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One-Step Synthesis of Highly Functionalized Monofluorinated Cyclopropanes from Electron-Deficient Alkenes

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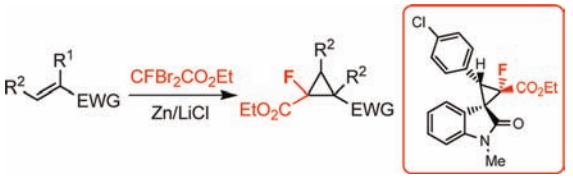
ABSTRACT



The unique combination of Zn/LiCl allowed generation of reactive zinc enolate from ethyl dibromofluoroacetate. This fluorinated enolate reacts efficiently with a wide range of functionalized electron-deficient alkenes to afford the corresponding monofluorinated cyclopropylcarboxylates in good yields.

Cyclopropane, the smallest cycloalkane with a unique structural feature, is the basis core of many natural products and biological compounds.[1] Incorporation of fluorine atoms into the biologically active molecules modulates their activity and often leads to substantial improvement in bioavailability and biochemical stability.[2] The combination of unique properties of cyclopropane and fluorine thus gives birth to fluorinated cyclopropanes which can be envisioned as new powerful scaffolds for building new therapeutic agents or crop protection molecules. In particular, monofluorinated cyclopropanes have received considerable attention over recent years due to their high potency in the treatment of neurological disorders.[3]

Reported methods for the synthesis of monofluorinated cyclopropanes include [2 + 1]-cycloaddition of fluorocarbenes to olefins,[4] cyclopropanation of fluoroalkenes,[5] radical addition of ethyl iodofluoroacetate,[6] or Pd-catalyzed allylation of ethyl 2-fluoroacetoacetate[7] with subsequent intramolecular nucleophilic substitution. Also, one example of 1,4-addition of fluorinated silyl ketene acetal to cyclopentenone was used for the construction of the 6-fluorobicyclo[3.1.0]hexane core.[6] Although the utility of existing methods was demonstrated by the synthesis of several types of biologically active compounds, the problem of a general approach to the variously substituted monofluorinated cyclopropanes has not yet been addressed.

In order to broaden the scope of accessible monofluorinated cyclopropanes we report here a new method based on the Michael addition of zinc enolate **2** derived from commercially available ethyl dibromofluoroacetate

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(3) (a) Chaki, S.; Yoshikawa, R.; Hirota, S.; Shimazaki, T.; Maeda, M.; Kawashima, N.; Yoshimizu, T.; Yasuhara, A.; Sakagami, K.; Okuyama, S.; Nakanishi, S.; Nakazato, A. *Neuropharmacology* **2004**, *46*, 457. (b) Sakagami, K.; Yasuhara, A.; Chaki, S.; Yoshikawa, R.; Kawakita, Y.; Saito, A.; Taguchi, T.; Nakazato, A. *Bioorg. Med. Chem.* **2008**, *16*, 4359. (c) Hruschka, S.; Rosen, T. C.; Yoshida, S.; Kirk, K. L.; Fröhlich, R.; Wibbeling, B.; Haufe, G. *Bioorg. Med. Chem.* **2008**, 7148. (d) Pessah, N.; Bialer, M.; Wlodarczyk, B.; Finnell, R. H.; Yagen, B. *J. Med. Chem.* **2009**, 2233.

(4) Brahms, D. L. S.; Dailey, W. P. *Chem. Rev.* **1996**, *96*, 1585.

(5) (a) Morikawa, T.; Sasaki, H.; Mori, K.; Shiro, M.; Taguchi, T. *Chem. Pharm. Bull.* **1992**, *40*, 3189. (b) Meyer, O. G. J.; Fröhlich, R.; Haufe, G. *Synthesis* **2000**, 1479. (c) 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) Saito, A.; Ito, H.; Taguchi, T. *Tetrahedron* **2001**, *57*, 7487.

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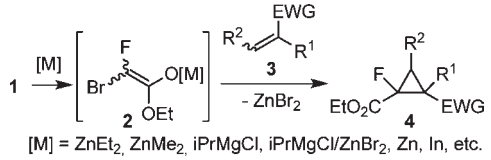
(EDBFA, **1**) followed by an in situ nucleophilic cyclization (Scheme 1).

Scheme 1. Michael-Initiated Cyclopropanation Using the Fluorinated Enolate **2**



In an initial set of experiments, we tried to generate pure enolate **2** according to a halogen−metal exchange, before adding the Michael acceptor, by the treatment of **1** with certain organometallics. Me_2Zn and Et_2Zn cannot give rise to pure **2** as they require generally high temperatures for metal−halogen exchange. On the other hand, iPrMgCl was found to react with **1** even at −94 °C; however **Mg-2** was found to be extremely unstable and undergoes self-condensation, while reaction with benzyl acrylate (**3a**, $R^1 = R^2 = H$, EWG = CO_2Bn) leads to elimination of benzyl alcohol as a result of a 1,2-addition. Only traces of cyclopropane **4a** ($R^1 = R^2 = H$, EWG = CO_2Bn) were obtained along with a complete degradation of both benzyl acrylate and EDBFA. Introduction of a Mg−Zn transmetalation step allowed us to reduce the 1,2-addition, and finally 20% of **4a** were isolated. To improve the low isolated yield and minimize the degradation, we decided to switch the order of addition of reagents to generate the reactive enolate **2** in the presence of a Michael acceptor (Table 1).

Diethylzinc, successfully used[8] in combination with **1** for the synthesis of fluoroalkenes[9] and oxiranes,[10] proved to be incompatible with benzyl acrylate (entries 1 and 2) probably due to the fast polymerization of the acceptor triggered by 1,4-addition of diethylzinc. Isopropylmagnesium chloride (entry 3) provided desired cyclopropane in a low yield which can be slightly improved by the Mg−Zn transmetalation (entry 4). Under these reaction conditions benzyl acrylate is subject to intense polymerization along with 1,2-addition (evidenced by formation of benzyl alcohol). In order to reduce the degradation of the Michael acceptor and increase the reaction yield, the non-nucleophilic Mg and Zn metals were used instead of organometallics (entries 5−10).

Table 1. Metalation of Ethyl Dibromofluoroacetate (**1**) in the Presence of Benzyl Acrylate **3a**

entry	[M][a]	yield **4a**,[b] %	dr[c]
1	$ZnEt_2$[d]	traces	–
2	$ZnEt_2/RhCl(PPh_3)_3$[d]	0	–
3	iPrMgCl (−94 to 0 °C)	17	3.8:1
4	iPrMgCl, $ZnBr_2$ (−94 to 0 °C)	30	2.4:1
5	Mg (60 °C)[e]	traces	–
6	Zn (60 °C)[e]	traces	–
7	Zn−Cu (rt)	0	–
8	$Mg/ZnCl_2$/LiCl (0 °C)	30	2.8:1
9	Rieke-Zn (−20 °C)	35	2.1:1
10	Zn/LiCl (−20 °C)	88	2.6:1

[a] 0.5−1 mmol **1**, 0.5 equiv of benzyl acrylate, THF. [b] Determined by ^1H NMR of the crude reaction mixture using DMF as internal standard. [c] Determined by ^{19}F NMR of the crude product. [d] Various temperatures in the range of −20 to 60 °C were tried. [e] No reaction was observed in a reasonable time at < 40 °C using standard metal activation procedures.

To our delight, the combination of zinc and lithium chloride[11] provided the best yield (88%) in very mild conditions[12] (entry 10) while the activated Mg and Zn metals were found to be unreactive in the conditions suitable for the cyclopropanation (with exception of Rieke-Zn, entry 9). To our knowledge, that is the first example of the application of the Zn/LiCl combination to the metalation of α-halocarbonyl compounds.

We observed that zinc activation is a crucial step for successful cyclopropanation; indeed insufficiently activated zinc requires a higher temperature for metalation leading to poor isolated yields. The standard protic acid activation was ineffective, while TMSCl/dibromoethane[11] and DIBAL-H[13] provided highly active zinc powder suitable for metalation at −20 °C. However, in our hands the best results and the most reproducible procedure were obtained after heating Zn/LiCl with 2 mol % DMSO and 2 mol % TMSCl in THF.

Thus, with this optimized procedure in hand, a variety of functionalized monofluorinated cyclopropanes **4** and **4′** was obtained in moderate to very good yields (Table 2).

2-Alkyl- and aryl-substituted acrylates were not reactive enough under the standard conditions but can be easily converted to the corresponding cyclopropanes by increasing the temperature[14] (30 °C). More reactive alkenes (**3c**, **3j**−**3l**) demand lower amounts of EDBFA. Noteworthy, the simple alkenyl substituent (**3e**) and aryl halogenides (**3g**, **3l**) are tolerated.[15]

(8) In one case (Boc-ΔAla(N-Boc)-OCH_3 **3h**), the expected cyclopropane was obtained in 60% yield (cis/trans ratio: 65/35) using diethylzinc in THF. In all other cases of Michael acceptor tested, the reaction failed. The cyclopropane adduct **4h** was used in a medicinal chemistry program for the synthesis of glutamate analogs (mGluR4 receptor ligands); application recently submitted for publication (BMC-D-12-00276).

(9) Lemonnier, G.; Zoute, L.; Dupas, G.; Quirion, J.-C.; Jubault, P. *J. Org. Chem.* **2009**, *74*, 4124.

(10) Lemonnier, G.; Zoute, L.; Quirion, J.-C.; Jubault, P. *Org. Lett.* **2010**, *12*, 844.

(11) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6040.

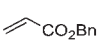
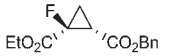
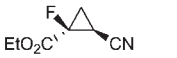
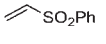
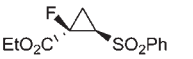
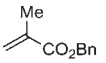
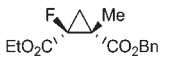
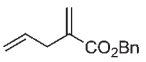
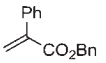
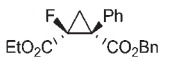
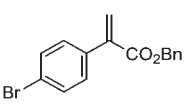
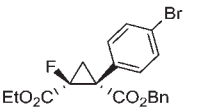
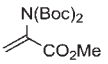
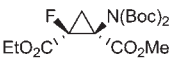
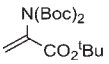
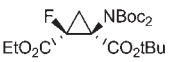
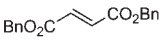
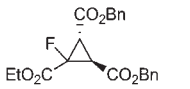
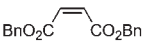
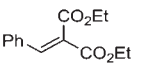
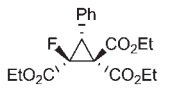
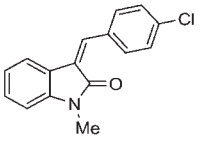
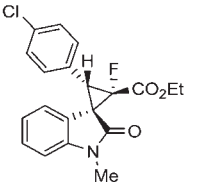
(12) THF provided the best yields compared to the other solvents (MeCN, toluene, DCM, dioxane, DME, ether, DMF, DMSO, not exceeding 20%). Other additives (LiBr, LiI, CsF, CsCl, $ZnCl_2$, $ZnBr_2$, $MgCl_2$, NEt_3BnCl, HMPA) failed to promote the metalation of **1** in THF at temperatures below 40 °C.

(13) Girgis, M. J.; Liang, J. K.; Du, Z.; Slade, J.; Prasad, K. *Org. Process Res. Dev.* **2009**, *13*, 1094.

(14) See Supporting Information for optimization details.

(15) By contrast, metalation of **1** was inhibited in the presence of β-nitrostyrene, *N*-acryloyloxazolidinone, and *N*,*N*-dimethylacrylamide.

Table 2. Scope of the Cyclopropanation Reaction Using Zn/LiCl in THF

entry	substrate (**3**)		major isomer (**4**)		yield[a]	*dr*[b]
1		**3a**		**4a**	80[c]	72:28
2		**3b**		**4b**	47[c]	53:47
3		**3c**		**4c**	72[d]	67:33
4		**3d**		**4d**	61[c]	70:30
5		**3e**		**4e**	68[c]	73:27
6		**3f**		**4f**	76[c]	76:24
7		**3g**		**4g**	80[e]	78:22
8		**3h**		**4h**	78[f] 93[g]	59:41
9		**3i**		**4i**	73[f]	84:16
10		(*E*)-**3j**		**4j**	66[d]	100:0
11		(*Z*)-**3j**			61[d]	100:0
12		**3k**		**4k**	72[d]	69:31
13		**3l**		**4l**	70[h]	53:36:7:4

[a] Overall isolated yield (see Supporting Information for the isolated yields of individual isomers). [b] Based on ^{19}F NMR of the crude product. [c] 2 equiv of **1**, −20 °C. [d] 1.1 equiv of **1**, −20 °C. [e] 3 equiv of **1**, 30 °C. [f] 2 equiv of **1**, 0 °C. [g] Large-scale procedure: 0.1 mol of Michael acceptor, 1.6 equiv of **1**, 0 °C. [h] 1.1 equiv of **1**, 0 °C.

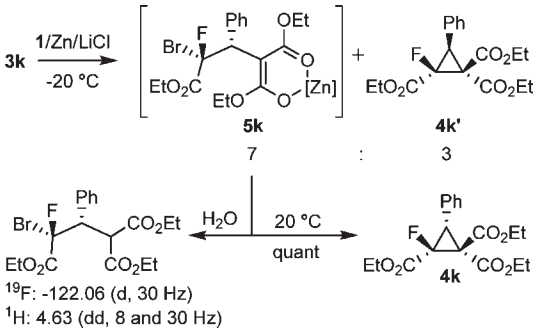
Remarkably, our method was successfully applied to the synthesis of the fluorinated amino acid **4h** on a 0.1 mol scale (30.1 g of Michael acceptor) with 93% isolated yield. A similar amino acid **4i** was synthesized with a better dr due to the more sterically demanding *tert*-butyl ester group. In contrast, when *tert*-butyl dibromofluoroacetate instead of ethyl dibromofluoroacetate was used during the cyclopropanation process, no improvement of diastereoselectivity was observed[16] (benzyl acrylate **3a**: dr 75:25 for ^{t}Bu-DBFA, 72:28 for EDBFA; diethyl benzylidenemalonate **3k**: dr 64:36 for ^{t}Bu-DBFA, 69:31 for EDBFA).

Reactions with both dibenzyl fumarate (*E*)-**3j** and dibenzyl maleate (*Z*)-**3j** lead to exclusive formation of the same *trans*-isomer of **4j** with comparable yields. In a control experiment no *cis*−*trans* isomerization of dibenzyl maleate (*Z*)-**3j** was observed under the reaction conditions (standard protocol except using $ZnBr_2$ in place of **1**). Then, we tried to isolate the intermediate using diethyl benzylidene malonate **3k**. Quenching the reaction at −20 °C leads to the exclusive formation of a minor isomer of cyclopropane **4k′** along with the noncyclized intermediate **5k** which can be trapped by protonation upon aqueous workup (Scheme 2). When allowed to warm to rt, this intermediate is converted quantitatively into the major isomer of cyclopropane **4k**. Based on the above experiments, we can assume that cyclopropanation with EDBFA-Zn/LiCl proceeds via the 1,4-addition-nucleophilic substitution and does not involve the formation of the corresponding ethoxycarbonylfluorocarbene.

Interestingly, reaction with oxyindol derivative **3l** leads to the formation of the same mixture of four stereoisomers when either (*Z*)-**3l** or (*E*)-**3l** is used. Unlike dibenzyl maleate, (*Z*)-**3l** and (*E*)-**3l** undergo interconversion under reaction conditions. Therefore, identical stereochemical outcomes for both isomers of **3l** can result from the equilibrium of the reactive and nonreactive isomers of **3l**.[17]

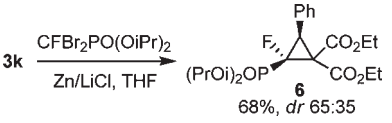
(16) Independence of stereoselectivity on the size of R in silyl ketene acetals derived from $CFBr_2CO_2R$ (R = Me, Et, *i*Pr) was reported earlier for 1,2-addition to aldehydes: Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *55*, 2225.

Scheme 2. Stepwise Cyclopropanation of Diethyl Benzylidenemalonate **3k**



The scope of the Zn/LiCl-promoted cyclopropanation can be further extended to the highly valuable fluorinated cyclopropylphosphonates as exemplified by the synthesis of an α-fluoro-phosphonate **6** (Scheme 3).

Scheme 3. Synthesis of Fluorinated Cyclopropyl Phosphonate **6**



The stereochemistry of the products **4** and **6** was elucidated based on the known trends of H−F and C−F spin−spin coupling in fluorinated cyclopropanes and $^{1}H-^{19}F$ HOESY (**4h**, **4h′**) and was independently confirmed by the X-ray analysis of oxyindole derivative **4l** (Figure 1). This type of spiro-oxyindols is of particular interest because of the biological activity of similar nonfluorinated compounds[18] and possible use in the synthesis of indole alkaloids.[19] To our knowledge, this is the first example of spiro-oxyindole fluorinated in a nonaromatic position.

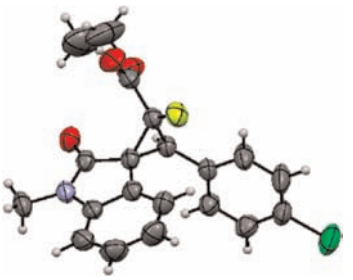


Figure 1. X-ray structure of **4l**.

In conclusion, a straightforward single step procedure for the preparation of monofluorinated cyclopropanes using ethyl dibromofluoroacetate **1** as a commercially available fluorine source was developed. The combination of Zn and LiCl proved to be essential for the generation of a highly reactive organozinc reagent **2** for the cyclopropanation of a wide range of Michael acceptors. Further developments especially devoted to an asymmetric version of this cyclopropanation process are currently under investigation in our laboratory.

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Supporting Information Available. Detailed experimental procedures, spectral data for the new compounds, crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(17) Under identical reaction conditions (addition of EDBFA over 40 min) a 61% yield was obtained from (*E*)-**3l** compared to 71% for (*Z*)-**3l**. Diastereomeric composition of cyclopropane was the same for both (*E*)-**3l** and (*Z*)-**3l**. See Supporting Information for mechanistic proposal.

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