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Gem-Difluorinated Homoallyl Alcohols, *β*-Hydroxy Ketones, and *syn*- and *anti*-1,3-Diols via *γ*,*γ*-Difluoroallylboronates

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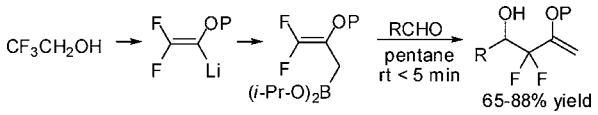
ABSTRACT



***γ*,*γ*-Difluoroallylboronates have been prepared from trifluoroethanol and utilized for the allylboration of a variety of aldehydes to provide *gem*-difluorinated homoallylic alcohols. α-Chiral aldehydes were allylborated in 4:1–13:1 diastereoselectivity favoring the *anti*-isomer. A representative series of difluorinated hydroxyl enol ethers were converted to the corresponding α,α-difluoro-*β*-hydroxy ketones. Diastereoselective reduction of one of these to either *syn*- and *anti*-1,3-diol was also studied.**

Fluorine often influences the delivery and metabolism of pharmaceuticals.[1] Geminal difluoromethylated molecules are valued intermediates and targets in drug design owing to their unique biological properties, such as enzyme inhibition.[1] The preparation of fluoro-aromatic and trifluoromethylated aliphatic compounds are becoming commonplace, whereas *gem*-difluorinated aliphatic compounds warrant further development.[2] Allylation is frequently utilized by synthetic chemists for stitching together simple and complex natural and unnatural molecules.[3] The preparation and reaction of *gem*-difluorinated homoallyl alcohols via allylmetals, such as allylsilanes,[4] -lithium,[5] -tin,[6] -zinc,[7] -indium,[8] etc. have been described. Although allylboranes are readily synthesized and possess demonstrated advantages,[9] there has been no report of fluorine-containing allylboranes or -boronates. Herein we describe the first synthesis of *γ*,*γ*-difluoroallylboronates from trifluoroethanol and their applications for tailored gem-difluorinated synthons.

Allylboranes can be prepared via transmetalation, hydroboration of allenes, Pd-catalyzed addition of boron to 1,3-dienes, allylic acetates, conjugate-addition elimination, and homologation of vinylmetals.[9] The availability of a variety of fluorovinylmetals[10] encouraged us to adopt the homologation approach for fluoroallylboranes. We sought to utilize Nakai's alkoxydifluorovinyllithium, readily accessed from trifluoroethanol,[11] for the eventual synthesis of difluorinated synthons (Scheme 1).

(1) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
(2) (a) Romanenko, V. D.; Kukhar, V. P. *Chem. Rev.* **2006**, *106*, 3868. (b) Ma, J. A.; Cahard, D. *Chem. Rev.* **2006**, *105*, 4581. (c) Tozer, M. J.; Herpinb, T. F. *Tetrahedron* **1996**, *52*, 8619.
(3) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(4) (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 4085. (b) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135.
(5) (a) Seyferth, D.; Simon, R. M.; Sepelak, D. J.; Klein, H. A. *J. Org. Chem.* **1980**, *45*, 2273. (b) Seyferth, D.; Simon, R. M.; Sepelak, D. J.; Klein, H. A. *J. Am. Chem. Soc.* **1983**, *105*, 4634.
(6) Seyferth, D.; Wursthorn, J. *J. Organomet. Chem.* **1979**, *182*, 455.
(7) Yang, Z.; Burton, D. J. *J. Org. Chem.* **1991**, *56*, 1037.
(8) Kirihara, M.; Takuwa, T.; Takizawa, S.; Momose, T.; Nemoto, H. *Tetrahedron* **2000**, *56*, 8275.
(9) For a review on pinane-based versatile "allyl" borane reagents, see: Ramachandran, P. V. *Aldrichim. Acta* **2002**, *35*, 23.
(10) Burton, D. J.; Yang, Z. Y.; Morken, P. A. *Tetrahedron* **1994**, *50*, 2993.
(11) (a) Tanaka, K.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1978**, *19*, 4809. (b) Nakai, T.; Tanaka, K.; Ishikawa, N. *Chem. Lett.* **1976**, 1263.

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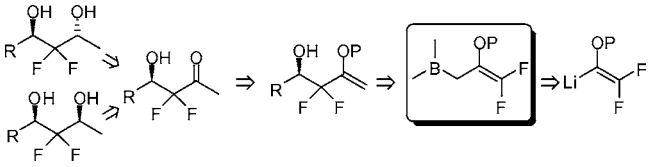
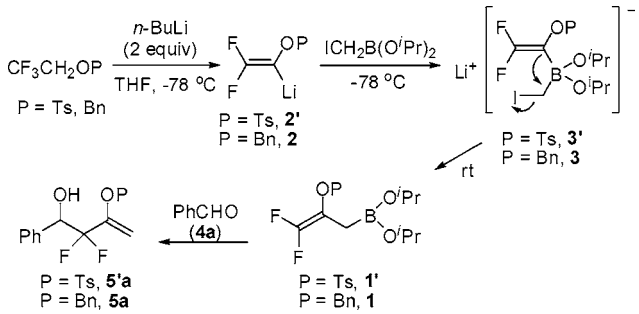
Scheme 1. Retrosynthesis of Difluoro-Synthons



Initially, we examined the homologation[12] of tosyloxydifluorovinyllithium (**2′**),[13] prepared from trifluoroethanol tosylate, with diisopropyl iodomethylboronate[14] at −78 °C. Gratifyingly, the resultant "ate complex" (**3′**) (^{11}B NMR spectrum: δ 2 ppm, singlet), upon warming to room temperature (rt), displaced the iodide with the tosyloxydifluorovinyl group to furnish the desired allylboronate (**1′**) within 12 h (Scheme 2, ^{11}B: δ 28 ppm). Subsequent

Scheme 2. Preparation and Reaction of γ,γ-Difluoroallyl-Boronates



allylboration of benzaldehyde (**4a**) revealed no reaction at rt, but proceeded to completion in 24 h under refluxing THF (^{11}B NMR shift from δ 28 to 18 ppm). Aqueous workup provided the corresponding difluorinated homoallylic alcohol **5′a** in 60% yield.

Presuming that the slow rate of allylboration could be the consequence of decreased electron-density on the alkene due to the tosyl group, we sought to commence the synthesis of the allylboronate with trifluoroethanol bearing other protecting groups. Due to the ease of its removal, benzyl 2,2,2-trifluoroethyl ether was treated with two equiv of *n*-butyllithium in THF to provide the difluorovinyllithium (**2**). This underwent facile homologation with diisopropyl iodomethylboronate within 1 h to provide β-benzyloxy-γ,γ-difluoroallylboronate **1**. An accelerated allylboration of **4a** was achieved *in situ*, within 1 h at rt, and an aqueous workup provided 3-benzyloxy-2,2-difluoro-1-phenyl-3-buten-1-ol (**5a**) in 45% isolated yield. The yield of the *in situ* allylboration could be improved to 76% by preparing the reagent **1** from benzyl 2,2-difluorovinyl ether. Indeed, the yield could be further improved to 82% by utilizing distilled **1**.

This new difluoroallylboration was then extended to a variety of aromatic, aliphatic, and fluorinated aldehydes. Electron-donating (**4b**) or withdrawing (**4c**−**d**) groups on the phenyl ring, the steric bulk of the aliphatic aldehydes (**4f**−**j**), or fluorine substitution (**4e**, **4k**) did not have a noticeable effect on the yields. All reacted within 1−5 h, except the bulky pivaldehyde (**4i**), which required 30 h for completion. This prompted a solvent study[15] and examination of pentane, toluene, and dichloromethane revealed that the reaction proceeded faster in these solvents. Noticeably, reagent **1** was consumed by all of the aldehydes almost instantaneously in pentane. The results are summarized in Table 1.

Having standardized the reagent preparation and reaction conditions, the diastereoselectivity of the difluoroallylboration of chiral aldehydes was probed. (*S*)-3-(tert-butyldimethylsilyloxy)-2-methylpropanal (**4l**), (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**4m**), and (*R*)-2-phenylpropanal (**4n**) underwent allylboration instantly at rt to provide the product alcohols with diastereoselectivity in the range 4:1 to 13:1 (Table 1, entry 12−14). The upfield resonance of the CF_2 group for the major isomers of **5l**−**n** in the ^{19}F NMR spectra revealed them to be *anti* on the basis of literature report.[16] The diastereomers of **5l** were separated by column chromatography to characterize the isomers. Conversion of the major isomer to the corresponding 3,5-dinitrobenzoate and examination by X-ray crystallography (Figure 1) confirmed it to be *anti*.

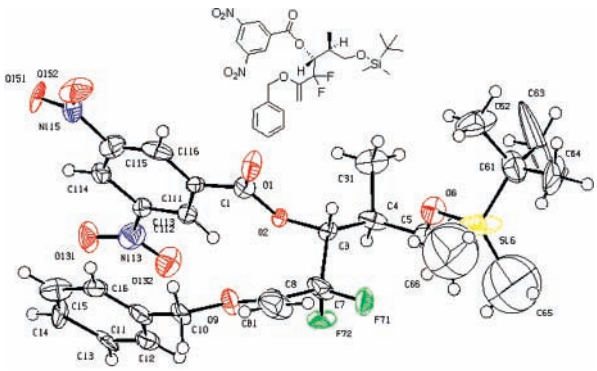
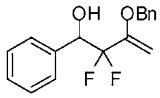
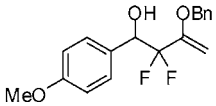
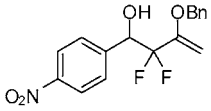
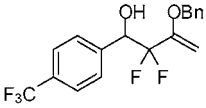
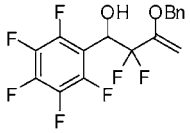
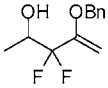
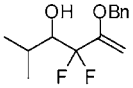
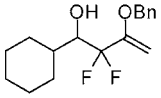
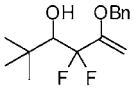
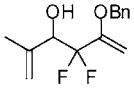
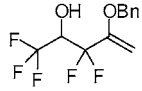
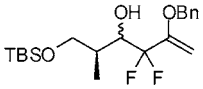
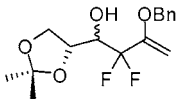
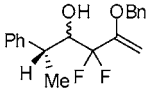


Figure 1. X-ray crystal structure of 3,5-dinitrobenzoate of the major isomer of **5l**.

Ishihara and co-workers have reported the synthesis of α,α-difluorinated-β-hydroxy ketones via the aldol reaction

(12) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398.
(13) (a) Ichikawa, J.; Kaneko, M.; Yokota, M.; Itonaga, M.; Yokoyama, T. *Org. Lett.* **2006**, *8*, 3167. (b) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 1641.
(14) (a) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100. (b) Wallace, R. H.; Zong, K. K. *Tetrahedron Lett.* **1992**, *33*, 6941.
(15) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.
(16) Zhang, X.; Xia, H.; Dong, X. C.; Jin, J.; Meng, W. D.; Qing, F. L. *J. Org. Chem.* **2003**, *68*, 9026.
(17) Kuroboshi, M.; Ishihara, T. *Tetrahedron Lett.* **1987**, *28*, 6481.
(18) Hydrogenation of the protected alcohol (**5a**) resulted in a 1:1 mixture of *syn* and *anti* diol which were separated as their cyclic acetal and characterized fully.

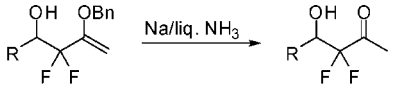
Table 1. Difluoroallylboration of Aldehydes with **1b**[a]

entry	RCHO no.	homoallyl alcohol	no.	yield[b] (%)
1	**4a**		**5a**	82
2	**4b**		**5b**	88
3	**4c**		**5c**	76
4	**4d**		**5d**	75
5	**4e**		**5e**	72
6	**4f**		**5f**	85
7	**4g**		**5g**	82
8	**4h**		**5h**	76
9	**4i**		**5i**	85
10	**4j**		**5j**	72
11	**4k**		**5k**	75
12	**4l**	 anti:syn = 4:1	**5l**[c]	72
13	**4m**	 anti:syn =4:1	**5m**[c]	84
14	**4n**	 anti:syn = 13:1	**5n**[c]	75

[a] Reactions were carried out in pentane at rt with 1.2 equiv reagent within 5 min. [b] Isolated yield of pure product. [c] *syn/anti* ratio determined using ^{19}F NMR spectrum of the crude reaction mixture.

of chlorodifluoromethyl ketones in the presence of zinc, a catalytic amount of copper(I) chloride or silver(I) acetate, and molecular sieves.[17] Having prepared a variety of α,α-difluorinated *β*-hydroxyl enol benzyl ethers in high yields, we undertook their conversion to a representative series of α,α-difluorinated-*β*-hydroxy ketones for further conversion to either the *syn* or *anti*-2,2-difluoro-1,3-diols.[18] While reagents, such as BF_3-Et_2O, 6N HCl, ceric ammonium nitrate, and DDQ debenzylated in poor to moderate yields, Na in liquid NH_3 provided the highest yield for the hydroxy ketone. Thus, the treatment of **5a** with Na in liquid NH_3[19] yielded 78% of the *β*-hydroxy ketone **6a**. This protocol was then extended to include **5b**, **5h**, and **5i**. The corresponding hydroxy ketones were obtained in 75−82% yields (Scheme 3).

Scheme 3. Preparation of α,α-Difluoro-*β*-hydroxy Ketones



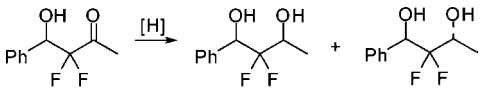
5a: R = Ph
5b: R = 4-MeO-Ph
5h: R = Chx
5i: R = *t*-Bu

6a: R = Ph, 78%
6b: R = 4-MeO-Ph, 75%
6h: R = Chx, 79%
6i: R = *t*-Bu, 82%

Diastereoselective reduction of *β*-hydroxyketones is a well studied topic in organic chemistry.[20] Kuroboshi and Ishihara had conducted a systematic study on the diastereoselective reduction of α,α-difluoro-*β*-hydroxy ketones to prepare the corresponding *syn*- and *anti*-1,3-diols, utilizing DIBALH in the presence of $ZnCl_2$-TMEDA and triisopropoxyaluminum, respectively.[21] They had observed that contrary to the reduction of non-fluorinated systems, *anti*-selective reagents DIBALH afforded the *syn*-diol predominantly and tetramethylammonium triacetoxyborohydride provided a complex mixture.

A variety of reducing agents were examined for the reduction of **6a** and the results are summarized in Table 2. Confirming Ishihara's results, we achieved the *syn*-diol (*syn*-**7a**) in high yields by reduction with DIBALH in the presence

Table 2. Diastereoselective Reduction of α, α-difluoro-*β*-hydroxy Ketone **6a**



6a *syn*-**7a** *anti*-**7a**

entry	reducing agent	temp (°C)	time, h	yield[a]	*syn*/*anti*[b]
1	$Me_4N(OAc)_3BH$	−40	24	90	25:75
2	$Na(OAc)_3BH$	−40	24	92	20:80
3	$Al(O^iPr)_3$	rt	48	94	19:81
4	$LiAl(^tBuO)_2H_2$	−78	6	85	59:41
5	$NaBH_4/Et_3B$/MeOH	rt	4	88	76:24
6	DIBAL-H/NMO	−78	8	89	87:13
7	DIBALH/$ZnCl_2$-TMEDA	−78	8	92	93:7

[a] Isolated yield of pure product. [b] Ratio determined by ^{19}F NMR of the crude reaction mixtures of the corresponding acetals.

of $ZnCl_2$-TMEDA and also with DIBALH-NMO.[22] Nevertheless, *anti*-**7a** was obtained predominantly with both tetramethylammonium and sodium triacetoxyborohydride (entry 1 and 2). Meerwein-Ponndorf-Verely reduction provided primarily the *anti*-isomer, whereas reduction under Narasaka's conditions[23] with sodium borohydride in the presence of triethylborane and methanol provided the *syn*-product as the major isomer.

In conclusion, the preparation of difluorinated allylborating agents in high yield and purity via the homologation of lithiated difluorovinyl ethers derived from trifluoroethanol has been described. A variety of aldehydes, including α-chiral aldehydes, were successfully allylborated almost instantly in pentane at rt to provide the *gem*-difluorinated homoallylic alcohols in good yields.[24] A representative series of difluorinated hydroxyl enol ethers were converted to the corresponding α,α-difluoro-*β*-hydroxy ketones, and one of these ketones was further reduced to either *syn*- and *anti*-1,3-diol in high diastereoselectivity. This methodology can be applied to the efficient preparation of various *gem*-difluoro-containing molecules, including sugars and lactones. This chemistry is currently being used to prepare chiral reagents, synthons, and targets.

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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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(19) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725.

(20) Brown, H. C.; Ramachandran, P. V. In *Reductions in Organic Chemistry*; ACS Sym. Ser. 641; Abdel Magid, A. F., Ed.; American Chemical Soc.: Washington, DC, 1996; Chapter 1.

(21) Kuroboshi, M.; Ishihara, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1185.

(22) Ramachandran, P. V.; Reddy, M. V.; Rudd, M. T. *Chem. Commun.* **1999**, 1979.

(23) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

(24) The preparation and representative reaction of **1** is as follows. (a) Preparation of benzyl-2,2,2-trifluoroethyl ether: Trifluoroethanol (20 g, 14.6 mL, 200 mmol) was added, slowly, to a suspension of NaH in THF (200 mL) (8.72 g, 55% dispersion in mineral oil, 200 mmol) at 0 °C and warmed to rt. When the hydrogen evolution ceased, benzyl bromide (30.8 g, 21.5 mL, 180 mmol) was added and refluxed for 3 h. The organic solvents were removed and the residue was washed with ether and the combined organics were washed with brine, dried (anhydrous $MgSO_4$), concentrated, and distilled to provide benzyl-2,2,2-trifluoroethyl ether as a colorless liquid (32 g, 94%). bp 80 °C/30 Torr. (b) Preparation of 1-benzyloxy-2,2-difluoroethene: Under vigorous stirring, at −100 °C, the above benzyl-2,2,2-trifluoroethyl ether (7.6 g, 40 mmol) was added, slowly over a period of 20 min, to a solution of *n*-BuLi (40 mL, 2.5 M solution in hexane, 100 mmol) in THF (120 mL) and kept stirring for another 2 h. The dark-red solution was quenched with methanol (12 mL) at this temperature, followed by the addition of aqueous saturated NH_4Cl solution (40 mL). The solution was warmed to rt and diluted with diethyl ether (200 mL). The ether layer was separated and the aqueous layer was washed with ether (3 × 20 mL). The combined ether layer was washed with brine, dried (anhydrous $MgSO_4$), and evaporated. The residue was distilled to yield 1-benzyloxy-2,2-difluoroethene as a colorless viscous liquid (5.2 g, 76%). bp. 70 °C/30 Torr. (c) Preparation of *β*-benzyloxy-*γ*,*γ*-difluoroallylboronate (**1**): *n*-BuLi (12.2 mL, 2.5 M solution in hexane, 30.4 mmol) was added, slowly at −78 °C, to a solution of 1-benzyloxy-2,2-difluoroethene (5.2 g, 30.4 mmol) in THF (60 mL) and at that temperature for 20 min. Diisopropyl iodomethylboronate (8.2 g, 30.4 mmol) was added slowly, at −78 °C, to the resultant red solution, left stirred for 0.5 h, allowed to warm to rt, and continued to stir for 2 h. The solvents were removed under vacuo, and the residue was triturated with dry pentane (30 mL). The supernatant was filtered through a short bed of celite under inert atmosphere. The residue was washed with pentane (4 × 20 mL), and the combined organics was concentrated and distilled to yield *β*-benzyloxy-*γ*,*γ*-difluoroallylboronate (**1**) as a colorless liquid. bp. 79−82 °C/0.2 Torr. (d) Representative procedure for allylboration: Allylboronate **1** (2.2 mL of 1 M solution in pentane, 2.2 mmol) was added to a solution of benzaldehyde (0.21 mL, 2 mmol) in pentane. Upon completion (^{11}B NMR spectroscopy: *δ* 28 to 18 ppm, 2 min), the reaction was quenched with 2 mL of sat. NH_4Cl solution. The product was extracted with ether (3 × 20 mL), dried (Na_2SO_4), concentrated, and purified by flash silica gel chromotography (hexane:ethyl acelate = 4:1) to yield homoallylic alcohol **5a** (0.48 g, 82 %) as a colorless viscous liquid.