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# Diastereoselective Fluorocyclopropanation of Chiral Allylic Alcohols Using an α-Fluoroiodomethylzinc Carbenoid

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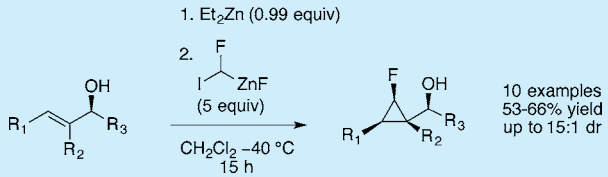
Supporting Information

**ABSTRACT:** Chiral fluorocyclopropyl carbinols were synthesized in high diastereoselectivities via a zinc mediated cyclopropanation reaction, using *sec*-allylic alcohols as simple building blocks. An enantioselective version of this transformation was achieved through *in situ* formation of chiral allylic zinc *sec*-alkoxides from the requisite aldehydes using Walsh's protocol.




Fluorocyclopropanes bring together the biologically beneficial properties of the fluorine atom[1] to the medicinally important cyclopropane scaffold.[2] The traditional methodologies to access monofluorocyclopropanes[3] involve (1) a Michael induced ring closure (MIRC) strategy using α-fluoro carbanions;[4] (2) the cyclopropanation of vinyl fluorides;[5] or (3) the use of fluorocarbenoids.[6] In comparison to other halocyclopropanations,[7] the stereoselective synthesis of fluorocyclopropanes from fluoro-substituted carbenoids is relatively understudied, mainly in part due to the lack of suitable methods for the efficient generation of the reagent. The diastereoselective transfer of carbenoids using chiral secondary allylic alcohols[8] is an efficient strategy to synthesize 1,2,3-substituted halocyclopropanes,[9,10] containing up to four stereocenters (Scheme 1). We reasoned that this strategy could be applied toward the stereoselective formation of fluoro-substituted cyclopropanes. The diastereoselective transfer of iodo-, bromo-, and chloromethyl carbenoids using chiral secondary allylic alcohols has previously been studied;[10b] however, to our knowledge, no examples are known for the transfer of fluoro-substituted carbenoids in such a system.

Our group recently described an efficient enantioselective synthesis of monofluorocyclopropanes from primary allylic alcohols using a chiral dioxaborolane ligand.[11] This methodology hinges on the formation of the active monofluoromethylene carbenoid **1** (Scheme 1) via a halogen scrambling of its difluoromethylene precursor, difluoroiodomethane, used in place of the customary diiodofluoromethane, an expensive and difficult to prepare reagent.

In this letter, we report the diastereoselective fluorocyclopropanation of chiral secondary allyl alcohols using a fluoro-substituted zinc carbenoid prepared from difluoroiodomethane.

We began our study by exposing the ethylzinc alkoxide of (±)-cyclohexyl-3-phenylpropenol **2** (Table 1, entry 1) to 2 equiv of the fluorocarbenoid **1** in dichloromethane at −40 °C. Encouragingly, this afforded the desired fluorocyclopropane **3** in 30% yield, with an 8:1 dr. We were pleased to find that, by simply adding a larger excess of the carbenoid,[8b] both the yield and the diastereoselectivity of **3** were improved (Table 1, entries 2−5). Ultimately, the use of 5 equiv of the carbenoid proved optimal, giving complete consumption of the starting material and affording **3** in 69% yield and a 15:1 dr. The use of more than 5 equiv of carbenoid led to an unclean reaction and the formation of nonpolar byproducts.

**Scheme 1. 1,2,3-Substituted Halocyclopropane Synthesis by Diastereoselective Carbenoid Transfer**

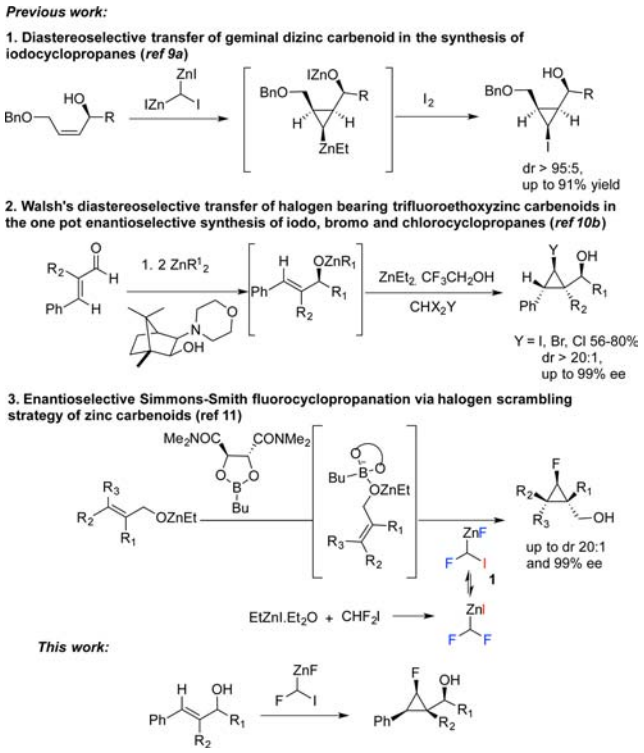



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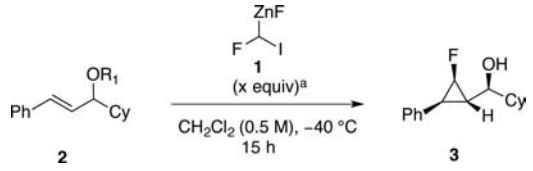
**Table 1. Screening of the Fluorocyclopropanation Conditions**




| entry | $R_1$ | $x$ | dr[b] | yield **3** (%)[c] | recovered **2** (%)[c] |
|---|---|---|---|---|---|
| 1 | ZnEt | 2 | 8:1 | 30 | 57 |
| 2 | ZnEt | 3 | 10:1 | 56 | 20 |
| 3 | ZnEt | 4 | 13:1 | 62 | 8 |
| 4 | ZnEt | 5 | 15:1 | 69 | 0 |
| 5 | ZnEt | 6 | 13:1 | 61 | 0 |
| 6 | H | 5 | 6:1 | 71 | 0 |
| 7[d] | ZnEt | 5 | 9:1 | 63 | 13 |

[a]Carbenoid prepared by mixing 1 M $CH_2Cl_2$ solution of EtZnI·$Et_2O$ with a 1 M $CH_2Cl_2$ solution of $CHF_2I$ at −78 °C. [b]Determined by $^{19}F$ NMR of the crude reaction mixture. [c]Isolated yields. [d]Reaction run in the presence of 15 equiv of PhMe.

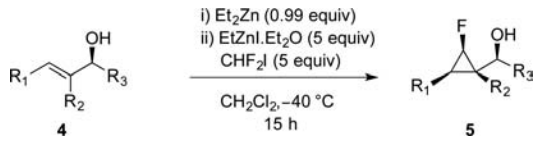
In related halocyclopropanation reactions of *sec*-allylic alcohols, the use of the dihalomethyl zinc trifluoroethoxide is necessary in order to achieve high yields and diastereoselectivities.[10b] In view of this, the high yield and diastereoselectivity observed with carbenoid **1** is particularly noteworthy. Submitting **2** to 5 equiv of the carbenoid **1** without preforming the ethylzinc alkoxide yielded **3** in 71% yield but with a reduced 6:1 dr (entry 5). This exemplified the importance of the preformation of the allylic zinc alkoxide on the diastereoselectivity of the fluorocyclopropanation. Furthermore, derivatization of **3** as its 3,5-dinitrobenzoate allowed isolation of a crystalline compound of suitable quality for X-ray crystallography. The obtained X-ray crystal structure confirmed the overall configuration of **3** to have a *trans* relationship between the fluorine and carbinol substituents (see Supporting Information).[12] Also, the presence of 15 equiv of toluene in this reaction led to a decreased 9:1 dr, suggesting $\pi$ type interactions between toluene and the fluorocarbenoid **1** (vide infra).

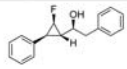
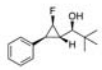
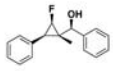
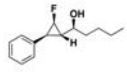
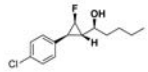
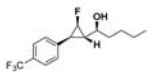
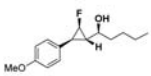
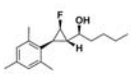
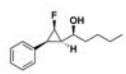
With the optimized conditions in hand, the scope of the reaction with a range of *sec*-allylic alcohols was examined. Gratifyingly, excellent diastereoselectivities (15:1) were obtained when $R_3$ was sterically demanding (Table 2, entries 1−2). The level of diastereoselection remained high for 2,3-trisubstituted allylic alcohol **4c** (entry 3).

A loss in dr to 2:1 was observed when the steric demand of $R_3$ was reduced (entry 4). The diastereoselectivity was regained when substrate **4e**, bearing a larger *n*-butyl chain, was used (entry 5). We next explored the effect of the electronic properties of $R_1$ on the outcome of the developed reaction. Interestingly, the presence of electron-deficient (entries 6 and 7) and electron-donating aryl groups in the $R_3$ position (entry 8) did not have any marked influence on the diastereoselectivity (which remained uniform at 7:1) and yield of the reaction. The presence of the bulkier mesityl group (entry 9) was also well tolerated, affording **5i** in 65% yield, with a 7:1 dr. In the case of the *cis* allylic alcohol (entry 10), the developed methodology afforded a diminished diastereoselectivity (1.5:1).

Keeping in view the improved diastereoselectivity with the increase in the equivalents of the fluorocarbenoid and the known precedents of Zn(II) interactions with $\pi$ systems,[13] we propose that Figure 1 likely best depicts the transition state model for this *trans* diastereoselective fluorocyclopropanation.

**Table 2. Scope of the Fluorocyclopropanation Using Optimized Conditions**




| entry | $R_1$ | $R_2$ | $R_3$ | product | yield[a] | dr[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | H | Bn |  5a | 62 | 15:1 |
| 2 | Ph | H | *t*-Bu |  5b | 64 | 15:1 |
| 3 | Ph | Me | Ph |  5c | 63 | 15:1 |
| 4 | Ph | H | Me |  5d | 58 | 2:1 |
| 5 | Ph | H | Bu |  5e | 62 | 7:1 |
| 6 | 4-ClPh | H | Bu |  5f | 64 | 7:1 |
| 7 | 4-$CF_3$Ph | H | Bu |  5g | 64 | 7:1 |
| 8 | OMe | H | Bu |  5h | 66 | 7:1 |
| 9 | mes | H | Bu |  5i | 65 | 7:1 |
| 10 | Ph | H | Bu |  5j | 53 | 1.5:1 |

[a]Isolated yield of the diastereomerically pure compound. [b]Determined by $^{19}F$ NMR of the crude reaction mixture.

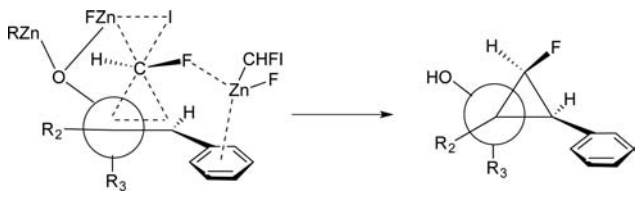



**Figure 1.** Transition state model for *trans* diastereoselective fluorocyclopropanation.

With the successful diastereoselective formation of fluorocyclopropanes starting from racemic allylic alcohols in



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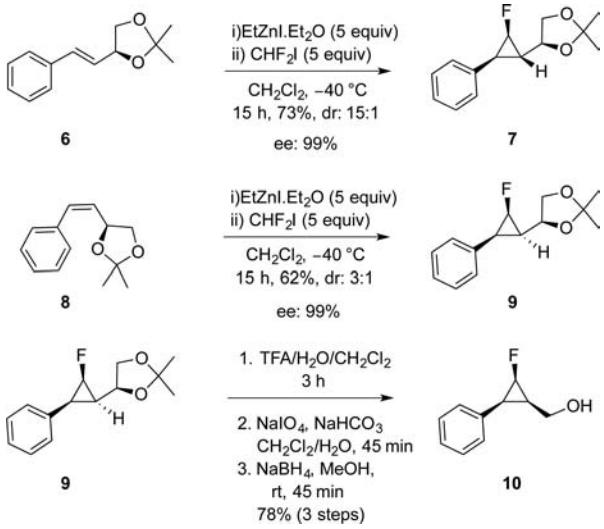
hand, we sought to further explore the possibilities for the development of a diastereoselective cyclopropanation of chiral allylic ethers. In such context, we decided to evaluate the stereochemical outcome of the fluorocyclopropanation of *trans*-styryldioxolane **6** derived from D-glyceraldehyde acetonide. We were delighted to find that the reaction of **6** with 5 equiv of the carbenoid **1** afforded the fluorocyclopropane **7** in 73% yield, in 15:1 dr and 99% ee, with the fluorine substituent being oriented *trans* to the dioxolane (Scheme 2). In the case of the *cis* isomer **8**,

**Scheme 2. Diastereoselective Fluorocyclopropanation Using Styryl Dioxolanes**[a,b]



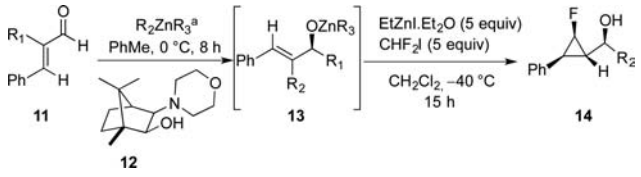

[a]Determined by $^{19}$F NMR of the crude reaction mixture. [b]Determined by $^{1}$H NMR of the crude reaction mixture.

the reaction proceeded with a 3:1 dr. The major isomer, isolated in 62% yield and 99% ee, was found to be the all-*cis* fluorocyclopropane **9**, the structure of which was confirmed by X-ray crystallography (see Supporting Information).[14] A sequence of acid catalyzed acetonide deprotection, periodate mediated cleavage, and sodium borohydride reduction of the resulting aldehyde then allowed access to the all-*cis* fluorocyclopropyl carbinol **10** in 78% yield over three steps.

Walsh et al. recently reported an excellent methodology for the one-pot synthesis of halocyclopropyl carbinols with high enanatio- and diastereocontrol (Scheme 1, eq 2).[10b] The methodology relies on the enantioselective addition of dialkyl zinc reagents to unsaturated aldehydes using chiral aminoalcohol MIB.[15] To the formed enantioenriched *sec*-allylic zinc alkoxide intermediates are then added halomethyl carbenoids furnishing enantioenriched iodo-, bromo-, and chlorocyclopropanes. In order to circumvent the preparation of enantiopure *sec*-allylic alcohols and seeking to further build on the success of the diastereoselective transfer of fluorocarbenoid **1**, we envisioned achieving the one-pot fluorocyclopropanation protocol under Walsh's protocol.

In our initial attempt, cinnamaldehyde was reacted with diethylzinc under MIB catalysis conditions in toluene at 0 °C to form the ethylzinc adduct. After removal of the volatiles under vacuum, dichloromethane and 5 equiv of the fluorocarbenoid **1** were added. We were pleased to find that the desired fluorocyclopropane **14a** (Table 3, entry 1) was isolated in 68% yield as a 8:1 diastereomeric mixture in 90% ee. Since electronic and steric effects on the aromatic ring did not seem to play a role

**Table 3. One-Pot Enantioselective Fluorocyclopropanation Using MIB Catalysis**




| entry | $R_1$ | $R_2$ | $R_3$ | product | yield[b] | dr[c] | ee[d] |
|---|---|---|---|---|---|---|---|
| 1 | H | Et | Et | **14a** | 68 | 8:1 | 90 |
| 2 | H | Bu | Bu | **14b** | 63 | 7:1 | 70 |
| 3 | H | Cy | Cy | **14c** | 58 | 15:1 | 90 |

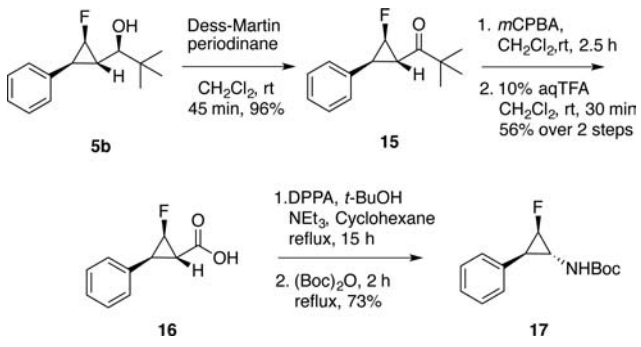
[a]Dialkylzinc reagents in entries 1, 2, and 3 were ethereal solutions. [b]Isolated yield of the diastereomerically pure compound. [c]Determined by $^{19}$F NMR of the crude reaction mixture. [d]Determined by SFC on a chiral stationary phase.

in the diastereoselective fluorocyclopropanation, two other dialkylzinc reagents[16] were evaluated within this one-pot fluorocyclopropanation protocol. The reaction using dibutylzinc delivered **14b** in 63% yield, with a 7:1 dr and in 90% ee (Table 3, entry 2). Some loss in yield in this reaction was attributed to the formation of a minor byproduct, arising from reduction of cinnamaldehyde during the addition reaction of dibutyl zinc.

While the diastereoselectivity with the more hindered dicyclohexyl zinc was high (Table 3, entry 3), the enantioselectivity dropped to 70%. The fluorocyclopropyl carbinols synthesized could be further functionalized to prepare various biologically important fluorocyclopropanes. Stereodefined fluorocyclopropylcarboxylic acid **16** was accessed from **5b** by a simple oxidation protocol involving a sequential Dess-Martin oxidation, Baeyer−Villiger reaction, and saponification (Scheme 3). A Curtius rearrangement of **16** in a reaction with diphenyl phosphorylazide gave access to the corresponding amino cyclopropane **17** in 73% yield.

In summary, we have successfully developed a new methodology for the fluorocyclopropanation of a range of racemic *sec*-

**Scheme 3. Synthesis of Fluorocyclopropane Carboxylic Acid and Fluoroaminocyclopropane**



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allylic alcohols and ethers in high yields and diastereoselectivities. The use of glyceraldehyde derived allyl ethers allows synthesis of the corresponding fluorocyclopropanes in excellent yields and enantioselectivities. The methodology could also be extended in a one-pot fluorocyclopropanation protocol using in situ generated enantioenriched allylic alkoxides to give access to chiral, nonracemic fluorocyclopropanes.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02097.

Experimental procedures, NMR spectra, and compound characterization data (PDF)
Crystallographic data for **9** (CIF)
Crystallographic data for **18** (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) Mueller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529.

(2) (a) Vuligonda, V.; Lin, Y.; Chandraratna, R. A. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 213. (b) Martin, S. F.; Austin, R. E.; Oalmann, C. J.; Baker, W. R.; Condon, S. L.; deLara, E.; Rosenberg, S. H.; Spina, K. P.; Stein, H. H.; Cohen, J.; Kleinert, H. D. *J. Med. Chem.* **1992**, *35*, 1710. (c) Martin, S. F.; Oalmann, C. J.; Liras, S. *Tetrahedron* **1993**, *49*, 3521. (d) Reichelt, A.; Martin, S. F. *Acc. Chem. Res.* **2006**, *39*, 433. (e) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103. (f) Ivashkin, P.; Lemonnier, G.; Tora, A. S.; Pin, J. P.; Goudet, C.; Jubault, P.; Pannecoucke, X. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2523. (g) Lemonnier, G.; Lion, C.; Quirion, J.-C.; Pin, J.-P.; Goudet, C.; Jubault, P. *Bioorg. Med. Chem.* **2012**, *20*, 4716.

(3) For reviews, see: (a) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. - Eur. J.* **2012**, *18*, 14904. (b) Dolbier, W. R., Jr.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071. (c) Akiba, T.; Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Terashima, S. *Tetrahedron* **1994**, *50*, 3905.

(4) (a) Shen, X.; Zhang, W.; Zhang, L.; Luo, T.; Wan, X.; Gu, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6966. (b) Milanole, G.; Couve-Bonnaire, S.; Bonfanti, J. F.; Jubault, P.; Pannecoucke, X. *J. Org. Chem.* **2013**, *78*, 212. (c) Ferrary, T.; David, E.; Milanole, G.; Besset, T.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 5598. (d) Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7487. (e) Zhang, F.; Song, Z. J.; Tschaen, D.; Volante, R. P. *Org. Lett.* **2004**, *6*, 3775. (f) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 5130.

(5) (a) Pons, A.; Beucher, H.; Ivashkin, P.; Lemonnier, G.; Poisson, T.; Charette, A. B.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2015**, *17*, 1790. (b) Morikawa, T.; Sasaki, H.; Mori, K.; Shiro, M.; Taguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 3189. (c) Meyer, O. G. J.; Frohlich, R.; Haufe, G. *Synthesis* **2000**, *2000*, 1479. (d) Nakazato, A.; Kumagai, T.; Sakagami, K.; Yoshikawa, R.; Suzuki, Y.; Chaki, S.; Ito, H.; Taguchi, T.; Nakanishi, S.; Okuyama, S. *J. Med. Chem.* **2000**, *43*, 4893.

(6) (a) Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Akiba, T.; Terashima, S. *Tetrahedron* **1994**, *50*, 3889. (b) Akiba, T.; Tamura, O.; Hashimoto, M.; Kobayashi, Y.; Katoh, T.; Nakatani, K.; Kamada, M.; Hayakawa, I.; Terashima, S. *Tetrahedron* **1994**, *50*, 3905.

(7) For reviews, see: (a) Charette, A. B.; Beauchemin, A. *Org. React. (N. Y.)* **2001**, *58*, 1. (b) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (c) Roy, M.-N.; Lindsay, V. N. G.; Charette. A. B. In *Stereoselective Synthesis: Reactions of Carbon-Carbon Double Bonds (Science of Synthesis Series)*; de Vries, J. G., Vol. Ed.; Thieme: Stuttgart, 2011; Vol. *1*, Chapter 1.14, pp 731−817.

(8) For earlier work on the diastereoselective cyclopropanation of acyclic allylic alcohols and ethers using zinc carbenoids, see: (a) Ratier, M.; Castaing, M.; Godet, J. Y.; Pereyre, M. *J. Chem. Res. (M)* **1978**, 2309. (b) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, *60*, 2966. (c) Charette, A. B.; Lacasse, M. C. *Org. Lett.* **2002**, *4*, 3351.

(9) (a) Fournier, J. F.; Mathieu, S.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 13140. (b) Charette, A. B.; Mathieu, S.; Fournier, J. F. *Synlett* **2005**, 1779.

(10) (a) Kim, H. Y.; Lurain, A. E.; Garcia-Garcia, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138. (b) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 954. (c) Infante, R.; Nieto, J.; Andres, C. *Org. Biomol. Chem.* **2014**, *12*, 345.

(11) Beaulieu, L.-P. B.; Schneider, J. F.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819.

(12) In the dinitrobenzoate derivative of **3**, as observed in the case of the related iodocyclopropanes, the *cis* disposed cyclopropane ring hydrogen atom relative to the fluoromethine hydrogen atom exhibits a higher $^{3}J_{\text{FCH-H}cis}$ proton coupling constant of 6.7 Hz, while the *trans* disposed hydrogen atom exhibits a lower $^{3}J_{\text{FCH-H}cis}$ coupling constant of 2.4 Hz. Also, the fluorine atom displays a strong $^{3}J_{\text{F-H}cis}$ coupling constant of 20.3 Hz and a smaller $^{3}J_{\text{F-H}trans}$ coupling constant of 6.9 Hz. These $^{1}$H and $^{19}$F coupling constants have been used to assign the stereochemistry of the fluorocyclopropane carbinols synthesized (see Supporting Information). For use of coupling constants in assignment of stereochemistry of halocyclopropanes, see: (a) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1500. (b) Miyano, S.; Matsumoto, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1975**, 364. (c) Seyferth, D.; Yamazaki, H.; Alleston, D. L. *J. Org. Chem.* **1963**, *28*, 703. (d) Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892. (e) Kim, H. Y.; Salvi, L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 954.

(13) (a) Marek, I.; Beruben, D.; Normant, J.-F. *Tetrahedron Lett.* **1995**, *36*, 3695. (b) Beruben, D.; Marek, I.; Normant, J. F.; Platzer, N. *J. Org. Chem.* **1995**, *60*, 2488. (c) Wooten, A.; Carroll, P. J.; Maestri, A. G.; Walsh, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 4624. (d) Guerrero, A.; Martin, E.; Hughes, D. L.; Kaltsoyannis, N.; Bochmann, M. *Organometallics* **2006**, *25*, 3311. (e) Walker, D. A.; Woodman, T. J.; Hughes, D. L.; Bochmann, M. *Organometallics* **2001**, *20*, 3772. (f) Bukhaltsev, E.; Goldberg, I.; Cohen, R.; Vigalok, A. *Organometallics* **2007**, *26*, 4015.

(14) The all *cis* fluorocyclopropyl dioxolane **9** displays a $^{3}J_{\text{FCH-H}cis}$ coupling constant of 6 Hz for the *cis* disposed cyclopropane ring protons. The *trans* disposed fluorine atom displays a $^{3}J_{\text{F-H}trans}$ coupling constant of 7.4 Hz (see Supporting Information).

(15) Nugent, W. A. *Chem. Commun.* **1999**, 1369.

(16) Côté, A.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 2771.




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