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Ag(II)-Mediated Synthesis of β-Fluoroketones via Oxidative Cyclopropanol Opening

Yuanlin Deng, Nabeelah I. Kauser, Shahidul M. Islam, and Justin T. Mohr*

Abstract: A regioselective synthesis of β-fluorinated ketones via silver(II)-mediated ring opening is described. Commercially available AgF_2 serves as both an oxidant and fluorine atom source. A variety of β-fluorinated ketones are efficiently prepared from tertiary cyclopropanol precursors, offering a straightforward approach for the introduction of a fluorine atom at a remote site. Selectivity is observed in the site of bond cleavage leading to fluorination at the more substituted site. A radical mediated sequential homolytic C–C bond cleavage and C–F bond formation is suggested.

Introduction

The synthesis of organofluorine compounds remains a significant and important challenge in organic chemistry.[1] The importance of fluorine in a range of pharmaceutical compounds particularly highlights the demand for novel methods for forging new C–F bonds.[2] Especially useful are fluorination reactions that install the new fluorine atom at a relatively remote site.[1e] Hand-in-hand with the pervasive reactivity concerns of fluorinating agents are issues of reagent cost and safe handling. This is a particular challenge for electrophilic F sources since these are frequently synthesized from highly reactive molecular fluorine[3] and the resulting reagents are often strong oxidants.[4] However, the oxidizing ability may also be viewed as an opportunity for cascade reactivity toward organofluorine compounds.

One convenient, commercially available source of electrophilic F is AgF_2.[5] This relatively low molecular weight solid compares favorably to other common sources of electrophilic F on a cost basis. For instance, at present AgF_2 ($110 for 10 g = $1.60 per mmol, Alfa Aesar) is nearly 20% less costly than the more common 1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor®) reagent[4j] ($135 for 25 g = $1.91 per mmol, Alfa Aesar) and nearly 50% less than *N*-fluorobenzenesulfonimide (NFSI)[4g] ($251 for 25 g = $3.17 per mmol, Alfa Aesar). An additional practical advantage of a Ag salt is that the byproducts may also serve to scavenge any HF produced during the reaction and therefore substantially reduce potential safety hazards or pH changes.[5] In the context of our broader program exploring remote functionalization reactions[6] and halogenation protocols,[7] we were particularly intrigued by the AgF_2 reagent that combines the potential to not only supply an electrophilic F, but also behave as a potent oxidant that could expand the scope of fluorination protocols.

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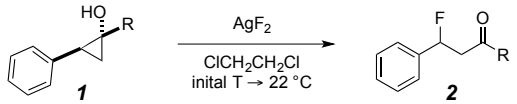
Results and Discussion

To explore the potential of AgF_2, we selected a strain-based strategy[8] for remote fluorination using cyclopropanols as substrates.[9] Some recent reports from Zhu,[10a] Murakami,[10b] and Loh,[10c] have found this type of transformation feasible with Ag(I) in the presence of superstoichiometric quantities of Selectfluor® as an electrophilic source of F (and perhaps also as an oxidant). Lectka[10d] has developed a related system based on photoredox catalysis in the presence of Selectfluor®. Related halogenative transformations using Mn[11] and Ag,[12] as well as C–C[13] and C–N[14] bond forming protocols based on Cu catalysts corroborate the versatility of cyclopropanols for a variety of metal-mediated transformations.[15] We hoped that the presumably different reactivity of Ag(II) might facilitate either a distinctive reaction pathway or expand the scope of the transformations reported previously.

With cyclopropanols readily available via the Kulinkovich protocol,[16] we commenced our study using AgF_2 and cyclopropanol **1a** as a model substrate (Table 1). We were pleased to find that a ring opening/fluorination cascade occurred readily to deliver the β-fluoroketone in fair yield as a single constitutional isomer, suggesting site selectivity in the putative C–C bond scission. Other fluoride salts such as AgF or alkali metal fluorides did not lead to fluorinated products under similar conditions, and high-valent transition metal fluorides MnF_3 and CoF_3 led to nonspecific decomposition. To optimize the reaction protocol we first examined the time of reaction, which proved a

Table 1. Optimization of reaction conditions.[a]



1 ***2***

Entry	Substrate	AgF_2 [equiv]	Initial T [°C]	Time at initial T [h]	Time at 22 °C [h]	Yield of ***2*** [%]
1	***1a*** (R = Me)	2	0	1	1	60
2	***1a***	2	0	1	4	60
3	***1a***	2	0	1	6	64
4	***1a***	2	0	1	8	57
5	***1a***	2	0	1	17	42
6	***1a***	2	–40	1	4	31
7	***1a***	2	–40	1	8	44
8	***1a***	2	–40	1	17	51
9	***1a***	1	–40	1	17	25
10	***1a***	4	–40	1	17	24
11	***1a***	2	–15	1	1	53
12[b]	***1b*** (R = *i*-Pr)	2	0	1	1	58
13[b]	***1b***	2	0	2	2	62
14[b]	***1b***	2	0	2	1	48
15[b]	***1b***	2	–15	1	1	72

[a] Reactions performed with 0.1 mmol of substrate **1** in $ClCH_2CH_2Cl$ (2 mL). Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. [b] Reaction performed with 0.3 mmol of substrate **1** in $ClCH_2CH_2Cl$ (6 mL).

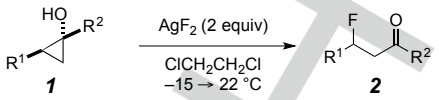
complex issue. Under our preliminary conditions the yield of fluoroketone increased only moderately over time, but decreased at extended reaction time (entries 1–5). Conducting the reaction at an initial temperature of –40 °C required long reaction times after warming to ambient temperature to obtain comparable yields (entries 6–8). Either increasing or decreasing the quantity of AgF_2 under these conditions was detrimental to the reaction (entries 8–10). A compromise was found by conducting the reaction at an initial temperature of –15 °C, leading to 53% yield of β-fluoroketone in 2 h overall (entry 11). Concurrently, we had observed that notably higher yield was obtained with substrate **1b** and we therefore validated our observations using this substrate, again finding the –15 °C initial temperature condition to be optimal (entries 12–15).[17]

With effective ring-opening conditions identified we next turned to examination of the scope of the reaction (Table 2). Increasing the steric bulk adjacent to the hydroxyl group did not adversely affect the reaction (entries 1–3). An aromatic substituent attached to the carbinol increased reaction efficiency substantially, however (entry 4). Substrates containing *p*-tolyl substituents (entries 5–7) led to *mono*-fluorinated products exclusively, suggesting that under the reaction conditions a simple benzylic fluorination mechanism is not likely and the site of fluorination is dependent on the ring-opening process. Encouraged by this result, we examined substrates where fluorination would occur at a non-benzylic site (entries 9–10). Products of ring-opening/fluorination were observed in these cases with no evidence of fluorination at other sites, although yields were somewhat reduced.

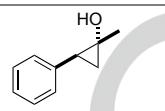
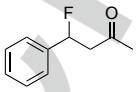
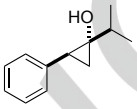
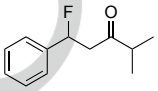
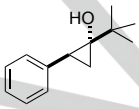
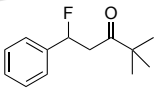
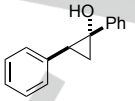
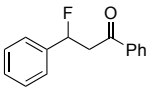
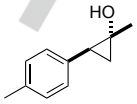
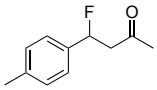
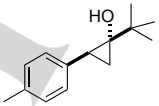
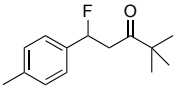
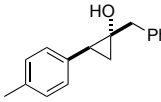
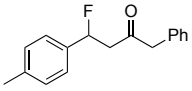
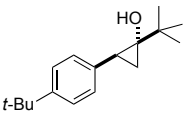
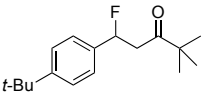
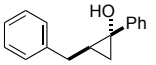
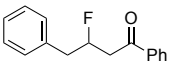
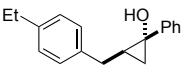
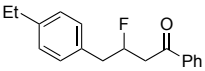
Purification of the fluoroketone products was complicated by the presence of α,β-unsaturated ketone in some cases. This contaminant exhibited similar chromatographic properties to the fluoroketone and care is needed to effectively separate the desired product. The enone is observable in ^{1}H NMR analysis of crude reaction mixtures and the desired fluoroketone is stable under chromatographic conditions on SiO_2. Isolated enone does not convert to β-fluoroketone under the reaction conditions. Although it is attractive to suggest that this conjugated compound arises from elimination HF from the fluoroketone, in control experiments we have not observed conversion of the fluoroketone to enone under typical reaction conditions. Together these observations suggest that enone likely arises from a competing reaction pathway perhaps involving a mechanistic intermediate en route to the fluoroketone.

Polar functional groups within the molecule pose a challenge both to substrate preparation via the Kulinkovich protocol. To study the effect of diverse functional groups in our Ag-mediated reaction, we carried out a "robustness" study[18] using a standard cyclopropanol and various additives (Table 3). The results show a limited scope of tolerated functional groups containing Lewis basic atoms. This could be due to strong Lewis acid–Lewis base interactions with the Ag center or possibly oxidation by the Ag. Some functional groups impede the ring-opening reaction moderately but are consumed in the course of the reaction. Others, such as an alkyne, cause a dramatic decrease in yield but survive the reaction largely intact. Further studies to understand these effects and expand the scope of this transformation are ongoing.[19]

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



1 **2**

Entry	Substrate		Product		Yield [%]
1		***1a***		***2a***	53 (51)
2		***1b***		***2b***	72 (69)
3		***1c***		***2c***	59
4		***1d***		***2d***	93
5		***1e***		***2e***	47
6		***1f***		***2f***	71 (55)
7		***1g***		***2g***	67 (47)
8		***1h***		***2h***	90
9		***1i***		***2i***	60
10		***1j***		***2j***	39 (42)

[a] Reactions were performed with 0.3 mmol of substrate **1** and AgF_2 (2 equiv) in $ClCH_2CH_2Cl$ (9 mL) for 2 h. Yields determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. Values in parentheses are isolated yields after chromatography.

Given the apparent improvement in reaction efficiency with aryl carbinols relative to aliphatic carbinols, we carried out a competition experiment to gain insight into the process and perhaps provide mechanistic insight (Scheme 1). In experiments with either 1 or 2 equiv of AgF_2 the benzylic alcohol outcompeted the aliphatic tertiary alcohol by a factor of ~4–5-fold. This is important in demonstrating that the improvement in efficiency with aryl carbinols is due, at least in part, to an increase in rate and not some undetermined factor such as product stability.

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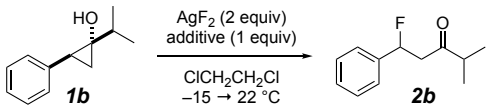
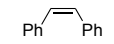
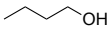
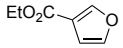
Table 3. Robustness study.[a]



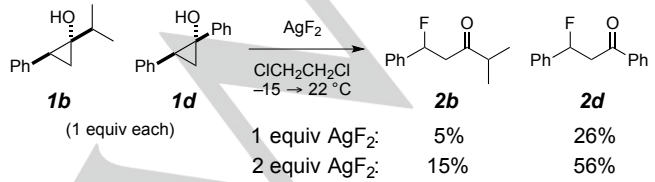
Entry	Additive	Yield **2b** [%]	Recovered Additive [%]	Entry	Additive	Yield **2b** [%]	Recovered Additive [%]
1	none	72	–	5		29	87
2		53	23	6		46	5
3	*t*-Bu–C≡N	57	18	7		8	95
4	pyridine	39	3	8		33	56

[a] See Table 2 for reaction conditions. Yields determined by NMR.

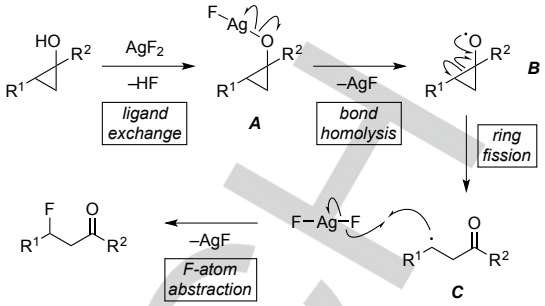
Although there are several plausible explanations for this difference in reactivity, the effect is likely best explained through an influence at an early stage of the mechanism. Whereas the aryl group proximal to the oxygen would likely stabilize a hypothetical O-centered or benzylic radical, an aryl group at this site would be expected to accelerate a mechanism involving single electron intermediates that could arise from oxidation or bond fission. To estimate the influence of the neighboring aryl group we referred to the bond dissociation energy (BDE) of *t*-BuO–O*t*-Bu (162.8 ± 2.1 kJ/mol) and Ph_3CO–$OCPh_3$ (131.4 kJ/mol).[20] The significantly weaker bond in the arylated peroxide may suggest a preference for a radical adjacent to the aromatic rings as a potential explanation for the increase rate in our competition experiment.[21]

Alternatively, the inductive effect of the aryl ring could facilitate the formation of a Ag–O interaction by increasing acidity of the hydroxyl group. To substantiate this possibility, we conducted theoretical calculations of the aqueous pK_a of the alcohol moieties is both **1b** and **1d**.[22] Using either an implicit solvation model or an implicit solvation model with explicit water molecules, the same trend is observed: the computed pK_a of **1d** is approximately two pK_a units lower than that of **1b**, which would be consistent with an increased rate of Ag–O coordination.

A potential mechanism for the fragmentation is shown in Scheme 2. Related processes have invoked Ag(III) as a key reactive intermediate,[10] although we predict that Ag(II) may be a viable promoter of fragmentation. Thus, initial ligand exchange electron oxidation via Ag–O bond homolysis. The resulting alkoxy radical **B** could undergo bond fission driven by strain



Scheme 1. Competition experiment between alkyl- and arylcarbinols.



Scheme 2. Mechanistic hypothesis for ring opening/fluorination.

release in the cyclopropane system leading to C-centered radical intermediate **C**. This step could account for the to form Ag–alkoxide complex **A** could be followed by single regioselectivity in fragmentation due to a preference for the formation of the secondary radical intermediate. Finally, F-atom abstraction from a second molecule of AgF_2 would lead to the β-fluoroketone product and account for the optimal reaction stoichiometry. The AgF and HF byproducts likely combine to form silver bifluoride ($AgHF_2$) mitigating changes in acidity.

Although oxidation of the intermediate radical **C** to the corresponding carbocation is also possible in the presence of Ag(II), we do not believe this to be the major pathway to the fluorinated products since we predict deprotonation to be more likely in this case to generate the undesired enone products that are observed in some cases. Potential radical inhibitors or trapping agents such as TEMPO, BHT, and Ph_3CCl all negate fluorination under our typical conditions, but the corresponding enone is observed in low yields with TEMPO or BHT. These experiments are consistent with a radical-based mechanism of C–F bond formation, but are not definitive. However, the observation of the enone under these conditions could be explained by either oxidation of the putative radical or trapping to form a β-heteroatom-containing intermediate that could undergo elimination to generate the conjugated system.

An alternative homoenolate-type mechanism involving a carbanion intermediate would appear at odds with observed the preference for opening at the secondary carbon site as this anion is predicted to be higher in energy than the alternative primary anion. An electrophilic mechanism initiated by a formal F^+ interacting with the cyclopropane would similarly contradict the empirical preference for introducing the F at the more substituted site due to expected steric interactions. We have noted that the cyclopropanol substrates are sensitive to strong base leading to mixtures with substantial quantities of nonfluorinated ketones even in the presence of fluorinating agents. Further mechanistic studies to elucidate the details of the mechanism are ongoing in our laboratories.

Conclusions

In conclusion, we have developed a protocol for the synthesis of β-fluoroketones using readily available cyclopropanols as

precursors. The transformation features the use of commercially available AgF_2 as both an oxidant and a source of F. Regioselectivity in the putative bond fission step enables selective generation of secondary organofluorides. The transformation is relatively insensitive to sterics and the presence of aryl groups affixed to the carbinol center appear to accelerate the reaction suggesting an influence of inductive withdrawing groups of resonance stabilizing groups. Applications of this methodology in the synthesis of valuable fluorinated target molecules are underway.

Experimental Section

General Methods: Unless otherwise stated, reactions were performed in oven-dried 20 mL plastic vials under a N_2 atmosphere using dry, deoxygenated solvents. Silver difluoride was purchased from Alfa Aesar and stored in a N_2-filled glovebox. Anhydrous 1,2-dichloroethane was purchased from Macron, distilled over CaH_2, followed by three freeze-pump-thaw degassing cycles. Starting materials were synthesized according to reported literature.[16c] Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification. Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde solutions. Flash chromatography[23] was performed using Silicycle SiliaFlashR P60 silica gel (40–63 μm particle size). Melting points were determined using a Mel-Temp electrothermal capillary melting point apparatus and the values reported are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sept = septet, m = multiplet, app. = apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). ^{19}F NMR spectra were recorded on a Bruker Avance DRX-400 at 376 MHz and are reported relative to the internal standard α,α,α-trifluorotoluene (δ –63.1 ppm). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). GC/MS analyses were performed on a Hewlett Packard Model 6890 gas chromatograph interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). High-resolution mass spectra (HRMS) were obtained from the University of Illinois at Urbana–Champaign Mass Spectral Facility. All the electronic structure calculations were carried out with Gaussian09[24] (see Supporting Information for details).

General Procedure for Ring-Opening Fluorination: An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (87.6 mg, 0.6 mmol, 2 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL). The mixture was cooled to –15 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M soln in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 1 h at –15 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

Specific quantities of reagents, procedural variations, and purification conditions may be found below in the entry containing the characterization data.

Procedure for Retreatment of Product Mixture with AgF_2: An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (24.5 mg, 0.168 mmol, 2 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (0.84 mL) via syringe. The suspension was cooled to –15 °C and stirred vigorously for 1 min. A solution comprising a 3.9:1 ratio of 3-fluoro-1,3-diphenylpropan-1-one (15.5 mg, 0.0679 mmol, quantity determined by ^{1}H NMR) and (*E*)-chalcone (3.6 mg, 0.0173 mmol, quantity determined by ^{1}H NMR) dissolved in anhydrous 1,2-dichloroethane (1.68 mL) was added in one portion to AgF_2 suspension and the mixture was then stirred for 1 h at –15 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and then stirred for 1 h. The reaction mixture was passed through a short silica gel plug to remove the solid residue and eluted with CH_2Cl_2 (2 x 1 mL). The vial was washed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as internal standard and a ^{19}F NMR spectrum was obtained to determine the yields. The residue was purified by flash chromatography (10:1 hexanes/acetone) on silica gel to afford a 8.6:1 mixture of fluoroketone and enone (16.6 mg total: 3-fluoro-1,3-diphenylpropan-1-one 14.1 mg, 0.0618 mmol and (*E*)-chalcone 1.5 mg, 0.0072 mmol, determined by ^{1}H NMR).

Procedure for Competition Experiments: An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (14.6 mg, 0.1 mmol, 1 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL) via syringe. The suspension was cooled to –15 °C and stirred vigorously for 1 min. A solution of 1-isopropyl-2-phenylcyclopropan-1-ol (17.6 mg, 0.1 mmol, 1 equiv) and 1,2-diphenylcyclopropan-1-ol (21.0 mg, 0.1 mmol, 1 equiv) dissolved in 1,2-dichloroethane (1 mL) was added at once and then the mixture was stirred for 1 h at –15 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short plug of SiO_2 to remove the solid residue and eluted with CH_2Cl_2 (2 x 1 mL) and then the vial was washed with CH_2Cl_2 (2 x 3 mL). The combined solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added into the residue as an internal standard and ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.) The experiment was also carried out with 0.2 mmol of AgF_2 (29.2 mg, 2 equiv) in a similar manner.

Procedure for Robustness Study: An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (87.6 mg, 0.6 mmol, 2 equiv) was added and the vial was then

sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL). The mixture was cooled to –15 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M soln in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) and a specific additive (0.3 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 1 h at –15 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) and dibromomethane (7.0 μL) were added to the residue as internal standards. ^{1}H and ^{19}F NMR spectra were obtained to determine the yield and the quantity of remaining additive.

Experimental Data for Cyclopropanols and β-Fluoroketones: Substrates were synthesized via the method previously reported by Cha and co-workers.[16c] Based on the spectra obtained using this method, all the substrates are single diastereomers and the relative configurations were assigned by analogy to the Cha work. Spectra for cyclopropanols **1a**,[25] **1d**,[26] **1e**[25c] and **2a**[10d] matched those in the literature.

*1-Isopropyl-2-phenylcyclopropan-1-ol (**1b**):* White powder; mp 60–62 °C; TLC (SiO_2) R_f = 0.33 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 2,43 (dd, *J* = 9.5, 7.5 Hz, 1H), 1.24–1.11 (m, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 128.3, 128.0, 125.8, 64.9, 31.9, 30.1, 18.5, 17.6, 16.7; IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}; GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%).

*1-(tert-Butyl)-2-phenylcyclopropan-1-ol (**1c**):* White powder; mp 58–59 °C; TLC (SiO_2) R_f = 0.37 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.22 (m, 4H), 7.20–7.15 (m, 1H), 2.49 (dd, *J* = 10.0, 8.0 Hz, 1H), 1.33 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.06 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 128.3, 128.0, 125.8, 64.9, 31.9, 30.1, 18.5, 17.6, 16.7; IR (neat) 3473, 3357, 2959, 1599, 1493, 1362, 1187, 1145, 774, 696, 608 cm^{-1}; GC/MS (*m/z*): 190.1 (6%), 133.0 (65%), 105.1 (100%), 91.0 (66%), 77.0 (19%), 57.1 (57%).

*1-(tert-Butyl)-2-(p-tolyl)cyclopropan-1-ol (**1f**):* White powder; mp 64–66 °C; TLC (SiO_2) R_f = 0.46 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.5 Hz, 2H), 7.06 (d, *J* = 8 Hz, 2H), 2.44 (dd, *J* = 18.5, 8.5 Hz, 1H), 2.31 (s, 3H), 1.30 (dd, *J* = 7.5, 5.5 Hz, 1H), 1.03 (dd, *J* = 10.5, 6.0 Hz, 1H), 0.80 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.5, 135.1, 129.5, 128.7, 66.4, 35.2, 31.7, 26.9, 21.1, 14.1; IR (neat) 3457, 2963, 2871, 1362, 1180, 1076, 907, 813, 550, 526 cm^{-1}; GC/MS (*m/z*): 204.1 (10%), 145.0 (41%), 119.1 (42%), 105.1 (100%), 91.0 (15%), 57.1 (44%).

*1-Benzyl-2-(p-tolyl)cyclopropan-1-ol (**1g**):* Clear colorless liquid; TLC (SiO_2) R_f = 0.39 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–6.96 (m, 9H), 2.86 (d, *J* = 14.5 Hz, 1H), 2.46 (dd, *J* = 9.5, 7.0 Hz, 2H), 2.36 (s, 3H), 1.32–1.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4, 135.7, 135.1, 129.5, 129.0, 128.5, 128.3, 126.6, 125.6, 61.0, 39.4, 30.0, 21.1, 18.0; IR (neat) 3395, 3027, 2924, 2364, 2332, 1516, 1492, 1450, 1092, 813, 699, 530 cm^{-1}; GC/MS (*m/z*): 238.1 (5%), 147.0 (20%), 119.0 (27%), 105.0 (100%), 91.0 (24%).

*1-(tert-Butyl)-2-(4-(tert-butyl)phenyl)cyclopropan-1-ol (**1h**):* White powder; mp 72–74 °C; TLC (SiO_2) R_f = 0.40 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.44 (dd, *J* = 10.5, 8.0 Hz, 1H), 1.30 (s, 10H), 1.03 (dd, *J* = 10.5, 6.0 Hz, 1H), 0.81 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 135.0, 129.2, 124.8, 35.2, 31.7, 31.4, 31.3, 31.2, 26.9, 14.1; IR (neat) 3366, 2956, 2904, 2869, 1515, 1362, 820, 611, 526 cm^{-1}; GC/MS (*m/z*): 246.1 (30%), 189.0 (26%), 175.1 (19%), 147.1 (100%), 133.0 (96%), 117.0 (19%), 91.0 (17%), 57.0 (82 %).

*2-Benzyl-1-phenylcyclopropan-1-ol (**1i**):* Clear colorless liquid; TLC (SiO_2) R_f = 0.43 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 2.53 (dd, *J* = 15.0, 2.5 Hz, 1H), 2.31 (s, 1H), 2.08 (dd, *J* = 15.0, 8.0 Hz, 1H), 1,82–1.75 (m, 1H), 1.25 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.14 (app. t, *J* = 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.1, 140.0, 128.3, 128.2, 128.1, 127.6, 125.8, 61.8, 35.2, 27.8, 18.6; IR (neat) 3314, 3060, 3027, 2920, 2852, 1600, 1492, 1450, 1190, 1060, 764, 692 cm^{-1}; GC/MS (*m/z*): 224.1 (24%), 209.0 (4%), 133.0 (48%), 120.0 (46%), 105.0 (100%), 91.1 (30%), 77.0 (49%).

*2-(4-Ethylbenzyl)-1-phenylcyclopropan-1-ol (**1j**):* Clear colorless liquid; TLC (SiO_2) R_f = 0.46 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 2.60 (q, *J* = 8.0 Hz, 2H), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.02 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.81–1.72 (m, 1H), 1.25 (app. t, *J* = 5.5 Hz, 1H), 1.22 (app. t, *J* = 7.5 Hz, 3H), 1.12 (app. t, *J* = 6.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.7, 140.1, 138.3, 128.3, 128.1, 128.1, 127.7, 127.6, 61.9, 34.8, 28.4, 28.0, 18.6, 15.6; IR (neat) 3336, 2963, 2930, 2859, 1682, 1512, 1447, 1190, 1060, 1024, 836, 758, 699 cm^{-1}; GC/MS (*m/z*): 252.1 (27%), 237.0 (11%), 132.1 (58%), 119.0 (44%), 105.0 (100%), 91.1 (23%), 77.0 (44%).

*4-fluoro-4-phenylbutan-2-one (**2a**):* The title compound was prepared with a ^{19}F NMR yield of 53%, and was isolated (25.2 mg, 51%). Spectral data matches with the reported data.[10d]

*1-fluoro-4-methyl-1-phenylpentan-3-one (**2b**):* The title compound was prepared with a ^{19}F NMR yield of 72% containing 10% enone (determined by ^{1}H NMR) and was isolated as a pale yellow liquid (40.2 mg, 69%). TLC (SiO_2) R_f = 0.52 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 5.99 (ddd, *J* = 46.5, 8.5, 4.0 Hz, 1H), 3.25 (ddd, *J* = 16.6, 14.5, 8.5 Hz, 1H), 2.81 (ddd, *J* = 31.5, 16.5, 4.0 Hz, 1H), 2.60 (sept, *J* = 6.5 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.5, 128.6, 125.5, 125.5, 100.1, 90.3 (d, *J* = 170.7 Hz), 47.6 (d, *J* = 26.3 Hz), 41.6, 17.7, 17.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –174.9 (ddd, *J* = 46.4, 31.6, 13.9 Hz, 1F); IR (neat) 2966, 2926, 2852, 1713, 1467, 1379, 1070, 1021, 985, 758, 699 cm^{-1}; GC/MS (*m/z*): 194.1 (2%), 174.0 (3%), 151.0 (19%), 131.0 (46%), 109.0 (100%), 77.0 (20%); HRMS (*m/z*) calc'd for $C_{12}H_{15}FONa$ $[M + Na]^+$: 217.1005, found 217.1001.

*1-fluoro-4,4-dimethyl-1-phenylpentan-3-one (**2c**):* The title compound was prepared with a ^{19}F NMR yield of 59% containing 23% enone (determined by ^{1}H NMR) and was isolated as a white solid. Mp 37–39 °C; TLC (SiO_2) R_f = 0.54 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.31 (m, 5H), 6.02 (ddd, *J* = 46.5, 8.5, 4.5 Hz, 1H), 3.33 (ddd, *J* = 17.0, 14.0, 8.5 Hz, 1H), 2.77 (ddd, *J* = 31.5, 17.0, 4.5 Hz, 1H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 128.6, 128.5, 125.5, 125.5, 90.5 (d, *J* = 170.4 Hz), 44.2 (d, *J* = 26.5 Hz), 26.3, 25.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ –175.7 (ddd, *J* = 46.2, 31.6, 13.9 Hz, 1F); IR (neat) 2972, 2930, 1694, 1609, 1473, 1369, 1086, 1028, 976, 855, 765, 699, 542 cm^{-1}; GC/MS (*m/z*): 208.1 (3%), 188.0 (2%), 131.0 (100%), 103.0 (38%), 57.0 (46%); HRMS (*m/z*) calc'd for $C_{13}H_{17}FONa$ $[M + Na]^+$: 231.1166, found 231.1161.

*3-fluoro-1,3-diphenylpropan-1-one (**2d**):* The title compound was prepared with a ^{19}F NMR yield of 93%, and was isolated as a white solid. Mp 63–65 °C; TLC (SiO_2) R_f = 0.39 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.0 Hz, 2H), 7.69–7.33 (m, 8H), 6.19 (ddd, *J* = 46.5, 8.0, 4.0 Hz, 1H), 3.81 (app. dt, *J* = 15.0, 8.5 Hz, 1H), 3.33 (ddd, *J* = 29.5, 17.0, 4.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.1, 144.9, 139.6, 139.4, 136.7, 133.5, 132.8, 130.6, 129.0, 128.7, 128.7, 128.5, 128.5, 128.2, 125.7, 125.6, 122.1, 90.3 (d, *J* = 171.2 Hz), 46.0 (d, *J* = 26.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –174.5 (ddd, *J* = 46.0, 30.0, 14.9 Hz, 1F); IR (neat) 3063, 3030, 2937, 1685, 1665, 1597, 1447, 1376, 1203, 995, 751, 687, 579, 547 cm^{-1}; GC/MS (*m/z*): 228.1 (16%), 207.1 (48%), 131.0 (20%), 105.0 (100%), 77.1 (78%); HRMS (*m/z*) calc'd for $C_{15}H_{13}FONa$ [M + Na]$^+$: 251.0848, found 251.0482.

*4-fluoro-4-(p-tolyl)butan-2-one (**2e**):* The title compound was prepared with a ^{19}F NMR yield of 47%, and was isolated as a pale yellow liquid. TLC (SiO_2) R_f = 0.37 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 11.0 Hz, 2H), 7.19 (d, *J* = 8.5, 2H), 5.91 (ddd, *J* = 47.0, 8.5, 4.5 Hz, 1H), 3.20 (ddd, *J* = 16.4, 14.8, 9.0 Hz, 1H), 2.81 (ddd, *J* = 32.0, 17.0, 4.0 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.9, 143.5, 138.6, 138.6, 129.3, 125.6, 125.6, 90.1 (d, *J* = 170.4 Hz), 50.6 (d, *J* = 26.5 Hz), 30.9, 29.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ –172.4 (ddd, *J* = 46.5, 31.9, 14.1 Hz, 1F); IR (neat) 2959, 2923, 2855, 1720, 1668, 1609, 1457, 1366, 1258, 1180, 1044, 800 cm^{-1}; GC/MS (*m/z*): 180.1 (11%), 160.1 (15%), 145.0 (100%), 115.0 (42%), 91.0 (17%); HRMS (*m/z*) calc'd for $C_{11}H_{13}FONa$ [M + Na]$^+$: 203.0848, found 203.0841.

*1-fluoro-4,4-dimethyl-1-(p-tolyl)pentan-3-one (**2f**):* The title compound was prepared with a ^{19}F NMR yield of 71%, and was isolated as a white solid (36.7 mg, 55%). Mp 34–36 °C; TLC (SiO_2) R_f = 0.22 in 20:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.98 (ddd, *J* = 46.5, 8.0, 4.0 Hz, 1H), 3.33 (ddd, *J* = 22, 13.5, 8.5 Hz, 1H), 2.76 (ddd, *J* = 31.0, 17.0, 4.0 Hz, 1H), 2.35 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 142.9, 138.4, 136.7, 136.5, 129.6, 129.2, 128.3, 125.6, 125.5, 119.7, 90.5 (d, *J* = 169.6 Hz), 44.1 (d, *J* = 27.2 Hz), 26.4, 25.9, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –173.8 (ddd, *J* = 46.1, 31.5, 13.6 Hz, 1F); IR (neat) 2966, 2926, 2871, 1708, 1604, 1369, 1080, 1002, 979, 817, 728, 543 cm^{-1}; GC/MS (*m/z*): 222.1 (8%), 202.1 (6%), 145.1 (100%), 123.1 (34%), 115.1 (22%), 91.1 (11%); HRMS (*m/z*) calc'd for $C_{14}H_{19}FONa$ [M + Na]$^+$: 245.1318, found 245.1323.

*4-fluoro-1-phenyl-4-(p-tolyl)butan-2-one (**2g**):* The title compound was prepared with a ^{19}F NMR yield of 67%, and was isolated as an off-white solid (36.3 mg, 47%). Mp 57–60 °C; TLC (SiO_2) R_f = 0.41 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 3H), 7.29 (d, *J* = 7 Hz, 2H), 7.24–7.15 (m, 4H), 5.92 (ddd, *J* = 46.5, 8.5, 4.0 Hz, 1H), 3.75 (d, *J* = 5.0 Hz, 2H), 3.23 (ddd, *J* = 16.3, 14.8, 9.0 Hz, 1H), 2.82 (ddd, *J* = 31.0, 16.5, 3.0 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.4, 197.4, 143.5, 141.1, 138.6, 136.1, 136.0, 134.6, 133.4, 131.7, 129.7, 129.5, 129.3, 128.8, 128.8, 128.4, 127.2, 127.1, 127.0, 125.7, 125.6, 124.3, 90.2 (d, *J* = 170.6 Hz), 51.0, 48.9 (d, *J* = 26.5 Hz), 48.3, 21.5, 21.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –172.5 (ddd, *J* = 46.2, 31.4, 13.9 Hz, 1F); IR (neat) 3027, 2963, 2920, 1713, 1603, 1496, 1450, 1334, 1220, 1073, 1028, 817, 741, 696, 543 cm^{-1}; GC/MS (*m/z*): 256.1 (3%), 165.0 (18%), 145.0 (13%), 123.1 (100%), 91.0 (22%); HRMS (*m/z*) calc'd for $C_{17}H_{17}FONa$ [M + Na]$^+$: 279.1161, found 279.1162.

*1-(4-(tert-butyl)phenyl)-1-fluoro-4,4-dimethylpentan-3-one (**2h**):* The title compound was prepared with a ^{19}F NMR yield of 90% containing 1% enone (determined by ^{1}H NMR) and was isolated as a white solid. Mp 49–50 °C; TLC (SiO_2) R_f = 0.26 in 20:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 10.5 Hz, 2H), 7.30 (d, *J* = 9.5 Hz, 2H), 6.00 (ddd, *J* = 58.5, 11.0, 5.0 Hz, 1H), 3.36 (ddd, *J* = 21.1, 17.3, 11.0 Hz, 1H), 2.75 (ddd, *J* = 40.5, 21.5, 5.0 Hz, 1H), 1.32 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 151.6, 136.6, 136.5, 125.5, 125.3, 125.3, 90.3 (d, *J* = 169.6 Hz),44.3, 44.0 (d, *J* = 27.0 Hz), 34.6, 31.3, 25.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ –174.0 (ddd, *J* = 46.4, 32.5, 13.8 Hz, 1F); IR (neat) 2960, 2928, 2905, 2868, 1704, 1476, 1364, 1082, 1002, 839, 582 cm^{-1}; GC/MS (*m/z*): 264.1 (4%), 249.1 (6%), 207.1 (6%), 187.1 (32%), 165.1 (31%), 131.0 (35%), 57.1 (100%); HRMS (*m/z*) calc'd for $C_{17}H_{25}FONa$ [M + Na]$^+$: 287.1787, found 287.1785.

*3-fluoro-1,4-diphenylbutan-1-one (**2i**):* The title compound was prepared with a ^{19}F NMR yield of 60%, and was isolated as an off-white solid. Mp 55–56 °C; TLC (SiO_2) R_f = 0.43 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 10.0, 1.0 Hz, 2H), 7.58 (app. tt, *J* = 9.0, 1.6 Hz, 1H), 7.46 (app. t, *J* = 10.0 Hz, 2H), 7.36–7.29 (m, 2H), 7.26 (app. d, *J* = 8.5 Hz, 3H), 5.40 (app. doublet of quintets, *J* = 59.0 7.0 Hz, 1H), 3.45 (ddd, *J* = 21.3, 19.0, 9.0 Hz, 1H), 3.18–3.04 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 136.8, 136.5, 133.4, 129.6, 128.7, 128.5, 128.1, 126.8, 90.4 (d, *J* = 171.7 Hz), 42.8 (d, *J* = 23.2 Hz), 41.2 (d, *J* = 21.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ –179.0 (app. ddt, *J* = 47.2, 23.1, 16.5 Hz, 1F); IR (neat) 3031, 2959, 2930, 1682, 1597, 1447, 1379, 1213, 1083, 1009, 744, 686, 511 cm^{-1}; GC/MS (*m/z*): 222.1 (15%), 115.0 (18%), 105.0 (100%), 91.1 (9%), 77.0 (32%); HRMS (*m/z*) calc'd for $C_{16}H_{15}FONa$ [M + Na]$^+$: 265.1005, found 265.1008.

*4-(4-ethylphenyl)-3-fluoro-1-phenylbutan-1-one (**2j**):* The title compound was prepared with a ^{19}F NMR yield of 39%, and was isolated as a pale yellow liquid (33.9 mg, 42%). TLC (SiO_2) R_f = 0.44 in 5:1 hexanes/acetone, *p*-anisaldehyde stain; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94–7.88 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.43 (m, 2H), 7.20–7.13 (m, 4H), 5.39 (app. doublet of quintet, *J* = 47.0, 6.0 Hz, 1H), 3.44 (ddd, *J* = 16.8, 15.5, 7.0 Hz, 1H), 3.17–3.02 (m, 3H), 2.64 (q, *J* = 7.5 Hz, 2H), 1.24 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 148.0, 142.8, 137.9, 136.8, 134.9, 133.6, 133.5, 133.4, 133.2, 132.6, 29.5, 128.8, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 126.7, 90.5 (d, *J* = 171.7 Hz), 42.8 (d, *J* = 23.3 Hz), 40.8 (d, *J* = 21.2 Hz), 28.5, 15.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –178.7 (app. ddt, *J* = 47.7, 23.9, 15.8 Hz, 1F); IR (neat) 2963, 2930, 2361, 2335, 1684, 1620, 1450, 1272, 1216, 1018, 983, 829, 754, 689 cm^{-1}; GC/MS (*m/z*): 250.1 (19%), 145.1 (12%), 117.1 (14%), 105.0 (100%), 91.1 (6%), 77.0 (29%); HRMS (*m/z*) calc'd for $C_{18}H_{19}FONa$ [M + Na]$^+$: 293.1318, found 293.1323.

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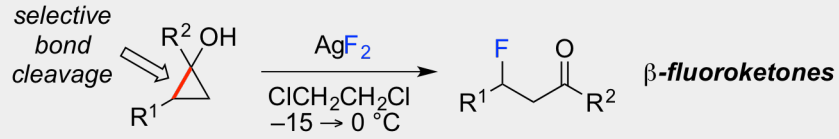

A practical methodology for the synthesis of fluoroketones using commercially available AgF_2 and cyclopropanols is described. The regioselective introduction of a remote C–F bond is enabled through a hypothetical oxidative radical mechanism. This approach provides convenient access to valuable fluorinated ketone building blocks.

Remote Fluorination

*Yuanlin Deng, Nabeelah I. Kauser, Shahidul M. Islam, and Justin T. Mohr**

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Ag(II)-Mediated Synthesis of β-Fluoroketones via Oxidative Cyclopropanol Opening