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Supporting Information

Taking Advantage of Lithium Monohalocarbenoids Intrinsic α-Elimination in 2-MeTHF: Controlled Epoxide Ring-Opening *en route* to Halohydrins

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Table of Contents

1. General Methods	3
2. General Procedures	4
3. Spectral and Characterization Data	5
4. Experimental procedures Scheme 3	20
5. References	21
6. Copies of ¹ H- and ¹³ C-NMR Spectra for all the compounds	22

1. General Methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ¹H, ¹³C, and ¹⁹F NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F) at 298 K using a directly detecting broadband observe (BBFO) probe. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (¹H in CDCl₃) and δ 77.0 ppm (¹³C in CDCl₃). ¹⁹F NMR spectra were referenced via the Ξ ratio (absolute referencing). Spin-spin coupling constants (*J*) are given in Hz. In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

THF was distilled over Na/benzophenone. Chemicals were purchased from Sigma-Aldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe, otherwise specified. Organolithium reagents were provided by Albemarle Corporation. Organolithium reagents were titrated immediately before the use according to established literature procedure.¹ The starting epoxides were commercially available or simply synthesized according to Corey Chaykosky procedure.² Solutions were evaporated under reduced pressure with a rotary evaporator. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Macherey-Nagel, Merck); the spots were visualized under UV light (λ = 254 nm) and/or KMnO₄ (aq.) was used as revealing system. Neutral Aluminium Oxide – Brockmann grade 2 (Alox-BG2) for chromatographic purifications was prepared as we previously reported.³

2. General procedure

To a cooled (-78 °C) solution of the suitable epoxide (1.0 equiv) in dry 2-MeTHF was added iodochloromethane (2.0 equiv). After 2 min, an ethereal solution of MeLi (1.8 equiv, 1.6 M) was added dropwise, using a syringe pump (flow: 0.200 mL/min). The resulting solution was stirred for one hour at -78 °C. A satured solution of NH₄Cl was added (2 mL/mmol substrate), then was extracted with Et₂O (2 x 5 mL) and washed with water (5 mL) and brine (10 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered and, after removal of the solvent under reduced pressure, the so-obtained crude mixture was subjected to chromatography silica gel to afford pure compounds.

3. Spectral and Characterization Data

2-(3-Chloro-2-hydroxypropyl)-1H-isoindole-1,3(2H)-dione (rac-2)⁴



By following the General Procedure **1**, starting from 2-[(oxiran-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (218 mg) as white solid (m.p.: 95 °C) after chromatography on silica gel (50:50 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.81 (m, 2H, Phthal H-4,7), 7.70 (m, 2H, Phthal H-5,6), 4.16 (brs, 1H, C<u>H</u>OH), 3.91 (dd, *J* = 14.3, 7.4 Hz, 1H, NCH₂), 3.83 (dd, *J* = 14.3, 4.4 Hz, 1H, NCH₂), 3.64 (dd, *J* = 11.5, 4.7 Hz, 1H, CH₂Cl), 3.59 (dd, *J* = 11.5, 5.5 Hz, 1H, CH₂Cl), 3.18 (brs, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ: 168.6 (Phthal C-1,3), 134.2 (Phthal C-5,6), 131.7 (Phthal C-3a,7a), 123.4 (Phthal C-4,7), 69.5 (CHOH), 47.2 (CH₂Cl) 41.5 (NCH₂).

HRMS (ESI), *m*/*z*: calcd. for C₁₁H₁₁ClNO₃⁺: 240.0422 [M+H]⁺; found: 240.0426.

Racemate:

Chiralpak IG, HEX:IPA 85:15, 254 nm, 23 °C, 1 ml/min



Enantioenriched (S):



Enantioenriched (R):



Datafile Name:LI-590_85%HEX_15IPA_01.lcd Sample Name:LI-590_85%HEX_15IPA_ Sample ID:LI-590_85%HEX_15IPA_

2-(3-Bromo-2-hydroxypropyl)-1H-isoindole-1,3(2H)-dione (rac-3)⁵



By following the General Procedure **1**, starting from 2-[(oxiran-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), ICH₂Br (442 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 89% yield (253 mg) as white solid (m.p.: 85 °C) after chromatography on silica gel (50:50 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.82 (m, 2H, Phthal H-4,7), 7.71 (m, 2H, Phthal H-5,6), 4.14 (m, 1H, C<u>H</u>OH), 3.92 (dd, *J* = 14.3, 7.4 Hz, 1H, NCH₂), 3.84 (dd, *J* = 14.3, 4.4 Hz, 1H, NCH₂), 3.52 (dd, *J* = 10.7, 4.6 Hz, 1H, CH₂Br), 3.46 (dd, *J* = 10.7, 5.6 Hz, 1H, CH₂Br), 3.09 (brs, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ: 168.5 (Phthal C-1,3), 134.2 (Phthal C-5,6), 131.7 (Phthal C-3a,7a), 123.4 (Phthal C-4,7), 69.1 (CHOH), 42.3 (NCH₂) 36.2 (CH₂Br).

HRMS (ESI), *m*/*z*: calcd. for C₁₁H₁₁BrNO₃⁺: 283.9917 [M+H]⁺; found: 283.9922.

Racemate:

Chiralpak IG, HEX:IPA 85:15, 254 nm, 23 °C, 1 ml/min



Enantioenriched (S):



Enantioenriched (R):



Datafile Name:LI-592_85%HEX_15IPA_02.lcd Sample Name:LI-592_85%HEX_15IPA_ Sample ID:LI-592_85%HEX_15IPA_

2-(2-Hydroxy-3-iodopropyl)-1H-isoindole-1,3(2H)-dione (rac-4)⁵



By following the General Procedure **1**, starting from 2-[(oxiran-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), ICH₂I (536 mg, 0.16 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (301 mg) as white solid (m.p.: 112 °C) after chromatography on silica gel (50:50 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.87 (m, 2H, Phthal H-4,7), 7.75 (m, 2H, Phthal H-5,6), 3.90 (m, 2H, NCH₂), 3.90 (m, 1H, C<u>H</u>OH), 3.37 (m, 1H, CH₂I), 3.30 (m, 1H, CH₂I), 2.77 (brs, 1H, OH).

¹³C NMR (100 MHz, CDCl₃) δ: 168.6 (Phthal C-1,3), 134.3 (Phthal C-5,6), 131.8 (Phthal C-3a,7a), 123.6 (Phthal C-4,7), 69.4 (CHOH), 43.5 (NCH₂), 10.8 (CH₂I).

HRMS (ESI), *m*/*z*: calcd. for C₁₁H₁₁INO₃⁺: 331.9779 [M+H]⁺; found: 331.9775.

Racemate:

Chiralpak IG, HEX:IPA 85:15, 254 nm, 23 °C, 1ml/min



Enantioenriched (S):



Enantioenriched (R):



2-Chloro-1-(4-chlorophenyl)ethanol (5)⁶



By following the General Procedure **1**, starting from 2-(4-chlorophenyl)oxirane (155 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 90% yield (172 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.34 (m, 2H, Ph H-3,5), 7.29 (m, 2H, Ph H-2,6), 4.84 (m, 1H, C<u>H</u>OH), 3.69 (dd, *J* = 11.3, 3.5 Hz, 1H, CH₂Cl), 3.59 (dd, *J* = 11.3, 8.5 Hz, 1H, CH₂Cl), 2.97 (m, OH).

¹³**C NMR** (100 MHz, CDCl₃) δ: 138.3 (Ph C-1), 134.1 (Ph C-4), 128.7 (Ph C-3,5), 127.4 (Ph C-2,6), 73.2 (CHOH), 50.4 (CH₂Cl).

HRMS (ESI), m/z: calcd. for C₈H₉Cl₂O⁺: 191.0025 [M+H]⁺; found: 191.0029.

2-Chloro-1-[2-(trifluoromethoxy)phenyl]ethanol (6)



By following the General Procedure **1**, starting from 2-[2-(trifluoromethoxy)phenyl]oxirane (204 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 85% yield (205 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.66 (m, 1H, Ph H-6), 7.37 (m, 1H, Ph H-4), 7.35 (m, 1H, Ph H-5), 7.26 (m, 1H, Ph H-3), 5.25 (dt, J_d = 8.6 Hz, J_t = 3.3 Hz, 1H, C<u>H</u>OH), 3.81 (dd, J = 11.2, 3.1 Hz, 1H, CH₂Cl), 3.60 (dd, J = 11.2, 8.6 Hz, 1H, CH₂Cl), 2.71 (d, J = 3.6 Hz, 1H, OH).

¹³**C NMR** (100 MHz, CDCl₃) δ: 146.1 (q, *J* = 1.6 Hz, Ph C-2), 132.0 (Ph C-1), 129.6 (Ph C-4), 127.8 (Ph C-6), 127.0 (Ph C-5), 120.4 (q, *J* = 258.5 Hz, OCF₃), 119.9 (q, *J* = 1.7 Hz, Ph C-3), 68.2 (CHOH), 49.6 (CH₂Cl).

¹⁹**F NMR** (470 MHz, CDCl₃) δ: -56.9 (s, CF₃).

HRMS (ESI), m/z: calcd. for C₉H₉ClF₃O₂⁺: 241.0238 [M+H]⁺; found: 241.0242.

2-(4-Bromophenyl)-1-chloro-2-propan-2-ol (7)



By following the General Procedure **1**, starting from 2-(4-bromophenyl)-2-methyloxirane (213 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 82% yield (205 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.50 (m, 2H, Ph H-3,5), 7.34 (m, 2H, Ph H-2,6), 3.79 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.73 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.60 (brs, 1H, OH), 1.61 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 143.2 (Ph C-1), 131.5 (Ph C-3,5), 126.8 (Ph C-2,6), 121.6 (Ph C-4), 73.6 (COH), 55.0 (CH₂Cl), 27.3 (CH₃).

HRMS (ESI), *m*/*z*: calcd. for C₉H₁₁BrClO⁺: 248.9676 [M+H]⁺; found: 248.9680.

1-Chloro-2-(4-iodophenyl)-2-propanol (8)



By following the General Procedure **1**, starting from 2-(4-iodophenyl)-2-methyloxirane (260 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 83% yield (246 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.70 (m, 2H, Ph H-3,5), 7.21 (m, 2H, Ph H-2,6), 3.79 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.73 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.60 (brs, 1H, OH), 1.60 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 144.0 (Ph C-1), 137.5 (Ph C-3,5), 127.1 (Ph C-2,6), 93.2 (Ph C-4), 73.7 (COH), 55.0 (CH₂Cl), 27.3 (CH₃).

HRMS (ESI), *m*/*z*: calcd. for C₉H₁₁ClIO⁺: 296.9538 [M+H]⁺; found: 296.9542.

1-Chloro-2-(4-fluorophenyl)-2-propanol (9)



By following the General Procedure **1**, starting from 2-(4-fluorophenyl)-2-methyloxirane (152 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 90% yield (170 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.44 (m, 2H, Ph H-2,6), 7.05 (m, 2H, Ph H-3,5), 3.79 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.73 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.59 (brs, 1H, OH), 1.63 (s, 3H, CH₃).

¹³**C NMR** (100 MHz, CDCl₃) δ: 162.1 (d, J = 246.2 Hz, Ph C-4), 139.9 (d, J = 3.1 Hz, Ph C-1), 126.8 (d, J = 8.1 Hz, Ph C-2,6), 115.2 (d, J = 21.4 Hz, Ph C-3,5), 73.5 (COH), 55.3 (CH₂Cl), 27.3 (CH₃).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -115.2 (m, F).

HRMS (ESI), *m*/*z*: calcd. for C₉H₁₁ClFO⁺: 189.0477 [M+H]⁺; found: 189.0481.

1-Chloro-2-(2,5-dichlorophenyl)propan-2-ol (10)



By following the General Procedure **1**, starting from 2-(2,5-dichlorophenyl)-2-methyloxirane (203 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 92% yield (220 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (200 MHz, CDCl₃) δ: 7.76 (d, *J* = 8.6 Hz, 1H, Ph H), 7.37 (d, *J* = 2.2 Hz, 1H, Ph H), 7.29 (dd, *J* = 8.6, 2.2 Hz, 1H, Ph H), 4.33 (d, *J* = 11.2 Hz, 1H, CH₂Cl), 4.01 (d, *J* = 11.2 Hz, 1H, CH₂Cl), 2.96 (brs, 1H, OH), 1.74 (s, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ: 139.5 (Ph C), 134.1 (Ph C), 131.1 (Ph C), 130.9 (Ph C), 129.6 (Ph C), 127.3 (Ph C), 74.4 (COH), 52.6 (CH₂Cl), 24.9 (CH₃).

HRMS (ESI), *m*/*z*: calcd. for C₉H₉Cl₃O⁺: 238.9792 [M+H]⁺; found: 238.9788.

1-Chloro-2-(2,4-difluorophenyl)-2-propanol (11)



By following the General Procedure **1**, starting from 2-(2,4-difluorophenyl)-2-methyloxirane (170 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M,

1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 87% yield (180 mg) as colourless oil after chromatography on silica gel (90:10 v/v, n-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.64 (m, 1H, Ph H-6), 6.91 (m, 1H, Ph H-5), 6.80 (m, 1H, Ph H-3), 4.02 (d, *J* = 11.1 Hz, 1H, CH₂Cl), 3.88 (dd, *J* = 11.1, 1.1 Hz, 1H, CH₂Cl), 2.77 (brs, 1H, OH), 1.65 (d, *J* = 1.2 Hz, 3H, CH₃).

¹³**C NMR** (100 MHz, CDCl₃) δ: 162.5 (dd, *J* = 249.0, 12.4 Hz, Ph C-4), 159.1 (dd, *J* = 247.8, 11.7 Hz, Ph C-2), 128.9 (dd, *J* = 9.5, 5.8 Hz, Ph C-6), 127.0 (dd, *J* = 12.6, 3.8 Hz, Ph C-1), 111.2 (dd, *J* = 20.6, 3.5 Hz, Ph C-5), 104.3 (dd, *J* = 27.6, 25.5 Hz, Ph C-3), 72.8 (d, *J* = 4.3 Hz, COH), 53.8 (d, *J* = 6.4 Hz, CH₂Cl), 25.9 (d, *J* = 3.6 Hz, CH₃).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -111.4 (m, Ph F), -109.7 (m, Ph F).

HRMS (ESI), *m*/*z*: calcd. for C₉H₁₀ClF₂O⁺: 207.0383 [M+H]⁺; found: 207.0388.

1-Chloro-2-(2,4,5-trifluorophenyl)-2-propanol (12)



By following the General Procedure **1**, starting from 2-methyl-2-(2,4,5-trifluorophenyl)oxirane (188 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (204 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.52 (ddd, *J* = 11.5, 9.0, 7.3 Hz, 1H, Ph H-6), 6.91 (m, 1H, Ph H-3), 4.01 (d, *J* = 11.2 Hz, 1H, CH₂Cl), 3.86 (dd, *J* = 11.2, 1.1 Hz, 1H, CH₂Cl), 2.79 (brs, 1H, OH), 1.64 (d, *J* = 1.2 Hz, 3H, CH₃).

¹³**C NMR** (100 MHz, CDCl₃) δ: 153.8 (ddd, J = 244.1, 9.3, 2.9 Hz, Ph C), 149.3 (ddd, J = 251.5, 14.6, 12.8 Hz, Ph C), 146.8 (ddd, J = 244.6, 12.0, 3.4 Hz, Ph C), 127.9 (dt, $J_d = 15.0$ Hz, $J_t = 4.4$ Hz, Ph C-1), 116.4 (ddd, J = 21.4, 5.9, 1.3 Hz, Ph C-6), 106.4 (dd, J = 29.9, 21.0 Hz, Ph C-3), 72.6 (d, J = 4.7 Hz, COH), 53.4 (d, J = 6.5 Hz, CH₂Cl), 25.8 (d, J = 3.5 Hz, CH₃).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -141.9 (m, F), -134.7 (m, F), -115.7 (m, F).

HRMS (ESI), *m*/*z*: calcd. for C₉H₉ClF₃O⁺: 225.0289 [M+H]⁺; found: 225.0286.

1-Chloro-2-[4-(trifluoromethyl)phenyl]-2-propanol (13)



By following the General Procedure **1**, starting from 2-methyl-2-[4-(trifluoromethyl)phenyl]oxirane (202 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 91% yield (203 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.63 (m, 2H, Ph H-3,5), 7.60 (m, 2H, Ph H-2,6), 3.84 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.78 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.68 (brs, 1H, OH), 1.64 (s, 3H, CH₃).

¹³**C NMR** (100 MHz, CDCl₃) δ: 148.2 (Ph C-1), 129.8 (q, *J* = 32.5 Hz, Ph C-4), 125.5 (Ph C-2,6), 125.4 (q, *J* = 3.8 Hz, Ph C-3,5), 124.0 (q, *J* = 272.0 Hz, CF₃), 73.8 (COH), 54.9 (CH₂Cl), 27.4 (CH₃).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -62.6 (s, CF₃).

HRMS (ESI), *m*/*z*: calcd. for C₁₀H₁₁ClF₃O⁺: 239.0445 [M+H]⁺; found: 239.0440.

4-Chloro-2-(1-chloro-2-hydroxy-2-propanyl)phenol (14)



By following the General Procedure **1**, starting from 4-chloro-2-(2-methyloxiran-2-yl)phenol [185 mg, 1.0 mmol, 1.0 equiv – previously deprotonated at -78 °C in 2-MeTHF with Meli (1.6 M, 0.6 mL, 0.95 mmol, 0.95 equiv)], ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 82% yield (181 mg) as white solid (m.p.: 105 °C) after chromatography on silica gel (80:20 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 8.67 (s, 1H, OH), 7.16 (dd, *J* = 8.7, 2.5 Hz, 1H, Ph H-5), 7.03 (d, *J* = 2.5 Hz, 1H, Ph H-3), 6.83 (d, *J* = 8.7 Hz, 1H, Ph C-6), 3.98 (d, *J* = 11.5 Hz, 1H, CH₂Cl), 3.69 (d, *J* = 11.5 Hz, 1H, CH₂Cl), 3.24 (s, 1H, OH), 1.73 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 154.7 (Ph C-1), 129.7 (Ph C-5), 127.2 (Ph C-2), 126.1 (Ph C-3), 124.6 (Ph C-4), 119.5 (Ph C-6), 76.9 (COH), 53.2 (CH₂Cl), 25.9 (CH₃).

HRMS (ESI), *m*/*z*: calcd. for C₉H₁₁Cl₂O₂⁺: 221.0131 [M+H]⁺; found: 221.0135.

2-Chloro-1-(4-fluorophenyl)-1-phenylethanol (15)



By following the General Procedure **1**, starting from 2-(4-fluorophenyl)-2-phenyloxirane (214 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 90% yield (225 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.43 (m, 2H, Ph2 H-2,6), 7.42 (m, 2H, Ph1 H-2,6), 7.36 (m, 2H, Ph2 H-3,5), 7.30 (m, 1H, Ph2 H-4), 7.03 (m, 2H, Ph1 H-3,5), 4.18 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.7 Hz, 1H, CH₂Cl), 4.16 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.7 Hz, 1H, CH₂Cl), 3.17 (brs, 1H, OH).

¹³**C NMR** (100 MHz, CDCl₃) δ: 162.2 (d, J = 246.9 Hz, Ph1 C-4), 143.0 (Ph2 C-1), 139.1 (d, J = 3.2 Hz, Ph1 C-1), 128.4 (Ph2 C-3,5), 128.3 (d, J = 8.2 Hz, Ph1 C-2,6), 127.9 (Ph2 C-4), 126.3 (Ph2 C-2,6), 115.2 (d, J = 21.4 Hz, Ph1 C-3,5), 77.5 (COH), 53.1 (CH₂Cl).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -114.7 (m, F).

HRMS (ESI), *m*/*z*: calcd. for C₁₄H₁₃ClFO⁺: 251.0633 [M+H]⁺; found: 251.0659.

2-Chloro-1-(4-methoxyphenyl)-1-phenylethan-1-ol (16)



By following the General Procedure **1**, starting from 2-(4-methoxyphenyl)-2-phenyloxirane (226 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 92% yield (229 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (200 MHz, CDCl₃) δ: 7.50-7.34 (m, 7H, Ph1 H-2,6, Ph2 H-2,3,4,5,6), 6.91 (m, 2H, Ph1 H-3,5), 4.19 (s, 2H, CH₂Cl), 3.80 (s, 3H, OCH₃), 3.22 (s, 1H, OH).

¹³**C NMR** (50 MHz, CDCl₃) δ: 158.9 (Ph1 C-4), 143.4 (Ph2 C-1), 135.4 (Ph1 C-1), 128.2 (Ph2 C-3,5), 127.6 (Ph1 C-2,6), 127.5 (Ph2 C-4), 126.3 (Ph2 C-2,6), 113.6 (Ph1 C-3,5), 77.6 (COH), 55.1 (OCH₃), 53.3 (CH₂Cl).

HRMS (ESI), *m*/*z*: calcd. for C₁₅H₁₆ClO₂⁺: 263.0833 [M+H]⁺; found: 263.0838.

1-Chloro-2-(4-methoxyphenyl)propan-2-ol (17)⁷



By following the General Procedure **1**, starting from 2-(4-methoxyphenyl)-2-methyloxirane (164 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 92% yield (229 mg) as colourless oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (200 MHz, CDCl₃) δ: 7.39 (d, *J* = 8.8 Hz, 2H, Ph H-2,6), 6.90 (d, *J* = 8.8 Hz, 2H, Ph H-3,5), 3.87-3.68 (m, 2H, CH₂Cl), 2.83 (s, 3H, OCH₃), 2.41 (brs, 1H, OH), 1.63 (s, 3H, CH₃).

¹³C NMR (50 MHz, CDCl₃) δ: 158.8 (Ph C-4), 136.2 (Ph C-1), 126.2 (Ph C-2,6), 113.7 (Ph C-3,5), 73.5 (COH), 55.4 (CH₂Cl), 55.2 (OCH₃), 27.2 (CH₃).

HRMS (ESI), m/z: calcd. for C₁₀H₁₃ClO₂⁺: [M+H]⁺; found: .

1-Chloro-2-phenyl-2-propanol (18)⁸



By following the General Procedure **1**, starting from 2-methyl-2-phenyloxirane (134 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 89% yield (152 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.47 (m, 2H, Ph H-2,6), 7.38 (m, 2H, Ph H-3,5), 7.30 (m, 1H, Ph H-4), 3.84 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.76 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.59 (brs, 1H, OH), 1.64 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 144.1 (Ph C-1), 128.4 (Ph C-3,5), 127.5 (Ph C-4), 124.9 (Ph C-2,6), 73.8 (COH), 55.4 (CH₂Cl), 27.3 (CH₃).

HRMS (ESI), m/z: calcd. for C₉H₁₂ClO⁺: 171.0571 [M+H]⁺; found: 171.0575.

3-Chloro-1,1,1-trifluoro-2-phenyl-2-propanol (19)



By following the General Procedure **1**, starting from 2-phenyl-2-(trifluoromethyl)oxirane (188 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 85% yield (191 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.59 (m, 2H, Ph H-2,6), 7.45 (m, 3H, Ph H-3,4,5), 4.18 (d, *J* = 12.0

Hz, 1H, CH₂Cl), 4.06 (d, *J* = 12.0 Hz, 1H, CH₂Cl), 3.29 (brs, 1H, OH).

¹³**C NMR** (100 MHz, CDCl₃) δ: 134.7 (Ph C-1), 129.3 (Ph C-4), 128.6 (Ph C-3,5), 126.2 (Ph C-2,6), 124.3 (q, *J* = 286.5 Hz, CF₃), 76.4 (q, *J* = 28.6 Hz, COH), 47.7 (CH₂Cl).

¹⁹**F NMR** (376 MHz, CDCl₃) δ: -76.9 (s, CF₃).

HRMS (ESI), *m*/*z*: calcd. for C₉H₉ClF₃O⁺: 225.0289 [M+H]⁺; found: 225.0285.

2-Methyl-2-propanyl 4-(1-chloro-2-hydroxy-2-propanyl)benzoate (20)



By following the General Procedure **1**, starting from *tert*-butyl 4-(2-methyloxiran-2-yl)benzoate (234 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 87% yield (236 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.99 (m, 2H, Ph H-2,6), 7.51 (m, 2H, Ph H-3,5), 3.84 (A-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 3.77 (B-part of an AB-system, ${}^{2}J_{AB}$ = 11.2 Hz, 1H, CH₂Cl), 2.64 (s, 1H, OH), 1.63 (s, 3H, CH₃), 1.59 (s, 9H, C(CH₃)₃).

¹³**C NMR** (100 MHz, CDCl₃) δ: 165.4 (C=O), 148.6 (Ph C-4), 131.3 (Ph C-1), 129.6 (Ph C-2,6), 124.9 (Ph C-3,5), 81.1 (<u>C</u>(CH₃)₃), 73.9 (COH), 55.0 (CH₂Cl), 28.2 (C(<u>C</u>H₃)₃), 27.4 (CH₃).

HRMS (ESI), *m*/*z*: calcd. for C₁₄H₂₀ClO₃⁺: 271.1095 [M+H]⁺; found: 271.1091.

1-Chloro-2-methyl-4-phenyl-3-butyn-2-ol (21)9



By following the General Procedure **1**, starting from 2-methyl-2-(phenylethynyl)oxirane (158 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 85% yield (165 mg) as colourless oil after chromatography on silica gel (80:20 v/v, *n*-hexane/ethyl acetate).

¹**H NMR** (400 MHz, CDCl₃) δ: 7.45 (m, 2H, Ph H-2,6), 7.32 (m, 3H, Ph H-3,4,5), 3.78 (A-part of an AB-system, ${}^{2}J_{AB}$ = 10.9 Hz, 1H, CH₂Cl), 3.69 (B-part of an AB-system, ${}^{2}J_{AB}$ = 10.9 Hz, 1H, CH₂Cl), 2.86 (s, 1H, OH), 1.68 (s, 3H, Me).

¹³**C NMR** (100 MHz, CDCl₃) δ: 131.8 (Ph C-2,6), 128.6 (Ph C-4), 128.2 (Ph C-3,5), 122.0 (Ph C-1), 89.5 (PhC=<u>C</u>), 84.5 (Ph<u>C</u>=C), 68.0 (CHOH), 54.1 (CH₂Cl), 26.9 (CH₃).

HRMS (ESI), m/z: calcd. for C₁₁H₁₁ClO⁺: 195.0571 [M+H]⁺; found: 195.0571.

(3E)-1-Chloro-2-methyl-3-hepten-2-ol (22)



By following the General Procedure **1**, starting from 2-methyl-2-[(1*E*)-pent-1-en-1-yl]oxirane (126 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (3 mL), the desired product was obtained in 92% yield (150 mg) as colourless oil after chromatography on silica gel (80:20 v/v, *n*-hexane/ethyl acetate).

¹**H NMR** (400 MHz, C₆D₆) δ : 5.64 (td, J_d = 15.5 Hz, J_t = 6.9 Hz, 1H, Hepten H-4), 5.30 (dt, J_d = 15.5 Hz, J_t = 1.5 Hz, 1H, Hepten H-3), 3.18 (A-part of an AB-system, ² J_{AB} = 10.8 Hz, 1H, Hepten H-1), 3.14 (B-part of an AB-system, ² J_{AB} = 10.8 Hz, 1H, Hepten H-1), 1.88 (s, 1H, OH), 1.87 (m, 2H, Hepten H-5), 1.28 (m, 2H, Hepten H-6), 1.13 (s, 3H, CH₃), 0.82 (t, J = 7.3 Hz, 3H, Hepten H-7).

¹³**C NMR** (100 MHz, C₆D₆) δ: 133.9 (Hepten C-3), 130.4 (Hepten C-4), 71.9 (Hepten C-2), 54.7 (Hepten C-1), 34.5 (Hepten C-5), 25.7 (CH₃), 22.6 (Hepten C-6), 13.7 (Hepten C-7).

HRMS (ESI), m/z: calcd. for C₈H₁₆ClO⁺: 163.0884 [M+H]⁺; found: 163.0880.

4. Experimental procedures Scheme 3

General Procedure scheme 3a with 1.8 equiv of LiCH₂Cl in 2-MeTHF

By following the General Procedure **1**, starting from 2-{[(2*S*)-oxiran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (353 mg, 0.15 mL, 2.0 mmol, 2.0 equiv), MeLi (1.6 M, 1.1 mL, 1.8 mmol, 1.8 equiv) and 2-MeTHF (5 mL), *rac-2* was obtained in 21% yield (50 mg) as white solid (m.p.: 95 °C) and compound **5** in 57% yield (109 mg) as yellow oil after chromatography on silica gel (80:20 *v/v*, *n*-hexane/diethyl ether). The experimental spectra match with those reported above.

General Procedure scheme 3a with 1.0 equiv of LiCH₂Cl in 2-MeTHF

By following the General Procedure **1**, starting from 2-{[(2*S*)-oxiran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (212 mg, 0.09 mL, 1.2 mmol, 1.2 equiv), MeLi (1.6 M, 0.6 mL, 1.0 mmol, 1.0 equiv) and 2-MeTHF (5 mL), *rac-2* was obtained in 10% yield (24 mg) as white solid (m.p.: 95 °C) and compound **5** in 25% yield (48 mg) as yellow oil after chromatography on silica gel (80:20 *v/v*, *n*-hexane/diethyl ether). The experimental spectra match with those reported above.

General Procedure scheme 3a with 1.0 equiv of LiCH₂Cl in THF

By following the General Procedure **1**, starting from 2-{[(2*S*)-oxiran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), 4-chlorobenzaldehyde (141 mg, 1.0 mmol, 1.0 equiv), ICH₂Cl (212 mg, 0.09 mL, 1.2 mmol, 1.2 equiv), MeLi (1.6 M, 0.6 mL, 1.0 mmol, 1.0 equiv) and THF (5 mL), compound **5** was formed in 77% yield (147 mg) as yellow oil after chromatography on silica gel (90:10 v/v, *n*-hexane/diethyl ether). The experimental spectra match with those reported above.

General Procedure scheme 3b with 1.8 equiv of LiCD₂Cl in 2-MeTHF

By following the General Procedure **1**, starting from 2-{[(2*S*)-oxiran-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione (203 mg, 1.0 mmol, 1.0 equiv), CD_2I_2 (324 mg, 0.1 mL, 1.2 mmol, 1.2 equiv), MeLi (1.6 M, 0.6 mL, 1.0 mmol, 1.0 equiv) and 2-MeTHF (3 mL), *rac-4* was formed in 84% yield (278 mg) as white solid (m.p.: 112 °C) after chromatography on silica gel (50:50 *v/v*, *n*hexane/diethyl ether). The experimental spectra match with those reported above.

5. References

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6. Copies of ¹H- and ¹³C-NMR Spectra for all the compounds

2-(3-Chloro-2-hydroxypropyl)-1H-isoindole-1,3(2H)-dione (2)

о но CI N ő

(¹H NMR, CDCI₃, 400 MHz)



2-(3-Bromo-2-hydroxypropyl)-1*H*-isoindole-1,3(2*H*)-dione (3)



(¹H NMR, CDCI₃, 400 MHz)







2-(2-Hydroxy-3-iodopropyl)-1*H*-isoindole-1,3(2*H*)-dione (4)

2-Chloro-1-(4-chlorophenyl)ethanol (5)



2-Chloro-1-[2-(trifluoromethoxy)phenyl]ethanol (6)







Br

ŌН _CI Me



∑ 3.81 3.78 3.77 3.71 - 2.60

(¹H NMR, CDCI₃, 400 MHz)





2-(4-Bromophenyl)-1-chloro-2-propan-2-ol (7)

1-Chloro-2-(4-iodophenyl)-2-propanol (8)





1-Chloro-2-(4-fluorophenyl)-2-propanol (9)

110 100 f1 (ppm)

.

1-Chloro-2-(2,5-dichlorophenyl)propan-2-ol (10)



1-Chloro-2-(2,4-difluorophenyl)-2-propanol (11)





(¹H NMR, CDCI₃, 400 MHz)



1-Chloro-2-(2,4,5-trifluorophenyl)-2-propanol (12)





1-Chloro-2-[4-(trifluoromethyl)phenyl]-2-propanol (13)

4-Chloro-2-(1-chloro-2-hydroxy-2-propanyl)phenol (14)



2-Chloro-1-(4-fluorophenyl)-1-phenylethanol (15)





(¹H NMR, CDCI₃, 200 MHz)



2-Chloro-1-(4-methoxyphenyl)-1-phenylethan-1-ol (16)





(¹H NMR, CDCI₃, 200 MHz)



1-Chloro-2-(4-methoxyphenyl)propan-2-ol (17)



1-Chloro-2-phenyl-2-propanol (18)



3-Chloro-1,1,1-trifluoro-2-phenyl-2-propanol (19)





(¹H NMR, CDCI₃, 400 MHz)



(¹³C NMR, CDCI₃, 100 MHz)





2-Methyl-2-propanyl 4-(1-chloro-2-hydroxy-2-propanyl)benzoate (20)

1-Chloro-2-methyl-4-phenyl-3-butyn-2-ol (21)



(3E)-1-Chloro-2-methyl-3-hepten-2-ol (22)

