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# Asymmetric Fluoroallylboration of Aldehydes

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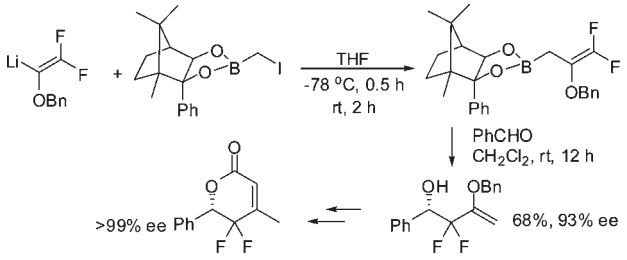
## ABSTRACT




**Contrary to previous reports, the homologation of benzyloxydifluorovinyllithium with bulky chiral iodomethylboronates readily provides a series of chiral $\gamma,\gamma$-difluoroallylboronates. Asymmetric fluoroallylboration of aldehydes with a 2-phenylbornane-2,3-diol-derived reagent provides *gem*-difluorinated homoallyl alcohols in good yields and 77−95% ee. Preparation of a chiral $\alpha$-pyrone in >99% ee has also been described.**

Asymmetric allylboration is an important carbon–carbon bond-forming reaction for organic syntheses.[1] Partially fluorinated biologically active molecules are often enhanced in their potency and bioavailability.[2] As part of our ongoing projects on fluoroorganic synthesis via boranes,[3] we had reported the preparation of chiral fluorinated homoallyl alcohols via the asymmetric allylboration of fluoro aldehydes.[4] We recently described the preparation of a fluorinated allylborating agent, $\beta$-benzyloxy-$\gamma,\gamma$-difluoroallylboronate (**1**),[5] for the synthesis of $\alpha$-*gem*-difluorinated homoallyl alcohols and dihydropyrones.[6] In continuation, we herein report the successful synthesis of chiral $\gamma,\gamma$-difluoroallylboronates and the subsequent allylboration of aldehydes for the preparation of highly enantioenriched *gem*-difluorinated homoallyl alcohols[7] and derivatives.

The simplest protocol envisioned to prepare the chiral analogues of the difluoroallylboronate reagent was to transesterify the isopropoxy groups with a chiral diol (Scheme 1).[8] On the basis of the success of the tartrate esters in allylborations,[9] diisopropyl tartrate (**2a**) was

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(4) Kumar, D. J. S.; Madhavan, S.; Ramachandran, P. V.; Brown, H. C. *Tetrahedron: Asymmetry* **2000**, *11*, 4629.

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(7) For reports on the preparation of optically active *gem*-difluoroohomoallyl alcohols via enzymatic resolution, see: (a) Kirihara, M.; Kawasaki, M.; Katsumata, H.; Kakuda, H.; Shiro, M.; Kawabata, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2283. (b) Itoh, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591. (c) You, Z.-W.; Jiang, Z.-X.; Wang, B.-L.; Qing, F.-L. *J. Org. Chem.* **2006**, *71*, 7261. (d) Itoh, T.; Kudo, K.; Yokota, K.; Tanaka, N.; Hayasa, S.; Renou, M. *Eur. J. Org. Chem.* **2004**, 406. (e) Kaneda, T.; Komura, S.; Kitazume, T. *J. Fluorine Chem.* **2005**, *126*, 17.

(8) (a) Nyzam, V.; Belaud, C.; Zammattio, F.; Villiéras, J. *Bull. Soc. Chim. Fr.* **1997**, *134*, 583. (b) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3250.

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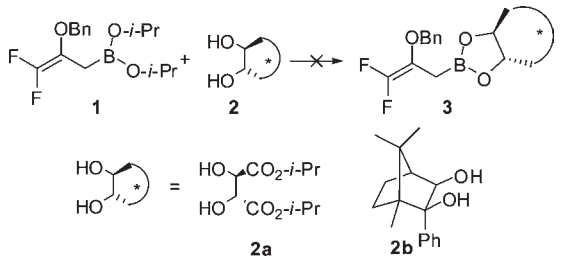
**Scheme 1.** Failed Trans-Esterification of Difluoroallylboronate

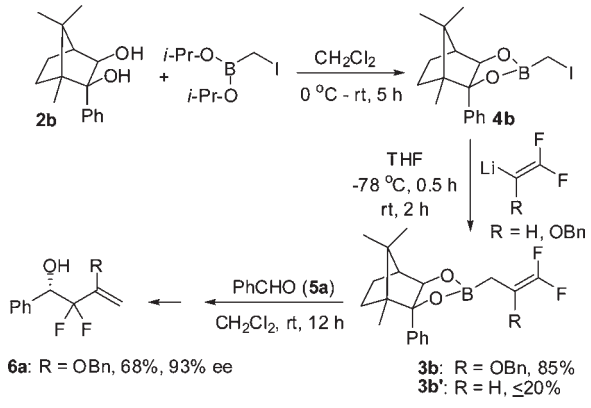



treated with **1** in tetrahydrofuran (THF) at room temperature (rt) for 4 h. However, there was no evidence of any transesterification even under reflux for 4 h. Changing the solvents also did not facilitate the reaction. Contrary to the report by Kennedy and Hall, transesterification with the (+)-camphor-derived 2-phenylbornane-2,3-diol **2b**[10] also met with the same fate.[11]

We then opted to prepare the chiral allylboronate via the homologation[12] of benzyloxydifluorovinyllithium (derived from trifluoroethanol)[5a] using the camphor diol iodomethylboronate **4b** reported previously.[11,13] Hall had reported the failed homologation of a vinylcuprate using **4b**.[11] Roush also had reported the failed homologation of silylvinylcuprate and silylvinyllithium employing **4b**.[13] However, we were interested in understanding the effect, if any, of the fluorine atoms or the benzyloxy group of the benzyloxydifluorovinyllithium on the homologation.

To our delight, the transesterification of diisopropyl iodomethylboronate[14] with **2b** followed by homologation of benzyloxydifluorovinyllithium in THF (Scheme 2) afforded the necessary reagent **3b**. To delineate the effect of the fluorine and benzyloxy groups on the success of the homologation reaction, we examined the preparation of the parent $\gamma,\gamma$-difluoroallylboronate reagent (**3b′**). Treatment of 2,2-difluorovinyllithium[15] (prepared by the reaction of 1,1-difluoroethylene and *sec*-butyllithium) with **4b** provided a very low yield (≤20%) of **3b′** (Scheme 2). This

**Scheme 2.** Preparation and Reaction of Chiral Difluoroallylboronate




result suggests that the ease of homologation of **4b** is attributable to the benzyloxy group on the vinyl moiety. Further examination of this phenomenon is necessary.

Allylboration of benzaldehyde (**5a**), monitored by $^{11}B$ NMR spectroscopy (disappearance of peak at $\delta$ 33.5 ppm and appearance of the peak at $\delta$ 22.5 ppm), proceeded to completion within 12 h. An oxidative workup provided the chiral difluorinated homoallyl alcohol **6a** in 68% isolated yield as an oil. Determination of the enantiomeric purity using gas chromatographic (GC) analysis on a CP-Chirasil-Dex CB column revealed an ee of 93% in the *S*-isomer (vide infra).

The constitutional isomer of the bornanediol chiral auxiliary **2c** (Figure 1) was also converted to the iodomethylboronate **4c** and allylboronate **3c** as before. Allylboration of benzaldehyde furnished 42% of the fluorinated homoallyl alcohol **6a** in 27% ee in the *R*-isomer.

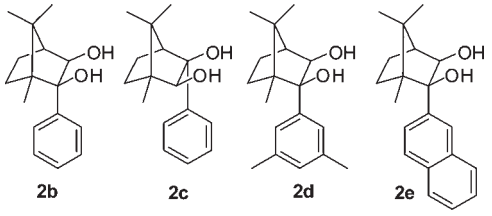


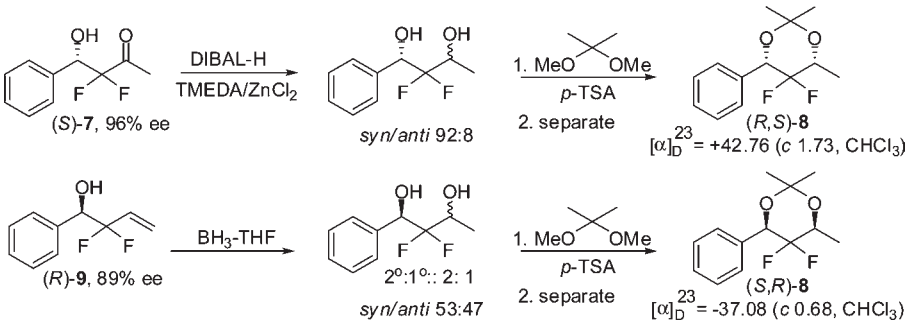

**Figure 1.** Camphor-derived chiral auxiliaries.

Clearly, the presence of the phenyl group adjacent to the bridgehead methyl group is important in achieving high ee. With the hope of improving the enantioselectivity in the asymmetric fluoroallylboration, novel bornanediols were prepared substituting the phenyl group in **2b** with a 3,5-dimethylphenyl (**2d**) and 2-naphthyl (**2e**) groups (Figure 1).[16] These were then converted to the chiral iodomethylboronates **4d** and **4e**, respectively, and eventually transformed to the corresponding fluoroallylborating agents **3d** and **3e**, respectively. Upon allylboration of benzaldehyde, the use of **3d** provided **6a** in 50% yield and 90% ee, whereas **3e** provided a 53% yield and 79% ee for the homoallyl alcohol. The results are summarized in Table 1.

We had previously reported a rapid fluoroallylboration in pentane with an achiral reagent.[5a] This prompted us to study the effect of solvents on the asymmetric

(10) Herold, T.; Schrott, U.; Hoffmann, R. W. *Chem. Ber* **1981**, *114*, 359.
(11) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412.
(12) Wuts, P. G. M.; Thompson, P. A.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398.
(13) Lira, R.; Roush, W. R. *Org. Lett.* **2007**, *9*, 4315.
(14) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100.
(15) Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 957.
(16) Lachance, H.; St-Onge, M.; Hall, D. G. *J. Org. Chem.* **2005**, *70*, 4180.
(17) Reist, E. J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725.
(18) See the Supporting Information for the ORTEP diagram of **7**.

**Scheme 3.** Stereochemical Correlation of **7** and **9**




fluoroallylboration. Benzaldehyde was reacted with **3b** in pentane, THF, and $CH_2Cl_2$. The reagent is only sparingly soluble in pentane, and the reaction in $CH_2Cl_2$ provided a slightly better yield and ee for **6a** than in THF (Table 1).

**Table 1.** Asymmetric Difluoroallylboration of Benzaldehyde (**5a**): Optimization of Reagent and Conditions[a]

| | | | homoallyl alcohol **6a** | | |
|---|---|---|---|---|---|
| entry | reagent **3** | solvent | yield[b] (%) | ee[c] (%) | isomer |
| 1 | **3b** | $CH_2Cl_2$ | 68 | 93 | *S*[d] |
| 2 | **3b** | THF | 62 | 92 | *S* |
| 3 | **3b** | pentane | [e] | | |
| 4 | **3c** | $CH_2Cl_2$ | 42 | 27 | *R*[f] |
| 5 | **3d** | $CH_2Cl_2$ | 50 | 90 | *S* |
| 6 | **3e** | $CH_2Cl_2$ | 53 | 79 | *S* |

[a] Reactions were carried out at rt with 1.5 equiv of crude reagent for 12 h. [b] Isolated yields of pure products. [c] Determined by GC analysis on a CP-Chirasil-Dex CB column. [d] On the basis of X-ray crystallographic analysis of **7** derived from **6a** and stereochemical correlation (Scheme 3). [e] No reaction due to the poor solubility of the reagent in pentane. [f] On the basis of GC analysis.

The stereochemistry of the homoallyl alcohol **6a**, obtained from **3d**–**e**, is the same as that obtained from **3b**, as determined by the GC analysis (vide supra). X-ray crystallographic analysis of the corresponding $\beta$-hydroxy ketone (3,3-difluoro-4-hydroxy-4-phenylbutan-2-one, **7**), obtained via debenzylation of **6a** with sodium in liquid ammonia,[5a,17] revealed it to be the *S*-isomer.[18] This was further confirmed by converting (*S*)-**7** to (*R*,*S*)-**8** as shown in Scheme 3 and comparing its optical rotation with that of (*S*,*R*)-**8**, prepared from the homoallylic alcohol (*R*)-**9**[7a] of known configuration.[19]

The formation of (S)-**7** can be rationalized by the transition-state model depicted in Figure 2.[11,20] It is noteworthy that the two fluorine atoms in the reagent have no influence in the stereochemical outcome of the reaction.[21]

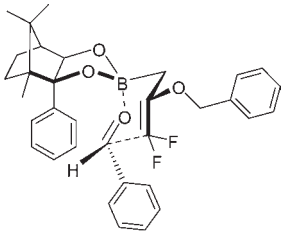


**Figure 2.** Transition-state model for the formation of **6a**.

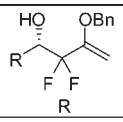
With the standardized conditions for achieving the optimal ee in hand, we probed the generality of reagent **3b** with a series of aldehydes of varying steric and electronic environments (Table 2). Strongly electron-withdrawing groups and steric demands affected the ee. Substitution of benzaldehyde at the *o*-, *m*-, and *p*-positions with an electron-donating methoxy group (**5b**–**d**) did not have any significant impact on the ee of the product alcohol. However, *p*-tolualdehyde (**5e**) provided an improved yield (79%) and 92% ee for the alcohol. Halogens, such as chlorine and fluorine in the *para*-position (**5h** and **5g**, respectively) also did not affect the ee. A *p*-$CF_3$ group (**5f**) decreased the ee slightly (88%), whereas a *p*-$NO_2$ group (**5i**) substantially lowered the ee to 78%. A decrease in ee was also observed when both the *ortho*-positions were blocked with methyl groups (**5j**). 1-Naphthaldehyde (**5k**) and an $\alpha,\beta$-unsaturated aldehyde, cinnamaldehyde (**5l**), afforded the alcohol in 89% and 93% ee, respectively. Hydrocinnamaldehyde (**5m**), a representative aliphatic aldehyde, also gave the product in 92% ee. Cyclohexanecarboxaldehyde (**5n**) increased the ee to 95%, and further increasing the bulk to a *tert*-butyl group [pivalaldehyde (**5o**)] decreased the ee to 78% (as that of **5j**). The yields were in the range of 45–79%, with the bulky aldehydes providing lowest yields. We believe that we have obtained

(19) (*R*)-**9** was prepared as described in ref 7a. For the preparation of **8**, see the Supporting Information.

(20) (a) Chataigner, I.; Lebreton, J.; Zammattio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719. (b) Mitra, S.; Gurrala, S. R.; Coleman, R. S. *J. Org. Chem.* **2007**, *72*, 8724.

(21) Compared to the *R*-homoallyl alcohol from the allylboration of benzaldehyde with the parent nonfluorinated allylborating agent,[21a] the *S*-isomer for the difluorinated homoallyl alcohol is an artifact of the Cahn–Ingold Prelog rules.[21b] (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (b) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem., Int. Ed.* **1966**, *5*, 385.

**Table 2.** Asymmetric Difluoroallylboration of Aldehydes with **3b**[a]

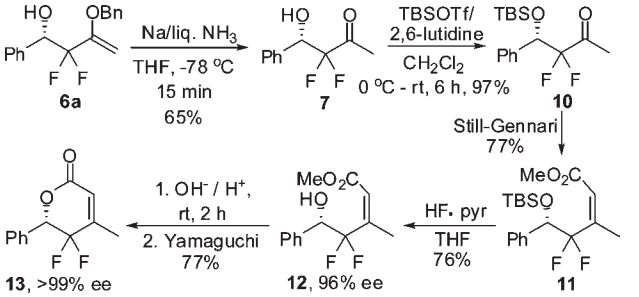
| entry | RCHO **5** |  | **6** | yield[b] (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | **5a** | $C_6H_5$ | **6a** | 68 | 93[c] |
| 2 | **5b** | 2-$CH_3O$-$C_6H_4$ | **6b** | 58 | 93[c] |
| 3 | **5c** | 3-$CH_3O$-$C_6H_4$ | **6c** | 55 | 94[c] |
| 4 | **5d** | 4-$CH_3O$-$C_6H_4$ | **6d** | 58 | 95[d] |
| 5 | **5e** | 4-$CH_3$-$C_6H_4$ | **6e** | 79 | 92[d] |
| 6 | **5f** | 4-$CF_3$-$C_6H_4$ | **6f** | 51 | 88[e] |
| 7 | **5g** | 4-F-$C_6H_4$ | **6g** | 57 | 93[e] |
| 8 | **5h** | 4-Cl-$C_6H_4$ | **6h** | 53 | 90[e] |
| 9 | **5i** | 4-$NO_2$-$C_6H_4$ | **6i** | 55 | 78[e] |
| 10 | **5j** | 2,6-$Me_2$-$C_6H_3$ | **6j** | 45 | 77[c] |
| 11 | **5k** | 1-Naphthyl | **6k** | 64 | 89[c] |
| 12 | **5l** | Cinnamyl | **6l** | 65 | 93[c] |
| 13 | **5m** | $C_6H_5$-$(CH_2)_2$ | **6m** | 67 | 92[c] |
| 14 | **5n** | Chx | **6n** | 54 | 95[d] |
| 15 | **5o** | *tert*-Bu | **6o** | 47 | 78[c] |

[a] Reactions were carried out in dichloromethane at rt with 1.5 equiv of crude reagent for 12 h. [b] Isolated yield of pure product. [c] Determined by GC analysis on a CP-Chirasil-Dex CB column. [d] Determined by HPLC analysis on a Chiralcel OD-H column. [e] Determined by HPLC analysis of the *p*-nitrobenzoyl derivative on a Chiralcel OD-H column.

the *S*-isomer in all of the cases, on the basis of the confirmed configuration of **6a**.

Having achieved the chiral difluoroallylboration of aldehydes, we demonstrated the application of this protocol for the preparation of chiral α-pyrones by following the sequence of reactions that we had reported recently (Scheme 4).[6] Thus, (*S*)-**7** (96% ee) was protected as the TBS ether **10** and converted to the protected δ-hydroxy olefinic ester **11** via a *Z*-stereospecific Still−Gennari olefination in 77% yield, as a single isomer without loss of optical activity. Deprotection of the TBS ether **11** with HF·pyridine gave the δ-hydroxy ester **12** in 96% ee, confirmed by HPLC analysis using a Chiralcel OD-H column (see the Supporting Information for details). The targeted chiral α-pyrone **13** was prepared in 77% yield by alkaline hydrolysis, followed by cyclization under Yamaguchi conditions. GC analysis using a CP-Chirasil-Dex CB column revealed an ee of >99%.

**Scheme 4.** Preparation of Chiral α-Pyrone **13**




In conclusion, we have herein reported the first successful preparation of chiral difluoroallylboronates, and have demonstrated their application for the difluoroallylboration of a series of aromatic and aliphatic aldehydes, yielding α-*gem*-difluorohomoallyl alcohols in good yields and 77−95% ee. A representative example of the benzyloxy-substituted difluorohomoallyl alcohol was converted to the corresponding chiral α-pyrone in >99% ee. Further applications of these fluorinated chiral building blocks will be reported in due course.

**Acknowledgment.** Financial support from the Herbert C. Brown Center for Borane Research is gratefully acknowledged.

**Supporting Information Available.** Experimental details and spectral data of compounds. The X-ray crystallographic data for **7** has been deposited with the Cambridge Crystallographic Data Center. This data (CCDC 832344) can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. This material is available free of charge via the Internet at http://pubs.acs.org