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ASYMMETRIC SYNTHESIS OF DIFLUOROCYCLOPROPANES

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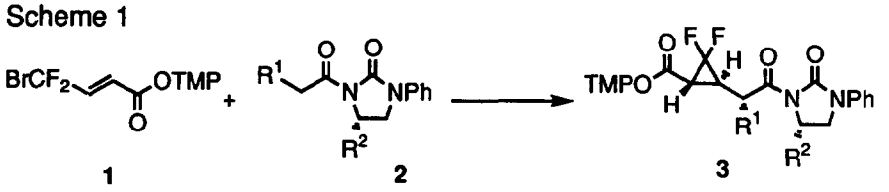
Abstract: A highly diastereoselective synthesis of functionalized *trans gem*-difluorocyclopropane carboxylate **3** was achieved through sequential Michael addition of lithium enolate of homochiral *N*-acylimidazolidinone **2** with 2,4,6-trimethylphenyl (TMP) 4-bromo-4,4-difluorocrotonate **1** and triethylborane-mediated intramolecular substitution reaction.

Recently we reported a regio- and stereoselective synthesis of *gem*-difluorocyclopropanes by using 2,4,6-trimethylphenyl (TMP) 4-bromo-4,4-difluorocrotonate **1** as a building block.[1] Such difluorocyclopropanes are needed in enantiomerically pure form to evaluate their biological responses. According to the reaction pathway,[1] it would be expected that the enantiomeric purity of the difluorocyclopropane formed depends on the degree of chiral induction of the Michael addition step. Highly potential utility of chiral acyl oxazolidinones for alkylations,[2] aldol condensations[3] or Michael additions[4] have been demonstrated originally by Evans and later by several other groups. The observed diastereoselectivities in reactions of *S* imide enolates with electrophiles were explained on the basis of the predominant formation of (*Z*)-enolate and the subsequent reactions on their sterically favourable *Si* face, if the metal is coordinated to the oxazolidinone carbonyl at the time of electrophilic attack. To achieve our purpose, chiral *N*-acylimidazolidinone **2**, instead of the oxazolidinone to lower the reactivity of the carbonyl group,[4c] was chosen as a Michael donor. In this paper, we report a highly diastereoselective synthesis of functionalized *trans gem*-difluorocyclopropane **3** through sequential Michael addition of lithium enolate of homochiral *N*-acylimidazolidinone **2** with 4-bromo-4,4-difluorocrotonate **1** and triethylborane-mediated intramolecular substitution reaction.

Scheme 1



1 **2** **3**

a R^1=OBn, R^2=Bn **b** R^1=OBn, R^2=*i* Pr **c** R^1=H, R^2=Bn

The cyclopropanation reaction was carried out by employing similar reaction conditions to those described previously; thus, reaction of the enolate, generated by treating **2** with LDA in THF at -78°C, with the crotonate **1** for 15 min at the same temperature followed by the addition of triethylborane and 1,3-dimethyl-2-imidazolidinone (DMI) and stirring for 2-3 hr at ca -20°C.[1] Results are summarized in Table 1. With benzyloxyacetyl derivatives **2a**, **2b**, high levels of diastereo- (2,3-asymmetric inductions were excellent from the ^{19}F-NMR (376 MHz) spectra of the crude reaction mixtures) and diastereofacial selecivties were observed to obtain the *trans* difluorocyclopropane **3a** of 76 % de in 48 % chemical yield and **3b** of 92 % de in 51 % chemical yield, respectively. With acetyl derivative **2c** (R^1=H, R^2=Bn), **3c** was obtained in 61 % chemical yield with 80 % de along with the isolation of the Michael adduct in 22 % yield.

Table 1. Preparation of Difluorocyclopropane **3**

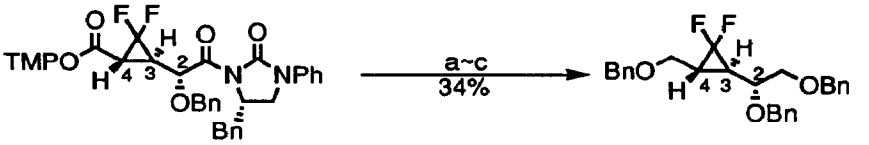
Entry	Difluorocyclopropane **3**	c.y. (%)[a]	de (%)[b]	Configuration[c]
1	**3a** R^1=OBn R^2=Bn	48[d]	76	2*R*,3*R*,4*R*
2	**3b** R^1=OBn R^2=*i*Pr	51	92	2*R*,3*R*,4*R*
3	**3c** R^1=H R^2=Bn	61[e]	80	3*S*,4*R*[f]

[a] Isolated Yield. [b] Determined by ^{19}F-NMR (376 MHz) spectrum of the reaction mixture. [c] Configuration of the major isomer is shown. Determination of the stereochemistry is described in the Text. [d] Michael adduct, 17% yield. [e] Michael adduct, 22% yield. [f] Tentatively assigned from the reaction mechanism.[9]

The stereochemistry of the cyclopropane **3a** was determined as follows. After the chromatographic purification and fractional recrystallization of **3a**, the major diastereomer was converted to the tribenzyl ether **4** in 34% overall yield by alkaline hydrolysis (LiOH, 30% H_2O_2-THF, rt), borane reduction (BH_3 DMS, THF) followed by benzylation (NaH, BnBr, DMF, rt) (Scheme 2). For the preparation of authentic samples, first, reaction of the (*E*)-allyl ether **5**[5] derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde with difluorocarbene generated from sodium chlorodifluoroacetate at 180°C in diglyme[6] was conducted to give a diastereomeric mixture of *trans* difluorocyclopropanes (**6** and **7**) in a ratio of 2.6:1. Each diastereomer could be obtained in pure form by MPLC separation and then was converted to the tribenzyl ether derivative **8** and **9**, respectively (Scheme 3).[7] The *p*-bromobenzoate **10**[8] derived from the minor isomer **7** provided suitable crystallines for X-ray analysis to reveal 2*S*,3*R*,4*R* configuration (Fig. 1), thereby major isomer **6** and its tribenzyl ether derivative **8** should have 2*S*,3*S*,4*S* configuration. Finally, by comparing NMR (^{1}H, ^{19}F and ^{13}C) data and $[\alpha]_D$ value of **4** with those of both **8** and **9**, it was concluded that the physical properties of **4** were identical with those of **8** except for the sign of $[\alpha]_D$ value; that is, **4** has 2*R*,3*R*,4*R* configuration.[9]

In conclusion, the asymmetric synthesis of difluorocyclopropanes described here shows a potential utility of the crotonate **1** as a building block. Further examinations with other Michael donors and applications to preparation of difluorocyclopropane derivatives of biological interest are currently investigated.

Scheme 2

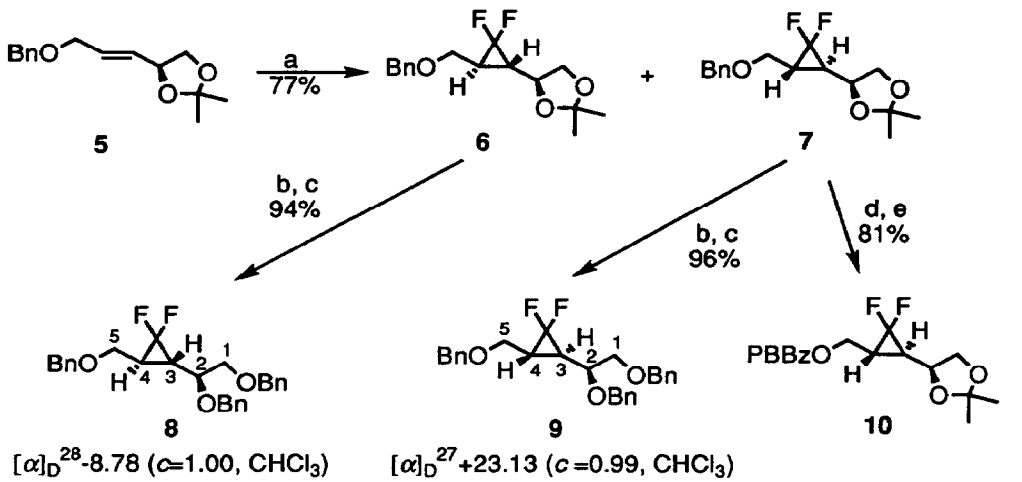


3a (major isomer)

4 $[\alpha]_D^{28}$+8.28 (c=0.99, $CHCl_3$)

(a) LiOH, 30%H_2O_2-THF, rt (b) BH_3-DMS, THF (c) NaH, BnBr, DMF

Scheme 3



5 **6** **7** **8** **9** **10**

$[\alpha]_D^{28}$-8.78 (c=1.00, $CHCl_3$) $[\alpha]_D^{27}$+23.13 (c=0.99, $CHCl_3$)

(a) $ClCF_2COONa$, diglyme, 180° (b) 10% HCl-MeOH (c) NaH, BnBr, DMF
(d) H_2/Pd-C, MeOH (e) p-BrBz-Cl, Et_3N

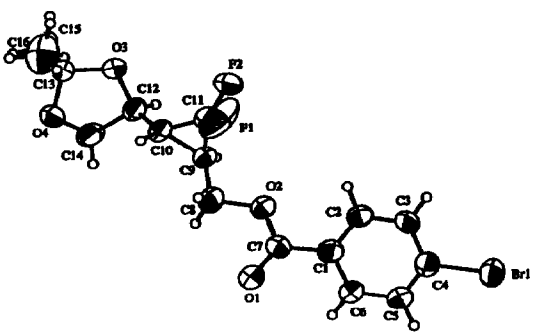


Fig.1 X-Ray Crystal Structure of **10**

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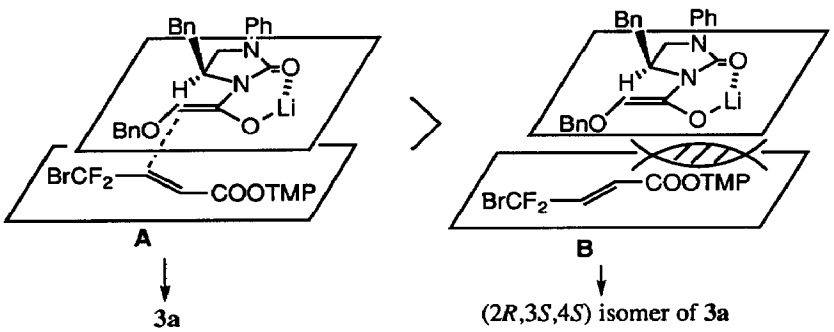
7. **8**, colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.67 (1H, ddd, J=14.8, 7.5, 7.5 Hz), 1.82 (1H, ddd, J=14.0, 13.8, 7.2 Hz), 3.45-3.70 (5H, m), 4.54 (2H, ABq, J=11.9 Hz), 4.60 (2H, ABq, J=14.6 Hz), 4.69 (2H, ABq, J=11.8 Hz), 7.20-7.45 (15H, m); ^{19}F-NMR (376 MHz, $CDCl_3$; relative to benzotrifluoride) δ: -73.6 (1F, dd, J=163.5, 13.8 Hz), -74.7 (1F, dd, J=163.5, 14.8 Hz); selected signals of ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 27.38 (t, J=9.94 Hz), 28.33 (t, J=9.42 Hz), 113.4 (t, J=287.1 Hz). **9**, colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.55-1.75 (2H, m), 4.45-4.75 (6H, m), 4.51 (2H, ABq, J=12.0 Hz), 4.55 (2H, ABq, J=12.2 Hz), 4.64 (2H, ABq, J=11.8 Hz), 7.20-7.40 (15H, m); ^{19}F-NMR ($CDCl_3$) δ: -72.0 (1F, dd, J=160.9, 13.5 Hz), -75.8 (1F, dd, J=160.9, 13.4 Hz); selected signals of ^{13}C-NMR ($CDCl_3$) δ: 25.69 (t, J=10.7 Hz), 28.32 (t, J=11.1 Hz), 114.2 (t, J=286.5 Hz).
8. **10**, colorless needles. mp 68-70.5°C, $[\alpha]_D^{26}$ +38.6 (*c*=1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, s), 1.44 (3H, s), 1.79 (1H, m), 1.91 (1H, m), 3.70 (1H, dd, J=8.26, 5.93 Hz), 3.94 (1H, ddd, J=8.49, 6.0, 6.0 Hz), 4.08 (1H, dd, J=8.26, 6.08 Hz), 4.39 (3H, m), 7.60 (2H, m), 7.90 (2H, m); ^{19}F-NMR ($CDCl_3$) δ: -74.99 (1F, dd, J=166, 11.3 Hz), -75.57 (1F, dd, J=166, 11.9 Hz).
9. The observed diastereoselectivity of the cyclopropane **3a** may be explained by considering a transition state model **A**, in which the reaction at the *Re* face of the (*Z*)-enolate of **2a** with **1** occurrs preferentially when **1** approaches in a way to minimize steric interaction between TMP ester part and the imidazolidinone part as shown below.[4]



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