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Diastereoselective Introduction of an EtO_2CCF_2- Group into Chiral Imide Enolates Mediated by Triethylborane

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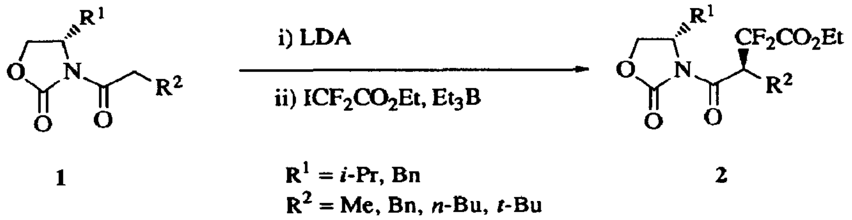
Abstract: *The introduction of an EtO_2CCF_2- group into lithium enolates of chiral N-acyloxazolidinones with ethyl difluoroiodoacetate mediated by triethylborane proceeds with good diastereomeric excess (86->98% de).*

The synthesis of chiral fluoroorganic compounds is an important aspect of organofluorine chemistry in relation to analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] This paper presents for the first time the diastereoselective introduction of an EtO_2CCF_2- group into lithium enolates of *N*-acyloxazolidinones **1** in 86->98% de using ethyl difluoroiodoacetate and triethylborane.

Triethylborane is an effective radical initiator for perfluoroalkyl iodide and induces the trifluoromethylation of acetylenes, olefins, silyl enol ethers and ketene silyl acetals, as previously reported by Oshima and Utimoto.[2] The diastereoselective trifluoromethylation of **1** with iodotrifluoromethane mediated by triethylborane was recently reported,[3] and Taguchi et al. successfully carried out the stereoselective synthesis of *gem*-difluorocyclopropanes by triethylborane mediated intramolecular reaction.[4]

Typically, chiral imide enolate, generated at -78 °C in THF by treatment of 2.0 mmol of **1** with 1.1 equiv of lithium diisopropylamide (LDA) for 60 min, was added to a solution of 1.3 equiv of ethyl difluoroiodoacetate[5] and 1.0 equiv of triethylborane in THF with a cannula at 5 °C over 12 min. The reaction mixture was stirred at 5 °C for 3 to 45 min prior to quenching with NH_4Cl.[6] α-Ethoxycarbonyldifluoromethyl carboximides **2** and their diastereomers were isolated by flash chromatography.[7] The results are summarized in Table 1.

The reaction was inhibited not only by lack of triethylborane (entry 1) but with a radical scavenger, galvinoxyl (entry 4). The new asymmetric center of **2a** was shown to have the (*S*)-configuration by conversion to the known α-trifluoromethyl carboximide **4**.[3] The hydrolysis of **2a** with $NaHCO_3$ in aqueous methanol gave the corresponding carboxylic acid **3** which was subsequently treated with xenon difluoride (XeF_2) to afford **4**.[8] Attack by the ethoxycarbonyldifluoromethyl radical may thus be considered to proceed with C(α)-*Si*-face preference to Li-chelated transition state **A**.



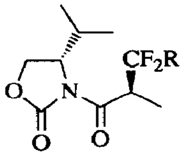
R^1 = *i*-Pr, Bn
R^2 = Me, Bn, *n*-Bu, *t*-Bu

(1)

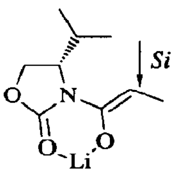
Table 1. Diastereoselective Introduction of an EtO_2CCF_2- Group into Chiral Imide Enolates (Eq. 1)

Entry	Imide 1 R^1	R^2		Reaction Time (min)	Et_3B (equiv)	Product 2 % de[a]	% yield(2 + its diastereomer)[b]	
1	*i*-Pr	Me	**(1a)**	30	0.0	-	0	
2	*i*-Pr	Me	**(1a)**	3	0.2	93 (*S*)[c]	20 (57)	**(2a)**
3	*i*-Pr	Me	**(1a)**	3	1.0	88 (*S*)[c]	74 (84)	**(2a)**
4[d]	*i*-Pr	Me	**(1a)**	3	1.0	90 (*S*)[c]	7 (49)	**(2a)**
5	*i*-Pr	Bn	**(1b)**	3	1.0	86	61 (75)	**(2b)**
6	*i*-Pr	*n*-Bu	**(1c)**	3	1.0	88	64 (76)	**(2c)**
7	*i*-Pr	*t*-Bu	**(1d)**	45	1.0	>98[e]	19 (22)[f]	**(2d)**
8	Bn	Me	**(1e)**	30	1.0	87	70 (84)	**(2e)**

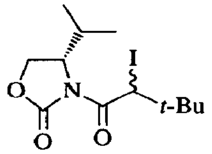
a) De's were determined by capillary GLC; b) All yields are those of isolated compounds. Values in parentheses indicate conversion yields; c) Configuration of the new asymmetric center of the major isomer; d) The reaction was carried out in the presence of 1.0 equiv of galvinoxyl; e) No minor isomer was detected; f) Iodocarboximide **5** was isolated in 53% yield. The ratio of the stereoisomers was determined to be 56:44 by ^1H NMR.



3 R = CO_2H
4 R = F



A



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This paper is the first presentation of the diastereoselective introduction of an EtO_2CCF_2- group into chiral imide enolates of **1** with ethyl difluoroiodoacetate mediated by triethylborane to produce carboximides **2** in 86->98% de. Application of the present results to synthesis of useful chiral fluoroorganic compounds is now being carried out.

References and Notes

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4. Taguchi, T.; Sasaki, H.; Shibuya, A.; Morikawa, T. *Tetrahedron Lett.* **1994**, *35*, 913.
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6. The reaction was too slow to be useful at -20 °C.
7. Even in the presence of 1.0 equiv of triethylborane, imides **1** were recovered in 12-18% yields.
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