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Stereoselective Michael Addition Reactions of Acylated Oxazolidinones to Ethyl 3-Trifluoromethylacrylate

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Michael addition reactions of acyl oxazolidinones to ethyl 3-trifluoromethylacrylate were found to proceed smoothly with a high degree of diastereo- as well as diastereofacial selectivity at the new carbon-carbon bond.

In the preceding paper, the utility of ethyl 3-trifluoromethylacrylate was clarified for the enolate-Michael addition[1] with various type of lithium enolates in a highly diastereoselective manner. This acceptor was also found to possess a special characteristics on its reactivity: thus the substituent of enolates from esters or ketones influences the reaction significantly. On the contrary, the fact that amide enolates worked well irrespective of the substitution pattern of enolates prompted us to utilize chiral amides from readily accessible optically active amino acids. Recently, Evans and co-workers[2] have reported the high ability of chiral acyl oxazolidinones for alkylations[2c] or aldol condensations.[2d] From their literature, the two inherent nature of lithium enolates from the acyl oxazolidinones were noted: i) predominant formation of (**Z**)-enolate, ii) reaction with electrophiles at its *Si* face without any exception (Fig. 1), both of which are of course very important factors to control stereoselectivity. In the present paper, the authors would like to describe the extension of our enolate-Michael addition to asymmetric synthesis by using chiral acylated oxazolidinones from L-valine, which furnished the desired 1,4-adducts in a highly stereoselective manner.

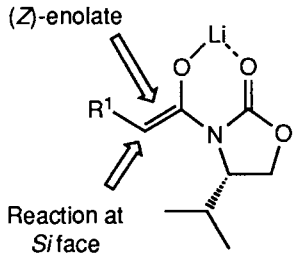
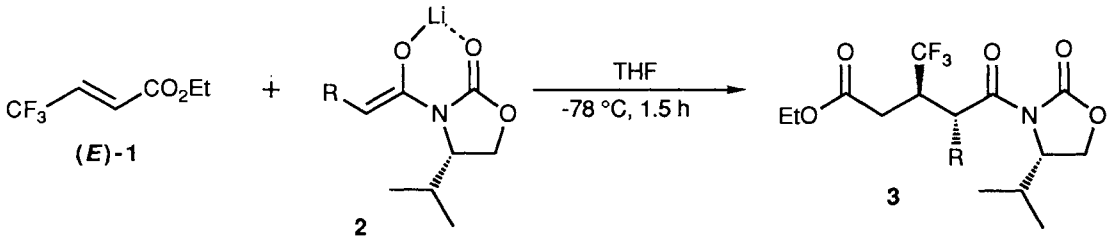


Fig. 1.

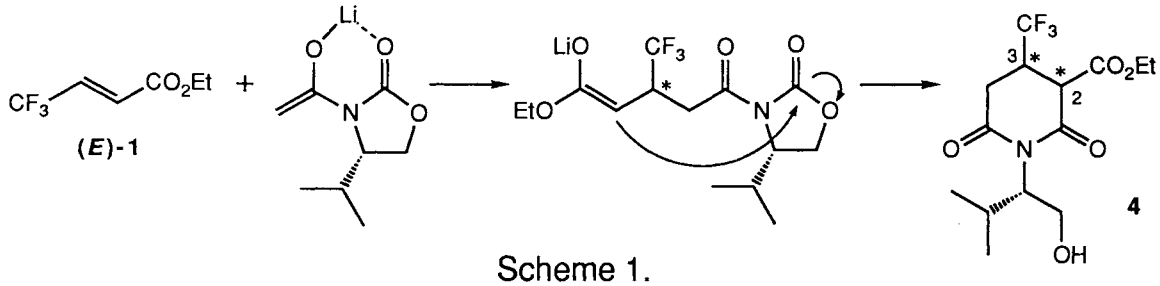
Basically the same reaction conditions were employed as in the preceding paper[3]; thus an enolate was generated with LDA in THF at -78 °C, followed by the addition of ethyl 3-trifluoromethylacrylate (***E*)-1** and stirring for 1.5 h at that temperature. As summarized in Table 1, optically active adducts were obtained in good to excellent yields with very high levels of diastereo- as well as diastereofacial selectivities. *Especially products **3a, 3b, and 3e** were obtained as single isomers, respectively, where four stereoisomers were possible* as determined by spectroscopic data (^{1}H, ^{13}C, and ^{19}F NMR) and capillary gas chromatographic analysis.[4] Reaction with acetylated oxazolidinone (Entry 1) was the special case, which furnished the cyclic product **4** presumably via nucleophilic attack of the resulting ester enolate to the carbonyl moiety of oxazolidinone ring (Scheme 1).[5] On the other hand, oxazolidinone with a phenylacetyl moiety did not give any adduct when the corresponding lithium enolate was employed, while the usage of potassium hexamethyldisilazide (KHMDS) affected the reaction to afford the desired product but with lower diastereoselectivity (30% de). In this instance, the information that removal of the chiral auxiliary from **3d** furnished the corresponding half acid with basically same de value (36% de) would be interpreted as the result of the predominant reaction of the enolate **2** (R:Ph) at

Table 1. Reaction of Ethyl 3-Trifluoromethylacrylate with Various Acyl Oxazolidinones



Entry	Product	R	Yield[a]/%	Diastereoselectivity[b]/% de
1	**4**	H	93	78
2	**3a**	Me	88	>98
3	**3b**	Et	52 (74)[c]	>98
4	**3c**	*i*-Pr	97	97
5[d]	**3d**	Ph	62	30
6	**3e**	$PhCH_2O$	36	>98

a) In the parenthesis was shown ^{19}F NMR using $PhCF_3$ as an internal standard. b) Unless otherwise noted, these diastereomers were resulted from CF_3-*C**-*C**-R, which was proved by removal of the chiral auxiliary. c) This gap is due to the close R_f values of the product and the starting amide. d) Potassium hexamethyldisilazide was employed for the generation of the enolate.

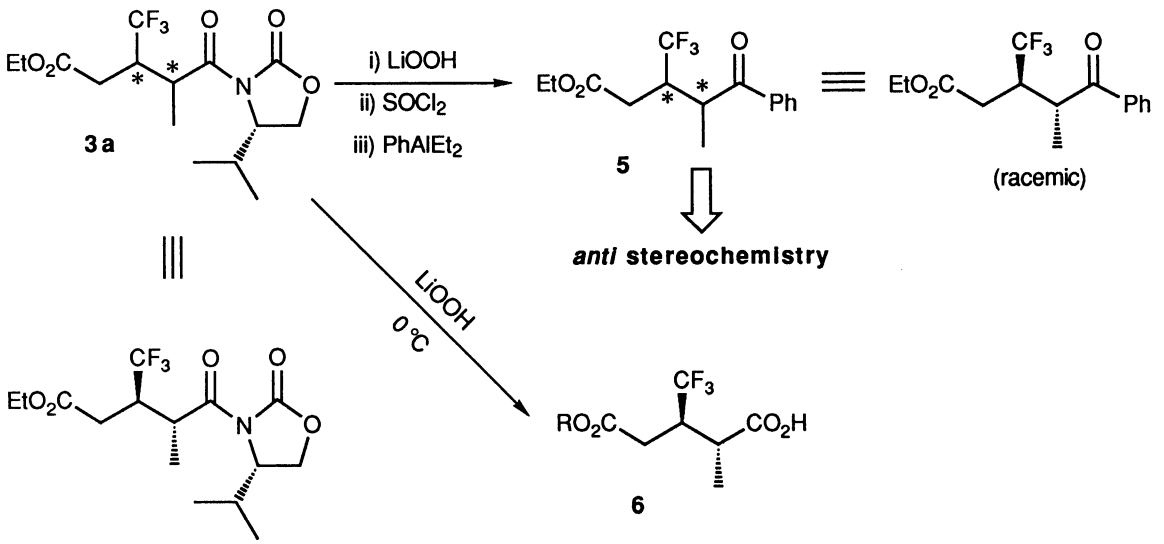


Scheme 1.

its *Si* face like other acyl oxazolidinones' cases but poor face matching of the Michael acceptor (***E***)-**1**.

For the clarification of the relative stereochemistry, the optically active Michael adduct **3a** was treated with LiOOH followed by the derivatization into acid chloride and its reaction with $PhAlEt_2$ furnished **5** without any evidence of epimerization by ^{19}F NMR (Scheme 2). *Anti* relative stereochemistry of **3a** was deduced from the fact that **5** had totally identical spectral properties to that of the same racemic compound synthesized in the preceding paper. Consideration of the characteristics of lithium enolates from acylated oxazolidinones as discussed above allows us to assume the absolute stereostructure of **3a** as shown in Scheme 2. The same sense of stereoselection for compounds **3b**, **3c**, and **3e** might be also expected by the assumption of their similar reaction courses.

The obtained Michael adducts **3** in almost diastereomerically as well as enantiomerically pure forms would be employed as useful chiral building blocks with a CF_3 group because, as is already shown, this chiral auxiliary can be removed under mild condition without epimerization. For example, compound **3a** can be easily



Scheme 2.

converted into the corresponding half acid **6a**[6] almost quantitatively, which contains two similar but readily distinguishable functionalities such as ester and carboxyl moieties. Reaction at the latter cite was realized, via its acid chloride or mixed anhydride, with such nucleophiles as alcohols, amines, or organometallics as shown in the preceding paper.[3,7]

Further examination of this Michael addition reaction with various kinds of donors and analysis of its reaction course are in progress in our laboratory.

References

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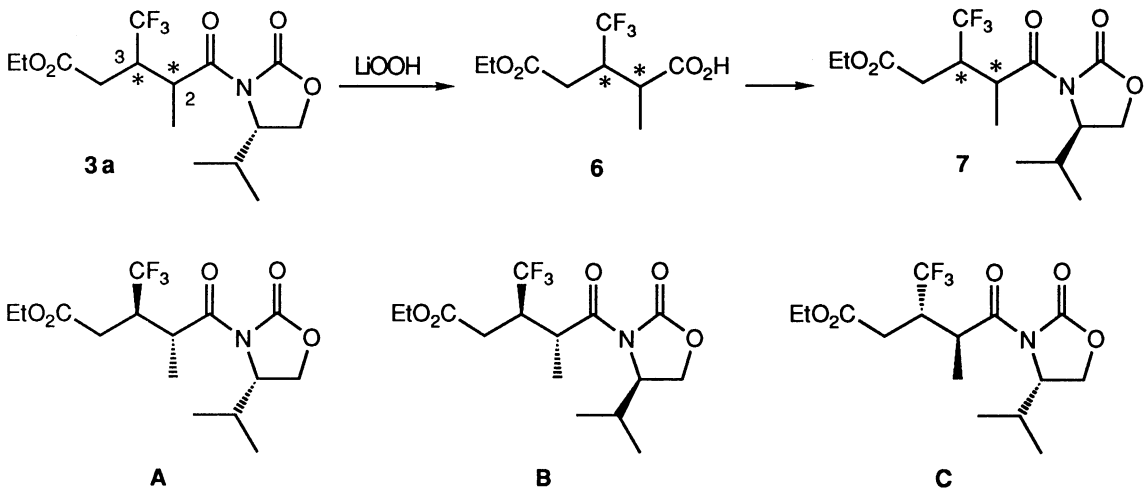
2) a) D. A. Evans, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3, p.1; b) D. A. Evans, *Aldrichimica Acta*, **15**, 23 (1982); c) D. A. Evans, M. D. Ennis, and D. J. Mathre, *J. Am. Chem. Soc.*, **104**, 1737 (1982); d) D. A. Evans, J. Bartroli, and T. L. Shih, *J. Am. Chem. Soc.*, **103**, 2127 (1981); e) D. A. Evans, T. C. Britton, and J. A. Ellman, *Tetrahedron Lett.*, **28**, 6141 (1987).

3) T. Yamazaki, J. Haga, T, Kitazume, and S. Nakamura, *Chem. Lett.*, preceding issue of this paper.

4) Empirically this type of structure, CF_3-*C**-*C**-R, usually gives two different peaks by ^{19}F NMR but only one peak was in fact observed not only from **3a** but also from **6** (See Scheme 2), the latter of which was obtained after removal of the chiral auxiliary by LiOOH[2e] with complete retention of the stereochemistry. On the basis of this fact, compound **3a** was considered to possess only one stereochemical relationship (thus, *syn* only or *anti* only) with respect to its 2 and 3 positions. Moreover, **3a** was condensed with oxazolidinone from D-valine via **6** to furnish the diastereomer **7**. Here, suppose that the stereostructure of **3a** is **A**, then **7** and **B** are equivalent, and the spectroscopic properties of the latter should be exactly the same as the ones of compound **C**. Comparison of their ^1H (200 MHz), ^{13}C (50 MHz), and ^{19}F NMR (60 MHz) showed totally different physical properties, which has led us to conclude that **3a** contained a single stereoisomer. The followings are the representative physical properties of compounds **3a** and **7**, from which these two are easily discriminated. **3a**: R_f 0.27 (hexane: AcOEt = 3:1). $[\alpha]_D^{22.0}$ +44.04° (*c* 1.10,



MeOH). GC retention time 22.0 min (GE XE-60 capillary column, 3 mm x 30 m at 180 °C). ^{1}H NMR δ 2.57 (2 H, d, J = 6.22 Hz, $CH_2C(O)$; *two equivalent hydrogens*). ^{13}C NMR δ 41.04 (q, J = 26.2 Hz, CF_3CH). ^{19}F NMR δ 8.8 (d, J = 8.7 Hz). HRMS calculated for $C_{15}H_{22}F_3O_5N$ *m/e* 353.1450, found 353.1423. **7**: R_f 0.42 (hexane:AcOEt = 4:1). $[\alpha]_D^{27.5}$ -71.72° (*c* 1.05, MeOH). GC retention time 15.7 min. ^{1}H NMR δ 2.54 (1 H, dd, J = 17.21, 5.29 Hz, $CH_2C(O)$), 2.67 (1 H, dd, J = 17.21, 6.84 Hz, $CH_2C(O)$; *non-equivalent AB pattern*). ^{13}C NMR δ 40.21 (q, J = 26.4 Hz, CF_3CH). ^{19}F NMR δ 8.3 (d, J = 9.5 Hz). HRMS calculated for $C_{15}H_{22}F_3O_5N$ *m/e* 353.1450, found 353.1441.

5) There are two possibilities for the interpretation of this relatively lower de value: i) perfect selection of diastereoface of Michael acceptor **(*E*)-1**, followed by less stereocontrolled intramolecular nucleophilic attack (thus 89:11 at 2-position and optically pure at 3-position of compound **4** in Scheme 1), or ii) the opposite mode of reaction course (optically pure at 2-position and 78% ee at its 3-position). However, since **4** possesses the acidic proton at its 2-position which might easily cause epimerization at this cite, the latter would be less probable. Investigations on this problem are currently under way.

6) The half acid **6a** was isolated in basically pure condition after usual work up procedure for carboxylic acids. $[\alpha]_D^{27.5}$ -7.25° (*c* 1.02, $CHCl_3$). ^{1}H NMR δ 1.26 (3 H, dq, J = 7.22, 0.85 Hz, $CH_3CHC(O)$), 1.27 (3 H, t, J = 7.14 Hz, CH_3CH_2O), 2.55 (1 H, dd, J = 16.67, 6.63 Hz, $CH_2C(O)$), 2.64 (1 H, dd, J = 16.67, 6.47 Hz, $CH_2C(O)$), 2.96 (1 H, dq, J = 7.15, 4.22 Hz, $CH_3CHC(O)$), 3.41 (1 H, dtq, J = 9.38, 6.62, 4.19 Hz, CF_3CH), 4.17 (2 H, q, J = 7.14 Hz, CH_3CH_2O), 8.3 (1 H, bs, OH). ^{13}C NMR δ 12.30 (s,$CH_3CHC(O)$), 14.06 (s, CH_3CH_2O), 30.15 (q, J = 2.4 Hz, $CH_2C(O)$), 37.55 (q, J = 2.0 Hz, $CH_3CHC(O)$), 41.18 (q, J = 26.6 Hz, CF_3CH), 61.59 (s, CH_3CH_2O), 127.51 (q, J = 281.2 Hz, CF_3), 171.33 (s, CO_2Et), 179.84 (s, CO_2H). ^{19}F NMR δ 7.8 (d, J = 8.8 Hz). IR (neat) ν 3300, 3000, 1745, 1720 cm^{-1}. HRMS calculated for $C_9H_{14}F_3O_4$ *m/e* 243.0844 (M+H), found 243.0855.

7) On the other hand, extention of the reaction time was found to give dicarboxylic acid in 80% yield after recrystallization from methylene chloride, which will be subjected to X-ray crystallographic analysis to confirm our hypothesis about its absolute configuration.

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