

Catalytic Domino Reaction of Ketones/Aldehydes with $\text{Me}_3\text{SiCF}_2\text{Br}$ for the Synthesis of α -Fluoroenones/ α -Fluoroenals

Xiaoning Song, Jian Chang, Dongsheng Zhu,* Jiaheng Li, Cong Xu, Qun Liu,* and Mang Wang*

Department of Chemistry, Northeast Normal University, Renmin Street 5268, Changchun 130024, P. R. China

Supporting Information

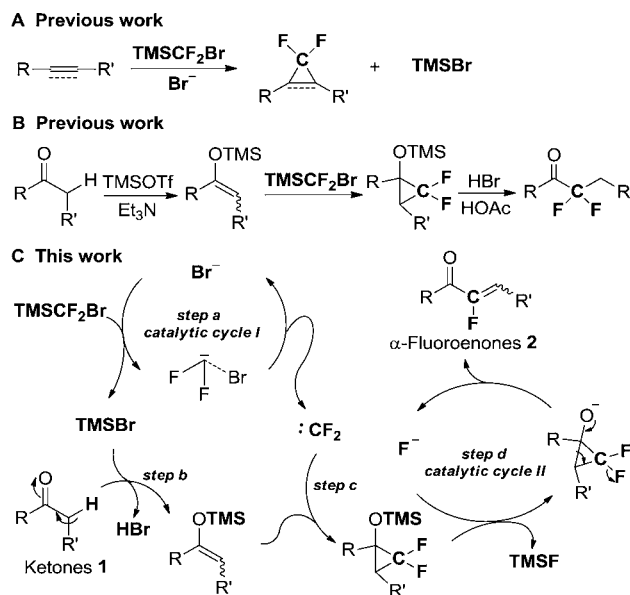
ABSTRACT: A unique domino reaction of enolizable carbonyl compounds with $\text{Me}_3\text{SiCF}_2\text{Br}$ to construct α -fluoroenones and α -fluoroenals is described to undergo the in situ formation of difluorocarbene and silyl enol ether, difluorocyclopropanation, desilylation, ring-opening, and defluorination sequence. In this tandem reaction, $\text{Me}_3\text{SiCF}_2\text{Br}$ acts as not only the difluorocarbene source but also the TMS transfer agent as well as internal bromide and fluoride anion catalyst. It allows the transformations to occur smoothly under only a catalytic amount of $n\text{-Bu}_4\text{NBr}$ as initiator.



Installation of fluorine-containing skeletons into organic molecules has become a powerful strategy in drug discovery and new material design. Efficient use of organofluorine reagents plays a key role for this purpose. The vinyl fluoride unit has been found to be an isostere of the peptide bond.^{2a} This structural feature gives monofluoroolefin derivatives highly important biological and pharmacological activities.^{2b,c} Among them, functionalized fluoroolefins have earned high interest^{3,4} due to their wide applications in the construction of various fluoroorganic compounds. Thus, developing a new and practical method for their synthesis is an important subject of this field.

Fluoroalkylsilanes are versatile fluoroalkylating reagents,^{5–10} among which easily available $\text{Me}_3\text{SiCF}_2\text{Br}$ (TMSCF_2Br) has been developed as an effective difluorocarbene reagent^{6a,7–9} since the pioneering work by Hu⁷ and Dilman.⁸ As described in Scheme 1A, the generation of difluorocarbene along with the release of TMSBr from bromide anion-activated TMSCF_2Br has been proven to be a decisive step in the difluorocyclopropanations of alkenes/alkynes.^{7b} Very recently, Dilman and co-workers reported a difluorocyclopropanation of silyl enol ethers with TMSCF_2Br which was an important step in the difluorohomologation of ketones (Scheme 1B).^{9a} In fact, although many difluorocyclopropanations of alkenes are known,^{11–13} the investigation of synthetic applications of *gem*-difluorocyclopropanes remains a challenge. To the best of our knowledge, there are only a few examples of difluorocyclopropanations of silyl enol ethers.^{9a,14} A little earlier, Amii et al. developed a difluorocyclopropanation of silyl enol ethers by using $\text{BrCF}_2\text{CO}_2\text{Na}$ as difluorocarbene source in a two-step synthesis of cyclic α -fluoroenones.^{14c} In their work, difluorohomologation products were obtained under basic conditions.^{14c}

During our latest study on the reaction of ketones with TMSCF_2Br as a part of our continuing interest in synthetic applications of fluoroalkylsilanes,^{5a,10} we hypothesized a catalytic domino transformation in which the side product, oxophilic TMSBr that formed along with difluorocarbene from TMSCF_2Br , might participate in the in situ generation of silyl enol ethers from ketones (Scheme 1C, step b). Thus, a

Scheme 1. Working Assumption on Catalytic Domino Reaction of Ketones with TMSCF_2Br 

difluorocyclopropanation (Scheme 1C, step c) might be possible and evolve by further desilylation and a ring-opening sequence (Scheme 1C, step d). To our delight, it was indeed the case. The cascade reaction occurred smoothly leading to α -keto monofluoroalkenes only catalyzed by $n\text{-Bu}_4\text{NBr}$ (TBAB) for initially activating TMSCF_2Br (Scheme 1C, catalytic cycle I) and in many instances assisted by an external fluoride anion for accelerating the desilylation of the resulting cyclic trimethylsilyl ether intermediate (Scheme 1C, catalytic cycle II).

Herein, we report this unique catalytic, domino reaction for the synthesis of α -fluoroenones.^{14c,15} The method can be extended to the synthesis of α -fluoroenals.¹⁶ Sufficient use of


Received: February 15, 2015

Published: March 23, 2015

TMSCF₂Br, broad scope of readily available starting materials, tolerance for various functionality, and efficient transformations made possible the development of a general and practical one-pot approach for the assembly of fluorine-containing fragment into the α -C–C bond in carbonyl compounds.

We initially chose 4-acetobiphenyl **1a** as a model substrate, and its reaction with TMSCF₂Br was investigated (Table 1).

Table 1. Screening the Reaction Conditions^a



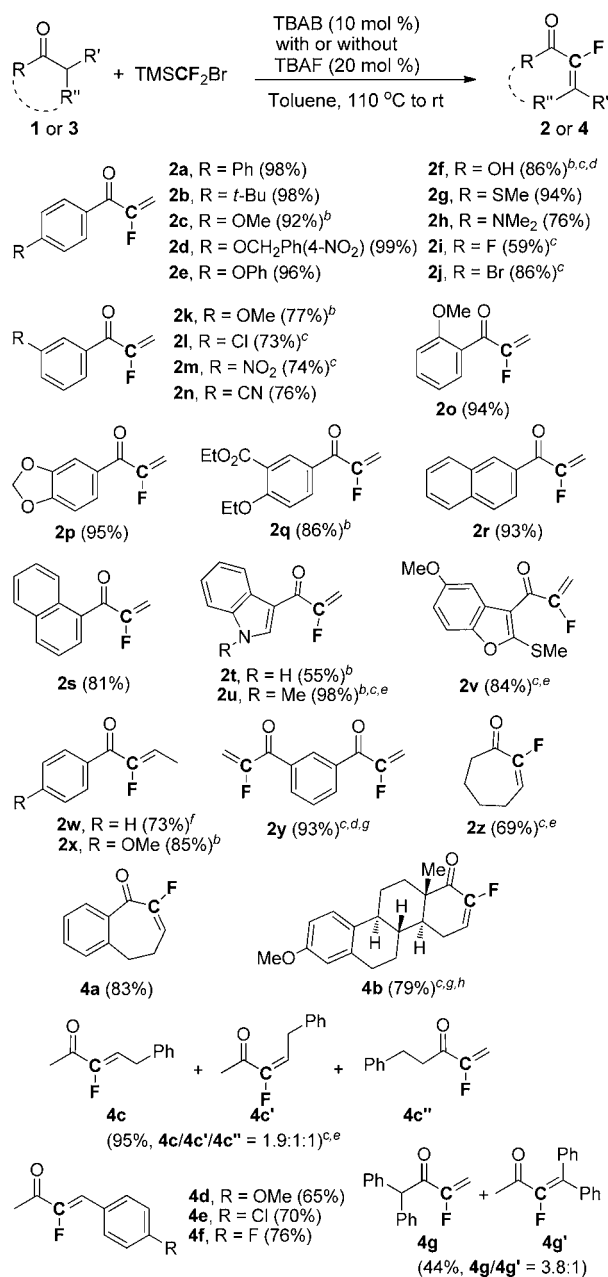
entry	TMSCF ₂ Br (equiv)	TBAB/TBAF (mol %)	temp (°C)	time (h)	yield ^b (%)
1	1.5	5/–	110	5	42
2	1.5	5/5	110/110	5/3	50
3	2	5/10	110/110	6/3	63
4	2.5	10/15	110/110	4/2	79
5 ^c	2.5	10/15	110/110	7/4	90
6 ^c	2.5	10/20	110/110	6/3	96
7 ^c	2.5	10/20	110/60	6/3	97
8 ^c	2.5	10/20	110/rt	6/3	98
9 ^c	2.5	10/20	90/rt	6/3	89
10 ^c	2.5	–/20	110	9	80
11 ^{c,d}	2.5	10/20	110/rt	6/3	trace
12 ^{c,e}	2.5	10/20	110/rt	6/3	41

^aConditions: **1a** (0.5 mmol), toluene (2.5 mL), in sealed tube. ^bIsolated yield. ^cTMSCF₂Br was added in two portions: 1.5 equiv of TMSCF₂Br for 2 h followed by 1 equiv of TMSCF₂Br for additional time. ^dIn DCE. ^eIn dioxane.

Generally, the reaction needed to be performed at around 110 °C in toluene, and excess TMSCF₂Br was added in two portions for better transformation. The addition of the catalysts was followed by the order of TBAB for the activation of TMSCF₂Br and *n*-Bu₄NF (TBAF) for the desilylation of cyclic intermediate. As described in Table 1, entry 1, the reaction of **1a** with TMSCF₂Br afforded **2a** in 42% yield when 5 mol % of TBAB was used. The use of 2 equiv of TMSCF₂Br along with 5 mol % of TBAB for 6 h and then with 10 mol % of TBAF for an additional 3 h afforded **2a** in 63% yield (Table 1, entry 3). Increasing the amount of TMSCF₂Br and catalysts provided a notable improvement (Table 1, entries 4–6). In the case of 10 mol % of TBAB and then 20 mol % of TBAF, **2a** was isolated in excellent yield (Table 1, entry 6). It was found that the desilylation and ring-opening process performed at room temperature also afforded satisfactory results (Table 1, entry 8). At this time, after **1a** (0.5 mmol) reacted with TMSCF₂Br (0.75 mmol) in 2 mL of toluene in the presence of TBAB (0.05 mmol) at 110 °C for 2 h, the additional TMSCF₂Br (0.5 mmol), which was predissolved in 0.5 mL of toluene, was added to the reaction mixture for another 4 h. Then, the reaction was allowed to cool to room temperature and a solution of TBAF in THF (0.1 mmol) was added to react 3 h. After a conventional workup, **2a** was isolated in 98% yield (for details, see the Supporting Information). By comparison, the difluorocyclopropanation at lower temperature was proven to be less efficient (Table 1, entry 9). Finally, a domino reaction catalyzed by TBAF (Table 1, entry 10) or performed in DCE or dioxane (Table 1, entries 11 and 12) was investigated but gave inferior results.

Clearly, synthesis of α -fluoroenones from ketones and TMSCF₂Br presents a promising synthetic strategy due to the readily available starting materials and simple organofluorine reagent. Thus, the scope of the reaction was thoroughly investigated under the optimized reaction conditions (Table 1, entry 8). As described in Scheme 2, the R substituents at the phenyl ring of aromatic ketones **1**, bearing either an electron-donating or electron-withdrawing group at the different

Scheme 2. Scope of Enolizable Ketones for Catalytic Domino Transformations^a



^aConditions: **1** (0.5 mmol), TMSCF₂Br (2.5 equiv), TBAB (10 mol %), TBAF (20 mol %), toluene (2.5 mL), in sealed tube, 110 °C then rt. TMSCF₂Br was added in two portions: 1.5 equiv of TMSCF₂Br for 2 h followed by additional 1 equiv of TMSCF₂Br for 4 h. Isolated yield. ^bWithout TBAF. ^cAt 100 °C. ^d4 equiv of TMSCF₂Br was used. ^e5 mol % of TBAB was used. ^f¹H NMR yield. ^g30 mol % of TBAF was used. ^h5 equiv of TMSCF₂Br was used.

positions, were compatible with the reaction to produce **2a–s** in good to high yields. It was noteworthy that this cascade reaction was successful in the presence of various functional groups including halogens (F, Cl, and Br), nitro, cyano, amino, alkoxy, alkylthio, and ester groups. Ketone **1f** bearing a phenolic hydroxyl functionality also underwent the domino process to give **2f** with comparable results, indicating that the method was tolerant to acidic hydrogen, whereas the reaction seemed to be sensitive to those ketones containing unprotected amino or pyridyl groups and led to a complex mixture though 3-acetylindole **1t**, giving acceptable results. In comparison, *N*-methyl-3-acetylindole **1u** afforded α -fluoroenone **2u** in 98% yields.

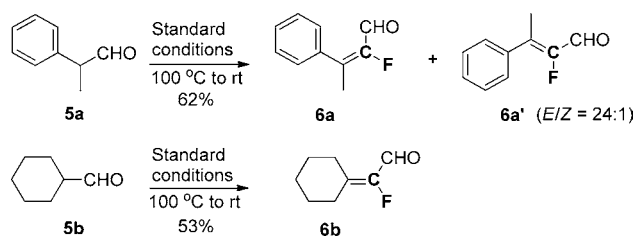
In addition, **2v** was isolated in 84% yield from 3-acetylbenzothiophene **1v**. Propiophenone derivatives gave **2w** and **2x** with a *cis* relationship of the methyl and fluorine as the major product. With double-acetyl benzene **1y** as the substrate, bisfluoroolefin **2y** was also obtained in excellent yield. For cyclic ketones, reactions afforded ring-expansion products **2z** and **4a** efficiently. Considering the significance of the modulation of drug intermediates by introducing a fluorine-containing skeleton, estrone **3b** was subjected to the identical reaction conditions. Delightfully, the desired α -fluoroenone **4b** was obtained in 79% yield. During the investigations, we also found that no TBAF was required for efficient transformations in the case of **1c**, **1f**, **1k**, **1q**, **1t**, **1u**, and **1x** as the substrates.¹⁷

The regioselectivity of the reactions for the ketones with two different sites for enolization was then investigated. As described in Scheme 2, 4-phenyl-2-butanone **3c** under the standard reaction conditions furnished a mixture of three isomers **4c**, **4c'**, and **4c''** in 95% overall yields. By comparison, 1-phenyl-2-propanones **3d–f** provided thermodynamic products (*Z*)-4-aryl-3-fluoro-3-buten-2-ones **4d–f** as the sole products. When 1,1-diphenyl-2-propanone **3g** was selected as the substrate, the main product was identified as 3-fluoro-1,1-diphenyl-3-buten-2-one **4g** resulting from the kinetic silyl enol ether. Steric hindrance of two phenyl rings may make difluorocyclopropanation difficult and leads to the kinetic product in selectivity.

Driven by the important properties and applications of α -fluorinated α,β -unsaturated carbonyl compounds in organic synthesis^{3,4} and the simplicity of the present method, our next effort targeted a series of investigations on broadening this method to aldehydes. Thus, 2-phenylpropanal **5a** and cyclohexanecarbaldehyde **5b** were subjected to the optimized conditions. The successful formation of α -fluoroal products **6** in reasonable yields indicated that the method could tolerate aldehydes (Scheme 3).¹⁶

In conclusion, an efficient assembly of a fluorine-containing unit into the α -C–C bond in enolizable carbonyl compounds has been described. The use of TMSCF₂Br as difluorocarbene source directly toward carbonyl compounds makes possible the in situ

Scheme 3. Catalytic Domino Reactions of Aldehydes with TMSCF₂Br



generation of two distinct reactive intermediates, difluorocarbene and silyl enol ether, which are combined into the final α -carbonyl fluoroolefins. The side product, TMSBr, along with Br⁻ and F⁻ released from TMSCF₂Br contributes to the catalytic domino procedures. The research provides a new and powerful example for highly efficient application of simple fluoroalkylsilanes in the construction of fluoroorganic compounds. Further work focused on the extension of this new synthetic strategy is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for all compounds **2**, **4**, and **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhuds206@nenu.edu.cn.

*E-mail: liuqun@nenu.edu.cn.

*E-mail: wangm452@nenu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge National Natural Sciences Foundation of China (21172031, 21272034 and 21372040), and National Natural Science Foundation of Jilin (20140101113JC) for financial support.

■ REFERENCES

- (1) (a) Kirsch, P. In *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, 2nd ed.; Wiley-VCH: Weinheim, 2013. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: Chichester, 2009.
- (2) (a) Abraham, R. J.; Ellison, S. L. R.; Schonholzer, P.; Thomas, W. A. *Tetrahedron* **1986**, *42*, 2101. (b) Uneyama, K. In *Organofluorine Chemistry*; Blackwell; Oxford, 2006. (c) Bégue, J.-P.; Bonnet-Delpon, D. In *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, 2008.
- (3) (a) Ojima, I.; McCarthy, J. R.; Welch, J. T. In *Biomedical Frontiers of Fluorine Chemistry*; ACS Symposium Series 639; ACS: Washington, DC, 1996. (b) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical Society: Washington, DC, 2005. (c) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151. Selected applications: (d) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290. (e) McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. *J. Am. Chem. Soc.* **1991**, *113*, 7439.
- (4) Landelle, G.; Bergeron, M.; Turcotte-Savard, M. O.; Paquin, J. F. *Chem. Soc. Rev.* **2011**, *40*, 2867.
- (5) Selected reviews on fluoroalkylsilanes: (a) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (b) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.
- (6) Recent reviews on difluorocarbene sources: (a) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842. (b) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465.
- (7) (a) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411. (b) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390.
- (8) Kosobokov, M. D.; Dilman, A. D.; Levin, V. V.; Struchkova, M. I. *J. Org. Chem.* **2012**, *77*, 5850.
- (9) (a) Kosobokov, M. D.; Levin, V. V.; Strichkova, M. I.; Dilman, A. D. *Org. Lett.* **2015**, *17*, 760. (b) Kosobokov, M. D.; Levin, V. V.;

Zemtsov, A. A.; Struchkova, M. I.; Korlyukov, A. A.; Arkhipov, D. E.; Dilman, A. D. *Org. Lett.* **2014**, *16*, 1438. (c) Zemtsov, A. A.; Kondratyev, N. S.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 818. (d) Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2014**, *16*, 3784. (e) Tsybmal, A. V.; Kosobokov, M. D.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 7831. (f) Smirnov, V. O.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Dilman, A. D. *J. Org. Chem.* **2014**, *79*, 11819. (g) Levin, V. V.; Zemtsov, A. A.; Struchkova, M. I.; Dilman, A. D. *Org. Lett.* **2013**, *15*, 917.

(10) (a) Xu, C.; Liu, J.; Ming, W.; Liu, Y.; Liu, J.; Wang, M.; Liu, Q. *Chem.—Eur. J.* **2013**, *19*, 9104. (b) Liu, X.; Xu, X.; Pan, L.; Zhang, Q.; Liu, Q. *Org. Biomol. Chem.* **2013**, *11*, 6703. (c) Liu, X.; Pan, L.; Dong, J.; Xu, X.; Zhang, Q.; Liu, Q. *Org. Lett.* **2013**, *15*, 6242. (d) Dong, J.; Pan, L.; Xu, X.; Liu, Q. *Chem. Commun.* **2014**, *50*, 14797.

(11) Selected reviews: (a) Dolbier, W. R., Jr.; Battiste, M. *Chem. Rev.* **2003**, *103*, 1071. (b) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099.

(12) For recent applications of *gem*-difluorocyclopropanes: (a) Nihei, T.; Hoshino, T.; Konno, T. *Org. Lett.* **2014**, *16*, 4170. (b) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. *Org. Lett.* **2014**, *16*, 2638. (c) Dolbier, W. R., Jr.; Cornett, E.; Martinez, H.; Xu, W. *J. Org. Chem.* **2011**, *76*, 3450. (d) Hang, X.-C.; Chen, Q.-Y.; Xiao, J.-C. *J. Org. Chem.* **2008**, *73*, 8598.

(13) For selected difluorocyclopropanations of enols, see: (a) Crabbé, P.; Cervantes, A.; Cruz, A.; Galeazzi, E.; Iriarte, J.; Velarde, E. *J. Am. Chem. Soc.* **1973**, *95*, 6655. (b) Bessard, Y.; Muller, U.; Schlosser, M. *Tetrahedron* **1990**, *46*, 5213. (c) Gassen, K.-R.; Bielefeldt, D.; Marhold, A.; Andres, P. *J. Fluorine Chem.* **1991**, *55*, 149. (d) Cai, X.; Zhai, Y.; Ghiviriga, I.; Abboud, K. A.; Dolbier, W. R., Jr. *J. Org. Chem.* **2004**, *69*, 4210. (e) Cai, X.; Wu, K.; Dolbier, W. R., Jr. *J. Fluorine Chem.* **2005**, *126*, 477.

(14) Reports involving difluorocyclopropanations of silyl enol ethers: (a) Oshiro, K.; Morimoto, Y.; Amii, H. *Synthesis* **2010**, 2080. (b) Amii, H.; Oshiro, K.; Morimoto, Y.; Matsuura, M. *PCT Int. Appl. WO 2011083612 A1 20110714*, 2011. (c) Kageshima, Y.; Suzuki, C.; Oshiro, K.; Amii, H. *Synlett* **2015**, *26*, 63.

(15) For selected reports on the synthesis of α -fluoroenones: (a) He, Y.; Zhang, X.; Shen, N.; Fan, X. *J. Fluorine Chem.* **2013**, *156*, 9. (b) de Haro, T.; Nevado, C. *Chem. Commun.* **2011**, *47*, 248. (c) Hopkinson, M. N.; Giuffredi, G. T.; Gee, A. D.; Gouverneur, V. *Synlett* **2010**, 2737. (d) Prakash, G. K. S.; Chacko, S.; Vaghoo, H.; Shao, N.; Gurung, L.; Mathew, T.; Olah, G. A. *Org. Lett.* **2009**, *11*, 1127. (e) Ghosh, A. K.; Banerjee, S.; Sinha, S.; Kang, S. B.; Zajc, B. *J. Org. Chem.* **2009**, *74*, 3689. (f) Dutheuil, G.; Paturel, C.; Lei, X.; Couve-Bonnaire, S.; Pannecoucke, X. *J. Org. Chem.* **2006**, *71*, 4316. (g) Hata, H.; Kobayashi, T.; Amii, H.; Uneyama, K.; Welch, J. T. *Tetrahedron Lett.* **2002**, *43*, 6099.

(16) For a few examples of the synthesis of α -fluoroenals: (a) Camps, F.; Coll, J.; Fabrias, G.; Cuerrero, A.; Riba, M. *Tetrahedron Lett.* **1983**, *24*, 3387. (b) Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 2453. (c) Hatanaka, F.; Tsuchiya, M.; Yoshimatsu, M. *Synlett* **2005**, 2191. (d) Zemmouri, R.; Kajjout, M.; Castanet, Y.; Eddarir, S.; Rolando, C. *J. Org. Chem.* **2011**, *76*, 7691.

(17) In these cases, HBr, which was produced from the reaction system, may initiate the desilylation of cyclopropoxytrimethylsilane intermediate^{9a} at the beginning. Once the desilylation took place, fluoride anion would be released for further catalytic cycle II (Scheme 1C).