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Synthesis of 2-fluorotetralones by oxidative radical cyclization of α-fluoroacetophenones and olefins

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Abstract—The oxidative radical cyclization of α-fluoroacetophenones in the presence of olefins offers an efficient access to 2-fluorotetralones. Fluorinated starting materials can be prepared from α-bromoacetophenones. The reaction was optimized with respect to a future application in the synthesis of 18-fluorine labeled compounds, where reaction times are a critical aspect.

Substituted 2-fluorotetralones are important precursors for the synthesis of vicinal fluorohydrins which have served as versatile building blocks and key intermediates for numerous bioactive compounds.[1] Effective enantioselective approaches by dynamic kinetic resolution,[2a] asymmetric protonation,[2b] and chelation-controlled diastereoselective reduction[2c] have been reported recently. The synthesis of 2-fluorotetralones has so far mostly been achieved by electrophilic fluorination of tetralone precursors or their corresponding enolates.[3] For asymmetric fluorination, camphorsultam-[4] and cinchona-based[5] agents have been developed.

Most reagents for electrophilic fluorination reactions cannot easily be applied for radiochemical syntheses, since elemental fluorine is not available with a high degree of labeling which later results in carrier-added products. In contrast [^{18}F]KF can be prepared with high specific radioactivity from 18-oxygen-enriched water. For this reason, a synthetic access to 2-fluorotetralones and further derivatives including a nucleophilic introduction of fluoride would be valuable. α-[^{18}F]Fluoroacetophenones, which had been obtained from the corresponding bromides, have successfully been used as precursors for the labeling of peptides.[6]

The conversion of α-bromoacetophenones to fluorides by nucleophilic substitution with activated potassium fluoride is a well established reaction for both 18- and 19-fluoride ions.[6,7] For the synthesis of tetralones from acetophenones and olefins radical addition–cyclization sequences have been shown to be valuable methods.[8] Especially the use of xanthates as radical precursors offers a convenient and simple access to tetralones.[9] Although α-chloro-[10] and α-nitro-acetophenones[11] were applied for radical carbon–carbon bond forming reactions under oxidative conditions, no α-fluorocarbonyl compounds have served as starting material for this purpose so far. In addition, the direct nucleophilic substitution of, for example, 2-bromotetralones by fluoride is troubled by elimination and naphthol formation.[12]

In order to evaluate the efficacy and selectivity of radical formation, a mixture of α-fluoroacetophenone (**1a**) and 1-octene was treated with different oxidants which are known to generate carbon-centered radicals in the α-position of carbonyls.[13] The expected reaction pathway, in which two oxidative steps are required for primary radical formation and final rearomatization, is depicted in Scheme 1. For that reason, at least 2 equiv of an one-electron oxidant are necessary. The results of the optimization are summarized in Table 1.

The most effective and versatile oxidants known for the desired radical formation are manganese(III) acetate[14,15] and ceric(IV) ammonium nitrate.[16,17] Changes in selectivity have been reported when these reagants are used in protic or aprotic solvents and when basic or acidic conditions were applied.[14,15] For the investigated reaction, simple heating under reflux did not lead to sufficient conversions (entry 1) in reasonable reaction times. This observation is in good agreement

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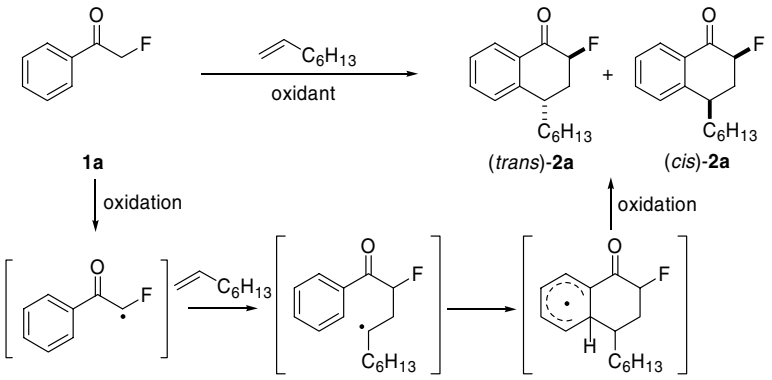


Scheme 1. Formation of 2-fluorotetralones from α-fluoroacetophenones.

Table 1. Formation of tetralone **2a** from α-fluoroacetophenone (**1a**) and 1-octene

Entry	Conditions (oxidant, solvents, temperature, time)	Conversion (%)
1	MAH (2 equiv), AcOH, reflux, 60 min	18
2	MAH (2 equiv), AcOH, MW (600 W), 130 °C, 30 min	41
3	MAH (4 equiv), AcOH, MW (600 W), 130 °C, 30 min	28
4	MAH (4 equiv), AcOH, sealed tube, 140 °C, 30 min	29
5	CAN (2 equiv), CH_3CN, sealed tube, 100 °C, 30 min	0
6	MAH (4 equiv), AcOH–Ac_2O, sealed tube, 140 °C, 30 min	18
7	MAH (5 equiv), AcOH–Ac_2O, sealed tube, 140 °C, 30 min	10
8	MAA (3 equiv), PhCl, sealed tube, 140 °C, 30 min	10
9	MAA (3 equiv), AcOH, sealed tube, 140 °C, 30 min	12
10	MAA (3 equiv), AcOH–KOAc, sealed tube, 140 °C, 30 min	47
11	MAH (3 equiv), AcOH–KOAc, sealed tube, 140 °C, 30 min	50
12	MAH (5 equiv), AcOH–KOAc, sealed tube, 140 °C, 15 min	100

All reactions were carried out with 0.5 mmol of acetophenone **1a**, conversions and diastereomeric ratios were determined by GC; MAH = $Mn(OAc)_3 \times 2H_2O$; MAA = $Mn_3O(OAc)_7$ (prepared by drying MAH over P_2O_5 in vacuo); CAN = $Ce(NH_4)_2(NO_3)_6$; MW = microwave.

with the relatively slow radical formation from α-chloroacetophenones[10] compared to more reactive 1,3-dicarbonyl compounds. Since attempts under microwave conditions gave varying results and did not exceed the product formation reached with pressure tube experiments, these conditions were not further applied (entries 2–4). The use of cerium(IV) as oxidant gave no product formation at all (entry 5). When shifting to non-aqueous conditions by either adding acetic anhydride or anhydrous manganese(III) acetate, no decisive improvements were observed. Satisfactory results were finally obtained by the addition of potassium acetate (entries 10–12). The slight decrease in acidity caused by this modification probably leads to an enhanced enolization of the α-fluoroacetophenone, which in turn facilitates the attack of the oxidant on the carbonyl oxygen.

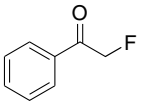
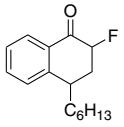
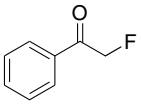
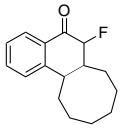
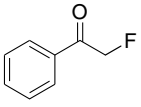
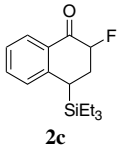
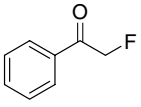
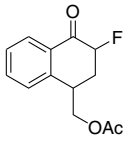
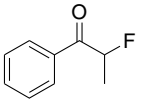
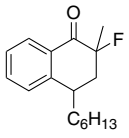
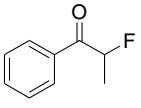
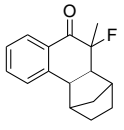
Most reactions shown in Table 1 are clean conversions. No major side products were observed in the crude NMR spectra before purification. The diastereomeric ratio, which can be easily determined by GC or ^1H NMR, was always close to a 1:1 mixture. With these optimized conditions in hand, different acetophenones and olefins were converted to tetralones.

All reactions summarized in Table 2 gave reasonable yields except for the attempt with allyl acetate (entry 4). In this case, the ester functionality was partially hydrolyzed under the reaction conditions and the corresponding alcohol was observed as by-product in 8% yield. For the reason of complete conversion, all reactions were run for 20 min though the experiments for optimization (Table 1, entry 12) indicate that the acetophenones are consumed even faster.[20] The relative stereochemistry of the major products was determined by ^1H NMR and NOESY interactions (Scheme 2).[21,22]

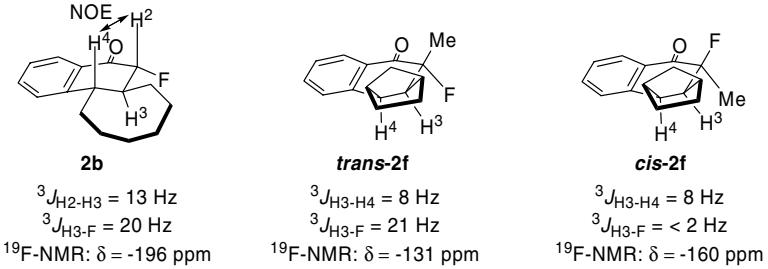
No tetralone formation was observed when the reaction was run with 4-pentenoic acid. In this case, the intermediate radical that arises from the addition of the α-carbonyl radical to the olefin (Scheme 1) is exclusively trapped by the manganese(III)-complexed carboxylate moiety before an addition to the aromatic core occurs.[24] The formation of γ-lactones from alkenes and acetic acid derivatives under oxidative conditions is a well known process and has been widely applied[14,15] (Scheme 3).

Since terminal alkynes have been successfully used in ring annulation reactions,[26] α-fluoroacetophenone (**1a**) was reacted with 1-octyne under standard conditions.[18] Due to the higher degree of unsaturation a 2-fluoronaphthol derivative was expected as reaction product instead of a tetralone. Surprisingly, the α,β-unsaturated aldehyde **4** was isolated from the reaction mixture as major product. The structure was confirmed by

Table 2. Synthesis of 2-fluorotetralones

Entry	α-Fluoroacetophenone (**1**)	Olefin	2-Fluorotetralone (**2**)	Yield (%) [diastereomeric ratio]
1	 **1a**	1-Octene	 **2a**	77 [50:50]
2	 **1a**	Cyclooctene	 **2b**	63 [58:26:8:8]
3	 **1a**	Vinyltriethylsilane	 **2c**	51 [67:33]
4	 **1a**	Allyl acetate	 **2d**	35 [55:45]
5	 **1b**	1-Octene	 **2e**	56 [60:40]
6	 **1b**	Norbornene	 **2f**	83 [63:37]

All reactions were carried out according to the standard procedure Ref. 18. Yields after isolation and purification by column chromatography. For analytical data, see Ref. 19.

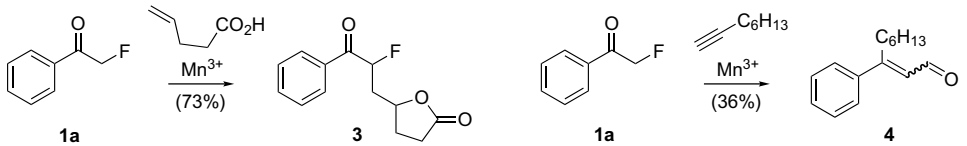


2b
$^3J_{H2\text{-}H3}$ = 13 Hz
$^3J_{H3\text{-}F}$ = 20 Hz
^{19}F-NMR: δ = -196 ppm

***trans*-2f**
$^3J_{H3\text{-}H4}$ = 8 Hz
$^3J_{H3\text{-}F}$ = 21 Hz
^{19}F-NMR: δ = -131 ppm

***cis*-2f**
$^3J_{H3\text{-}H4}$ = 8 Hz
$^3J_{H3\text{-}F}$ = < 2 Hz
^{19}F-NMR: δ = -160 ppm

Scheme 2. Selected ^{1}H-, NOESY-, and ^{19}F NMR data for tetralones **2b** and **2f**.[23]



1a **3** **1a** **4**

Scheme 3. Formation of γ-lactones[25a] and α,β-unsaturated aldehydes.[25b]

comparison with similar compounds[27] as well as 2D NMR techniques. For the formation of aldehyde **4**, a mechanism[28,29] similar to the radical Smiles arrangement reported by Zard[30] seems reasonable. If aldehyde **4** would arise from the oxidative degradation of the desired naphthol, then the fluorine atom should still be a part of the molecule.

In summary, a new access to 2-fluorotetralones from α-fluoroacetophenones by an oxidative radical addition–cyclization sequence has been developed. The reactions conditions, especially the short reaction times, are suitable for a future use in radiochemical syntheses. 2-Fluorotetralones are known as versatiles building blocks for the synthesis of biologically active fluorohydrins and fluoronaphthols.

Acknowledgments

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18. *General procedure for the synthesis of tetralones* **2**: A solution of α-fluoro-acetophenone **1** (1.00 mmol) in acetic acid (3 mL) was added to a mixture of $Mn(OAc)_3 \times 2H_2O$ (1.35 g, 5.0 mmol), potassium acetate (1.0 g) and olefin (1.0 mL) and heated in a pressure tube for 20 min (temperature of surrounding oil bath: 140 °C). The reaction mixture was cooled, diluted with water, and extracted twice with dichloromethane. The combined organic extracts were dried over sodium sulfate, concentrated and purified by flash column chromatography to give tetralones **2** as colorless oils.
19. (Table 2, entry 1) *cis*-2-Fluoro-4-hexyl-3,4-dihydro-2*H*-naphthalen-1-one (***cis*-2a**): ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.90 (t, $^3J = 6.8$ Hz, 3H), 1.22–1.42 (m, 8H), 1.69–1.80 (m, 1H), 1.96–2.11 (m, 2H), 2.58–2.67 (m, 1H), 3.13–3.22 (m, 1H), 5.15 (ddd, $^3J = 5.4$ Hz, $^3J = 13.0$ Hz, $^2J_{HF} = 48.2$ Hz, 1H), 7.36 (t, $^3J = 7.7$ Hz, 1H), 7.43 (d, $^3J = 7.7$ Hz, 1H), 7.57 (dt, $^6J_{HF} = 1.4$ Hz, $^3J = 7.7$ Hz, 1H), 8.06 (dd, $^5J_{HF} = 1.4$ Hz, $^3J = 7.7$ Hz, 1H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 34.3 (CH_2), 35.0 (d, $^2J_{CF} = 17.8$ Hz, CH_2), 36.3 (d, $^3J_{CF} = 9.9$ Hz, CH), 90.8 (d, $^1J_{CF} = 188.5$ Hz, CH), 126.7 (CH), 127.0 (CH), 127.9 (CH), 131.3 (d, $^3J_{CF} = 1.4$ Hz, C_q), 134.2 (CH), 146.2 (C_q), 193.8 (d, $^2J_{CF} = 14.5$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −189.7.
trans-2-Fluoro-4-hexyl-3,4-dihydro-2*H*-naphthalen-1-one (***trans*-2a**): ^{1}H NMR (360 MHz, $CDCl_3$): δ 0.88 (t, $^3J = 6.9$ Hz, 3H), 1.20–1.57 (m, 8H), 1.60–1.76 (m, 2H), 2.38–2.49 (m, 1H), 2.52–2.60 (m, 1H), 3.13–3.16 (m, 1H), 5.21 (ddd, $^3J = 5.4$ Hz, $^3J = 13.0$ Hz, $^2J_{HF} = 47.5$ Hz, 1H), 7.26 (d, $^3J = 7.5$ Hz, 1H), 7.35 (dt, $^4J = 1.1$ Hz, $^3J = 7.5$ Hz, 1H), 7.54 (dt, $^4J = 1.4$ Hz, $^3J = 7.5$ Hz, 1H), 8.06 (dd, $^4J = 1.4$ Hz, $^3J = 7.5$ Hz, 1H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.6 (CH_2), 28.2 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 33.3 (d, $^2J_{CF} = 17.8$ Hz, CH_2), 36.0 (CH_2), 37.8 (d, $^3J_{CF} = 11.5$ Hz, CH), 88.2 (d, $^1J_{CF} = 185.4$ Hz, CH), 127.1 (CH), 127.9 (d, $^4J_{CF} = 2.3$ Hz, CH), 128.7 (CH), 130.2 (C_q), 134.1 (CH), 147.6 (d, $^4J_{CF} = 1.6$ Hz, C_q), 193.4 (d, $^2J_{CF} = 14.2$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −195.6. MS (EI): m/z (%) = 248 (62) [M^+], 202 (12), 164 (63), 163 (37), 145 (19), 132 (22), 131 (100), 115 (23), 105 (55), 77 (92). HRMS (EI) Calcd for $C_{16}H_{21}FO$ (M^+) 248.1576. Found: 248.1577.
(Table 2, entry 2) (6*S*,6a*R*,12a*R*)- and (6*R*,6a*S*,12a*S*)-6-Fluoro-6a,7,8,9,10,11,12,12a-octahydro-6*H*-cycloocta[*a*]-naphthalen-5-one (**2b**) (major diastereoisomer):^{1}H NMR

(360 MHz, $CDCl_3$):δ 1.40–1.75 (m, 8H), 1.80–1.92 (m, 1H), 2.05–2.18 (m, 1H), 2.20–2.30 (m, 2H), 2.32–2.39 (m, 1H), 2.98–3.04 (m, 1H), 5.21 (dd, $^3J = 12.6$ Hz, $^2J_{HF} = 49.0$ Hz, 1H), 7.34 (t, $^3J = 7.6$ Hz, 1H), 7.42 (d, $^3J = 7.6$ Hz, 1H), 7.57 (dt, $^4J = 1.6$ Hz, $^3J = 7.5$ Hz, 1H), 8.03 (dd, $^4J = 1.6$ Hz, $^3J = 7.5$ Hz, 1H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 24.1 (CH_2), 26.0 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 27.8 (d, $^3J_{CF} = 3.8$ Hz, CH_2), 29.0 (d, $^4J_{CF} = 1.4$ Hz, CH_2), 41.7 (d, $^3J_{CF} = 7.0$ Hz, CH), 45.3 (d, $^2J_{CF} = 15.9$ Hz, CH), 94.6 (d, $^1J_{CF} = 191.0$ Hz, CH), 126.8 (d, $^5J_{CF} = 0.5$ Hz, CH), 126.9 (CH), 127.6 (d, $^4J_{CF} = 2.5$ Hz, CH), 131.4 (d, $J_{CF} = 1.5$ Hz, C_q), 134.2 (CH), 146.1 (d, $J_{CF} = 1.4$ Hz, C_q), 194.0 (d, $^2J_{CF} = 15.0$ Hz, C_q)^{19}F NMR (235.3 MHz, $CDCl_3$): δ −195.7. MS (EI): m/z (%) = 247 (18) [M^++H], 246 (100) [M^+], 228 (12), 213 (11), 189 (12), 176 (27), 175 (26), 163 (30), 162 (23), 145 (20), 131 (54), 118 (15), 115 (16), 103 (16), 91 (10), 77 (11). HRMS (EI) Calcd for $C_{16}H_{19}FO$ (M^+) 246.1420. Found: 246.1421.

(Table 2, entry 3) *cis*- and *trans*-2-Fluoro-4-triethylsilanyl-3,4-dihydro-2*H*-naphthalen-1-one (**2c**) (2:1 mixture of diastereoisomers):^{1}H NMR (major) (360 MHz, $CDCl_3$): δ 0.55–0.70 (m, 6H), 0.89 (t, $^3J = 7.9$ Hz, 9H), 2.53–2.61 (m, 2H), 2.80–2.87 (m, 1H), 5.20 (ddd, $^3J = 7.6$ Hz, $^3J = 12.6$ Hz, $^2J_{HF} = 47.9$ Hz, 1H), 7.10 (d, $^3J = 7.6$ Hz, 1H), 7.24 (m, 1H), 7.45 (m, 1H), 8.07 (dd, $^4J = 1.4$ Hz, $^3J = 7.9$ Hz, 1H). ^{13}C NMR (major) (90.6 MHz, $CDCl_3$): δ 3.6 ($3\times CH_2$), 7.3 ($3\times CH_3$), 26.8 (d, $^3J_{CF} = 11.9$ Hz, CH), 32.5 (d, $^2J_{CF} = 18.6$ Hz, CH_2), 90.1 (d, $^1J_{CF} = 187.1$ Hz, CH), 125.5 (CH), 127.6 (CH), 128.4 (d, $^4J_{CF} = 2.4$ Hz, CH), 130.4 (C_q), 133.8 (CH), 147.5 (C_q), 193.2 (d, $^2J_{CF} = 13.9$ Hz, C_q). ^{19}F NMR (major) (235.3 MHz, $CDCl_3$): δ −188.1. ^{1}H NMR (minor) (360 MHz, $CDCl_3$): δ 0.55–0.70 (m, 6H), 0.90 (t, $^3J = 7.9$ Hz, 9H), 2.27–2.59 (m, 2H), 2.80–2.87 (m, 1H), 5.12 (ddd, $^3J = 5.2$ Hz, $^3J = 10.3$ Hz, $^2J_{HF} = 49.0$ Hz, 1H), 7.21–7.28 (m, 2H), 7.46 (m, 1H), 7.99 (dd, $^4J = 1.3$ Hz, $^3J = 7.7$ Hz, 1H). ^{13}C NMR (minor) (90.6 MHz, $CDCl_3$): δ 2.9 ($3\times CH_2$), 7.4 ($3\times CH_3$), 23.7 (d, $^3J_{CF} = 5.4$ Hz, CH), 29.8 (d, $^2J_{CF} = 18.7$ Hz, CH_2), 90.5 (d, $^1J_{CF} = 186.7$ Hz, CH), 125.6 (CH), 127.9 (CH), 128.2 (d, $^4J_{CF} = 1.7$ Hz, CH), 131.2 (C_q), 133.7 (CH), 146.1 (C_q), 193.0 (d, $^2J_{CF} = 14.9$ Hz, C_q). ^{19}F NMR (minor) (235.3 MHz, $CDCl_3$): δ −190.0. MS (EI): m/z (%) = 278 (5) [M^+], 249 (4), 178 (6), 145 (14), 144 (100), 143 (16), 116 (30), 115 (24), 105 (11), 87 (36), 77 (20). HRMS (EI) Calcd for $C_{16}H_{23}FOSi$ (M^+) 278.1502. Found: 278.1499.

(Table 2, entry 4) *cis*- and *trans*-Acetic acid 3-fluoro-4-oxo-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl ester (**2d**) (1:1 mixture of diastereoisomers): ^{1}H NMR (360 MHz, $CDCl_3$): δ 2.05 (s, 3H), 2.06 (s, 3H), 2.22–2.35 (m, 1H), 2.43–2.55 (m, 1H), 2.59–2.72 (m, 2H), 3.43–3.56 (m, 2H), 4.33–4.46 (m, 2H), 4.42 (ddd, $^4J_{HF} = 1.3$ Hz, $^3J = 6.5$ Hz, $^2J = 11.3$ Hz, 1H), 4.55 (ddd, $^4J_{HF} = 1.4$ Hz, $^3J = 4.7$ Hz, $^2J = 11.3$ Hz, 1H), 5.17 (ddd, $^3J = 5.4$ Hz, $^3J = 12.6$ Hz, $^2J_{HF} = 48.2$ Hz, 1H), 5.41 (ddd, $^3J = 5.6$ Hz, $^3J = 12.8$ Hz, $^2J_{HF} = 47.5$ Hz, 1 H), 7.34–7.44 (m, 4H), 7.55–7.60 (m, 2H), 8.05–8.10 (m, 2H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 21.2 (CH_3), 21.2 (CH_3), 32.0 (d, $^2J_{CF} = 19.3$ Hz, CH_2), 33.6 (d, $^2J_{CF} = 19.1$ Hz, CH_2), 36.5 (d, $^3J_{CF} = 10.3$ Hz, CH), 37.5 (d, $^3J_{CF} = 11.8$ Hz, CH), 66.6 (CH_2), 67.0 (CH_2), 88.4 (d, $^1J_{CF} = 185.6$ Hz, CH), 90.4 (d, $^1J_{CF} = 188.1$ Hz, CH), 126.5 (CH), 127.8 (CH), 128.0 (d, $^4J_{CF} = 2.7$ Hz, CH), 128.0 (CH), 128.2 (d, $^4J_{CF} = 2.3$ Hz, CH), 128.8 (CH), 131.1 (d, $^4J_{CF} = 1.0$ Hz, C_q), 131.3 (d,$^4J_{CF} = 1.3$ Hz, C_q), 134.4 ($2\times CH$), 141.6 (d, $^3J_{CF} = 1.4$ Hz, C_q), 142.0 (d, $^3J_{CF} = 1.6$ Hz, C_q), 170.5 (C_q), 170.7 (C_q), 193.6 (d, $^2J_{CF} = 14.4$ Hz, C_q), 193.7 (d, $^2J_{CF} = 14.6$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −189.3, −194.1. MS (EI): m/z (%) = 237 (6) [M^++H], 176 (63), 164 (18), 148 (26), 122 (19), 105 (33), 77 (19), 49 (18), 43 (100). HRMS (EI) Calcd for $C_{11}H_9FO$ (M^+–$C_2H_4O_2$) 176.0637. Found: 176.0637. HRMS (EI) Calcd for $C_{13}H_{14}FO_3$ (M^++H) 237.0927. Found: 237.0930.

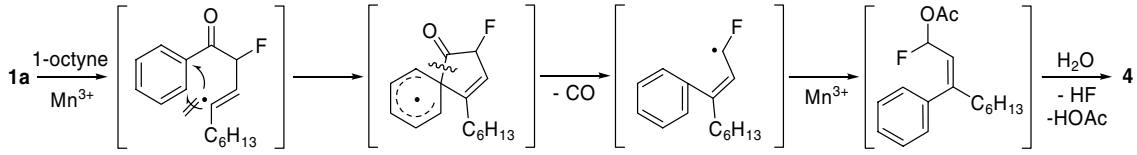
(Table 2, entry 5) (2*R*,4*S*)- and (2*S*,4*R*)-2-Fluoro-4-hexyl-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one (**2e**) (major diastereoisomer): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.88 (t, $^3J = 7.0$ Hz, 3H), 1.10–1.60 (m, 8H), 1.55 (d, $^3J_{HF} = 22.0$ Hz, 3H), 1.62–1.76 (m, 1H), 1.80–2.03 (m, 1H), 2.18 (ddd, $J = 10.5$ Hz, $J = 10.7$ Hz, $J = 12.5$ Hz, 1H), 2.39 (ddd, $^3J = 5.0$ Hz, $J = 12.5$ Hz, $J = 12.7$ Hz, 1H), 3.01–3.15 (m, 1H), 7.32–7.46 (m, 2H), 7.57 (t, $^3J = 7.5$ Hz, 1H), 8.06 (dd, $^4J = 1.3$ Hz, $^3J = 7.5$ Hz, 1H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 14.4 (CH_3), 21.8 (d, $^2J_{CF} = 26.1$ Hz, CH_3), 22.6 (CH_2), 26.0 (CH_2), 29.4 (CH_2), 31.7 (CH_2), 35.1 (d, $^4J_{CF} = 1.1$ Hz, CH_2), 36.1 (d, $^3J_{CF} = 8.8$ Hz, CH), 39.6 (d, $^2J_{CF} = 20.6$ Hz, CH_2), 94.1 (d, $^1J_{CF} = 182.1$ Hz, C_q), 127.0 (CH), 127.1 (CH), 128.3 (d, $^4J_{CF} = 1.8$ Hz, CH), 130.7 (d, $J_{CF} = 1.6$ Hz, C_q), 134.1 (CH), 145.9 (d, $J_{CF} = 1.3$ Hz, C_q), 195.4 (d, $^2J_{CF} = 16.9$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −148.5. MS (EI): m/z (%) = 262 (38) [M^+], 202 (18), 192 (18), 178 (29), 145 (20), 132 (23), 131 (100), 129 (14), 105 (17), 103 (8), 77 (10). HRMS (EI) Calcd for $C_{17}H_{23}FO$ (M^+) 262.1733. Found: 262.1731.

(Table 2, entry 6) (1*R*,4*S*,4a*R*,10*R*,10a*S*)- and (1*S*,4*R*,4a*S*,10*S*,10a*R*)-10-Fluoro-10-methyl-1,4-methylene-2,3,4,4a,10,10a-hexahydro-1*H*-phenanthren-9-one (***trans*-2f**) (major diastereoisomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (d, $^2J = 10.8$ Hz, 1H), 0.99 (d, $^2J = 10.8$ Hz, 1H), 1.30–1.70 (m, 4H), 1.65 (d, $^3J_{HF} = 23.0$ Hz, 3H), 2.13–2.18 (m, 2H), 2.41 (dd, $^3J = 7.8$ Hz, $^3J_{HF} = 21.0$ Hz, 1H), 3.20 (d, $^3J = 7.8$ Hz, 1H), 7.27–7.34 (m, 2H), 7.53 (t, $^3J = 7.5$ Hz, 1H), 7.76 (d, $^3J = 7.5$ Hz, 1H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 19.6 (d, $^2J_{CF} = 23.9$ Hz, CH_3), 28.3 (CH_2), 31.5 (CH_2), 32.6 (CH_2), 38.4 (d, $^3J_{CF} = 11.3$ Hz, CH), 46.2 (CH), 47.0 (CH), 52.0 (d, $^3J_{CF} = 22.8$ Hz, CH), 94.1 (d, $^1J_{CF} = 164.8$ Hz, C_q), 126.2 (CH), 126.3 (CH), 128.8 (d, $^4J_{CF} = 0.5$ Hz, CH), 132.7 (d, $J_{CF} = 1.4$ Hz, C_q), 133.5 (CH), 145.8 (d, $J_{CF} = 1.1$ Hz, C_q), 195.4 (d, $^2J_{CF} = 26.3$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −130.9. MS (EI): m/z (%) = 244 (100) [M^+], 216 (34), 176 (40), 158 (55), 145 (44), 133 (25), 125 (30), 115 (28). HRMS (EI) Calcd for $C_{16}H_{17}FO$ (M^+) 244.1263. Found: 244.1262.

(1*R*,4*S*,4a*R*,10*S*,10a*S*)- and (1*S*,4*R*,4a*S*,10*R*,10a*R*)-10-Fluoro-10-methyl-1,4-methylene-2,3,4,4a,10,10a-hexahydro-1*H*-phenanthren-9-one (***cis*-2f**) (minor diastereoisomer): ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (d, $^2J = 11.0$ Hz, 1H), 1.11 (d, $^2J = 11.0$ Hz, 1H), 1.30–1.75 (m, 4H), 1.41 (d, $^3J_{HF} = 22.0$ Hz, 3H), 2.17 (s, 1H), 2.34 (d, $^3J = 8.0$ Hz, 1H), 2.67 (s, 1H), 3.24 (d, $^3J = 8.0$ Hz, 1H), 7.28–7.35 (m, 2H), 7.55 (t, $^3J = 7.3$ Hz, 1H), 7.77 (d, $^3J = 7.3$ Hz, 1H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 27.0 (d, $^2J_{CF} = 26.3$ Hz, CH_3), 28.1 (CH_2), 31.1 (CH_2), 32.2 (CH_2), 36.9 (d, $^4J_{CF} = 6.7$ Hz, CH), 47.4 (d, $^4J_{CF} = 6.7$ Hz, CH), 47.7 (d, $^5J_{CF} = 0.8$ Hz, CH), 51.6 (d, $^3J_{CF} = 19.9$ Hz, CH), 94.9 (d, $^1J_{CF} = 189.6$ Hz, C_q), 125.8 (d, $^4J_{CF} = 2.1$ Hz, CH), 126.5 (CH), 128.9 (CH), 132.4 (d, $J_{CF} = 2.1$ Hz, C_q), 134.0 (CH), 143.8 (C_q), 197.6 (d, $^2J_{CF} = 17.8$ Hz, C_q). ^{19}F NMR (235.3 MHz, $CDCl_3$): δ −159.9.

20. An experiment with α-fluoroacetophenone (**1a**) and 1-octene run under the conditions described in the general procedure Ref. 18 showed complete disappearance of **1a** after 8 min.
21. For vicinal proton–fluorine spin–spin couplings, see: Williamson, K. L.; Hsu, Y.-F. L.; Hall, F. H.; Swager,

S.; Coulter, M. S. *J. Am. Chem. Soc.* **1968**, *90*, 6717–6722.
22. For vicinal *endo–endo* and *exo–exo* spin–spin couplings in norbornanes, see: Marshall, J. L.; Walter, S. R.; Barfield, M.; Marchand, A. P.; Marchand, N. W.; Segre, A. L. *Tetrahedron* **1976**, *32*, 537–542.
23. ^{1}H NMR spectra are referenced to TMS (0.0 ppm), ^{19}F NMR spectra are referenced to $CFCl_3$ (0.0 ppm).
24. For lactone formation, both a radical attack on the carbonyl oxygen atom and on the manganese have been proposed: (a) Fristad, W. E.; Peterson, J. R. *J. Org. Chem.* **1985**, *50*, 10–18; (b) Snider, B. B. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds., 1st ed.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 198–218.
25. (a) 5-(2-Fluoro-3-oxo-3-phenyl-propyl)-dihydro-furan-2-one (**3**) (major diastereoisomer): ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.87–1.98 (m, 1H), 2.18–2.28 (m, 2H), 2.42–2.50 (m, 1H), 2.58–2.63 (m, 2H), 4.82–4.88 (m, 1H), 5.92 (ddd, $^{3}J = 5.2$ Hz, $^{3}J = 7.2$ Hz, $^{2}J_{HF} = 48.9$ Hz, 1H), 7.50 (t, $^{3}J = 7.7$ Hz, 2H), 7.62 (t, $^{3}J = 7.7$ Hz, 1H), 7.96 (d, $^{3}J = 7.7$ Hz, 2H). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 28.1 (CH_2), 28.6 (CH_2), 38.4 (d, $^{2}J_{CF} = 20.6$ Hz, CH_2), 76.1 (d, $^{3}J_{CF} = 2.0$ Hz, CH), 89.5 (d, $^{1}J_{CF} = 182.0$ Hz, CH), 128.8 (d, $^{4}J_{CF} = 3.0$ Hz, $2 \times$ CH), 128.9 (CH), 133.7 (C_q), 134.2 ($2 \times$ CH), 176.3 (C_q), 195.0 (d, $^{2}J_{CF} = 18.5$ Hz, C_q) MS (EI): m/z (%) = 236 (2) [M^+], 209 (1), 194 (1), 153 (1), 149 (1), 138 (4), 106 (9), 105 (100), 77 (25). HRMS (EI) Calcd for $C_{13}H_{13}FO_3$ (M^+) 236.0849. Found: 236.0849.; (b) 3-Phenyl-non-2-enal (**4**) (1:1 mixture of *E*/*Z*-isomers): ^{1}H NMR (*E*) (500 MHz, $CDCl_3$): δ 0.89 (t, $^{3}J = 7.0$ Hz, 3H), 1.10–1.45 (m, 8H), 3.05 (t, $^{3}J = 7.8$ Hz, 2H), 6.30 (d, $^{3}J = 8.0$ Hz, 1H), 7.28–7.30 (m, 2H), 7.41–7.44 (m, 2H), 7.50–7.53 (m, 1H), 10.18 (d, $^{3}J = 8.0$ Hz, 1H). ^{1}H NMR (*Z*) (500 MHz, $CDCl_3$): δ 0.89 (t, $^{3}J = 7.0$ Hz, 3H), 1.10–1.45 (m, 8H), 2.60 (t, $^{3}J = 7.5$ Hz, 2H), 6.13 (d, $^{3}J = 8.5$ Hz, 1H), 7.28–7.30 (m, 2H), 7.41–7.44 (m, 2H), 7.50–7.53 (m, 1H), 9.47 (d, $^{3}J = 8.5$ Hz, 1H). ^{13}C NMR (*E*/*Z*) (90.6 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 27.4 (CH_2), 28.8 (CH_2), 29.1 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 31.5 (CH_2), 39.7 (CH_2), 126.6 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.8 (CH), 128.9 (CH), 129.8 (CH), 137.9 (C_q), 139.9 (C_q), 163.3 (C_q), 166.7 (C_q), 191.0 (CH), 193.7 (CH) (signals missing due to overlap). MS (EI): m/z (%) = 216 (100) [M^+], 215 (61), 159 (79), 145 (71), 131 (80), 118 (74), 117 (38), 115 (48), 103 (27), 91 (57), 77 (25). HRMS (EI) Calcd for $C_{15}H_{20}O$ (M^+) 216.1514. Found: 216.1517.
26. Santi, R.; Bergamini, F.; Citterio, A.; Sebastiano, R.; Nicolini, M. **1992**, *57*, ; pp 4250–4255.
27. For a characterization of (*Z*)-3-phenyl-2-pentenal, see: Chou, S.-S. P.; Kuo, H.-L.; Wang, C.-J.; Tsai, C.-Y.; Sun, C.-M. *J. Org. Chem.* **1989**, *54*, 868–872.
28. For cyclizations of vinyl radicals on aryl rings, see: Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1998**, *63*, 537–542.
29. For the formation of aldehyde **4**, the following mechanism is proposed:



30. For the radical Smiles-type rearrangement, see: Bacque, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817–3820.