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Letter

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Me_3SiCF_2Br-Self-Assisted Domino Reaction: Catalytic Synthesis of α,α-Difluorocyclopentanones from Methylvinylketones

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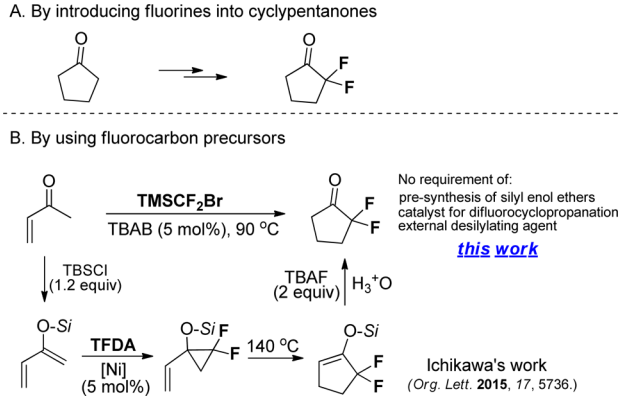
Supporting Information

ABSTRACT: A complete self-assistance strategy based on Me_3SiCF_2Br was used in the domino conversion of methylvinylketones into α,α-difluorinated cyclopentanones. Initiated by 5 mol % of nBu$_4$NBr, the multistep reaction occurred in one pot under mild conditions via the *in situ* formation of silyl dienol ethers, difluorocyclopropanation, thermal vinylcyclopropane−cyclopentene rearrangement, and desilylation. The process takes advantage of the multitasking capability of Me_3SiCF_2Br as the difluorocarbene source, a silicon-based transfer agent, and a bromine anion releaser.

Domino reactions allow for rapid construction of complex molecules from simple substrates in an economically favorable way.[1] In this regard, the cascade sequences achieved by means of a catalytic self-assistance strategy of the reactant undoubtedly provide a more ecologically and remarkably desirable approach to organic synthesis. Here, we reported a catalytic domino transformation of methylvinylketones to α,α-difluorinated cyclopentanones by the use of Me_3SiCF_2Br ($TMSCF_2Br$). The process takes advantage of the multitasking capability of $TMSCF_2Br$ as the $:CF_2$ source, a TMS transfer agent, and the Br^- releaser. The method avoids the presynthesis of silyl dienol ethers and also does not require either the catalyst for difluorocyclopropanation or an external desilylating reagent.

α,α-Difluorinated ketone is a privileged subset of medicinal and bioactive molecules.[2−4] Among them, cyclic α,α-difluorinated ketones are notable examples.[4a−c] As a consequence, reliable methods for their synthesis are valuable for developing new drug candidates and biological probes. However, current work is limited to the construction of difluorinated ketone scaffolds.[3a,5,6] A facile and efficient approach for the synthesis of cyclic analogs has not been established. It was reported that α,α-difluorocyclopentanones could be prepared via the fluorinations of the corresponding cyclopentanones (Scheme 1A), including either by a direct nucleophilic α-fluorination[5b,7] or by a deoxygenative fluorination−oxidation sequence.[8] This kind of strategy requires the preconstruction of a cyclopentanone skeleton and usually suffers from hazardous fluorinating reagents. Moreover, the regioselectivity of the fluorination, in the case of those cyclopentanones bearing multiple reaction sites as the substrates, still remains a challenging issue. On the other hand, the synthesis of α,α-difluoroketones from readily available fluorocarbon precursors represents a complementary route.[3a,6] However, this strategy is seldom applied for the synthesis of difluorinated cyclic ketones though it is versatile and more convergent in essence, and is also suited for regioselective synthesis of libraries of fluorinated chemicals.

Scheme 1. Strategies for the Synthesis of α,α-Difluorocyclopentanones



In 2015, Ichikawa and co-workers reported a preparation of α,α-difluorocyclopentanones starting from methylvinylketones by use of trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl) acetate (TFDA, Scheme 1B, Ichikawa's work).[9] The conversion was achieved via four separate steps including presynthesis of silyl dienol ethers, Ni-catalyzed difluorocyclopropanation, thermal vinylcyclopropane−cyclopentene (VCP) rearrangement,[10,11] and desilylation. During our research on the synthetic applications of fluoroalkylsilanes,[12,13] we have described a nBuN$_4$Br (TBAB)-catalyzed difluorocyclopropanation of enolizable ketones[13] by using $TMSCF_2Br$ as a difluorocarbene source. We then successfully carried out a ring-opening and defluorination reaction to prepare α-fluoroenones[13a] and o-fluoronaphthols[13b] by treating the resulting siloxyldifluoro-

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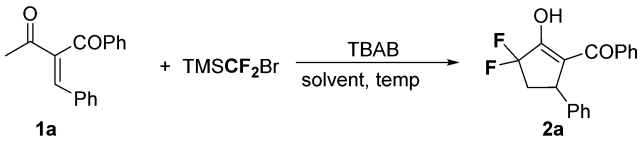
cyclopropanes with nBuN$_4$F (TBAF). Lately, we developed a well-controlled ring-opening and intramolecular S_NV type reaction of siloxyldifluorocyclopropanes in the presence of stoichiometric Cu or Ag salt via a metal difluorohomoenolate species for the synthesis of α,α-difluorocyclopentenones.[13c] We anticipated that further advances in the unique chemistry of TMSCF$_2$Br would enable a catalytic domino transformation[1] for the incorporation of a difluoromethylene fragment into the α-position of the carbonyl by utilizing a complete self-assistance strategy. Considering the ready availability of methylvinylketones and the possibility of the VCP rearrangement of siloxylvinyldifluorocyclopropane,[9] we explore the reaction of methylvinylketones with TMSCF$_2$Br (Scheme 1B, this work). In this letter, we report that this catalytic process could indeed be achieved, allowing the development of a direct and efficient route to a wide range of functionalized α,α-difluorocyclopentanone derivatives.

Initially, the reaction of (*Z*)-3-benzoyl-4-phenyl-3-buten-2-one **1a** with TMSCF$_2$Br was selected as a model system to identify the reaction conditions. Delightfully, upon treatment of **1a** with 2.5 equiv of TMSCF$_2$Br in the presence of 2.5 mol % TBAB in toluene at 100 °C, the desired 5-benzoyl-2,2-difluoro-4-phenylcyclopentanone could be obtained in its enolic form (Table 1) according to its NMR, MS spectra, and further by its

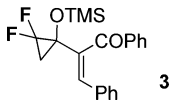
Table 1. Screening of the Reaction Conditions[a]



1a **2a**

entry	TBAB (mol %)	solvent	temp (°C)	yield[b] (%)
1	2.5	toluene	100	73
2	5	toluene	100	84
3	10	toluene	100	85
4	5	1,4-dioxane	100	76
5	5	MeCN	100	86
6	5	DCE	100	trace
7	5	toluene	90	86 (86)
8	5	toluene	80	75[c]
9	5	MeCN	90	53[d]
10	5	toluene	110	86

[a]General reaction conditions: **1a** (0.2 mmol), TMSCF$_2$Br (2.5 equiv), solvent (1.0 mL), in a sealed tube, 7 h. [b]^{1}H NMR yield by using 1,3,5-trimethoxybenzene as internal standard. Isolated yield was in parentheses. [c]13% yield of **3** was obtained. [d]24% of **1a** was recovered along with 7% yield of **3**.

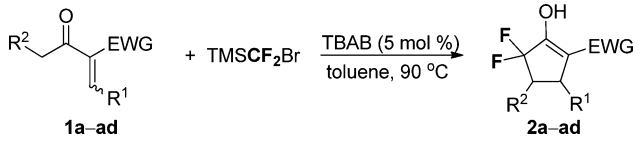


3

X-ray data.[14] By increasing the amount of the TBAB catalyst, the yield of the cyclic enol product **2a** could reach 85% (entries 2 and 3). A screen of other solvents revealed that both 1,4-dioxane and MeCN could give **2a** in good yield (entries 4 and 5), but DCE was inert for the reaction (entry 6). A lower temperature led to somewhat less efficiency of the conversion from siloxyldifluorovinylcyclopropane intermediate **3** to the final product **2a** (entries 7–9), while a higher temperature did not provide a better experimental result (entry 10).

With the optimized reaction conditions (Table 1, entry 7), we then evaluated the reactivities of various structurally diverse methylvinylketones **1** by using TMSCF$_2$Br as a fluorocarbon precursor. As presented in Table 2, most tested conversions

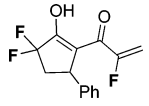
Table 2. Catalytic Synthesis of 2 from 1 and TMSCF$_2$Br[a]



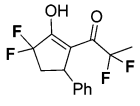
1a–ad **2a–ad**

entry	R^1	EWG	R^2	yield[b] (%)
1	Ph	PhCO	H	**2a**, 86 (86)
2	4-MeC$_6$H$_4$	PhCO	H	**2b**, 80 (89)
3	4-MeOC$_6$H$_4$	PhCO	H	**2c**, 76 (92)
4	3-MeOC$_6$H$_4$	PhCO	H	**2d**, 80 (82)
5	2-MeOC$_6$H$_4$	PhCO	H	**2e**, 71 (90)
6	4-BnOC$_6$H$_4$	PhCO	H	**2f**, 70 (95)
7	2-naphthyl	PhCO	H	**2g**, 90 (94)
8	4-FC$_6$H$_4$	PhCO	H	**2h**, 80 (94)
9	2-FC$_6$H$_4$	PhCO	H	**2i**, 79 (85)
10	4-ClC$_6$H$_4$	PhCO	H	**2j**, 89 (91)
11	4-BrC$_6$H$_4$	PhCO	H	**2k**, 85 (93)
12	4-CNC$_6$H$_4$	PhCO	H	**2l**, 69 (82)
13	3-CNC$_6$H$_4$	PhCO	H	**2m**, 76 (84)
14	4-NO$_2$C$_6$H$_4$	PhCO	H	**2n**, 60 (65)
15	4-MeO$_2$CC$_6$H$_4$	PhCO	H	**2o**, 70 (73)
16	4-CF$_3$C$_6$H$_4$	PhCO	H	**2p**, 61 (85)
17	*N*-Me-3-indolyl	PhCO	H	**2q**, 71 (88)
18	2-furyl	PhCO	H	**2r**, 76 (87)
19	2-thienyl	PhCO	H	**2s**, 73 (89)
20	cyclopropyl	PhCO	H	**2t**, 64 (73)[c]
21[d]	4-MeOC$_6$H$_4$	CO$_2$Me	H	**2u**, 84 (89)
22[d]	4-MeOC$_6$H$_4$	CO$_2$Et	H	**2v**, 80 (90)
23[d]	4-MeOC$_6$H$_4$	CO$_2$Bn	H	**2w**, 85 (92)
24[d]	2-naphthyl	CO$_2$Me	H	**2x**, 59 (93)
25[d]	3-ClC$_6$H$_4$	CO$_2$Me	H	**2y**, 65 (80)
26[d]	4-CNC$_6$H$_4$	CO$_2$Me	H	**2z**, 55 (77)
27[d]	4-MeOC$_6$H$_4$	CO$_2$Me	Me	**2aa**, 67 (83)
28[d]	4-MeOC$_6$H$_4$	CO$_2$Me	Et	**2ab**, 43 (60)
29	Ph	COMe	H	**2ac**, (40)[e]
				2ac′, **2ac″** (75)[f]
30	Ph	CN	H	complex

[a]General reaction conditions: **1** (0.2 mmol), TMSCF$_2$Br (2.5 equiv), toluene (1.0 mL), in a sealed tube, 7 h. [b]Isolated yields. ^{1}H NMR yields were in parentheses by using 1,3,5-trimethoxybenzene as an internal standard. [c]A mixture of two keto–enol isomers was obtained. [d]The reaction was performed in MeCN (1.0 mL), at 100 °C for 8 h. [e]Trace amount of **2ac′** was detected. 50% of **1ac** remained. [f]TMSCF$_2$Br (5 equiv). **2ac′** and **2ac″** were obtained in 1:5 mixture.



2ac'



2ac''

from **1** to **2** are highly efficient, while the isolated yields of **2** are somewhat low in some cases (such as Table 2, entries 3, 5, 6, 12, and 13) due to the inefficient chromatographic purification process. In general, there is to be a lack of significant electron effects of the R^1 substituent in **1** on the reaction efficiency. α-Benzoyl methylvinylketones **1b–g** bearing electron-donating aromatic R^1 afforded the desire **2b–g** in 82–95% NMR yields (entries 2–7). And substrates **1h–p** with electron-deficient aromatic R^1 also gave **2h–p** in 73–94% NMR yields (entries 8–16). By comparison, those substrates with a stronger

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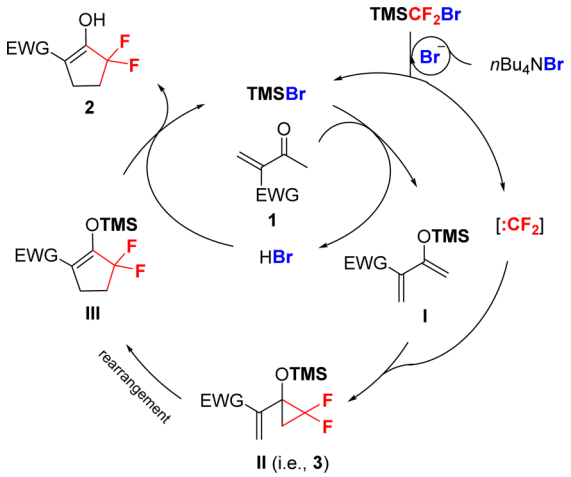
electron-deficient substituent (such as NO_2 or CO_2Me) on the phenyl ring gave **2** in relatively lower yields (entries 14 and 15). Heteroaromatic ring-substituted methylvinylketones **1q−s** could be used for the present domino reactions (entries 17−19). In the case of **1t** having an aliphatic cyclopropyl group, the reaction worked well furnishing a mixture of **2t** and its keto isomer **2t′** in good yield (entry 20). In addition, when α-alkoxycarbonyl methylvinylketones **1u−ab** were prepared for the reaction, corresponding α,α-difluorocyclopentanones **2u−ab** were also obtained (entries 21−28). R^2-Substituted vinylketones **1aa** and **1ab** gave **2aa** and **2ab** in lower yields under the identical reaction conditions (entries 27 and 28). When α-acetylated methylvinylketone **1ac** was selected as the substrate, **2ac** along with **2ac′**[15] was obtained (entry 29). By increasing the amount of $TMSCF_2Br$, the reaction gave **2ac′** and **2ac″**[16] as the products (entry 29). Moreover, α-cyano methylvinylketone **1ad** could not provide the desired product (entry 30) despite further efforts in optimizing the reaction conditions.

On the basis of our previous work[13] and the VCP rearrangement reactions,[9−11] it was reasonable to propose a catalytic domino mechanism for the above transformation. As described in Scheme 2, Br^--activated $TMSCF_2Br$ first produced

Scheme 2. Proposed Mechanism

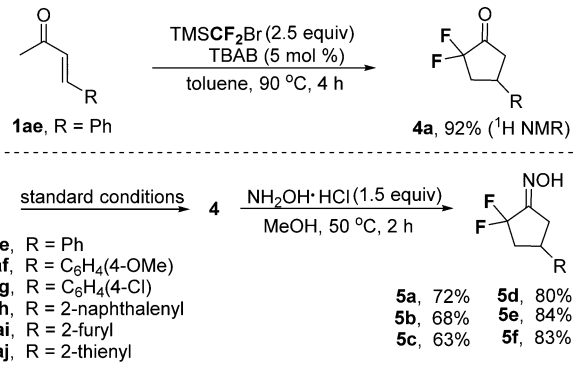


CF_2 and TMSBr. Silyl dienol ether **I** was then formed *in situ* by the reaction of methylvinylketone **1** and TMSBr along with releasing HBr to the reaction mixture. Next, difluorocyclopropanation of **I** with CF_2 gave vinyldifluorocyclopropane **II** followed by a thermal ring opening and recyclization (VCP rearrangement) leading to cyclic difluorinated silyl enol ether **III**. Finally, α,α-difluorocyclopentanone **2** was obtained by the desilylation with the assistance of HBr resulted from the former step.

Compared with the method developed by Ichikawa' group,[9] the present work described a remarkably simple and catalytic domino transformation of methylvinylketones to α,α-difluorinated cyclopentanones. Notably, our method does not need any catalysts for either difluorocyclopropanation or desilylation. Once $TMSCF_2Br$ is initially activated by a catalytic amount of TBAB, the cascade reaction will occur in a self-assisted manner. Besides generating difluorocarbene, the internal "TMS" and "Br" can be released from $TMSCF_2Br$ during the reaction for all the following steps.

Encouraged by the above experimental results, we further investigated the domino conversion of methylvinylketones **1ae−aj** without an α-substituent and made a comparison with Ichikawa' work (Scheme 3).[9] By using $TMSCF_2Br$ as the

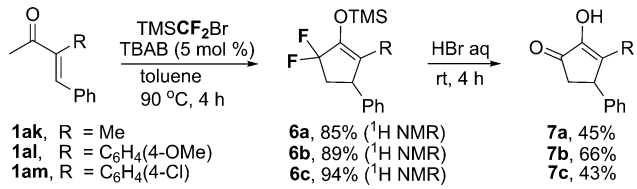
Scheme 3. Synthesis of 4/5 from 1 and $TMSCF_2Br$



difluorocarbene agent and TBAB as the initiator, **1ae** could smoothly undergo a tandem enolization−silylation, difluorocyclopropanation, VCP rearrangement, and desilylation sequence to furnish α,α-difluorocyclopentanone **4a** in 92% NMR yield. It was true that **4a** was sensitive toward chromatographic purification as observed in Ichikawa's experiments and, thus, had to be derivatized to oxime **5a** by further reacting with a 1.5 equiv amount of hydroxylamine hydrochloride for isolation. Similarly, **1af−aj** also gave the corresponding oximes **5b−f** in good yields by the reaction with $TMSCF_2Br$ and then with hydroxylamine hydrochloride in one pot. Clearly, a direct and easy transformation from readily available methylvinylketones to α,α-difluorocyclopentanones[9] was realized in the present work by the use of 5 mol % of TBAB without any additional silylation agent, metal catalyst for difluorocyclopropanation, and desilylation agent.

Additionally, when methylvinylketones **1ak−am** with an α-alkyl or α-aryl substituent were prepared and treated with $TMSCF_2Br$ under standard reaction conditions, the reactions stopped at the cyclic difluorinated silyl enol ethers **6a−c**, a type of intermediate **III** as described in Scheme 2, by analyzing the ^1H NMR spectra of the reaction mixture (Scheme 4). No

Scheme 4. Synthesis of 6/7 from 1 and $TMSCF_2Br$



desired α,α-difluorocyclopentanones were detected. However, decompositions of **6** during chromatography purification resulted in less than 10% isolated yields of **6**. Interestingly, a small amount of byproducts were isolated and identified to be the oxygenated cyclopentenones **7**, which were likely formed via the desilylation of **6**, defluorination, and hydrolysis sequence.[17] Considering that TBAB or HBr that existed in the reaction mixture was the potential initiator for the desilylation of **6**, either TBAB (1.5 equiv) or HBr (47% aqueous) was added to the reaction mixture after **1ak−am** were consumed. As we expected, **7a−c** were isolated in moderate to

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good yields, respectively, by using aqueous HBr and stirring at room temperature for 4 h (Scheme 4).

In conclusion, we have successfully developed a simple and efficient domino transformation of methylvinylketones to α,α-difluorocyclopentanone derivatives using unique $TMSCF_2Br$ as a difluorocarbene agent. A complete self-assistance strategy based on $TMSCF_2Br$ enables the conversion to occur smoothly under the catalysis of 5 mol % of TBAB via the *in situ* formation of silyl dienol ethers, difluorocyclopropanation, thermal ring opening and recyclization rearrangement, and desilylation. This process represents the first example for the catalytic synthesis of difluorinated cyclic compounds from fluorocarbon precursors. The reliable installation of a difluoromethylene fragment at the α-position of readily available ketones makes the method well-suited for wide applications in organic synthesis and drug design. Further work on the application and extension of the scope of the protocol are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00611.

Experimental procedures, analytical data for new compounds (PDF)

Crystallographic data for **2a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233. (d) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442.

(2) (a) Inhibition of Enzymes by Fluorinated Compounds. Béguè, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley: Hoboken, NJ, 2008; Chapter 7, p 246. (b) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: West Sussex, 2009; p 29. (c) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley: Chichester, 2009.

(3) (a) Han, C.; Salyer, A. E.; Kim, E. H.; Jiang, X.; Jarrard, R. E.; Powers, M. S.; Kirchhoff, A. M.; Salvador, T. K.; Chester, J. A.; Hockerman, G. H.; Colby, D. A. *J. Med. Chem.* **2013**, *56*, 2456. (b) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813. (c) Takahashi, L. H.; Radhakrishnan, R.; Rosenfield, R. E.; Meyer, E. F.; Trainor, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 3368.

(4) (a) Dan, N.; Bhakat, S. *Eur. J. Med. Chem.* **2015**, *95*, 324. (b) Fah, C.; Hardegger, L. A.; Baitsch, L.; Schweizer, W. B.; Meyer, S.; Bur, D.; Diederich, F. *Org. Biomol. Chem.* **2009**, *7*, 3947. (c) Persch, E.; Dumele, O.; Diederich, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 3290. (d) Fah, C.; Hardegger, L. A.; Ebert, M.-O.; Schweizer, W. B.; Diederich, F. *Chem. Commun.* **2010**, *46*, 67.

(5) (a) Peng, W.; Shreeve, J. M. *J. Org. Chem.* **2005**, *70*, 5760. (b) Pravst, I.; Zupan, M.; Stavber, S. *Synthesis* **2005**, *2005*, 3140. (c) Singh, R. P.; Majumder, U.; Shreeve, J. M. *J. Org. Chem.* **2001**, *66*, 6263.

(6) (a) Yang, M.-H.; Orsi, D. L.; Altman, R. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2361. (b) Ge, S.; Chaladaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149. (c) Han, C.; Kim, E. H.; Colby, D. A. *J. Am. Chem. Soc.* **2011**, *133*, 5802.

(7) (a) Shimada, Y.; Taniguchi, N.; Matsuhisa, A.; Sakamoto, K.; Yatsu, T.; Tanaka, A. *Chem. Pharm. Bull.* **2000**, *48*, 1644. (b) Baudoux, J.; Cahard, D. *Org. React.* **2007**, *69*, 347.

(8) Meegalla, S. K.; Doller, D.; Liu, R.; Sha, D.; Lee, Y.; Soll, R. M.; Wisnewski, N.; Silver, G. M.; Dhanoa, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1702.

(9) Aono, T.; Sasagawa, H.; Fuchibe, K.; Ichikawa, J. *Org. Lett.* **2015**, *17*, 5736.

(10) (a) Hudlický, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165. (c) Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197.

(11) Orr, D.; Percy, J. M.; Tuttle, T.; Kennedy, A. R.; Harrison, Z. A. *Chem. - Eur. J.* **2014**, *20*, 14305.

(12) (a) Liu, X.; Xu, C.; Wang, M.; Liu, Q. *Chem. Rev.* **2015**, *115*, 683. (b) Xu, C.; Liu, J.; Ming, W.; Liu, Y.; Liu, J.; Wang, M.; Liu, Q. *Chem. - Eur. J.* **2013**, *19*, 9104. (c) Zheng, G.; Ma, X.; Li, J.; Zhu, D.; Wang, M. *J. Org. Chem.* **2015**, *80*, 8910.

(13) (a) Song, X.; Chang, J.; Zhu, D.; Li, J.; Xu, C.; Liu, Q.; Wang, M. *Org. Lett.* **2015**, *17*, 1712. (b) Chang, J.; Song, X.; Huang, W.; Zhu, D.; Wang, M. *Chem. Commun.* **2015**, *51*, 15362. (c) Song, X.; Tian, S.; Zhao, Z.; Zhu, D.; Wang, M. *Org. Lett.* **2016**, *18*, 3414.

(14) CCDC 1521772 contains the supplementary crystallographic data for **2a** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.uk/data_request/cif.

(15) **2ac′** was formed by further difluorocyclopropanation, ring opening, and defluorination of the acetyl group of **2ac**.

(16) **2ac″** was formed by further difluorocyclopropanation, ring opening, and protonation of the acetyl group of **2ac**.

(17) Fuchibe, K.; Takayama, R.; Yokoyama, T.; Ichikawa, J. *Chem. - Eur. J.* **2017**, *23*, 2831.

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Org. Lett. XXXX, XXX, XXX−XXX