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Effect of Allylic $CH_{3-n}F_n$ Groups (n = 1–3) on π-Facial Diastereoselection

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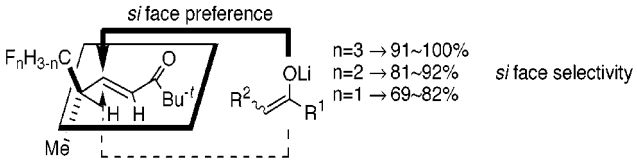
ABSTRACT

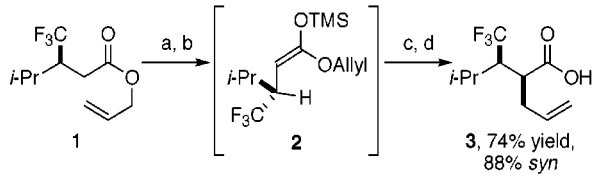


Michael addition of various enolates toward γ-$CH_{3-n}F_n$-α,β-unsaturated ketones (n = 1–3) was proven to smoothly furnish the 1,4-adducts with high *si* face selectivities which monotonously decreased by reduction in the number of fluorines. Although the Felkin–Anh model correctly anticipates the present stereochemical outcome only with *E*-acceptors, the hyperconjugative stabilization of transition states by electron donation from the allylic substituents (the Cieplak rule) successfully explains the π-facial preference of both acceptors at least in a qualitative level.

Stereoselective construction of organic molecules has been one of the central topics in synthetic organic chemistry, and a large number of challenges have been encountered in this field, especially in the diastereotopic π-facial discrimination at sp^2 hybridized carbon atoms.[1] One of the most significant factors for successfully obtaining a satisfactory outcome is, of course, to fix substrate conformations in an effective manner so as to attain maximum discrimination between both π faces by the steric and/or electrostatic effects of neighboring allylic substituents.

During the course of study on the development of novel preparation methods to access fluorine-containing materials in a stereoselective manner,[2] we have recently revealed highly diastereoselective Ireland−Claisen rearrangements (Scheme 1).[3] When a THF solution of ketene silyl acetal **2**[4] was refluxed for 6 h in the presence of a Pd catalyst,[5] the carboxylic acid **3** was produced with 88% *syn* selectivity. Taking into account the fact that the steric size of a CF_3

Scheme 1[a]



[a] (a) LDA/THF; (b) TMSCl; (c) 2.5 mol % $PdCl_2$·$(PhCN)_2$; (d) reflux.

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(1) Gung, B. W.; le Noble, B. Guest editors for the special thematic issue on diastereoselection. *Chem. Rev.* **1999**, *99*, 1067.

(2) (a) Yamazaki, T.; Umetani, H.; Kitazume, T. *Isr. J. Chem.* **1999**, *39*, 193. (b) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Fluorine Chem.* **1999**, *97*, 91. (c) Yamazaki, T.; Hiraoka, S.; Kitazume, T. *Tetrahedron: Asymmetry* **1997**, *8*, 1157.

(3) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140.

(4) The independent reaction demonstrated that the *E*,*Z* ratio of **2** was 92:8 in favor of the *E* isomer. Details will be published elsewhere.

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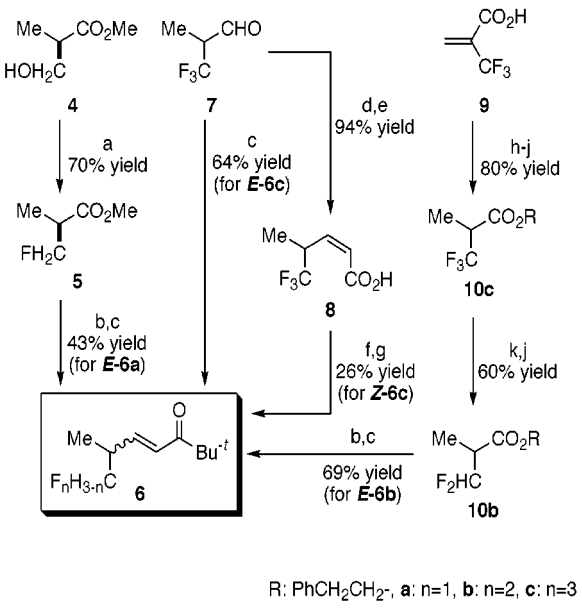
group is regarded to be between *i*-Pr and *i*-Bu moieties,[6] this relatively high *syn* preference should stem from the electrostatic environmental difference between two π-faces. This intriguing example encouraged us to investigate other systems for confirming its generality, and we at first selected Michael addition reactions to substrates with fluorine-containing methyl groups at their allylic positions. In this communication were described the experimental results of enolate-Michael addition to (*E*)-γ-$CH_{3-n}F_n$-α,β-unsaturated ketones **6** ($n = 1-3$) as the representative substrates, which as expected showed a clear correlation between the number of fluorine atoms and diastereofacial selectivities, monotonously decreasing the latter by successive reduction of the former.[7]

Preparation of variously fluorinated Michael acceptors **6** was performed as depicted in Scheme 2. Thus, after

Scheme 2[a]



[a] (a) $Et_2NCF_2CHFCF_3/CH_2Cl_2$; (b) DIBAL/$Et_2O$; (c) $(EtO)_2P(O)$-CH_2−C(O)*t*-Bu, *n*-BuLi/Et_2O; (d) $(PhO)_2P(O)CH_2CO_2Et$, NaH/THF; (e) NaOH/THF−H_2O; (f) AcCl, Et_3N/CH_2Cl_2; (g) *t*-BuMgCl/THF; (h) $C_6H_4(COCl)_2$; (i) $PhCH_2CH_2OH$, pyridine/CH_2Cl_2; (j) 10% Pd/C/ MeOH; (k) LDA/THF.

fluorination of the hydroxy group in **4**,[8] partial reduction followed by in situ condensation of the resultant hemiacetal intermediate[9] furnished the monofluorinated acceptor *E*-**6a** in 30% total yield by way of the Hörner−Wadsworth−Emmons (HWE) reaction. For the synthesis of the corresponding F_3 molecule, direct reaction of commercially available 3,3,3-trifluoro-2-methylpropionaldehyde[10] with the same phosphonate produced *E*-**6c** in 64% yield. On the other hand, construction of the difluorinated counterpart *E*-**6b** was found not to be straightforward. Our first synthetic plan was to start with the S_N2'-type substitution of fluorine in **9** (as the sodium salt) for the hydride[11] and then hydrogenation after derivatization into the corresponding ester. However, because of the detection of an appreciable amount of impurities, we have devised a new route involving deprotonation of the readily available **10c** from **9** as the key step.[12] Close examination of the reaction conditions proved that slow addition of LDA in THF to **10c** dissolved in the same solvent at −78 °C was quite effective in suppressing the possible formation of undesirable byproducts, and the subsequent hydrogenolysis with 10% Pd/C under 0.5 MPa pressure of hydrogen allowed us to isolate the desired **10b** in 60% total yield from **10c**. Its transformation into *E*-**6b** was attained successfully by the similar HWE protocol. In addition to the three types of *E*-**6** thus obtained, the corresponding *Z*-**6c** was also prepared for comparison. Several trials indicated that (diphenyl-phosphono)acetate[13] was the reagent of choice, and the intermediary α,β-unsaturated carboxylic acid **8** was isolated in 86% overall yield as the sole *Z*-isomer.[14] *Z*-**6c** was finally obtained by *tert*-BuMgCl reaction with the corresponding mixed anhydride in 24% yield.

With four requisite acceptors *E*-**6a**−**c** and *Z*-**6c** in hand,[15] enolate-Michael addition reactions were carried out with three representative lithium enolates from propiophenone, ethyl (methylthio)acetate,[16] and *N*,*N*-dimethyl-propionamide whose results are summarized in Table 1. As a general trend, chemical yields as well as diastereomeric ratios of products have a qualitatively proportional relationship with the number of fluorine atoms in the acceptors *E*-**6**. Theoretical molecular orbital calculation[17] of *E*-**6c** suggested its LUMO level of −2.055 eV at the B3LYP/6-31+G* level of theory, about 0.43 eV lower than the corresponding nonfluorinated counterpart, would be at least in part responsible for the higher reactivity of *E*-**6c** compared to the others.

Although all possible four diastereomers were formed when *E*-**6** was treated with the amide enolate, only two isomers were observed for the adducts **11** and **12** from the ketone and ester enolates, respectively. The isomeric acceptor *Z*-**6c** was apparently less reactive, possibly as a result of its

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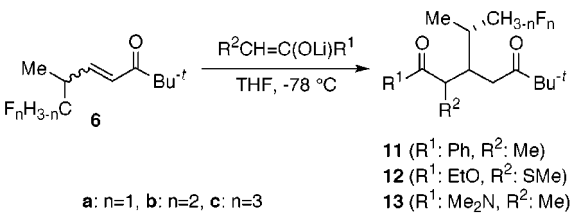
(6) (a) MacPhee, J. A.; Panaye, A. Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553. (b) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha, Gordon, and Breach Science Publisher: Tokyo, 1998; Chapter 1. See also: Béguin, C. G.; Schlosser, M. In *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V., Ed.; John Wiley and Sons: New York, 1999; pp 601 and 613, respectively.
(7) For the discussion of the number of fluorines and stereoselectivity, see: Soloshonok, V. A.; Kacharov, A. D.; Avilov, D. V.; Ishikawa, K.; Nagashima, N.; Hayashi, T. *J. Org. Chem.* **1997**, *62*, 3470.
(8) O'Hagan, D. *J. Fluorine Chem.* **1989**, *43*, 371.
(9) Lanier, M.; Haddach, M.; Pastor, R.; Riess, J. G. *Tetrahedron Lett.* **1993**, *34*, 2469 and references therein.
(10) Distillation with a few drops of BF_3·OEt_2 was required just prior to use for reproducible results.
(11) Fuchikami, T.; Shibata, Y.; Suzuki, Y. *Tetrahedron Lett.* **1986**, *27*, 3173.
(12) Recently, preparation of 3,3-difluoroacrylate was reported; see: Botteghi, C.; Paganelli, S.; Sbrogiò, F.; Zarantonello, C. *Tetrahedron Lett.* **1999**, *40*, 8435 and references therein.
(13) Ando, K. *J. Org. Chem.* **1999**, *64*, 8406.
(14) Initial *E*:*Z* ratio was 3:97 at the HWE step (determined by ^{19}F NMR) while the minor isomer was removed after hydrolysis.
(15) Throughout the text, the configuration of the $CH_{3-n}F_n$-attached carbon in **6** is conveniently fixed as *S* for the simpler stereochemical discussion despite employment of their racemic forms except for the case of *E*-**6a**.
(16) This donor was selected because no 1,4- or 1,2-adducts were provided when ethyl propionate was used.

Table 1. Enolate-Michael Addition Reactions toward **6**[a]



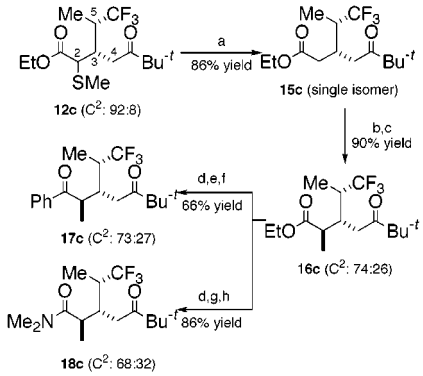
n	R^1	R^2	product	yield (%)	diastereomeric ratio[b]
3	Ph	Me	**11c**	95.0	2.8:97.2
2			**11b**	80.5	7.6:92.4
1			**11a**	76.3	17.6:82.4
3[c]				0[d]	
3	OEt	SMe	**12c**	quant	7.7:92.3 [1 isomer]
2			**12b**	86.0	15.1:84.9 [16.7:83.3]
1			**12a**	76.3	30.9:69.1 [26.3:73.7]
3[c]			**12c**	45.9	<1.0:>99.0
3	NMe_2	Me	**13c**	87.5	3.6: 5.1:30.4:60.9
2			**13b**	74.4	5.0:13.8:30.9:50.3
1			**13a**	78.8	15.6:16.3:34.0:34.1
3[c]			**14c**[e]	87.6	2.2:16.6:28.4:52.8

[a] Two equivalents of an enolate, prepared from a carbonyl compound and LDA in THF at −78 °C, was reacted with an acceptor at −78 °C for 2 h. [b] In the bracket is shown the diastereomeric ratio of **15** observed after removal of the methylthio group from **12**. [c] *Z*-acceptor was employed. [d] No reaction occurred. [e] The corresponding 1,2-adduct was obtained as sole product in the diastereomeric ratio depicted above.

severe steric congestion, and complete recovery of the starting material was observed for the reaction with the propiophenone enolate. On the other hand, high regioselectivity was noticed for the amide enolate, leading to the formation of the undesired 1,2-adduct in high yield. The ester enolate, different from other two enolates, realized the conjugate addition to afford **12c** basically as a single diastereoisomer, which was proven to be identical to the major isomer prepared from *E*-**6c** by spectroscopic comparison.

Stereochemical clarification was carried out as shown in Scheme 3. At first, *n*-Bu_3SnH-mediated removal of a MeS group was performed for obtaining direct information on the π-facial selectivity. This procedure for **12c** yielded **15c** as a single stereoisomer, while the corresponding mono- and difluorinated adducts, **12a** and **12b**, furnished **15a** and **15b** as diastereomeric pairs with the same isomeric ratios, respectively. Thus, **12c** contained two epimeric stereoisomers at C2, but two isomers of **12a** and **12b** were formed as the result of the different π-facial selection.

Scheme 3[a]



[a] (a) *n*-Bu_3SnH, cat. AIBN/PhH; (b) LDA/THF; (c) HMPA, MeI; (d) LiOH/THF−H_2O; (e) DAST; (f) PhMgBr/THF; (g) *t*-BuC(O)Cl, pyridine/ CH_2Cl_2; (h) 50% $HNMe_2$ aq.

At the next stage, methylation of the ketoester **15c** obtained above was carried out, and **16c** was produced as a 74:26 diastereomer mixture, which without further purification was independently converted into **17c** and **18c** with almost complete retention of the original stereochemical integrity (Scheme 3). Spectroscopic comparison of **18c** with the Michael adduct **13c** demonstrated that the major and minor **18c** corresponded to the major and the second major isomers of **13c**, respectively. On the other hand, ready chromatographic separation of the major **13c** enabled us to determine its relative stereochemical relationship as (2*R**,3*R**,5*S**) by the crystallographic technique.[18] These data led to the conclusion that the major and the second major isomers of **13c** should possess (2*R**,3*R**,5*S**) and (2*S**,3*R**,5*S**) stereochemistries, respectively, and the minor two isomers should be (3*S**,5*S**). On the other hand, while the major **17c** was proven to be identical to the major **11c**, the corresponding minor isomers were different from each other, suggesting that two isomers of **11c** were yielded as the result of the opposite diastereofacial selection.

The unambiguous stereochemical assignment for the CF_3 adducts **11c**−**13c** and analogous consideration for the others demonstrated a good to excellent level of *si*-face selection in every instances. These results are summarized in Table 2 along with some parameters of interest in regard to fluorine-possessing methyl groups.

For the reactions with *E*-**6** where R^1 = *t*-BuC(O) and R^2 = H, the Felkin-Anh (FA)-type transition state models are usually employed for the explanation of the product stereochemistry. As shown in Figure 1, because of the undesired steric repulsive interaction between incoming nucleophiles and the allylic substituents, **TS-FA-*si*** is regarded to be more preferable than **TS-FA-*re***. Moreover, an increase in the number of fluorine atoms increases the steric size of $CH_{3-n}F_n$ groups as well as their electron-withdrawing ability (see Table 2), and thus **TS-FA-*si*** preference becomes

(17) *Gaussian 98*, Revision A.7; Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1998.

(18) Crystallographic data for the major diastereomer of **13c** has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 166764.

Table 2. Relationship between Steric Bulkiness of $CH_{3-n}F_n$ Groups vs Diastereofacial Selectivities

				si face selectivity (%)[d]		
n	steric factor[a]	pK_a[b]	$^3J_{H-H}$ (Hz)[c]	ketone	ester	amide
3	−1.90	0.23	8.5[e]	97.2	100	91.3
2	−1.47	1.24	7.4	>92.4	84.9	<81.2
1	−1.32	2.59	7.0	>82.4	69.1	<68.1
0	−1.12	4.76	6.9[f]			
H[g]	0.00	3.75	6.5[f]			

[a] The larger negative value expresses its bulkier steric requirement. See ref 6a. Representative values for the nonfluorinated alkyl groups are as follows.: Et, −1.20; *n*-Pr, −1.43; *i*-Pr, −1.60; *i*-Bu, −2.05; *sec*-Bu, −2.12. [b] The values for $CH_{3-n}F_nCO_2H$ as an index for estimation of the electron-withdrawing ability of the fluorine-containing alkyl groups. [c] Coupling constants between allylic H and carbonyl β-H. [d] Inequality signs were used since the relative stereochemistries were not determined yet. [e] A value of 9.7 Hz was observed for the corresponding *Z*-**6c**. [f] See ref 19. [g] H instead of a $CH_{3-n}F_n$ group.

more pronounced to attain the better diastereoselectivity. This is totally in accord with the experimental results discussed

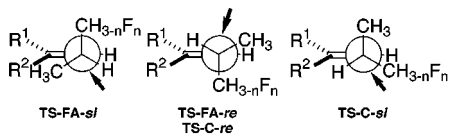


Figure 1. The Felkin-Anh and Cieplak models.

above. However, this is not the case for the corresponding *Z*-**6c**: significant steric disturbance between R^2 (*t*-BuC(O)) and the allylic Me moiety allows **TS-FA-*re*** to be the alternative route, resulting in the erroneous prediction of the diastereoisomers actually obtained if nucleophiles are assumed to approach from the less hindered side.[20]

In constrast, instead of the the FA model, the Cieplak (C) rule is also applicable where hyperconjugation is considered to play a central role in stabilizing transition states by electron donation from the allylic substituents to the incipient antibonding orbital.[21,22] In connection to the fact that Michael additions have been reported to be generally exothermic[23] and their TSs should be early and reactant-like,[24] the two major models to be considered would be **TS-C-*si*** and **-*re***, both stemming from the energetically most favorable conformation with the smallest hydrogen atom located at the inside position. Then, **TS-C-*si***, where the electron-donating methyl group occupies the antiperiplanar position with respect to the incoming nucleophiles, would be more preferable than **TS-C-*re***, almost identical in appearance to **TS-FA-*re***, with an electron-withdrawing fluorine-containing methyl group *anti* to the nucleophiles. Moreover, increasing the number of fluorines will increase the gap in electron-donating ability between Me and $CH_{3-n}F_n$ groups, which also reasonably dictates the observed diastereoselectivity variation. The $^3J_{H-H}$ values shown in Table 2, coupling constants between vinylic H β to the carbonyl group and the allylic H, demonstrated a quite interesting trend, and constant addition of fluorine affects the monotonic increase of the $^3J_{H-H}$ values. This is understood as the result of the larger population of such conformations with inside hydrogen as **TS-FA-*re***, **TS-C-*re***, and **TS-C-*si***, and considering that the transition states really resemble the substrates, it is the Cieplak rule, at least in the present system, which consistently explains the observed π-face selective nucleophilic attack of enolates from the face where bulkier F-containing methyl groups are located.[25]

Supporting Information Available: Experimental procedure for the preparation of acceptors *E*-**6a**−**c** and *Z*-**6c**, as well as their reactions with enolates to yield the corresponding adducts **11**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL016401G

(19) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132.

(20) In the case of nonfluorinated systems, the Felkin-Anh model for the *E*-acceptors and the 1,3-allylic strain concept for the *Z*-acceptors have been successfully employed for the explanation of the product stereochemistry; see, Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

(21) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265.

(22) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(23) (a) Wong, S. S.; Paddon-Row: M. N.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 8679. (b) Tatsukawa, A.; Kawatake, K.; Kanemasa, S.; Rudzinski, J. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2525. See also: Bernardi, A.; Capelli, A. M.; Cassinari, A.; Comotti, A.; Gennari, C.; Scolastico, C. *J. Org. Chem.* **1992**, *57*, 7029.

(24) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(25) One reviewer suggested that Li···F chelation is also applicable for the explanation of the present results, but this was ruled out here because of our previous experience on diastereoselectivity independent from the number of fluorines; see: Yamazaki, T.; Ando, M.; Kitazume, T.; Kubota, T.; Omura, M. *Org. Lett.* **1999**, *1*, 905.