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Fluoroamination of Alkenes Mediated by Hypervalent Iodine to Access 3-Functionalized Azetidines

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Keywords: Azetidine, Hypervalent Iodine, fluoroamination

Abstract

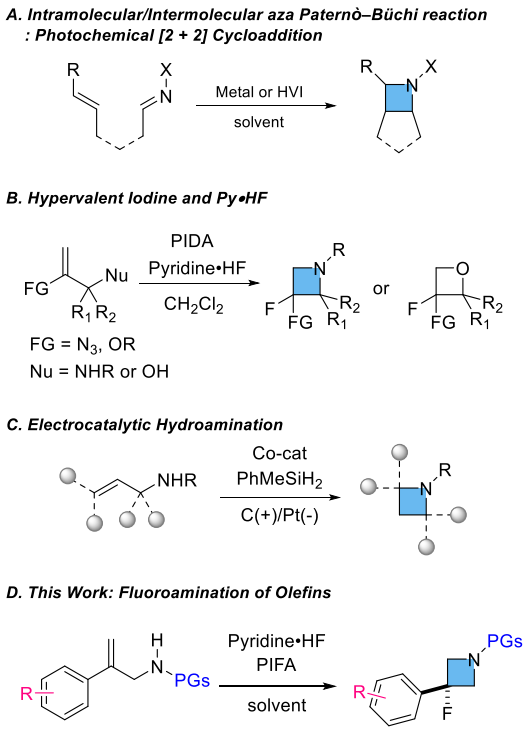
Azetidine motifs are valuable for the synthesis of a wide range of biologically active molecules and drug candidates. We report the construction of 3-functionalized azetidines through hypervalent iodine–mediated fluoroamination using pyridine·HF. Two complementary protocols enable simultaneous C–F and C–N bond formation under simple conditions. The reaction tolerates a broad range of *N*-protected 2-aryl allylamines, affording fluorinated azetidines in moderate-to-good yields.

1. Introduction

Azetidines, which are four-membered nitrogen-containing heterocycles, have attracted increasing attention in medicinal and synthetic chemistry because of their significant ring strain and unique three-dimensional architectures.[1-5] These features often result in an enhanced binding affinity, metabolic stability, and conformational rigidity, making azetidine motifs valuable in a wide range of biologically active molecules and drug candidates.[6, 7] Accordingly, azetidines have been explored in diverse therapeutic areas, including enzyme inhibition,[8, 9] cardiovascular diseases,[10-12] and central nervous system disorders,[10-13] and are now recognized as important building blocks in modern drug design.[14] Despite their importance, the synthesis of substituted azetidines remains challenging because of the intrinsic ring strain of four-membered heterocycles. Conventional methods often rely on multistep sequences, prefunctionalized starting materials, or harsh reaction conditions, which limit their efficiency and structural diversity.[15, 16] To address these limitations, various strategies have been developed, including intramolecular cyclizations of β-amino alcohols or β-amino esters,[17-19] ring contraction/expansion processes, and cycloaddition approaches.[20-25] Among the available approaches, photochemical [2+2] cycloaddition is a powerful route to four-membered rings with high regio- and stereocontrol.[26-30] The aza Paternò–Büchi reaction, which involves the photochemical [2+2] cycloaddition of an imine with an alkene, represents one of the most well-established and extensively developed strategies for the direct construction of azetidine frameworks. This reaction proceeds through photoexcitation of either the imine or the alkene component, generating a reactive excited state that undergoes stepwise or concerted [2+2] cycloaddition to furnish a strained four-membered nitrogen heterocycle. The overall transformation is highly attractive from a synthetic standpoint, enabling the simultaneous formation of C–C and C–N bonds in a single photochemical step (Scheme 1A).[27, 31, 32] Scheme 1B demonstrates the successful use of hypervalent iodine-mediated fluorocyclization to construct strained four-membered heterocycles, providing access to 3-functionalized oxetanes and azetidines from readily available allylic alcohols and amines.[33] By generating $PhIF_2$ in situ from PIDA and HF, the authors achieve high-yielding cyclizations across a broad range of substrates, including both cyclic and acyclic systems, and further validate the practicality of the method through gram-scale synthesis. Kim et al. reported the first electrocatalytic intramolecular hydroamination of allylic sulfonamides for the direct synthesis of azetidines, a transformation that had remained elusive despite the widespread availability of allylic amines as synthetic precursors (Scheme 1C).[34] By combining cobalt catalysis with electrochemistry, this strategy enables the regioselective generation of key carbocationic intermediates through

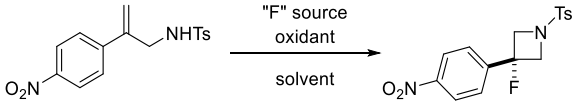
sequential metal hydride atom transfer (MHAT) and anodic oxidation, thereby overcoming the intrinsic kinetic limitations associated with four-membered ring formation. Herein, we report the hypervalent iodine-mediated fluorocyclization of *N*-sulfonyl-2-aryl allylamines, which provides a direct route to fluorinated azetidines. Although the fluorocyclization strategy of Wu (Scheme 1B) relies on a mandatory electron-donating group (−N_3 or −OR) at the α-position to polarize the C=C bond and facilitate four-membered ring formation, the present work employs *N*-sulfonyl-2-aryl allylamines in which the sulfonamide moiety directly serves as the intramolecular nucleophile, eliminating the need for pre-activation of the alkene. Unlike the method of Wu, which retains a pendant functional group, our approach forms both C–F and C–N bonds in a single step by directly inserting nitrogen into the azetidine ring. This method employs PIFA in combination with pyridine (Py)·HF to enable simultaneous C–F bond formation and ring closure under mild conditions, affording *trans*-configured fluorinated azetidines with a broad substrate scope.

Scheme 1. Synthesis of Azetidines



2. Results and discussion

Table 1. Reaction Optimization



1a 2a

entry	"F" source (equiv)	oxidant (equiv)	solvent	yield (%) [b]
1	Py•HF (2)	PIFA (1.2)	DCM	52
2	Py•HF (5)	PIFA (1.2)	DCM	57
3	Py•HF (5)	PIFA (2)	DCM	61
4	Et_3N•HF (5)	PIFA (2)	DCM	N.D.
5	Py•HF (5)	PIFA (2)	toluene	53
6	Py•HF (5)	PIFA (2)	dioxane	N.D.
7	Py•HF (5)	PIFA (2)	THF	N.D.
8	Py•HF (5)	PIFA (2)	CH_3CN	N.D.
9	Py•HF (5)	PIFA (2)	DMF	N.D.
10	Py•HF (5)	PIFA (2)	DMSO	N.D.
11	Py•HF (5)	PIFA (2)	TFE	46
12	Py•HF (5)	PIFA (2)	chlorobenzene	67
13	Py•HF (5)	PIDP (2)	chlorobenzene	61
14	Py•HF (5)	PIDA (2)	chlorobenzene	55

[a] All reactions were performed using 0.1 mmol (0.2 M) and a standard 18-40 h reaction time.
[b] Isolated yield.

Initially, we used (4-nitrophenyl)allyl)benzenesulfonamide (1a) as a model substrate and examined the effects of the fluoride source, oxidant, and solvent on the fluoroamination of alkenes (Table 1). Initial studies employing Py·HF (2 equiv.) as the fluoride source in combination with PIFA (1.2 equiv.) in DCM afforded desired product 2a in a 52% yield, confirming the feasibility of the transformation (entry 1). Increasing the amount of Py·HF to 5 equiv. under otherwise identical conditions led to a modest improvement in the yield (57%, entry 2), and a further increase in the oxidant loading to 2.0 equiv. resulted in a slightly higher yield (61%, entry 3). The nature of the fluoride source was critical, and the replacement of Py·HF with Et_3N·HF completely suppressed product formation under the same conditions

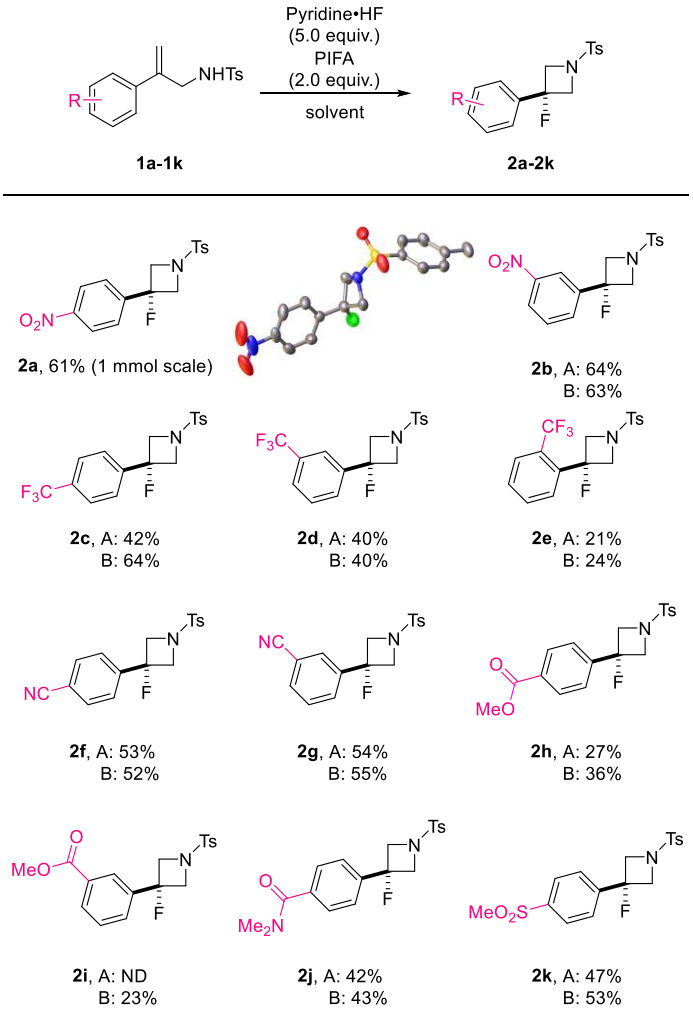
(entry 4). Solvent effects were then examined using Py·HF (5 equiv.) and PIFA (2 equiv.). Whereas toluene supported the reaction to a moderate extent (53% yield, entry 5), other solvents such as dioxane, THF, CH_3CN, DMF, and DMSO were ineffective, resulting in no detectable product formation (entries 6–10). In contrast, the use of TFE restored reactivity to some extent, delivering the product in a 46% yield (entry 11). Notably, a significant improvement was observed when chlorobenzene was employed as the solvent, affording the desired product in a 67% yield, which was the best result obtained during the optimization study (entry 12). Under these solvent conditions, alternative hypervalent iodine oxidants were also evaluated; the substitution of PIFA with PIDP or PIDA resulted in slightly diminished but still appreciable yields of 61% and 55%, respectively (entries 13 and 14). Based on these studies, the combination of Py·HF (5 equiv.) and PIFA (2 equiv.) in chlorobenzene was identified as the optimal conditions for the fluoroamination reaction and was therefore adopted for subsequent investigations.

A para-methoxycarbonyl group furnished 2h in moderate yields (A: 27%, B: 36%), whereas no product was detected under condition A for the para-ethoxycarbonyl analog, which gave 2i only under condition B (23%), implying sensitivity to the steric bulk of the ester moiety under condition A. A para-dimethylaminocarbonyl substrate delivered 2j in moderate yields under both conditions (A: 42%, B: 43%), demonstrating tolerance for amide functionalities. Finally, a para-methylsulfonyl group, a strongly electron-withdrawing and pharmaceutically relevant motif, afforded 2k in 47% and 53% yields under conditions A and B, respectively, further highlighting the broad functional group compatibility of this method.

To examine the effect of substrate electronics on the reactivity, natural population analysis (NPA) charge calculations (M06-2X/6-311++G(d,p), SMD/DCM) were performed on representative substrates bearing various electron-withdrawing aryl groups (Scheme 3). NPA charge analysis revealed that a range of electron-withdrawing aryl substituents induced consistently high polarization of the alkene, which correlated with the uniformly moderate-to-good reaction yields observed experimentally. Despite differences in electronic properties, all substituents examined ($-NO_2$, $-CF_3$, −CN, ester, amide, and $-SO_2Me$) exhibited a narrow Δe range, indicating sufficient activation of the C=C bond toward electrophilic fluorination by hypervalent iodine species. Minor variations, such as the slightly lower polarization for the $-NO_2$ group, aligned with comparable experimental outcomes, while ester-, amide-, and sulfonyl-substituted substrates showed consistently reliable performance. In contrast, substrates bearing electron-neutral (H, S1) or electron-donating substituents (Me, S2; OMe, S3) failed to

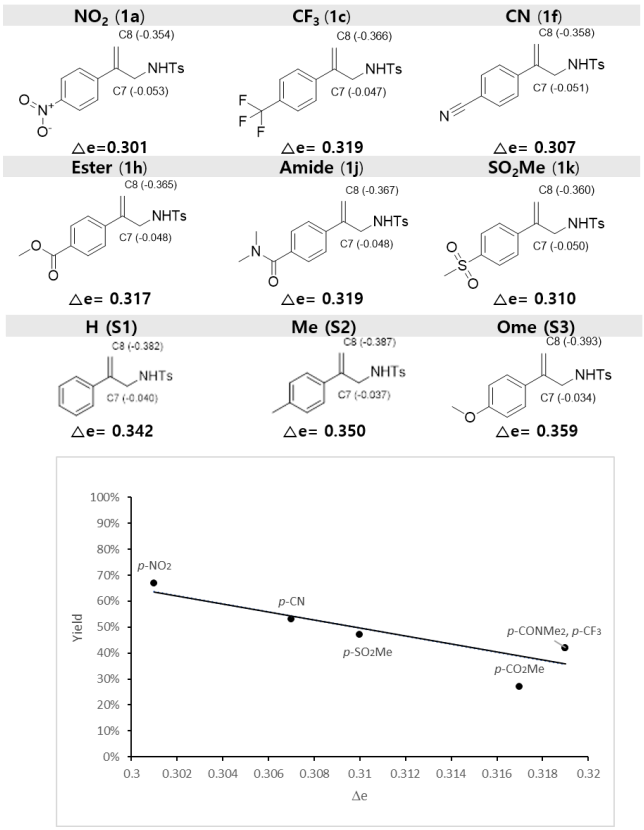
afford the desired products under the optimized reaction conditions. These substituents are expected to decrease alkene polarization relative to electron-withdrawing groups, thereby diminishing its susceptibility toward electrophilic activation by the iodine(III) reagent (see supporting information for details). Overall, these results support the conclusion that aryl substituents modulate alkene polarization, which directly influences the reactivity and efficiency of fluoroamination cyclization.

Scheme 2. Scope of Substituted Allylamines



[a]Reaction condition A: **1** (0.1 mmol), Pyridine•HF (0.5 mmol), and PIFA (0.2 mmol) in chlorobenzene (5.0 mL), rt, 3-6 h. [b]Reaction condition B: **1** (0.1 mmol), Pyridine•HF (0.5 mmol), and PIFA (0.2 mmol) in DCM (5.0 mL), rt, 3-6 h.

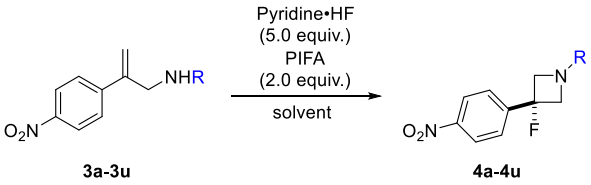
Scheme 3. Effect of Substrate Electronics



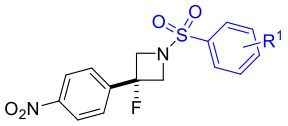
Having established the substrate scope with respect to the aryl group on the alkene, we investigated the influence of the *N*-sulfonyl substituent on the fluorocyclization reaction using a fixed *para*-nitrophenyl-substituted allylic amine framework (Scheme 4). A diverse array of sulfonamide-derived substrates **3a–3u** were evaluated under both reaction conditions, affording the corresponding fluorinated azetidines **4a–4u**. First, arylsulfonyl groups bearing electron-withdrawing substituents on the nitrogen were examined. The *para*-nitrophenylsulfonyl substrate afforded **4a** in good yields (A: 57%, B: 65%), whereas the *meta*-nitro analog delivered **4b** with comparable efficiency (A: 47%, B: 69%). A 4-chloro-3-nitro arylsulfonyl group afforded **4c** (A: 60%, B: 57%), and the *tert*-butyl-substituted arylsulfonyl substrate furnished **4d** in good yields (A: 74%, B: 69%). A *meta*-methyl arylsulfonyl group afforded **4e** (A: 55%, B: 55%), and a *para*-fluoro derivative delivered **4f** in moderate yields (A: 55%, B: 65%). The unsubstituted phenylsulfonyl substrate afforded **4g** in the highest yields observed in this series (A: 69%, B: 75%), suggesting that simplified arylsulfonyl groups are particularly well suited for this transformation. The scope was further extended to aliphatic and structurally diverse sulfonamides. Among simple alkylsulfonyl substrates, a methylsulfonyl group afforded **4h** in good yields under both conditions (A: 59%, B: 56%), while the isopropylsulfonyl analog gave

4i in reduced yields (A: 24%, B: 30%), reflecting the steric sensitivity of the branched alkyl substituents at the nitrogen. A butylsulfonyl group delivered **4j** in moderate yields (A: 49%, B: 52%), and a cyclopropylsulfonyl substrate furnished **4k** in the highest yields among the alkyl/cycloalkyl sulfonyl series (A: 69%, B: 56%), suggesting that the conformationally rigid cyclopropyl group is particularly well suited for this transformation. Sulfonamides incorporating heteroatom-containing rings were also evaluated. A morpholinylsulfonyl substrate afforded **4l** in good yields (A: 59%, B: 64%), and a dimethylaminosulfonyl derivative afforded **4m** in moderate yields (A: 36%, B: 39%), indicating that *N*,*N*-dialkyl amino substituents were tolerated, albeit with diminished efficiency, likely due to the electron-donating character of the dimethylamino group, which attenuated the electrophilic activation. A piperidinylsulfonyl substrate delivered **4n** (A: 52%, B: 49%) and a pyrrolidinylsulfonyl analogue gave **4o** in comparable yields (A: 52%, B: 50%), demonstrating that both six- and five-membered cyclic amine-derived sulfonyl groups participated effectively in the fluorocyclization. A secondary methylaminosulfonyl substrate afforded **4p** in moderate yields (A: 51%, B: 52%), further confirming tolerance for *N*-monoalkyl sulfonamide variants. Finally, *N*-benzoyl-derived substrates bearing aryl substituents at various positions were investigated. A *para*-methyl benzoyl substrate gave **4q** in low yields (A: 31%, B: 20%), and a *para*-tert-butyl analog afforded **4r** in similar yields (A: 34%, B: 20%). A *para*-chlorobenzoyl substrate gave **4s** in only a 10% yield under condition A, with no product detected under condition B, whereas a *meta*-nitro-benzoyl group delivered **4t** in moderate yields (A: 45%, B: 36%). The *para*-nitrobenzoyl substrate **4u** gave no detectable product under either condition, indicating that strongly electron-withdrawing *para*-nitro substitution on the benzoyl group was incompatible with the present fluorocyclization, likely due to the diminished nucleophilicity of the sulfonamide nitrogen impairing the intramolecular ring closure step. Overall, this broad survey of sulfonamide substituents demonstrates the versatility of fluorocyclization using a wide range of *N*-sulfonyl groups, with arylsulfonyl and simple alkylsulfonyl substrates generally providing superior yields relative to sterically demanding or strongly electron-deficient variants.

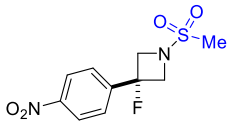
Scheme 4. Scope of N-sulfonyl substituted allylamines



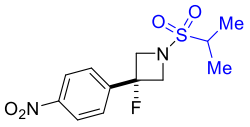
3a-3u **4a-4u**



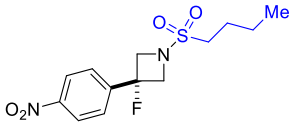
4a, R^1 = 4-NO_2, A 57%, B 65%
4b, R^1 = 3-NO_2, A 47%, B 69%
4c, R^1 = 3-NO_2, 4-Cl A 60%, B 57%
4d, R^1 = 4-^{t}Bu, A 74%, B 69%
4e, R^1 = 3-Me, A 67%, B 65%
4f, R^1 = 4-F, A 55%, B 65%
4g, R^1 = H, A 69%, B 75%



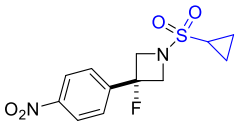
4h, A 59%
B 56%



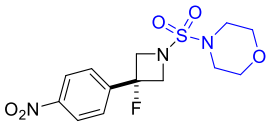
4i, A 24%
B 30%



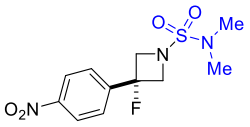
4j, A 49%
B 52%



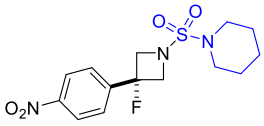
4k, A 69%
B 56%



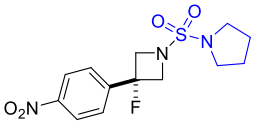
4l, A 59%
B 64%



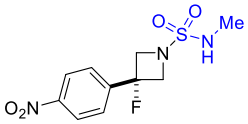
4m, A 36%
B 39%



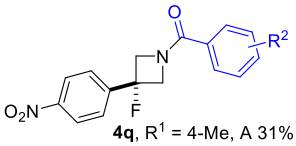
4n, A 52%
B 49%



4o, A 52%
B 50%



4p, A 51%
B 52%



4q, R^1 = 4-Me, A 31%, B 20%
4r, R^2 = 4-^{t}Bu, A 34%, B 20%
4s, R^2 = 4-Cl, A 10%, B N.D.
4t, R^2 = 2-NO_2, A 45% B 36%
4u, R^2 = 4-NO_2, A, B N.D.

[a]Reaction condition A: **3** (0.2 mmol), Pyridine•HF (1.0 mmol), and PIFA (0.4 mmol) in chlorobenzene (2.0 mL), rt, 3-6 h. [b]Reaction condition B: **3** (0.2 mmol), Pyridine•HF (1.0 mmol), and PIFA (0.4 mmol) in DCM (2.0 mL), rt, 3-6 h.

3. Conclusion

In conclusion, we have developed a mild hypervalent iodine-mediated fluoroamination of alkenes using Py·HF as the fluoride source. The reaction proceeds under oper-ationally simple conditions and tolerates a broad range of functional groups, enabling the simultaneous formation of C–F and C–N bonds. Systematic optimization identified PIFA and chlorobenzene as the optimal reaction compo-nents, and two closely related protocols (methods A and B) provided complementary reactivity profiles depending on the substrate electronics. The generality of this trans-formation was demonstrated across a wide array of N-protected 2-aryl allylamine substrates, delivering the fluorinated products in moderate to good yields. Notably, electron-deficient, electron-rich, and sterically demanding substrates, including heteroatom-containing systems, are compatible with the reaction conditions. The scalability of this process and its broad substrate scope underscore the synthetic utility of this methodology for the construc-tion of fluorinated azetidines. Given the prevalence of fluorinated motifs in pharmaceuticals and agrochemicals, this protocol offers an approach for the late-stage fluoro-amination of alkenes and is expected to find broad appli-cations in medicinal chemistry and related fields.

4. Experimental Section/Methods

Method 1: All reactions were conducted in 5 mL polyethylene (PE) vials to ensure compatibility with fluorine reagents. To a solution of 1a-k (0.1 mmol, 1.0 eq) and PIFA (88.7 mg, 0.2 mmol, 2.0 eq) in chlorobenzene (0.5 mL, 0.2 M) was added Pyridine•HF (64.4 μL, 0.5 mmol, 5.0 eq). The reaction mixture was stirred at r.t for 18 h. The resulting mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The mixture was then filtered and concentrated under reduced pressure. The residue was purified flash column chromatography on silica gel (hexane/EtOAc) to afford the desired fluorinated products.

Method 2: All reactions were conducted in 5 mL polyethylene (PE) vials to ensure compatibility with fluorine reagents. To a solution of 1a-k (0.1 mmol, 1.0 eq) and PIFA (88.7 mg, 0.2 mmol, 2.0 eq) in DCM (0.5 mL, 0.2 M) was added Pyridine•HF (64.4 μL, 0.5 mmol, 5.0 eq). The reaction mixture was stirred at r.t for 18 h. The resulting mixture was diluted with EtOAc, washed with sat. $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine and dried over Na_2SO_4. The mixture was then filtered and concentrated under

reduced pressure. The residue was purified flash column chromatography on silica gel (hexane/EtOAc) to afford the desired fluorinated products.

[CCDC 2521696 contains the supplementary crystallographic data for this study. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailingdata_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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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

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