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Ring-opening Fluorination of Cyclobutanols and Cyclopropanols Catalyzed by Silver

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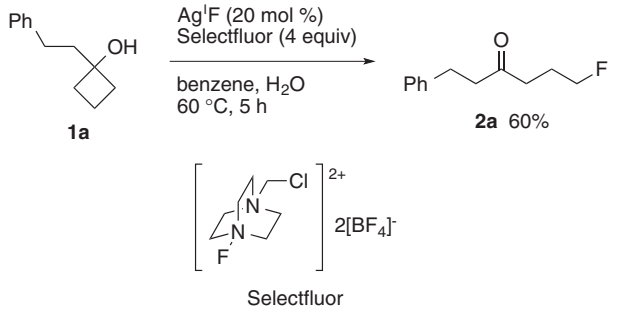
Cyclobutanols and cyclopropanols underwent ring-opening fluorination upon treatment with Selectfluor in the presence of a substoichiometric amount of a silver salt. The reaction provides an efficient method to synthesize γ- and β-fluoroalkyl ketones.

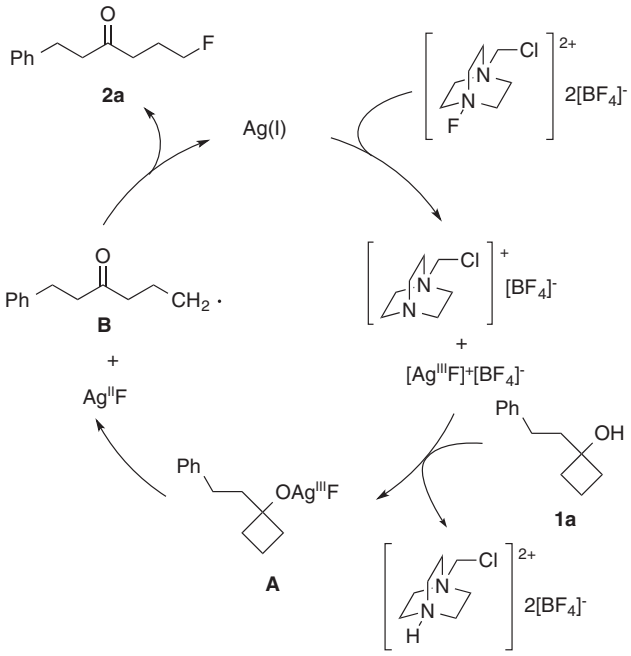
Organofluorine compounds have attracted significant attention in pharmaceuticals, agrochemicals, and materials science.[1] The strong demand for organofluorine compounds has spurred the development of new synthetic means for organofluorine compounds.[2,3] Herein we report a ring-opening fluorination reaction of cyclobutanols and cyclopropanols catalyzed by silver. A fluorine atom is introduced in a site-selective manner to afford the γ- and β-fluoroalkyl ketones.

Cyclobutanols are facilely prepared by well-established methods such as [2+2] cycloaddition of alkenes with ketenes followed by an addition reaction of Grignard reagents.[4] They undergo ring-opening reactions upon treatment with transition-metal catalysts.[5] Oxidation of cyclobutanols also induces ring opening.[6] As a continuation of our previous studies on the ring-opening reactions of cyclobutanol derivatives,[7] we examined a reaction with fluorinating agents to find that cyclobutanol **1a** underwent a ring-opening fluorination reaction when treated with Selectfluor (4 equiv)[8] in the presence of $Ag^{I}F$ (20 mol %) in a benzene/water biphasic solvent at 60 °C for 5 h (Scheme 1).[3c] γ-Fluoroalkyl ketone **2a** was obtained in 60% isolated yield. Other Ag(I) salts like $AgBF_4$ and $AgNO_3$ exhibited comparable reactivities, and no reaction took place in the absence of Ag(I) salts. Fluorinating agents such as *N*-fluorobenzenesulfonimide and *N*-fluoropyridinium salts were totally ineffective. Treatment of **1a** with a stoichiometric amount of either $Ag^{I}F$ or $Ag^{II}F_2$ in the absence of Selectfluor failed to induce any reactions, suggesting that a reactive species is generated in situ from $Ag^{I}F$ and Selectfluor to initiate the ring-opening fluorination reaction.

The formation of **2a** from **1a** can be explained by assuming a radical-type reaction mechanism depicted in Scheme 2, although we have no experimental evidence for it.[9] Initially, Ag(I) is oxidized to Ag(III) by Selectfluor. The resulting Ag(III)



Scheme 1. Ring-opening fluorination of **1a**.

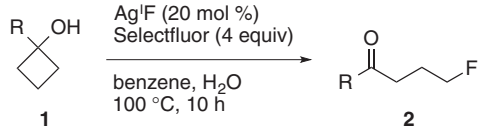


Scheme 2. Proposed mechanism.

reacts with cyclobutanol **1a** to furnish silver cyclobutanolate **A**. One-electron transfer from the cyclobutanolate moiety to Ag(III), i.e., homolytic cleavage of the Ag–O bond induces ring opening to give the alkylradical intermediate **B** together with $Ag^{II}F$ species. Finally, the carbon-centered radical **B** is fluorinated with the $Ag^{II}F$, resulting in the formation of **2a** and Ag(I) species, the latter of which re-enters the next cycle.

The ring-opening fluorination reaction was significantly dependent on the substituent at the 1-position of cyclobutanols. No reaction was observed with the 1-octadecylcyclobutanol. When a phenyl group is present in the 1-substituent, however, the fluorination reaction took place. 1-Phenylcyclobutanol (**1b**) underwent the ring-opening fluorination to produce the corresponding γ-fluoroalkyl ketone **2b** in 77% yield (Table 1). 1-Benzylcyclobutanol (**1c**) was also reactive (83% conversion) and **2c** was obtained in 30% yield along with various unidentified by-products. The reaction of 1-(3-phenylpropyl)cyclobutanol (**1d**) was sluggish and transformed only partially under the same reaction conditions. 1-[2-(4-Methoxyphenyl)ethyl]cyclobutanol (**1e**) was so reactive that 1.2 equiv of Selectfluor was enough for full conversion. On the other hand, 1-[2-(4-chlorophenyl)ethyl]-cyclobutanol (**1f**) was unreactive under the same reaction conditions. These results may indicate that the electron-donating phenyl group located in proximity to the hydroxy group facilitates the approach of the catalytically active silver species to the hydroxy group.[10]

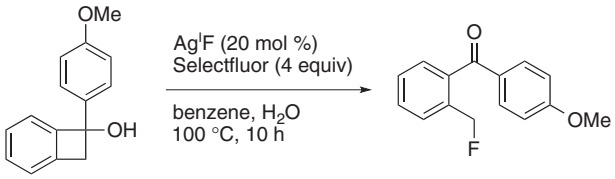
Table 1. Ring-opening fluorination of 1-substituted cyclobutanols[a]



1 2

Entry	R	Conversion of **1**/%[b]	Yield of **2**/%[c]
1	Ph– (**1b**)	100	77
2	$PhCH_2$– (**1c**)	83	30
3	$Ph(CH_2)_3$– (**1d**)	23	<10
4[d]	4-$MeOC_6H_4(CH_2)_2$– (**1e**)	100	40
5	4-$ClC_6H_4(CH_2)_2$– (**1f**)	<5	<5

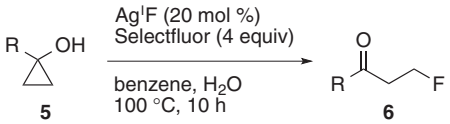
[a]Reaction conditions: cyclobutanol **1** (0.20 mmol), AgF (0.04 mmol, 20 mol %), Selectfluor (0.8 mmol, 4 equiv), benzene (1 mL), H_2O (1 mL), 100 °C, 10 h. [b]Determined by NMR analysis of the crude reaction mixture. [c]Isolated yield. [d]1.2 equiv of Selectfluor was used.



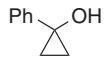
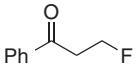
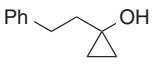
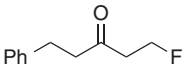
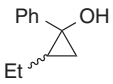
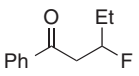
3 4 85%

Scheme 3. Ring-opening fluorination of **3**.

Table 2. Ring-opening fluorination of cyclopropanols[a]



5 6

Entry	Cyclopropanol **5**	β-Fluorinated ketone **6**[b]
1	 **5a**	 **6a** 78%
2	 **5b**	 **6b** 55%
3	 **5c** dr = 3:1	 **6c** 50%

[a]Reaction conditions: cyclopropanol **5** (0.20 mmol), AgF (0.04 mmol, 20 mol %), Selectfluor (0.8 mmol, 4 equiv), benzene (1 mL), H_2O (1 mL), 100 °C, 10 h. [b]Isolated yields are shown.

When benzocyclobutenol **3** was subjected to the standard reaction conditions in place of cyclobutanol **1**, benzyl fluoride **4** was selectively obtained in 85% isolated yield (Scheme 3). A product derived from cleavage of the $C(sp^2)$–$C(sp^3)$ bond[11] was not detected in the reaction mixture. This site-selectivity accords with the reported result of the oxidative ring-opening reaction of benzocyclobutenols; a benzocyclobutenoxyl radical undergoes ring opening with site-selective cleavage of the $C(sp^3)$–$C(sp^3)$ bond to give a benzylic radical intermediate.[12]

Phenyl-substituted cyclopropanols **5a**–**5c** also underwent the ring-opening fluorination reaction under the same reaction conditions to afford β-fluoroalkyl ketones (Table 2).[13] In the case of unsymmetrical cyclopropanol **5c**, the ring opening took place site-selectively at the more substituted position to afford *sec*-alkyl fluoride **6c**. This result is consistent with the proposed radical mechanism, since generation of a more substituted carbon radical would be favored.

In conclusion, we have described the silver-catalyzed ring-opening fluorination reaction of cyclobutanols and cyclopropanols. The site-selectivity of the ring-opening process can be rationalized by assuming a radical-type mechanism; the C–C bond is cleaved to generate a more stabilized carbon radical. The present reaction offers a convenient way to synthesize γ- and β-fluorinated ketones.

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Supporting Information is available electronically on J-STAGE.

References and Notes

1 a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881. b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320. c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359. d) M. Cametti, B. Crousse, P. Metrangolo, R. Milani, G. Resnati, *Chem. Soc. Rev.* **2012**, *41*, 31.

2 For reviews, see: a) M. Shimizu, T. Hiyama, *Angew. Chem., Int. Ed.* **2005**, *44*, 214. b) S. Rozen, *Eur. J. Org. Chem.* **2005**, 2433. c) G. Sandford, *J. Fluorine Chem.* **2007**, *128*, 90. d) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305. e) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465. f) M. Tredwell, V. Gouverneur, *Angew. Chem., Int. Ed.* **2012**, *51*, 11426. g) Y. Li, Y. Wu, G.-S. Li, X.-S. Wang, *Adv. Synth. Catal.* **2014**, *356*, 1412. h) A. F. Brooks, J. J. Topczewski, N. Ichiishi, M. S. Sanford, P. J. H. Scott, *Chem. Sci.* **2014**, *5*, 4545. i) M. G. Campbell, T. Ritter, *Chem. Rev.* **2015**, *115*, 612.

3 For selected recent examples of fluorination reactions forming alkyl fluorides: a) W. Liu, X. Huang, M.-J. Cheng, R. J. Nielsen, W. A. Goddard, III, J. T. Groves, *Science* **2012**, *337*, 1322. b) M. Rueda-Becerril, C. C. Sazepin, J. C. T. Leung, T. Okbinoglu, P. Kennepohl, J.-F. Paquin, G. M. Sammis, *J. Am. Chem. Soc.* **2012**, *134*, 4026. c) F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401. d) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem., Int. Ed.* **2012**, *51*, 10580. e) T. J. Barker, D. L. Boger, *J. Am. Chem. Soc.* **2012**, *134*, 13588. f) Y. Amaoka, M. Nagatomo, M. Inoue, *Org. Lett.* **2013**, *15*, 2160. g) S. Mizuta, I. S. R. Stenhagen, M. O'Duill, J. Wolstenhulme, A. K. Kirjavainen, S. J. Forsback, M. Tredwell, G. Sandford, P. R. Moore, M. Huiban, S. K. Luthra, J. Passchier, O. Solin, V. Gouverneur, *Org. Lett.* **2013**, *15*, 2648. h) H. Shigehisa, E. Nishi, M. Fujisawa, K. Hiroya, *Org. Lett.* **2013**, *15*, 5158. i) M.-G. Braun, A. G. Doyle, *J. Am. Chem. Soc.* **2013**, *135*, 12990.

j) J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494. k) S. Halperin, H. Fan, S. Chang, R. E. Martin, R. Britton, *Angew. Chem., Int. Ed.* **2014**, *53*, 4690. l) P. Xu, S. Guo, L. Wang, P. Tang, *Angew. Chem., Int. Ed.* **2014**, *53*, 5955. m) H. Wang, L.-N. Guo, X.-H. Duan, *Chem. Commun.* **2014**, *50*, 7382. n) C. W. Kee, K. F. Chin, M. W. Wong, C.-H. Tan, *Chem. Commun.* **2014**, *50*, 8211. o) W. Zi, Y.-M. Wang, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 12864. See ref 2i for aryl fluorides.

4 For discussion on the synthesis of cyclobutanols, see: N. Cramer, T. Seiser, *Synlett* **2011**, 449.

5 For selected examples: a) T. Nishimura, K. Ohe, S. Uemura, *J. Am. Chem. Soc.* **1999**, *121*, 2645. b) T. Matsuda, M. Makino, M. Murakami, *Org. Lett.* **2004**, *6*, 1257. c) T. Seiser, N. Cramer, *Angew. Chem., Int. Ed.* **2008**, *47*, 9294. d) A. Ziadi, R. Martin, *Org. Lett.* **2012**, *14*, 1266.

6 a) K. Meyer, J. Roček, *J. Am. Chem. Soc.* **1972**, *94*, 1209. b) S. Tsunoi, I. Ryu, Y. Tamura, S. Yamasaki, N. Sonoda, *Synlett* **1994**, 1009. c) B. M. Casey, C. A. Eakin, R. A. Flowers, II, *Tetrahedron Lett.* **2009**, *50*, 1264. d) H. Fujioka, H. Komatsu, A. Miyoshi, K. Murai, Y. Kita, *Tetrahedron Lett.* **2011**, *52*, 973.

7 Recent examples: a) N. Ishida, S. Sawano, M. Murakami, *Nat. Commun.* **2014**, *5*, 3111. b) N. Ishida, Y. Shimamoto, T. Yano, M. Murakami, *J. Am. Chem. Soc.* **2013**, *135*, 19103. c) N. Ishida, Y. Nakanishi, M. Murakami, *Angew. Chem., Int. Ed.* **2013**, *52*, 11875, and references cited therein.

8 When 2 equiv of Selectfluor was used, **2** was obtained in 55% yield and 21% of **1** was recovered.

9 TEMPO suppressed the ring-opening fluorination reaction of **2a** significantly, suggesting that a radical intermediate may be involved in the reaction pathway.

10 For interaction between $Ag(I)^+$ and arenes, see: a) Y.-P. Ho, Y.-C. Yang, S. J. Klippenstein, R. C. Dunbar, *J. Phys. Chem. A* **1997**, *101*, 3338. b) T. K. Dargel, R. H. Hertwig, W. Koch, *Mol. Phys.* **1999**, *96*, 583. c) H.-B. Yi, H. M. Lee, K. S. Kim, *J. Chem. Theory Comput.* **2009**, *5*, 1709.

11 a) R. V. Stevens, G. S. Bisacchi, *J. Org. Chem.* **1982**, *47*, 2396. b) M. Brands, H. G. Wey, H. Butenschön, *J. Chem. Soc., Chem. Commun.* **1991**, 1541. c) A. Gokhale, P. Schiess, *Helv. Chim. Acta* **1998**, *81*, 251. d) A. Chtchemelinine, D. Rosa, A. Orellana, *J. Org. Chem.* **2011**, *76*, 9157. e) N. Ishida, S. Sawano, Y. Masuda, M. Murakami, *J. Am. Chem. Soc.* **2012**, *134*, 17502. f) Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang, J. Wang, *J. Am. Chem. Soc.* **2014**, *136*, 3013.

12 K. Kobayashi, M. Itoh, H. Suginome, *Tetrahedron Lett.* **1987**, *28*, 3369.

13 Reviews of ring-opening reactions of cyclopropanols: a) I. Kuwajima, E. Nakamura, in *Small Ring Compounds in Organic Synthesis IV* in *Topics in Current Chemistry*, ed. by A. deMeijere, Springer, **1990**, Vol. 155, p. 1. doi:10.1007/3-540-52422-3_1. b) N. Nithiy, D. Rosa, A. Orellana, *Synthesis* **2013**, *45*, 3199. Recent examples: c) J. Jiao, L. X. Nguyen, D. R. Patterson, R. A. Flowers, II, *Org. Lett.* **2007**, *9*, 1323. d) P. P. Das, K. Belmore, J. K. Cha, *Angew. Chem., Int. Ed.* **2012**, *51*, 9517. e) A. Ilangovan, S. Saravanakumar, S. Malayappasamy, *Org. Lett.* **2013**, *15*, 4968. f) N. Nithiy, A. Orellana, *Org. Lett.* **2014**, *16*, 5854.

