Supporting Information

Two-step Conversion of Carboxylic Esters into Distally Fluorinated Ketones via Ring Cleavage of Cyclopropanol Intermediates: Application of Sulfinate Salts as Fluoroalkylating Reagents

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Table of Contents

I. Preparation of cyclopropanols S2
II. Selected NMR spectra of the reaction mixtures S5
III. Mechanism proving experiments S6
IV. X-Ray data for compound 5 S9
V. Copies of $^1$H, $^{13}$C and $^{19}$F NMR spectra of fluorinated ketones S11
VI. Copies of $^1$H, $^{13}$C NMR for cyclopropanols S37
I. Preparation of cyclopropanols

General procedure for cyclopropanation of carboxylic esters. Preparation of cyclopropanols 1a-c, 1g, 1i. To a stirred solution of ester (25 mmol) and titanium(IV) isopropoxide (0.74 mL, 2.5 mmol, 10 mol%) in diethyl ether (50 mL) was added slowly over 2–3 h at room temperature a solution of EtMgBr (60 mmol) in diethyl ether (60 mL). The reaction mixture was stirred for additional 30 min and then cooled with an ice bath. The reaction mixture was hydrolyzed by slow addition of cold 10% H\textsubscript{2}SO\textsubscript{4} solution (50 mL) and then extracted with ether (3 × 40 mL). The combined organic layers were washed with saturated NaHCO\textsubscript{3} solution, brine and dried (MgSO\textsubscript{4}). After evaporation of solvent under reduced pressure the cyclopropanol products can be purified using distillation or column chromatography on silica gel. However, in most cases they are pure enough to be used directly in the next step. The following cyclopropanol product were synthesized using the procedure described above:

1-Benzylcyclopropanol (1a), starting from isopropyl phenylacetate. Yield 88%. Purified using short-column silica gel chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta = 7.37$−7.22 (m, 5H), 2.89 (s, 2H), 1.93 (s, 1H), 0.82 (m, 2H), 0.64 (m, 2H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): $\delta =$ 138.73, 129.57, 128.68, 126.79, 56.30, 44.26, 13.41.

1-Amylcyclopropanol (1b), starting from methyl hexanoate. Yield 95%. Used as obtained without any purification. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta = 1.82$ (br s, 1H), 1.57−1.46 (m, 4H), 1.36−1.27 (m, 4H), 0.90 (m, 3H), 0.72 (m, 2H), 0.43 (m, 2H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): $\delta =$ 56.02, 38.41, 32.02, 25.74, 22.86, 14.20, 13.64.

1-(3-Chloropropyl)cyclopropanol (1c), starting from ethyl 4-chlorobutanoate. Yield 86%. Purified using short-column silica gel chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta = 3.64$ (t, $J = 6.5$ Hz, 2H), 2.04 (m, 2H), 1.80 (br s, 1H), 1.70 (m, 2H), 0.77 (m, 2H), 0.49 (m, 2H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): $\delta =$ 55.25, 45.22, 35.63, 29.34, 13.82.

1-(2-Phenylethyl)cyclopropanol (1g), starting from ethyl 2-phenylpropanoate. Yield 97%. Purified using short-column silica gel chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta =$ 7.32−7.16 (m, 5H), 2.86 (m, 2H), 1.88 (m, 2H), 1.80 (s, 1H), 0.76 (m, 2H), 0.46 (m, 2H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): $\delta =$ 142.33, 128.57, 128.55, 125.99, 55.96, 40.57, 32.65, 13.85.
1-(9-Decenyl)cyclopropanol (1j), starting from methyl 10-undecenoate. Yield 84%. Purified using short-column silica gel chromatography. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 5.81$ (ddt, $J = 17.0$, 10.2, 6.7 Hz, 1H), 4.99 (ddt, $J = 17.0$, 2.2, 1.7 Hz, 1H), 4.93 (ddt, $J = 10.2$, 2.2, 1.2 Hz, 1H), 2.04 (m, 2H), 1.75 (s, 1H), 1.58–1.44 (m, 4H), 1.43–1.23 (m, 10H), 0.73 (m, 2H), 0.44 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 139.38$, 114.26, 56.05, 38.44, 33.96, 29.81, 29.78, 29.59, 29.28, 29.08, 26.06, 13.67.

Preparation of cyclopropanols 1h, 1d, 1f, 1e. To a stirred solution of ester (10 mmol) and titanium(IV) isopropoxide (0.75 mL, 2.5 mmol, 25 mol%) in THF (60 mL) was added slowly over 3–4 h at room temperature a solution of EtMgBr (25 mmol) in THF (25 mL). The reaction mixture was stirred overnight and then hydrolyzed with water (1–2 mL) and filtered to afford compound 1h after evaporation of the solvent. For compounds 1d-e, solvent (THF) was evaporated under reduced pressure prior the hydrolysis. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL), cooled with ice bath, hydrolyzed with water (1–2 mL) and filtered through layer of silica. The filter cake was thoroughly washed with CH$_2$Cl$_2$ or ethyl acetate (5 × 40 mL). After evaporation of solvent under reduced pressure the cyclopropanol products were purified by column chromatography on silica gel, recrystallization or used directly in the next step without any purification.

1-(tert-Butyldiphenylsiloxymethyl)cyclopropanol (1h), starting from ethyl tert-butyldiphenylsiloxycetate. Yield 97%. Used as obtained without any purification. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.73–7.65$ (m, 4H), 7.48–7.36 (m, 6H), 3.69 (s, 2H), 2.69 (s, 1H), 1.08 (s, 9H), 0.79 (m, 2H), 0.44 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 135.74$, 133.53, 129.92, 127.89, 69.49, 56.62, 27.04, 19.47, 11.53.

1-(Tetrahydro-2H-pyran-4-yl)cyclopropanol (1d), starting from the corresponding ethyl ester. Yield 83%. Purified using short-column silica gel chromatography. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 4.02$ (dt, $J = 11.0$, 3.2 Hz, 2H), 3.45–3.27 (m, 2H), 2.12 (s, 1H), 1.67–1.52 (m, 4H), 1.33–1.21 (m, 1H), 0.71 (m, 2H), 0.47 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 68.16$, 58.66, 42.22, 28.84, 12.35.

tert-Butyl 4-(1-hydroxycyclopropyl)piperidine-1-carboxylate (1f), starting from the corresponding ethyl ester. Yield 68%. Purified by recrystallization from cyclohexane (mp 118 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 4.19$ (br s, 2H), 2.63 (br t, $J = 12.9$ Hz, 2H), 1.81 (br s,

S3
$^1$H, 1.71–1.63 (m, 2H), 1.55–1.35 (m, 2H), 1.46 (s, 9H), 1.12 (tt, $J = 12.1, 3.5$ Hz, 1H), 0.73 (m, 2H), 0.48 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 154.97, 79.50, 58.74, 44.00, 43.50, 28.62, 28.09, 12.77$.

1-(2,2-Diethoxyethyl)cyclopropanol (1e).$^6$ Yield 90%. Used as obtained without any purification.$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 4.80$ (t, $J = 5.8$ Hz, 1H), 3.79–3.67 (m, 2H), 3.62–3.52 (m, 3H), 1.89 (d, $J = 5.8$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 6H), 0.76 (m, 2H), 0.45 (m, 2H).

Preparation of 1-(3-methoxyphenyl)cyclopropanol (1i).$^7$ A 1.5 M solution of MeMgBr in diethyl ether (20 mL, 30 mmol) was added within 5 min to a solution of titanium isopropoxide (5.68 g, 20 mmol) in Et$_2$O. The resulting yellow solution was cooled to 0 °C and methyl 3-methoxybenzoate (20 mmol, 3.32 g, in 10 mL of Et$_2$O) was then added. EtMgBr (30 mL of a 1 M solution in Et$_2$O, 30 mmol) was added over 30–40 min. The resulting reaction mixture was allowed to warm to room temperature, then stirred for an additional hour, quenched at 0 °C by careful addition of cold 10% H$_2$SO$_4$ solution (80 mL), and was extracted with Et$_2$O (3 × 20 mL). The combined organic layers were washed with saturated NaHCO$_3$ solution, brine and dried (MgSO$_4$). After evaporation of solvent under reduced pressure the cyclopropanol product was isolated by column chromatography on silica gel (petroleum ether/EtOAc). Yield 45% (1.5 g). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.24$ (t, $J = 8.0$ Hz, 1H), 6.91 (dd, $J = 2.6, 1.8$ Hz, 1H), 6.83 (ddd, $J = 8.0, 1.8, 0.9$ Hz, 1H), 6.76 (ddd, $J = 8.0, 2.6, 0.9$ Hz, 1H), 3.81 (s, 3H), 2.39 (br s, 1H), 1.26 (m, 2H), 1.04 (m, 2H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta = 159.85, 146.27, 129.52, 116.64, 111.82, 110.62, 56.71, 55.37, 18.19$.

References:

II. Selected NMR spectra of the reaction mixtures

Produced from 1-amylcyclopropanol (1b) after extraction with pentane:

Produced from 1-benzylcyclopropanol (1a) after extraction with pentane:
III. Mechanism proving experiments

**TEMPO inhibition experiment.** A 5 mL vial was charged with Cu(OAc)$_2$·H$_2$O (40 mg, 0.2 mmol, 100 mol%), TEMPO (94 mg, 0.6 mmol) and CF$_3$SO$_2$Na (94 mg, 0.6 mmol). Then a solution of cyclopropanol 1b (0.2 mmol) and internal standard (1,3-bis(trifluoromethyl)-5-bromobenzene) in CD$_2$OD (1 mL) was added. After that, *tert*-butyl hydroperoxide solution (70% in water, 0.08 mL, 0.6 mmol) was added dropwise via syringe (without a metal needle). The reaction mixture was then filtered through a thin layer of MgSO$_4$ atop of short layer of SiO$_2$ into a NMR tube and examined by $^{19}$F NMR. The internal standard was employed to calculate yields of TEMPO-CF$_3$ adduct and $\beta$-trifluoromethyl ketone 3b. After 24h, the solution was diluted with 1 mL of D$_2$O, extracted with CDCl$_3$ and passed through a thin layer of MgSO$_4$ again to remove traces of paramagnetic Cu$^{II}$ species. $^{19}$F NMR spectrum was measured again to refine the initial data.
$^{19}$F NMR spectrum of reaction mixture produced from 2-butyl-1-methylcyclopropanol:

Direct monitoring of reaction in NMR tube. Detection of CuCF$_3$ species.

$^{19}$F NMR spectra were acquired in DMF-$d_7$ after addition of 1 equiv. of TBHP (spectrum A), 3 equiv. of TBHP (spectrum B), and after 48 h (spectrum C).
IV. X-Ray data for compound 6

Single crystal X-ray diffraction analysis

Crystal data for 6:
C_{18}H_{17}BrF_{2}O, \( M_r = 367.22 \) g/mol, orthorhombic, \( Pnma \) (no. 62), \( a = 34.5876(4) \) Å, \( b = 9.19962(10) \) Å, \( c = 4.92247(5) \) Å, \( V = 1566.29(3) \) Å\(^3\), \( Z = 4 \), \( T = 123.0 \) K, \( \mu (\text{Cu-K}α) = 3.762 \) mm\(^{-1}\), \( \rho_{\text{calc}} = 1.557 \) g/cm\(^3\), 13397 reflections measured (5.11° \( \leq 2\Theta \leq 134.43° \)) of which 1462 unique (\( R_{int} = 0.0195, R_{sigma} = 0.0074 \)), final \( R_1 \) [\( F^2 > 2\sigma(F^2) \)] = 0.0235, \( wR_2 = 0.0627 \). The crystallographic data is deposited with the Cambridge Crystallographic Data Centre (CCDC 1536256) and can be obtained free of charge from The Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

Single crystals of 6 were obtained as large colourless blocks, by slow evaporation of a solution of 6 in Et\(_2\)O and pentane. Single crystal X-ray diffraction data was collected at 123.0K on a Rigaku Compact HomeLab diffractometer, equipped with a Saturn 944 HG CCD detector and Oxford Cryostream cooling system using monochromatic Cu-K\(\alpha\) radiation (1.54178Å) from a MicroMax\(^\text{TM}\)-003 sealed tube microfocus X-ray source. The strategy for data collection was calculated using Rigaku CollectionStrategy [1]. Data was collected using \( \omega \)-scans. CrysAlisPro [2] was used for data reduction and empirical absorption correction using spherical harmonics implemented in SCALE3 ABSPACK scaling algorithm [3]. The structure was solved using SHELXT [4] and refined by full-matrix least-squares method against \( F^2 \) with SHELXL-2014 [4] through OLEX2 [5] program package. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen atoms were treated as riding on parent atoms, using isotropic displacement parameters \( U_{iso}(H) = 1.2U_{iso}(C) \) for CH and CH\(_2\). The asymmetric unit contains only half of the molecule, which is situated on a mirror plane (perpendicular to [0, 1, 0]). A part of the molecule was found to be disordered around the mirror plane and was modelled in one position with 50% occupancy, with the other disorder component generated by the symmetry element (Figure S1). Restraints were applied to the geometry of the disordered phenyl ring (FLAT, SADI) and to the sp\(^2\) carbon C9 with the atoms bound to it (FLAT). Anisotropic atomic displacement parameters were also restrained (RIGU). The figure was drawn using the program Mercury CSD 3.9 [6] and POV-Ray 3.7 [7].

Figure S1. The molecule of 6 in the crystal structure, showing the mirror plane (perpendicular to [0, 1, 0]) in light blue. The symmetry-generated disorder component is drawn in light aquamarine, symmetry code: i) \( x, \frac{1}{2} - y, z \). The atomic displacement ellipsoids are drawn at 50% probability level.
V. Copies of $^1$H, $^{13}$C and $^{19}$F NMR spectra of fluorinated ketones
VI. Copies of $^1$H, $^{13}$C NMR for cyclopropanols