Organic LETTERS

Letter

pubs.acs.org/OrgLett

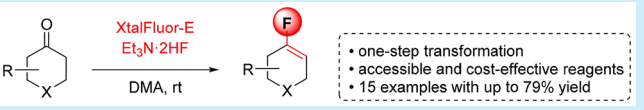
Eliminative Deoxofluorination Using XtalFluor-E: A One-Step Synthesis of Monofluoroalkenes from Cyclohexanone Derivatives

Mathilde Vandamme and Jean-François Paquin*

CGCC, PROTEO, Département de chimie, Université Laval, 1045 Avenue de la Médecine, Québec, Québec G1V 0A6, Canada

Supporting Information

ABSTRACT: The eliminative deoxofluorination of cyclohexanone derivatives using XtalFluor-E is described. The corresponding monofluoroalkenes are obtained in up to 79% yield. Notably, this one-step procedure occurs at room temperature using readily accessible and cost-effective reagents.

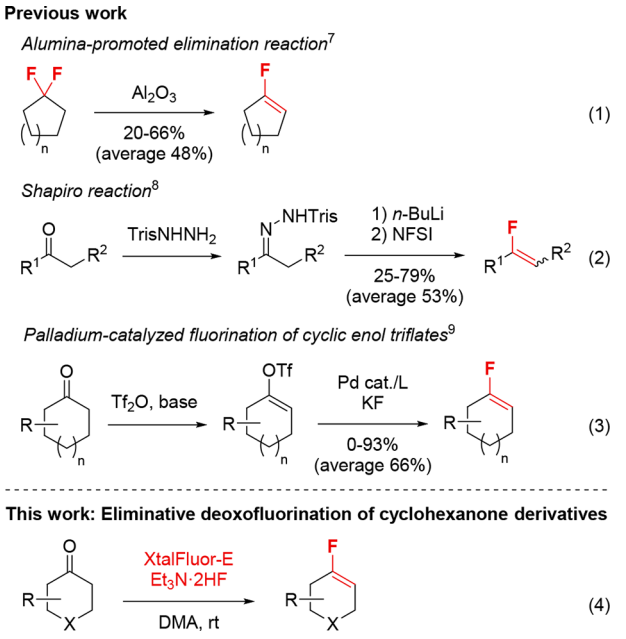


Alkenes bearing one or more fluorine atoms represent a valuable subclass of fluorine-containing molecules. Indeed, monofluoroalkenes are utilized in medicinal chemistry as, among other things, amide isosteres[1,2] and enol mimics.[3] Fluoroalkenes also have potential applications in material sciences,[4] and they can be used in synthetic organic chemistry as fluorinated building blocks for further functionalization.[5] The synthesis of monofluorinated alkenes, despite their potential uses in various fields, still remains a synthetic challenge.[6] An attractive strategy would be the direct conversion of a ketone to the corresponding fluoroalkene. Toward this end, three synthetic approaches have been reported. In the first case, an alumina-promoted elimination of difluorocycloalcanes was described (Scheme 1, eq 1).[7] In the second approach, the Shapiro reaction was used as the key step (Scheme 1, eq 2).[8] Ketones were first transformed into hydrazones using 2,4,6-triisopropylbenzenesulfonyl hydrazide ($TrisNHNH_2$). Reaction with *n*-BuLi followed by fluorination of the resulting vinyl lithium species using NFSI afforded the fluoroalkenes. More recently, the palladium-catalyzed fluorination of cyclic vinyl triflates was reported (Scheme 1, eq 3).[9] In this case, ketones were first converted to their corresponding vinyl triflates, which were then fluorinated using a newly developed phosphine ligand, a palladium source, $TESCF_3$ as an additive, and KF as the fluoride source. While all reactions represent key contributions, they suffer from issues limiting their applications. Indeed, in the first case, the source of alumina was found to be critical. In the last two reactions, the starting ketone must be transformed into an appropriate precursor which results in a lower overall yield. Additionally, in the case of the Shapiro reaction, both the hydrazine and fluorinating agent are expensive[10] and the basic conditions employed limit the functional groups tolerated. In the case of the Pd-catalyzed fluorination, not all the ligands employed are commercially available, and the reaction requires 30 mol % of $TESCF_3$, an expensive additive,[9] but most importantly, the fluorination step needs to be performed in a glovebox under strictly anhydrous conditions. Given those limitations, the development of additional complementary methods is necessary.

Our inspiration for the present work was the report that fluoroalkenes were sometimes observed as side products for the deoxofluorination of ketones using XtalFluor-E ($[Et_2NSF_2]$-BF_4)[11,12] or with other related reagents.[13−15] We imagine that if conditions favoring the formation of the fluoroalkene could be found, it would represent a practical one-step alternative to the above methods. Herein, we report the direct conversion of cyclohexanone derivatives to monofluoroalkene using XtalFluor-E (Scheme 1, eq 4).[16] Notably, this one-step procedure occurs at room temperature using readily accessible and cost-effective reagents[10] without the need for a glovebox.

An extensive optimization of the reaction conditions was undertaken, and selected key results are shown in Table 1.[17] Under conditions reported for the deoxofluorination of ketone

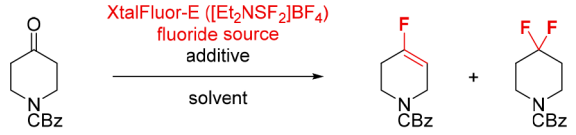
Scheme 1. Previous and Current Work



Received: May 25, 2017

DOI: 10.1021/acs.orglett.7b01581
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Key Optimization Results for the Eliminative Deoxofluorination of 4a Using XtalFluor-E[a]



4a **5a** **6a**

entry	XtalFluor-E (equiv)	fluoride source (equiv)[b]	solvent	additive (equiv)	temp (°C)	time (h)	conversion (%)[c]	ratio **5a**/**6a**[c]	yield (%)[d]
1	1.5	$Et_3N{\cdot}2HF$ (3)	CH_2Cl_2	–	rt	16	100	1:6.7	13
2	1.5	$Et_3N{\cdot}2HF$ (3)	toluene	–	rt	16	100	1:2.4	22
3	1.5	$Et_3N{\cdot}2HF$ (3)	EtOAc	–	rt	16	90	1:4.7	14
4	1.5	$Et_3N{\cdot}2HF$ (3)	Et_2O	–	rt	16	100	1:5.5	13
5	1.5	$Et_3N{\cdot}2HF$ (3)	THF	–	rt	16	86	1:1.8	24
6	1.5	$Et_3N{\cdot}2HF$ (3)	CH_3CN	–	rt	16	100	1:2.9	12
7	1.5	$Et_3N{\cdot}2HF$ (3)	DMF	–	rt	16	100	2.5:1	33
8	1.5	$Et_3N{\cdot}2HF$ (3)	DMA	–	rt	16	100	5:1	15
9	2	$Et_3N{\cdot}2HF$ (3)	DMA	–	rt	16	87	5.7:1	34
10	**3**	**$Et_3N{\cdot}2HF$ (3)**	**DMA**	**–**	**rt**	**16**	**100**	**6.8:1**	**75 (79)**[e]
11	3	$Et_3N{\cdot}2HF$ (3)	DMA	–	60	2	100	4.6:1	23
12	3	$Et_3N{\cdot}2HF$ (1.5)	DMA	–	rt	120	98	9.1:1	73
13	3	$Et_3N{\cdot}3HF$ (3)	DMA	–	rt	16	100	5.4:1	70
14	3	$Et_3N{\cdot}3HF$ (2)	DMA	DBU (1)	rt	16	94	5.5:1	60
15	3	$Et_3N{\cdot}3HF$ (2)	DMA	*i*-Pr_2EtN (1)	rt	16	97	5.8:1	70
16	3	$Et_3N{\cdot}3HF$ (2)	DMA	Me-imidazole (1)	rt	16	97	5.5:1	44
17[f]	3	$Et_3N{\cdot}3HF$ (2)	DMA	–	rt	16	97	3.2:1	19
18[g]	3	$Et_3N{\cdot}3HF$ (2)	DMA	–	rt	16	89	2.9:1	29

[a]See the Supporting Information for the detailed experimental procedures. [b]$Et_3N{\cdot}2HF$ is generated *in situ* by adding Et_3N (1 equiv) to $Et_3N{\cdot}3HF$ (2 equiv). [c]Determined by ^{19}F NMR analysis of the crude mixture after workup. [d]Yield of **5a** determined by ^{19}F NMR analysis of the crude mixture after workup. [e]Isolated yield of **5a** contaminated with inseparable **6a** (**5a**/**6a** = 5.9:1). [f]Me-DAST was used instead of XtalFluor-E. [g]Deoxofluor was used instead of XtalFluor-E.

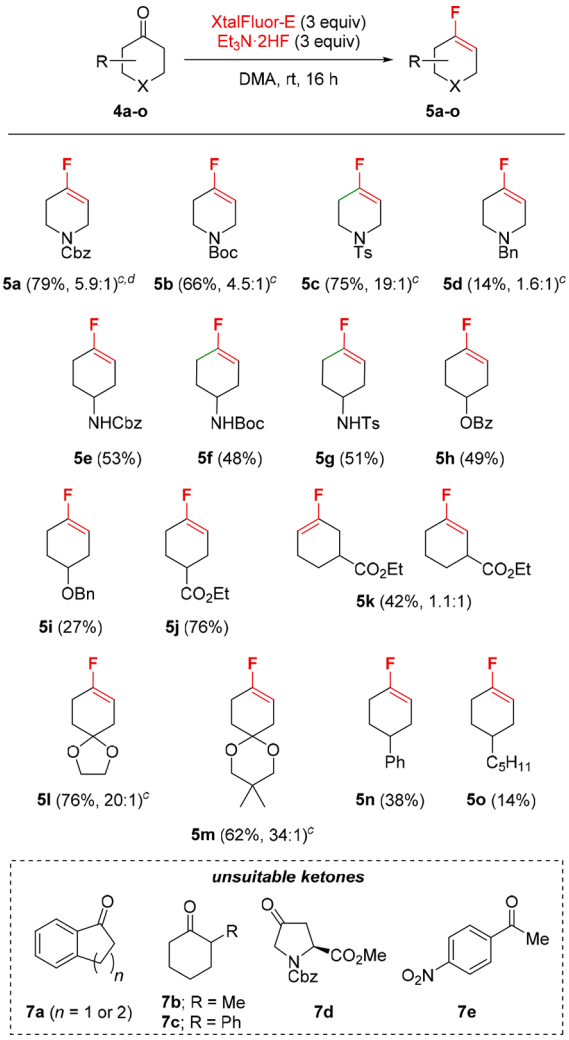
using XtalFluor-E (Table 1, entry 1),[11] a 13% NMR yield of the monofluoroalkene **5a** was observed, yet the major product was the difluoromethylene compound **6a** (ratio **5a**/**6a** = 1:6.7). Next, different solvents were tested including toluene, EtOAc, Et_2O, THF, or CH_3CN (Table 1, entries 2–6).[17] For all of them, low NMR yields of **5a** were detected (13–24%), and in all cases, product **6a** was the major compound with the best **5a**/**6a** observed with THF (1:1.8). Interestingly, when DMF was ratio employed as the solvent, a reversal of the selectivity was observed, as **5a** was now the major product (**5a**/**6a** = 2.5:1) with an NMR yield of 33% (Table 1, entry 7). Using a related solvent, dimethylacetamide (DMA), improved the **5a**/**6a** ratio to 5:1, but at the expense of the yield (15% by NMR) (Table 1, entry 8). Increasing the amount of XtalFluor-E to 3 equiv (Table 1, entries 9–10) resulted in a 75% NMR yield of the desired monofluoroalkene **5a** with a **5a**/**6a** ratio of 6.8:1. Diluting the reaction in CH_2Cl_2 using various ratios (9:1, 1:1, or 1:9) of a CH_2Cl_2/DMA mixture did not furnish better results (not shown). Similarly, conducting the reaction at 60 °C resulted in a lower NMR yield of **5a** (23%) (Table 1, entry 11). Reducing the amount $Et_3N{\cdot}2HF$ to 1.5 equiv resulted in a much slower reaction. Nonetheless, after 5 days, a 73% NMR yield of **5a** was observed with a higher **5a**/**6a** ratio of 9.1:1 (Table 1, entry 12). When $Et_3N{\cdot}3HF$ was used as the fluoride source, a slightly inferior NMR yield was observed (70%) (Table 1, entry 13) most likely due to the lower nucleophilicity of $Et_3N{\cdot}3HF$ compared to $Et_3N{\cdot}2HF$.[18] Replacing the added Et_3N by other amine bases (DBU, *i*-Pr_2EtN, or Me-imidazole) had limited effect on conversion and on the **5a**/**6a** ratio (Table 1, entries 14–16). Other fluoride sources such as TBAF (1 M soln in THF), $TBAF{\cdot}3H_2O$, or DMPU·HF[19] (with or without added Et_3N) were ineffective (not shown). Also, various additives[17] were tested, but none offered significantly better results (not shown). Finally, for comparison, Me-DAST and Deoxofluor, two classical deoxofluorinating agents, were tested (Table 1, entries 17–18). In both cases, a low yield (19–29%) and lower selectivity (up to 3.2:1) were obtained, demonstrating the unique reactivity of XtalFluor-E. Overall, the conditions shown in Table 1, entry 10 were chosen to be optimimal.

We next evaluated the reactivity of various cyclohexanone derivatives under the optimized conditions (Scheme 2). 4-Piperidone bearing various amine protecting groups performed well. In this case, monofluoroalkenes bearing a carbamate or sulfonyl-based protecting groups (**5a**–**c**) were isolated in better yields than the one having a benzyl group (**5d**). Cbz-, Boc-, or Ts-protected 4-aminocyclohexanone also provided the corresponding monofluoroalkenes (**5e**–**g**) in moderate yields. In the case of protected 4-hydroxycyclohexanone, the use of a benzoyl group furnished the monofluoroalkene **5h** in a better yield than when using a benzyl group (**5i**). An ethyl ester substituent is well tolerated at both the 4- and 3-position. In the former, monofluoalkene **5j** is isolated in 76% yield. In the latter, the product **5k** is isolated in moderate yield as a mixture of inseparable monofluoroalkenes in a ratio of 1.2:1 favoring the alkene distal to the ester moiety. Monofluoroalkenes derived from 1,4-cyclohexanedione monoacetal (**5l** and **5m**) were obtained in good yield. Finally, cyclohexanone bearing a phenyl group or a *n*-pentyl chain at the 4-position provided the desired products **5n** and **5o** in 38% and 14% respectively.

A number of other ketones were also tested, but did not provide the desired monofluoroalkenes. For instance, for 1-tetralone, no conversion was observed whereas, for 1-indanone,

DOI: 10.1021/acs.orglett.7b01581
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Eliminative Deoxofluorination of Various Cyclohexanone Derivatives Using XtalFluor-E[a,b]

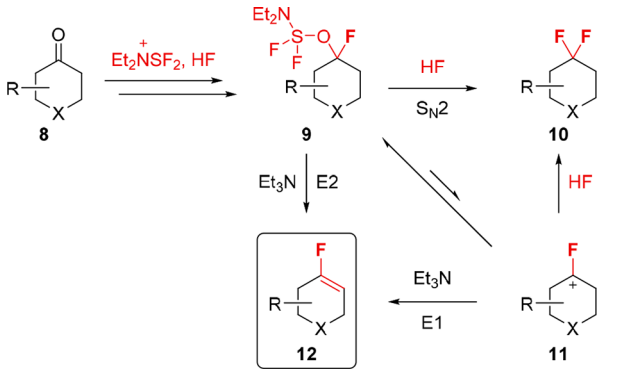


[a]See the Supporting Information for the detailed experimental procedures. [b]Isolated yield. [c]Monofluoroalkene/difluoromethylene ratio determined by ^{19}F NMR in the purified product when complete separation by flash chromatography was not possible. [d]On a 1 mmol scale, 75% (ratio **5a**/**6a** = 6.1:1) of **5a** was obtained.

<20% conversion was observed by NMR, but no fluorinated products were formed. When using α-substituted cyclohexanones, some conversion (23% and 72% for **7b** and **7c** respectively) was observed, but no fluorinated products could be detected. A moderate conversion (69%) was obtained for a five-membered ring derivative (**7d**), but no fluorinated products were formed. Finally, when using an acyclic ketone such as **7e**, only degradation was observed and no fluorinated products were observed.

Our current mechanistic hypothesis is shown in Scheme 3. First, the ketone (**8**) would get converted to the fluoroalkoxy-*N*,*N*-diethylaminodifluorosulfane (**9**).[20] This could occur either through HF addition to the carbonyl and reaction of the resulting α-fluoro alcohol with XtalFluor-E as claimed for DAST[21] or, alternatively, via reaction of the ketone with XtalFluor-E followed by addition of HF as proposed for SF_4.[22] In any case, from intermediate **9**, two related pathways would be possible for the formation of difluoromethylene **10** and monofluoroalkene **12**. For difluoromethylene **10**, an S_N2

Scheme 3. Mechanistic Hypothesis[a]



[a]The BF_4^- counterion has been omitted for clarity.

reaction on intermediate **9** with HF would produce **10** directly. Alternatively, ionization would lead to the fluorine-stabilized carbocation **11**,[23] which could then react with HF to produce **10**. For monofluoroalkene **12**, the first possibility would involve an E2 mechanism triggered by Et_3N conducting directly to **12**. Or else, ionization to carbocation **11** followed by elimination (E1 pathway) would also lead to monofluoroalkene **12**. While the current conditions do not allow us to discriminate between the two pathways, the observation that substrates bearing an electron-withdrawing substituent performed better suggest that the mechanism involving the carbocation is likely not the main pathway. Concerning the role of DMA (or DMF) for the control of the selectivity between monofluoroalkene (**12**) and difluoromethylene (**10**), our current hypothesis[24] points toward a possible role for the hydrogen bond acceptor ability of the solvent. Indeed, both DMA and DMF are strong hydrogen bond acceptors (pK_{BHX} = 2.44 and 2.10 respectively) whereas all the other solvents are a significantly weaker hydrogen bond acceptor (pK_{BHX} = −0.36 (toluene) to 1.28 (EtOAc)).[25] Hence, with HF being an excellent hydrogen bond donor, a significant interaction between HF with DMA would slow down the S_N2 attack of HF onto intermediate **9** (to produce **10**) and would thus favor the elimination pathway instead (leading to **12**).

In summary, we have described the eliminative deoxofluorination of cyclohexanone derivatives using XtalFluor-E. Notably, this one-step procedure for the synthesis of monofluoroalkenes occurs at room temperature using readily accessible and cost-effective reagents without the need for a glovebox. Overall, this new approach complements the previous reported methods. Mechanistic studies and extension of the reaction to other ketones, including acyclic ones, are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01581.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jean-francois.paquin@chm.ulaval.ca.

DOI: 10.1021/acs.orglett.7b01581
Org. Lett. XXXX, XXX, XXX−XXX

ORCID

Jean-François Paquin: 0000-0003-2412-3083

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada, the Fonds de recherche du Quebec−Nature et technologies, OmegaChem, and the Université Laval. Eliane Soligo (Université Laval) is thanked for preliminary experiments.

■ REFERENCES

(1) (a) Taguchi, T.; Yanai, H. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Blackwell Publishing Inc.: 2009; pp 257−290. (b) Choudhary, A.; Raines, R. T. *ChemBioChem* **2011**, *12*, 1801−1807.

(2) For selected recent applications, see: (a) Villiers, E.; Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Tetrahedron* **2015**, *71*, 7054−7062. (b) Nadon, J.-F.; Rochon, K.; Grastilleur, S.; Langlois, G.; Dao, T. T. H.; Blais, V.; Guérin, B.; Gendron, L.; Dory, Y. L. *ACS Chem. Neurosci.* **2017**, *8*, 40−49.

(3) Weintraub, P. M.; Holland, A. K.; Gates, C. A.; Moore, W. R.; Resvick, R. J.; Bey, P.; Peet, N. P. *Bioorg. Med. Chem.* **2003**, *11*, 427−431.

(4) For selected examples, see: (a) Cardone, A.; Martinelli, C.; Losurdo, M.; Dilonardo, E.; Bruno, G.; Scavia, G.; Destri, S.; Cosma, P.; Salamandra, L.; Reale, A.; Di Carlo, A.; Aguirre, A.; Milián-Medina, B.; Gierschnerf, J.; Farinola, G. M. *J. Mater. Chem. A* **2013**, *1*, 715−727. (b) Milad, R.; Shi, J.; Aguirre, A.; Cardone, A.; Milián-Medina, B.; Farinola, G. M.; Abderrabba, M.; Gierschner, J. *J. Mater. Chem. C* **2016**, *4*, 6900−6906.

(5) For selected recent examples, see: (a) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2016**, *531*, 459−465. (b) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. *Science* **2016**, *352*, 569−575. (c) Guérin, D.; Dez, I.; Gaumont, A.-C.; Pannecoucke, X.; Couve-Bonnaire, S. *Org. Lett.* **2016**, *18*, 3606−3609. (d) Rousée, K.; Schneider, C.; Bouillon, J.-P.; Levacher, V.; Hoarau, C.; Couve-Bonnaire, S.; Pannecoucke, X. *Org. Biomol. Chem.* **2016**, *14*, 353−357.

(6) For reviews on their synthesis, see: (a) van Steenis, J. H.; van der Gen, A. J. *Chem. Soc., Perkin Trans. 1* **2002**, 2117−2133. (b) Zajc, B.; Kumar, R. *Synthesis* **2010**, *2010*, 1822−1836. (c) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867−2908. (d) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, *2011*, 5939−5954. (e) Hara, S. *Top. Curr. Chem.* **2012**, *327*, 59−86. (f) Pfund, E.; Lequeux, T.; Gueyrard, D. *Synthesis* **2015**, *47*, 1534−1546. (g) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073−9174.

(7) Strobach, D. R.; Boswell, G. A., Jr. *J. Org. Chem.* **1971**, *36*, 818−820.

(8) Yang, M.-H.; Matikonda, S. S.; Altman, R. A. *Org. Lett.* **2013**, *15*, 3894−3897.

(9) Ye, Y.; Takada, T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 15559−15563.

(10) The price per mmol (in American dollars) for the following reagent was calculated using the largest amount available from a single provider (February 2017): $TrisNHNH_2$ ($18.96), NFSI ($4.87), $TESCF_3$ ($17.37), XtalFluor-E ($0.77), $Et_3N{\cdot}3HF$ ($0.21).

(11) (a) Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; Laflamme, F.; L'Heureux, A. *Org. Lett.* **2009**, *11*, 5050−5053. (b) L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75*, 3401−3411. (c) Mahe, O.; L'Heureux, A.; Couturier, M.; Bennett, C.; Clayton, S.; Tovell, D.; Beaulieu, F.; Paquin, J.-F. *J. Fluorine Chem.* **2013**, *153*, 57−60.

(12) For other contributions from our group using XtalFluor-E, see: (a) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 988−993. (b) Pouliot, M.-F.; Angers, L.; Hamel, J.-D.; Paquin, J.-F. *Tetrahedron Lett.* **2012**, *53*, 4121−4123. (c) Mahé, O.; Desroches, J.; Paquin, J.-F. *Eur. J. Org. Chem.* **2013**, *2013*, 4325−4331. (d) Pouliot, M.- F.; Mahé, O.; Hamel, J.-D.; Desroches, J.; Paquin, J.-F. *Org. Lett.* **2012**, *14*, 5428−5431. (e) Keita, M.; Vandamme, M.; Mahé, O.; Paquin, J.-F. *Tetrahedron Lett.* **2015**, *56*, 461−464. (f) Desroches, J.; Champagne, P. A.; Benhassine, Y.; Paquin, J.-F. *Org. Biomol. Chem.* **2015**, *13*, 2243−2246. (g) Keita, M.; Vandamme, M.; Paquin, J.-F. *Synthesis* **2015**, *47*, 3758−3766. (h) Vandamme, M.; Bouchard, L.; Gilbert, A.; Keita, M.; Paquin, J.-F. *Org. Lett.* **2016**, *18*, 6468−6471. (i) Lebleu, T.; Paquin, J.-F. *Tetrahedron Lett.* **2017**, *58*, 442−444.

(13) Monofluoroalkenes were observed when the deoxofluorination of cyclohexanone (72% GC yield) and 4-methoxyacetophenone (15% GC yield) were performed using 2,2-difluoro-1,3-dimethylimidazolidine (DFI); see Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T. *Chem. Commun.* **2002**, 1618−1619.

(14) A patent describing the eliminative deoxofluorination using DAST under strong acidic conditions was reported; see: Boswell, G. A., Jr. Preparation of vinylene fluorides. U.S. Patent 4,212,815, 1980.

(15) The deoxofluorination of *β*-diketones with *N*,*N*-diethyl-*α*,*α*-difluoro-*m*-methylbenzylamine provides *β*-fluoro-*α*,*β*-unsaturated ketones, see: (a) Sano, K.; Fukuhara, T.; Hara, S. *J. Fluorine Chem.* **2009**, *130*, 708−713. Reaction of cyclohexanone with the same reagent provides fluorocyclohexane in 58% yield along with 32% of difluorocyclohexane, see: (b) Hara, S.; Fukuhara, T. Method of fluorination. U.S. Patent 20060014972, 2006.

(16) For selected recent alternative approaches to monofluoroalkene-containing cyclohexane derivatives, see: (a) Furuya, T.; Ritter, T. *Org. Lett.* **2009**, *11*, 2860−2863. (b) Alonso, P.; Pardo, P.; Fañanás, F. J.; Rodríguez, F. *Chem. Commun.* **2014**, *50*, 14364−14366. (c) Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2014**, *136*, 14381−14384. (d) Nihei, T.; Kubo, Y.; Ishihara, T.; Konno, T. *J. Fluorine Chem.* **2014**, *167*, 110−121. (e) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 10330−10335. (f) Hamel, J.-D.; Cloutier, M.; Paquin, J.-F. *Org. Lett.* **2016**, *18*, 1852−1855.

(17) Additional optimization results can be found in the Supporting Information.

(18) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527−6530.

(19) Okoromoba, O. E.; Han, J.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2014**, *136*, 14381−14384.

(20) A related alkoxy-*N*,*N*-dialkylaminodifluorosulfane has been isolated and characterized; see: Sutherland, A.; Vederas, J. C. *Chem. Commun.* **1999**, 1739−1740.

(21) (a) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574−578. (b) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578.

(22) Pustovit, Y. M.; Nazaretian, V. P. *J. Fluorine Chem.* **1991**, *55*, 29−36.

(23) (a) Blint, R. J.; McMahon, T. B.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 1269−1278. (b) Williamson, A. D.; LeBreton, P. R.; Beauchamp, T. B. *J. Am. Chem. Soc.* **1976**, *98*, 2705−2709.

(24) We cannot exclude the potential role of DMA (or DMF) as a weak base; see ref 20a.

(25) Laurence, C.; Brameld, K. A.; Graton, J.; Le Questel, J.-Y.; Renault, E. *J. Med. Chem.* **2009**, *52*, 4073−4086.

DOI: 10.1021/acs.orglett.7b01581
Org. Lett. XXXX, XXX, XXX−XXX