Enantioselective Organocatalytic α-Fluorination of Cyclic Ketones

Piotr Kwiatkowski, Teresa D. Beeson, Jay C. Conrad
and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University,
Princeton, New Jersey 08544

dmacmill@princeton.edu

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Silicycle silica gel SiliaFlash F60 230-400 mesh according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on Silicycle 0.25 mm silica gel F-254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by using *p*-anisaldehyde or ceric ammonium molybdate (CAM). Gas Liquid Chromatography (GLC) and Supercritical Fluid Chromatography (SFC) assays to determine enantiometric excess were developed using racemic samples.

^{1}H, ^{13}C and NMR spectra were recorded on Bruker Ultrashield™ Plus 500 (500 MHz, 125 MHz) and ^{19}F NMR spectra were recorded on Varian Mercury 300 (282 MHz) as noted, and are internally referenced to residual protio solvent signals (note: $CDCl_3$ referenced at δ 7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C). Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum 100 FTIR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass spectra were obtained from the Princeton University Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard

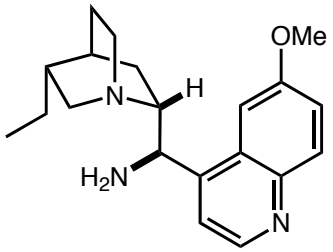
---

[1] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd edition; Pergamon Press; Oxford, 1988.

[2] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column. Supercritical Fluid Chromatography (SFC) was perfomed on a Berger Minigram equipped with a diode array UV detector (λ = 214–258 nm) using a Chiralpak® ADH and ASH column (25 cm x 0.46 mm, 5 cm x 0.46 mm guard) as noted (4.0 mL/min). Optical rotations were recorded on a Jasco P-1010 polarimeter.

Starting Materials



9-amino(9-deoxy)epi-dihydroquinidine (9-epi-DHQDA): The triple HCl salt was prepared from hydroquinidine according to the procedure of McCooey and Connon.[3] Isolation of the pure salt was accomplished by dissolving the residue (15 mmol scale reaction) in approx. 250 mL of MeOH while heating to 55 ºC. EtOAc was dripped into the hot solution until the first signs of a fine powder begin to form. The solution was cooled to rt, then placed in a –20 ºC freezer overnight. Care must be taken not to crash out the powder by adding additional EtOAc, which results in impure catalyst. The triple salt was free-based by partitioning between 1N NaOH and DCM, extracting 3 x with DCM, and drying over Na_2SO_4. 1.9g obtained, 29% yield.

[3] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

Other primary cinchona amines: 9-amino(9-deoxy)epi-quinidine (9-epi-QDA), 9-amino(9-deoxy)epi-cinchonine (9-epi-CA), pseudoenantiomeric 9-amino(9-deoxy)epi-cinchonidine (9-epi-CDA) were prepared according to procedure for 9-epi-DHQDA. 9-epi-DHQDA can be also easily prepared from 9-epi-QDA by simple hydrogenation in MeOH on Pd/C.

Ketones: 4,4-diphenylcyclohexanone,[4] 4-isopropylidenecyclohexanone,[5] dihydro-2*H*-pyran-3(4*H*)-one,[6] (3a*R*,7a*S*)-7a-methylhexahydro-1*H*-indene-1,5-dione[7] were prepared according to the literature methods. Other ketones: cyclohexanone, 4,4-dimethylcyclohexanone, 3,3-dimethylcyclohexanone, 1,4-cyclohexanedione monoethylene acetal (1,4-dioxaspiro[4.5]decan-8-one), 4-phenylcyclohexanone, tetrahydro-4*H*-pyran-4-one, 1-(*tert*-butoxycarbonyl)-4-piperidone, 5α-cholestan-3-one, 5α-pregnane-3,20-dione, cycloheptanone, cyclopentanone are commercially available.

Racemic samples of α-fluoroketones: 2-fluorocyclohexanone, 2-fluoro-4,4-dimethylcyclohexanone, 2-fluoro-4,4-diphenylcyclohexanone, 2-fluoro-5,5-dimethylcyclohexanone and 2-fluoro-3,3-dimethylcyclohexanone (4:1 mixture), mixture of *trans*- and *cis*-2-fluoro-4-phenylcyclohexanone, mixture of *cis*/*trans*-(5*R*)-2-fluoro-5-methylcyclohexanone and *cis*/*trans*-(3*R*)-2-fluoro-3-methylcyclohexanone (7:3 mixture), 2-fluorocycloheptanone, 2-fluorocyclopentanone were obtained directly from corresponding ketones and Selectfluor (1.2 equiv) in MeCN by heating

---

[4] Freeman, P. K.; Tafesh, A. M.; Clapp, G. E. *J. Org. Chem.* **1989**, *54*, 782.

[5] Revial, G.; Jabin, I.; Pfau, M. *Tetrahedron: Asymmetry*, **2000**, *11*, 4975.

[6] Avi, M.; Fechter, M.H.; Gruber, K.; Belaj, F.; Pöchlauer, P.; Griengl, H. *Tetrahedron*, **2004**, *60*, 10411.

[7] Shi, H. *Synth. Commun. etrahedron*, **2006**, *36*, 237.

in sealed tube at 70-80 °C for 12-24h.[8] This method does not work with heterocyclic ketones, 1,4-cyclohexanedione monoethylene acetal and 4-isopropylidene-cyclohexanone (decomposition of ketones was observed). Racemic 1-(*tert*-Butoxycarbonyl)-3-fluoro-4-piperidone[9] and 2-fluoro-1,4-dioxaspiro[4.5]decan-8-one were prepared by fluorination of trimethylsilyl enol ethers of corresponding ketones with Selectfluor in MeCN at 0–20° C. Racemic 3-fluorotetrahydro-4*H*-pyran-4-one, 4-fluorodihydro-2*H*-pyran-3(4*H*)-one and 2-fluoro-4-isopropylidenecyclohexanone were prepared from optically active samples by racemization with DBU in DCM at room temperature.

General Procedure for the Asymmetric α-Fluorination of Ketones: A 7 mL vial equipped with a magnetic stir bar and charged with *N*-fluorobenzenesulfonimide (NFSI) (325 mg, 1.00 mmol, 97%), dry Na_2CO_3 (160 mg, 1.5 mmol) and 3.0 mL of THF was cooled to –20 °C. Then 10 mol% of freshly prepared cinchona primary amine·acid·H_2O (1:1.05:1) in 1.0 mL of THF (0.1 M solution) was added. The mixture was stirred for 10 min and ketone (2.0 mmol, 2 equiv w.r.t. NFSI) was added and the reaction mixture stirred at –20 ºC. After 24 h the reaction was filtered through a short pad of silica gel, eluting with Et_2O, concentrated and purified by silica gel chromatography. The enantioselectivity was determined either by chiral GLC or SFC analysis. The GC yield/conversion was determined using methyl cyclohexanecarboxylate as an internal standard and calculated with a GC response factor.

---

[8] (a) Stavber, S.; Zupan, M. *Tetrahedron Lett.* **1996**, *37*, 3591. (b) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609.

[9] Castro, J. L.; Collins, I.; Russell, M. G. N.; Watt, A. P.; Sohal, B.; Rathbone, D.; Beer, M. S.; Stanton, J. A. *J. Med. Chem.* **1998**, *41*, 2667.

Catalyst solution (0.1 M **9-epi-DHQDA·TCA·H_2O** in THF). A 10 mL flask equipped with a magnetic stir bar was charged with 0.5 mmol of 9-epi-DHQDA free amine (163 mg), 0.525 mmol of trichloroacetic acid (86 mg, 1.05 equiv) and dissolved at room temperature in 5.0 mL of dry THF. Finally 0.5 mmol of water (9.0 μL) was added. The solution should be used within 2 h. Addition of water in some reactions (as noted) can decrease the amount of difluorinated by-product.

High-throughput Catalyst Evaluation

Catalysts were evaluated using a chemspeed accelerator robotic platform. Reactions were carried out under an inert atmosphere in 2 mL double jacketed reactors at –10 °C. The reactions were carried out on 52 ul cyclohexanone scale (0.5 mmol, 2 equiv). The general reaction sequence used to optimize the reaction was programmed as follows.

1. $NaHCO_3$ (42 mg, 2 equiv) was delivered by the solid dispensing unit.
2. Solvent was added to make 0.1 M
3. The reactors were cooled to –10 °C
4. Stock solutions of catalyst (0.2 equiv), TFA (0.2 equiv) and cyclohexanone (52 ul, 2 equiv) were added.
5. Internal standard (20 ul cyclohexanecarbxaldehyde) was added
6. NFSI was added as a solid (79 mg, 1 equiv)
7. The reactions were sealed under nitrogen and vortexed at 800 rpm and –10 °C for 24 h.
8. The reactions were diluted with 1 ml of ether.
9. The white precipitate was removed by filtering through an SPE cartridge
10. The sample was then diluted to ~0.01 M and analyzed by GC-FID (see below for details on ee determination)

Table S1. Yield of catalyst evaluation for the fluorination of cyclohexanone.

%Yield

Catalyst	THF	EtOAc	CHCl3	Toluene	DMF	MeCN
2	8	0	8	0	1	9
4	7	0	0	0	1	0
5	6	1	0	0	0	1
6	85	65	51	52	36	92
7	33	25	36	14	3	36
8	62	50	47	26	91	73
9	10	0	0	0	0	0
10	0	0	0	0	0	0
11	0	0	0	0	0	0
12	2	0	0	0	0	0
13	20	0	0	2	0	0
14	20	8	5	4	55	11
15	16	13	2	2	31	25
16	29	24	7	6	49	37
17	12	3	2	2	40	7
18	13	0	0	0	5	1
19	12	0	0	0	0	0
20	0	0	0	0	0	0
21	1	0	0	0	0	0
22	0	0	0	0	0	0
23	0	0	0	0	0	0
24	0	0	0	0	0	0
25	0	0	0	0	0	0
26	0	0	0	0	0	0
27	9	1	0	0	30	3
28	18	1	5	0	22	55
29	45	21	1	1	33	64
30	4	0	0	0	67	1
31	64	43	5	5	17	52
32	0	0	0	0	0	0
33	20	0	0	0	0	1
34	33	34	27	21	25	70

Table S2. Enantiomeric excess of catalyst evaluation for the fluorination of cyclcohexanone.

%ee

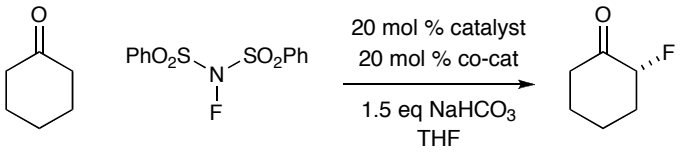
Catalyst	THF	EtOAc	$CHCl_3$	Toluene	DMF	MeCN
2	0	0	7	0	13	16
4	0	0	0	0	5	0
5	55	27	0	0	0	18
6	31	29	22	26	18	19
7	64	63	64	61	18	52
8	28	36	27	36	25	28
9	0	0	0	0	0	0
10	5	0	0	0	0	10
11	13	0	0	0	0	0
12	11	32	8	0	0	0
13	73	0	0	24	0	0
14	10	23	22	33	7	23
15	25	36	0	0	11	3
16	4	13	21	21	17	22
17	1	37	0	0	31	21
18	0	0	0	0	5	5
19	0	0	0	0	0	0
20	14	11	0	0	0	0
21	0	0	0	0	0	0
22	0	0	0	0	0	0
23	0	0	0	0	0	0
24	0	0	0	0	0	0
25	0	0	0	0	0	0
26	0	0	0	0	0	0
27	22	23	0	0	56	18
28	43	36	3	0	68	50
29	54	55	17	20	75	67
30	9	4	0	0	33	24
31	34	37	14	9	53	50
32	0	0	0	0	0	0
33	13	0	0	0	0	36
34	90	66	76	83	74	49

Table S3. Factored catalyst evaluation for the fluorination of cyclcohexanone.

(% yield)(% ee)^2

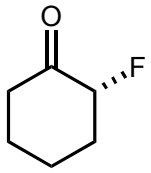
Catalyst	THF	EtOAc	$CHCl_3$	Toluene	DMF	MeCN
2	0	0	0	0	0	0
4	0	0	0	0	0	0
5	2	0	0	0	0	0
6	8	5	2	4	1	3
7	13	10	14	5	0	10
8	5	7	3	3	6	6
9	0	0	0	0	0	0
10	0	0	0	0	0	0
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	11	0	0	0	0	0
14	0	0	0	0	0	1
15	1	2	0	0	0	0
16	0	0	0	0	1	2
17	0	0	0	0	4	0
18	0	0	0	0	0	0
19	0	0	0	0	0	0
20	0	0	0	0	0	0
21	0	0	0	0	0	0
22	0	0	0	0	0	0
23	0	0	0	0	0	0
24	0	0	0	0	0	0
25	0	0	0	0	0	0
26	0	0	0	0	0	0
27	0	0	0	0	9	0
28	3	0	0	0	10	14
29	13	6	0	0	19	29
30	0	0	0	0	7	0
31	7	6	0	0	5	13
32	0	0	0	0	0	0
33	0	0	0	0	0	0
34	27	15	15	15	13	16

Table S4. Catalyst, co-catalyst and temperature optimization for the fluorination of cyclohexanone.



entry	catalyst (%)		co-catalyst	temp. °C	% Yield	% ee[a]
1[b]	**34**	20	TFA	–10	33	90
2	**34**	20	TFA	–10	70	95
4	**34**	10	pTSA	–10	80	97
5	**34**	10	TCA	–10	80	98
6	**34**	10	TCA	–20	84	97
7	**35**	10	TCA	–20	88	99
8	**35**	2.5	TCA	–10	71	97
9	**epi-34**	10	TCA	–20	84	98[c]
10	**epi-35**	10	TCA	–20	78	99[c]

[a] Determined by chiral GC-FID, S enantiomer. [b] Result from high throughput screen. [c] *S* enantiomer.

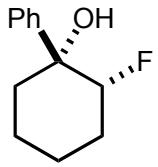


(*R*)-(+)-2-Fluorocyclohexanone (Table 1, entry 1): Prepared according to the general procedure. A 20 mL round-bottom flask equipped with a magnetic stir bar was charged with 2 mmol of NFSI (651 mg, 97%), 3 mmol of Na_2CO_3 (319 mg), and 6.0 mL of THF. The mixture was cooled to –20 °C and 10 mol% of catalyst 9-epi-DHQDA·TCA·H_2O in 2 mL of THF (freshly prepared 0.1 M solution in THF) was added, followed by cyclohexanone (416 μL, 4 mmol). After stirring for 24 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. GC analysis of crude mixture: 88% GC yield w.r.t. NFSI, 98.5–99% ee, contain ~5% of *trans*-2,6-difluorocyclohexanone). Filtrate was carefully concentrated, diluted with pentane and chromatographed on silica gel (10–30% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, Rf_{product} = 0.4, $Rf_{\text{starting material}}$ = 0.5; visualization with *p*-anisaldehyde) afforded (*R*)-2-fluorocyclohexanone as a colorless oil (129 mg, 55% yield, 88% GC yield, 98.5% ee). IR (film) 2947, 2870, 1729, 1452, 1431, 1316, 1086, 1067, 951, 913, 880, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.87 (ddd, *J* = 48.9, 11.5, 6.3 Hz, 1H, CF**H**), 2.57–2.49 (m, 1H, O=CC**H**$_2$), 2.45–2.36 (m, 1H, FCHC**H**$_2$), 2.35–2.27 (m, 1H, O=CC**H**$_2$), 2.05–1.91 (m, 2H, CH_2C**H**$_2$), 1.89–1.77 (m, 1H, FCHC**H**$_2$), 1.74–1.59 (m, 2H, CH_2C**H**$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0 (d, *J* = 14.3 Hz), 92.9 (d, *J* = 190.3 Hz), 40.4, 34.4 (d, *J* = 18.1 Hz), 27.1, 22.9 (d, *J* = 10.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –188.7 (dm, *J* = 48.4 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_6H_{10}FO$) requires *m/z* 117.0710, found *m/z*

117.0710. $[\alpha]_D$ = +49.6 (c = 0.90, C_6H_6).[10] With pseudoenantiomeric 9-epi-CDA as a catalyst (*S*)-2-fluorocyclohexanone was obtained with 98% ee and 82% GC yield. Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 45 min): (*S*) isomer t_r = 34.8 min and (*R*) isomer t_r = 35.3 min.

Selected data for ***trans*-2,6-difluorocyclohexanone** (~5% was usually formed in the reaction): TLC analysis (petroleum ether/Et_2O 7:3, Rf = 0.2); Selected NMR data for hydrated *trans*-2,6-difluorocyclohexanone: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (dm, *J* = 48.2 Hz, 2H, CF**H**), 3.32 (bs, 2H, $C(OH)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 92.7 (d, *J* = 184.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –200.6 (bs). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 45 min): t_r = 24.3 min.

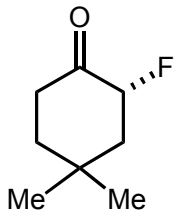
[10] (*R*)-2-Fluorocyclohexanone $[\alpha]_D$ = +54.8 (c = 0.68, C_6H_6): Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.



(1*R*,2*R*)-(–)-2-Fluoro-1-phenylcyclohexanol (Table 1, entry 1): [11] (2*R*)-2-Fluorocyclohexanone was prepared using 2 mmol of cyclohexanone and 1 mmol of NFSI according to the general procedure with 10 mol% of 9-epi-DHQDA·TCA·H_2O as a catalyst. After stirring for 24 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated to ca. 5 mL volume. Crude mixture of 2-fluorocyclohexanone and cyclohexanone was diluted with dry THF to 10 mL volume, cooled to –78 °C and phenylmagnesium bromide (2.0 mL of 3.0 M solution in Et_2O, 6.0 mmol, ~3 equiv) was added and mixture was slowly warmed to 0 °C. After 1 h at 0 °C mixture was cooled to ca –10 °C and water (2 mL) followed by saturated aqueous solution of NH_4Cl (2 mL) were added and extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel chromatography (5–30% Et_2O in petroleum ether; TLC analysis: petroleum ether/Et_2O 7:3, Rf = 0.75, visualization with CAM) to provide the title compound and more polar 1-phenylcyclohexanol. The fluoroalcolol was isolated with 66% yield (128 mg) w.r.t. NFSI, and 98% ee as a white solid. IR (film) 3568, 3455, 2939, 2862, 1446, 1356, 1297, 1072, 1028, 992, 969, 864, 755, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.6 Hz, 2H, **Ph**), 7.38 (t, *J* = 7.6 Hz, 2H, **Ph**), 7.29 (t, *J* = 7.5 Hz, 1H, **Ph**), 4.96 (ddd, *J* = 47.4, 8 Hz, 1H, CF**H**), 2.32 (bs, 1H, OH), 2.07–1.84 (m, 4H, CFH**CH_2**, CH_2C**H_2**, $CFHCH_2$**CH_2**), 1.77–1.67 (m, 1H, CH_2**CH_2**), 1.66–1.49 (m, 2H, CH_2**CH_2**), 1.45–1.34 (m, 1H, $CFHCH_2$**CH_2**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6 (d, *J* = 1.1

[11] Relative configuration confirmed by X-ray analysis: Billings, D.; Woerpel, S. *J. Org. Chem.* **2006**, *71*, 5171.

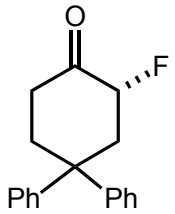
Hz), 128.6, 127.4, 125.1, 95.2 (d, J = 177.9 Hz), 75.1 (d, J = 17.9 Hz), 39.2 (d, J = 3.3 Hz), 27.7 (d, J = 18.1 Hz), 23.8 (d, J = 11.4 Hz), 21.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ: –186.3 (d, J = 46.8 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{15}FONa$) requires m/z 217.0999, found m/z 217.1003; $[\alpha]_D$ = –9.2 (c = 1.01, $CHCl_3$). Enantiopurity was determined by SFC analysis using a Chiralpak® AS-H column (5-10% of MeOH): (1*S*,2*S*) isomer (minor) t_r = 4.0 min and (1*R*,2*R*) isomer (major) t_r = 4.4 min.



(+)-2-Fluoro-4,4-dimethylcyclohexanone (Table 1, entry 2):[12] Prepared according to the general procedure using 1 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of 4,4-dimethylcyclohexanone (253 mg) in 4 mL of total volume of THF. After stirring at –20 ºC for 24 h the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated and diluted with pentane. Purification on silica gel (5–20% Et_2O in pentane; TLC analysis (petroleum ether/Et_2O 7:3, Rf $_{product}$ = 0.45, Rf $_{starting\ material}$ = 0.6; visualization with *p*-anisaldehyde) afforded (+)-2-fluoro-4,4-dimethylcyclohexanone as colorless volatile crystals (117 mg, 81% yield, 94% GC yield, 98% ee). IR (film) 2959, 2933, 2866, 1727, 1474, 1458, 1424, 1390, 1316, 1179, 1129, 1115, 1083, 1048, 1016, 998, 911, 855, 732, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (dddd, J = 48.4, 12.5, 6.6, 0.8 Hz, 1H, CF**H**), 2.54–2.46 (m, 1H, O=CC**H$_2$**), 2.45–2.39 (m, 1H, O=CC**H$_2$**), 2.17 (dddd, J = 12.5, 6.8, 5.6, 3.2, 1H,

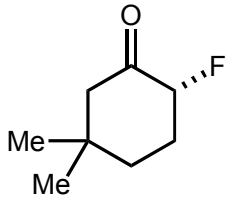
[12] ^{1}H NMR: Cruciani, G.; Margaretha, P. *J. Fluorine. Chem.* **1990**, *49*, 269.

CFHC**H**$_2$), 1.81–1.64 (m, 3H, CFHC**H**$_2$, O=CCH$_2$C**H**$_2$), 1.23 (s, 3H, C**H**$_3$), 1.09 (s, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.3 (d, *J* = 13.4 Hz), 90.6 (d, *J* = 189.3 Hz), 46.4 (d, *J* = 15.7 Hz), 39.5, 36.8, 32.5 (d, *J* = 10.0 Hz), 31.4, 25.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ –193.9 (dm, *J* = 48.4 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{14}FO$) requires *m/z* 145.1023, found *m/z* 145.1022. $[\alpha]_D$ = +46.4 (c = 1.02, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 40 min): (+) enantiomer (major) t_r = 26.4 min and (–) enantiomer (minor) t_r = 28.4 min.



(+)-2-Fluoro-4,4-diphenylcyclohexanone (Table 1, entry 3): Prepared according to the general procedure. A 7 mL vial equipped with a magnetic stir bar was charged with 1.0 mmol of NFSI (325 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), and 2.0 mmol of 4,4-diphenylcyclohexanone (501 mg) in 3 mL of THF. The mixture was cooled to –20 °C and 10 mol% of catalyst 9-epi-DHQDA·TCA·H_2O in 1 mL of THF (freshly prepared 0.1 M solution) was added. After stirring at –20 ºC for 24 h the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, concentrated and dissolved in DCM/petroleum ether 1:1. Purification on silica gel (40–100% DCM in petroleum ether; TLC analysis: DCM, Rf_{product} = 0.5, $Rf_{\text{starting material}}$ = 0.4; visualization with *p*-anisaldehyde) afforded (+)-2-fluoro-4,4-diphenylcyclohexanone as a white solid (234 mg, 87% yield, 99% ee). IR (film) 3059, 2960, 1738, 1496, 1447, 1073, 1033, 886, 841, 751, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.54 (m, 2H, **Ph**), 7.50–7.46 (m, 2H, **Ph**), 7.37–7.33 (m, 1H,

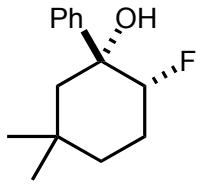
Ph), 7.31–7.27 (m, 2H, **Ph**), 7.22–7.16 (m, 3H, **Ph**), 5.01 (ddd, *J* = 48.2, 12.7, 6.1 Hz, 1H, CF**H**), 3.45–3.38 (m, 1H, CFHC**H**$_2$), 3.04–2.97 (m, 1H, O=CCH$_2$C**H**$_2$), 2.64–2.54 (m, 3H, CFHC**H**$_2$, O=CCH$_2$C**H**$_2$, O=CC**H**$_2$), 2.41–2.33 (m, 1H, O=CC**H**$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1 (d, *J* = 13.4 Hz), 147.3, 142.2, 129.6, 128.8, 127.3, 127.0, 126.8, 126.0, 90.5 (d, *J* = 190.3 Hz), 47.5 (d, *J* = 10.0 Hz), 43.5 (d, *J* = 18.1 Hz), 37.5, 37.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ –192.5 (d, *J* = 49.0 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{18}H_{17}FONa$) requires *m/z* 291.1156, found *m/z* 291.1156; $[\alpha]_D$ = +2.5 (c = 1.1, $CHCl_3$). Enantiopurity was determined by SFC analysis (Chiralpak® ADH 5-50% CH_3CN): (–) enantiomer (minor) t_r = 3.7 min and (+) enantiomer (major) t_r = 4.0 min.



(+)-2-Fluoro-5,5-dimethylcyclohexanone (Table 1, entry 4): Prepared according to the general procedure using 1 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of 3,3-dimethylcyclohexanone (278 μL) in 4 mL of total volume of THF. After stirring for 24 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated and diluted with pentane. Purification on silica gel (5–20% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, $Rf_{product}$ = 0.55, $Rf_{starting\ material}$ = 0.65; visualization with *p*-anisaldehyde) afforded (+)-2-fluoro-5,5-dimethylcyclohexanone as colorless volatile oil (87 mg, 60% yield, 85% GC yield, >50:1 regioselectivity, 98.5% ee). IR (film) 2957, 2874, 1732, 1462, 1370,

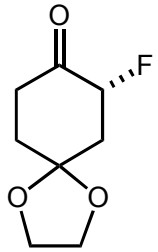
1285, 1220, 1169, 1099, 1067, 986, 935, 871, 666 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (ddd, *J* = 49.0, 11.1, 6.8 Hz, 1H, CF**H**), 2.34–2.23 (m, 3H, CFHC**H$_2$,** O=CC**H$_2$**), 2.05–1.94 (m, 1H, CFHC**H$_2$**), 1.74–1.65 (m, 2H, $CFHCH_2C$**H$_2$**), 1.07 (s, 3H, C**H$_3$**), δ 0.95 (s, 3H, C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7 (d, *J* = 14.8 Hz), 92.6 (d, *J* = 189.8 Hz), 52.9, 36.9, 35.7 (d, *J* = 9.5 Hz), 30.9, 29.7 (d, *J* = 18.6 Hz), 25.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –191.2 (dm, *J* = 49.0 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{14}FO$) requires *m/z* 145.1023, found *m/z* 145.1023; $[\alpha]_D$ = +66.5 (c = 0.62, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): (–) enantiomer (minor) t_r = 22.20 min and (+) enantiomer (major) t_r = 24.39 min.

2-Fluoro-3,3-dimethylcyclohexanone (1-2% in the reaction mixture was detected; identified by comparison with reference sample by GLC analysis). Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.58 (d, *J* = 49.3 Hz, 1H, CF**H**), 1.15 (s, 3H, C**H$_3$**), δ 0.91 (s, 3H, C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 99.2 (d, *J* = 195.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –203.0 (d, *J* = 49.3 Hz); GLC analysis: minor enantiomer t_r = 15.8 min and major enantiomer t_r = 16.1 min.

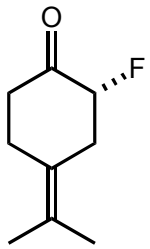


(1*R*,2*R*)-(+)-2-Fluoro-5,5-dimethyl-1-phenylcyclohexanol (Table 1, entry 4):

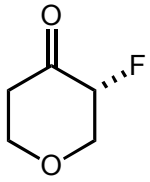
Prepared according to the procedure for phenylmagnesium bromide addition to 2-fluorocyclohexanone. (+)-2-Fluoro-5,5-dimethylcyclohexanone was prepared according to general procedure using 1 mmol of NFSI, 2 mmol of 3,3-dimethylcyclohexanone and 10 mol% of 9-epi-DHQDA·TCA·H_2O. Phenylmagnesium bromide was added to crude mixture of (+)-2-fluoro-5,5-dimethylcyclohexanone and 3,3-dimethylcyclohexanone in THF. Purification on silica gel (5–20% Et_2O in petroleum ether; TLC analysis: petroleum ether/Et_2O 7:3, Rf = 0.9) afforded white solid (171 mg, 77% yield, >99% ee). IR (film) 3587, 2949, 1456, 1446, 1366, 1353, 1295, 1077, 1035, 1025, 975, 844, 768, 699, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55–7.52 (m, 2H, Ar**H**), 7.42–7.37 (m, 2H, Ar**H**), 7.32–7.28 (m, 1H, Ar**H**), 5.04 (ddd, *J* = 47.0, 11.4, 4.9 Hz, 1H, CF**H**), 2.36 (m, 1H, O**H**), 2.34–2.24 (m, 1H, CFH**CH$_2$**), 1.98–1.91 (m, 1H, CFH**CH$_2$**), 1.81 (ddd, *J* = 14.9, 8.0, 3.2 Hz, 1H, PhC(OH)C**H$_2$**), 1.66–1.60 (m, 1H, CFHCH$_2$C**H$_2$**), 1.51 (dd, *J* = 14.9, 2.1 Hz, 1H, PhC(OH)C**H$_2$**), 1.48–1.40 (m, 1H, CFHCH$_2$C**H$_2$**), 1.28 (s, 3H, C**H$_3$**), 0.93 (s, 3H, C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 128.6, 127.3, 125.1, 95.7 (d, *J* = 177.4 Hz), 76.2 (d, *J* = 17.9 Hz), 51.3, 37.2 (d, *J* = 11.4 Hz), 33.6, 31.1, 26.9, 24.5 (d, *J* = 18.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –190.3 (d, *J* = 47.2 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{14}H_{19}FONa$) requires *m/z* 245.1312, found *m/z* 245.1316; $[\alpha]_D$ = +9.5 (c = 1.02, $CHCl_3$). Enantiopurity was determined by SFC analysis using a Chiralpak® AS-H column (5-10% of MeOH,); (1*S*,2*S*) isomer (minor) t_r =2.5 min and (1*R*,2*R*) isomer (major) t_r = 2.9 min.



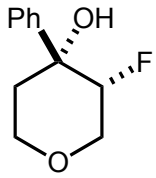
(+)-2-Fluoro-1,4-dioxaspiro[4.5]decan-8-one (Table 1, entry 5): Prepared according to the general procedure using 1 mmol of NFSI (327 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of 1,4-dioxaspiro[4.5]decan-8-one (313 mg) in 4 mL of total volume of THF. After stirring at –20 ºC for 24 h the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, concentrated and dissolved in small volume of DCM. Purification on silica gel (DCM to 2–10% Et_2O in DCM; TLC analysis: 5% Et_2O in DCM, Rf_{product} = 0.5, $Rf_{\text{starting material}}$ = 0.3; visualization with *p*-anisaldehyde) afforded (+)-2-fluoro-1,4-dioxaspiro[4.5]decan-8-one as a colorless crystalline solid (143 mg, 82% yield, 94% GC yield, 97-98% ee). IR (film) 2938, 2904, 1737, 1443, 1353, 1310, 1244, 1146, 1123, 1089, 1047, 984, 951, 931, 845, 707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.10 (dm, *J* = 48.4 Hz, 1H, CF**H**), 4.12–3.98 (m, 4H, $(OC\mathbf{H_2})_2$), 2.67–2.58 (m, 1H, O=CC$\mathbf{H_2}$), 2.56–2.49 (m, 1H, CFHC$\mathbf{H_2}$), 2.49–2.41 (m, 1H, O=CC$\mathbf{H_2}$), 2.20–2.11 (m, 1H, CFHC$\mathbf{H_2}$), 2.06–1.94 (m, 2H, O=$CCH_2C\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.6 (d, *J* = 14.3 Hz), 107.4 (d, *J* = 13.8 Hz), 89.8 (d, *J* = 191.2 Hz), 65.1, 65.1, 41.7 (d, *J* = 17.6 Hz), 35.3, 34.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –194.1 (dm, *J* = 48.1 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{11}FO_3Na$) requires *m/z* 197.0584, found *m/z* 197.0588; $[\alpha]_D$ = +44.5 (c = 1.00, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 60 min): (+) enantiomer (major) t_r = 50.4 min and (–) enantiomer (minor) t_r = 51.5 min.



(+)-2-Fluoro-4-isopropylidenecyclohexanone (Table 1, entry 6): Prepared according to the general procedure using 1 mmol of NFSI (327 mg, 97%), 1.5 mmol of Na_2CO_3 (159 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of 4-isopropylidenecyclohexanone (277 mg, liquid) in 4 mL of total volume of THF. After stirring at **–10 ºC** for 24 h the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated and diluted with pentane. Purification on silica gel (5–20% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, $Rf_{product} = 0.5$, $Rf_{starting\ material} = 0.6$; visualization with *p*-anisaldehyde) afforded (+)-2-fluoro-4-isopropylidenecyclohexanone as a colorless oil (solidified in refrigerator) (110 mg, 70% yield, 78% GC yield, 98% ee). IR (film) 2983, 2918, 2859, 1734, 1450, 1376, 1295, 1105, 1070, 1026, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 (ddd, *J* = 49.3, 11.9, 6.6 Hz, 1H, CF**H**), 3.32–3.24 (m, 1H, CFHC**H**$_2$), 2.86–2.79 (m, 1H, O=CCH$_2$C**H**$_2$), 2.57–2.51 (m, 1H, O=CC**H**$_2$), 2.40–2.28 (m, 2H, CFHC**H**$_2$, O=CC**H**$_2$), 2.23–2.15 (m, 1H, O=CCH$_2$C**H**$_2$), 1.78 (s, 3H, C**H**$_3$), 1.76 (s, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.9 (d, *J* = 13.8 Hz), 129.1, 123.1, 91.8 (d, *J* = 193.6 Hz), 39.4, 36.5 (d, *J* = 19.6 Hz), 28.6, 20.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ –188.2 (dm, *J* = 49.3 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_9H_{13}FONa$) requires *m/z* 179.0843, found *m/z* 179.0844; $[\alpha]_D$ = +1.7 (c = 1.05, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 60 min): (–) enantiomer (minor) t_r = 46.7 min and (+) enantiomer (major) t_r = 49.0 min.

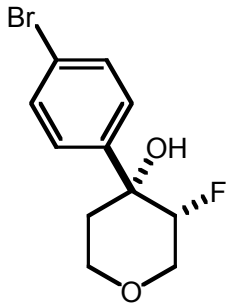


3-Fluoro-tetrahydropyran-4-one (Table 1, entry 7): Prepared according to the general procedure using 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of tetrahydro-4*H*-pyran-4-one (201 mg, 186 μL) in **2 mL** of total volume of THF. After stirring at –20 ºC for **48 h** the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated and diluted with DCM/pentane. Purification on silica gel (20–60% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 1:1, Rf_{product} = 0.3, $Rf_{\text{starting material}}$ = 0.4; visualization with *p*-anisaldehyde) afforded hydrated 3-fluoro-tetrahydropyran-4-one as colorless volatile oil which solidified (98 mg, 72% yield calculated for hydrated product, 95% conversion by GC, 98% ee after PhMgBr addition). IR (mixture of fluoroketone and its hydrated form, film) 3403, 2975, 2873, 1733, 1208, 1109, 1085, 1066, 971, 893, 844, 703 cm^{-1}; IR of hydrated product (after 2 min, only hydrated form was observed – no 1733 cm^{-1} band, film) 3375, 1298, 1113, 1029, 989, 876, 842, 704 cm^{-1}; ^1H NMR for fluoroketone (500 MHz, $CDCl_3$) δ 4.93 (dddd, *J* = 48.1, 9.6, 6.7, 0.9 Hz, 1H, O=CCF**H**), 4.37 (dddd, *J* = 11.0, 6.1, 4.5, 1.3 Hz, 1H, CFHC$\mathbf{H}_2$), 4.20–4.15 (m, 1H, O=CCH_2C$\mathbf{H}_2$), 3.69 (ddd, *J* = 11.1, 11.1, 3.3 Hz, 1H, O=CCH_2C$\mathbf{H}_2$), 3.62 (ddd, *J* = 11.0, 9.8, 5.4 Hz, 1H, CFHC$\mathbf{H}_2$), 2.72–2.66 (m, 1H, O=CC$\mathbf{H}_2$), 2.64–2.58 (m, 1H, O=CC$\mathbf{H}_2$), (hydrated product is poorly soluble in chloroform: δ 4.61 (dm 47.5 Hz, $(HO)_2$CCF**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5 (d, *J* = 14.3 Hz), 89.2 (d, *J* = 194.1 Hz), 70.8 (d, *J* = 26.2 Hz), 68.4, 42.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –203.0 (dm, *J* = 48.1 Hz); HRMS (EI) exact mass calculated for $[M]^+$ ($C_5H_7FO_2$) requires *m/z* 118.0430, found *m/z* 118.0431.



(3*R*,4*R*)-(–)-3-Fluoro-4-phenyltetrahydro-2*H*-pyran-4-ol (Table 1, entry 7): Prepared according to the procedure for phenylmagnesium bromide addition to 2-fluorocyclohexanone. 3-Fluoro-tetrahydropyran-4-one was prepared according general procedure using 1 mmol of NFSI, 2 mmol of tetrahydro-4*H*-pyran-4-one and 10 mol% of 9-epi-DHQDA·TCA·H_2O. After stirring for 48 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated to ca. 3 mL volume. Crude mixture of 3-fluoro-tetrahydropyran-4-one and tetrahydropyran-4-one (~1:1.2 by GC) was diluted with dry THF to 10 mL volume, cooled to –78 °C and phenylmagnesium bromide (2.0 mL of 3.0 M solution in Et_2O, 6.0 mmol, ~3 equiv) was added and mixture was slowly warmed to 0 °C. After 1 h at 0 °C mixture was cooled to ca –10 °C and water (2 mL) followed by saturated aqueous solution of NH_4Cl (2 mL) were added and extracted with Et_2O (3 × 10 mL). The combined organics were dried over $MgSO_4$, concentrated *in vacuo*. Purification on silica gel (20–50% Et_2O in petroleum ether; TLC analysis: petroleum ether/Et_2O 1:1, $Rf_{\text{product}} = 0.7$, $Rf_{\text{4-phenyltetrahydro-2}H\text{-pyran-4-ol}} = 0.3$, visualization with CAM) afforded (3*R*,4*R*)-3-fluoro-4-phenyltetrahydro-2*H*-pyran-4-ol as a white solid (116 mg, 60% yield, 98% ee). IR (film) 3396, 2960, 2877, 1447, 1388, 1290, 1225, 1113, 1074, 1033, 1009, 979, 883, 819, 759, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$). δ 7.52 (d, *J* = 7.4 Hz, 2H, **Ph**), 7.41 (t, *J* = 7.8 Hz, 2H, **Ph**), 7.34–7.30 (m, 1H, **Ph**), 5.06 (ddd, *J* = 46.7, 10.1, 5.4 Hz, 1H, CF**H**), 4.01 (dd, *J* = 10.6, 5.3 Hz, 1H, CFHC$\mathbf{H_2}$O), 3.88–3.81 (m, 2H, CFHC$\mathbf{H_2}$O, $CH_2C\mathbf{H_2}O$), 3.79–3.73 (m, 1H, $CH_2C\mathbf{H_2}O$), 2.48 (m, 1H, O**H**), 2.07–1.98 (m, 1H, $OCH_2C\mathbf{H_2}$), 1.97–1.90 (m, 1H,

$OCH_2C\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9 (d, *J* = 0.9 Hz), 128.8, 127.9, 125.1, 89.6 (d, *J* = 181.2 Hz), 73.0 (d, *J* = 17.6 Hz), 64.7 (d, *J* = 29.1 Hz), 63.7, 39.5 (d, *J* = 2.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –204.7 (d, *J* = 46.8 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{11}H_{13}FO_2Na$) requires *m/z* 219.0792, found *m/z* 219.0786; $[\alpha]_D$ = –16.7 (c = 1.00, $CHCl_3$). Enantiopurity was determined by SFC analysis using a Chiralpak® AD-H column (5-50% MeCN): (3*R*,4*R*) isomer (major) t_r = 2.6 min and (3*S*,4*S*) isomer (minor) t_r = 2.9 min.



(3*R*,4*R*)-(-)-4-(4-bromophenyl)-3-fluorotetrahydro-2H-pyran-4-ol (Table 1, entry 7 absolute stereochemistry determination): Prepared according to the procedure of *para*-bromophenyllithium addition to ketones.[13] To a –78 °C solution of dibromobenzene (925 mg, 3.9 mmol) in THF (10 mL) was added *n*-BuLi (1.8 ml of 2.2 M, 3.9 mmol) keeping the temperature below –70 °C. The resulting reaction mixture was stirred at –78 °C for 30 minutes followed by addition of hydrated 3-fluoro-tetrahydropyran-4-one[14] (200 mg, ~1.4 mmol) in 2 mL of THF and slowly warmed to –10 °C. The reaction was quenched with saturated NH_4Cl (2 mL) and extracted with diethyl ether, dried over $MgSO_4$, filtered and concentrated. Purification on silica gel (10–50% Et_2O in petroleum ether, visualization with CAM) afforded (3*R*,4*R*)-(-)-4-(4-bromophenyl)-3-fluorotetrahydro-2H-pyran-4-ol as a white solid (138 mg, ~35%, reaction was not optimized). Crystallization from chloroform/diethyl ether give crystals appropriate for X-ray analysis. IR (film) 3401, 2961, 2878, 1488,

---

[13] Caron, S.; Do, N. M. *Synlett* **2004**, 1440.

[14] Optically pure 3-fluoro-tetrahydropyran-4-one used in *para*-bromophenyllithium addition reaction was prepared according general procedure using 9-epi-DHQDA·TCA·H_2O as a catalyst.

1388, 1290, 1223, 1151, 1116, 1077, 1038, 1009, 980, 888, 814, 739, 621 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.54-7.51 (m, 2H, **Ph**), 7.40-7.37 (m, 2H, **Ph**), 4.99 (ddd, *J* = 46.7, 10.2, 5.4 Hz, 1H, CF**H**), 4.00 (dd, *J* = 10.7, 5.4 Hz, 1H, CFHC$\mathbf{H_2}$O), 3.86–3.73 (m, 3H, CFHC$\mathbf{H_2}$O, $CH_2C\mathbf{H_2}O$), 2.45 (m, 1H, O**H**), 2.01–1.94 (m, 1H, $OCH_2C\mathbf{H_2}$), 1.92–1.89 (m, 1H, $OCH_2C\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 131.9, 127.0, 121.9, 89.4 (d, *J* = 180.8 Hz), 72.9 (d, *J* = 17.5 Hz), 64.7 (d, *J* = 28.5 Hz), 63.6, 39.4 (d, *J* = 2.3 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ –204.8 (dm, *J* = 46.5 Hz); HRMS (EI+) exact mass calculated for $[M]^+$ ($C_{11}H_{12}BrFO_2$) requires *m/z* 274.0005, found *m/z* 274.0015; $[\alpha]_D$ = –11.8 (c = 1.00, $CHCl_3$). The absolute stereochemistry was assigned by X-ray analysis.

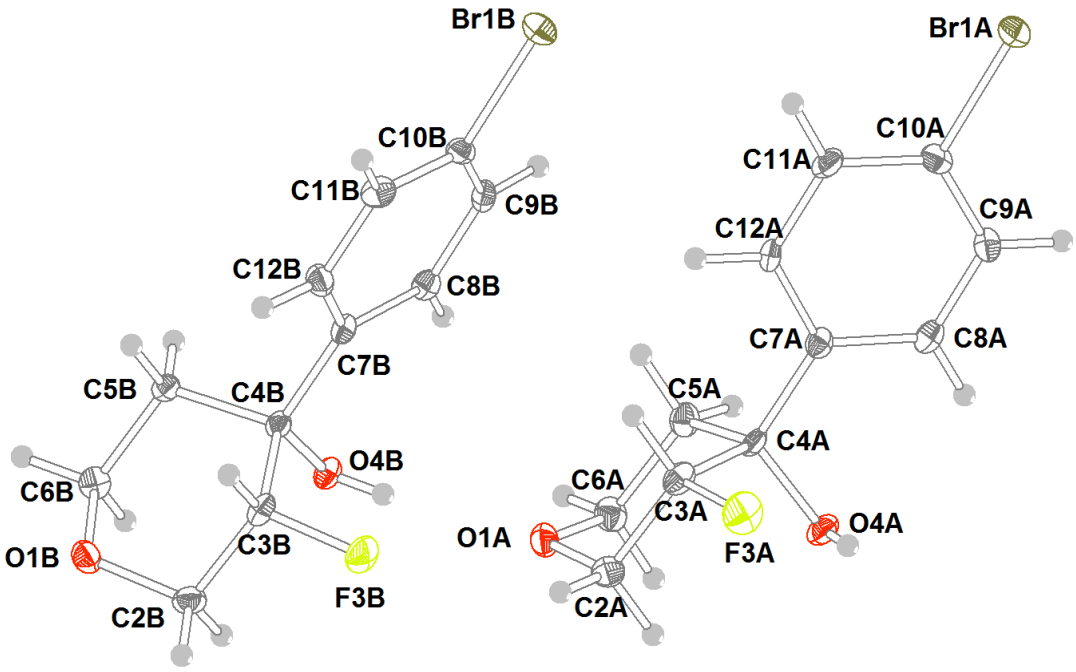
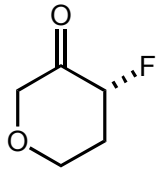
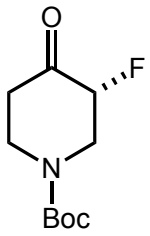


Figure S1. ORTEP drawing of (3*R*,4*R*)-(-)-4-(4-bromophenyl)-3-fluorotetrahydro-2H-pyran-4-ol.



4-Fluoro-dihydro-2*H*-pyran-3(4*H*)-one (Table 1, entry 8): Prepared according to the general procedure using 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), 10 mol% of 9-epi-DHQDA·TCA·H_2O and 2 mmol of dihydro-2*H*-pyran-3(4*H*)-one (201 mg; liquid) in **2 mL** of total volume of THF. After stirring at –20 ºC for **48 h** the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, carefully concentrated and diluted with DCM/pentane. Purification on silica gel (20–100% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 1:1, Rf $_{\text{product}}$ = 0.1, Rf $_{\text{starting material}}$ = 0.5; visualization with *p*-anisaldehyde) afforded very polar hydrated 4-fluoro-dihydro-2*H*-pyran-3(4*H*)-one as colorless oil (105 mg, ~77% yield calculated for hydrated product, 92% conversion by GC, 98-97% ee): IR (mixture with hydrated form, film) 3394, 2974, 2869, 1745, 1438, 1326, 1244, 1136, 1096, 1081, 1046, 976, 910, 865, 669 cm^{-1}; IR for hydrated product (after 2 min no 1745 cm^{-1} band, film) 3363, 2969, 2870, 1447, 1291, 1100, 1072, 1046, 963, 927, 669 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 (ddd, *J* = 47.9, 11.1, 6.9, Hz, 1H, CF**H**), 4.20 (dd, *J* = 15.0, 4.6, Hz, 1H, O=CC$\mathbf{H_2}$O), 4.14–4.08 (m, 1H, $CH_2C\mathbf{H_2}O$), 4.00 (d, *J* = 15.0 Hz, 1H, O=CC$\mathbf{H_2}$O), 3.86–3.80 (m, 1H, $CH_2C\mathbf{H_2}O$), 2.61–2.54 (m, 1H, CFHC$\mathbf{H_2}$), 2.36–2.25 (m, 1H, CFHC$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0 (d, *J* = 13.8 Hz), 89.8 (d, *J* = 194.1 Hz), 74.3, 64.9 (d, *J* = 9.5 Hz), 34.5 (d, *J* = 18.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –192.1 (dm, *J* = 48.1 Hz); ^{1}H NMR of hydrated fluoroketone (500 MHz, $CDCl_3$) δ 4.7 (bs, 1H, OH), 4.58 (ddd, *J* = 49.3, 7.6, 4.0 Hz, 1H, CF**H**), 4.5 (bs, 1H, OH), 3.87–3.80 (m, 1H, $CH_2C\mathbf{H_2}O$), 3.71 (dd, *J* = 12.1, 5.9 Hz, 1H, O=CC$\mathbf{H_2}$O), 3.62–3.57 (m, 1H, $CH_2C\mathbf{H_2}O$), 3.42 (d, *J* = 12.1 Hz, 1H,

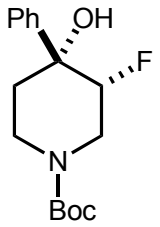
O=CC**H**$_2$O), 2.17–1.94 (m, 2H, CFHC**H**$_2$); ^{13}C NMR of hydrated fluoroketone δ 91.0 (d, *J* = 19.5 Hz), 90.9 (d, *J* = 181.2 Hz), 71.7, 64.1 (d, *J* = 6.2 Hz), 29.6 (d, *J* = 19.1 Hz); ^{19}F NMR of hydrated fluoroketone (282 MHz, $CDCl_3$) δ –196.6 (bd); HRMS (EI) exact mass calculated for $[M]^+$ ($C_5H_7FO_2$) requires *m/z* 118.0430, found *m/z* 118.0432. Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 40 min): major enantiomer t_r = 26.2 min and minor enantiomer t_r = 28.7 min.



(+)-1-(*tert*-Butoxycarbonyl)-3-fluoro-4-piperidone (Table 1, entry 9):[15] Prepared according to the general procedure using 0.5 mmol of NFSI (163 mg, 97%), 0.75 mmol of Na_2CO_3 (80 mg), 1 mmol of 1-(*tert*-butoxycarbonyl)-4-piperidone (200 mg) and 20 mol% of 9-epi-DHQDA·TCA·H_2O in 2 mL of total volume of THF. After stirring at **–10 ºC** for 24 h the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with AcOEt, concentrated and dissolved in DCM. Purification on silica gel (10–40% AcOEt in petroleum ether; TLC analysis: petroleum ether/AcOEt 3:2, Rf_{product} = 0.4, $Rf_{\text{starting material}}$ = 0.6, visualization with CAM) afforded (+)-1-(*tert*-butoxycarbonyl)-3-fluoro-4-piperidone as a white solid (100 mg, ~85% yield calculated for hydrated product, 91% conversion by GC, 94.5%

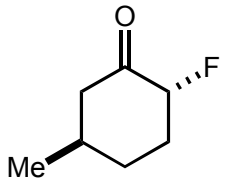
[15] (a) Castro, J. L.; Collins, I.; Russell, M. G. N.; Watt, A. P.; Sohal, B.; Rathbone, D.; Beer, M. S.; Stanton, J. A. *J. Med. Chem.* **1998**, *41*, 2667. (b) van Niel, M. B.; Collins, I.; Beer, M. S.; Broughton, H. B.; Cheng, S. K. F.; Goodacre, S. C.; Heald, A.; Locker, K. L.; MacLeod, A. M.; Morrison, D.; Moyes, C. R.; O'Connor, D.; Pike, A.; Rowley, M.; Russell, M. G. N.; Sohal, B.; Stanton, J. A.; Thomas, S.; Verrier, H.; Watt, A. P.; Castro, J. L. *J. Med. Chem.* **1999**, *42*, 2087. (c) Sun, A.; Lankin, D. C.; Hardcastle, K.; Snyder, J. P. *Chem. Eur. J.* **2005**, *11*, 1579.

ee determined after reaction with phenylmagnesium bromide). IR (film) 2978, 2931, 1739, 1693, 1477, 1415, 1367, 1309, 1270, 1231, 1158, 1116, 1085, 969, 885, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 (bd, *J* = 47.4, Hz, 1H, CF**H**), 4.67–4.33 (m, 1H, CFHC**H**$_2$N), 4.27–4.12 (bs, 1H, CH_2C**H**$_2$N), 3.40–3.10 (m, 2H, CFHC**H**$_2$N, CH_2C**H**$_2$N), 2.67–3.47 (m, 2H, O=CCH_2C**H**$_2$N) 1.49 (s, 3H, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.3 (d, *J* = 14.8 Hz), 154.3, 88.9 (d, *J* = 194.1 Hz), 81.6, 40.5, 28.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –197.9 (m); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{16}FNO_3Na$) requires *m/z* 240.1006, found *m/z* 240.1008; $[\alpha]_D$ = +12.7 (c = 1.00, $CHCl_3$).



(3*R*,4*R*)-1-(*tert*-Butoxycarbonyl)-3-fluoro-4-phenylpiperidin-4-ol (Table 1, entry 9): Prepared according to the procedure for phenylmagnesium bromide addition to 2-fluorocyclohexanone. 1-(*tert*-Butoxycarbonyl)-3-fluoro-4-piperidone (50 mg, ~0.21 mmol) was dissolved in 5.0 mL of THF, cooled to –78 °C and phenylmagnesium bromide (0.25 mL of 3.0 M solution in Et_2O, ~3 equiv) was added and mixture was slowly warmed to 0 °C. After 1 h at 0 °C mixture was cooled to ca –10 °C and water (2 mL) followed by saturated aqueous solution of NH_4Cl were added and extracted with Et_2O (3 × 5 mL). The combined organics were dried over $MgSO_4$, concentrated *in vacuo*. Purification on silica gel (5–30% AcOEt in petroleum ether; TLC analysis: petroleum ether/AcOEt 3:2, Rf = 0.8; visualization with CAM) afforded product as a white solid (43 mg, 68% yield, 94.5% ee). IR (film) 3439, 2923, 2853, 1676, 1423, 1366, 1248, 1215, 1162, 1149, 1032, 996, 880, 758, 699 cm^{-1}; ^1H NMR (500 MHz,

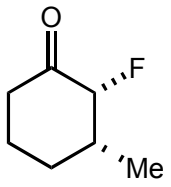
$CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 2H, Ph), 7.39 (t, *J* = 7.6 Hz, 2H, Ph), 7.33–7.29 (m, 1H, Ph), 4.95 (d, *J* = 44.3 Hz, 1H, CF**H**), 4.45–4.18 (m, 1H, CFHC**H**$_2$N), 4.05–4.79 (m, 1H, CH_2C**H**$_2$N), 3.38–3.06 (m, 2H, CFHC**H**$_2$N, CH_2C**H**$_2$N), 2.44 (bs, 1H, O**H**), 1.94–1.76 (m, 2H, C**H**$_2$$CH_2$N), 1.49 (s, C(C**H**$_3$)$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 143.9, 128.9, 127.9, 125.0, 90.1 (bd, *J* = 199 Hz), 80.5, 73.7 (d, *J* = 17.9 Hz), 38.8 (bs), 28.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –199.0 (d, *J* = 46.5 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{16}H_{22}FNO_3Na$) requires *m/z* 318.1476, found *m/z* 318.1480; $[\alpha]_D$ = +1.7 (c = 0.45, $CHCl_3$). Enantiopurity was determined by SFC analysis using a Chiralpak® AS-H column (5-10% of MeCN): (–) enantiomer (minor)t_r = 3.1 min and (+) enantiomer (major) t_r = 4.2 min.



(+)-(2*R*,5*R*)-2-Fluoro-5-methylcyclohexanone (Table 1, entry 10): Prepared according to the general procedure using 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), **20 mol%** of catalyst 9-epi-DHQDA·TCA and 2 mmol of (3*R*)-3-methylcyclohexanone (245 μL, 2 equiv) in 4 mL of total volume of THF. After stirring at –20 ºC for **48 h** the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. GC analysis of crude mixture: (5*R*)-2-fluoro-5-methylcyclohexanones (98% de) / (3*R*)-2-fluoro-3-methylcyclohexanones (89% de) 7:1 regioselectivity, 87% overall GC yield. Filtrate was carefully concentrated, diluted with pentane and chromatographed on silica gel (5–30% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, Rf $_{\text{major product}}$ = 0.45, Rf $_{\text{starting material}}$ = 0.6; visualization with *p*-anisaldehyde) afforded (2*R*,5*R*)-2-fluoro-5-methylcyclohexanone

as a volatile oil (90 mg, 69% yield, 75% GC yield). Minor regioisomer (2*R*,3*R*)-2-fluoro-5-methylcyclohexanone was isolated as a mixture with starting material.

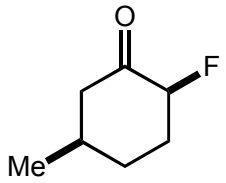
(+)-(2*R*,5*R*)-2-Fluoro-5-methylcyclohexanone: IR (film) 2957, 2874, 1731, 1455, 1336, 1270, 1087, 1048, 1015, 899, 860, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (ddd, *J* = 48.9, 12.3, 6.9 Hz, 1H, CF**H**), 2.52–2.40 (m, 2H, O=CC$\mathbf{H_2}$, CFHC$\mathbf{H_2}$), 2.06 (dd, *J* = 13.2 Hz, 1H, O=CC$\mathbf{H_2}$), 1.97–1.76 (m, 3H, $CH_3C\mathbf{H}$, CFHC$\mathbf{H_2}$, $CFHCH_2C\mathbf{H_2}$), 1.50–1.40 (m, 1H, $CFHCH_2C\mathbf{H_2}$), 1.04 (d, *J* = 6.3 Hz, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (d, *J* = 13.4 Hz), 92.6 (d, *J* = 191.7 Hz), 48.4, 34.9, 32.9 (d, *J* = 18.1 Hz), 31.6 (d, *J* = 10.5 Hz), 22.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ –191.2 (dm, *J* = 48.7Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_7H_{11}FONa$) requires *m/z* 153.0686, found *m/z* 153.0688; $[\alpha]_D$ = +60.9 (c = 1.0, $CHCl_3$). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 35.8 min. The stereochemistry was assigned based on comparison with NMR data in the literature[16] as well as observed nOe enhancement. 2D NOESY spectra showed cross-peaks between CF**H** and equatorial methyl group what suggest that fluorine atom is in equatorial position.



Selected data for minor regioisomer **(2*R*,3*R*)-2-fluoro-5-methylcyclohexanone** (isolated as a mixture with starting material)**:** TLC analysis (petroleum ether/Et_2O 7:3, $Rf_{product}$ = 0.6); Selected NMR data: ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 50.2, 4.4 Hz, 1H, CF**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9 (d, *J* = 17.2 Hz), 95.8 (d, *J*

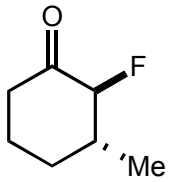
[16] Bensoam, J.; Mathey, F. *Tetrahedron Lett.* **1977**, *18*, 2797.

= 189.8 Hz), 39.4, 38.2 (d, J = 19.1 Hz), 28.7 (d, J = 6.2 Hz), 23.4, 13.7 (d, J = 3.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –198.0 (dd, J = 49.9, 16.7 Hz). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 16.2 min.

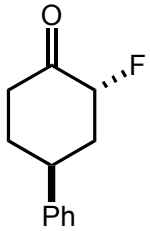


(–)-(2*S*,5*R*)-2-Fluoro-5-methylcyclohexanone (Table 1, entry 11): Prepared according to the general procedure using 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), **20 mol%** of pseudoenantiomeric catalyst **9-epi-CDA·TCA** and 2 mmol of (3*R*)-3-methylcyclohexanone (245 μL, 2 equiv) in 4 mL of total volume of THF. After stirring at –20 ºC for **48 h** the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. GC analysis of crude mixture: (5*R*)-2-fluoro-5-methylcyclohexanones (98% de) / (3*R*)-2-fluoro-3-methylcyclohexanone (98% de) 8:1 regioselectivity, 90% overall GC yield. Purification on silica gel (first chromatography – isolation of products mixture: 30–80% DCM in pentane; second chromatography – purification of major isomer: 5–30% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, $Rf_{\text{major product}}$ = 0.55, $Rf_{\text{minor product}}$ = 0.4, $Rf_{\text{starting material}}$ = 0.6; visualization with *p*-anisaldehyde) (81 mg, 62% yield, 78% GC yield). **(–)-(2*S*,5*R*)-2-Fluoro-5-methylcyclohexanone:** IR (film) 2958, 2878, 1732, 1459, 1428, 1331, 1274, 1079, 1056, 967, 916, 874, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.76 (ddd, J = 50.0, 8.2, 4.7 Hz, 1H, CF**H**), 2.47–2.39 (m, 2H, O=CC**H$_2$**), 2.24–2.14 (m, 2H, CFHC**H$_2$**, CH_3C**H**), 2.11–2.00 (m, 1H, CFHC**H$_2$**), 1.86–1.79 (m, 1H, $CFHCH_2$C**H$_2$**), 1.75–1.67 (m, 1H, $CFHCH_2$C**H$_2$**), 1.02 (d, J = 6.9

Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7 (d, *J* = 17.6 Hz), 92.6 (d, *J* = 185.0 Hz), 46.7, 33.4, 30.8 (d, *J* = 20.5 Hz), 28.4 (d, *J* = 6.2 Hz), 20.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ –188.4 (dm, *J* = 49.9 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_7H_{11}FONa$) requires *m/z* 153.0686, found *m/z* 153.0686; $[\alpha]_D$ = –61.6 (c = 0.85, $CHCl_3$). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 16.8 min.



Selected data for minor regioisomer **(2*S*,3*R*)-2-Fluoro-3-methylcyclohexanone (Table 1, entry 11):** TLC analysis (petroleum ether/Et_2O 7:3, Rf $_{\text{minor product}}$ = 0.4); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 49.1, 11.3 Hz, 1H, CF**H**), 2.55–2.48 (m, 1H, O=CC**H**$_2$), 2.37–2.29 (m, 1H, O=CC**H**$_2$), 2.06–1.90 (m, 3H, CFHC**H**CH_3, O=CCH_2C**H**$_2$, O=CCH_2CH_2C**H**$_2$), 1.70–1.60 (m, 1H, O=CCH_2C**H**$_2$), 1.54–1.45 (m, 1H, O=CCH_2CH_2C**H**$_2$), 1.19 (d, *J* = 6.3 Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5 (d, *J* = 14.3 Hz), 97.8 (d, *J* = 193.6 Hz), 41.0 (d, *J* = 17.6 Hz), 40.4, 32.1 (d, *J* = 8.1 Hz), 25.6, 18.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ –196.0 (dm, *J* = 49.3 Hz). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 22.5 min.

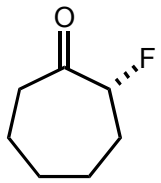


2-Fluoro-4-phenylcyclohexanone (Table 1, entry 12): Prepared according to the general procedure using 1.0 mmol of NFSI (328 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), **20 mol%** of catalyst 9-epi-DHQDA·TCA·H_2O and 2.0 mmol of 4-phenylcyclohexanone (349 mg) in **2 mL** of total volume of THF. After stirring for **48 h** at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O, concentrated and dissolved in DCM/petroleum ether 1:1. Purification on silica gel (40–100% DCM in petroleum ether; TLC analysis: DCM, Rf $_{trans\text{-product}}$ = 0.6, Rf $_{cis\text{-product}}$ = 0.45, Rf $_{\text{starting material}}$ = 0.4; visualization with *p*-anisaldehyde) afforded a colorless crystals of *trans- and cis*-product with 68% overall yield and 4:1 *trans*/*cis* ratio.

***trans*-(+)-2-Fluoro-4-phenylcyclohexanone** (107 mg, 55% yield, 97% ee): IR (film) 2943, 1728, 1496, 1455, 1428, 1320, 1248, 1063, 1017, 972, 935, 758, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (m, 2H, **Ph**), 7.30–7.26 (m, 3H, **Ph**), 4.78 (bd, *J* = 50.3 Hz, 1H, CF**H**), 3.49–3.41 (m, 1H, PhC**H**), 3.04–2.96 (m, 1H, O=CCH$_2$C**H$_2$**), 2.59–2.52 (m, 1H, CFHC**H$_2$**), 2.52–2.46 (m, 1H, O=CC**H$_2$**), 2.31–2.13 (m, 2H, CFHC**H$_2$** O=CC**H$_2$**), 2.09–1.99 (m, 1H, O=CCH$_2$C**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9 (d, *J* = 20.4 Hz), 143.0, 129.0, 127.1, 126.9, 92.3 (d, *J* = 178.3 Hz), 40.4 (d, *J* = 21.5 Hz), 37.9 (d, *J* = 1.9 Hz), 37.0 (d, *J* = 3.3 Hz), 34.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ –186.8 (m); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_{12}H_{14}FO$) requires *m/z* 193.1023, found *m/z* 193.1023; $[\alpha]_D$ = +36.9 (c = 1.04, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc

(50 m x 0.25 mm) column (120 °C, 15 min; 175 ºC, 120 min): (–)-*trans*-enantiomer (minor) t_r = 40.5 min and (+)-*trans*-enantiomer (major) t_r = 42.1 min.

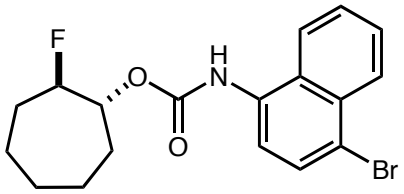
***cis*-2-Fluoro-4-phenylcyclohexanone - minor product** (25 mg, 13% yield, 85% ee): IR (film) 2943, 1736, 1497, 1455, 1108, 1059, 863, 762, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H, **Ph**), 7.30–7.24 (m, 3H, **Ph**), 5.14 (ddd, *J* = 48.2, 12.5, 6.8 Hz, 1H, CF**H**), 3.24–3.16 (m, 1H, PhC**H**), 2.72–2.61 (m, 2H, CFHC$\mathbf{H_2}$, O=CCH_2C$\mathbf{H_2}$), 2.57 (td, *J* = 14.0, 6.0 Hz, 1H, O=CC$\mathbf{H_2}$), 2.28–2.22 (m, 1H, O=CC$\mathbf{H_2}$), 2.21–2.11 (m, 1H, CFHC$\mathbf{H_2}$), 1.97–1.88 (m 1H, O=CCH_2C$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2 (d, *J* = 13.8 Hz), 142.8, 129.0, 127.3, 126.8, 91.9 (d, *J* = 193.1 Hz), 41.4 (d, *J* = 10.0 Hz), 40.9 (d, *J* = 18.1 Hz), 39.6, 34.4; ^{19}F NMR (282 MHz, $CDCl_3$) δ –189.4 (dm, *J* = 48.4 Hz)**;** HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{12}H_{13}FONa$) requires *m/z* 215.0843, found *m/z* 215.0845. Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 175 ºC, 120 min): major *cis*-enantiomer t_r = 105.4 min and minor *cis*-enantiomer t_r = 108.5 min.



(–)-2-Fluorocycloheptanone (Table 1, entry 13): A 7 mL vial equipped with a magnetic stir bar was charged with 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), and 3.0 mL of THF. The mixture was cooled to –20 °C and 10 mol% of catalyst 9-epi-DHQDA·TCA in 1 mL of THF (freshly prepared 0.1 M solution in THF; no water was added – addition of even small amount of water (10 mol%) decrease ee and yield) were added followed by cycloheptanone (355 μL, 3 equiv). After stirring for 24 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. GC analysis of crude mixture: 58% GC yield w.r.t. NFSI, 98-98.5% ee, monofluoro/difluoro-product ratio 4:1, 90% overall GC yield w.r.t. NFSI). Reaction mixture was carefully concentrated, diluted with pentane and chromatographed on silica gel (5–10% Et_2O in pentane; very difficult to separate from *trans*-2,7-difluorocyclohexanone; TLC analysis: petroleum ether/Et_2O 7:3, $Rf_{\text{product}} = 0.6$, $Rf_{\text{starting material}} = 0.5$) afforded 2-fluorocyclohexanone (59 mg, 45% yield, 98% ee) contaminated with ~5% of *trans*-2,7-difluorocycloheptanone as a colorless liquid. IR (film) 2934, 2862, 1721, 1455, 1158, 1031, 1009, 932, 895, 834 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.05 (dm, J = 48.5 Hz, 1H, CF**H**), 2.63–2.46 (m, 2H, O=CC**H$_2$**), 2.04–1.91 (m, 2H, C**H$_2$**), 1.87–1.76 (m, 2H, C**H$_2$**), 1.73–1.61 (m, 3H, C**H$_2$**), 1.57–1.48 (m, 1H, C**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9 (d, J = 18.6 Hz), 95.5 (d, J = 184.5 Hz), 40.1, 31.4 (d, J = 21.5 Hz), 28.4, 25.3 (d, J = 6.7 Hz), 23.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –184.8 (m); HRMS (EI) exact mass calculated for $[M]^+$ ($C_7H_{11}FO$) requires m/z 130.0794, found m/z 130.0794. $[\alpha]_D$ = –35.7 (contain ~5% of difluoro by NMR , c = 0.61, $CHCl_3$), $[\alpha]_D$ = –33.8 (c =

0.6, benzene). Enantiopurity was determined by GC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): major enantiomer t_r = 19.8 min and minor enantiomer t_r = 22.7 min.

Selected data for ***trans*-2,7-difluorocycloheptanone**: TLC analysis (petroleum ether/Et_2O 7:3, Rf = 0.65); Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.31 (dm, *J* = 52.0 Hz, 1H, 2×CF**H**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 94.5 (d, *J* = 183.6 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –195.2 (m). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 18.1 min.



(1*R*,2*R*)-2-fluorocycloheptyl 4-bromonaphthalen-1-ylcarbamate (Table 1, entry 13 absolute stereochemistry determination) A 50 mL vial equipped with a magnetic stir bar was charged with 3.17 mmol of NFSI (1 g, 97%), 4.76 mmol of Na_2CO_3 (504 mg), and 12.7 mL of THF. The mixture was cooled to –20 °C and 10 mol% of catalyst 9-epi-DHQDA·TCA in 1 mL of THF (freshly prepared 0.1 M solution in THF) were added followed by cycloheptanone (1.12 mL, 3 equiv). After stirring for 24 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. The filtrate was then treated with 5 equiv $NaBH_4$ (3 g) and 5 mL of EtOH was added. The reaction was stirred for 1 h then quenched with sat aq NH_4Cl (100 mL). The organic layer was then extracted with ethyl acetate and washed with brine (3 × 100 mL) and dried with $MgSO_4$. Separation of 2-fluorocycloheptanol from cycloheptanone was achieved by column chromatography (t_r 0.5, 40% EtOAc/hexane) and the isolated as a 1:1 mixture of diasteromers. A

portion of 2-fluorocycloheptanol (30 mg, 0.227 mmol) was then treated with 1-bromo-4-isocyanato-naphthalene (1.1 equiv, 62 mg, 0.25 mmol) and NEt_3 (1.1 equiv, 35 μL, 0.25 mmol). The product was purified by column chromatography (20% EtOAc/hexane) and isolated as a white powder (trans: 50 mg, 58%; cis: 23%). Crystals of the trans diasteromer suitable for X-ray diffraction were grown by slow evaporation of a saturated ether solution. IR (film) 3304, 2934, 2864, 1703, 1535, 1496, 1456, 1378, 1362, 1328, 1222, 1126, 1086, 1002, 917, 830, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 7.9, 1H), 7.87 (d, *J* = 8.1, 1H), 7.79 – 7.70 (m, 2H), 7.61 – 7.56 (m, 2H), 7.02 (br s, 1H), 5.05 – 4.89 (m, 2H), 2.16 – 1.98 (m, 2H), 1.88 – 1.45 (m, 6H);); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 132.6, 132.4, 130.0, 128.3, 127.7, 127.3, 121.1, 121.0, 93.9 (d, *J* = 174.5), 77.0 (d, *J* = 19.3), 30.2 (d, *J* = 21.1), 27.3 (d, *J* = 6.7), 26.5, 23.1, 21.7 (d, *J* = 6.0); ^{19}F NMR (282 MHz, $CDCl_3$) δ –190.2 (s). $[\alpha]_D = -7.0$ (c = 1.0, $CDCl_3$).

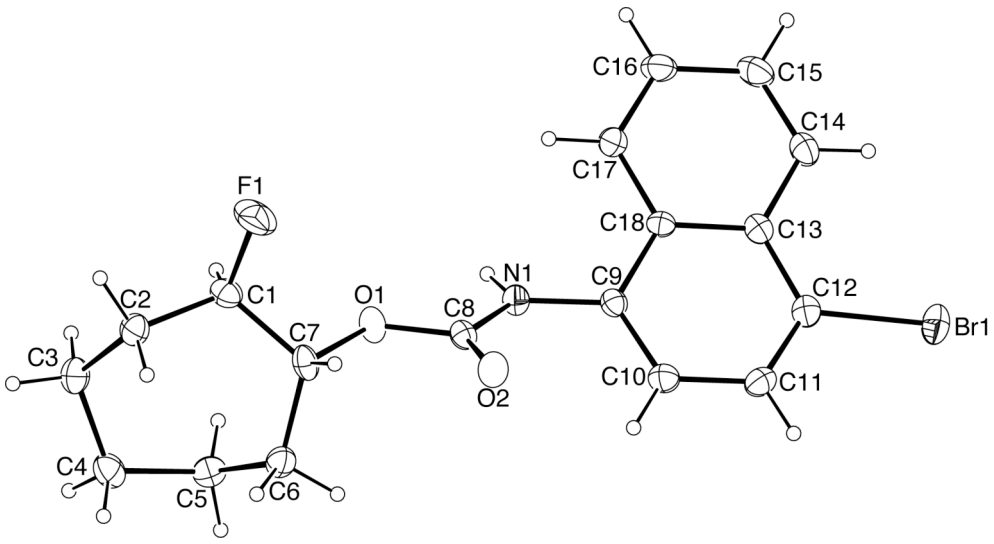
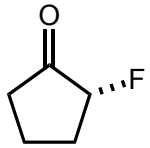


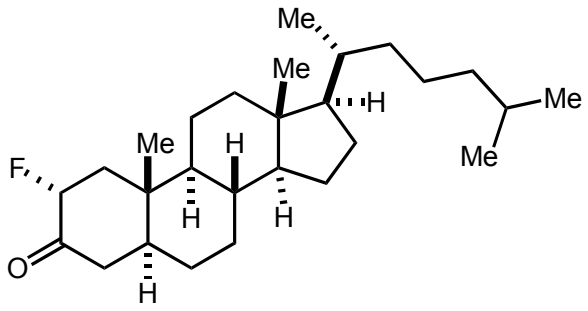
Figure S2. ORTEP drawing of (1*R*,2*R*)-2-fluorocycloheptyl 4-bromonaphthalen -1-ylcarbamate.



2-Fluorocyclopentanone (Table 1, entry 14): A 7 mL vial equipped with a magnetic stir bar was charged with 1.0 mmol of NFSI (326 mg, 97%), 1.5 mmol of Na_2CO_3 (160 mg), and 2.55 mL of THF. The mixture was cooled to –20 °C and 10 mol% of catalyst 9-epi-DHQDA·TCA in 1 mL of THF (freshly prepared 0.1 M solution in THF) and 0.45 mL of H_2O (25 equiv; reaction without water addition resulted in formation of difluorocyclopentanone as a major product) were added followed by cyclopentanone (266 μL, 3 equiv). After stirring for 48 h at –20 ºC the reaction was diluted with Et_2O, filtered through a short pad of silica gel, eluting with Et_2O. GC analysis of crude mixture: 54% GC yield w.r.t. NFSI, 86-90% ee, monofluoro/difluoro-product ratio 5:1, ~75% overall yield w.r.t. NFSI. Filtrate was carefully concentrated, diluted with pentane and chromatographed on silica gel (10–20% Et_2O in pentane; TLC analysis: petroleum ether/Et_2O 7:3, Rf_{product} = 0.4, $Rf_{\text{starting material}}$ = 0.5; visualization with *p*-anisaldehyde) afforded analytical sample of very volatile 2-fluorocyclopentanone as a colorless liquid. IR (film) 2980, 1753, 1404, 1353, 1273, 1146, 1099, 1013, 945, 817, 719 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (dm, *J* = 50.9 Hz, 1H, FC**H**), 2.46–2.23 (m, 3H, CHFC$\mathbf{H_2}$, O=CC$\mathbf{H_2}$), 2.17–2.06 (m, 1H, O=CCH$_2$C$\mathbf{H_2}$), 2.06–1.94 (m, 1H, CHFC$\mathbf{H_2}$), 1.89–1.79 (m, 1H, O=CCH$_2$C$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.4 (d, *J* = 13.4 Hz), 92.3 (d, *J* = 192.2 Hz), 34.5 (d, *J* = 1.0 Hz), 29.3 (d, *J* = 17.6 Hz), 16.3 (d, *J* = 8.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –195.7 (dm, *J* = 50.8 Hz); HRMS (EI) exact mass calculated for $[M]^+$ (C_5H_7FO) requires *m/z* 102.0481, found *m/z* 102.0482. Enantiopurity was determined by GC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm)

column (120 °C, 15 min; 150 ºC, 30 min): minor enantiomer t_r = 27.2 min and major enantiomer t_r = 28.6 min.

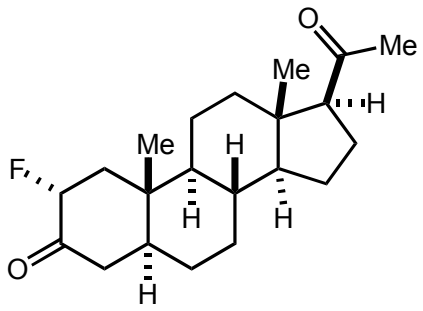
Selected data for **2,5-difluorocyclopentanone** (isolated as a hydrate): TLC analysis (petroleum ether/Et_2O 7:3, Rf = 0.25); Selected NMR data: ^{1}H NMR (500 MHz, $CDCl_3$). δ 4.79 (dm, *J* = 51.4 Hz, 1H, FC**H**), 3.84 (bs, 2H, $C(OH)_2$), 2.32–2.20 (m, 2H, CH_2), 1.90–1.77 (m, 2H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.6 (d, *J* = 184.1 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –193.2 (m). GC analysis using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min): t_r = 21.4 min.



(2*R*)-(+)-2α-Fluoro-5α-cholestan-3-one (Figure 2): A 7 mL vial equipped with a magnetic stir bar was charged with 5α-cholestan-3-one (194 mg, 0.5 mmol), 1.25 equiv of NFSI (203 mg, 0.62 mmol), Na_2CO_3 (99 mg, 0.93 mmol) and 1.0 mL of THF. The mixture was cooled to –20 °C and 20 mol% of 9-epi-DHQDA·TCA in 1.0 mL of THF was added (freshly prepared 0.1 M solution of catalyst; no water addition is required). The mixture was stirred at –20 ºC for 36 h, and then filtered through a short pad of silica gel, eluting with Et_2O and concentrated. GC analysis of crude mixture: conversion 93%; selectivity 96:4 (4% is a sum of 3 minor products). Purification of the resulting mixture on silica gel (30–100% DCM in petroleum ether; TLC analysis: DCM, Rf_{product} = 0.6, $Rf_{\text{starting material}}$ = 0.45; visualization with CAM) afforded (2*R*)-2α-fluoro-5α-cholestan-3-one as a white solid (174 mg, 85% yield,

97% purity by GC). IR (film) 2927, 2862, 1733, 1466, 1447, 1382, 1086, 1028, 907, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (ddd, *J* = 48.0, 12.5, 7.0 Hz, 1H, CF**H**), 2.50 (ddd, *J* = 11.7, 6.9, 4.4 Hz, 1H, CF**H**), 2.36 (dd, *J* = 14.2, 1H, O=CC**H**$_2$), 2.23 (ddd, *J* = 14.2, 6.3, 3.8 Hz, 1H, O=CC**H**$_2$), 2.00 (dm, *J* = 12.7 Hz, 1H), 1.86–1.78 (m, 1H), 1.70 (dm, *J* = 13.1 Hz, 1H), 1.60-1.20 (m, 14H), 1.08 (s, 3H, CH_3–C19), 0.89 (d, 3H, *J* = 6.5 Hz, CH_3–C21), 0.86 (d, 3H, *J* = 6.6 Hz, CH_3–C26), 0.85 (d, 3H, *J* = 6.6 Hz, CH_3–C27), 0.67 (s, 3H, CH_3–C18), 1.17-0.78 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.5 (d, *J* = 13.4 Hz), 91.5 (d, *J* = 189.3 Hz), 56.3, 56.2, 53.9, 47.8, 46.0 (d, *J* = 15.7 Hz), 43.6, 42.8, 39.9, 39.7, 37.7 (d, *J* = 9.5 Hz), 36.3, 36.0, 34.7, 31.7, 28.5, 28.4, 28.2, 24.4, 24.0, 23.0, 22.8, 21.8, 18.8, 13.0, 12.2; ^{19}F NMR (282 MHz, $CDCl_3$) δ –194.4 (dm, *J* 48.1 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_{27}H_{46}FO$) requires *m/z* 405.3527, found *m/z* 405.3529; $[\alpha]_D$ = +61.8 (c = 1.05, $CHCl_3$). The stereochemistry on C2 was assigned based on comparison with NMR data in the literature[17] as well as observed nOe enhancement. 2D NOESY spectra shoved cross-peaks between CF**H** and axial methyl group in C-19 position what suggest that fluorine atom is in equatorial position. Use of pseudo-enantiomeric 9-epi-CDA instead 9-epi-DHQDA resulted in non-selective reaction.

[17] (a) Thomas, M. G.; Suckling, C. J.; Pitt, A. R.; Suckling, K. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3191. (b) Sato, S.; Yoshida, M.; Hara, S. *Synthesis* **2005**, 2602. (c) Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2002**, 2609.



(2*R*)-(+)-2α-Fluoro-5α-pregnane-3,20-dione (Figure 2): A 7 mL vial equipped with a magnetic stir bar was charged with 0.5 mmol of 5α-pregnane-3,20-dione (159 mg), 1.5 equiv of *N*-fluorobenzenesulfonimide (244 mg, 0.75 mmol), 1.5 equiv of Na_2CO_3 (81 mg, 0.75 mmol) and dissolved in THF (0.5 mL) and DCM (1.5 mL) to improve solubility of diketone. The mixture was cooled to –10 °C and 20 mol% of 9-epi-DHQDA·TCA in 1 mL of THF was added (freshly prepared 0.1 M solution of catalyst). The reaction was stirred at –10 ºC for 48 h, and then filtered through a short pad of silica gel, eluting with Et_2O/DCM 1:1 and concentrated. GC analysis of crude mixture: conversion 97%; selectivity 93:7 (7% is a sum of 3 minor products). Purification of the resulting mixture on silica gel (DCM to 2–10% Et_2O in DCM; TLC analysis (5% Et_2O in DCM, Rf_{product} = 0.6, $Rf_{\text{starting material}}$ = 0.5; visualization with CAM) afforded the title compounds as a white solid (153 mg, 91% yield, 95% purity by GC). IR (film) 2940, 2853, 1731, 1697, 1450, 1440, 1360, 1200, 1156, 1090, 1026, 994, 902, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01 (ddd, *J* = 47.9, 12.3, 7.0 Hz, 1H, CF**H**), 2.55–2.47 (m, 2H, CF**H**), 2.37 (dd, *J* = 14.1, 1H, O=CC**H**$_2$), 2.25 (ddd, *J* = 14.3, 6.2, 3.7 Hz, 1H, O=CC**H**$_2$), 2.19–2.11 (m, 1H), 2.11 (s, 3H, C**H**$_3$C=O), 2.07–1.98 (m, 1H), 1.75–1.12 (m, 13H), 1.08 (s, 3H, CH_3–C19), 1.00–0.82 (m, 2H), 0.62 (s, 3H, CH_3–C18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 205.2 (d, *J* = 13.4 Hz), 91.3 (d, *J* = 189.4 Hz), 63.8, 56.3, 53.7, 47.8, 45.9 (d, *J* = 16.2 Hz), 44.3, 43.5, 38.9, 37.7 (d, *J* = 9.5 Hz), 34.6, 31.8, 31.6, 28.3, 24.5, 22.9, 21.8, 13.6, 13.0; ^{19}F NMR (282

MHz, $CDCl_3$) δ −194.5 (dm, J = 48.0 Hz); HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_{21}H_{32}FO_2$) requires m/z 335.2381, found m/z 335.2384; $[\alpha]_D$ = +134.6 (c = 1.00, $CHCl_3$). The relative stereochemistry on C2 was assigned based on 2D NOESY and X-ray analysis. 2D NOESY spectra shoved cross-peaks between FC**H** and axial methyl group (C-19) and axial α-proton of O=CC**H**$_2$, what suggest that fluorine atom is in equatorial position. Use of pseudo-enantiomeric 9-epi-CDA instead 9-epi-DHQDA resulted in non-selective reaction.

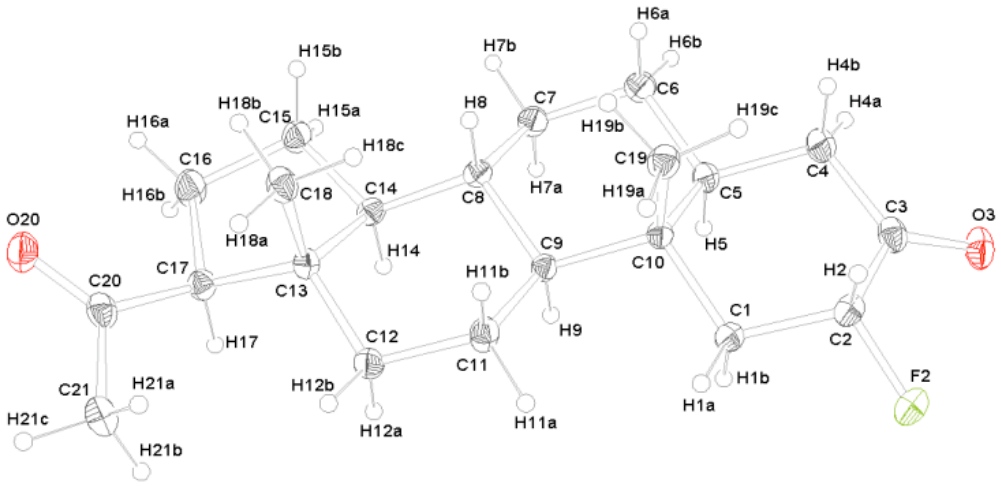
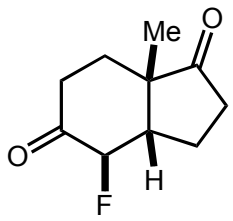


Figure S3. ORTEP drawing of (2*R*)-(+)-2α-Fluoro-5α-pregnane-3,20-dione.



(3a*R*,4*R*,7a*S*)-(+)-4-Fluoro-7a-methylhexahydro-1*H*-indene-1,5-dione (Figure 2): A 7 mL vial equipped with a magnetic stir bar was charged with 1.0 mmol of (3a*R*,7a*S*)-7a-methylhexahydro-1*H*-indene-1,5-dione (166 mg), 1.1 equiv of *N*-fluorobenzenesulfonimide (357 mg, 1.1 mmol), Na_2CO_3 (175 mg, 1.65 mmol) and 3 mL of THF. The mixture was cooled to –20 °C and after 10 min 10 mol% of 9-epi-DHQDA·TCA in 1 mL of THF (freshly prepared 0.1 M solution of catalyst) was added. The mixture was stirred at –20 ºC for 24 h, and then filtered through a short pad of silica gel, eluting with Et_2O/DCM 1:1 and concentrated. GC analysis of crude mixture: conversion 92%; selectivity 9:1 (10% is a sum of 3 minor products). Purification of the resulting mixture on silica gel (20–40% AcOEt in petroleum ether; TLC analysis (petroleum ether/ AcOEt 3:2, Rf_{product} = 0.55, $Rf_{\text{starting material}}$ = 0.45, visualization with CAM) afforded the title compounds as a white solid (137 mg, 74% yield, >98% purity by GC). IR (film) 2969, 2926, 1731, 1445, 1410, 1162, 1142, 1095, 1056, 1023, 908, 858 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.57 (dd, *J* = 48.6, 9.5 Hz, 1H, CF**H**), 2.58–2.39 (m, 4H, CFHC**H,** O=CC**H_2**), 2.34–2.19 (m, 3H, O=CC**H_2**, O=CCH_2C**H_2**), 2.13–2.06 (m, 1H, O=CCH_2C**H_2**), 1.76–1.68 (m, 1H, O=CCH_2C**H_2**), 1.16 (s, 3H, C**H_3**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 218.7, 205.3 (d, *J* = 14.8 Hz), 92.3 (d, *J* = 191.7 Hz), 51.3 (d, *J* = 20.0 Hz), 49.6 (d, *J* = 7.2 Hz), 35.8, 33.4, 30.8, 23.0, 21.2 (d, *J* = 1.4 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –194.0 (ddd, *J* = 48.4, 17.1, 5.0 Hz); HRMS (ES) exact mass calculated for $[M+Na]^+$ ($C_{10}H_{13}FO_2Na$) requires *m/z* 207.0792, found *m/z* 207.0792; $[\alpha]_D$ = +78.5 (c = 1.00, $CHCl_3$). The relative stereochemistry on C4 was assigned based on 2D NOESY spectra which

showed no cross-peaks between CF**H** and axial methyl group, what suggest that fluorine atom is in axial position. The same direction of fluorination was observed with steroid systems (e.g. 5β-pregnane-3,20-dione) having *cis*-configuration of A-B rings (fluorination on C4). Use of pseudo-enantiomeric 9-epi-CDA instead 9-epi-DHQDA resulted in non-selective reaction.