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Catalytic Enantioselective Protonation of Monofluorinated Silyl Enol Ethers towards Chiral α-Fluoroketones

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ABSTRACT Described herein is an organocatalytic enantioselective protonation of monofluorinated silyl enol ethers, affording an array of optically active α-secondary α-fluoroketones in good to high yields and enantioselectivities, under the catalysis of bifunctional cinchonidine derived squaramide **C4**. It represents a rare example of facile synthesis of enantioenriched α-secondary α-fluoroketones. With D_2O as the deuterium source and MeOD as the solvent, the first highly enantioselective preparation of chiral α-deuterated α-fluoroketones in >92 % deuteration is developed.

KEY WORDS Enantioselective Protonation, Monofluorinated Silyl Enol Ethers, Chiral α-Fluoroketone, Organocatalysis

Introduction

The selective incorporation of a fluorine or fluorinated moiety into organic molecules has been identified as a fruitful tool to improve the pharmacological properties in drug discovery,[1] because the presence of a fluorine moiety often brings about beneficial effects such as the enhancement in bioavailability, lipophilicity, and metabolic stability.[2] Consequently, efficient and selective introduction of fluorine atoms or fluoroalkyl groups is much sought after in medicinal research.[3] Among various fluorinated motifs, optically active α-fluorocarbonyl compounds represent a type of privileged scaffolds, owing to their occurrence in bioactive molecules (fluasterone,[4a] and 12-fluoroforskolin[4b] for example) and chiral catalyst[4c] (Figure 1). In addition, they can serve as versatile fluorinated synthons.[4d]

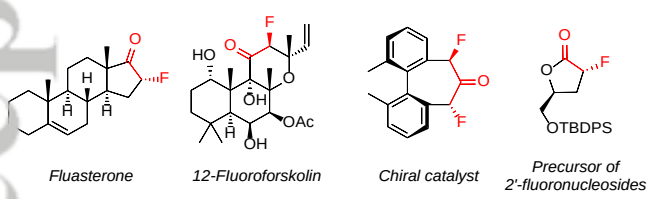

Figure 1 Selected compounds featuring α-fluorocarbonyl unit.

In the past decade, much attention has gone to the catalytic enantioselective synthesis of α-fluorocarbonyl compounds. Some synthetic strategies are developed, including electrophilic fluorination[5a-e], nucleophilic fluorination[5f-g], functionalization of α-fluoroenolate equivalents[5h-l] or other α-fluorinated substrates[5m-n] (Scheme 1A).[3b] However, despite ongoing progress, catalytic asymmetric synthesis of α-secondary α-fluoro carbonyl compounds is largely undeveloped.[6] On the other hand, while enantioselective protonation of prochiral enolate derivatives allows facile synthesis of chiral α-monosubstituted carbonyl compounds,[7] few attention is paid to the application of this strategy to access α-fluoroketones. In 2003, Hénin et al tried a decarboxylative protonation of benzyl 2-fluoro-1-tetralone-2-carboxylate **1a**, with 66% ee obtained.[8a] In 2006, Stoltz et al achieved up to 88% ee in the synthesis (*S*)-2-fluoro-1-tetralone via the decarboxylative protonation.[8b] Later, Levacher and Oudeyer attempted organocatalytic protonation of monofluorinated silyl enol ether (m-FSEE) **2d**, and found chiral amine $(DHQ)_2AQN$ could afford **3d** in 75% ee.[8c,d] Nevertheless, all the three reports only disclosed the synthesis of α-fluoro tetralone **3d**, and the catalytic asymmetric protonation to structurally diverse α-fluoroketones waits for further exploration in terms of enantioselectivity and substrate scope.

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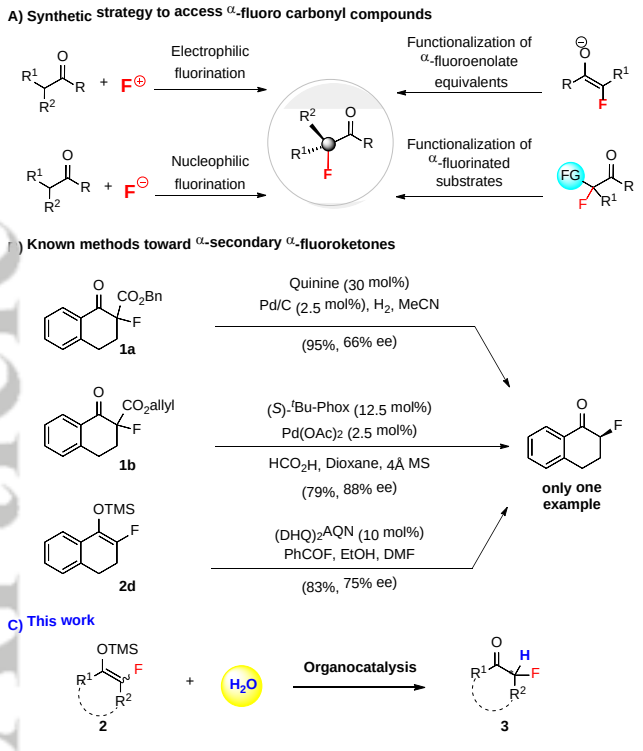
Scheme 1 Known synthetic strategies and this work



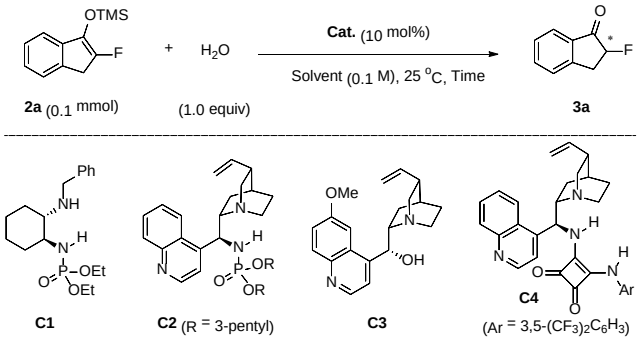
Monofluorinated silyl enol ethers **2**, as readily available α-fluorinated enolate precursors, have received growing attention for the diversity-oriented synthesis of chiral α-fluoroketones.[9] The past decade has witnessed a variety of elegant protocols based on m-FSEEs, including allylation,[10] arylation,[11] aldol,[12] Michael[13] and Mannich reaction,[14] as well as olefination.[15] Since the Paquin group pioneered a Pd-catalyzed enantioselective allylation reaction of m-FSEEs **2** in 2007,[10a] m-FSEEs have found increasing application in asymmetric catalysis. As a continuation in exploring diversity-oriented synthesis using fluorinated silyl enol ethers,[12-16] we have found chiral bifunctional amine catalysts were able to efficiently activate m-FSEEs for the aldol reaction of isatins,[12a] Mannich reaction with cyclic *N*-sulfonyl ketimines,[14a] and Michael addition to isatylidene malononitriles.[13a] Based on these results, we wonder whether it is possible to extend bifunctional amine catalysis to enantioselective protonation of m-FSEEs, providing a facile entry to structurally diverse chiral α-fluoroketones. Herein, we wish to report a cinchona alkaloid derived bifunctional squaramide catalyzed highly enantioselective protonation of m-FSEEs to chiral α-secondary α-fluoroketones.

Results and Discussion

Our study commenced with the investigation of different bifunctional chiral amine catalysts for the enantioselective hydrolysis of indanone derived m-FSEE **2a**. All the reactions were performed in anhydrous acetone at room temperature (Table 1). The use of 10 mol% chiral phosphoramide-secondary amine bifunctional catalyst **C1** that we developed for Michael reaction involving m-FSEEs afforded product **3a** in 90% yield with only 6% ee after 1 day (entry 1). Our phosphoramide-tertiary amine catalyst **C2** exhibited much lower reactivity, but the ee value was improved to 47% (entry 2). Cinchona alkaloid derived bifunctional catalyst **C3** further increased the enantioselectivity to 53% (entry 3). To our pleasure, cinchonidine derived squaramide catalyst **C4** enabled the reaction to furnish **3a** in up to 76% ee with 69% yield, albeit with prolong reaction time (entry 4). Then we examined solvent effects to improve the reactivity and enantioselectivity (entries 5-12). While the use of toluene, CH_2Cl_2, THF, EtOAc, and MeCN all led to low ee values, alcoholic solvents proved to be capable of enhancing the enantioselectivity, and trifluoroethanol (TFE) turned out to be the best in terms of enantioselectivity and reactivity, as the reaction could finish within 1 day to afford the desired product **3a** in up to 77% yield and 86% ee (entry 12). Considering that alcoholic solvents might act as the proton source, so we conducted the reaction in the absence of H_2O. However, a diminished 75% ee for product **3a** was detected, indicating the indispensable role of H_2O in achieving high enantioselectivity (entry 13 *vs* 12).[17] Besides, lowering the reaction temperature to 0 °C, the enantioselectivity of **3a** was increased to 89% (entry 14). Furthermore, decreasing the usage of catalyst **C4** from 10 mol% to 5 mol% furnished the α-fluoroindanone **3a** in 81% yield and 90% ee (entry 15).

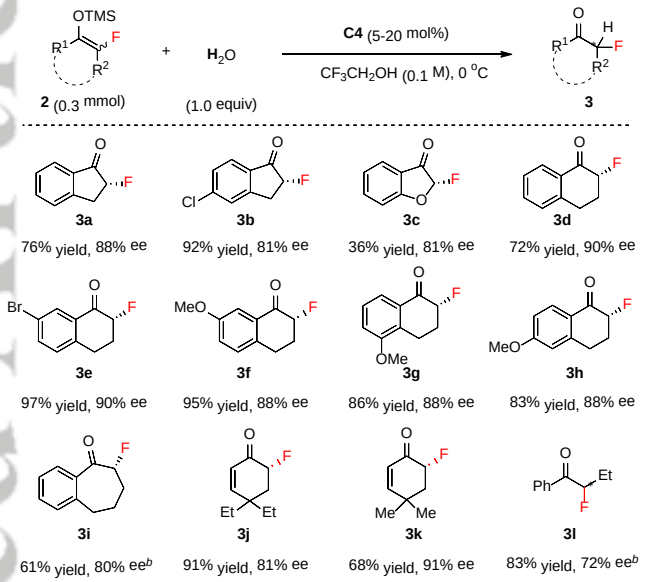
Based on these optimizations, we determined to run the catalytic enantioselective protonation of m-FSEEs in CF_3CH_2OH (0.1 M) at 0 °C, in the presence of 5 mol% catalyst **C4**. We studied the substrate scope with respect to differently substituted monofluorinated silyl enol ethers, and all the reactions were run on a 0.3 mmol scale. As shown in Table 2, five-membered cyclic monofluorinated silyl enol ethers were first examined. It was found that α-fluoroindanones derived m-FSEEs **2a** and **2b** worked well to afford the corresponding product **3a** and **3b** in 76% and 92% yield, 88% and 81% ee, respectively. The α-fluoro benzofuranone **3c** could be obtained in 81% ee, albeit with 36% yield, due to the formation of side aldol byproduct.[18]

Table 1 Condition optimization [a]



We next turned our attention to investigate the performance of six-membered cyclic m-FSEEs. Differently substituted α-fluorotetralone derived silyl enol ethers all proceeded well to produce the target products **3d**-**h** with 72-97% yields and 88-90% ee. However, the use of 10 mol% or 20 mol% catalyst was required to ensure satisfactory yields. Additionally, seven-membered α-fluoro 1-benzosuberone **3i** was also obtained in 61% yield with 80% ee. And optically enriched 6-fluoro cyclohexenones **3j-k** could also be produced with 68-91% yield and 81-91% ee values, from the simply cyclohexenone derived m-FSEEs. Notably, 2-fluorobutyrophenone derived acyclic fluorinated silyl enol ether **2l** (*E*/*Z* >20:1) also turned out to be a viable substrate, providing the desired optically active acyclic α-fluoroketones **3l** in 83% yield and 72% ee.[19]

Table 2 Substrate scope [a]



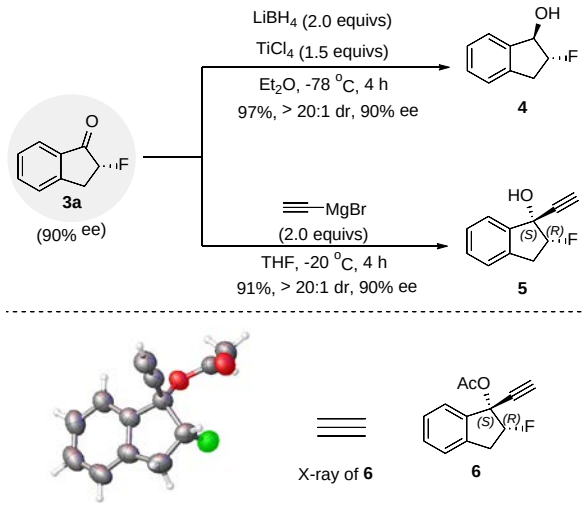
[a] Unless otherwise noted, all reactions were run on a 0.3 mmol scale in CF_3CH_2OH (0.1 M) at 0 °C; 5 mol% **C4** for **3a**-**c**, 10 mol% **C4** for **3i**, 20 mol% **C4** for **3d**-**h**, **3j**-**n**; [b] At 25 °C.

The synthetic utility of this method was illustrated by the synthesis of optically active β-fluoroalcohols (Scheme 2). For example, the product **3a** could be readily reduced by $LiBH_4$ to produce *anti*-β-fluoroalcohol **4** in 97% yield, >20:1 dr with 90% ee, in the presence of $TiCl_4$.[20] Treatment of **3a** with ethynylmagnesium bromide in THF at -20 °C delivered β-fluoro propargyl alcohol **5** in 91% yield and >20:1 dr, without any loss of ee value. The relative and absolute configuration of **5** was assigned to be (1*S*, 2*R*) by single crystal X-ray analysis of its *O*-Ac protected derivative **6**.[21] The absolute configuration of the product **3a**-**c** was tentatively assigned to be *R* based on the absolute configuration of **6**. And absolute configuration of products **3d**-**k** was determined by comparing optical rotation values with the literature data.[22]

Entry	Cat.	Solvent	H_2O	Time (d)	Yield (%)	Ee (%)
1	**C1**	Acetone	1.0	1	90	6
2	**C2**	Acetone	1.0	5	88	47
3	**C3**	Acetone	1.0	5	97	53[b]
4	**C4**	Acetone	1.0	7	69	76
5	**C4**	Toluene	1.0	7	31	47
6	**C4**	CH_2Cl_2	1.0	7	61	64
7	**C4**	THF	1.0	7	37	49
8	**C4**	EtOAc	1.0	7	49	64
9	**C4**	MeCN	1.0	7	49	67
10	**C4**	MeOH	1.0	3	82	87
11	**C4**	^{i}PrOH	1.0	7	47	79
12	**C4**	CF_3CH_2OH	1.0	1	77	86
13	**C4**	CF_3CH_2OH	0	1	87	75
14[c]	**C4**	CF_3CH_2OH	1.0	4	83	89
15[c,d]	**C4**	CF_3CH_2OH	1.0	6	81	90

[a] Unless noted, all reactions were run on a 0.1 mmol scale at room temperature, with 10 mol% chiral catalyst ; isolated yield was reported; ee was determined by chiral HPLC analysis. [b] Opposite enantiomer. [c] At 0 °C. [d] 5 mol% **C4** used.

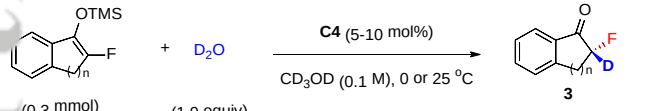
Scheme 2 Synthetic elaborations.



Given the replacement of hydrogen with deuterium in the bioactive molecules emerges as a promising strategy to improve

the pharmacological properties in medicinal research. Since FDA approved the first deuterated drug, Austedo, in 2017,[23] many deuterated compounds have become clinical drugs, such as DRX-065[24] and DRX-164.[25] In this light, the development of efficient synthetic approaches for the preparation of deuterated compounds is very much in demand. Accordingly, we tried to incorporate deuterium into α-fluoroketone to access deuterated α-fluoroketones[26] a type of molecules of important potential value in drug discovery. To our delight, with D_2O as the deuterium source, the reaction of α-fluoro indanone or tetralone derived m-FSEEs proceeded smoothly under the catalysis of **C4** in MeOD, delivering α-deuterated α-fluoroindanone **3m** and α-fluorotetralone **3n** in 90% ee, 98% yield with 95% D, and 90% ee, 57% yield with 92% D, respectively (Scheme 3). Notably, this represents the first highly enantioselective catalytic synthesis of enantioenriched α-deuterated α-fluoroketones.

Scheme 3 Synthesis of chiral α-deuterated α-fluoroketones.



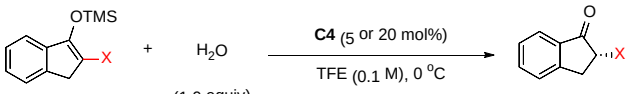
(0.3 mmol)
2a (n = 1)
2d (n = 2)

(1.0 equiv)

n = 1: 98% yield, 90% ee, 95% D (**3m**)
n = 2: 57% yield, 90% ee, 92% D (**3n**)

Interestingly, obvious fluorine effect was observed in the current enantioselective protonation reaction, as the use of chlorinated silyl enol ether **2o** only produced the corresponding product **3o** in 0% ee and 81% yield, in sharp contrast to 88% ee with 76% yield for **3a**. Although the origin of this strong fluorine effect is not clear by now, we speculated that it might be related to the possible C-F···H-X interactions in the transition state, which have been found to strongly influence of organic reaction by us and other groups.[27] Based on this speculation, together with our results in the activation of FSEEs by amine catalysis for reaction development,[12a,13a,14a,16ab] we proposed a transition state in which the tertiary amine part of catalyst **C4** activated silyl enol ethers **2** via the n-σ* interaction between the silicon and nitrogen atom, whilst the squaramide moiety interacted with proton source. The C-F···H-X interaction between the water bonded to the two N-H bonds of squaramide[28] and the C-F bond of the m-FSEE activated by tertiary amine moiety of **C4** stabilized a favorable transition, allowing the proton to attack the *Si* face. Without such a subtle interaction, it is difficult to realize face discrimination to achieve high to excellent enantioselectivity, as supported by the result obtained by using chlorinated silyl ether **2o**. Subsequently, the silyl enol ethers attached the proton to provide the optically pure α-fluoroketones.

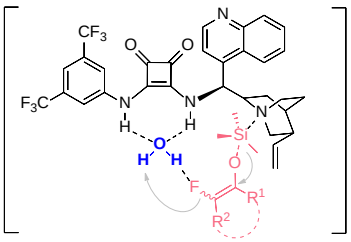
Scheme 4 Fluorine effects and proposed transition state.



2a: X = F
2o: X = Cl

X = F, 5 mol% **C4**: 76% yield, 88% ee (**3a**)
X = Cl, 20 mol% **C4**: 81% yield, 0% ee (**3o**)

Proposed transition state



Conclusions

In conclusion, we have developed a highly enantioselective protonation of m-FSEEs by using a bifunctional cinchonidine derived squaramide **C4** and water as the proton source. This provides a facile synthesis of structurally diverse enantioenriched α-secondary α-fluoroketones. The resulting chiral α-fluoroketones can be readily elaborated into the corresponding β-fluoroalcohols without the loss of enantioselectivity. Notably, chiral α-deuterated α-fluoroketones of important potential applications in medicinal research, could be achieved with excellent enantioselectivity by this protocol. The study of the detailed reaction mechanism and the extension of scope toward other diversified chiral α-fluorinated ketones are now ongoing in our laboratory.

Experimental

General information

Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. Infrared (IR) spectra were obtained using SHIMADZU TRT racer-100. The $[\alpha]_D$ was recorded using PolAAr 3005 High Accuracy Polarimeter and Anton Paar MCP 5500. ^1H, ^{19}F, ^{13}C NMR spectra were obtained using a Bruker DPX-400 and 300 MHz spectrometers. Chemical shifts are reported in ppm from $CDCl_3$ with the solvent resonance or $(CH_3)_4Si$ as the internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad. Coupling constants (*J*) are reported in Hertz. All reactions were run in air except noted. Anhydrous THF and toluene were prepared by distillation over sodium-benzophenone ketyl prior to use. Anhydrous CH_2Cl_2 and CH_3CN were prepared by first distillation over P_2O_5 and then from CaH_2. Anhydrous EtOAc and acetone was prepared by first distillation over activated $CaSO_4$ and then stored in 5Å molecular sieves. The

monofluorinated enol silyl ethers **2a-2c**, **2m** and **2p** were prepared according to literature reports,[14a,15a] **2d-2l** were prepared according to literature reports.[10a,11b] PE and TFE are the abbreviation of petroleum ether and 2,2,2-trifluoroethanol, respectively.

General procedure

To a 5.0 mL vial were added chiral squaramides **C4** (5-20 mol%) and monofluorinated silyl enol ethers **2** (0.3 mmol, the structure and numbering of **2** was shown in the supporting information), followed by the addition of TFE (3.0 mL). The resulting mixture was stirred at the indicated temperature (0 or 25 °C) for about 30 min before distilled water H_2O (0.30 mmol, 1.0 equiv) was added. After full conversion of **2** by TLC analysis, the reaction mixture was directly subjected to flash column chromatography to afford the desired chiral α-fluoroketones **3**, using the indicated eluent. (Note: the reaction for synthesis of deuterated products **3m-n** was performed under N_2 atmosphere)

(*R*)-2-Fluoro-2,3-dihydro-1*H*-inden-1-one (**3a**): Prepared by the general procedure from **2a** (65.4 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (9.0 mg, 0.015 mmol, 5 mol%), stirred at 0 °C for 7 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3a** in 76% yield as white solid.[29] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 9.57 min, t_r (major) = 11.48 min) gave the isomeric composition of the product: 87% ee, $[\alpha]^{27}_D$ = -3.0 (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.70-7.65 (m, 1H), 7.48-7.41 (m, 2H), 5.27 (ddd, *J* = 51.0 Hz, *J* = 7.8 Hz, *J* = 4.5 Hz, 1H), 3.69-3.58 (m, 1H), 3.31-3.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.96 (d, *J* = 15.0 Hz, 1C), 149.69 (d, *J* = 5.0 Hz, 1C), 136.39, 133.91, 128.46, 126.84 (d, *J* = 2.0 Hz, 1C), 124.75, 90.51 (dd, *J* = 186.0 Hz, *J* = 3.0 Hz, 1C), 33.46 (d, *J* = 21.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -193.98 (s, 1F).

(*R*)-5-Chloro-2-fluoro-2,3-dihydro-1*H*-inden-1-one (**3b**): Prepared by the general procedure from **2b** (76.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (9.0 mg, 0.015 mmol, 5 mol%), stirred at 0 °C for 7 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3b** in 81% yield as white solid.[30] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 11.53 min, t_r (major) = 15.79 min) gave the isomeric composition of the product: 80% ee, $[\alpha]^{27}_D$ = -2.7 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.46-7.39 (m, 2H), 5.26 (ddd, *J* = 51.0 Hz, *J* = 7.8 Hz, *J* = 4.2 Hz, 1H), 3.66-3.55 (m, 1H), 3.28-3.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.40 (d, *J* = 15.0 Hz, 1C), 151.16 (d, *J* = 6.0 Hz, 1C), 142.94, 132.34, 129.32, 127.06, 125.93 (d, *J* = 1.0 Hz, 1C), 90.18 (d, *J* = 193.0 Hz, 1C), 33.22 (d, *J* = 22.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$): -193.01~-193.22 (m, 1F).

(*S*)-2-Fluorobenzofuran-3(2*H*)-one (**3c**): Prepared by the general procedure from **2c** (67.2 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (9.0 mg, 0.015 mmol, 5 mol%), stirred at 0 °C for 2 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3c** in 36% yield as yellow oil. HPLC analysis (Chiralpak OJ-H, ^{i}PrOH/hexane = 3/97, 1.0 mL/min, 205 nm; t_r (minor) = 14.35 min, t_r (major) = 16.56 min) gave the isomeric composition of the product: 84% ee, $[\alpha]^{27}_D$ = -4.3 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.67 (m, 2H), 7.20-7.14 (m, 2H), 5.79 (d, *J* = 58.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.99 (d, *J* = 14.0 Hz, 1C), 171.41 (d, *J* = 3.0 Hz, 1C), 139.47, 124.59 (d, *J* = 157.0 Hz, 1C), 118.31, 113.49, 104.23 (d, *J* = 4.0 Hz, 1C), 101.87 (d, *J* = 3.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -139.84 (s, 1F). GC-MS: 152 (M^+, 94), 151 (7), 124 (17), 104 (69), 96 (11), 76 (100), 63 (8), 50 (35); HRMS (EI): Exact mass calcd for $C_8H_5FO_2$ $[M]^+$: 152.0274, Found: 152.0270.

(2′*S*)-2,2'-Difluoro-3'-hydroxy-2',3'-dihydro-[2,3'-bibenzofuran] -3(2*H*)-one (**A**): during the protonation reaction of monofluorinated silyl enol ether **2c**, a byproduct **A** generated from the aldol reaction of **2c** with product **3c** was observed, and isolated (PE/CH_2Cl_2 = 10:1) as a white solid in 54% yield, m. p. 116-118 °C. HPLC analysis revealed that the dr vlues is 1.5:1, HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; major diastereomer: t_r (minor) = 12.55 min, t_r (major) = 17.97 min, minor diastereomer: t_r (major) = 15.10 min, t_r (minor) = 20.54 min) gave the isomeric composition of the major diastereomer: 81% ee and the minor diastereomer: 83% ee, $[\alpha]^{27}_D$ = -108.1 (c = 1.0, $CHCl_3$); ^{1}H NMR for the major diastereomer (400 MHz, $CDCl_3$): δ 7.76-7.69 (m, 2H), 7.65 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.41 (td, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.23-7.20 (m, 2H), 7.14 (td, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H), 7.02-7.00 (m, 1H), 6.93 (dd, *J* = 62.4 Hz, *J* = 1.6 Hz, 1H), 3.03 (br, 1H); ^{13}C NMR for the major diastereomer (100 MHz, $CDCl_3$): δ 192.85 (d, *J* = 18.0 Hz, 1C), 170.96 (d, *J* = 2.0 Hz, 1C), 158.32, 139.51, 132.27, 126.76, 125.47, 123.98, 123.22, 122.56, 119.11, 113.29, 111.15, 108.49 (d, *J* = 236.0 Hz, 1C), 107.50 (dd, *J* = 239.0 Hz, *J* = 6.0 Hz, 1C), 82.39 (dd, *J* = 35.0 Hz, *J* = 9.0 Hz, 1C); ^{19}F NMR for the major diastereomer (376 MHz, $CDCl_3$): -127.99 (s, 1F), -137.99 (s, 1F). IR (neat): 3447, 1715, 1617, 1473, 1457, 1091, 753, 505; HRMS (ESI): Exact mass calcd for $C_{16}H_{10}F_2NaO_4$ $[M+Na]^+$: 327.0439, Found: 327.0442.

(*R*)-2-Fluoro-3,4-dihydronaphthalen-1(2*H*)-one (**3d**): Prepared by the general procedure from **2d** (70.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 4 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3d** in 72% yield as white solid.[29] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 9.20 min, t_r (major) = 12.31 min) gave the isomeric composition of the product: 91% ee, $[\alpha]^{27}_D$ = +53.1 (c = 1.00, $CHCl_3$) or $[\alpha]^{20}_D$ = +40.4 (c = 1.00, *p*-dioxane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08-8.06 (m, 1H), 7.55-7.50 (m, 1H), 7.38-7.33 (m, 1H), 7.28-7.26 (m, 1H), 5.15 (ddd, *J* = 48.0 Hz, *J* = 12.6 Hz, *J* = 5.1 Hz, 1H), 3.16-3.11 (m, 2H), 2.61-2.53 (m, 1H), 2.40-2.32 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.36 (d, *J* = 15.0 Hz, 1C), 143.03, 134.19, 131.23, 128.67, 127.83 (d, *J* = 1.0 Hz, 1C), 127.15, 91.21 (d, *J* = 187.0 Hz, 1C), 30.14 (d, *J* = 19.0 Hz, 1C), 27.01 (d, *J* = 11.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$): -190.33~ -190.36 (m, 1F). Its absolute configuration was determined to be *R* by comparing the optical rotation value with the literature data[8a]: $[\alpha]^{25}_D$ = +64.9 (c = 0.43, *p*-dioxane) for (*R*)-configurated **3d** in the reported literature. Based on this, the absolute configuration of products **3e-k** were tentatively deduced by analogy.

(*R*)-7-Bromo-2-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (**3e**): Prepared by the general procedure from **2e** (94.2 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 6 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3e** in 97% yield as yellow solid.[31] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 10.24 min, t_r (major) = 15.39 min) gave the isomeric composition of the product: 90% ee, $[\alpha]^{26}_D$ = +28.6 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.8 Hz, 1H), 7.64-7.61 (m, 1H), 7.16 (d, *J* = 11.2 Hz, 1H), 5.13 (ddd, *J* = 47.7 Hz, *J* = 12.6 Hz, *J* = 5.1 Hz, 1H), 3.10-3.05 (m, 2H), 2.58-2.53 (m, 1H), 2.41-2.31 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.09 (d, *J* = 15.0 Hz, 1C), 141.78, 136.98 (d, *J* = 7.0 Hz, 1C), 132.73, 130.54, 130.45, 121.20, 90.88 (d, *J* = 184.0 Hz, 1C), 29.88 (d, *J* = 19.0 Hz, 1C), 26.55 (d, *J* = 5.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$): -190.75~ -190.79 (m, 1F).

(*R*)-2-Fluoro-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3f**): Prepared by the general procedure from **2f** (79.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 6 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3f** in 95% yield as white solid.[32] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 10.25 min, t_r (major) = 13.92 min) gave the isomeric composition of the product: 88% ee, $[\alpha]^{20}_D$ = +78.4 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 2.4 Hz, 1H), 7.18-7.16 (m, 1H), 7.10-7.08 (m, 1H), 5.12 (ddd, *J* = 48.0 Hz, *J* = 12.8 Hz, *J* = 5.2 Hz, 1H), 3.83 (d, *J* = 0.8 Hz, 3H), 3.07-3.04 (m, 2H), 2.58-2.52 (m, 1H), 2.36-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.35 (d, *J* = 15.0 Hz, 1C), 158.67, 135.68, 132.06, 129.94, 122.72, 109.37, 91.33 (d, *J* = 186.0 Hz, 1C), 55.59, 30.37 (d, *J* = 19.0 Hz, 1C), 26.26 (d, *J* = 12.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -190.37 (s, 1F).

(*R*)-2-Fluoro-5-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3g**): Prepared by the general procedure from **2g** (79.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 7 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3g** in 86% yield as white solid.[33] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 10.34 min, t_r (major) = 12.75 min) gave the isomeric composition of the product: 88% ee, $[\alpha]^{20}_D$ = +60.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.12 (ddd, *J* = 48.4 Hz, *J* = 13.2 Hz, *J* = 5.2 Hz, 1H), 3.87 (s, 3H), 3.28-3.22 (m, 1H), 2.84-2.75 (m, 1 H), 2.59-2.53 (m, 1 H), 2.29-2.23 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.75 (d, *J* = 15.0 Hz, 1C), 156.70, 132.26, 131.96 (d, *J* = 2.0 Hz, 1C), 127.79, 119.07 (d, *J* = 2.0 Hz, 1C), 114.89, 91.12 (d, *J* = 187.0 Hz, 1C), 55.73 (d, *J* = 2.0 Hz, 1C), 29.23 (d, *J* = 18.0 Hz, 1C), 21.02 (d, *J* = 11.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -191.00 (s, 1F).

(*R*)-2-Fluoro-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**3h**): Prepared by the general procedure from **2h** (79.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (18.0 mg, 0.03 mmol, 10 mol%), stirred at 0 °C for 5 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3h** in 83% yield as white solid.[11b] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 21.53 min, t_r (major) = 33.65 min) gave the isomeric composition of the product: 88% ee, $[\alpha]^{26}_D$ = +29.0 (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.7 Hz, 1H), 6.89-6.85 (m, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 5.09 (ddd, *J* = 48.0 Hz, *J* = 12.3 Hz, *J* = 5.1 Hz, 1H), 3.87 (s, 3H), 3.10-3.07 (m, 2H), 2.59-2.50 (m, 1H), 2.41-2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.94 (d, *J* = 14.0 Hz, 1C), 164.25, 145.59 (d, *J* = 1.0 Hz, 1C), 130.31 (d, *J* = 2.0 Hz, 1C), 124.67, 113.82, 112.51, 90.94 (d, *J* = 185.0 Hz, 1C), 55.55 (d, *J* = 4.0 Hz, 1C), 30.13 (d, *J* = 19.0 Hz, 1C), 27.23 (d, *J* = 11.0 Hz, 1C); ^{19}F NMR (282 MHz, $CDCl_3$): -190.33~ -190.40 (m, 1F).

(*R*)-6-Fluoro-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one (**3i**): Prepared by the general procedure from **2i** (75.0 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C to rt for 10 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3i** in 61% yield as yellow oil.[33] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (minor) = 7.20 min, t_r (major) = 8.01 min) gave the isomeric composition of the product: 80% ee, $[\alpha]^{20}_D$ = -5.1 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.45-7.41 (m, 1H), 7.34-7.30 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 5.24 (ddd, *J* = 56.4 Hz, *J* = 12.8 Hz, *J* = 7.6 Hz, 1H), 3.02-2.94 (m, 2H), 2.38-2.30 (m, 1H), 2.15-1.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.31 (d, *J* = 19.0 Hz, 1C), 141.89, 135.93, 132.38, 130.17, 129.26 (d, *J* = 1.0 Hz, 1C), 126.79, 94.81 (d, *J* = 183.0 Hz, 1C), 34.30, 30.61 (d, *J* = 21.0 Hz, 1C), 23.00 (d, *J* = 8.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -182.63 (s, 1F).

(*R*)-4,4-Diethyl-6-fluorocyclohex-2-en-1-one (**3j**): Prepared by the general procedure from **2j** (72.6 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 7 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3j** in 91% yield as yellow solid. HPLC analysis (Chiralpak OD-H, ^{i}PrOH/hexane = 3/97, 1.0 mL/min, 205 nm; t_r (minor) = 10.85 min, t_r (major) = 11.58 min) gave the isomeric composition of the product: 81% ee, $[\alpha]^{20}_D$ = +50.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (d, *J* = 10.0 Hz, 1H), 5.94 (dd, *J* = 10.4 Hz, *J* = 4.4 Hz, 1H), 5.08 (ddd, *J* = 48.4 Hz, *J* = 13.2 Hz, *J* = 6.0 Hz, 1H), 2.24-2.18 (m, 1H), 2.06-1.97 (m, 1H), 1.66-1.46 (m, 4H), 0.95 (t, *J* = 7.6 Hz, 3H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.71 (d, *J* = 14.0 Hz, 1C), 158.69, 126.08, 88.10 (d, *J* = 185.0 Hz, 1C), 41.79 (d, *J* = 10.0 Hz, 1C), 36.69 (d, *J* = 17.0 Hz, 1C), 31.48, 30.04, 8.82, 7.95; ^{19}F NMR (376 MHz, $CDCl_3$): -194.38 (s, 1F); IR (neat): 3302, 2970, 2854, 2168, 1728, 1493, 1463, 752; HRMS (ESI): Exact mass calcd for $C_{10}H_{15}FNaO$ $[M+Na]^+$: 193.0999, Found: 193.0999.

(*R*)-6-Fluoro-4,4-dimethylcyclohex-2-en-1-one (**3k**): Prepared by the general procedure from **2k** (64.2 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 7 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3k** in 68% yield as white solid.[10a] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 15/85, 1.0 mL/min, 205 nm; t_r (major) = 11.60 min, t_r (minor) = 13.52 min) gave the isomeric composition of the product: 91% ee, $[\alpha]^{20}_D$ = +1.7 (c = 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.64 (d, *J* = 10.0 Hz, 1H), 5.84-5.80 (m, 1H), 5.04 (ddd, *J* = 47.6 Hz, *J* = 13.2 Hz,

J = 5.6 Hz, 1H), 2.25-2.19 (m, 1H), 2.06-1.98 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.40 (d, *J* = 14.0 Hz, 1C), 159.71, 124.36, 87.98 (d, *J* = 185.0 Hz, 1C), 42.26 (d, *J* = 16.0 Hz, 1C), 35.47 (d, *J* = 11.0 Hz, 1C), 30.47, 26.11; ^{19}F NMR (376 MHz, $CDCl_3$): -195.74 (s, 1F).

2-Fluoro-1-phenylbutan-1-one (**3l**): Prepared by the general procedure from **2l** (71.4 mg, 0.3 mmol, *E*/*Z* > 20:1)[34] and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 25 °C for 5 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3l** in 83% yield as yellow oil.[35] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 20/80, 1.0 mL/min, 205 nm; t_r (minor) = 4.52 min, t_r (major) = 5.70 min) gave the isomeric composition of the product: 72% ee, $[\alpha]^{20}_D$ = -7.5 (c = 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.6 Hz, 2H), 7.62-7.58 (m, 1H), 7.50-7.46 (m, 2H), 5.52 (ddd, *J* = 49.2 Hz, *J* = 7.6 Hz, *J* = 4.4 Hz, 1H), 2.11-1.93 (m, 2H), 1.08 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.87 (d, *J* = 19.0 Hz, 1C), 134.43, 133.76, 128.86 (d, *J* = 4.0 Hz, 1C), 128.75, 94.80 (d, *J* = 182.0 Hz, 1C), 26.13 (d, *J* = 22.0 Hz, 1C), 9.08; ^{19}F NMR (376 MHz, $CDCl_3$): -191.12 (s, 1F).

(*R*)-2-Fluoro-2,3-dihydro-1*H*-inden-1-one-2-*d* (**3m**): Prepared by the general procedure from **2a** (65.4 mg, 0.3 mmol) and D_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (9.0 mg, 0.015 mmol, 5 mol%) in MeOD (3 mL), stirred at 25 °C for 1.5 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3m** in 98% yield with 95% D at α-atom as a white solid (m.p. 50-51 °C). HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 10/90, 1.0 mL/min, 230 nm; t_r (minor) = 11.04 min, t_r (major) =13.41 min) gave the isomeric composition of the product: 90% ee, $[\alpha]^{20}_D$ = -8.6 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.68-7.64 (m, 1H), 7.47-7.41 (m, 2H), 5.26 (ddd, *J* = 50.8 Hz, *J* = 7.6 Hz, *J* = 4.4 Hz, 0.06H), 3.62 (dd, *J* = 17.2 Hz, *J* = 7.2 Hz, 1H), 3.22 (dd, *J* = 23.2 Hz, *J* =17.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.95 (d, *J* = 15.0 Hz, 1C), 149.74 (d, *J* = 5.0 Hz, 1C), 136.38, 133.95, 128.45, 126.84 (d, *J* = 2.0 Hz, 1C), 124.76 (d, *J* = 2.0 Hz, 1C), 90.29-88.94 (m, 1C), 33.36 (d, *J* = 21.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -194.58 (t, 1F). GC-MS: 152 (M^+, 10), 151 (100), 123 (60), 102 (23), 97 (13), 76 (31), 63 (6), 50 (12); HRMS (EI): Exact mass calcd for C_9H_6DFO $[M]^+$: 151.0544, Found: 151.0546.

(*R*)-2-Fluoro-3,4-dihydronaphthalen-1(2*H*)-one-2-*d* (**3n**): Prepared by the general procedure from **2d** (70.8 mg, 0.3 mmol) and D_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (9.0 mg, 0.015 mmol, 10 mol%) in MeOD (3 mL), stirred at 0 °C for 8 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3n** in 57% yield with 92% D at α-atom as brown oil. HPLC analysis (Chiralpak AD-H, ^{i}PrOH/hexane = 5/95, 1.0 mL/min, 205 nm; t_r (minor) = 9.28 min, t_r (major) = 9.84 min) gave the isomeric composition of the product: 90% ee, $[\alpha]^{20}_D$ = +55.5 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 5.16 (ddd, *J* = 48.4 Hz, *J* = 12.8 Hz, *J* = 5.2 Hz, 0.11H), 3.15-3.12 (m, 2H), 2.61-2.54 (m, 1H), 2.40-2.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.39 (d, *J* = 15.0 Hz, 1C), 143.05, 134.19, 131.25, 128.67, 127.83 (d, *J* = 2.0 Hz, 1C), 127.15, 91.93-89.62 (m, 1C), 30.03 (d, *J* = 19.0 Hz, 1C), 26.97 (d, *J* = 11.0 Hz, 1C); ^{19}F NMR (376 MHz, $CDCl_3$): -191.10 (t, 1F). GC-MS: 165 (M^+, 89), 134 (8), 118 (100), 109 (3), 90 (98), 77 (5), 63 (22), 51 (11); HRMS (EI): Exact mass calcd for $C_{10}H_8DFO$ $[M]^+$: 165.0700, Found: 165.0699.

2-Chloro-2,3-dihydro-1*H*-inden-1-one (**3o**): Prepared by the general procedure from **2o** (71.4 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 3 d and column chromatography (PE/CH_2Cl_2 = 20:1) afforded the product **3o** in 81% yield as yellow oil.[36] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 20/80, 1.0 mL/min, 205 nm; t_r = 8.51 min, t_r = 12.30 min) gave the isomeric composition of the product: 0% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.8 Hz, 1H), 7.68-7.63 (m, 1H), 7.46-7.39 (m, 2H), 4.55 (dd, *J* = 7.8 Hz, *J* = 4.2 Hz, 1H), 3.81-3.73 (m, 1H), 3.31-3.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.27, 150.79, 136.11, 133.82, 128.35, 126.44, 124.99, 55.76, 37.55.

2-(Trifluoromethyl)-3,4-dihydronaphthalen-1(2*H*)-one (**3p**): Prepared by the general procedure from **2p** (85.8 mg, 0.3 mmol) and H_2O (5.5 uL, 0.3 mmol, 1.0 equiv) with **C4** (36.0 mg, 0.06 mmol, 20 mol%), stirred at 0 °C for 3 d and column chromatography (PE/CH_2Cl_2 = 20:1 to 10:1) afforded the product **3p** in 99% yield as yellow oil.[37] HPLC analysis (Chiralpak AS-H, ^{i}PrOH/hexane = 20/80, 1.0 mL/min, 254 nm; t_r = 5.19 min, t_r = 6.70 min) gave the isomeric composition of the product: 0% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.2 Hz, 1H), 3.32-3.22 (m, 1H), 3.14-3.03 (m, 2H), 2.53-2.47 (m, 1H), 2.32-2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.23, 143.11, 134.20, 131.94, 128.80, 127.83, 127.10, 125.11 (q, *J* = 278.0 Hz, 1C), 50.90 (q, *J* = 26.0 Hz, 1C), 27.53, 23.44; ^{19}F NMR (376 MHz, $CDCl_3$): -67.54 (s, 1F).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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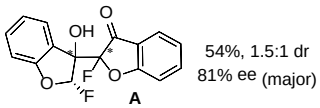
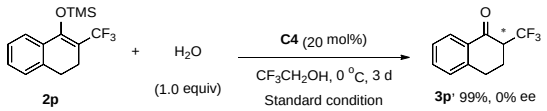
[17] Water was identified to be best proton source, because several other proton sources all gave inferior outcomes in CF_3CH_2OH under other same condition. Typical results for the investigation of proton sources as illustrated below: H_2O (89% ee); PhOH (72% ee); citric acid (9% ee); $PhCO_2H$ (3% ee); AcOH (14% ee).

[18] Along with the formation of product **3c**, an aldol reaction of silyl enol ether **2c** with product **3c**, would be take place in this case, which afforded a byproduct **A** with 54% yield, 1.5:1 dr and 81% ee (major).



[19] We would like to thank one reviewer for suggesting us to test the performance of substrates bearing α-CF_3 substitution. However, when α-trifluoromethyl substituted enol silyl ether **2p** was prepared and subjected to the standard condition, we found to our regret that only racemic desired product **3p** was obtained, as shown below.



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[21] Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC: 1904673).

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Entry for the Table of Contents

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Catalytic Enantioselective Protonation of Monofluorinated Silyl Enol Ethers toward Chiral α-Fluoroketones

Lui Liao,[a] Xiao-Si Hu,[a] Ren-Yi Zhu,[a] Ruo-Han Rao,[b] Jin-Sheng Yu,*[a] Feng Zhou,[a] and Jian Zhou*[a, c]

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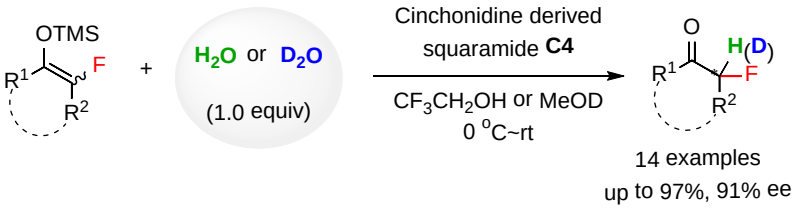

We report a highly organocatalytic enantioselective protonation of monofluorinated silyl enol ethers with water as proton source, which represents a rare example of facile synthesis of optically active α-secondary α-fluoroketones. Moreover, with D_2O as the deuterium source and MeOD as the solvent, the first highly enantioselective catalytic synthesis of enantioenriched α-deuterated α-fluoroketones is developed.

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