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Modular and Chemoselective Strategy for the Direct Access to α-Fluoroepoxides and Aziridines via the Addition of Fluoroiodomethyllithium to Carbonyl-Like Compounds

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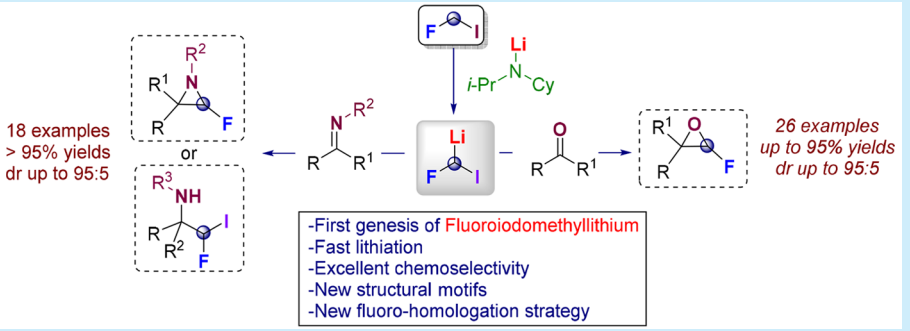
Supporting Information



ABSTRACT: An expeditious, high-yielding synthesis of rare α-fluoroepoxides and α-fluoroaziridines through the addition of the unkown fluoroiodomethyllithium (LiCHIF)—formed via deprotonation the commercially available fluoroiodomethane with a lithium amide base—to carbonyl-like compounds is documented. The ring-closure reactions, leading to α-fluorinated three-membered heterocycles, rely on the diversely reactive C−I and C−F bonds. Excellent chemoselectivity was observed in the presence of highly sensitive functionalities—aldehyde, ketone, nitrile, alkene—which remained untouched during the homologation sequence.

Fluorine-containing chemicals are unique entities whose behavior is dominated by the particular features of this halogen which finely modulates their physicochemical parameters.[1] These properties are advantageously exploited for designing valuable scaffolds attracting wide interest within the pharmaco-biological, material, or agricultural communities.[2] From a synthetic perspective the elaboration of fluoro-containing skeletons is a highly significant challenge.[3] Although a series of conceptually different tactics became available for the efficient introduction of this halogen, the use of fluorinated carbanions remained for a long time elusive and problematic.[4] Unfortunately, their intrinsic instability caused by the α-elimination (even at −130 °C)[5] dramatically limited the innate potential of simple and well-established nucleophilic−electrophilic transfer operations (Scheme 1a). Overcoming degradative issues was achieved through the installation on the putative carbanion of stabilizing groups—usually strongly electron-withdrawing[6] or silicon-containing[5,7] functionalities—which required appropriate removal at the end of the synthetic sequence (Scheme 1b).[6b] Arguably, the introduction and the subsequent removal of such stabilizing groups could make unsuitable the tactic for routine and extensive applications. Although significant advancements have been realized in radical monofluoromethylation of heteroatoms (O, S, N, P), the transformation proved to be not compatible with carbon species.[8] In 2017 our group documented the first straightforward generation and preparative use of fluoromethyllithium ($LiCH_2F$; Scheme 1c).[9] Despite its pronounced chemical instability,[10] the fine-tuning of the reaction conditions allowed us to employ it in direct transfers of the CH_2F unit to a wide range of carbon electrophiles. Pivotal for accomplishing such a challenging task was individuating the commercially available fluoroiodomethane (ICH_2F, bp 52 °C)[11] as a convenient and versatile precursor for the carbenoid which could be generated via iodine−lithium exchange reaction. We reasoned that switching the carbenoid formation event from the I/Li exchange to a deprotonation process[12] would form a more complex and bivalent fluoroiodomethyl carbanion suitable for introducing the CHIF fragment into an organic electrophile (Scheme 1c). At the outset of our investigations, we envisioned the potential of designing a concerted carbonyl homologation/ring closure by taking advantage of the constitutive different reactivity of the C−I and C−F bonds. In fact, the selective involvement of the C−I

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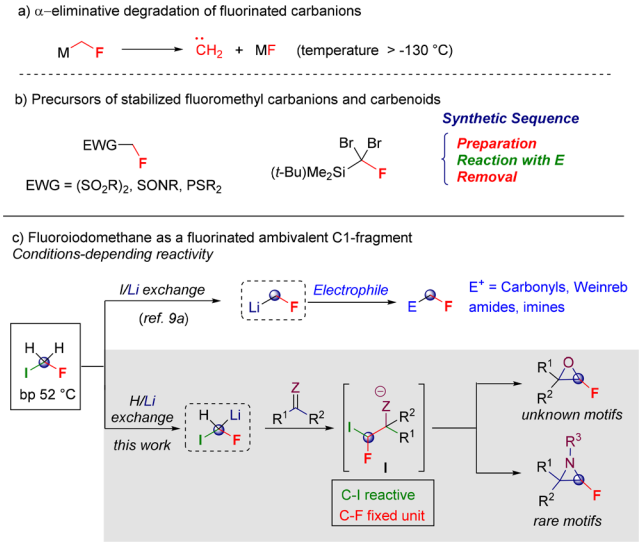
Scheme 1. Fluoro Homologations: State-of-the-Art

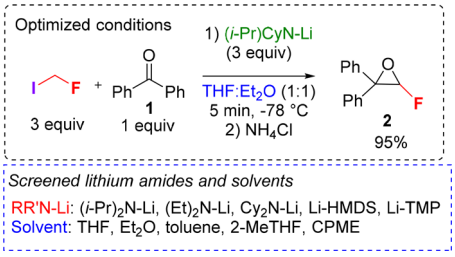


bond, and its inherent excellent leaving group capability, would have led to rather uncommon α-fluoroepoxides. Interestingly, trisubstituted α-fluoroepoxides have not been previously synthesized, and to the best of our knowledge, representative examples of this motif are limited to the fully substituted analogues (i.e., tetrasubstituted) accessible via protected fluorinated carbanions,[5,7,13] via the epoxidation of fluoroalkenes[14] or through ring closure of fluorohalohydrins.[15] Cognizant of the difficulties for preparing α-fluoroaziridines,[16] we thought that this approach would have been adaptable for facing this challenge, as well. The transfer of fluorocarbene to imines first introduced by Seyferth in 1973 represented the only available strategy for a long time:[17] however, the presence of elemental lead,[18] and the poor efficiency, severely limited its widespread application.[19] To date, the protocol developed by Verniest and De Kimpe involving the use of halofluoroamines followed by ring closure represents a reliable methodology to prepare *N*-alkyl analogues.[20] Herein, we document a conceptually simple homologation method for rapidly assembling trisubstituted fluoro-epoxides and aziridines starting from widely available carbonyl-like precursors and fluoroiodomethyllithium.

Benzophenone **1** was selected as a model electrophile for ascertaining the feasibility of the process and optimization. Crucial for the generation of the unknown carbenoid LiCHIF was identifying suitable reaction conditions in terms of solvent and lithium amide base. An extensive optimization study was conducted using Barbier-type conditions at −78 °C, and several lithium amides were screened, as well as different solvents (see Table S1, Supporting Information). Gratifingly, the best results for the sequential homologation−ring closure were achieved using lithium *i*-propyl-cyclohexyl amide (3 equiv) in a 1:1 (v/v) mixture of THF/Et_2O as the reaction's solvent and 3 equiv of fluoroiodomethane (Scheme 2). Under these conditions, fluoroepoxide **2** was isolated in an excellent 95% yield upon chromatography on basic alumina (Brockmann grade 2).[21]

Negligible differences were observed when the lithium amide was generated with different alkyllithiums, whereas the change to a magnesium base resulted in complete recovery of the starting material (Table S1). Although $BrCH_2F$ was amenable of deprotonation and could be used for preparing **2**,

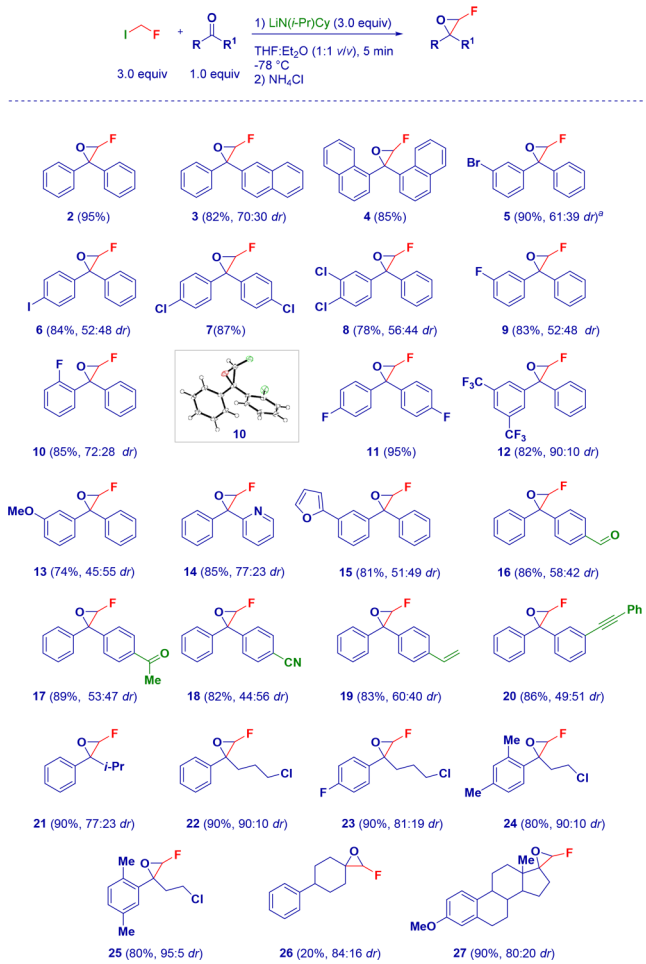
Scheme 2. Model Reaction: Optimization



low yields were observed likely for the difficult manipulation it required (bp 19 °C), thus making fluoroiodomethane as the ideal carbenoid precursor for this transformation. With the optimized conditions in hand, the scope of the reaction was explored (Scheme 3). A series of diaryl-ketones smoothly underwent the homologation−ring closure sequence providing the corresponding α-fluoroepoxides in excellent yields and moderate to very good diastereoselectivity.

Accordingly, the protocol could be applied to variously substituted systems decorated with a plethora of substituents ranging from aromatic (**3**−**4**) to halogen-containing ones

Scheme 3. Scope of the Reaction: Synthesis of α-Fluoroepoxides[b]



[a]Reaction run on 1.5 mmol gave 88% yield (62:38 dr). [b]Otherwise indicated: isolated yields. Diasteromeric ratio (dr) determined by ^{19}F NMR analysis.

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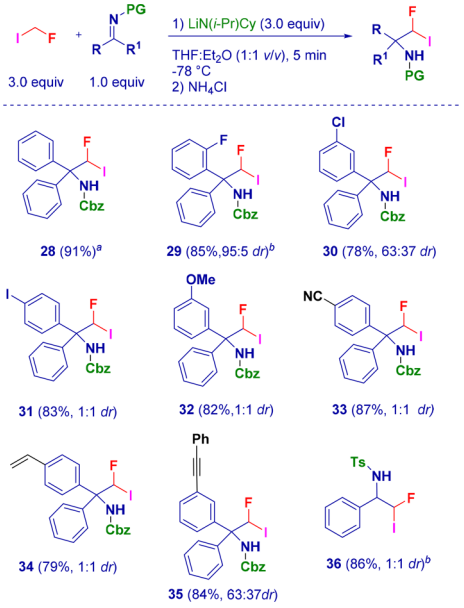
including bromine (**5**), iodine (**6**), chlorine (**7**–**8**), fluorine (**9**–**11**), or trifluoromethyl (**12**). Notably, the reaction leading to **5** could be scaled up to 1.5 mmol with comparable chemo- and stereocontrol. The X-ray analysis of fluoroepoxide **10** unambigously confirmed the structure for this previously unknown motif.[22] Ketones bearing an electron-donating group (OMe, **13**) on the aromatic ring or heterocycles (2-pyridyl **14** and 2-furyl **15**) were found to be fully compatible. The chemoselectivity toward the addition to a diarylketone functionality was superb as showcased with the formyl-substituted derivative (**16**) or the acyl-substituted epoxide **17**.[23] Moreover, selective transfer of the CHIF unit was also observed in the case of a nitrile (**18**) or unsaturated moieties such as an olefin (**19**) and an alkyne (**20**). The employment of aryl-alkyl ketones allowed us to assemble fluoroepoxides with uniformly higher dr values (up to 95:5) compared to those of diarylketones: the presence of sterical elements on the aromatic ring of aryl-alkylketones could rationalize this behavior. Some additional points merit mention: (1) The presence of an activated chloroalkyl substituent does not interfere with the targeted delivery of the CHIF unit to the carbonyl (**22**–**25**). (2) Dialkyl-ketones undergo the transformation, though in some instance with limited efficiency (**26**). However, a biologically relevant steroidic analogue was amenable for the transformation, giving fluoroepoxide **27** in excellent yield. The substantial reactivity analogy between ketones and imines prompted us to extend the methodology toward the synthesis of rare α-fluoroaziridines. We conceived that our strategy could serve as a platform for forming the new C–C bond through the addition of the mixed fluoroiodocarbenoid to an imine, followed by the ring closure. Pleasingly, under our optimized conditions N-activated imines were susceptible to the attack of LiCHIF, giving the corresponding β-fluoroiodoamines in very high to excellent yields (Scheme 4). Similarly to the previously mentioned ketones, aromatic substituents such as fluorine (**29**), chlorine (**30**), iodine (**31**), and methoxy (**32**) were allowed. Again, running the process at higher scale allowed us to completely preserve the efficiency (**28**). The chemoselective transfer of LiCHIF was further confirmed in the presence of a nitrile (**33**), olefin (**34**), or alkyne (**35**). It is worth mentioning that also an aldimine (**36**) could be employed in this process.

Significantly, the low propensity of lithiated fluoroiodoamides to undergo intramolecular cyclization allowed isolating highly functionalized β-fluoroiodoamines. Remarkably, the ring closure could be triggered in the presence of NaH in DMF: pleasingly, this two-step procedure showed a general applicability, giving access to challenging α-fluoroaziridines with high efficiency (Scheme 5). In the case of **37**—scalable also at the 1.34 mmol scale—single-crystal X-ray analysis confirmed the beauty of this unusual molecular motif.[22] *N*-Sulfonyl-protected ketimine underwent a very smooth homologation ring closure, giving compound **45** in an excellent 90% yield (Scheme 5).

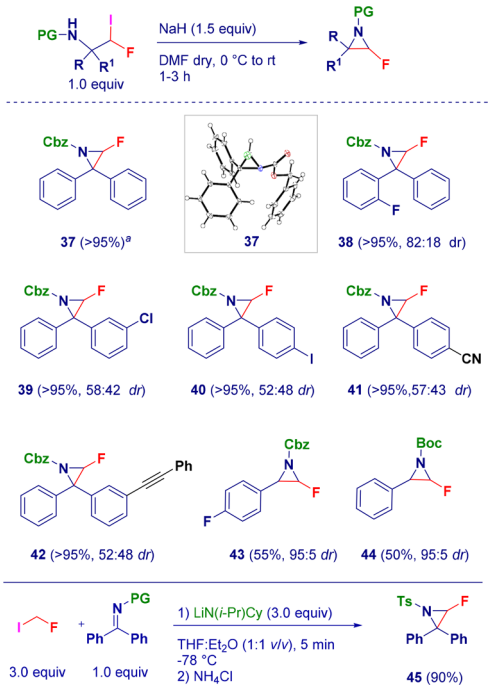
In order to acquire additional insights into the reactivity of the new synthesized compounds, we succeeded in realizing a sequential homologation–ring closure concerted with the 1,2-fluorine migration previously developed by Hu in the case of fully substituted α-fluoroepoxides (Scheme 6a).[13b] It should be observed that the herein studied trisubstituted α-fluoroepoxide resulted in the formation of the quaternary fully substituted α-fluoroaldehyde **47**. The presence of a reactive halogen on the aromatic ring of both α-fluoroepoxide (**5**) and α-fluoroaziridine (**40**) could be advantageously exploited for accomplishing the recently described Feringa's palladium-catalyzed cross-coupling with organolithiums (Scheme 6b,c).[24] Accordingly, the polyaromatic systems **48** and **49** were rapidly assembled

Scheme 4. Synthesis of α-Fluoroiodoamines



[a]Reaction run on 1.5 mmol gave 90% yield. [b]Diasteromeric ratio determined by ^{19}F NMR analysis. [c]Otherwise indicated: isolated yields. Diasteromeric ratio (dr) was determined by ^{1}H NMR analysis.

Scheme 5. Synthesis of α-Fluoroaziridines



[a]Reaction run on 1.35 mmol gave 94% yield. [b]Otherwise indicated: isolated yields. Diasteromeric ratio (dr) determined by ^{19}F NMR analysis.

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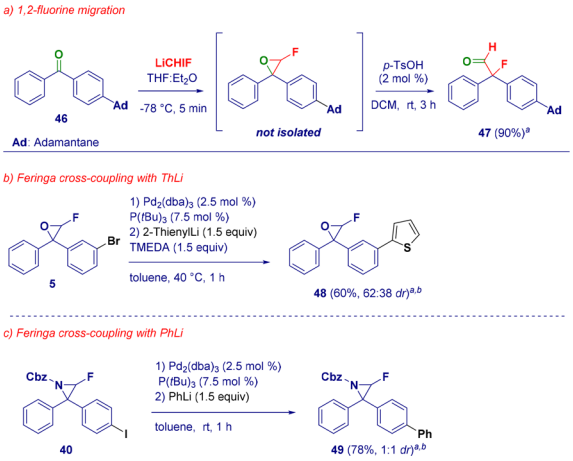
Scheme 6. Manipulation of α-Fluoroepoxides and Aziridines



[a]Isolated yields. [b]Diasteromeric ratio determined by ^{19}F NMR analysis. [c]Otherwise indicated: isolated yields. Diasteromeric ratio (dr) determined by ^{19}F-NMR analysis.

with full preservation of the sensitive α-fluorinated three-membered heterocyclic units.

In conclusion, we have developed an expeditious synthesis of α-fluoroepoxides and α-fluoroaziridines starting from ketones and imine-type derivatives (aldimines and ketimines), respectively. The proposed strategy relies on the introduction of an unknown fluorocarbenoid—fluoroiodomethyllithium—which acting in nucleophilic mode selectively attacks the carbonyl-like electrophilic center. The inherent different reactivities of the two C—halogen bonds connected to the inserted carbon allow the exclusive expulsion of iodine, thus leaving—after the ring closure—the fluorine atom in the final compound. In the case of imines, a two-step sequence is required, with the ring-closure step occurring on the (isolable) fluoroiodoamines. Remarkably, fluoroiodomethyllithium acts with superb chemoselectivity as evidenced in the presence of additional electrophilic sites across the molecular core: the full preservation of an aldehyde, a ketone, a nitrile, or an alkene nicely highlights the unique reactivity pattern of this new mixed, bis-functionalized carbenoid.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b04001.

Experimental procedure, NMR spectra, and analytical data for all the compounds (PDF)

Accession Codes

CCDC 1879398−1879399 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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