A Facile Synthesis of α-Fluoro Ketones Catalyzed by $[Cp^*IrCl_2]_2$

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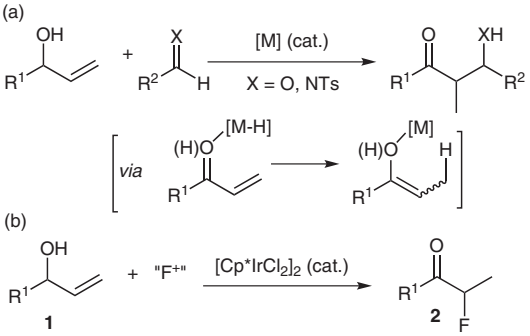
Abstract: Allylic alcohols are isomerized into enolates (enols) by $[Cp^*IrCl_2]_2$. The enolates react with Selectfluor present in the reaction media. This method produces α-fluoro ketones as single constitutional isomers in high yields.

Key words: iridium, fluorine, isomerization, alcohols, fluoro ketones

Generation of enolates from noncarbonyl precursors is an attractive strategy that overcomes some of the limitations of the classical methods. One of these advantages is that enolates can be formed in a regiocontrolled manner. For example, enones can be transformed into enolates by reduction with lithium in liquid ammonia.[1] During the last decade, transition-metal complexes have been used to promote enolate formation from enones or allylic alcohols. The enolates generated under such catalytic conditions can react with electrophiles present in the reaction mixture (e.g., aldehydes).[2] Furthermore, since the reactions are run under neutral conditions, base-sensitive electrophiles can be present from the reaction outset. In the case of enones, reductants such as hydrogen[3] or silanes[4,5] are needed, whereas when allylic alcohols are used, the enolate may be formed through an internal oxidation/reduction sequence (Scheme 1a).[6] Several research groups,[7–9] including our own,[10] have reported catalytic systems able to combine allylic alcohol isomerizations with carbon–carbon bond-forming reactions using electrophiles such as aldehydes and imines (Scheme 1a). Most of these systems use complexes of ruthenium, rhodium, iron, or nickel as catalysts.

The development of new methods to synthesize fluorinated compounds under mild reaction conditions is a highly desirable goal. A high percentage of the drugs produced by pharmaceutical industries contain fluorine atoms. The presence of fluorine can improve the biological activity and influence the pharmacokinetics of certain drugs.[11] In the last few years, transition-metal-catalyzed electrophilic fluorination has been used as an efficient tool to prepare a variety of fluorinated aromatic[12] and aliphatic[13,14] compounds. Fluorination of carbonyls has been extensively developed,[15] including asymmetric fluorinations of β-keto esters using chiral transition-metal complexes of titanium, ruthenium, and palladium, among other metals.[13] However, there are very few reports on the regioselective synthesis of α-fluoro ketones containing similar substituents at both sides of the carbonyl moiety.[16]



Scheme 1 Transition-metal-catalyzed regiospecific synthesis of (a) aldols and Mannich type products, and (b) α-fluoro ketones from allylic alcohols

Very recently, we have reported the synthesis of α-fluoro ketones from allylic alcohols (Scheme 1b)[17] using $[Cp^*IrCl_2]_2$ as the catalyst in combination with an electrophilic fluorine source (Selectfluor®, Figure 1). Compatibility of all the reagents and in particular the stability of the transition-metal catalyst under the reaction conditions was essential to achieve this tandem transformation.

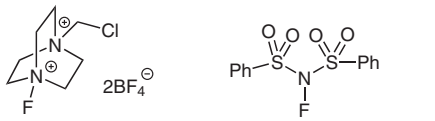


Figure 1 Electrophilic fluorinating reagents

In this article, we report our further investigations on the iridium-catalyzed tandem isomerization/fluorination reaction of allylic alcohols (Scheme 1b). Herein, the compatibility of the fluorinating catalytic system with different substrates containing various functional groups, such as aromatic rings with different electronic properties, enolizable methylene groups, and ketone or alcohol functionalities is evaluated.

In our preliminary studies, various complexes of ruthenium(II) and rhodium(I) were tested to obtain α-fluoro ketones **2** by reacting allylic alcohols **1** with *N*-fluorobenzenesulfonimide (NFSI) or Selectfluor® (SelectF) (Figure 1). Although the complexes tested were known to catalyze isomerizations (Scheme 2) and tandem isomer-

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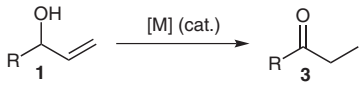
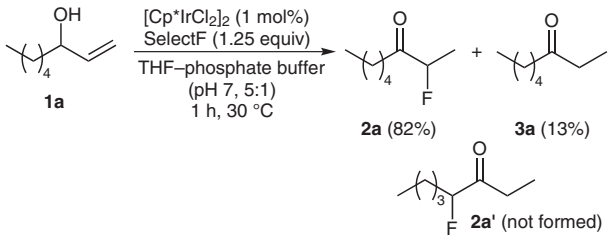
ization/aldol reactions,[7–10] they decomposed in the presence of the electrophilic fluorinating reagents or afforded only traces of fluorinated ketones **2**.



Scheme 2 Isomerization of allylic alcohols catalyzed by transition-metal complexes

Only complexes of a higher oxidation state, such as $[Cp^*RhCl_2]_2$ and $[Cp^*IrCl_2]_2$ gave preliminary good results.[17] After screening different reaction conditions, the best results were obtained with $[Cp^*IrCl_2]_2$. Only 1 mol% of this catalyst was sufficient to fluorinate allylic alcohol **1a** in 82% yield in the presence of SelectF when phosphate buffer (pH 7) or water–tetrahydrofuran mixtures (1:5 v/v) were used as reaction media (Scheme 3). The reaction is not sensitive to oxygen, and thus it can be run under an atmosphere of air. The formation of nonfluorinated ketones **3** could not be completely suppressed.



Scheme 3 Optimized reaction conditions for the tandem isomerization/fluorination of **1a**

Several aliphatic allylic alcohols **1a–f** were subjected to the optimized reactions conditions (Table 1, entries 1–6). The C–F bond is formed exclusively at the alkenylic carbon of the starting allylic alcohol in all cases **1a–f** (i.e., **2a′** is not formed). Next, our attention turned to the synthesis of α-fluoro ketones bearing enolizable methylene groups, such as 1,3-dicarbonyl compounds. Since these compounds are in equilibrium with their tautomeric form, fluorination at the acidic methylene is easily achieved in the presence of electrophilic fluorine sources.[13] Using the tandem isomerization/fluorination we aimed at introducing the fluorine exclusively at the less acidic position. When the allylic alcohol **1g** was subjected to the reaction conditions, monofluorinated β-keto ester **2g** was formed in 80% yield together with ketone **3g** (20%) after one hour (Table 1, entry 7). Introduction of fluorine at the enolizable methylene group was not detected (i.e., **4g** or **5g** was not formed, Figure 2). However, if the mixture was not worked up, but left stirring for prolonged reaction times, **4g** and **5g** were formed. Nevertheless, if the reaction time is controlled, high yields of the desired product can be obtained. Similar results were obtained with allylic alcohol **1h** (Table 1, entry 8), which afforded 61% yield of fluorinated diketone **2h**. Aromatic aldol **1i** was converted into the desired product **2i** in 58% yield (Table 1, entry 9). Along with fluoro ketone **2i**, products arising from fluorination at the activated methylene were also formed, albeit in trace amounts (4% **4i**, Figure 2). The fluorination method is compatible with the presence of an additional hydroxyl functional group within the molecule (Table 1, entry 10). Also, **1k** underwent isomerization/fluorination to give **2k** with a quaternary fluorinated carbon (Table 1, entry 11). Cyclic allylic alcohol **1l** was fluorinated in moderate yield after prolonged reaction times (entry 12).

Table 1 Fluorination of Aliphatic Allylic Alcohols **1a–l**[a]

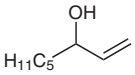
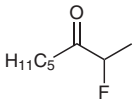
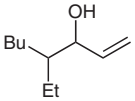
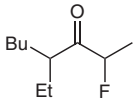
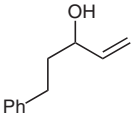
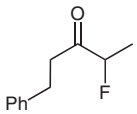
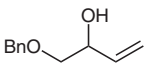
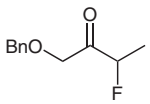
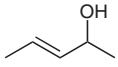
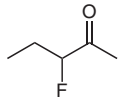
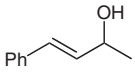
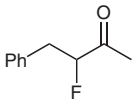
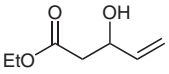
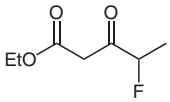
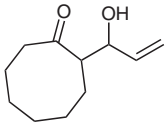
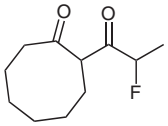
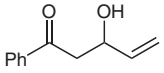
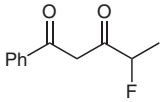
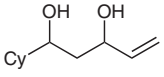
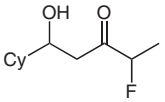
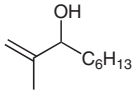
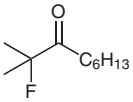
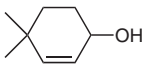
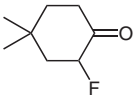
Entry	Allylic alcohol **1**		α-Fluoro ketone **2**		Time (h)	Yield **2/3** (%)[b]
1	**1a**		**2a**		1	82/13
2[c]	**1b**		**2b**		4	78/19
3	**1c**		**2c**		2	91 (77)/5
4	**1d**		**2d**		8	92 (74)/5
5	**1e**		**2e**		1	69/15

Table 1 Fluorination of Aliphatic Allylic Alcohols **1a–l**[a] (continued)

Entry	Allylic alcohol **1**		α-Fluoro ketone **2**		Time (h)	Yield **2/3** (%)[b]
6[c]	**1f**		**2f**		2	78 (67)/15
7[d–f]	**1g**		**2g**		1	80 (63)/20
8[d–g]	**1h**		**2h**		1	61/32
9[d–f,h]	**1i**		**2i**		1	58 (43)/30
10[d–f]	**1j**		**2j**		0.5	61/39
11[i]	**1k**		**2k**		15	60/11
12[d–f]	**1l**		**2l**		24	57/13

[a] Unless otherwise noted, reactions were run with $[IrCp^*Cl_2]_2$ (1 mol%), allylic alcohol **1** (1 mmol), SelectF (1.25 mmol) in THF (5 mL)–deionized H_2O (1 mL) [or a buffer $K/NaPO_4^{2-}$ (pH 7) for entries 1 and 2] at 30 °C. Full conversion into **2** and **3** was achieved, unless otherwise noted.
[b] Determined by NMR spectroscopy with 1,4-dimethoxybenzene, 1,4-di-*tert*-butylbenzene, or fluorobenzene as internal standard. Isolated yields in parenthesis.
[c] With 2 equiv SelectF.
[d] $[Cp^*IrCl_2]_2$ (2.5 mol%).
[e] THF–deionized water = 10:1.
[f] Reaction run at 25 °C.
[g] Conversion: 93%. Product **2h** formed as a mixture of diastereomers.
[h] Product **4i** was formed in 4%.
[i] With 3 mol% of $[Cp^*IrCl_2]_2$.

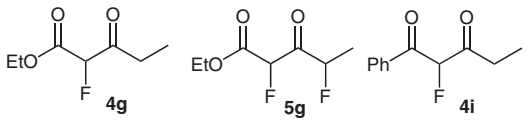
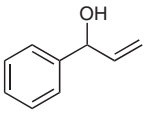
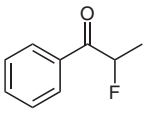
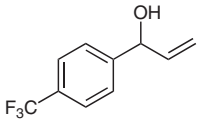
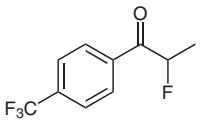
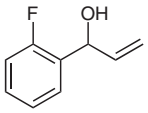
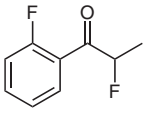
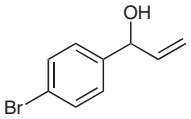
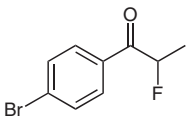
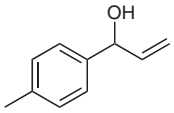
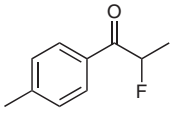
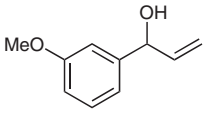
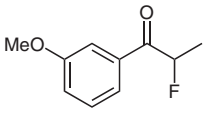
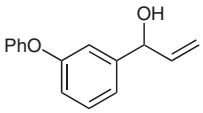
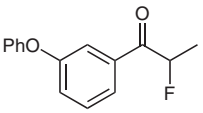
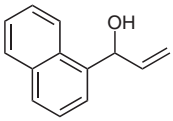
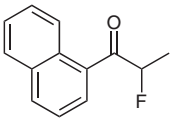
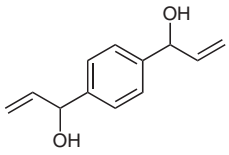
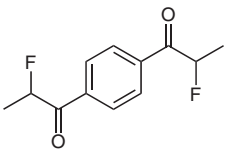


Figure 2 By-products formed in the fluorination of **1g** and **1i**

Next a variety of aromatic allylic alcohols with different electronic properties were tested (Table 2). In general, the fluorination of aromatic allylic alcohols required longer reaction time than that of aliphatic allylic alcohols and for some substrates a higher catalyst loading was needed (Table 1 vs Table 2). α-Vinylbenzyl alcohol (**1m**) was fluorinated in high yield (Table 2, entry 1). Aromatic allylic alcohol **1n**, with an electron-withdrawing substituent, was also transformed into the corresponding α-fluoro ketone **2n** (Table 2, entry 2). Other functional groups such as fluoro, bromo, methyl, methoxy, or phenoxy are well tolerated, and the corresponding fluoro ketones were formed in high yields (Table 2, entries 3–7). A more sterically hindered substrate, such as α-naphthyl-substituted alcohol **1t** afforded **2t** in excellent yield (Table 2, entry 8). Double fluorination was achieved when the starting material contains two allylic alcohol functionalities as in **1u** (Table 2, entry 9). Fluorination of the aromatic ring was never detected.

The fluorination reaction did not give satisfactory results with several allylic alcohols having certain functional groups, such as pyridine, furan, and amide. Allylic alcohols bearing a primary hydroxyl group (e.g., cinnamyl alcohol) afforded considerable amounts of the corresponding α,β-unsaturated aldehyde (cinnamaldehyde) together with the desired product, and homoallylic alcohols decomposed under the reaction conditions. Allylic alcohols bearing a trisubstituted double bond did not

Table 2 Fluorination of Aromatic Allylic Alcohols **1m–u**[a]

Entry	Allylic alcohol **1**	α-Fluoro ketone **2**	Time (h)	Yield **2/3** (%)[b]
1	**1m** 	**2m** 	15	82 (67)/8
2	**1n** 	**2n** 	16	81 (69)/4
3[c]	**1o** 	**2o** 	6	93 (54)/7
4	**1p** 	**2p** 	16	97 (70)/3
5[c]	**1q** 	**2q** 	16	85/15
6[c]	**1r** 	**2r** 	16	91 (75)/8
7	**1s** 	**2s** 	16	91 (82)/9
8	**1t** 	**2t** 	16	91 (81)/9
9[d]	**1u** 	**2u** 	48	81/0[e]

[a] Unless otherwise noted, reactions were run with $[Cp^*IrCl_2]_2$ (1 mol%), allylic alcohol **1** (1 mmol), SelectF (1.25 mmol) in THF (5 mL)–H_2O (0.5 mL) [or a buffer K/$NaPO_4^{2-}$ (pH 7) for entries 3, 7, and 8] at 25 °C. Full conversion into **2** and **3** was achieved, unless otherwise noted.
[b] Determined by ^1H NMR with 1,4-dimethoxy benzene, 1,4-di-*tert*-butylbenzene, or fluorobenzene as internal standard. Isolated yields in parenthesis.
[c] $[Cp^*IrCl_2]_2$ (2.5 mol%).
[d] With SelectF (2.2 equiv) and $[Cp^*IrCl_2]_2$ (2.5 mol%), THF–aq K/$NaPO_4^{2-}$ (pH 7) (5:1). See Supporting Information for a detailed description.
[e] Monofluorinated diketone was formed in 14% yield.

afford the desired product either. The substrates that failed to give good results in the tandem isomerization/fluorination are shown in Figure 3.

We propose the mechanism shown in Scheme 4 based on deuterium labeling studies and cross-over experiments.[17] The first step is an oxidation of the allylic alcohol to the corresponding α,β-unsaturated carbonyl compound (intermediate **I**). An iridium-hydride complex is formed, which reduces the double bond of **I** forming an enolate interme-

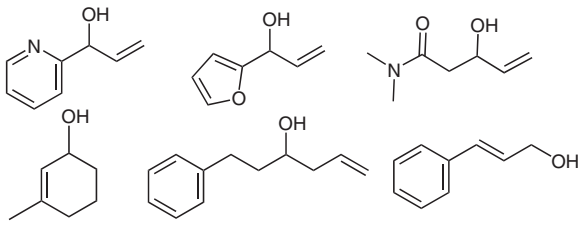
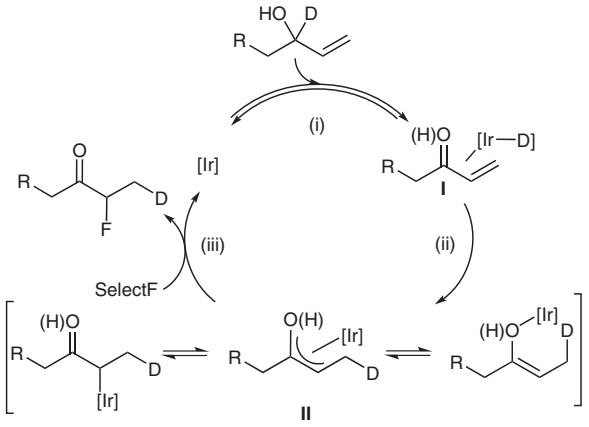


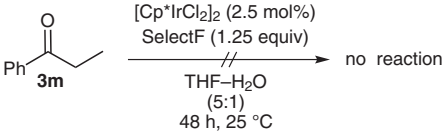
Figure 3 Unsuccessful alcohols in tandem isomerization/fluorination reaction

diate **II**.[8f,18] In the last step, the iridium enolate reacts with SelectF yielding the α-fluoro ketone.



Scheme 4 Proposed catalytic cycle

An alternative mechanism in which the allylic alcohol **1** is first isomerized to the corresponding ketone **3**, followed by fluorination of this ketone **3** with SelectF can be ruled out since the reaction with aliphatic substrates is regiospecific and thus, the products are formed as single regioisomers. In the case of aromatic allylic alcohols, a control experiment in which propiophenone (**3m**) was subjected to the reaction conditions (Table 2, entry 1) for 48 hours confirmed that fluorination of aromatic ketones does not proceed under these mild conditions (Scheme 5).



Scheme 5 Control experiment

In conclusion, we have developed a straightforward method to synthesize α-fluoro ketones from allylic alcohols using iridium catalysis and SelectF as the fluorine source. This methodology is characterized by the following features: (a) the reaction is regiospecific. Thus, the new C–F bond is formed exclusively at the olefinic carbon of the starting material; (b) aliphatic and aromatic allylic alcohols can be transformed into α-fluoro ketones in good yields; (c) this method can be used to synthesize α′-fluorinated 1,3-dicarbonyl compounds, with the fluorine substituent at the less acidic α-carbon; (d) the reactions are run under an atmosphere of air, under mild reaction conditions (25–30 °C) and are simple to perform; (e) fluorination of aromatic rings is not observed; (f) the system is not compatible with certain nitrogen containing functional groups on the substrates, and primary allylic alcohols, homoallylic alcohols, and hindered allylic alcohols give low yields of the desired products, and (g) a mechanism via enone intermediates formed by oxidation of the allylic alcohol with concomitant formation of an iridium hydride is proposed. We are currently performing further mechanistic investigations to have a better understanding of this tandem isomerization/fluorination reaction.

Air and moisture sensitive reactions were carried out under an atmosphere of dry N_2. Ir-catalyzed reactions were run under an atmosphere of air. Reagents were used as obtained from commercial suppliers without further purification. THF was used as obtained from supplier (puriss. p. a., stabilized with 2,6-di-*tert*-butyl-4-methylphenol ~250 mg/L). The undistilled THF used in the reactions tested negative for peroxides (0% by Quantofix peroxide). A KH_2PO_4/Na_2HPO_4 buffer (pH 7; per liter: 3.54 g KH_2PO_4/14.7g Na_2HPO_4) was used as obtained from supplier. Flash chromatography was carried out on 60 Å (35–70 μm) silica gel. Spectra were recorded at 400 or 500 MHz for ^{1}H NMR, at 100 or 125 MHz for ^{13}C NMR, and at 376 MHz for ^{19}F NMR on a Bruker Avance spectrometer. ^{1}H and ^{13}C NMR chemical shifts (δ) are reported in ppm from TMS with the solvent resonance as the internal standard, ($CDCl_3$: δ_H 7.26 and δ_C 77.16). ^{19}F NMR chemical shifts (δ) (^{1}H-decoupled) are reported in ppm from $CFCl_3$ with C_6H_5F (δ –113.15) as the internal standard. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF ESI-TOF mass spectrometer.

Alcohols **1a**, **1e**, 3-methylcyclohex-2-enol, and cinnamyl alcohol were used as obtained from supplier (Aldrich). 4-Ethyloct-1-en-3-ol (**1b**),[17] 5-phenylpent-1-en-3-ol (**1c**),[19] 1-(benzyloxy)but-3-en-2-ol (**1d**),[17] (*E*)-4-phenylbut-3-en-2-ol (**1f**),[20] ethyl 3-hydroxypent-4-enoate (**1g**),[21] 1-phenyl-1-oxo-3-hydroxypent-4-ene (**1i**),[22] 2-methylnon-1-en-3-ol (**1k**),[17] 4,4-dimethylcyclohex-2-en-1-ol (**1l**),[23] 1-phenylprop-2-en-1-ol (**1m**),[2a] 1-(4-trifluoromethylphenyl)prop-2-en-1-ol (**1n**),[24] 1-(2-fluorophenyl)prop-2-en-1-ol (**1o**),[25] 1-(4-bromophenyl)prop-2-en-1-ol (**1p**),[26] 1-(*p*-tolyl)prop-2-en-1-ol (**1q**),[27] 1-(3-methoxyphenyl)prop-2-en-1-ol (**1r**),[28] 1-(2-furyl)prop-2-en-1-ol,[24] 1-(3-phenoxyphenyl)prop-2-en-1-ol (**1s**),[29] 1-(α-naphthyl)prop-2-en-1-ol (**1t**)[30] 1-phenylhex-5-en-3-ol,[31] and 1-(2-pyridyl)prop-2-en-1-ol[32] were prepared as described in the literature.

Allylic Alcohols 1b–d,k,m–u; General Procedure

A solution of the corresponding alkenyl/alkylmagnesium bromide (1 M in THF, 1.1 equiv, 2.2 equiv in the case of **1v**) was added to the corresponding aldehyde (1 equiv) at 0 °C. The reaction mixture was slowly warmed up to r.t. On consumption of the aldehyde (as monitored by TLC: EtOAc–pentane, 1:20), the reaction was quenched with aq NH_4Cl (1 mL/mmol of alcohol), extracted with EtOAc (10 mL/mmol of alcohol) and the combined organic extracts were washed with brine (5 mL/mmol of alcohol). The combined organic phases were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc–pentane, 1:20–1:5) afforded the pure allylic alcohols.

1,4-Bis(prop-2-en-1-ol)benzene (1u)[33]

Yield 51%; white solid; mixture of 2 diastereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (s, 4 H), 6.01 (ddd, *J* = 16.7, 10.5, 6.3 Hz, 2 H), 5.32 (dt, *J* = 16.7, 1.4 Hz, 2 H), 5.20–5.15 (m, 4 H), 2.33 (br s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.1, 140.2, 126.6, 115.2, 75.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{14}O_2$ + Na: 213.0886; found: 213.0892.

Aldol Allylic Alcohols 1g–j; General Procedure

n-BuLi (6.8 mL, 11 mmol, 1.6 M solution in hexanes) was added to a stirred solution of distilled $(i\text{-Pr})_2NH$ (1.54 mL, 11 mmol) in anhyd THF (50 mL) at –78 °C. After 15 min, the corresponding ketone or amide (10 mmol) was added slowly, and the mixture was stirred for another 45 min. Distilled acrolein (0.67 mL, 10 mmol) in THF (5 mL) was added dropwise. After 10 min at –78 °C, sat. aq

NH_4Cl (2 mL) and H_2O (15 mL) were added. After extraction with Et_2O (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), filtered, and the solvent was evaporated. Purification by column chromatography (SiO_2) afforded alcohols **1g–j**.

2-(Prop-2-en-1-ol)cyclooctanone (1h)
Following the general procedure, the reaction was performed with cyclooctanone (1.3 g, 10 mmol) and acrolein (0.67 mL, 10 mmol). The product was purified by column chromatography (SiO_2; pentane–EtOAc, 4:1), and isolated as a yellowish oil (1.52 g, 84% as a mixture of distereomers 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82 (m, 1 H), 5.30 (m, 1 H), 5.18 (m, 1 H), 4.23–4.37 (m, 1 H), 2.99 (m, 1 H), 2.83 (m, 1 H), 2.32–2.48 (m, 2 H), 1.95–2.61 (m, 1 H), 1.14–1.86 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.31, 23.68, 24.80, 24.87, 25.05, 25.21, 28.02, 28.17, 28.48, 31.66, 44.10, 44.97, 53.70, 54.00, 73.15, 75.23, 115.93, 116.53, 138.00, 138.79

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}NO_2$ + Na: 205.1199; found: 205.1192.

1-Cyclohexylpent-4-ene-1,3-diol (1j)
This compound was prepared in two steps from 1-cyclohexylethanone. Following the general procedure, the reaction was performed with 1-cyclohexylethanone (1.26 g, 10 mmol) and acrolein (0.67 mL, 10 mmol). The product, 1-cyclohexyl-3-hydroxypent-4-en-1-one, was purified by column chromatography over silica gel (pentane–EtOAc, 4:1), and isolated as a yellowish oil (1.55 g, 85%) as a mixture of diastereomers (1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (m, 1 H), 5.31 (m, 1 H), 5.14 (m, 1 H), 4.57 (m, 1 H), 3.19 (m, 1 H), 2.32–2.38 (m, 2 H), 2.35 (m, 1 H), 1.68–1.88 (m, 5 H), 1.19–1.40 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.54, 25.77, 28.20, 46.51, 51.38, 68.64, 114.90, 139.07, 214.70.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{18}NO_2$ + Na: 205.1199; found: 205.1191.

To a solution of 1-cycohexyl-3-hydroxypent-4-en-1-one (0.32 g, 1.75 mmol) in MeOH (5 mL) was added $NaBH_4$ (0.08 g, 2.1 mmol) slowly. The resulting mixture was stirred at r.t. for 1 h. After completion of the reaction (as confirmed by TLC analysis; pentane–EtOAc, 7:3), the solvent was evaporated. After extractive workup (H_2O–Et_2O), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated. Product **1j** was obtained as a colorless oil (270 mg, 84%). Its characterization data was identical to that reported in the literature.[34]

Isomerization/Fluorination of Allylic Alcohols 1; General Procedure
$[Cp^*IrCl_2]_2$ (4 mg, $5\cdot10^{-3}$ mmol, 1 mol%) was dissolved in a mixture of THF (2.5 mL) and H_2O (0.25–0.5 mL) at 25–30 °C. Selectfluor® (0.63 mmol, 1.25 equiv) and the corresponding allylic alcohol **1** (0.5 mmol) were added to the reaction mixture. The mixture was stirred at 25–30 °C for the time indicated in Tables 1 and 2. On completion (as monitored by TLC; EtOAc–pentane, 1:10), H_2O (1 mL) was added and the mixture was extracted with Et_2O (3 × 2 mL), and the combined Et_2O extracts were dried ($MgSO_4$). Evaporation of the solvent afforded a mixture of α-fluorinated ketone **2** and nonfluorinated ketone **3**. The yield and F/H ratios were determined by ^{1}H NMR using 1,4-dimethoxybenzene (0.25 mmol) as an internal standard. Isolated products were purified by column chromatography (EtOAc–pentane or Et_2O–pentane 1:40–1:20). TLC plates were developed with $KMnO_4$ or cerium molybdate (Hanessian's stain). The preparation of α-fluoro ketones **2a–f**, **2k**, and **2m** has been previously reported by us.[17]

Ethyl 4-Fluoro-3-oxopentanoate (2g)
Yield: 63%; colorless oil; **2g** exists as a mixture of dicarbonyl and enolized forms.

^{1}H NMR (400 MHz, $CDCl_3$): δ (keto form) = 5.00 (dq, $^2J_{H,F}$ = 49.6 Hz, *J* = 6.9 Hz, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 3.65 (m, 2 H), 1.54 (dd, $^3J_{H,F}$ = 24.0 Hz, *J* = 6.9 Hz, 3 H), 1.30 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (keto form) = 202.9 (d, $^2J_{C,F}$ = 27.1 Hz), 166.7 (d, $^4J_{C,F}$ = 2.2 Hz), 92.4 (d, $^1J_{C,F}$ = 191.2 Hz), 61.5, 44.9, 17.3 (d, $^2J_{C,F}$ = 21.6 Hz), 14.1.

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (keto form) = –183.5 (dqt, $^2J_{H,F}$ = 49.6 Hz, $^3J_{H,F}$ = 24.0 Hz, $^4J_{H,F}$ = 4.0 Hz).

^{1}H NMR (400 MHz, $CDCl_3$): δ (enol form) = 12.03 (d, $^4J_{H,F}$ = 2 Hz, 1 H), 5.32 (dd, $^4J_{H,F}$ = 2.0 Hz, *J* = 1 Hz, 1 H), 5.02 (dqd, $^2J_{H,F}$ = 48.0, *J* = 6.9 Hz, *J* = 1 Hz, 1 H), 4.24 (q, *J* = 7.3 Hz, 2 H), 1.56 (dd, $^3J_{H,F}$ = 23.0 Hz, *J* = 6.9 Hz, 3 H), 1.32 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (enol form) = 174.8 (d, $^2J_{C,F}$ = 24.1 Hz), 172.7 (d, $^3J_{C,F}$ = 1.5 Hz), 86.8 (d, $^1J_{C,F}$ = 174.4 Hz), 87.5 (d, $^4J_{C,F}$ = 7.9 Hz), 60.4, 19.1 (d, $^2J_{C,F}$ = 22.6 Hz), 14.2.

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (enol form) = –185.3 (dqt, $^2J_{H,F}$ = 49.6 Hz, $^3J_{H,F}$ = 23.0 Hz, $^4J_{H,F}$ = 2.0 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_7H_{11}FO_3$ + Na: 185.0584; found: 185.0584.

4-Fluoro-1-phenylpentane-1,3-dione (2i)
Yield: 43%; colorless oil; **2i** was obtained as a mixture of enolized and dicarbonyl forms in a ratio of 96:4 (contaminated with <5% of **3i**).

^{1}H NMR (400 MHz, $CDCl_3$): δ (keto form) = 8.01–7.89 (m, 2 H), 7.72–7.45 (m, 3 H), 5.06 (dq, $^2J_{H,F}$ = 48.7 Hz, *J* = 6.9 Hz, 1 H), 4.37 (dd, *J* = 16.3 Hz, $^4J_{H,F}$ = 4.5 Hz, 1 H), 4.26 (dd, *J* = 16.3 Hz, $^4J_{H,F}$ = 4.5 Hz, 1 H), 1.54 (dd, $^3J_{H,F}$ = 24.1 Hz, *J* = 6.9 Hz, 3 H).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (keto form) = –182.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ (enol form) = 15.91 (s, 1 H), 7.98–7.93 (m, 2 H), 7.61–7.55 (m, 1 H), 7.52–7.47 (m, 2 H), 6.57 (d, $^4J_{H,F}$ = 3.0 Hz, 1 H), 5.11 (dq, $^2J_{H,F}$ = 48.6 Hz, *J* = 6.9 Hz, 1 H), 1.64 (dd, $^3J_{H,F}$ = 24.5 Hz, *J* = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ (enol form) = 195.4 (d, $^2J_{C,F}$ = 23.4 Hz), 183.7 (d, $^3J_{C,F}$ = 1.0 Hz), 134.2, 132.8, 128.7, 127.2, 91.7 (d, $^4J_{C,F}$ = 6.7 Hz), 89.3 (d, $^1J_{C,F}$ = 179 Hz), 18.8 (d, $^2J_{C,F}$ = 22 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (enol form) = –184.8, (dqd, $^2J_{H,F}$ = 48.6 Hz, $^3J_{H,F}$ = 24.5 Hz, $^4J_{H,F}$ = 3.0 Hz).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}FO_2$ + Na: 217.0635; found: 217.0625.

2-Fluoro-1-(4-trifluoromethylphenyl)propan-1-one (2n)
Yield: 69%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.06 (m, 2 H), 7.78–7.73 (m, 2 H), 5.66 (dq, $^1J_{H,F}$ = 48.4 Hz, *J* = 6.8 Hz, 1 H), 1.68 (dd, $^2J_{H,F}$ = 24.1 Hz, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.5 (d, $^2J_{C,F}$ = 20.9 Hz), 137.0, 135.1 (q, $^2J_{C,F}$ = 32.8 Hz), 129.6 (d, $^3J_{C,F}$ = 4.5 Hz, 2 C), 125.9 (q, $^3J_{C,F}$ = 3.7 Hz, 2 C) 123.6 (q, $^1J_{C,F}$ = 272.8 Hz), 90.9 (d, $^1J_{C,F}$ = 180.7 Hz), 18.2 (d, $^2J_{C,F}$ = 23.0 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = – 63.3 (3 F), –180.8.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_8F_4O$ + Na: 243.0403; found: 243.0398.

2-Fluoro-1-(2-fluorophenyl)propan-1-one (2o)
Yield: 54%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 1 H), 7.58 (m, 1 H), 7.29 (m, 1 H), 7.16 (m, 1 H), 5.70 (dqd, $^2J_{H,F}$ = 48.5 Hz, J = 7 Hz, $^5J_{H,F}$ = 2.3 Hz, 1 H), 1.64 (ddd, $^3J_{H,F}$ = 23.7 Hz, J = 7 Hz, J = 1.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8 (dd, $^2J_{C,F}$ = 20.2 Hz,$^3J_{C,F}$ = 4.2 Hz), 161.3 (d, $^1J_{C,F}$ = 254.7 Hz), 135.3 (d, $J_{C,F}$ = 9.0 Hz), 131.5 (t, $J_{C,F}$ = 2.8 Hz), 124.9 (d, $J_{C,F}$ = 2.9 Hz), 123.0 (d, $J_{C,F}$ = 14.3 Hz), 116.5 (d, $^2J_{C,F}$ = 23.5 Hz), 91.5 (dd, $^1J_{C,F}$ = 180.3 Hz, $^4J_{C,F}$ = 8.4 Hz), 17.5 (dd, $^2J_{C,F}$ = 23.0 Hz, $^5J_{CF}$ = 1.9 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –108.82 (d, $^5J_{F,F}$ = 13.5 Hz), –183.37 (d, $^5J_{F,F}$ = 13.5 Hz).

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_9H_{81}F_2O$ + Na: 193.0435; found: 193.0429.

1-(4-Bromophenyl)-2-fluoropropan-1-one (2p)
Yield: 70%; colorless oil (contaminated with <5% of **3p**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–7.85 (m, 2 H), 7.69–7.62 (m, 2 H), 5.65 (dq, $^2J_{H,F}$ = 48.6 Hz, J = 6.9 Hz, 1 H), 1.67 (dd, $^3J_{H,F}$ = 24.3 Hz, J = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.1 (d, $^2J_{C,F}$ = 20.3 Hz), 132.7 (d, $^3J_{C,F}$ = 2.8 Hz), 132.1, 130.6 (d, $^4J_{C,F}$ = 4.4 Hz), 129.1, 90.6 (d, $^1J_{C,F}$ = 180.5 Hz), 18.2 (d, $^2J_{C,F}$ = 22.6 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –180.5.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_9H_8{}^{79}BrFO$ + Na: 252.9635; found: 252.9629.

2-Fluoro-1-(3-methoxyphenyl)propan-1-one (2r)
Yield: 75%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 2 H), 7.39 (t, J = 7.9 Hz 1 H), 7.17–7.13 (m, 1 H), 5.71 (dq, $^1J_{H,F}$ = 48.7 Hz, J = 6.8 Hz, 1 H), 3.86 (s, 3 H), 1.66 (dd, $^2J_{H,F}$ = 24.0 Hz, J = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.8 (d, $^2J_{C,F}$ = 19.3 Hz), 160.0, 135.4, 129.9, 121.9 (d, $^4J_{C,F}$ = 4.2 Hz), 120.5, 113.3 (d, $^4J_{C,F}$ = 3.2 Hz), 90.3 (d, $^1J_{C,F}$ = 180.3 Hz), 55.6, 18.6 (d, $^2J_{C,F}$ = 22.8 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –181.5.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{11}H_9FO$ + Na: 205.0635; found: 205.0626.

2-Fluoro-1-(3-phenoxyphenyl)propan-1-one (2s)
Yield: 82%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74–7.70 (m, 1 H), 7.64–7.61 (m, 1 H), 7.47 (t, J = 7.7 Hz, 1 H), 7.43–7.36 (m, 2 H),7.29–7.24 (m, 1 H), 7.21–7.16 (m, 1 H), 7.09–7.03 (m, 2 H), 5.67 (dq, $^2J_{H,F}$ = 49.0 Hz, J = 6.8 Hz, 1 H), 1.67 (dd, $^3J_{H,F}$ = 24.1 Hz, J = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.3 (d, $^2J_{C,F}$ = 19.8 Hz), 157.9, 156.4, 135.7 (d, $^3J_{C,F}$ = 1.5 Hz), 130.1, 130.0, 124.0, 123.9 (d, $^4J_{C,F}$ = 4.4 Hz), 123.6, 119.2 (d, $^4J_{C,F}$ = 2.9 Hz), 118.7, 90.3 (d, $^1J_{C,F}$ = 180.1 Hz), 18.3 (d, $^2J_{C,F}$ = 22.7 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –181.2.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{15}H_{13}FO_2$ + Na: 267.0792; found: 267.0791.

2-Fuoro-1-(α-naphthyl)propan-1-one (2t)
Yield: 81%; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50–8.45 (m, 1 H), 8.10–8.04 (m, 1 H), 7.95–7.90 (m, 1 H), 7.90–7.84 (m, 1 H), 7.70–7.50 (m, 3 H), 5.80 (dq, $^2J_{H,F}$ = 49.0 Hz, J = 6.9 Hz, 1 H), 1.69 (dd, $^3J_{H,F}$ = 23.7 Hz, J = 6.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.9 (d, $^2J_{C,F}$ = 20.1 Hz), 134.0, 133.2, 132.6, 130.6, 128.6, 128.2, 127.9 (d, $^4J_{C,F}$ = 4.6 Hz), 126.7, 125.3, 124.2, 90.7 (d, $J_{C,F}$ = 180 Hz), 18.2 (d, $^2J_{C,F}$ = 22.7 Hz).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –179.8.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{13}H_{11}FO$ + Na: 225.0686; found: 225.0679.

Selected NMR Data of α-Fluoro Ketones 2h and 2l
α-Fluoro ketones **2c**,**d**,**h**,**l**,**q** were not isolated due to difficult separation from the nonfluorinated ketones **3** and their volatility. In these cases, the yields reported in Tables 1 and 2 were calculated using 1,4-dimethoxybenzene, 1,4-di-*tert*-butylbenzene, or fluorobenzene as the internal standard. For compounds that have not been reported previously, selected ^{1}H and ^{19}F NMR peaks are listed below:

2-(2-Fluoropropanoyl)cyclooctanone (2h)
The spectra were recorded with a crude sample, which was a mixture of diastereoisomers 51% (dr = 2:1) together with enolized form 10% and ketone **3h** (32%). Selected NMR signals:

^{1}H NMR (400 MHz, $CDCl_3$): δ (keto form) = 4.90 [dq, $^2J_{H,F}$ = 48 Hz, J = 6.9 Hz, 1 H (minor)], 4.87 [dq, $^2J_{H,F}$ = 49 Hz, J = 6.9 Hz, 1 H (major)], 4.23 [dt, J = 11.6 Hz, $^4J_{H,F}$ = 3.6 Hz, J = 3.6 Hz, 1 H (major) + 1 H (minor)], 1.48 [dd, $^3J_{H,F}$ = 24.5 Hz, J = 6.9 Hz, 3 H, (major)], 1.47 [dd, $^3J_{H,F}$ = 24.3 Hz, J = 6.9 Hz, 3 H (minor)].

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (keto form) = –183.6 (major), –183.6 (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ (enol form) = 5.32 (dq, $^2J_{H,F}$ = 48 Hz, J = 6.9 Hz, 1,H), 1.57 (dd, $^3J_{H,F}$ = 24.3 Hz, J = 6.9 Hz, 3 H).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ (enol form) = –181.5.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{11}H_{17}FO_2$ + Na: 223.1105; found: 223.1100.

1-Cyclohexyl-4-fluoro-1-hydroxypentan-3-one (2j)
This compound was obtained as a mixture of 2 diastereoisomers (dr = 56:43), which could not be separated from **3j**. Selected NMR signals:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 [dq, $^2J_{H,F}$ = 49.3 Hz, J = 6.9 Hz, 1 H, (major)], 4.91 [dq, $^2J_{H,F}$ = 49.3 Hz, J = 6.9 Hz, 1 H, (minor)], 3.94–3.82 [m, 1 H (major) + 1 H (minor)], 2.87–2.71 [m, 1 H (major) + 1 H (minor)], 1.51 [dd, $^3J_{H,F}$ = 23.9 Hz, J = 6.9 Hz, 3 H, (major)], 1.51 [dd, $^3J_{H,F}$ = 23.9 Hz, J = 6.9 Hz, 3 H (minor)].

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –184.1 (minor), –184.3 (major).

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{11}H_{19}FO_2$ + Na: 225.1216; found: 225.1252.

2-Fluoro-4,4-dimethylcyclohexanone (2l)[13h]
^{1}H NMR and ^{19}F NMR spectra were identical to those previously reported.

2-Fluoro-1-(*p*-tolyl)propan-1-one (2q)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.17–7.13 (m, 1 H), 5.69 (dq, $^1J_{H,F}$ = 48.7 Hz, J = 6.8 Hz, 1 H), 2.42 (s, 3 H), 1.65 (dd, $^2J_{H,F}$ = 24.0 Hz, J = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.6 (d, $^2J_{C,F}$ = 19.2 Hz), 144.9, 131.6 (d, $^3J_{C,F}$ = 1.2 Hz, 2 C), 129.1 (d, $^4J_{C,F}$ = 4.1 Hz, 2 C), 90.3 (d, $^1J_{C,F}$ = 179.9 Hz), 21.7, 18.6 (d, $^2J_{C,F}$ = 22.8 Hz).

^{19}F NMR ($CDCl_3$, 376.4 MHz): δ = –181.3.

HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{10}H_{11}FO$ + Na: 189.0686; found: 189.0688.

1,1′-(1,4-Phenylene)bis(2-fluoropropan-1-one) (2u)
Product **2u** was formed as a mixture of 2 diastereoisomers not distinguishable by NMR spectroscopy.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 4 H), 5.67(dq, $^1J_{H,F}$ = 48.4, Hz, J = 6.8 Hz, 2 H), 1.65 (dd, $^2J_{H,F}$ = 24.1 Hz, J = 6.8 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.7 (d, $^2J_{C,F}$ = 20.7 Hz, 2 C), 137.8 (d, $^3J_{C,F}$ = 1.7 Hz, 2 C), 129.3 (d, $^4J_{C,F}$ = 4.1 Hz, 4 C), 90.7 (d, $^1J_{C,F}$ = 180.6 Hz, 2 C), 18.1 (d, $^2J_{C,F}$ = 22.5 Hz, 2 C).

^{19}F NMR (376.4 MHz, $CDCl_3$): δ = –181.3.

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{12}F_2O_2$ + Na: 249.0698; found: 249.0703.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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