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Communication

Highly Enantioselective Simmons-Smith Fluorocyclopropanation of Allylic Alcohols via the Halogen Scrambling Strategy of Zinc Carbenoids

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Highly Enantioselective Simmons-Smith Fluorocyclopropanation of Allylic Alcohols via the Halogen Scrambling Strategy of Zinc Carbenoids

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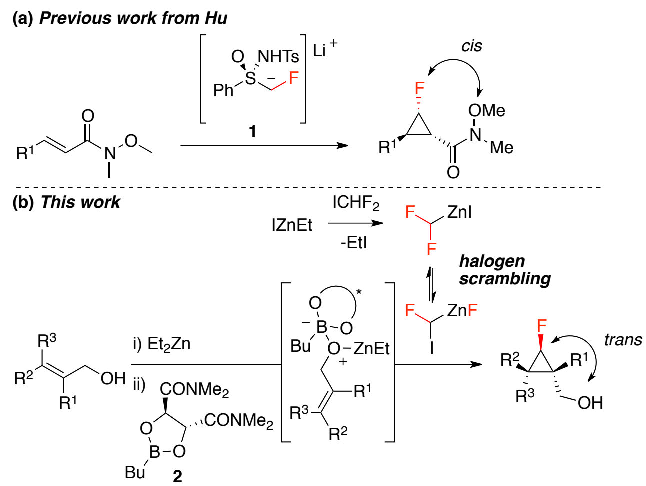
Supporting Information Placeholder

ABSTRACT: Highly enantio- and diastereoenriched monofluorocyclopropanes were accessed via the Simmons-Smith fluorocyclopropanation of allylic alcohols using difluoroiodomethane and ethylzinc iodide as the substituted carbenoid precursors. The scrambling of halogens at the zinc carbenoid led to the formation of the fluorocyclopropanating agent (fluoroiodomethyl)zinc(II) fluoride. This strategy circumvented the ongoing limitation in Simmons-Smith fluorocyclopropanations relying on the use of the relatively inaccessible and expensive carbenoid precursor fluorodiiodomethane.

Organofluorine compounds elicit significant interest in medicinal and agrochemistry as they display enhanced metabolic stability, lipophilicity and have distinctive physicochemical properties when compared to their isosteric dehalogenated analogues. There is also a growing body of evidence pointing towards a marked increase in binding efficacy and selectivity in pharmaceuticals comprising fluorine atoms.[1] As a testament to the promise of organofluorine chemistry, nearly 20% of all pharmaceuticals and 40% of agrochemicals under development contain fluorine.[2] It is therefore increasingly necessary to develop synthetic routes for the incorporation of fluorine atoms into organic scaffolds in order to study the effect of hydrogen to fluorine substitutions.

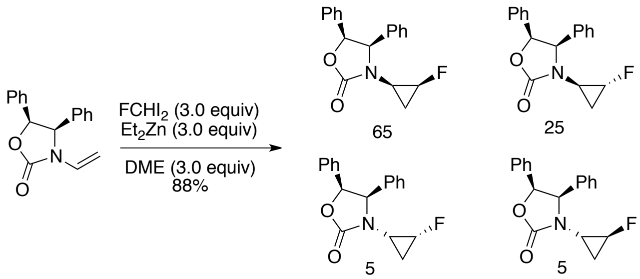
Monofluorocyclopropanes have become prime synthetic targets as they combine the advantages of organofluorine compounds with the added structural rigidity and metabolic stability of cyclopropanes, which act as alkene[3] and peptide bond[4] bioisosteres. In spite of the considerable efforts to develop methodologies for the preparation of monofluorocyclopropanes, limited progress has been accomplished for their asymmetric synthesis, which relies in most cases on the cyclopropanation of alkenyl fluorides.[5,6] Hu and collaborators have recently reported the first enantioselective monofluorocyclopropanation reaction through a Michael-induced ring closure (MIRC) reaction involving the chiral carbanion (**1**) generated by fluorinating (NFSI) a sulfoximine auxiliary and α,β-unsaturated Weinreb amides (Scheme 1(a)).[7] While this major contribution enables the enantioselective formation of monofluorocyclopropanes where the fluorine atom and the amide group have a *cis* relationship, developing a methodology to access the *trans* diastereomer as well would result in a significant advance in the field. Herein we disclose the first highly stereoselective Simmons-Smith monofluorocyclopropanation, which takes advantage of the scrambling of halogens at the zinc carbenoid and leads to the *trans* diastereomer (Scheme 1(b)).



Scheme 1. Highly enantioselective monofluorocyclopropanation reactions

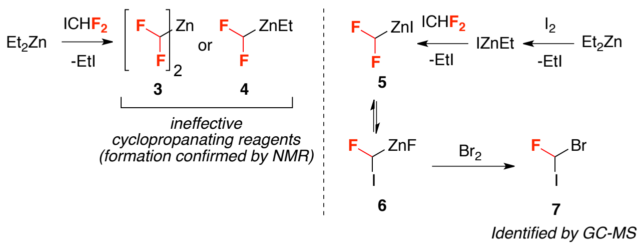
Our group has lately been interested in the enantioselective Simmons-Smith monohalocyclopropanation of allylic alcohols using a dioxaborolane chiral ligand (**2**),[8] leading to the cyclopropane products in which the halogen atom has a *trans* relationship to the proximal basic alcohol group. Highly stereoselective iodo- and chlorocyclopropanation reactions have thus been achieved with substituted zinc carbenoids derived from diethylzinc and the corresponding haloform (CHI_3 and $ClCHI_2$, respectively,).[9]

While numerous Simmons-Smith monoiodo-, bromo- and chlorocyclopropanation reactions have been reported,[10] there is a dearth of monofluorocyclopropanation reactions in the literature. This is ascribed to the difficult preparation of the carbenoid precursor $FCHI_2$ from CHI_3, involving stoichiometric amounts of highly toxic HgF_2,[11] or expensive AgF.[12,13] One notable application of this reaction is the fluorocyclopropanation reported by Terashima that leads to a mixture of four diastereomers en route to the antibiotic sitafloxacin (Scheme 2).[14]



Scheme 2. Diastereoselective Simmons-Smith fluorocyclopropanation reaction

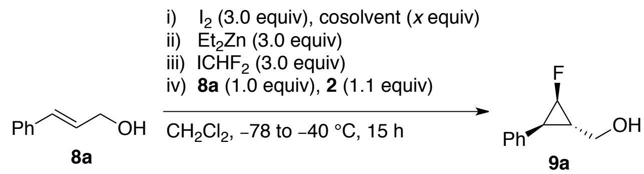
Conversely, since difluoroiodomethane ($ICHF_2$) is readily accessed in one step from inexpensive chlorodifluoroacetic acid ($ClCF_2COOH$), CuI and KI,[15] we envisioned that it would constitute an optimal fluorocarbenoid precursor. Our investigation began by treating cinnamyl alcohol with preformed fluoromethylzinc carbenoid **3** or **4** (Scheme 3), obtained from diethylzinc and difluoroidomethane, and dioxaborolane ligand **2**. Unfortunately, although the reagent was formed in solution (as observed by ^{1}H NMR), quantitative recovery of cinnamyl alcohol was observed thus indicating that neither reagent **3** or **4** is a suitable cyclopropanating reagent (Table 1, entry 1). In our studies of Simmons-Smith monohalocyclopropanation reactions, we have observed scrambling of halogen atoms in dihalomethylzinc halide species.[9] We then sought to capitalize on this interesting observation to generate the iodofluoromethylzinc carbenoid **6** in situ from iodoethylzinc iodide and $ICHF_2$. To confirm that the halogen exchange was indeed taking place, $IZnCHF_2$ was prepared using the optimal conditions (Table 2, entry 7) and then quenched with Br_2 (Scheme 3). Bromofluoroiodomethane (**7**) formation was observed by GC/MS and ^{1}H NMR,[16] indicating that the halogen scrambling was operative.



Scheme 3. Flurohalomethylzinc Reagents

This reagent procedure was then used in the enantioselective cyclopropanation of cinnamyl alcohol in the presence of the dioxaborolane ligand **2** (Table 1, entries 2-7). The first set of conditions using this reagent led to conversion to fluorocyclopropane **7a** with very high diastereoselectivity but low yield (Table 1, entry 2).[17] The reaction mixture was heterogeneous throughout the reaction period. We then surmised that the incorporation of a cosolvent might provide a homogeneous reaction mixture and thus increase the rate of the halogen scrambling and/or the cyclopropanation event.[18] The addition of two equivalents of Et_2O relative to diethylzinc led to complete consumption of the allylic alcohol and an encouraging enantiomeric ratio (entry 3). The use of DME or THF completely suppressed reactivity, presumably because of their higher Lewis basicity when compared to Et_2O (entries 4 and 5).[19] The complexation of such stronger Lewis bases to the zinc atom would decrease the electrophilicity and hence the reactivity of the zinc carbenoid towards the allylic alkoxide.[20] In an effort to increase the enantioselectivity of the reaction, the amount of Et_2O relative to Et_2Zn was lowered from 2 to 1 equivalent, as the cosolvent may compete with the chiral ligand for complexation with the zinc carbenoid (entry 6).[21] Unfortunately, this did not result in significant changes in stereoselectivity. However, the preformation of the zinc alkoxide derived from Et_2Zn and cinnamyl alcohol followed by its complexation with the dioxaborolane ligand **2** and reaction with the fluoromethylzinc carbenoid led to excellent ee and dr (entry 7). These conditions were used to elaborate the scope of the reaction (Table 2).

Table 1. Optimization of the enantioselective monofluorocyclopropanation reaction

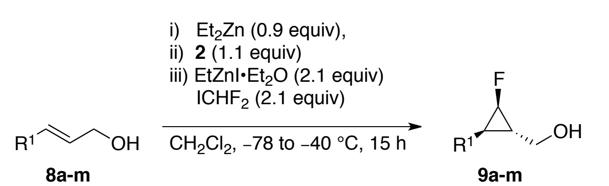


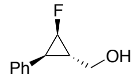
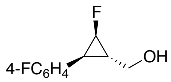
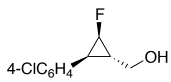
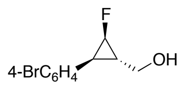
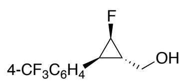
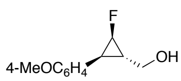
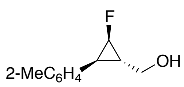
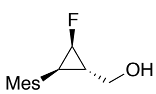
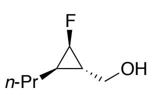
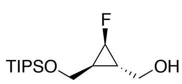
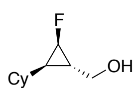
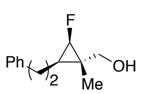
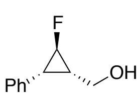
entry	cosolv.	x (equiv)	yield (%)[a]	recov. (%)[a]	dr[b]	ee (%)[c]
1[d]	Et_2O	3	0	100	-	-
2	none	-	25	58	≥20:1	-
3	Et_2O	6	76	0	≥20:1	82
4	DME	3	0	100	-	-
5	THF	6	0	100	-	-
6	Et_2O	3	79	0	≥20:1	83
7[e]	Et_2O	3	75(71)	≤5	≥20:1	96

[a] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as the internal standard, isolated yield in brackets. [b] Determined by ^{1}H NMR from the crude mixture. [c] Determined by SFC on a chiral stationary phase. [d] Reagent formation was conducted with Et_2Zn (3.0 equiv)/$ICHF_2$ (3.0 equiv) instead of EtZnI/ $ICHF_2$ (3.0 equiv). [e] Reaction conducted by preforming the zinc alkoxide derived from **8a** and Et_2Zn, followed by complexation with **2** and reaction with the fluoromethylzinc carbenoid.

Gratifyingly, the reaction displayed high diastereo- and enantioselectivities for various cinnamyl alcohol derivatives bearing electron-withdrawing groups (Table 2, entries 2-5) and electron-donating groups (entries, 6-8). While the fluorocyclopropanation of 4-methoxy derivative **8f** led to decreased enantioselectivity at –40 °C (85% ee, entry 6), its stereoselectivity could be increased by performing the reaction at –63 °C (94% ee), albeit at the expense of reaction conversion.[16] The reaction was also compatible with allylic alcohols substituted with primary or secondary alkyl groups (entries 9-10 and 11, respectively). Unsurprisingly, 2,3-trisubstituted allylic alcohol **8l** gave decreased enantioselectivity due to destabilizing 1,3-allylic strain interactions in both reactive conformations of the allylic alkoxide leading to either enantiomers (entry 12).[22] Interestingly, (*Z*)-cinnamyl alcohol **8m** displayed increased diastereoselectivity favoring the *trans* diastereomer **9m** (4:1 dr) when compared to the homologous chlorocyclopropanation (1:1 dr) and iodocyclopropanation (1:3 dr) reactions.[9b]

Table 2. Scope of the enantioselective monofluorocyclopropanation reaction



entry	product		yield (%)[a]	dr[b]	ee (%)[c]
1		**9a**	71	≥20:1	96
2		**9b**	60	≥20:1	95
3		**9c**	66	≥20:1	98[d]
4		**9d**	75	≥20:1	97
5		**9e**	69	≥20:1	98
6		**9f**	49	≥20:1	85
7		**9g**	74	≥20:1	96
8		**9h**	62	≥20:1	99
9		**9i**	62	≥20:1	94
10		**9j**	70	≥20:1	96
11		**9k**	72	≥20:1	95
12		**9l**	73	≥20:1	82
13		**9m**	46	4:1	98

[a] Isolated yield of the diastereomerically pure material. [b] Determined by ^{1}H NMR from the crude mixture. [c] Determined by SFC on a chiral stationary phase. [d] The absolute configuration of its *O*-3,5-dinitrobenzoyl derivative was determined by X-ray crystallography.

In summary, we have reported the first highly enantioselective monofluorocyclopropanation reaction of allylic alcohols. The reaction features a broad scope and gives access to biologically relevant monofluorocyclopropane units from readily available precursors. Quenching experiments have confirmed the halogen scrambling at the zinc carbenoid, which precedes the cyclopropanation event. This contribution has overcome the ongoing limitation in Simmons-Smith monofluorocyclopropanations involving the use of $FCHI_2$ as carbenoid precursor. Further applications of this strategy are ongoing and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, compound characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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16 See Supporting Information
[17] See Supporting Information for complete details relative to reaction optimization.
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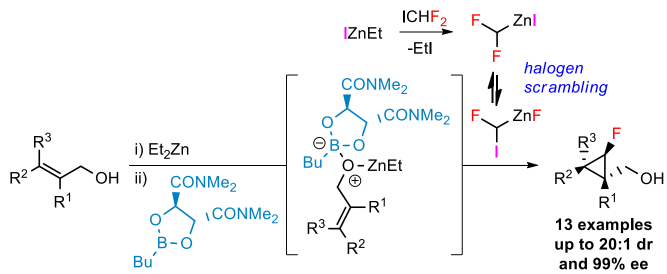
IZnEt
ICHF2
-EtI
ZnI
halogen scrambling
ZnF
i) Et2Zn
ii)
CONMe2
B-O
Bu
O-ZnEt
OH
13 examples
up to 20:1 dr
and 99% ee