is parentheses. [c] LDA, LHMDS, and NaHMDS were employed instead of KHMDS in entries 1, 2, and 3, respectively. [d] In Et_2O. [e] Reaction was conducted at 0 °C. [f] 3.0, 10.0, or 1.0 equiv of HMPA (entries 8, 9, or 14) was added prior to addition of KHMDS, respectively.

Table 2. Representative Reaction Results

	isolated yield (%) [DS, % de]			steric factors[a]	
R	MeI	$PhCH_2Br$	allyl-I	Es	Es′
CF_3 (**1a**)	67 [90]	79 [80]	82 [68]	−1.16	−0.78
CHF_2 (**1b**)	58 [88]	45 [84]	61 [72]	−0.67	−0.32
CH_2F (**1c**)	50 [82]	41 [84]	49 [62]	−0.24	−0.20
i-Pr (**1d**)	50 [56]	31 [48]	77 [28]	−0.47	−0.48

[a] Es: Taft steric constant with reference to a methyl group (Me: 0.00). Es': revised Taft steric constant by Dubois and co-workers. Me: 0.00. Ph: −2.31.

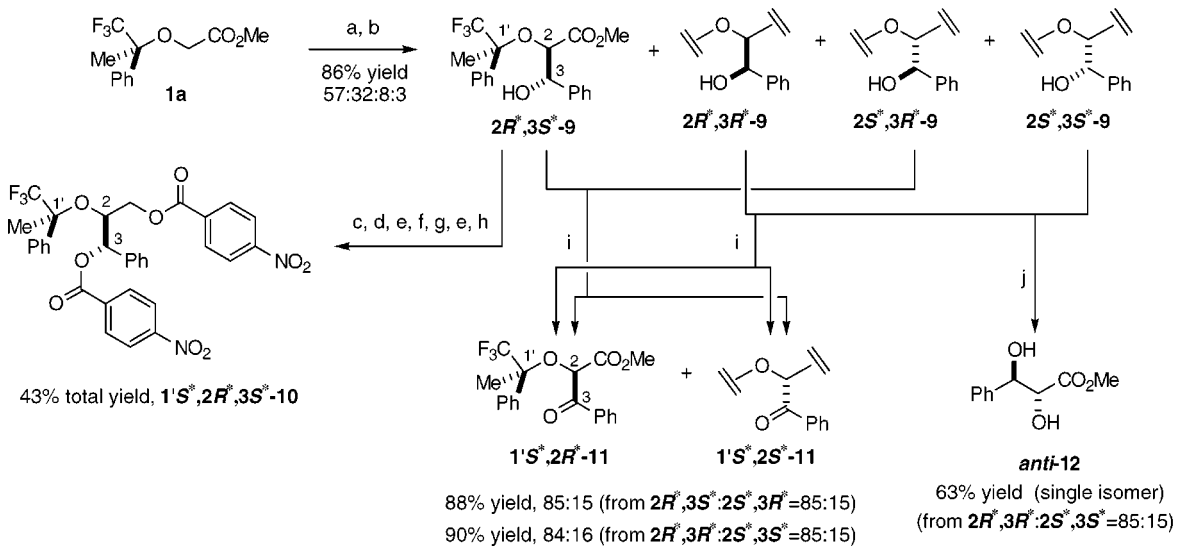
A similar diastereofacial preference was demonstrated when benzaldehyde was employed as an electrophile. Thus, as shown in Scheme 2, **1a** furnished all possible stereoisomeric mixtures of **9**[8] in a ratio of 57:32:8:3 which were chromatographically separated into two groups consisting of the first and third compounds (**2*R**,3*S**-9** and **2*S**,3*R**-9**, respectively) and the second and fourth isomers (**2*R**,3*R**-9** and **2*S**,3*S**-9**, respectively). Independent oxidation of these two groups by PDC did not affect the original isomeric ratios,

(6) (a) Weseloh, G.; Wolf, C.; König, W. A. *Chirality* **1996**, *8*, 441. (b) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618. See also: Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *Chem. Pharm. Bull.* **1991**, *39*, 233.

(7) KHMDS was used after evaporation of the original solvent, toluene, under reduced pressure.

(8) All new products showed satisfactory spectral as well as analytical data.

Scheme 2[a]



[a] Reagents and conditions: (a) KHMDS/THF, (b) PhCHO, (c) DHP, PPTS/CH_2Cl_2, (d) LAH/Et_2O, (e) *p*-TsOH/MeOH, (f) $Me_2C(OMe)_2$, *p*-TsOH/DMF, (g) chromatographic separation, (h) *p*-NO_2-$C_6H_4C(O)Cl$, pyridine/CH_2Cl_2, (i) PDC, Ac_2O/CH_2Cl_2, (j) BCl_3/CH_2Cl_2

and BCl_3-mediated removal of the CF_3-containing auxiliary from the latter combination yielded a single anti isomer, ***anti*-12**.[13] Moreover, the relative stereostructure of bis-*p*-nitrobenzoate **10** derived from the major diastereomer **(2*R**,3*S**)-9** was unambiguously determined as (1′*S**,2*R**,3*S**) by X-ray crystallographic analysis.[12] These three independent transformations led to unambiguous confirmation of relative stereochemical relationship of **9** as (2*R**,3*R**), (2*S**,3*R**), and (2*S**,3*S**) for the second to fourth isomers, respectively. Consequently, this result demonstrated that the enolate diastereofacial selectivity was 89:11, again in favor of the *re* face attack.

To obtain further mechanistic insight, **1a** was transformed into the corresponding ketene silyl acetal and NMR analysis of the crude product indicated the formation of a single stereoisomer.[14] Considering the fact that 2-alkoxy esters in general furnish *Z*-enolates in a preferential fashion,[15,16] the present diastereoselectivity would be the reflection of the exclusive formation of *Z*-potassium enolate from **1a**, followed by the preferential reaction at its *re* face.

(9) A solution of **1a** (0.5 mmol) in THF (1.5 mL) was added dropwise to a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene (*removed prior to use*), 1.2 mL, 0.6 mmol) in THF (0.5 mL) at −78 °C. After 30 min, methyl iodide (0.60 mmol) was added, and the mixture was stirred at that temperature. After the reaction was quenched with saturated aqueous NH_4Cl, extraction was carried out with ethyl acetate three times, and the combined organic layers were washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, and concentrated. The desired material was obtained after purification by silica gel chromatography (hexane:AcOEt = 9:1): combined yield 79% (a 90:10 diastereoisomer mixture); ^{1}H NMR major isomer δ 1.68−1.72 (3 H, m), 3.01 (1 H, dd, J = 5.5, 13.5 Hz), 3.08 (1 H, dd, J = 8.0, 14.0 Hz), 3.67 (3 H, s), 3.96 (1 H, dd, J = 5.5, 8.5 Hz), 7.11−7.35 (5 H, m); minor isomer (representative peaks are shown) δ 1.79−1.81 (3 H, m), 3.49 (3 H, s), 4.22 (1 H, dd, J = 5.5, 8.0 Hz); ^{13}C NMR δ 17.48, 40.05, 51.58, 74.23, 80.67 (q, J = 28.5 Hz), 124.56 (q, J = 283.1 Hz), 126.77, 127.75, 127.85, 128.00, 128.19, 128.83, 129.60, 134.87, 135.71, 172.97; ^{19}F NMR major isomer δ 82.05 (s); minor isomer δ 83.44 (s); IR (neat) ν 3060, 3030, 2950, 1760 cm^{-1}. Anal. Calcd for $C_{19}H_{19}O_3F_3$: C, 64.77; H, 5.43. Found: C, 64.40; H, 5.20.

(10) For Es value, see: Taft, R. W., Jr. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley & Sons: New York, 1956; p 556. For the revised Es value, Es', see: MacPhee, J. A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553.

(11) 2 N aqueous NaOH (0.75 mL) was added to a solution of **2a** (0.36 g, 1.0 mmol) in MeOH (1.0 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 1 d. Crude carboxylic acid thus obtained was treated with $(COCl)_2$ (0.18 mL, 2.0 mmol) and a catalytic amount of DMF, and the solution was stirred overnight and then reacted with 2.5 mmol of benzylamine. Usual workup and chromatographic purification furnished **8a** in 47% total yield (a 90:10 diastereoisomer mixture): mp 128−129 °C; ^{1}H NMR major isomer δ 1.39 (3 H, d, J = 6.8 Hz), 1.68−1.72 (3 H, m), 3.87 (1 H, q, J = 6.8 Hz), 4.45 (1 H, dd, J = 5.9, 14.7 Hz), 4.50 (1 H, dd, J = 6.1, 14.7 Hz), 6.87−6.92 (1 H, m), 7.26−7.53 (10 H, m); minor isomer (representative peaks are shown) δ 1.46 (3 H, d, J = 6.8 Hz), 1.79−1.81 (3 H, m); ^{13}C NMR δ 16.96, 20.49, 42.86, 71.47, 80.65 (q, J = 28.3 Hz), 124.60 (q, J = 282.7 Hz), 127.39, 127.50, 127.62, 128.17, 128.57, 129.21, 135.61, 137.79, 173.41; ^{19}F NMR major isomer δ 81.49 (s); minor isomer δ 82.58 (s); IR (KBr) ν 3240, 3090, 2950, 1650, 1570 cm^{-1}. Anal. Calcd for $C_{19}H_{20}F_3NO_2$: C, 64.95; H, 5.74; N, 3.99. Found: C, 64.95; H, 5.35; N, 3.92.

(12) **(1′*S**,2*R**)-8a**: $C_{19}H_{20}F_3NO_2$, M = 351.37, colorless prism, orthorhombic, a = 17.215(4) Å, b = 22.638(4) Å, c = 9.416(3) Å, V = 3669(1) Å^3, T = 299.0 K, space group *Pbca* (no. 61), Z = 8, R = 0.036, R_w = 0.036, GOF = 1.75. **(1′*S**,2*R**)-8b**: $C_{19}H_{21}F_2NO_2$, M = 333.38, colorless prism, monoclinic, a = 9.913(4) Å, b = 22.067(5) Å, c = 9.277(4) Å, β = 117.8988°, V = 1793.7(10) Å^3, T = 296.0 K, space group $P2_1/a$ (no. 14), Z = 4, R = 0.031, R_w = 0.031, GOF = 1.67. **(1′*S**,2*R**,3*S**)-10**: $C_{32}H_{25}F_3N_2O_9$, M = 638.55, colorless prism, monoclinic, a = 8.701(4) Å, b = 11.891(3) Å, c = 28.513(4) Å, β = 98.48(2)°, V = 2917(1) Å^3, T = 296.0 K, space group $P2_1/n$ (no. 14), Z = 4, R = 0.041, R_w = 0.042, GOF = 1.44.

(13) Matthews, B. R.; Jackson, W. R.; Jacobs, H. A.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 1195.

(14) Spectroscopic data of the crude mixture was as follows: ^{1}H NMR δ 0.25 (9 H, s), 1.75−1.78 (3 H, m), 3.37 (3 H, s), 5.06 (1 H, s), 7.29−7.45 (3 H, m), 7.48−7.57 (2 H, m); ^{13}C NMR δ 0.09, 18.10, 55.17, 80.97 (q, J = 27.7 Hz), 102.69, 124.96 (q, J = 282.9 Hz), 127.67, 128.06, 128.63, 136.33, 152.66; ^{19}F NMR δ 82.20 (s).

(15) In this text, *E*,*Z* nomenclature for enolates refers to the relative relationship between OR moieties at the 2 position and OM (M: metal) groups.

(16) Since Kanemasa and co-workers reported that methyl 2-(1,1-dimethylethoxy)acetate yielded the ketene silyl acetal in favor of the *Z* isomer (*E*/*Z* = 17/83), our ketene silyl acetal from **1a**, obtained as a single stereoisomer, was believed to have the same stereoisomeric preference. See: Kanemasa, S.; Nomura, M.; Wada, E. *Chem. Lett.* **1991**, 1735.

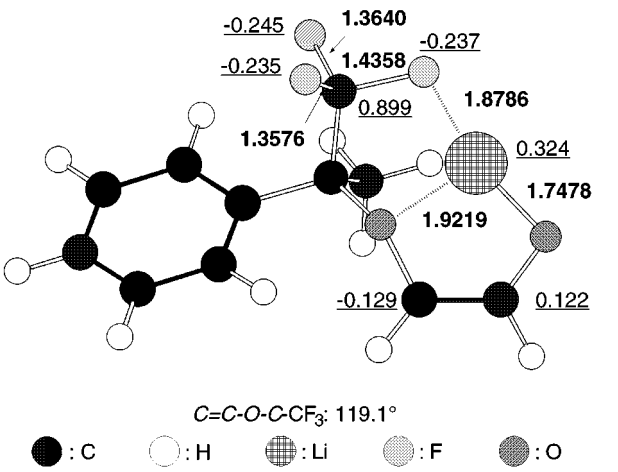


Figure 1. Most stable conformation of the model lithium enolate. Representative **bond lengths (Å)** and Mulliken charges are shown.

We have also performed ab initio computation[17] of the model enolate of **1a**. The Chem3D model of the most stable conformer is depicted in Figure 1. It was quite apparent from this model that, along with the expected intramolecular interaction of α-oxygen and lithium, one of the fluorine atoms in the CF_3 group formed a strong chelation with Li. This was supported by the Li···F distance of 1.879 Å, 0.043 Å shorter than the Li···O distance.[18] Such interaction led to significant elongation of the C−F bond length at the same time (0.072−0.078 Å). The bicyclo[3.3.0] system formed allowed the auxiliary to effectively cover the *si* face with a *C*═*C*−*O*−*C*−CF_3 dihedral angle of 119.1°.[4] The second most stable conformer also included similar Li···F and ···α-O chelation likewise causing steric hindrance around the *si* face, but the auxiliary of the third isomer proved to shield the opposite *re* face of the enolate. Since the energy difference from the most stable form was 0.041 and 0.858 kcal/mol, respectively, the diastereofacial selectivity was anticipated to be as high as 94.6:5.4 at −78 °C, which, at least qualitatively, supported the present stereochemical results.[19]

The present paper describes the high potency of fluorine-containing auxiliaries effectively attaining good to excellent diastereoselectivities where, as we expected, metal···fluorine intramolecular interaction is most likely to successfully fix the enolate conformations. Although extremely high selectivity has not been attained yet, *it is especially worthwhile to note that although the second smallest element, fluorine, merely imposes minimum steric modification, introduction of even one fluorine atom to the prototypical achiral donor* ***1*** *(R = CH_3) realizes effective discrimination between enolate π faces in a ratio of up to 92:8.*

Since the auxiliaries could be removed with complete retention of the original stereochemistry as shown in Scheme 2 (see the conversion of a mixture of **2*R**,3*R**-** and **2*R**,3*R**-9** to ***anti*-12**) and the structurally similar trifluorinated tertiary alcohol was already resolved by O'Hagan's group,[20] the present method could be readily extended to the construction of optically active molecules. Further application of this metal···fluorine interaction along with the judicious design of auxiliaries for improvement of diastereofacial selectivities is underway in our laboratory

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(17) Because of computational limitation, we have considered the *lithium* enolate from **1a** with substitution of an ester methoxy group for hydrogen. This metal change from potassium (actual species) to lithium might be valid as long as this model is employed for the explanation of the diastereofacial selectivity because of their same propensity in the enolate π-facial selection despite poor yield (see entries 1 and 4 in Table 1). All structures were fully optimized with the ab initio software Mulliken implemented in CAChe Worksystem (SONY/Tektronix Corporation) on an IBM RS-6000-3CT workstation at the asdfsadfasMB3LYP/3-21G level of theory.

(18) Since the van der Waals radius of fluorine is 0.05 Å smaller than that of oxygen, interaction of lithium with fluorine would be roughly estimated to be as strong as that with oxygen.

(19) As shown in Table 1, when HMPA was added, the DS values were slightly decreased with the same sense of diastereofacial preference. Computation of the "naked" enolate was also performed to determine that the auxiliary of the most stable conformer covered the *si* face, but the opposite face was shielded by the second most stable isomer, 2.76 kcal/mol higher in energy. These results led to the anticipation that the alkylation would preferentially occur from the *re* face even in the presence of HMPA. Details will be published elsewhere.

(20) O'Hagan, D.; Zaidi, N. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 947.