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Bis-*exo*-2-norbornylboron Triflate for Stereospecific Enolization of 3,3,3-Trifluoropropionates

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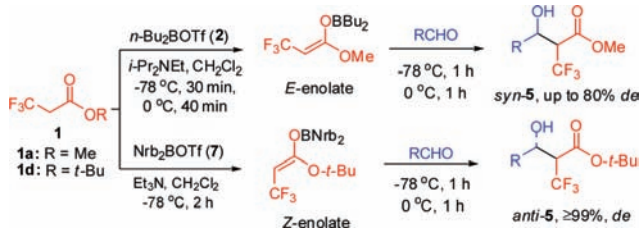
ABSTRACT



The first boron-mediated enolization−aldolization of 3,3,3-trifluoropropionates has been reported. The preparation and application of bis-*exo*-bicyclo[2.2.1]heptan-2-ylboron triflate as a superior reagent for diastereospecific enolization has also been described.

Altering the biological properties of organic molecules via fluorine substitution has been an efficient strategy in the design and development of effective drugs.[1] This trend has motivated synthetic chemists to develop novel methods to stereo- and regioselectively place fluoroalkyl groups in organic molecules.[2] The stereocontrolled cross-aldol reaction is a powerful synthetic tool. However, the metal enolates of α-CF_3 ketones often underwent defluorination, leading to the formation of α,β-unsaturated difluorocarbonyls.[3] Successful reports of enolate preparation of a CF_3-ketone involve either DIBAL-H reduction of alkenyl phosphate[4] or treatment with $TiCl_4$ in the presence of Et_3N.[3] The latter protocol requires the addition of Ti(O-*i*-Pr)$_4$ during the aldolization step, lest the yield is very poor.

One of the hallmarks of the boron-mediated cross-aldol reaction is the high level of stereocontrol,[5] although the enolborinates of fluorocarbonyls have rarely been described.[6] The enolboration of esters remained relatively unexplored[7] until Abiko and Masamune described the efficacy of dialkylboron triflates for the diastereoselective and substrate-controlled enantioslective aldol reaction.[8] An efficient reagent-controlled enantioselective enolboration−aldolization of propionates was executed by us to prepare the synthons of the potent antitumor agent (−)-dictyostatin.[9] As part of our program on fluoroorganic synthesis via boranes,[10] we were

(1) (a) Filler, R.; Saha, R. *Future Med. Chem.* **2009**, *1*, 777. (b) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: West Sussex, U.K., 2009.

(2) (a) Cao, L. L.; Gao, B. L.; Ma, S. T.; Liu, Z. P. *Curr. Org. Chem.* **2010**, *14*, 889. (b) Cahard, D.; Xu, X.; Couve-Bonnaire, S.; Pannecoucke, X. *Chem. Soc. Rev.* **2010**, *39*, 558. (c) Prakash, G. K. S.; Wang, F.; Stewart, T.; Mathew, T.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2009**, *106*, 4090. (d) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817.

(3) Ito, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174.

(4) Ishihara, T.; Kuroboshi, M.; Yamaguchi, K.; Okada, Y. *J. Org. Chem.* **1990**, *55*, 3107.

(5) Cowden, C. J.; Paterson, I. *Org. React. (N.Y.)* **1997**, *51*, 1.

(6) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1191.

(7) (a) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (b) Brown, H. C.; Ganesan, K. *Tetrahedron Lett.* **1992**, *33*, 3421. (c) Ganesan, K.; Brown, H. C. *J. Org. Chem.* **1994**, *59*, 2336.

(8) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Org. Chem.* **1996**, *61*, 2590. (b) Abiko, A. *Acc. Chem. Res.* **2004**, *37*, 387. (c) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250. (d) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

(9) Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2009**, *11*, 1467.

(10) Ramachandran, P. V.; Chatterjee, A. *Org. Lett.* **2008**, *10*, 1195.

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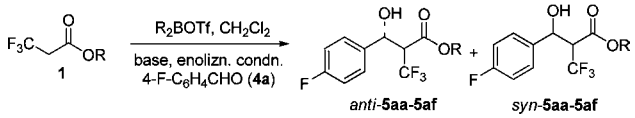
interested in the synthesis of dictyostatin wherein the C6-methyl is swapped for a trifluoromethyl group.[11] Consequently, we examined the enolboration−aldolization of 3,3,3-trifluoropropionates (**1**).[12,13] Herein, we describe the development of bis-*exo*-2-norbornylboron triflate as a reagent for the facile, diastereospecific incorporation of *anti*-α-trifluoromethyl *β*-hydroxy moieties.

As a first step, we set out to optimize the conditions for the diastereoselective enolboration to realize either the *syn*- or *anti*-aldols from 3,3,3-trifluoropropionates. Accordingly, we prepared the methyl (**1a**), ethyl (**1b**), isopropyl (**1c**), *tert*-butyl (**1d**), benzyl (**1e**), and phenyl (**1f**) esters from 3,3,3-trifluoropropionic acid[14] and examined their enolboration with di-*n*-butylboron triflate (*n*-Bu_2BOTf, **2**) in the presence of diisopropylethylamine (conditions A) and dicyclohexylboron triflate (Chx_2BOTf, **3**) in the presence of triethylamine (conditions B).[15] Upon aldolization of 4-fluorobenzaldehyde (**4a**), the *syn*- and *anti*-aldols,[16] respectively, were obtained from these enolates (Table 1). On the basis of the aldol

Table 1. Effect of R Group of Ester on Enolization with **2** and **3**

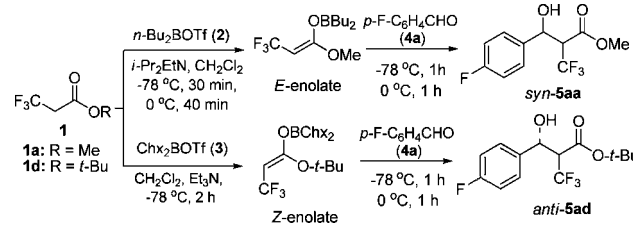


				aldol		
no.	**1**	R	enol. conditions[a]	**5**[b]	yield[c] (%)	*syn*/*anti*[d]
1	**1a**	Me	A	**5aa**	69	86:14
2	**1a**	Me	B	**5aa**	71	21:79
3	**1b**	Et	A	**5ab**	71	84:16
4	**1b**	Et	B	**5ab**	80	10:90
5	**1c**	iPr	A	**5ac**	52	76:24
6	**1c**	iPr	B	**5ac**	72	6:94
7	**1d**	tBu	A	**5ad**	62	53:47
8	**1d**	tBu	B	**5ad**	76	5:95
9	**1e**	Bn	A	**5ae**	65	82:18
10	**1e**	Bn	B	**5ae**	81	6:94
11	**1f**	Ph	A	**5af**	61	60:40
12	**1f**	Ph	B	**5af**	20	50:50

[a] A: **2**, *i*-Pr_2NEt, −78 °C, 30 min, 0 °C, 40 min. B: **3**, Et_3N, −78 °C, 2 h. [b] The first letter refers to the aldehyde, and the second letter refers to the ester. [c] Combined yield of *syn* and *anti* isomers. [d] *Syn* and *anti* ratios were determined by ^{19}F NMR spectroscopy.[16]

stereochemistry, we deduce that the optimal conditions were achieved with an ester−reagent combination of **1a** and **2** for *E*-enolates and **1d** and **3** for *Z*-enolates (Scheme 1).[17] In contrast with the nonfluorinated alkyl propionates,[8a] the *syn*-

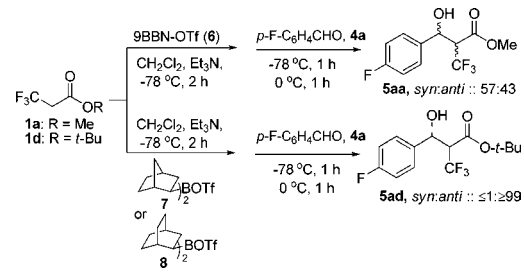
Scheme 1. Optimization of Enolization Conditions Using **2** and **3**



aldols were obtained with lower diastereoselectivity, although the *anti*-aldols were realized with relatively high selectivity.[18]

The effect of the alkyl groups of the dialkylboron triflates was then examined[19] to improve the diastereoselectivity for the enolization and aldolization. 9-Borabicyclo[3.3.1]nonyl trifluoromethanesulfonate (9-BBN-OTf, **6**), a reagent with lower steric requirements for the *E*-selective enolboration,[17,19] was examined with the expectation of better selectivity for the *syn*-aldols. Unexpectedly, enolization of the *syn*-favoring ester **1a** with **6** in the presence of *i*-Pr_2NEt decreased the selectivity to 57:43 (Scheme 2). An examina-

Scheme 2. Enolboration−Aldolization with Reagents **6**−**8**



tion of the ^{19}F NMR spectrum of the 9-BBN enolate revealed an isomeric ratio of 53:47, which essentially corresponds to the aldol stereoisomeric ratio. We are further investigating this.

Since the C6−C7 relationship in C6-CF_3-dictyostatin is *anti*, we focused our attention on bulkier boron triflates to achieve the maximum selectivity of *anti*-aldols.[19] To this end, we prepared two novel reagents, bis-*exo*-bicyclo[2.2.1]heptan-2-ylboron triflate (bis-*exo*-2-norbornylboron triflate, Nrb_2BOTf, **7**) and bis-*exo*-bicyclo[2.2.2]octan-2-ylboron triflate (Bco_2BOTf, **8**), from the corresponding dialkylboranes. Upon enolization of the *anti*-favoring ester **1d** with both of these reagents (Scheme 2), followed by aldolization, the *anti*-aldols were obtained *exclusively*, thus identifying **7** and **8** as superior reagents for the *Z*-selective[17] enolization of *tert*-butyl 3,3,3-trifluoropropionate. Reagent **7** was chosen for further studies due to the ready availability of norbornene.

(11) (a) Curran and co-workers have shown that the 6-methyl group influences the potency of (−)-dictyostatin. Hence, the preparation of 6-CF_3-dictyostatin: (b) Raccor, B. S.; Vogt, A.; Sikorski, R. P.; Madiraju, C.; Balachandran, R.; Montgomery, K.; Shin, Y.; Fukui, Y.; Jung, W.-H.; Curran, D. P.; Day, B. W. *Mol. Pharmacol.* **2008**, *73*, 718.

(12) For the aldolization of 3,3,3-trifluoropropanamides via silyl enolates, see: Shimada, T.; Yoshioka, M.; Konno, T.; Ishihara, T. *Org. Lett.* **2006**, *8*, 1129.

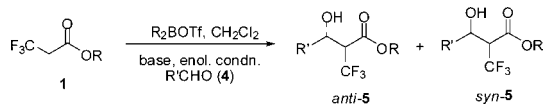
(13) For the aldolization of 3,3,3-trifluoropropanamides via titanium enolates, see: Franck, X.; Seon-Meniel, B.; Figadere, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 5174.

(14) Komata, T.; Akiba, S.; Hosoi, K.; Ogura, K. *J. Fluorine Chem.* **2008**, *129*, 35.

(15) The reagent−amine combination was selected on the basis of Abiko's study; see ref 8a.

With the above optimized conditions, the generality of our process was examined with a selected series of aldehydes with **2** (conditions A: *i*-Pr_2NEt, −78 °C, 30 min, 0 °C, 40 min) and **7** (conditions C: Et_3N, −78 °C, 2 h) and compared with **3** (conditions B: Et_3N, −78 °C, 2 h) (Table 2). The

Table 2. Examination of Aldehydes for the Aldol Reaction



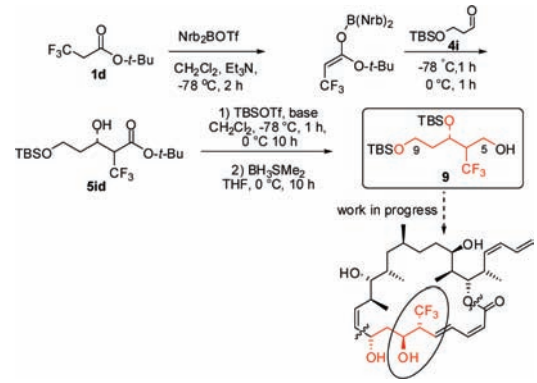
	R′CHO			aldol		
no.	**4**	R′	enol. conditions[a]	**5**[b]	yield,%[c]	*syn*/*anti*[d]
1	**4a**	*p*-FC_6H_4	A	**5aa**	69	86:14
2	**4a**	*p*-FC_6H_4	B	**5ad**	76	5:95
3	**4a**	*p*-FC_6H_4	C	**5ad**	74	≤**1:≥99**
4	**4b**	Ph	A	**5ba**	64	86:14
5	**4b**	Ph	B	**5bd**	79	6:94
6	**4b**	Ph	C	**5bd**	87	≤**1:≥99**
7	**4c**	*p*-NO_2 C_6H_4	A	**5ca**	67	86:14
8	**4c**	*p*-NO_2 C_6H_4	B	**5cd**	90	9:91
9	**4c**	*p*-NO_2 C_6H_4	C	**5cd**	76	≤**1:≥99**
10	**4d**	*p*-MeO C_6H_4	A	**5da**	70	86:14
11	**4d**	*p*-MeO C_6H_4	B	**5dd**	81	4:96
12	**4d**	*p*-MeO C_6H_4	C	**5dd**	95	≤**1:≥99**
13	**4e**	*E*-PhCH=CH	A	**5ea**	50	90:10
14	**4e**	*E*-PhCH=CH	B	**5ed**	72	12:88
15	**4e**	*E*-PhCH=CH	C	**5ed**	75	≤**1:≥99**
16	**4f**	*n*-Pr	A	**5fa**	48	57:43
17	**4f**	*n*-Pr	B	**5fd**	65	8:92
18	**4f**	*n*-Pr	C	**5fd**	52	≤**1:≥99**
19	**4g**	*i*-Pr	A	**5ga**	63	75:25
20	**4g**	*i*-Pr	B	**5gd**	65	8:92
21	**4g**	*i*-Pr	C	**5gd**	73	≤**1:≥99**
22	**4h**	*t*-Bu	A	**5ha**	61	54:46
23	**4h**	*t*-Bu	B	**5hd**	40	9:91
24	**4h**	*t*-Bu	C	**5hd**	70	≤**1:≥99**

[a] A: R = Me, **2**, *i*-Pr_2NEt, −78 °C, 30 min, 0 °C, 40 min. B: R = *t*-Bu, **3**, Et_3N, −78 °C, 2 h. C: R = *t*-Bu, **7**, Et_3N, −78 °C, 2 h. [b] The first letter refers to the aldehyde, and the second letter refers to the ester. [c] Combined yield of *syn* and *anti* isomers. [d] *Syn* and *anti* ratios were determined by ^{19}F NMR spectroscopy.[16]

diastereomeric excess (de) for *syn*-aldols with reagent **2** is in the 72−80% range for aromatic aldehydes and lower for aliphatic aldehydes. Reagent **3** provided *anti*-aldols in 76−92% de. The bulky reagent **7** provided *anti*-aldols exclusively (≥99%) for all classes of aldehydes examined, thus confirming its control.

Pursuing our goal, we examined reagent **7** for the preparation of the CF_3-containing racemic substructure of C6-CF_3 dictyostatin. 1,3-Propanediol was monoprotected as the TBS ether and oxidized with DMP to the aldehyde (**4i**). Ester **1d** was converted to the *Z*-enolate with **7** and treated with **4i** to obtain the aldol **5id** in 88% yield and ≥99% selectivity. This hydroxy ester was protected as the TBS ether and reduced with BH_3·SMe_2 to the corresponding alcohol **9**. This constitutes the synthesis of the racemic C5−C9 framework of our target (Scheme 3).

Scheme 3. Preparation of Racemic C5−C9 Framework of 6-CF_3-dictyostatin



In conclusion, our investigations concentrated on the boron-mediated enolization of 3,3,3-trifluoromethylpropionates, and we have described the first successful enolboration−aldolization of these fluoroesters. Contrary to the

(16) (a) The diastereomer ratio (dr) was determined by ^{19}F NMR spectroscopy. (b) For the assignment of the *syn* and *anti* configuration, see: Sakamoto, T.; Takahashi, K.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1999**, *64*, 9467.

(17) Note that the *E*-enolate for the esters is similar to the *Z*-enolate for ketones.

(18) In comparison, the $TiCl_4$-catalyzed aldol reaction of silicon enolates (ref 12) and TMEDA-assisted aldol reaction of titanium enolates (ref 13) of trifluoropropanamides provide *syn*-products selectively.

(19) Brown and co-workers have shown that decreased bulk on boron favors *syn*-aldol and increased bulk favors *anti*-aldols for ketone enolization−aldolization. Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem.* **1992**, *57*, 3767.

(20) **Typical Procedure for the *Anti*-Selective Aldol Reaction.** Bis-*exo*-2-norbornylborane (Nrb_2BH) (2.5 mmol), prepared from norbornene and BH_3·SMe_2, was transferred to an oven-dried 50 mL round-bottom flask in a glove bag. Methylene chloride (5 mL) was added, and the mixture was cooled to 0 °C, followed by the addition of trifluoromethanesulfonic acid (2.8 mmol). The reaction mixture was stirred at ambient temperature for 1 h and cooled to −78 °C, and triethylamine (3.6 mmol) was added dropwise via syringe, followed by the addition of *tert*-butyl 3,3,3-trifluoropropionate (1 mmol). The resulting solution was stirred at this temperature for 2 h. The aldehyde (1.5 mmol) in methylene chloride (1 mL) was then added, dropwise, to the above enolate solution and stirred for an additional 1 h, followed by stirring at 0 °C for 1 h. The reaction was quenched by the addition of pH 7 buffer solution (2 mL). The mixture was diluted with MeOH (2 mL), followed by the careful addition of 30% hydrogen peroxide (2 mL), and stirred vigorously for 6−8 h. The reaction mixture was partitioned between water (4 mL) and methylene chloride (20 mL), the aqueous layer was extracted with methylene chloride, and the combined organics were washed with brine (5 mL), dried (anhydrous Na_2SO_4), filtered, concentrated, and purified by silica gel chromatography to obtain the pure *anti*-aldol product. **Typical Procedure for the *Syn*-Selective Aldol Reaction.** 3,3,3-Trifluoropropionates (1 mmol) and methylene chloride (4 mL) were transferred to an oven-dried 50-mL round-bottom flask under nitrogen. This solution was cooled to −78 °C, and a solution of *n*-butylboron triflate in dichloromethane (2 mmol) was added, followed by the dropwise addition of diisopropylethylamine (3 mmol). The resulting solution was stirred at this temperature for 30 min and 0 °C at 40 min. The aldehyde (0.75 mmol) in methylene chloride (1 mL) was added dropwise to the enolate solution. The reaction mixture was stirred for 1 h at −78 °C and 1 h at 0 °C and quenched by addition of pH 7 buffer solution (2 mL). The mixture was diluted with MeOH (2 mL), followed by the careful addition of 30% hydrogen peroxide (2 mL), and stirred vigorously for 6−8 h. The reaction mixture was partitioned between water (4 mL) and methylene chloride (20 mL). The aqueous layer was extracted with methylene chloride, and the combined organics were washed with brine (5 mL), dried (anhydrous Na_2SO_4), filtered, concentrated, and purified by silica gel chromatography to obtain the pure *syn*-aldol product.

nonfluorinated propionates, the *syn*-aldols were obtained in relatively lower de. The high de for the *anti*-aldols were improved further by utilizing a bulkier reagent for enolization. The preparation and application of bis-*exo*-2-norbornylboron triflate as a superior reagent for diastereospecific enolization has been described[20] in conjunction with the preparation of the critical subunit of C6-CF_3-dictyostatin. This process should find application in the efficient preparation of trifluoromethyl analogues of various pharmacologically active compounds bearing an α-methyl hydroxyl unit. Further investigations are in progress to improve the *syn*-selectivity and to develop a substrate- and reagent-controlled enantioselective reaction.

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Supporting Information Available: Experimental details and spectral data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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