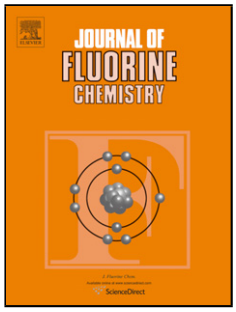

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Enantioselective electrophilic fluorination of α-aryl-tetralones using a preparation of *N*-fluoroammonium salts of cinchonine

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Graphical Abstract

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Enantioselective electrophilic fluorination of α-aryl-tetralones using a preparation of *N*-fluoroammoniumsalts of cinchonine

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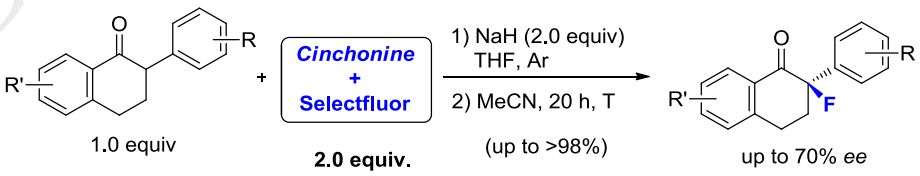

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ABSTRACT

The enantioselective electrophilic fluorination of α-aryl-tetralones is promoted by cinchonine/selectfluor combinations. This strategy allows a facile synthesis of the corresponding 2-fluoro-2-aryl-1-tetralones with excellent yields (up to >98%) and moderate to good enantioselectivity (up to74%).

1. Introduction

Several bioactive chiral compounds bearing stereogenic centers at the α-position of carbonyl groups, with one enolizable hydrogen, can suffer rapidly epimerization under physiological conditions [1]. For example, in propionic acid derivatives, known as profens (**1**) (Figure 1), the α-CH_3 group increases cyclooxygenase inhibitory activity, the *S*-(+)-enantiomer being much more potent. Fortunately, *R*-(-)-enantiomers are *in vivo* stereospecifically transformed to the active S-(+)-enantiomers [2]. Thalidomide (**2**) is an important example of how the same molecule has different effects depending on the enantiomer. (R)-enantiomer (**2a**) causes the clinically effective sedative hypnotic effects and the (S)-enantiomer (**2b**) is responsible for the teratogenic side effects [3]. Another interesting example of epimerization occurs in the biosynthesis of isoflavonoids. Genistein, the main isoflavanone of soybean, is stereospecifically reduced to (*R*)-dihydrogenistein (**3**) (Figure 1), which is further isomerized to (*S*)-dihydrogenistein by enzymatic or biological keto-enol tautomerization, such as occurs in daidzein metabolism [4]. Both (*R*)-dihydrogenistein (**3**) and its enantiomer are biotransformed into tetracyclic isoflavonoids, as pterocarpans.

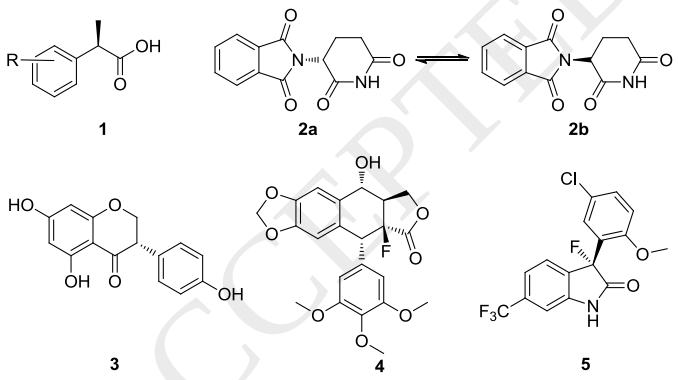
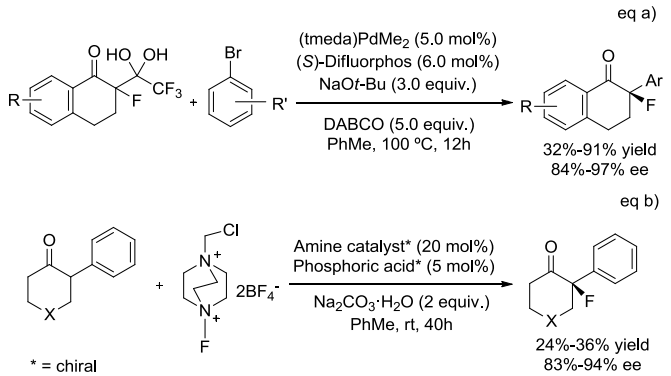


Figure 1. Propionic acid derivatives (**1**), (R)-thalidomide (**2a**), (S)-thalidomide (**2b**), (*S*)-dihydrogenistein (**3**), 2-fluoropodophyllotoxin (**4**) and potassium ion channel modulator MaxiPost (BMS-204352) (**5**).

In the last decades fluorine-containing compounds have attracted the attention of medicinal chemists and pharmaceutical industry [5]. The replacement of a hydrogen atom by a fluorine atom in bioactive compounds promote changes in the stability, lipophilicity and reactivity [6]. In the particular case of fluorination at the α-position of carbonyl groups, bearing a tertiary stereogenic center, the obtained substances containing configurationally stable quaternary stereogenic centers, prevented the epimerization process [7]. For example, in 2-fluoropodophyllotoxin (**4**) (Figure 1), an antitumor agent, the fluorination promotes metabolic stability [8]. In the potassium ion channel modulator MaxiPost (BMS-204352) (**5**) (Figure 1) the absolute configuration is important for the biological activity and this compound was used as a pure enantiomer [9]. In consequence, chirality plays a key role in the efficacy of many compounds and thus enantioselective synthesis is an important strategy in pharmaceutical industry to access these compounds in enantiomerically pure form [10].

The electrophilic fluorination of the α-carbonyl center is one of the most common forms to generate fluorine-containing compounds [11].Some methods to generate enantioselective α-fluoro-α-aryl cyclic carbonyl compounds can be divided in two strategies: one is the enantioselective α-arylation of α-fluoroketones demonstrated by Hartwig and co-workers[12] using palladium catalysts and chiral ligands (Scheme 1, eq a). The other one is the enantioselective α-fluorination of α-aryl-ketones with selectfluor, via cooperative catalysis of enamine and chiral anionic phase-transfer described by Toste and co-workers [13] (Scheme 1, eq b).



Scheme 1. Synthesis of enantiopure α-fluoro-α-aryl cyclic carbonyl compounds: (eq a) enantioselective α-arylation of fluoro-ketones and (eq b) enantioselective α-fluorination of α-aryl-ketones.

The α-aryl cyclic carbonyl moiety is present in the structure of many biological active compounds and is also found in many natural products like isoflavonoids, which are secondary

metabolites present in *Leguminosae* family [7]. An example is cajanol **6** (Figure 2), an isoflavanone which has antiproliferative activity towards MCF-7 human breast cancer cells, promoting disruption of the cell cycle in the G2/M phase and induction of apoptosis through ROS-mediated mitochondrial pathway [14]. Bonfield *et al*. [15] and Amato *et al*. [16] synthesized isoflavanone analogues (**7a** and **7b**) which acted as aromatase inhibitors. Compound **7** showed antiproliferative properties in MCF7 cells in culture (Figure 2). Carba-analogues of isoflavanones, like **8** (Figure 2), were also synthesized and evaluated as hepatitis C virus inhibitors by Manvar *et al*. [17]. The biological properties of all these compounds were studied in the racemic form.

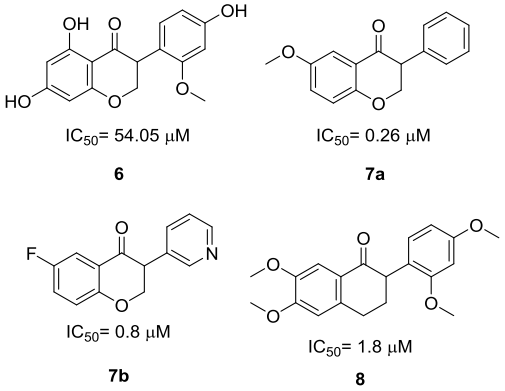


Figure 2. Cajanol (**6**), aromatase inhibitors (**7a**,**b**) and hepatitis C virus inhibitor (**8**)

So, according to all these precedents, we combined all them in this work with the idea of synthesizing enantioenriched 2-aryl-2-fluoro-1-tetralones by enantioselective α-fluorination of *o*-substituted α-aryl-tetralones using ammonium salts from *Cinchona* alkaloids.

2. Results and discussion

Previous studies on the fluorination of α-benzyl cyclic carbonyl compounds, including α-benzyl indanones and α-benzyl tetralones, using achiral *N*-fluorosulfonamide agents [18], chiral Pd-complexes [8b] and *N*-fluoroammonium salts of *Cinchona* alkaloid derivatives [5,10b,[19] have been reported in the literature.

Several steps are required for synthesizing chiral *N*-fluorosulfonamide agents and most common involves the formation of the N-F bond using elemental fluorine or $FClO_3$ at low temperatures (-78 ºC), using strong bases (LDA or LiHMDS) [16]. In contrast, the reactions using *N*-fluoroammonium salts of *Cinchona* alkaloids and their derivatives are performed under milder conditions. So we examined initially the reaction employing catalytic amounts (20 mol%) of *Cinchona* alkaloids and α-(2-methoxyphenyl)tetralone (**9a**) [15]. A sodium enolate of **9a**, generated by using sodium hydride in THF, was treated with selectfluor and NFSI as fluorinating agents and substoichiometric amounts of quinine, quinidine, cinchonidine, cinchonine and $(DHQN)_2PHAL$ as chiral sources (Figure 3).

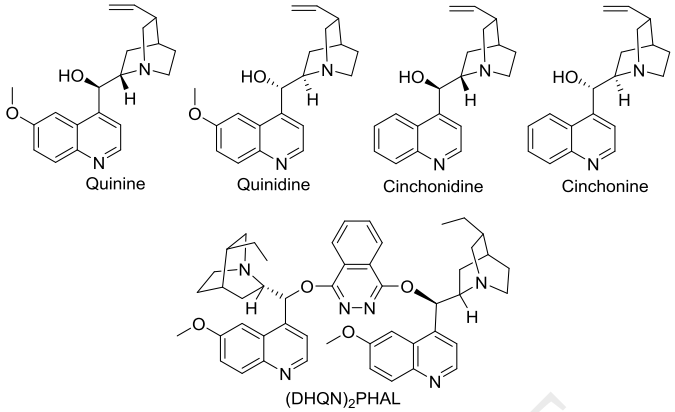
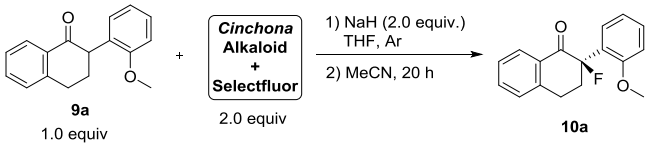


Figure 3. *Cinchona* derived alkaloids used in this work.

Using these last reaction conditions no conversion was observed. Indeed, this problem was solved by using 2 equiv of *Cinchona* derivatives in an equimolar mixture with selectfluor, like Cahard *et al*. [10b]. The conditions were optimized by changing temperature and the *Cinchona* alkaloids (Table 1). The highest ee for product **10a** was observed when cinchonine was used as alkaloid at 0 ºC (Table 1, entry 9) although the yields were higher decreasing the temperature (Table 1, entries 10-13). No reaction was observed neither when $(DHQN)_2PHAL$ was used (Table 1, entry 14) nor when quinidine was employed at -20 ºC (not depicted in Table 1). So, we extended these reaction conditions (cinchonine/0ºC) to other α-aryl tetralones with changes in the A or in the C rings (Scheme 2). The reaction performed with *O*-allylated cinchonine or *O*-allylated hydrocinchonine afforded racemic compounds (not shown in Table 1).

Table 1.

Fluorination of the enolate of α-(2-methoxyphenyl)tetralone (**9**).

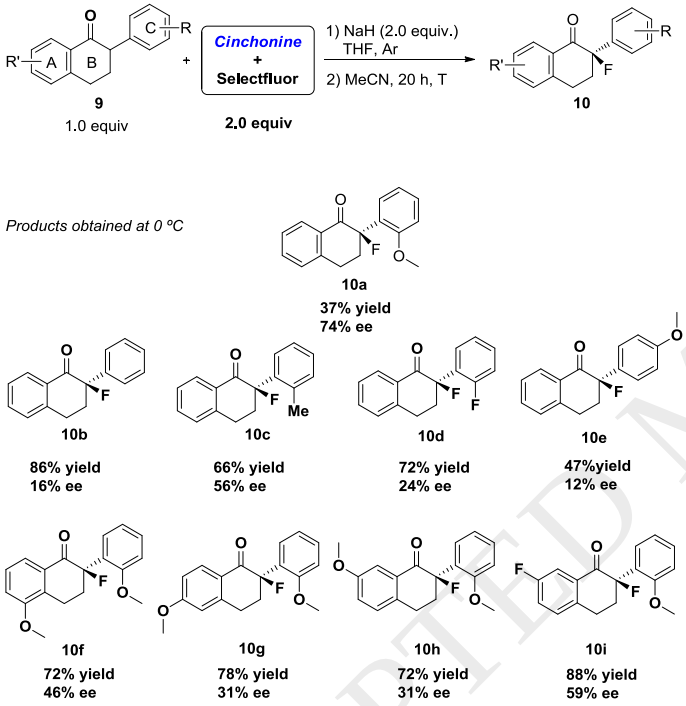


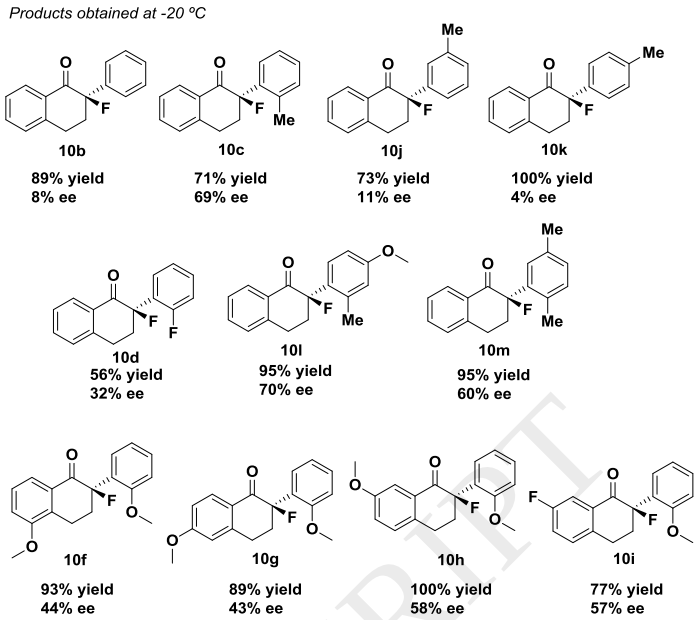
Entry	Alkaloid	T (ºC)	Yield (%)[a]	ee (%)[b]
1	Quinine	rt	57	22
2	Quinine	0	59	0
3	Quinine	-20	67	8
4	Cinchonidine	rt	64	6
5	Cinchonidine	0	73	20
6	Cinchonidine	-20	82	6
7	Cinchonine	rt	11	44
8	Cinchonine	0	37	74
9	Cinchonine	-5	74	57
10	Cinchonine	-10	86	55
11	Cinchonine	-20	99	60
12	Cinchonine	-30	81	59
13	Quinidine	rt	22	20

14	$(DHQD)_2PHAL$	rt	NR	--

[a] Isolated yield after column chromatography.
[b]Determined by HPLC using Daicel-Chiralpak AD-H column (Hex:IPA 5%).

Compounds **10a-i** were obtained at 0 ºC from low to moderate ee, achieving the maximum 74% ee when **9a** was used as starting compound (Scheme 2). So, the reaction performed with cinchonine at -20 ºC was next tested for these starting tetralones and others (Scheme 2). Under these reaction conditions the ee was higher or remained unaltered with respect to the others obtained at 0 ºC. The better ee was obtained for the *ortho*-methyl derivatives **10c** and **10l**, with 69% ee and 70% ee, respectively. By changing the α-aryl substituents from *ortho*- to *meta*- and *para*-positions the enantiomeric excesses decreased (products **10c**, **10j** and **10k**). It was noted that changing the A ring substituents, compounds with substituents at C-7 position, products **10h** and **10i** kept almost the same results of the model substrate at -20 ºC with 58% ee and 57% ee, respectively. Substituents in other positions induced a small decrement of ee.





Scheme 2. Some different products obtained by enantioselective α-fluorination using the selected conditions at different temperatures.

The absolute configuration was assigned by measurement of the optical rotation and using the octant rule that is compared with reported values [1,[20]. Also, vibrational circular dichroism (VCD) analysis of compound **10l** confirmed the (*R*)-configuration. The calculated and experimental VCD spectra of 2-Fluoro-2-(4-methoxy-2-methylphenyl)tetralone is illustrated in Figure 4. It is found that the predicted spectra have a clear and crucial similarity with the experimental one in the region of the carbonyl group vibration (~1700 cm^{-1}). The fingerprint region of the vibrational optical activity spectra (not shown in Figure 4) did not completely match due to the presence of a 85:15 ratio of enantiomers in the sample.

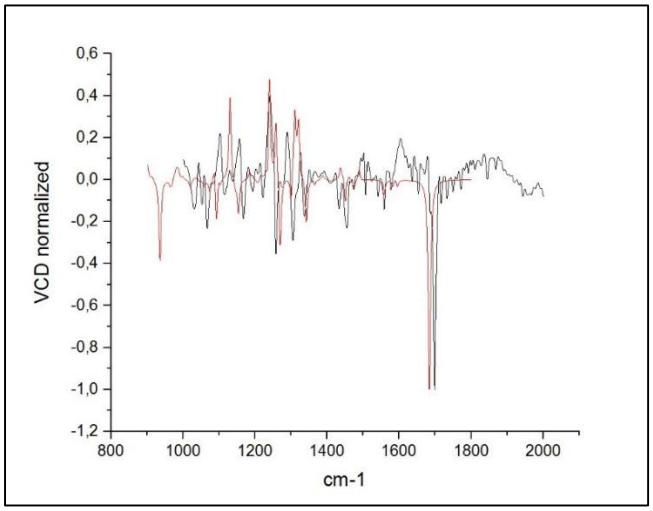


Figure 4. VCD analysis of molecule **10l**. Calculated plot for the (*R*)-enantiomer in red, and experimental spectra in black.

A known effect in medicinal chemistry is the *ortho*-effect, which is the result of a conformational change forced by the introduction of a bulky group [21]. Much work is in process to

build a molecular model for justifying this stereoselective behavior with the transition states developed by Lam and Houk (2014) [22], which described a stereoselective model for *Cinchona* alkaloid-derived primary amines to control the fluorinations of cyclic ketones by the cyclic TS in chair and boat conformations.

2. Conclusions

In this work, we have screened different combination of *N*-fluoroammonium salts of *Cinchona* alkaloid derivatives at various temperatures for the enantioselective electrophilic fluorination of α-aryl-α-tetralones using an unusual substrate as model, α-(2-methoxyphenyl)tetralone, due to the importance of o-substituent compounds in the pharmaceutical chemistry and synthesis of natural products. The enantioselectivity in this reaction showed a strong dependence of the substituent in C ring for electron-donor *o*-substituent. Although moderately efficient from the point of view of enantioselectivity (up to 70% ee). These reactions are highly sensitive to the structure of *Cinchona* derivatives, to the nature of the substrates and to the temperature. To complete the reaction, the sodium enolate of the corresponding tetralone was allowed to react with fluorinated agent formed by the most appropriate chiral base cinchonidine and selectfluor (both used in stoichiometric amounts) in acetonitrile at 0 or -20 ºC

4. Experimental

4.1. General

Reagents and dry solvents were obtained commercially (Aldrich and Alfa aesar) and used without further purification. CEM Discovery and Explorer-Coolmate accessory were employed in the microwave-assisted reactions for the generation of α-ayltetralones. NMR spectra were recorded in deuterated chloroform, with tetramethylsilane (TMS) as internal standard, unless otherwise stated. The samples were analyzed at 300 and 400 MHz ^{1}H NMR and 75 and 101 MHz ^{13}C NMR using a Bruker AV300 and a Bruker AV400, respectively. Chemical shifts are reported as δ values (ppm). The following abbreviations are used for the multiplicities: s: singlet, d: doublet, dd: doublet of doublet, t: triplet, q: quadruplet, m: multiplet. Melting points were uncorrected. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using an Agilent 6890N Network GC system and Agilent 5973 Network Mass Selective Detector. High resolution mass spectra (GC-EI) were recorded using a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Vibrational Circular Dichroism analysis was performed in a VCD Jasco FVS-6000 incorporating MCT-V detector. Optical rotations were measured with a Perkin-Elmer 341 polarimeter. The progress of reactions was monitored by ^{1}H NMR and column chromatography was carried out on silica gel, the flash column chromatography silica gel 60 (40-60 mm) was employed. Analytical thin layer chromatography (TLC) was done using ALUGRAM® Xtra SIL G/ UV_{254} silica gel plates, and the spots were determined under UV light (λ = 254 nm). The enantiomeric excesses of products were determined by chiral HPLC analysis at 254 nm using the indicated chiral phase column.

4.2. General procedure for the synthesis of α-aryl-tetralones

In a microwave tube were added a suspension of $Pd(dba)_2$ (5mol%), tBu$_3$PHBF$_4$ (10mol%), NaOH (2eq), aryl bromide (1.2eq) and α-tetralone (1.0eq) in a mixture of degassed dioxane/water (4:1, v/v, 2-4 mL) and heated under Ar and microwave irradiation (100W of initial power, 100 ºC, 60 min, infrared probe). Then, the mixture was allowed to cool to rt, diluted in AcOEt, washed with saturated NH_4Cl solution, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column with *n*-hexane:AcOEt (95:5) as solvent.

Compounds ***9a*** [15], ***9b*** [23], ***9c*** [23], ***9d*** [24], ***9e*** [23], ***9f*** [15], ***9g*** [15], ***9h*** [15], ***9j*** [23] and ***9k*** [23] are known, new compounds follow:

*4.2.1. 7-Fluoro-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (**9i**)*: yellow solid (24 mg, 90%). Mp = 79-82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.29–7.23 (m, 2H), 7.18 (td, *J* = 8.3, 2.6 Hz, 1H), 7.09 (d, *J* = 7.4 Hz, 1H), 6.92 (dd, *J* = 15.3, 7.8 Hz, 2H), 3.99 (dd, *J* = 12.4, 4.6 Hz, 1H), 3.73 (s, 3H), 3.11 – 3.03 (m, 1H), 2.98 (dt, *J* = 16.3, 3.8 Hz, 1H), 2.48 (ddd, *J* = 24.7, 12.5, 4.4 Hz, 1H), 2.26 (ddd, *J* = 12.9, 8.4, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.05 (d, *J* = 1.8 Hz), 161.55 (d, *J* = 245.7 Hz), 156.95, 139.76 (d, *J* = 3.0 Hz), 134.65 (d, *J* = 6.1 Hz), 130.43 (d, *J* = 7.1 Hz), 129.42, 128.89, 128.29, 120.76, 120.33 (d, *J* = 22.2 Hz), 113.43 (d, *J* = 21.9 Hz), 111.09, 55.41, 49.87, 29.89, 28.75. HRMS (ESI): *m/z* calcd. for $C_{17}H_{15}FO_2$: 270.1058; found: 270.1054.

*4.2.2. 2-(4-Methoxy-2-methylphenyl)-3,4-dihydronaphthalen-1(2H)-one (**9l**)*: brown solid (231.7 mg, yield 87%). Mp = 77-79 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.49 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 (t, *J*= 7.6 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.77 (d, *J* = 2.7 Hz, 1H), 6.71 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.90 (dd, *J* = 11.9, 4.8 Hz, 1H), 3.77 (s, 3H), 3.19 – 3.10 (m, 1H), 3.05 (dt, *J* = 16.6, 4.2 Hz, 1H), 2.48 – 2.30 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.35, 158.25, 144.10, 137.95, 133.38, 133.06, 130.87, 128.80, 128.52, 127.76, 126.74, 116.14, 111.35, 55.17, 50.89, 30.56, 29.53, 20.18. HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O_2$ $[M]^+$ = 266.1307, found 266.1310.

*4.2.3. 2-(2,5-Dimethylphenyl)-3,4-dihydronaphthalen-1(2H)-one (**9m**)*: yellow solid (27.4 mg, yield 55%). Mp = 66-68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.51 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (dd, *J* = 16.1, 7.8 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.99 (dd, *J* = 7.7, 1.8 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 3.94 (dd, *J* = 12.1, 4.8 Hz, 1H), 3.24 – 3.01 (m, 2H), 2.41 (dddd, *J* = 13.3, 8.8, 3.5, 2.5 Hz, 2H), 2.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.21, 144.10, 138.49, 135.47, 133.38, 133.31, 133.08, 130.44, 128.77, 128.39, 127.79, 127.69, 126.77, 51.62, 30.49, 29.58, 21.11, 19.48. HRMS (ESI): *m/z* calcd for $C_{18}H_{18}O$ $[M]^+$= 250,1358, found 250.1348.

4.3. General procedure for the synthesis of 2-fluoro-2-aryl-1-tetralones

A mixture of cinchonine (58.88 mg, 0.2 mmol) and selectfluor (70.85 mg, 0.2 mmol) in dry MeCN (1 mL) was stirred for 1h at rt. This mixture was added to another mixture containing α-aryltetralone (0.1mmol) and NaH (4.8 mg, 0.2 mmol) in THF (1 mL) under Ar, which was stirred previously 30 min at -20ºC. The resulting mixture was stirred at -20ºC for 20 h and then water was added (5 mL) extracted with AcOEt (3x5 mL). The organic phase was washed with saturate $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by silica gel column with *n*-hexane:diethyl ether (90:10) as solvent.

*4.3.1. 2-Fluoro-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (**10a**):* yellow solid (10 mg, 37%, ee 74%). Mp = 110-112 °C. $[\alpha]_D^{25}$ = -41.88 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J*= 7.8 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.52

(t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.33 (dd, *J* = 12.3, 4.8 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.86 (t, *J* = 8.9 Hz, 1H), 3.56 (s, 3H), 3.34 – 3.23 (m, 1H), 2.97 – 2.79 (m, 2H), 2.45 (ddd, *J* = 17.8, 9.1, 4.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.31 (d, *J* = 18.1 Hz), 154.91 (d, *J* = 6.1 Hz), 143.31, 133.43, 131.80, 129.52 (d, *J* = 1.0 Hz), 128.99 (d, *J* = 22.6 Hz), 128.45, 128.17, 126.93, 126.13 (d, *J* = 13.3 Hz), 121.10 (d, *J* = 1.7 Hz), 111.57, 94.76 (d, *J* = 177.6 Hz), 55.38, 34.85 (d, *J* = 24.0 Hz), 25.14 (d, *J* = 4.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -162.87 (dd, *J* = 37.5, 13.4 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R= 8.69 min (minor), t_R = 11.20 min (major). GC-MS (EI): *m/z* calcd. for $C_{17}H_{15}FO_2$: 270.1056; found: 270.1052.

4.3.2. 2-Fluoro-2-phenyl-3,4-dihydronaphthalen-1(2H)-one ***(10b)*** [1,21,22]: yellow oil (20.7 mg, yield 89%, ee 16%). $[\alpha]_D^{23}$ = +42.35 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.45 – 7.41 (m, 1H), 7.37 (s, 5H), 7.26 (d, *J* = 7.7 Hz, 1H), 3.18 – 3.06 (m, 1H), 2.92 – 2.66 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.87 (d, *J* = 18.3 Hz), 143.14, 136.75 (d, *J* = 22.6 Hz), 134.23, 132.18, 129.13 (d, *J* = 2.3 Hz), 128.84, 128.62, 128.11 (d, *J* = 1.4 Hz), 127.22, 126.09 (d, *J* = 5.8 Hz), 96.02 (d, *J* = 184.4 Hz), 35.52 (d, *J* = 25.0 Hz), 26.38 (d, *J* = 9.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -144.94 (t, *J* = 10.5 Hz).HPLC (Chiralpack AS-H column, hex/i-PrOH= 99/1, 1.0 mL/min, 254 nm) t_R = 17.45 min (major), t_R = 23.66 min (minor). GC-MS (*m/z*, relative intensity): 240.1 (M^+, 18), 118.1 (100), 90.1 (51).

4.3.3.2-Fluoro-2-(o-tolyl)-3,4-dihydronaphthalen-1(2H)-one (***10c)*** [22]: yellow solid (18 mg, yield 71%, ee 69%). Mp = 69-73 °C. $[\alpha]_D^{25}$ = -66.59 (*c* 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.24 – 7.19 (m, 2H), 7.19 – 7.06 (m, 2H), 3.26 – 3.14 (m, 1H), 2.91 – 2.73 (m, 2H), 2.62 – 2.49 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.92 (d, *J* = 19.0 Hz), 143.50, 136.34 (d, *J* = 20.9 Hz), 135.59, 134.21, 132.29, 131.98, 128.78, 128.57, 128.38, 127.29, 126.12 (d, *J* = 11.3 Hz), 125.62, 96.90 (d, *J* = 180.6 Hz), 34.90 (d, *J* = 24.5 Hz), 25.83 (d, *J* = 7.0 Hz), 21.34 (d, *J* = 4.4 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -154.22 (dd, *J* = 23.8, 10.9 Hz).HPLC (Chiralcel OD-H column, hex/iPrOH = 99:1, 1.0 mL/min, 254 nm) t_R= 12.94 min (minor), t_R = 16.13 min (major).GC-MS (*m/z*, relative intensity): 254.2 (M^+, 6), 234.1 (40), 118.1 (100), 90.1 (56).

4.3.4. 2-Fluoro-2-(2-fluorophenyl)-3,4-dihydronaphthalen-1(2H)-one ***(10d)*** [22]: yellow solid (14.5 mg, yield 56%, ee 32%). Mp = 74-76ºC. $[\alpha]_D^{25}$ = -31.70 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.45 – 7.34 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.22 (td, *J* = 7.6, 1.1 Hz, 1H), 7.12 – 7.04 (m, 1H), 3.35 (ddd, *J* = 15.4, 8.7, 4.0 Hz, 1H), 3.03 – 2.80 (m, 2H), 2.68 – 2.54 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.60 (d, *J* = 19.2 Hz), 159.06 (dd, *J* = 247.1, 5.4 Hz), 143.46, 134.15, 131.03, 130.42 (d, *J* = 8.3 Hz), 128.68, 127.36 (d, *J* = 3.6 Hz), 127.19, 126.28 (dd, *J* = 23.7, 12.7 Hz), 124.27 (d, *J* = 2.5 Hz), 115.92 (d, *J* = 21.8 Hz), 94.27 (dd, *J* = 181.5, 2.9 Hz), 34.95 (dd, *J* = 24.0, 3.0 Hz), 25.25 (d, *J* = 6.0 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -110.95 – -111.10 (m), 161.51 (dd, *J* = 33.5, 10.8 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R= 8.36 min (minor), t_R = 11.78 min (major). GC-MS (*m/z*, relative intensity): 258.1 (M+, 22), 118.1 (100), 90.1 (44).

4.3.5. 2-Fluoro-2-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one ***(10e)*** [22]: orange oil (24.5 mg, yield 91%, ee 6%). $[\alpha]_D^{26}$ = +15.91 (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (dd, *J* = 12.9, 5.1 Hz, 1H), 7.36 – 7.30 (m, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 6.92 – 6.85 (m, 2H), 3.80 (d, *J* = 2.2 Hz, 3H), 3.09 (ddd, *J* = 11.0, 6.4, 4.0 Hz, 1H), 2.93 – 2.61 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.27 (d, *J* = 18.3 Hz), 160.23 (d, *J* = 2.2 Hz), 142.94, 134.14, 132.15, 128.78, 128.01 (d, *J* = 0.7 Hz), 127.90 (d, *J* = 4.8 Hz), 127.15, 114.04, 95.86 (d, *J* = 184.6 Hz), 55.27, 34.97 (d, *J* = 25.5 Hz), 26.66 (d, *J* = 9.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -145.71 (t, *J* = 10.7 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 99:1, 1.0 mL/min, 254 nm) t_R = 25.22 min (major), t_R = 29.76 min (minor). GC-MS (*m/z*, relative intensity): 270.1 (M^+, 9), 250.1 (100), 235.1 (14), 207.1 (18), 178.1 (48), 152.1 (18), 118.1 (66), 90.1 (32).

4.3.6. *2-Fluoro-5-methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one* ***(10f)****:* yellow solid (28 mg, yield 93%, ee 44%). Mp = 122-126 ºC. $[\alpha]_D^{23.8}$ = -12.50 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.57 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.11 – 7.04 (m, 2H), 6.92 – 6.87 (m, 1H), 3.90 (s, 3H), 3.62 (s, 3H), 3.01 (dd, *J* = 7.5, 4.7 Hz, 2H), 3.00 – 2.78 (m, 1H), 2.54 – 2.39 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.58 (d, *J* = 18.4 Hz), 156.41, 155.26 (d, *J* = 5.7 Hz), 132.79, 132.40, 129.62 (d, *J* = 1.1 Hz), 128.58 (d, *J* = 22.4 Hz), 127.22, 126.38 (d, *J* = 12.7 Hz), 121.07 (d, *J* = 1.4 Hz), 119.78, 114.34, 111.68 (d, *J* = 1.2 Hz), 94.70 (d, *J* = 178.0 Hz), 55.72, 55.47, 34.01 (d, *J* = 24.0 Hz), 18.56 (d, *J* = 4.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -161.44 (dd, *J* = 36.2, 12.6 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R = 10.40 min (minor), t_R = 14.64 min (major).GC-MS (EI): *m/z* calcd for $C_{18}H_{17}FO_3$ (M^+Na^+): 323.1053, found: 323.1057.

4.3.7. *2-Fluoro-6-methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one* ***(10g)****:* yellow solid (26.6 mg, yield 89%, ee 43%). Mp = 89-90 °C. $[\alpha]_D^{24.5}$ = -11.49 (*c* 0.8, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.6, 4.7 Hz, 1H), 7.58 (ddd, *J* = 11.7, 6.3, 5.6 Hz, 1H), 7.39 – 7.31 (m, 1H), 7.11 – 7.03 (m, 1H), 6.95 – 6.87 (m, 2H), 6.77 (d, *J* = 2.4 Hz, 1H), 3.90 (d, *J* = 3.1 Hz, 3H), 3.62 (d, *J* = 3.2 Hz, 3H), 3.31 (ddd, *J* = 15.7, 11.5, 4.5 Hz, 1H), 3.05 – 2.76 (m, 2H), 2.50 – 2.31 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.86 (d, *J* = 18.5 Hz), 163.66, 155.01 (d, *J* = 6.1 Hz), 145.89, 130.78, 129.38, 126.12 (d, *J* = 13.7 Hz), 125.18, 121.02 (d, *J* = 1.8 Hz), 120.54, 113.53, 112.31, 111.58 (d, *J* = 1.5 Hz), 94.78 (d, *J* = 177.2 Hz), 55.46 (2 overlapped signals), 34.72 (d, *J* = 24.0 Hz), 25.50 (d, *J* = 4.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -163.30 (dd, *J* = 38.1, 13.2 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R = 10.88 min (minor), t_R = 15.35 min (major).GC-MS (EI): *m/z* calcd for $C_{18}H_{17}FO_3$ (M^+Na^+): 323.1053, found: 323.1060.

4.3.8. *2-Fluoro-7-methoxy-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one* ***(10h)****:* yellow solid (30.2 mg, yield 100%, ee 58%). Mp = 130-133 °C. $[\alpha]_D^{25}$ = -37.61 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 2.7 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 3.89 – 3.81 (m, 3H), 3.57 (s, 3H), 3.24 – 3.15 (m, 1H), 2.91 – 2.72 (m, 2H), 2.41 (ddd, *J* = 17.8, 9.1, 4.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.17 (d, *J* = 18.4 Hz), 158.55 (s), 154.96 (d, *J* = 6.0 Hz), 136.00 (s), 132.52 (s), 129.72 (s), 129.50 (s), 128.98 (d, *J* = 22.8 Hz), 126.18 (d, *J* = 13.3 Hz), 121.73 (s), 121.09 (d, *J* = 1.7 Hz), 111.55 (d, *J* = 1.0 Hz), 110.17 (s), 94.67 (d, *J* = 177.7 Hz), 55.56 (s), 55.45 (s), 35.02 (d, *J* = 24.0 Hz), 24.37 (d, *J* = 4.5 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -162.74 (dd, *J* = 37.2, 13.2 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R = 14.84 min (minor),

t_R = 21.55 min (major).GC-MS (EI): *m/z* calcd for $C_{18}H_{17}FO_3$ (M^+): 300.1162, found: 300.1159.

4.3.9. *2,7-Difluoro-2-(2-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one (**10i**):* yellow solid (23.1 mg, yield 77%, ee 57%). Mp = 104-107 °C. $[\alpha]_D^{25}$ = -32.02 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 3.56 (s, 3H), 3.27 – 3.18 (m, 1H), 2.92 – 2.76 (m, 2H), 2.48 – 2.39 (m, 1H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 190.40 (dd, *J* = 18.4, 1.7 Hz), 161.72 (d, *J* = 246.2 Hz), 154.75 (d, *J* = 6.1 Hz), 139.07 (d, *J* = 3.1 Hz), 133.33 (d, *J* = 6.2 Hz), 130.34 (d, *J* = 7.2 Hz), 129.65 (s), 128.70 (d, *J* = 22.8 Hz), 126.07 (d, *J* = 13.2 Hz), 121.18 (d, *J* = 1.6 Hz), 120.81 (d, *J* = 22.2 Hz), 113.91 (d, *J* = 22.0 Hz), 111.55 (d, *J* = 1.5 Hz), 94.26 (d, *J* = 177.8 Hz), 55.38 (s), 34.91 (d, *J* = 24.1 Hz), 24.46 (d, *J* = 4.3 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -114.52 (dd, *J* = 13.8, 8.1 Hz), -163.11 (dd, *J* = 38.0, 13.3 Hz). HPLC (Chiralcel OD-H column, hex/iPrOH = 95:5, 1.0 mL/min, 254 nm) t_R = 7.77 min (minor), t_R = 10.64 min (major). GC-MS (EI): *m/z* calcd for $C_{17}H_{14}F_2O_2$ (M^+): 288.0962, found: 288.0958.

4.3.10. *2-Fluoro-2-(m-tolyl)-3,4-dihydronaphthalen-1(2H)-one* (***10j***): brown solid (18.6 mg, yield 73%, ee 11%). Mp = 56-59 ºC. $[\alpha]_D^{24}$ = +28.67 (*c* 0.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28 – 7.12 (m, 5H), 3.18 – 3.05 (m, 1H), 2.94 – 2.66 (m, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.03 (d, *J* = 18.1 Hz), 143.17, 138.43, 136.51 (d, *J* = 22.4 Hz), 134.19, 132.17, 129.97 (d, *J* = 2.2 Hz), 128.83 (d, *J* = 28.0 Hz), 128.45, 128.12, 127.19, 126.78 (d, *J* = 5.7 Hz), 123.19 (d, *J* = 5.5 Hz), 96.07 (d, *J* = 184.2 Hz), 35.42 (d, *J* = 25.1 Hz), 26.45 (d, *J* = 9.3 Hz), 21.56; ^{19}F NMR (470 MHz, $CDCl_3$) δ -144.19 (t, *J* = 10.5 Hz). HPLC (Chiralpack AD-H column, hex/i-PrOH= 99/1, 1.0 mL/min, 254 nm) t_R = 11.06 min (major), t_R = 14.94 min (minor). GC-MS (EI): *m/z* calcd for $C_{17}H_{15}FO$ (M^+): 254.1107, found: 254.1110.

4.3.11. *2-Fluoro-2-(p-tolyl)-3,4-dihydronaphthalen-1(2H)-one (**10k**)* [22]*:* brown oil (25.4 mg, yield 100%, ee 4%). $[\alpha]_D^{25}$ = +8.79 (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H), 7.41 (dd, *J* = 11.3, 3.9 Hz, 1H), 7.27 (ddd, *J* = 13.2, 6.9, 4.6 Hz, 3H), 7.20 – 7.15 (m, 2H), 3.17 – 3.04 (m, 1H), 2.93 – 2.65 (m, 3H), 2.35 (d, *J* = 1.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.17 (d, *J* = 18.1 Hz), 143.06, 139.20 (d, *J* = 2.4 Hz), 134.16, 133.36 (d, *J* = 22.7 Hz), 132.19, 129.34, 128.82, 128.05, 127.17, 126.20 (d, *J* = 5.2 Hz), 96.01 (d, *J* = 184.4 Hz), 35.22 (d, *J* = 25.2 Hz), 26.54 (d, *J* = 9.4Hz), 21.19; ^{19}F NMR (470 MHz, $CDCl_3$) δ -142.84 (t, *J* = 9.5 Hz). HPLC (Chiralpack AD-H column, hex/i-PrOH = 99/1, 1.0 mL/min, 254 nm) t_R = 12.44 min (major), t_R = 17.61 min (minor). GC-MS (*m/z*, relative intensity): 254.1 (M^+, 16), 234.1 (47), 118.1 (100), 90.1 (37).

4.3.12. *2-Fluoro-2-(4-methoxy-2-methylphenyl)-3,4-dihydronaphthalen-1(2H)-one (**10l**):* brown oil (27.1 mg, yield 95%, ee 70%). $[\alpha]_D^{25}$ = -104.28 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.43 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 6.79 (d, *J* = 2.6 Hz, 1H), 6.62 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.79 (s, 3H), 3.23 – 3.12 (m, 1H), 2.93 – 2.75 (m, 2H), 2.64 – 2.53 (m, 1H), 2.41 (d, *J* = 2.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.67 (d, *J* = 18.9 Hz), 159.44, 143.46, 138.02, 134.13, 132.14, 128.75, 128.25, 128.09 (d, *J* = 21.9 Hz), 127.80 (d, *J* = 9.8 Hz), 127.24, 118.19, 110.21, 97.12 (d, *J* = 181.3 Hz), 55.15, 34.98 (d, *J* = 24.9 Hz), 26.11 (d, *J* = 7.6 Hz), 21.42 (d, *J* = 4.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ -151.55 (dd, *J* = 19.9, 10.1 Hz). HPLC (Chiralpack AS-H column, hex/i-PrOH= 99/1, 1.0 mL/min, 254 nm) t_R = 18.42 min (minor), t_R = 20.57 min (major). GC-MS (EI): *m/z* calcd for $C_{18}H_{17}FO_2$ (M^+): 284.1213, found: 284.1218.

4.3.13. *2-(2,5-Dimethylphenyl)-2-fluoro-3,4-dihydronaphthalen-1(2H)-one (**10m**):* yellow solid (25.4 mg, yield 95%, ee 60%). Mp = 96-99 ºC. $[\alpha]_D^{25}$ = -87.75 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.43 (dd, *J* = 11.3, 3.9 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.11 (dd, *J* = 9.0, 4.9 Hz, 1H), 7.09 (d, *J* = 2.5 Hz, 2H), 3.33 – 3.21 (m, 1H), 2.93 – 2.77 (m, 2H), 2.63 – 2.52 (m, 1H), 2.30 (d, *J* = 1.3 Hz, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.76 (d, *J* = 19.1 Hz), 143.56, 136.38 (d, *J* = 20.7 Hz), 135.10, 134.19, 132.14, 132.02 (d, *J* = 2.6 Hz), 131.89, 129.21, 128.77, 128.45, 127.28, 126.68 (d, *J* = 11.8 Hz), 96.72 (d, *J* = 179.4 Hz), 34.98 (d, *J* = 24.6 Hz), 25.72 (d, *J* = 6.6 Hz), 21.09, 20.94 (d, *J* = 3.7 Hz); ^{19}F NMR (470 MHz, $CDCl_3$) δ -154.96 (dd, *J* = 27.1, 11.3 Hz). HPLC (Chiralpack AS-H column, hex/i-PrOH= 99/1, 1.0 mL/min, 254 nm) t_R = 7.94 min (minor), t_R = 10.53 min (major). GC-MS (EI): *m/z* calcd for $C_{18}H_{17}FO$ (M^+): 268.1263, found: 268.1271.

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