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Diastereoselective Bromodifluoromethylation of Chiral Imide Enolates via Insertion of Difluorocarbene

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Abstract: *The bromodifluoromethylation of lithium enolates of chiral N-acyloxazolidinones via the insertion of difluorocarbene proceeds with good diastereomeric excess (68-92% de).*

The synthesis of selectively fluorinated homochiral molecules is now an important aspect of organofluorine chemistry in connection with analytical and medicinal chemistry and opto-electric substances such as liquid crystals.[1] This paper presents for the first time the diastereoselective bromodifluoromethylation of lithium enolates of *N*-acyloxazolidinones **1** to α-bromodifluoromethyl carboximides **2** in 68-92% de via the insertion of difluorocarbene .

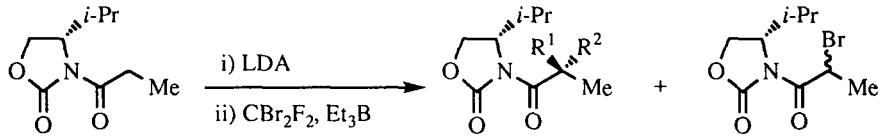
Triethylborane is an effective radical initiator of perfluoroalkyl iodide and induces the trifluoromethylation of acetylenes, olefins, silyl enol ethers and ketene silyl acetals, as previously reported by Oshima and Utimoto.[2] Recently, the authors reported the diastereoselective trifluoromethylation (CF_3)[3] and ethoxycarbonyldifluoromethylation (EtO_2CCF_2)[4] of **1** with iodotrifluoromethane and ethyl difluoroiodoacetate, respectively, mediated by triethylborane. Taguchi et al. successfully achieved the stereoselective synthesis of *gem*-difluorocyclopropanes using triethylborane mediated intramolecular reaction.[5] Triethylborane also induces the *radical* addition of dibromodifluoromethane to terminal acetylenes and olefins.[2]

N-Propionyloxazolidinone **1a** was used in the initial optimization study in that the stereochemistry of the major product **2a**[6] has been established (Table 1). Lithium enolate derived *in situ* from **1a** and lithium diisopropylamide (LDA) in tetrahydrofuran was treated with dibromodifluoromethane and triethylborane to afford α-bromodifluoromethyl carboximides, **2a** and **3a**, but unfortunately, in only limited yields (entry 1). It should be pointed out, however, that the products were obtained in 10% yield even *in the absence of triethylborane* (entry 2). It was found that product yield could be improved by adjusting the concentration of the lithium enolate *in vacuo* at -20 °C followed by the addition of dibromodifluoromethane.[7] Bromodifluoromethylation of the concentrated enolate in the absence of triethylborane proceeded at -20 °C with product yields of 43% (entry 3). Dilution of the concentrated enolate with tetrahydrofuran prior to the addition of dibromodifluoromethane gave better results (entry 4). The highest chemical yield (59% yield) was achieved using dimethoxyethane as the diluent (entry 5). Triethylborane was not a determinant of the amount of diastereomeric excess or chemical yield (entry 6). The addition of diisopropylamine greatly suppressed the formation of products (entry 7). In all cases, the starting imide **1a** could be partially recovered from 11% to 82%. α-Bromo carboximide **4a**[8] was obtained as a by-product in the range of 0.8-8% yield.

Results of the diastereoselective bromodifluoromethylation of a variety of *N*-acyloxazolidinones **1** with dibromodifluoromethane under optimal conditions (Table 1, entry 5)[9] are summarized in Table 2.

Diastereomeric excess (92% de) was greatest in reaction with **1d** (R^1 = *i*-Pr, R^2 = *t*-Bu, entry 4). α-Bromo carboximide **4** was obtained in all cases.[10]

Table 1. Bromodifluoromethylation of Imide **1a** under Various Conditions

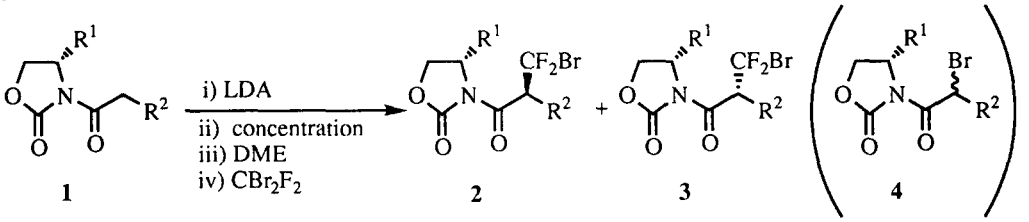


1a — **2a** $R^1 = CF_2Br$, $R^2 = H$; **3a** $R^1 = H$, $R^2 = CF_2Br$ — **4a**

Entry	Reaction Conditions[a]	Solvent	Et_3B (equiv.)	Product (**2a**, **3a**) % de[b]	% yield(**2a** + **3a**)[c]	By-product **4a** % yield
1	A	THF	1.0	61	9 (30)	1
2	A	THF	0.0	60	10 (31)	1
3	B	none	0.0	69	43 (52)	<1
4	C	THF	0.0	66	51 (59)	6
5	C	DME	0.0	68	59 (66)	8
6	C	DME	1.0	68	58 (65)	6
7[d]	C	DME	0.0	66	<1 (5)	<1

a) In Method A, lithium enolate derived from **1a** and LDA in THF was treated with CBr_2F_2 in the presence or absence of Et_3B at -78 °C. The resultant solution was allowed to warm to 0 °C over 3 h. In Method B, the lithium enolate was concentrated *in vacuo* at -20 °C followed by the addition of CBr_2F_2, and the system was stirred at -20 °C for 1 h. In Method C, the concentrated enolate in Method B was diluted with THF or DME followed by the addition of CBr_2F_2. This solution was stirred in the presence or absence of Et_3B at -20 °C for 1 h; b) Des were determined by capillary GLC. The major product was **2a**; c) Yields of all isolated compounds are indicated. Conversion yields are shown in parentheses; d) Diisopropylamine (5 equiv.) was added to the enolate solution prior to CBr_2F_2.

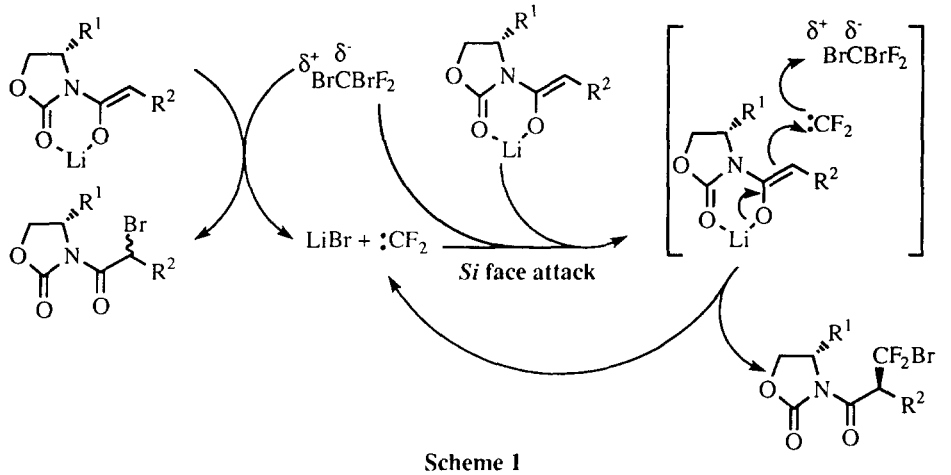
Table 2. Diastereoselective Bromodifluoromethylation of Lithium Enolates Derived from *N*-Acyloxazolidinones (**1**)



1 — **2** — **3** — **4**

Entry	Imide **1** R^1	R^2		Product (**2**, **3**) % de[a]	% yield(**2** + **3**)[b]	
1	*i*-Pr	Me	(**1a**)	68 (*S*)[c]	59 (66)	(**2a**)
2	*i*-Pr	Bn	(**1b**)	67	52 (59)	(**2b**)
3	*i*-Pr	*n*-Bu	(**1c**)	67	60 (68)	(**2c**)
4	*i*-Pr	*t*-Bu	(**1d**)	92	42 (52)	(**2d**)
5	Bn	Me	(**1e**)	71	55 (61)	(**2e**)

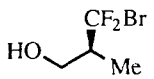
a) Des were determined by capillary GLC; b) All yields are those of isolated compounds. Conversion yields are shown in parentheses; c) Configuration of the new asymmetric center of the major isomer.



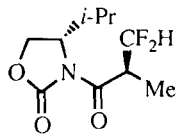
Scheme 1

It is considered from the above results that present diastereoselective bromodifluoromethylation of *N*-acyloxazolidinones **1** with dibromodifluoromethane proceeds not *via a radical mechanism involving bromodifluoromethyl radical*[2a] but *via an ionic chain mechanism involving the insertion of difluorocarbene.*[11] The proposed mechanism is illustrated in Sheme 1 and is supported by the following observations: 1) Triethylborane was not necessary for the present reaction.[2a] 2) Diisopropylamine dramatically suppressed the reaction.[12,13] 3) α-Bromo carboximide **4** was obtained.[11]

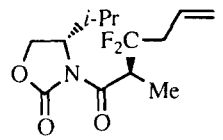
Finally, the reduction of α-bromodifluoromethyl carboximide **2a** with lithium borohydride in tetrahydrofuran at room temperature gave β-bromodifluoromethyl alcohol **5a** without racemization. Treatment of **2a** with tributyltin hydride and allyltributyltin in the presence of 2,2'-azobis(isobutyronitrile) during reflux with benzene gave **6a** and **7a** in 90% and 88% yield, respectively.



5a



6a



7a

This paper presents the first examples of the diastereoselective bromodifluoromethylation of *N*-acyloxazolidinones **1** via insertion of difluorocarbene to give α-bromodifluoromethyl carboximides **2** in 68-92% de. This reaction is presently being applied to the synthesis of important chiral fluoroorganic compounds.

References and Notes

1. Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661 and references cited therein.
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3. a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169; b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961.
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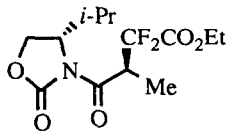
6. α-Ethoxycarbonyldifluoromethyl carboximide **8** (See ref. 4) was converted to **2a** as follows. The hydrolysis of **8** with $NaHCO_3$ in aqueous methanol (room temperature, 12 h) gave the corresponding carboxylicacid **9** which was subsequently treated with bromine in CH_2Cl_2 in the presence of xenone difluoride and sodium fluoride at room temperature for 6 h to afford **2a** in 42% overall yield.
7. Not only the solvent, THF, but also diisopropylamine can be removed through adjustment of concentration.
8. Diastereomeric excess of α-bromo carboximide **4a** ranges from 34% to 68%.
9. To a solution of diisopropylamine (2.2 mmol) in THF (4 ml) at 0 °C was added *n*-BuLi (2.2 mmol). After 30 min at 0 °C, the solution was cooled to -78 °C, followed by adding a solution of **1a** (2.0 mmol) in THF (6 ml). After 1 h at -78 °C, the mixture was concentrated *in vacuo* (0.3 mmHg) at -78 °C for 10 min and at -20 °C for 2 h. To the concentrated lithium enolate was added DME (10 ml) and CBr_2F_2 (10 mmol). After being stirred at -20 °C for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The combined etheral extracts were washed with brine, dried and filtered. Following evaporation of the solvent, chromatography of the residue with *n*-hexane-CH_2Cl_2 as eluent gave the less polar isomer (9%), more polar isomer (50%) and starting material **1a** (11%).
10. With **1d** (R^1 = *i*-Pr, R^2 = *t*-Bu), α-bromo carboximide **4d** was obtained in 20% yield.
11. a) Bey, P.; Vevert, J.P. *Tetrahedron Lett.* **1978**, 1215; b) Rico, I.; Cantacuzene, D.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1063 and references cited therein.
12. Diisopropylamine completely suppressed the cyclopropanation of 2-methyl-2-butene with difluorocarbene as follows. To a solution of triphenylphosphine (20 mmol) in triglyme (30 ml) was added CBr_2F_2 (20 mmol) at room temperature. After 30 min at the same temperature, 2-methyl-2-butene (20 mmol) and KF (80 mmol) were added, and the system was stirred at room temperature for 20 h to give difluorocyclopropane **10** in 44% yield. The addition of diisopropylamine (20 mmol) prior to 2-methyl-2-butene provided **10** in only trace amount, see: Burton, D.J.; Naae, D.G. *J. Am. Chem. Soc.* **1973**, *95*, 8467.
13. Diisopropylamine failed to inhibit addition of the trifluoromethyl radical to olefins mediated by triethyborane according to the following reaction scheme: A solution of 1-dodecene (2 mmol), CF_3I (10 mmol), Et_3B (2 mmol) and diisopropylamine (2 mmol) in *n*-hexane (10 ml) was stirred at -30 °C for 5 h to give **11** in 80% yield. See ref. 2a.



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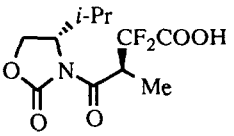

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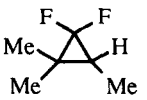

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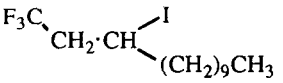

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