Highly Diastereoselective Sequential Enolate–Michael Addition–Ireland Claisen Rearrangement

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We recently reported the highly diastereoselective Michael addition reactions of lithium enolates derived from various types of ketones, esters, or amides toward ethyl 3-(trifluoromethyl)acrylate.[1] The *ab initio* molecular orbital calculation unambiguously demonstrated that the intramolecular interaction between lithium and fluorine(s)[2] plays an important role for the significant stabilization of the intermediary ester enolates.[1b] This effect was considered to be the strong driving force for the smooth conjugate addition, especially with ketone enolates, which usually undergo the retro-Michael pathway when a nonfluorinated ester is employed as an acceptor. Formation of the ketene silyl acetal (**2**) basically as a single isomer[3] by trapping this Michael intermediate also supported the above theoretical calculation.

Such suitably stereocontrolled ketene silyl acetals, especially the ones prepared from acylated oxazolidinones as the donors, would be interesting and promising intermediates for introducing the additional chiral centers. As a further representative utilization, we have focused our attention on [3,3]-sigmatropic rearrangements[5] because the rearrangement system can be easily constructed by simply modifying the original ethyl ester functionality as the corresponding allylic ester. Here we would like to describe our preliminary results on the sequential Michael addition–Ireland Claisen reactions,

Scheme 1

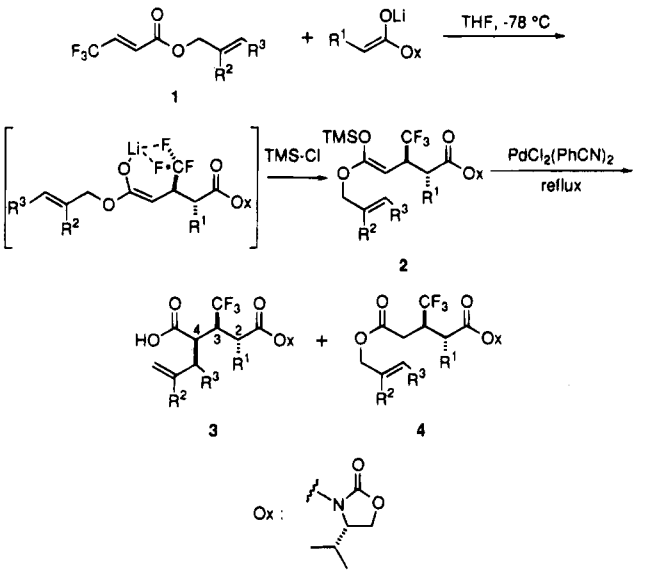

Table 1. Sequential Enolate Michael Addition–Ireland Claisen Rearrangement with Allylic 3-(Trifluoromethyl)acrylate as an Acceptor[a]

						isolated yield[b] %)	
entry	acceptor	R^1	R^2	R^3	product	**3**	**4**
1[d]	**1a**	Me	H	H	**3a**	55	22
2	**1a**	Me	H	H	**3a**	65 (44)	22 (45)
3[e]	**1a**	Me	H	H	**3a**	47	16
4	**1a**	Et	H	H	**3b**	63	32
5	**1a**	*i*-Pr	H	H	**3c**	60	32
6	**1b**	Me	Me	H	**3d**	65	21
7	**1b**	Et	Me	H	**3e**	74	34[c]
8	**1b**	*i*-Pr	Me	H	**3f**	62	45[c]
9	**1c**	Me	H	Me	**3g**	0	79

[a] The Ireland–Claisen rearrangement was carried out at reflux for 6 h after addition of a Pd(II) catalyst to ketene silyl acetal obtained *in situ*. [b] The yields obtained in the absence of a Pd(II) catalyst are shown in parentheses. [c] These yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [d] Reflux for 4 h. [e] Reflux for 11 h.

which enabled us to readily and effectively control the three consecutive stereocenters in a one pot reaction.

Preparation of lithium enolates under the standard conditions (30 min in THF at −78 °C under the action of LDA) followed by the addition of the allylic ester acceptor **1** has led to the smooth conjugate addition (within 1–2 h), whose stereoselectivity was independently confirmed as >98% de in every case (Scheme 1). Formation of the ketene silyl acetal **2** was effected by the reaction of the Michael intermediate with freshly distilled trimethylsilyl chloride (TMS-Cl),[6] and the resultant mixture was then heated without further purification to furnish the rearranged carboxylic acid **3** in moderate to good yields as a single stereoisomer along with the unrearranged Michael adduct **4** (Table 1). Addition of palladium dichloride–benzonitrile complex[7] at the rearrangement step was found to effectively suppress the unfavorable formation of the side products (see entry 2 in Table 1). Moreover, the yields appeared to be dependent on the reaction time,

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(1) (a) Shinohara, N.; Haga, J.; Yamazaki, T.; Kitazume, T.; Nakamura, S. *J. Org. Chem.* **1995**, *60*, 4363. (b) Yamazaki, T.; Haga, J.; Kitazume, T.; Nakamura, S. *Chem. Lett.* **1991**, 2171. (c) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175.

(2) The same type of interaction was recently reported. (a) Harder, S.; Streitwieser, A.; Petty, J. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1995**, *117*, 3253. (b) Canepa, C.; Antoniotti, P.; Tonachini, G. *Tetrahedron* **1994**, *50*, 8073. (c) Boche, G.; Bosold, F.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, *126*, 1873. (d) van Eikema Hommes, N. J. R.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 755. (e) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (f) Dixon, D. A.; Smart, B. E. In *Selective Fluorination in Organic and Bioorganic Chemistry*; Welch, J. T., Ed.; ACS Symposium Series No. 456; American Chemical Society: Washington, D.C., 1991; p 18.

(3) We assumed the geometry at the olefinic bond of lithium enolate as *E* which was on the basis of the Li–F interaction as well as the predominant formation of the same *E* intermediate for the nonfluorinated species reported by Heathcock and co-workers.[4a,b] The ^{13}C NMR chemical shift of the ketene silyl acetal **2** (ethyl ester, δ 67.66 (q, J = 3.03 Hz, *C*H=C(OTMS)OEt) also supported this hypothesis because the same carbon atom of the *Z* ketene silyl acetal from ethyl propionate appeared at 70.4 ppm (possessing the same olefinic geometry as the *E* lithium enolate in spite of the different *E*/*Z* nomenclature), while the same signal was observed at about 10 ppm lower field (δ 80.6 ppm) for the corresponding *E* isomer.[4c]

(4) (a) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132. (b) Oare, D. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 157. (c) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650.

(5) For a recent review, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1424 and references cited therein.

(6) Use of bulkier silylating agents such as *tert*-butyl- or thexyldimethylsilyl chlorides has led to the formation of the unidentified product mixture, and no rearranged material was obtained.

(7) (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *Synth. Commun.* **1989**, *19*, 2109. (b) Yasui, K.; Fugami, K.; Tanaka, S.; Tamaru, Y.; Li, A.; Yoshida, Z.; Saidi, M. R. *Tetrahedron Lett.* **1992**, *33*, 789.

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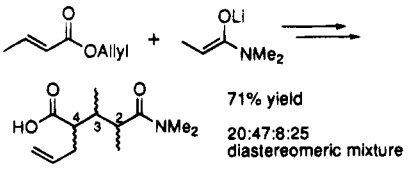
Scheme 2



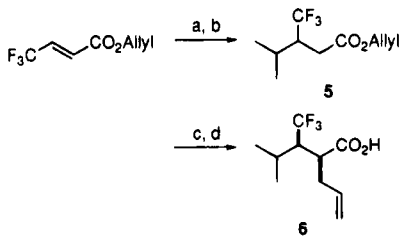
and heating the reaction mixture at reflux for 6 h proved to be the condition of choice. The allyl terminus was sensitive toward substitution, and introduction of a methyl group led to the total failure of the rearrangement (entry 9).

This sequential procedure was also applicable to a nonfluorinated combination such as *N,N*-dimethylpropionamide and allyl crotonate; the product was obtained in 71% yield but with much lower stereoselectivity (Scheme 2). This disappointing result arose from the low diastereofacial selectivity of the Ireland Claisen rearrangement because quenching of the reaction at the Michael addition step provided an 81.7:18.3 (*syn* major) mixture.[8]

The high stereoselectivity of the Michael addition step (Scheme 1) was well-understood in the same manner as the aldol reaction and alkylation of acylated oxazolidinones previously reported by Evans and co-workers.[1b] Then, what factor was responsible for the realization of the high diastereofacial selectivity of the Claisen rearrangement step? For the explanation of the 2*S*,3*S*,4*R* absolute stereochemistry of **3b** determined by X-ray crystallographic analysis, the well-accepted two types of chairlike transition state models, TS-*re* and TS-*si*, were considered: the former was the transition state with the preferential attack of the allyl group at the *re*-face of the vinyl part, whose conformation would be fixed so as to minimize the steric hindrance around the silyl group based on the allylic 1,3-strain concept.[10] Since a CF_3 moiety is recognized as the steric equivalent to a nonfluorinated isopropyl group,[11] substitution of an *i*-Pr group in both TSs for R would constitute the sterically close environment at both diastereotopic faces. Thus, ketene silyl acetal from allyl 4-methyl-3-(trifluoromethyl)-pentanoate (**5**) is considered as a good probe to know how important the steric requirement is in our instance. The requisite ester **5**, prepared by Michael addition of 2-nitropropane to allyl 3-(trifluoromethyl)acrylate followed by denitration, was transformed into the desired ketene silyl acetal, which furnished the rearranged product **6** in 74% yield with 88% *syn* preference (determined by the crystallographic analysis after conversion of **6** to the corresponding *N,N*-dimethylamide). Thus, this model experiment unambiguously demonstrated that the stereoelectronic effect was the dominant factor responsible for the present high stereoselectivity (Scheme 3).

On the basis of the Cieplak effect,[12] the preferential attack at an sp^2 site occurs from the face, effectively stabilizing the developing electron deficient $\sigma_{\ddagger}^*$ orbital by the neighboring σ orbital. As shown in Figure 1, σ_{C-R} and σ_{C-CF3} are the orbitals playing an important role in TS-*re* and TS-*si*, respectively, due to the partial pyramidalization at the vinyl ether terminus. Because of the well-known strongly electron-withdrawing property of the trifluoromethyl moiety, it would be readily understood that the rearrangement preferentially proceeds from the opposite side of the more potent electron-donating σ_{C-R} orbital, leading to the construction of the 3,4-*syn* stereochemical relationship via TS-*re*. This hypothesis was supported by the result of the nonfluorinated counterpart already shown in Scheme 2. Thus, as described above, the sequential procedure for nonfluorinated allyl crotonate and *N,N*-dimethylpropionamide failed to attain high selectivity especially at the rearrangement step. The TSs taken into account in this case should be the ones containing a CH_3 group instead of a CF_3 moiety, and the orbitals interacted with the developing $\sigma_{\ddagger}^*$ are both σ_{C-R}, leading to the close electronic contribution.

Scheme 3



[a] Key: (a) *i*-$PrNO_2$, DBU/MeCN; (b) *n*-Bu_3SnH, cat AIBN/PhH; (c) LDA, TMSCl; (d) $PdCl_2(PhCN)_2$, Δ.

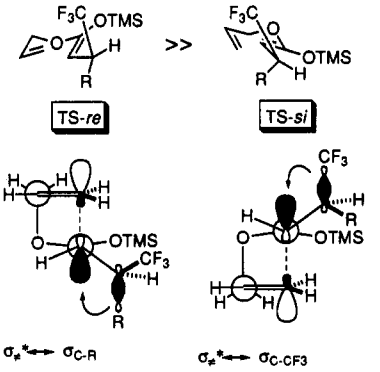


Figure 1.

As shown above, we have succeeded in developing a novel pathway as the sequential enolate Michael addition–Ireland Claisen rearrangement, which realized the ready construction of three consecutive chiral centers with an exceptionally high degree of stereoselectivity. The discrimination of the diastereotopic olefinic faces was successfully carried out as the result of the electron-withdrawing character of the CF_3 moiety. This effect effectively lowered the electron-donating ability of σ_{C-CF3} to make TS-*si* with a $C-CF_3$ bond antiperiplanar to the incoming allylic part less important. Related work utilizing ketene silyl acetals of type **2** is in progress in our laboratory.

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Supporting Information Available: A listing of experimental procedures and crystallographic data of compounds **3b** and **5** (12 pages).

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(8) Yamaguchi and co-workers previously reported the selectivity as 2:1 (*syn* major)[9] when ethyl crotonate was employed as the acceptor, while, in our case, exactly the same system afforded the 90:10 ratio.

(9) Yamaguchi, M.; Hasebe, K.; Tanaka, S.; Minami, T. *Tetrahedron Lett.* **1986**, *27*, 959.
(10) For a review, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(11) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.
(12) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.