Supporting Information

Chemo- and Regioselective Oxygenation of C(sp³)–H Bonds in Aliphatic Alcohols Using a Covalently Bound Directing Activator and Atmospheric Oxygen

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1. General method

$^1$H NMR spectra were recorded on JEOL ECX-500 (500.16 MHz for $^1$H NMR and 125.77 MHz for $^{13}$C NMR), and JEOL ECS-400 (391.78 MHz for $^1$H NMR, 98.52 MHz for $^{13}$C NMR, 125.70 MHz for $^{11}$B NMR, and 368.64 MHz for $^{19}$F NMR) spectrometers. Chemical shifts were reported downfield from tetramethylsilane ($\delta = 0$ ppm) for $^1$H NMR. For $^1$H and $^{13}$C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference ($\delta = 7.26$ and 77.00 ppm (CDCl$_3$), 2.04 and 29.80 ppm (acetone-$d_6$); $^1$H and $^{13}$C NMR respectively). Chemical shifts for $^{11}$B NMR and $^{19}$F NMR were reported in the scale relative to PhB(OH)$_2$ ($\delta = 31.00$ ppm) and C$_6$F$_6$ ($\delta = -164.90$ ppm) respectively as an external standard. Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. ESI-MS spectra were measured on a Waters ZQ4000 spectrometer (for LRMS), and a JEOL JMS-T100LC AccuTOF spectrometer (for HRMS). Column chromatography was performed with silica gel Merck 60 (230-400 mesh ASTM). Gel permeation chromatography (GPC) purification was conducted on a Japan Analytical Industry Co., Ltd. LC9210NEXT equipped with JAIGEL-1H and JAIGEL-2H, and CHCl$_3$ was used as an eluent. HPLC was conducted by JASCO HPLC systems (pump: PU-2080; detector: UV-2075, measured at 254 nm). All reactions other than substrates synthesis were carried out in normal solvents without any purification (purchased from Aldrich or Wako Pure Chemical Industries, Ltd.) unless otherwise noted. Reagents whose preparations are not described in this manuscript were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd., and used without further purification except for triethylamine, which was distilled from CaH$_2$. NMR yields were calculated by $^1$H NMR of crude products using 1,1,2,2-tetrachloroethane as an internal standard. The oxygenated compounds 2a, 2d + 2d', 2h, 2i, 2k, 2m, and 2s were isolated by silica gel column chromatography (eluents: hexane/EtOAc); other products were isolated by preparative TLC (eluents: hexane/EtOAc).
2. Typical experimental procedure

(A) The oxygenation of secondary C(sp³)-H bonds:

Oxygenation of 1a: To a test tube were added Co(OAc)₂ (0.89 mg, 0.005 mmol), Mn(OAc)₃•2H₂O (1.34 mg, 0.005 mmol), 1a (R = Me, 28.9 mg, 0.1 mmol), and 2,2,2-trifluoroethanol (TFE, 1 mL, 0.1 M). The mixture was stirred at 40 °C after replacing the air inside the tube with O₂ (1 atm, balloon). After 1a was consumed, which was checked on TLC, TFE was removed by evaporation and then EtOAc was added. The EtOAc solution was passed through silica gel to remove the metals. EtOAc was removed from the filtrate by evaporation and the residue was dried under reduced pressure to afford the crude mixture. NMR yield was calculated as 67% from the ¹H NMR spectra of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (EtOAc/hexane = 1/1) afforded 2a as a colorless sticky liquid (18.6 mg, 62%).

2a: ¹H NMR (500 MHz, CDCl₃) δ: 8.83 (brs, 1H), 7.87 (d, 1H, J = 7.5 Hz), 7.58-7.68 (m, 3H), 3.57 (dt, 1H, J = 3.5 Hz, 9.8 Hz), 2.93 (ddd, 1H, J = 3.5 Hz, 9.2 Hz, 18.9 Hz), 2.63 (dt, 1H, J = 18.9 Hz, 3.5 Hz), 2.23 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ: 208.3, 163.8, 133.9, 133.0, 131.7, 130.5, 124.2, 124.1, 121.7 (q, J = 286.7 Hz), 90.5 (q, J = 32.4 Hz), 57.7, 42.1, 30.4; ¹⁹F NMR (369 MHz, CDCl₃) δ: –78.2; IR (neat, cm⁻¹) ν: 3213, 2952, 1719, 1469, 1363, 1304, 1197; LRMS (ESI): m/z 326 [M+Na]+; HRMS (ESI): m/z calcd for C₁₃H₁₂F₃NO₄Na [M+Na]⁺ 326.0611, Found 326.0620.

(B) The oxygenation of tertiary or benzylic C(sp³)-H bonds:

Oxygenation of 1h: To a test tube were added 1h (R¹ = R² = Me, 30.3 mg, 0.1 mmol) and TFE (1 mL, 0.1 M). Me₂S (9 μL, 0.12 mmol) was added after replacing the air inside the tube with O₂ (1 atm, balloon) and finally Co(OAc)₂ (0.5 M DMSO solution, 2 μL, 0.001 mmol) was added. The mixture was stirred at 40 °C and after 1h was consumed, which was checked on TLC, TFE was removed by evaporation and then EtOAc was added. The EtOAc solution was passed through silica gel to remove the metal and DMSO. EtOAc was removed from the filtrate by evaporation and the residue was dried under reduced pressure to afford the crude mixture. NMR yield was calculated as 100% from the ¹H NMR spectra of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. Purification by silica gel column chromatography (EtOAc/hexane = 1/1) afforded 2h as a colorless sticky liquid (29.6 mg, 93%).

2h: ¹H NMR (500 MHz, CDCl₃) δ: 9.88 (s, 1H), 7.84 (d, 1H, J = 7.5 Hz), 7.64 (dd, 1H, J = 7.5 Hz, 7.5 Hz), 7.59-7.64 (m, 2H), 3.80 (brs, 1H), 3.55 (dt, 1H, J = 4.0 Hz, 9.8 Hz), 3.25-3.32 (m, 1H), 1.93-2.02 (m, 1H).
1.69 (dt, 1H, $J = 14.9$ Hz, 4.1 Hz), 1.37 (s, 3H), 1.25 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 164.9, 134.4, 133.0, 131.6, 130.3, 124.1, 124.0, 121.8 (q, $J = 286.7$ Hz), 90.9 (q, $J = 32.4$ Hz), 70.7, 60.8, 40.9, 30.0; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.2; IR (neat, cm$^{-1}$) v: 3395, 3172, 2972, 1722, 1470, 1381, 1305, 1199; LRMS (ESI): $m/z$ 342 [M+Na$^+$]; HRMS (ESI): $m/z$ calcd for C$_{14}$H$_{16}$F$_3$NO$_4$Na [M+Na$^+$] 342.0924, Found 342.0921.
3. Typical synthetic procedure for directing-activator-anchored alcohols

Procedure A: for all the substrates except for ones listed below

![Diagram of Procedure A]

Procedure B: for 1o, 1v, 1x, 1aa, 1ab, 1ac and 1ad

![Diagram of Procedure B]

Procedure C: for 1p

![Diagram of Procedure C]

Typical experimental procedure for Procedure A: O-benzyl-N-hydroxyphthalimide (S1)

To a stirred mixture of N-hydroxyphthalimide (97.8 g, 600 mmol, 1 eq) and benzyl bromide (79 mL, 660 mmol, 1.1 eq) in DMF (1.2 L, 0.5 M) was added DBU (108 mL, 720 mmol, 1.2 eq) over 30 minutes at ambient temperature. After completion of the addition, 2.4 L of HCl (1 N in water) was added, and the white precipitate was filtered off and washed with water to afford wet S1. Azeotropic removal of remained water with toluene (twice) afforded S1 as white solid (147.6 g, 97% yield).

\[^1\text{H} \text{NMR (500 MHz, CDCl}_3 \delta: 7.80 (dd, 2H, J = 2.9 \text{ Hz}, 5.2 \text{ Hz}), 7.72 (dd, 2H, J = 2.9 \text{ Hz}, 5.2 \text{ Hz}), 7.53 (dd, 2H, J = 4.0 \text{ Hz}, 7.5 \text{ Hz}), 7.36-7.40 (m, 3H), 5.21 (s, 2H); ^1\text{C} \text{NMR (126 MHz, CDCl}_3 \delta: 163.4, 134.4, 133.6, 129.8, 129.3, 128.8, 128.5, 123.4, 79.8; IR (KBr, cm}^{-1} \nu: 3076, 3034, 2954, 2887, 1789, 1731, 1464; \text{LRMS (ESI): m/z } 276 \text{ [M+Na]}; \text{HRMS (ESI): m/z calcd for C}_{15}\text{H}_{11}\text{NO}_3\text{Na [M+Na]^{+} 276.0631,}}

S5
Found 276.0630.

**N-benzyloxy-3-hydroxy-3-trifluoromethyl-isindo1inone (S2)**

To a stirred mixture of S1 (139 g, 550 mmol, 1 eq) and TMSCF3 (98 mL mL, 660 mmol, 1.2 eq) in dry DMF (550 mL, 1 M) was added CsF (100 g, 660 mmol, 1.2 eq) at 0 °C, and the reaction mixture was stirred for one hour. 1 N HCl aq. (500 mL) was added and the mixture was extracted with ethyl acetate/hexane (1/1). The organic layer was washed with water and saturated NaCl aq. solution, and dried over Na2SO4. The solution was passed through short silica gel pad and evaporation of the solvent afforded S2 as light yellow solid (169.3 g, 95% yield). S2 was used in the next step without further purification.

1H NMR (500 MHz, acetone-d6) δ: 7.78-7.85 (m, 3H), 7.72-7.76 (m, 1H), 7.59 (d, 2H, J = 7.5 Hz), 7.37-7.45 (m, 3H), 5.34 (d, 1H, J = 9.8 Hz), 5.22 (d, 1H, J = 9.8 Hz); 13C NMR (126 MHz, acetone-d6) δ: 164.9, 139.1, 136.0, 134.5, 132.5, 130.2, 130.0, 129.5, 129.1, 125.0, 124.2, 123.9 (q, J = 286.7 Hz), 88.0 (q, J = 32.4 Hz), 80.5; 19F NMR (369 MHz, acetone-d6) δ: –79.5; IR (KBr, cm−1) ν: 3223, 3031, 1719, 1618, 1470, 1378, 1261, 1195; LRMS (ESI): m/z 346 [M+Na]+; HRMS (ESI): m/z calcd for C16H12F3NO3Na [M+Na]+ 346.0662, Found 346.0674.

**N-benzyloxy-3-chloro-3-trifluoromethyl-isindo1inone (S3)**

To a stirred mixture of S2 (169 g, 523 mmol, 1 eq) and triethylamine (117 mL, 836 mmol, 1.6 eq) in CH2Cl2 (45 mL, 1 M) was added methanesulfonyl chloride (61 mL, 784 mmol, 1.5 eq) at 0 °C. The mixture was stirred for three hours before water was added. The separated organic layer was washed with water and saturated NaCl aq. solution, and dried over Na2SO4. The solution was passed through short silica gel pad, and evaporation of the solvent afforded S3 as light yellow liquid (179 g, 100% yield). For practical use, S3 is stored as 1 M solution in heptane, or S3 is solidified by seeding.

1H NMR (400 MHz, CDCl3) δ: 7.90 (d, 1H, J = 7.2 Hz), 7.71-7.76 (m, 2H), 7.63-7.70 (m, 1H), 7.55-7.61 (m, 2H), 7.37-7.46 (m, 3H), 5.41 (d, 1H, J = 9.4 Hz), 5.25 (d, 1H, J = 9.4 Hz); 13C NMR (126 MHz, CDCl3) δ: 164.5, 137.9, 134.2, 133.9, 131.8, 129.6, 129.1, 128.5, 127.3, 124.4, 124.1, 121.7 (q, J = 284.3 Hz), 79.7, 79.5 (q, J = 36.4 Hz); 19F NMR (369 MHz, CDCl3) δ: –75.8; IR (neat, cm−1) ν: 1755, 1469, 1258, 1197; LRMS (ESI): m/z 364 [M+Na]+; HRMS (ESI): m/z calcd for C16H11ClF3NO2Na [M+Na]+ 364.0323, Found 364.0325.

**N-benzyloxy-3-butoxy-3-trifluoromethyl-isindo1inone (S4a)**

To a light-protected mixture of AgOTf (6.9 g, 26.7 mmol, 1.5 eq), 1-butanol (2.0 mL, 21.4 mmol, 1.2 eq), and triethylamine (3.2 mL, 23.1 mmol, 1.3 eq) in toluene (17.8 mL) was added S3 (1 M solution in toluene, 17.8 mL, 17.8 mmol, 1 eq) at ambient temperature. The reaction mixture was stirred overnight and saturated NaCl aq. solution was added. After filtration over Celite pad to remove the silver salts, the organic layer was separated, washed with water and saturated NaCl aq. solution, and dried over Na2SO4.
Evaporating the solvent afforded the crude oily liquid. Purification by silica gel column chromatography (hexane/EtOAc = 10/1) afforded S4a (R = Bu) as slightly yellow liquid (5.7 g, 84%).

$^1$H NMR (500 MHz, CDCl$_3$) δ: 7.90 (d, 1H, $J = 7.7$ Hz), 7.69 (dd, 1H, $J = 6.9$ Hz, 7.8 Hz), 7.60-7.66 (m, 2H), 7.57 (d, 2H, $J = 6.9$ Hz), 7.35-7.43 (m, 3H), 5.32 (d, 1H, $J = 9.8$ Hz), 5.16 (d, 1H, $J = 9.8$ Hz), 3.28 (dt, 1H, $J = 8.6$ Hz, 6.3 Hz), 2.95 (dt, 1H, $J = 8.6$ Hz, 6.3 Hz), 1.44-1.59 (m, 2H), 1.23-1.39 (m, 2H), 0.83 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.6, 135.3, 134.6, 133.4, 131.6, 130.0, 129.3, 128.8, 128.4, 124.2, 124.1, 122.2 (q, $J = 286.7$ Hz), 91.0 (q, $J = 32.4$ Hz), 79.1, 63.8, 31.0, 18.9, 13.6; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.1; IR (neat, cm$^{-1}$) ν: 2960, 1746, 1468, 1294, 1195; LRMS (ESI): $m/z$ 402 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{20}$F$_3$NO$_3$Na [M+Na]$^+$ 402.1288, Found 402.1284.

3-butoxy-N-hydroxy-3-trifluoromethyl-isouindolinone (1a)

A stirred mixture of S4a (2.6 g, 6.8 mmol, 1 eq) and Pd/C (10 wt%, 362 mg, 0.34 mmol, 0.05 eq) in ethanol (14 mL, 0.5 M) was exposed to H$_2$ (balloon pressure) at ambient temperature. The reaction mixture was stirred for two hours and then H$_2$ was removed. Filtration over Celite pad and evaporation of the filtrate afforded a crude oily liquid. Purification by silica gel column chromatography (hexane/EtOAc = 4/1) afforded 1a as slightly orange liquid. The liquid was gradually solidified into white solid (1.8 g, 92%).

$^1$H NMR (500 MHz, CDCl$_3$) δ: 9.88 (s, 1H), 7.79 (d, 1H, $J = 7.8$ Hz), 7.66 (dd, 1H, $J = 7.4$ Hz, 6.9 Hz), 7.61 (d, 3H, $J = 7.4$ Hz), 7.60 (dd, 1H, $J = 6.9$ Hz, 7.8 Hz), 3.43 (dt, 1H, $J = 8.6$ Hz, 6.6 Hz), 2.98 (dt, 1H, $J = 8.6$ Hz, 6.6 Hz), 1.54-1.68 (m, 2H), 1.29-1.46 (m, 2H), 0.88 (t, 3H, $J = 7.2$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.9, 135.3, 133.2, 131.5, 130.0, 124.0, 123.8, 121.9 (q, $J = 286.7$ Hz), 91.0 (q, $J = 32.4$ Hz), 64.1, 31.1, 19.0, 13.7; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.5; IR (KBr, cm$^{-1}$) ν: 3435, 3136, 2964, 1878, 1719, 1472, 1305, 1201; LRMS (ESI): $m/z$ 312 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{13}$H$_{14}$F$_3$NO$_3$Na [M+Na]$^+$ 312.0818, Found 312.0831.

Typical experimental procedure for Procedure B

![Chemical diagram](image-url)

$O$-(4-methoxybenzyl)-$N$-hydroxyphthalimide (S1')
To a stirred mixture of N-hydroxyphthalimide (8.16 g, 50 mmol, 1 eq) and DBU (9.7 mL, 65 mmol, 1.3 eq) in DMF (50 mL, 1 M) was added 4-methoxybenzyl chloride (6.6 mL, 55 mmol, 1.1 eq) at 0 °C. After two hours, 100 mL of HCl (1 N in water) was added. White precipitate was filtered off, washed with cold water, and then dissolved in CH₂Cl₂. Drying the solution over Na₂SO₄ and evaporating the solvent afforded S₁' as white solid (11.0 g, 78% yield).

\[ ^1H \text{NMR (500 MHz, CDCl}_3) \delta: 7.79 (dd, 2H, J = 5.4 Hz, 3.2 Hz), 7.72 (dd, 2H, J = 5.4 Hz, 3.2 Hz), 7.44 (d, 2H, J = 8.6 Hz), 6.88 (d, 2H, J = 8.6 Hz), 5.14 (s, 2H), 3.79 (s, 3H); ^{13}C \text{NMR (126 MHz, CDCl}_3) \delta: 163.5, 160.4, 134.3, 131.6, 128.9, 125.8, 123.4, 113.9, 79.4, 55.2; \text{IR (KBr, cm}^{-1}) \nu: 2945, 1725, 1611, 1516, 1386, 1259; \text{LRMS (ESI): } m/z \text{ 306 [M+Na]}^+; \text{HRMS (ESI): } m/z \text{ calcld for C}_{16}H_{13}NO_4Na [M+Na]}^+ 306.0737, \text{ Found 306.0745.}

3-hydroxy-N-((4-methoxybenzyl)oxy)-3-(trifluoromethyl)isoindolinone (S₂')

The same procedure as the conversion of S₁ to S₂ afforded S₂' as light yellow solid (13 g, 97%) from 11 g of S₁'. S₂' was also used in the next step without further purification.

\[ ^1H \text{NMR (500 MHz, acetone-d}_6) \delta: 7.76-7.84 (m, 3H), 7.70-7.75 (m, 1H), 7.51 (d, 2H, J = 8.0 Hz), 5.26 (d, 1H, J = 9.2 Hz), 3.82 (s, 3H); ^{13}C \text{NMR (126 MHz, acetone-d}_6) \delta: 164.8, 161.1, 139.2, 134.4, 132.4, 132.0, 130.2, 128.1, 124.9, 124.2, 123.9 (q, J = 286.7 Hz), 114.5, 88.0 (q, J = 32.8 Hz), 80.2, 55.5; ^{19}F \text{NMR (369 MHz, acetone-d}_6) \delta: -79.5; \text{IR (KBr, cm}^{-1}) \nu: 3233, 1703, 1616, 1517, 1254, 1200; \text{LRMS (ESI): } m/z \text{ 376 [M+Na]}^+; \text{HRMS (ESI): } m/z \text{ calcld for C}_{17}H_{14}F_3NO_4Na [M+Na]}^+ 376.0767, \text{ Found 376.0773.}

3-chloro-N-((4-methoxybenzyl)oxy)-3-(trifluoromethyl)isoindolinone (S₃')

The same procedure as the conversion of S₂ to S₃ afforded S₃' as yellow solid (11 g, 79%) from 13 g of S₂'.

\[ ^1H \text{NMR (400 MHz, CDCl}_3) \delta: 7.89 (d, 1H, J = 7.6 Hz), 7.62-7.77 (m, 3H), 7.50 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 5.33 (d, 1H, J = 9.0 Hz), 5.17 (d, 1H, J = 9.0 Hz), 3.82 (s, 3H); ^{13}C \text{NMR (100 MHz, CDCl}_3) \delta: 164.5, 160.3, 137.9, 134.1, 131.8, 131.5, 127.4, 126.2, 124.4, 124.1, 121.7 (q, J = 284.4 Hz), 113.9, 79.6 (q, J = 36.3 Hz), 79.4, 55.2; ^{19}F \text{NMR (369 MHz, CDCl}_3) \delta: -75.7; \text{IR (KBr, cm}^{-1}) \nu: 1755, 1612, 1517, 1199; \text{LRMS (ESI): } m/z \text{ 394 [M+Na]}^+; \text{HRMS (ESI): } m/z \text{ calcld for C}_{17}H_{13}ClF_3NO_3Na [M+Na]}^+ 394.0428, \text{ Found 394.0425.}

N-((4-methoxybenzyl)oxy)-3-(oct-4-yn-1-yloxy)-3-trifluoromethyl-isoindolinone (S₄'aa)

The same procedure as the conversion of S₃ to S₄a afforded S₄'aa as light yellow liquid (256.6 mg, 60%) from 116.1 mg of S₃'.

\[ ^1H \text{NMR (400 MHz, CDCl}_3) \delta: 7.87-7.92 (m, 1H), 7.60-7.71 (m, 3H), 7.45-7.51 (m, 2H), 6.90-6.95 (m,
2H), 5.25 (d, 1H, J = 9.4 Hz), 5.08 (d, 1H, J = 9.4 Hz), 3.82 (s, 3H), 3.38 (dt, 1H, J = 9.4 Hz), 3.04-3.13 (m, 1H), 2.17-2.29 (m, 2H), 1.95-2.01 (m, 2H), 1.61-1.80 (m, 2H), 1.32-1.42 (m, 2H), 0.86 (t, 3H, J = 7.4 Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ: 165.3, 160.0, 134.9, 133.2, 131.5, 131.0, 130.0, 126.7, 124.2, 123.9, 122.0 (q, J = 286.4 Hz), 113.6, 90.9 (q, J = 32.9 Hz), 80.7, 78.7, 78.5, 62.3, 55.0, 28.3, 22.1, 20.4, 15.0, 13.2; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) δ: –78.0; IR (neat, cm\(^{-1}\)) ν: 2960, 1744, 1613, 1516, 1468, 1252, 1186; LRMS (ESI): m/z 484 [M+Na]\(^+\); HRMS (ESI): m/z calcd for C\(_{25}\)H\(_{26}\)F\(_3\)NO\(_4\)Na [M+Na]\(^+\) 484.1706, Found 484.1707.

\(N\)-hydroxy-3-(oct-4-yn-1-yloxy)-3-trifluoromethyl-isooindolinone (1aa)

![Chemical structure of 1aa]

To a stirred mixture of S\(_4\)‘aa (250 mg, 0.54 mmol, 1 eq), pentamethylbenzene (326 mg, 2.2 mmol, 4 eq; a cation scavenger\(^1\)) in CH\(_2\)Cl\(_2\) (3 mL, 0.2 M) was added trifluoroacetic acid (267 μL, 10 wt% to the solvent). After half a day, saturated NaHCO\(_3\) aq. solution was added. The organic layer was washed with water and saturated NaCl aq. solution, and dried over Na\(_2\)SO\(_4\). Evaporating the solvent afforded a crude liquid. Purification by silica gel column chromatography (hexane/EtOAc = 3/1) afforded 1aa (R = oct-4-yn-1-yl) as yellow liquid (151 mg, 82%).

\(^1\)H NMR (500 MHz, CDCl\(_3\)) δ: 9.28 (brs, 1H), 7.82 (d, 1H, J = 6.9 Hz), 7.57-7.68 (m, 3H), 3.44-3.50 (m, 1H), 3.13-3.18 (m, 1H), 2.29-2.34 (m, 2H), 1.72-1.85 (m, 2H), 0.88 (t, 3H, J = 7.4 Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) δ: 165.4, 135.0, 133.1, 131.5, 130.1, 124.2, 123.9, 121.9 (q, J = 286.7 Hz), 90.9 (q, J = 33.2 Hz), 81.3, 79.0, 62.5, 28.2, 22.3, 20.6, 15.1, 13.4; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) δ: –78.4; IR (neat, cm\(^{-1}\)) ν: 3419, 2962, 1718, 1469, 1192; LRMS (ESI): m/z 364 [M+Na]\(^+\); HRMS (ESI): m/z calcd for C\(_{17}\)H\(_{18}\)F\(_3\)NO\(_3\)Na [M+Na]\(^+\) 364.1131, Found 364.1138.

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**Typical experimental procedure for Procedure C**

![Chemical diagram]

2-(2-(trimethylsilyl)ethoxy)isoindoline-1,3-dione (S1'')

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\(^1\)K. Okano, K.-i. Okuyama, T. Fukuyama, H. Tokuyama Synlett 2008, 1977-1980.
To a stirred mixture of N-hydroxyphthalimide (24.5 g, 150 mmol, 1 eq), 2-trimethylsilyl ethanol (21.4 mL, 150 mmol, 1 eq), and Ph₃P (43.3 g, 165 mmol, 1.1 eq) in anhydrous CHCl₃ (300 mL, 0.5 M) was added dropwise diethyl azodicarboxylate (2.2 M in toluene, 72 mL, 157 mmol, 1.05 eq) at 0 ºC. After completion of the addition, the cold bath was removed and the mixture was allowed to stir at room temperature for about 12 hours. The reaction mixture was diluted with hexane/Et₂O (5/1) and was passed through SiO₂. Evaporation of the solvent afforded a crude mixture. Purification by silica gel column chromatography (hexane/Et₂O = 5/1) afforded S1'' as gray solid (24.6 g, 62% yield).

**3-hydroxy-3-(trifluoromethyl)-2-(2-(trimethylsilyl)ethoxy)isoindolin-1-one (S2'')**

The same procedure as the conversion of S1 to S2 afforded S2'' as yellow solid (22.2 g, 71%) from 24.6 g of S1''.

**3-chloro-3-(trifluoromethyl)-2-(2-(trimethylsilyl)ethoxy)isoindolin-1-one (S3'')**

The same procedure as the conversion of S2 to S3 afforded S3'' as yellow liquid (23.4 g, 100%) from 22.2 g of S2''.

**3-((3-methyloct-7-en-1-yl)oxy)-3-trifluoromethyl-N-(2-(trimethylsilyl)ethoxy)-isoindolinone (S4''p, diastereomixture)**

The same procedure as the conversion of S3 to S4a afforded S4''p as colorless liquid (670.6 mg, 83%) from 619.1 mg of S3''.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.87 (d, 1H + 1H, $J$ = 6.9 Hz), 7.60-7.69 (m, 2H + 2H), 7.58 (d, 1H + 1H, $J$ = 7.4 Hz), 5.72-5.82 (m, 1H + 1H), 4.90-5.00 (m, 2H + 2H), 4.33-4.40 (m, 1H + 1H), 4.15-4.22 (m, 1H + 1H), 3.30-3.38 (m, 1H + 1H), 2.93-3.01 (m, 1H + 1H), 1.95-2.05 (m, 2H + 2H), 1.49-1.68 (m, 2H + 2H), 1.00-1.44 (m, 7H + 7H), 0.81 (d, 3H, $J$ = 6.9 Hz), 0.77 (d, 3H, $J$ = 6.3 Hz), 0.06 (s, 9H + 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 165.52, 165.56, 138.93, 138.91, 135.3, 135.2, 133.2, 131.5, 130.3, 124.12, 124.07, 122.1 (q, $J$ = 286.1 Hz), 114.31, 114.28, 90.8 (q, $J$ = 32.7 Hz), 75.2, 62.4, 36.4, 36.1, 36.0, 35.9, 33.9, 29.5, 29.4, 26.1, 19.6, 19.3, 17.08, 17.05, −1.5; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: −78.3; IR (neat, cm$^{-1}$) $\nu$: 3078, 2953, 1747, 1641, 1615, 1468, 1187; LRMS (ESI): $m/z$ 480 [M+Na]$^+$; HRMS (ESI): $m/z$ calc'd for C$_{23}$H$_{34}$F$_3$NO$_3$SiNa [M+Na]$^+$ 480.2152, Found 480.2153.

**$\textit{N}$-hydroxy-$3'$-((3-methyloct-7-en-1-yl)oxy)-3'-trifluoromethyl-isoindolinone (1p, diastereomixture)**

To a stirred mixture of S4''p (642 mg, 1.4 mmol, 1 eq) in THF (3 mL, 0.5 M) was added tetrabutylammonium fluoride trihydrate (1.3 g, 4.2 mmol, 3 eq). After three hours, saturated NH$_4$Cl aq. solution was added. The organic layer was washed with water and saturated NaCl aq. solution, and dried over Na$_2$SO$_4$. Evaporating the solvent afforded the crude liquid. Purification by silica gel column chromatography (hexane/EtOAc = 3/1) afforded 1p (R = 3-methyloct-7-en-1-yl) as colorless liquid (470 mg, 93%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.69 (brs, 1H), 9.68 (brs, 1H), 7.77-7.82 (m, 1H + 1H), 7.57-7.69 (m, 3H + 3H), 5.72-5.85 (m, 1H + 1H), 4.90-5.02 (m, 2H + 2H), 3.42-3.51 (m, 1H + 1H), 2.95-3.05 (m, 1H + 1H), 1.95-2.05 (m, 2H + 2H), 1.51-1.75 (m, 2H + 2H), 1.18-1.49 (m, 4H + 4H), 1.02-1.18 (m, 1H + 1H), 0.85 (d, 3H, $J$ = 6.3 Hz), 0.80 (d, 3H, $J$ = 6.7 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 165.8, 139.02, 138.99, 135.31, 135.30, 133.2, 131.5, 130.0, 124.0, 123.9, 121.9 (q, $J$ = 286.1 Hz), 91.0 (q, $J$ = 32.9 Hz), 62.68, 62.66, 36.4, 36.2, 36.0, 35.9, 33.95, 33.91, 29.5, 29.4, 26.14, 26.13, 19.5, 19.3; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: −78.6; IR (neat, cm$^{-1}$) $\nu$: 3148, 2930, 1718, 1478, 1458, 1406, 1200; LRMS (ESI): $m/z$ 380 [M+Na]$^+$; HRMS (ESI): $m/z$ calc'd for C$_{18}$H$_{22}$F$_3$NO$_3$Na [M+Na]$^+$ 380.1444, Found 380.1457.

4. **The procedure for gram-scale oxidation and the removal of the directing activator**

There is difference from the typical procedure in the equivalent of the reagents.
To a light-protected round-bottom flask (dried by heat gun under reduced pressure) were added AgOTf (2.16 g, 8.39 mmol, 1.5 eq), dry toluene (11 mL, 0.5 M), 3-methyl-1-butanol (609 μL, 5.59 mmol, 1 eq), triethylamine (930 μL, 6.71 mmol, 1.2 eq), and finally dry toluene solution of S3 (about 3 mL, 5.87 mmol, 1.05 eq) at ambient temperature. The reaction mixture was stirred overnight and saturated NaCl aq. solution was added. After filtration over Celite pad to remove the silver salts, the organic layer was washed with water and saturated NaCl aq. solution, and dried over Na2SO4. Evaporating the solvent afforded the crude oily liquid. Purification by silica gel column chromatography (hexane/EtOAc = 10/1) afforded S4h (R = isopentyl) as slightly yellow liquid (2.17 g, 97%).

1H NMR (500 MHz, CDCl3) δ: 7.91 (d, 1H, J = 7.5 Hz), 7.69 (dd, 1H, J = 7.2 Hz, 8.1 Hz), 7.61-7.67 (m, 2H), 7.57 (d, 2H, J = 6.3 Hz), 7.35-7.43 (m, 3H), 5.33 (d, 1H, J = 9.7 Hz), 5.16 (d, 1H, J = 9.7 Hz), 3.31 (dt, 1H, J = 9.2 Hz, 6.3 Hz), 2.98 (dt, 1H, J = 9.2 Hz, 6.3 Hz), 1.62-1.72 (m, 1H), 1.35-1.50 (m, 2H), 0.81 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz); 13C NMR (126 MHz, CDCl3) δ: 165.6, 135.3, 134.6, 133.4, 131.6, 130.0, 129.3, 128.4, 124.1, 122.2; 19F NMR (369 MHz, CDCl3) δ: -78.1; IR (neat, cm⁻¹) ν: 2957, 1745, 1643, 1468, 1190; LRMS (ESI): m/z 416 [M+Na]+; HRMS (ESI): m/z calcd for C21H22F3NO3Na [M+Na]+ 416.1444, Found 416.1456.

N-hydroxy-3-isopentyloxy-3-trifluoromethyl-isooindolinone (1h)

A stirred mixture of S4h (2.17 g, 5.39 mmol, 1 eq) and Pd/C (10 wt%, 170 mg, 0.16 mmol, 0.03 eq) in ethanol (11 mL, 0.5 M) was exposed to H2 (balloon pressure) at ambient temperature. The reaction mixture was stirred for two hours and then H2 was removed. Filtration over Celite pad and evaporation of the filtrate afforded the crude oily liquid. Purification by silica gel column chromatography (hexane/EtOAc = 10/1) afforded 1h as slightly orange liquid. The liquid was gradually solidified into white solid (1.56 g, 95%).

1H NMR (500 MHz, CDCl3) δ: 9.93 (brs, 1H), 7.79 (d, 1H, J = 6.9 Hz), 7.65-7.67 (m, 1H), 7.57 (d, 2H, J = 6.3 Hz), 3.47 (dt, 1H, J = 9.2 Hz, 6.9 Hz), 3.00 (dt, 1H, J = 9.2 Hz, 6.9 Hz), 2.98 (dt, 1H, J = 9.2 Hz, 6.9 Hz), 1.62-1.72 (m, 1H), 1.35-1.50 (m, 2H), 0.81 (d, 3H, J = 6.9 Hz), 0.79 (d, 3H, J = 6.9 Hz); 13C NMR (126 MHz, CDCl3) δ: 165.9, 135.3, 133.2, 131.5, 130.0, 124.0, 123.9, 121.9 (q, J = 286.7 Hz), 91.0 (q, J = 33.6 Hz), 62.8, 37.8, 24.8, 22.6,
22.3; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.5; IR (KBr, cm$^{-1}$) ν: 3137, 2959, 1718, 1507, 1472, 1194; LRMS (ESI): m/z 326 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{14}$H$_{16}$F$_3$NO$_3$Na [M+Na]$^+$ 326.0975, Found 326.0966.

$N$-hydroxy-3-(3-hydroxy-3-methylbutoxy)-3-trifluoromethyl-isoindolinone (2h)

To a round-bottom flask were added 1h (1.00 g, 3.30 mmol, 1 eq) and TFE (33 mL, 0.1 M). Me$_2$S (289 μL, 3.96 mmol, 1.2 eq) was added after replacing the air inside the tube with O$_2$ (1 atm, balloon) and finally Co(OAc)$_2$ (0.5 M solution in DMSO, 59.4 μL, 0.0297 mmol, 0.9 mol%) was added. The mixture was stirred at 40 °C and after 1h was consumed, which was checked on TLC, TFE was removed by evaporation and then EtOAc was added. The EtOAc solution was passed through silica gel to remove the metal and DMSO, and EtOAc was removed from the filtrate by evaporation. The residue was dried under reduced pressure to afford the crude mixture. Purification by silica gel column chromatography (EtOAc/hexane = 1/1) afforded 2h as a colorless sticky liquid (840 mg, 80%).

Removal of directing activator

LiAlH$_4$ conditions

To a round-bottom flask (dried by heat gun under reduced pressure) were added 2h (840 mg, 2.3 mmol, 1 eq) and dry THF (13 mL, 0.2 M), and the mixture was cooled at −78 °C. LiAlH$_4$ (200 mg, 2 eq) was added to the reaction mixture in three portions (65 mg; 70 mg; 65 mg), and 15 minutes later the reaction temperature was raised to 0 °C. Two hours later water (200 μL), 4 M NaOH aq. (200 μL), and water (600 μL) were added successively to the reaction mixture, with vigorous stirring. Insoluble materials were removed by filtration over Celite pad and the filtrate was dried under reduced pressure to obtain the crude mixture. Purification by silica gel column chromatography (hexane/EtOAc = 1/2) and Kugelrohr distillation afforded 3-methyl-1,3-butanediol as colorless liquid (221 mg, 81%).

$^1$H NMR (500 MHz, CDCl$_3$) δ: 3.90 (t, 2H, $J = 5.7$ Hz), 2.22 (bs, 2H), 1.75 (t, 2H, $J = 5.7$ Hz), 1.30 (s, 6H); LRMS (ESI): m/z 127 [M+Na]$^+$: identical to a commercial material.

SmI$_2$ conditions

To a flask containing 2i (18.0 mg, 0.05 mmol, 1 eq) were added SmI$_2$ in THF (freshly prepared just before use as reported$^3$ 4 mL, ca. 0.4 mmol, 8 eq), Et$_3$N (500 μL, 3.6 mmol, 72 eq), and water (65 μL, 36 mmol, 72 eq) at room temperature under argon atmosphere. After three hours, excess SmI$_2$ was oxidized by bubbling air through the reaction mixture. Filtration over Celite pad and evaporation of the filtrate afforded the crude mixture (69.4 mg, 84% NMR yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ: 3.82 (t, 2H, $J = 5.7$ Hz), 3.71 (s, 12H), 3.23 (s, 1H), 1.68 (t, 2H, $J = 5.7$ Hz), 1.52-1.62 (m, 4H), 1.35-1.50 (m, 5H), 1.23-1.32 (m, 1H); LRMS (ESI): m/z 167 [M+Na]$^+$: identical to a commercial material.

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$^2$ M. Szostak, M. Spain, A. J. Eberhart, D. J. Procter J. Am. Chem. Soc. 2014, 136, 2268-2271.

$^3$ M. Szostak, M. Spain, D. J. Procter J. Org. Chem. 2012, 77, 3049-3059.
Removal of directing activator from 2aa and 2ae is also successfully demonstrated.

oct-4-yne-1,3-diol: $^1$H NMR (500 MHz, CDCl$_3$) δ: 4.64 (s, 1H), 3.94–4.02 (m, 1H), 3.81–3.89 (m, 1H), 2.51 (s, 1H), 2.19 (td, 2H, $J = 7.2$ Hz, 1.9 Hz), 2.17 (s, 1H), 1.88–2.02 (m, 2H), 1.49–1.57 (m, 2H), 0.98 (t, 3H, $J = 7.4$ Hz); $^{13}$C NMR (126 MHz, acetone-$d_6$) δ: 84.2, 83.3, 60.3, 59.5, 42.0, 22.9, 21.0, 13.6; IR (neat, cm$^{-1}$) ν: 3347, 2961, 1717, 1430, 1050; LRMS (ESI): $m/z$ 165 [M+Na]$^+$; HRMS (ESI): $m/z$ calcld for C$_8$H$_{14}$O$_2$Na [M+Na]$^+$ 165.0886, Found 165.0886.

1-(1-tosyl-1H-indol-3-yl)propane-1,3-diol: $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.98 (d, 1H, $J = 8.6$ Hz), 7.77 (d, 2H, $J = 8.0$ Hz), 7.60 (d, 1H, $J = 8.0$ Hz), 7.55 (s, 1H), 7.30–7.34 (m, 1H), 7.20–7.25 (m, 3H), 5.20–5.25 (m, 1H), 3.85–3.95 (m, 2H), 2.99 (s, 1H), 2.34 (s, 3H), 2.27 (s, 1H), 2.06–2.20 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 145.0, 135.5, 135.2, 129.9, 128.6, 126.8, 125.6, 124.9, 123.2, 122.7, 120.2, 113.8, 68.0, 61.4, 38.4, 21.6; IR (neat, cm$^{-1}$) ν: 3375, 2925, 1597, 1447, 1367, 1276, 1173; LRMS (ESI): $m/z$ 368 [M+Na]$^+$; HRMS (ESI): $m/z$ calcld for C$_{18}$H$_{19}$NO$_4$SNa [M+Na]$^+$ 368.0908.

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$^4$ T. He, W.-C. Gao, W.-K. Wang, C. Zhang Adv. Synth. Catal. 2014, 356, 1113-1118.
5. Experimental details

5.1. Optimization of the oxygenation conditions

5.1.1. Investigation of Directing Activator (DA)

We synthesized several DA (A-G) bound-alcohols and compared their reactivity under condition A [Co(OAc)$_2$ (5 mol%), Mn(OAc)$_3$·2H$_2$O (5 mol%) in 2,2,2-trifluoroethanol (TFE, 0.1 M) under O$_2$ (1 atm) at 40 °C] (Table S1).

With A, benzylic C–H oxygenation produced the corresponding phenyl ketone product in only 8% yield. A more challenging methylene C($sp^3$)–H oxygenation did not proceed at all. In both cases, the efficiency of the C–H oxygenation was much lower than that of N-hydroxyphthalimide itself. Because the reactivity of N-oxyl radicals is in accord with their electron-deficiency, we next designed B bearing a CF$_3$ group at the α-carbon of the nitrogen atom to enhance the reactivity of the DA. As a result, B promoted simple methylene C($sp^3$)–H oxygenation to produce γ-oxo product in 67% yield. Although the α-C($sp^3$)–H bond adjacent to the ether oxygen atom is the innate reactive site, the less reactive γ-C($sp^3$)–H was predominantly oxygenated. Under the same conditions, benzylic C($sp^3$)–H oxygenation also proceeded well (85% yield). Introducing an additional CF$_3$ substituent at the benzene ring (C), however, did not further improve the yield. Additional structural modifications (D, E, F, or G) were not successful, resulting in complex mixtures and/or decomposition of the DA during the reaction. Thus, B proved to be the best DA.

5.1.2. Secondary C($sp^3$)-H oxygenation

Solvents, metal salts, and additives were screened for higher yields of secondary C($sp^3$)-H oxygenation. Tested additives such as some acids, bases, molecular sieves, and reductants all brought no improvements.

The screening of the solvents for 1-pentanol oxygenation is shown below. As shown in Table S2, TFE (2,2,2-trifluoroethanol) and HFIP (1,1,1,3,3,3-hexafluoropropanol) accelerated the reaction to almost the same degree and produced almost the same yields, so the cheaper TFE was employed as the best solvent.
Then, metal salts were screened using B-anchored 1-butanol instead of B-anchored 1-pentanol because B-anchored 1-butanol gave only one regioisomer and made the analysis easier.

As shown in Table S3, the combination of Co(OAc)$_2$ and Mn(OAc)$_3$·2H$_2$O produced the best result. The role of Mn(OAc)$_3$·2H$_2$O is not clear, but we suppose that the main role of Mn(OAc)$_3$·2H$_2$O is to trap reversibly reactive intermediates such as peroxy radicals and alkoxy radicals to suppress unfavorable side reactions, considering the fact that the reaction rate became lower by adding Mn(OAc)$_3$·2H$_2$O than when Co(OAc)$_2$ alone was used as a metal source even though Mn(OAc)$_3$·2H$_2$O itself was able to catalyze the reaction.

The 1-butanol oxygenation was conducted at 30, 40, or 50 °C. The reaction didn't complete at 30 °C, and became slightly complicated at 50 °C compared to that at 40 °C. Therefore, 40 °C was revealed to be the best reaction temperature.

Then, the optimal conditions for secondary C($sp^3$)-H oxygenation were these: Co(OAc)$_2$ (5 mol%), Mn(OAc)$_3$·2H$_2$O (5 mol%), O$_2$ (1 atm), TFE (0.1 M), 40 °C.
5.1.3. Tertiary C(sp³)-H oxygenation

Although 67% NMR yield was obtained for 1-butanol oxygenation under condition A, the reaction became complicated and only 20% NMR yield was obtained for 3-methyl-1-butanol oxygenation (1h) under the same conditions. It was probably because condition A was too harsh for tertiary C(sp³)-H oxygenation, so the reaction conditions had to be refined for higher yields. The goal was accomplished by reducing the amount of the metal salts. Lower reaction temperatures and different solvents were not effective. The best reaction conditions were these: Co(OAc)₂ (1 mol%), Me₂S (1.2 eq), O₂ (1 atm), TFE (0.1 M), 40 °C.

5.2. Absolute configuration of DA-anchored (+)-menthol (1k)

X-ray analysis of less polar diastereomer of O-(4-nitrobenzyl)-1k was conducted to determine the absolute configuration of DA-anchored (+)-menthol. The configuration of the hemiaminal center was revealed to be (R), which accords with that of reactive isomer in aerobic C-H oxygenation.

![Chemical Structure](image)

Crystallization procedure: less polar diastereomer of O-(4-nitrobenzyl)-1k was dissolved in MeCN and the solvent was gradually evaporated under air at room temperature. After a few days a needle crystal was obtained.

The supposed reason for the difference in the reactivity is depicted in the figure below.
According to molecular modeling, there is no steric repulsion during the abstraction of the red hydrogen in \((R)-1k\) and it proceeds smoothly; whereas in the case of \((S)-1k\) there is a steric repulsion between CF\(_3\) and the axial \(\alpha\)-hydrogen of the oxygen atom in menthol that makes it difficult for the \(N\)-oxyl radical to access the red hydrogen.

5.3. **Comparison of reaction speed in benzylic C–H oxygenation**

The chemical yield after 30 min was compared for \(\beta\)-, \(\gamma\)-, and \(\delta\)-C–H oxygenation. Reaction speed of \(\beta\)-C–H oxygenation is significantly slower than \(\gamma\)- and \(\delta\)-C–H oxygenation. The difference between \(\gamma\)- and \(\delta\)-C–H oxygenation is, however, not large. This low \(\gamma/\delta\) selectivity is a current limitation of our method.
6. Selective ultra-remote C-H oxygenation

6.1. Synthesis of substrate 3

To a round bottom flask were added S5 (2.15 g, 8.3 mmol), \( p \)-acetylaniline (1.07 g, 7.9 mmol) and pyridine (42 mL, 0.2 M). The mixture was stirred at reflux for 18 h. Pyridine was removed by evaporation. The obtained crude mixture was purified by silica gel column chromatography (EtOAc/hexane = 2/1) to afford S6 with inseparable byproducts as a colorless sticky liquid (2.98 g). This mixture was used for next step.

Synthetic procedure from S6 to S7

To a round bottom flask were added acid impure S6 (566 mg, ca. 1.6 mmol), 3-(4-ethylphenyl)propan-1-ol (286 mg, 1.74 mmol), diethyl azodicarboxylate (2.5 M solution in toluene, 0.759 mL, 1.90 mmol), PPh\(_3\) (456 mg, 1.90 mmol) and CH\(_2\)Cl\(_2\) (8.7 mL, 0.2 M). The mixture was stirred at room temperature for 2.5 h, followed by all the volatiles were removed by evaporation. The obtained crude mixture was purified by silica gel column chromatography (EtOAc/hexane = 1/2) to afford S7 as a colorless sticky liquid (532 mg, 69%, 2 steps).

\[ \text{1H NMR (392 MHz, CD}_{3}\text{OD)} \delta: 7.99 (d, 2H, } J = 8.1 \text{ Hz), 7.27 (d, 2H, } J = 8.1 \text{ Hz), 7.01 (d, 2H, } J = 7.6 \text{ Hz), 6.96 (d, 2H, } J = 7.6 \text{ Hz), 3.99 (t, 2H, } J = 6.1 \text{ Hz), 2.71 (d, 2H, } J = 13.9 \text{ Hz), 2.60 (s, 3H), 2.51-2.60 (m, 2H+2H), 2.24 (d, 1H, } J = 13.5 \text{ Hz), 1.70-1.80 (m, 2H), 1.58 (d, 1H, } J = 13.5 \text{ Hz), 1.42 (d, 2H, } J = 13.9 \text{ Hz), 1.30 (s, 3H), 1.27 (s, 3H), 1.18 (t, 3H, } J = 7.6 \text{ Hz); } \text{13C NMR (126 MHz, CDCl}_{3}\text{)} \delta: 197.6, 176.1, 176.1, \ldots \]

\[ a \] Q. Ye, I. V. Komarov, A. J. Kirby, M. Jones, Jr. J. Org. Chem. 2002, 67, 9288-9294. (b) T. J. Dale, J. Rebek, Jr. J. Am. Chem. Soc. 2006, 128, 4500-4501.
142.0, 140.2, 138.4, 136.3, 128.9, 128.8, 128.4, 128.0, 64.9, 44.0, 31.7, 31.1, 30.1, 28.5, 26.8, 26.1, 15.8; IR (neat, cm⁻¹) ν: 2964, 1721, 1689, 1602, 1460, 1357, 1321, 1265, 1174; LRMS (ESI): m/z 526 [M+Na]^+; HRMS (ESI): m/z calcd for C₃₁H₃₇NO₅Na [M+Na]^+ 526.2564, Found 526.2541.

**Synthetic procedure from S7 to S8**

To solution of ketone S7 (288 mg, 0.588 mmol) in CH₂Cl₂ (2.94 mL, 0.2 M) were added triethylamine (0.590 mL, 4.23 mmol) and TBSOTf (0.494 mL, 2.82 mmol). The mixture was stirred at room temperature for 40 min. After ketone was consumed, which was checked on TLC, pentane and H₂O were added. The organic layer was separated and washed with 10% aqueous CuSO₄ solution and 5% NaHCO₃ aq. solution, and then dried over Na₂SO₄. Filtration followed by evaporating the solvent at room temperature afforded the crude mixture containing the corresponding enol silyl ether.

To a round bottom flask were added the all amount of the crude mixture, S3” (0.394 mL, 1.18 mmol), Et₃N (0.246 mL, 1.76 mmol) and toluene (5.88 mL, 0.1 M), followed by AgOTf (376 mg, 1.47 mmol). The mixture was stirred at room temperature for 18 h, and saturated NaCl aq. solution was added. After filtration over Celite pad to remove the silver salts, the organic layer was separated and washed with water and saturated NaCl aq. solution, and dried over Na₂SO₄. After filtration, all the volatiles were removed by evaporation. The obtained crude mixture was purified by silica gel column chromatography (EtOAc/hexane = 2/5) to afford S8 as colorless sticky liquid (421 mg, 87% yield).

**Synthetic procedure from S8 to 3**

To a solution of S8 (421 mg, 0.514 mmol) in THF (0.590 mL, 4.23 mmol) was added tetrabutylammonium fluoride (1.0 M solution in THF, 1.54 mL, 1.54 mmol). The mixture was stirred at room temperature. After S8 was consumed, which was checked on TLC, water was added. The organic layer was separated and the water layer was extracted by EtOAc two times. The combined organic layer was dried over Na₂SO₄. After filtration, all the volatiles were removed by evaporation. The obtained crude mixture was purified by silica gel column chromatography (EtOAc/hexane = 2/3) to afford 3 as colorless sticky liquid (287 mg, 78% yield).

**1H NMR (500 MHz, CD₃OD) δ:** 7.85-7.90 (m, 1H), 7.84 (d, 2H, J = 8.6 Hz), 7.60-7.66 (m, 3H), 7.22 (d, 2H, J = 8.6 Hz), 7.00 (d, 2H, J = 8.0 Hz), 6.96 (d, 2H, J = 8.0 Hz), 4.60 (brs, 1H), 4.37-4.43 (m, 1H), 4.09-4.20 (m, 3H), 3.91-3.97 (m, 2H), 2.69 (d, 2H, J = 13.7 Hz), 2.54 (q, 2H, J = 7.4 Hz), 2.49 (t, 2H, J = 7.4 Hz), 2.21 (d, 1H, J = 13.2 Hz), 1.67-1.73 (m, 2H), 1.56 (d, 1H, J = 13.2 Hz), 1.39 (d, 2H, J = 13.7 Hz), 1.28 (s, 6H), 1.25 (s, 3H), 1.16 (t, 3H, J = 7.4 Hz), 0.90-1.10 (m, 2H), -0.01 (s, 9H); **13C NMR (126 MHz, CD₃OD) δ:** 194.4, 178.3, 178.3, 178.0, 170.9, 143.1, 142.4, 140.00, 139.8, 137.2, 134.7, 131.9, 131.5, 130.4, 129.6, 129.3, 129.0, 126.1 (q, J = 283.1 Hz), 124.9, 124.3, 76.4, 69.0 (q, J = 30.1 Hz), 66.1, 44.9, 43.9, 43.6, 42.05, 42.03, 32.8, 31.40, 31.36, 29.6, 26.3 17.9, 16.5, -1.25; **19F NMR (369 MHz, CDCl₃) δ:** -76.1; IR (neat, cm⁻¹) ν: 2963, 1733, 1693, 1602, 1463, 1356, 1321, 1273, 1178, 1092; LRMS (ESI): m/z 841 [M+Na]^+; HRMS (ESI): m/z calcd for C₄₃H₅₃F₃N₂O₇SiNa [M+Na]^+ 841.3466, Found 841.3436.
2H, J = 8.0 Hz), 6.96 (d, 2H, J = 8.0 Hz), 4.17-4.22 (m, 2H), 3.96 (t, 2H, J = 6.3 Hz), 2.69 (d, 2H, J = 13.7 Hz), 2.55 (q, 2H, J = 7.7 Hz), 2.21 (d, 1H, J = 13.2 Hz), 1.68-1.75 (m, 2H), 1.56 (d, 1H, J = 13.2 Hz), 1.40 (d, 2H, J = 13.7 Hz), 1.28 (s, 6H), 1.16 (t, 3H, J = 7.7 Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 193.4, 176.30, 176.27, 147.25, 142.21, 141.1, 138.6, 137.3, 133.1, 130.7, 129.3, 129.1, 128.9, 128.6, 128.2, 128.0, 125.7, 124.5 (q, J = 289.5 Hz), 123.4, 121.1, 68.2 (q, J = 27.2 Hz), 65.1, 44.6, 44.5, 44.1, 42.5, 41.2, 34.5, 32.0, 31.2, 30.3, 30.1, 28.7, 26.3, 16.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): -75.5; IR (neat, cm\(^{-1}\)) \(\nu\): 3432, 2929, 1690, 1605, 1463, 1358, 1321, 1273, 1178, 1093; LRMS (ESI): \(m/z\) 755 \([\text{M}+\text{Na}]^+\); HRMS (ESI): \(m/z\) calcd for C\(_{40}\)H\(_{39}\)F\(_3\)N\(_2\)O\(_7\)Na \([\text{M}+\text{Na}]^+\) 755.2537, Found 755.2537.

6.2. Oxygenation of 3 (ultra-remote position-selective aerobic C-H oxygenation)

To a test tube were added 3 (30.0 mg, 41.7 \(\mu\)mol) and TFE (0.42 mL, 0.1 M). Me\(_2\)S (6.71 \(\mu\)L, 91.8 \(\mu\)mol) was added after replacing the air inside the tube with O\(_2\) (1 atm, balloon), and finally Co(OAc)\(_2\) (0.2 M solution in DMSO, 2.1 \(\mu\)L, 0.42 \(\mu\)mol) was added. The mixture was stirred at room temperature. After 1.5 h, Co(OAc)\(_2\) (0.2 M solution in DMSO, 2.1 \(\mu\)L, 0.42 \(\mu\)mol) and Me\(_2\)S (6.71 \(\mu\)L, 91.8 \(\mu\)mol) were added. After 3 was consumed, which was checked on TLC, TFE was removed by evaporation and water was added. The aqueous layer was extracted by EtOAc three times. The combined organic layer was dried over Na\(_2\)SO\(_4\). After filtration, all the volatiles were removed by evaporation. The yield was determined as 66\% by \(^1\)H NMR of the crude mixture with 1,1,2,2-tetrachloroethane as the internal standard. Purification by neutral silica gel column chromatography (EtOAc/hexane = 2/3) afforded 4 as a white solid (16.3 mg, 53%).

\(^1\)H NMR (500 MHz, CD\(_2\)OD) \(\delta\): 7.80-7.88 (m, 3H), 7.78 (d, 2H, J = 8.0 Hz), 7.55-7.65 (m, 3H), 7.23 (d, 2H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 4.10-4.16 (m, 2H), 3.92-4.00 (m, 2H), 2.68 (d, 1H, J = 14.3 Hz), 2.61 (t, 2H, J = 7.4 Hz), 2.51 (s, 3H), 2.15-2.23 (m, 1H), 1.70-1.79 (m, 2H), 1.57 (d, 1H, J = 13.2 Hz), 1.40 (d, 1H, J = 14.3 Hz), 1.29 (s, 6H), 1.25 (s, 3H); \(^{13}\)C NMR (126 MHz, CD\(_2\)OD) \(\delta\): 203.3, 178.0, 177.6, 169.2, 148.7, 142.0, 137.1, 136.0, 133.7, 132.2, 131.0, 130.0, 129.7, 129.5, 129.0, 125.7 (d, J = 278.3 Hz), 124.3, 123.9, 65.6, 44.5, 43.5, 43.2, 41.7, 34.9, 32.8, 31.0, 30.6, 30.5, 29.3, 26.5, 25.9; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): -75.5; IR (neat, cm\(^{-1}\)) \(\nu\): 3432, 2929, 1690, 1605, 1463, 1358, 1321, 1273, 1178, 1093; LRMS (ESI): \(m/z\) 755 \([\text{M}+\text{Na}]^+\); HRMS (ESI): \(m/z\) calcd for C\(_{40}\)H\(_{39}\)F\(_3\)N\(_2\)O\(_7\)Na \([\text{M}+\text{Na}]^+\) 755.2551, Found 755.2537.

6.3. Removal of directing activator
To a test tube were added 4 (2.8 mg, 3.8 μmol) and THF/H₂O (3/1, 80 μL, 0.05 M). To the mixture were added LiOH (1 M solution in H₂O, 20 μL, 20 μmol) and H₂O₂ (10 M in H₂O, 3.2 μL, 32 μmol). After stirring for 21 h, LiOH (1 M solution in H₂O, 20 μL, 20 μmol) and H₂O₂ (10 M in H₂O, 3.2 μL, 32 μmol) were further added. The mixture was stirred at 40 °C for 24 h. After 4 was consumed, which was checked on TLC, water was added. The aqueous layer was extracted by EtOAc three times. The combined organic layer was dried over Na₂SO₄. After filtration, all the volatiles were removed by evaporation to afford the crude mixture. The yield was determined to be 79% by ¹H NMR of the obtained crude mixture with 1,1,2,2-tetrachloroethane as the internal standard.

¹H NMR (500 MHz, CDCl₃) δ: 7.89 (d, 2H, J = 8.0 Hz), 7.30 (d, 2H, J = 8.0 Hz), 3.68 (t, 2H, J = 6.3 Hz), 2.78 (t, 2H, J = 2.78 Hz), 2.59 (s, 3H), 1.85-1.95 (m, 2H), LRMS (ESI): m/z 201 [M+Na]⁺; identical to a reported data.⁶

6.4. Structural analysis of oxygenated products

After aerobic oxygenation of 3, ¹H NMR chart of the crude mixture was carefully analyzed. No triplet peak was observed around 3.00-3.50 ppm, which corresponds to the α-methylene protons of phenyl ketone 4’ (marked in red in 4’ of the above scheme), while a singlet peak at 2.58 ppm was observed, which corresponds to the α-methyl protons of phenyl ketone of 4 (marked in red in 4). For comparison, oxidized

⁶ Z.-L. Shen, K. K. K. Goh, Y.-S. Yang, Y.-C. Lai, C. H. A. Wong, H.-L. Cheong, T.-P. Loh, Angew. Chem. Int. Ed. 2011, 50, 511.
products of model substrate S11 afforded α-methylene protons of phenyl ketone S12' observed at 3.35 ppm as triplet (marked in red in S12' of the scheme below), and α-methyl protons of ketone S12 observed at 2.58 ppm as singlet (marked in red in S12). This fact indicates that regioisomer 4' did not generate at all. Thus, we concluded that the oxygenation of 3 occurred exclusively at the remote benzylic position.

The intermolecular oxygenation of model compound S11 produced a 2 : 1 regiomixture of S12 and S12' at 60 °C. This result, combined with the contrasting and exclusive remote-regioselectivity in oxygenation of 3, further supported the notion that oxygenation of 3 proceeded in an intramolecular manner controlled by the “long-arm linker” directing activator.
7. Analytical data

Full spectroscopic data were described for S4, 1, and 2 related to Table 1.

\textit{N}-benzylxy-3- ((2-methylpentan-2-yl)oxy)-3-trifluoromethyl-isoindolinone (S4b)

\begin{align*}
\text{colorless liquid; } ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta: & \quad 7.88 (dd, 1H, J = 6.0 Hz, 2.0 Hz), 7.61-7.73 (m, 3H), 7.56 (d, 2H, J = 6.9 Hz), 5.45 (d, 1H, J = 9.2 Hz), 5.06 (d, 1H, J = 9.2 Hz), 1.32-1.50 (m, 4H), 1.03 (s, 3H), 0.93 (s, 3H), 0.79-0.84 (m, 3H); \quad \text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3\text{)} \delta: & \quad 165.1, 137.3, 134.8, 132.6, 131.4, 130.3, 129.2, 128.6, 128.4, 125.4, 123.9, 122.7 (q, J = 286.0 Hz), 89.1 (q, J = 32.3 Hz), 82.3, 78.5, 46.1, 27.3, 26.0, 16.9, 14.3; \quad \text{\textsuperscript{19}F NMR (369 MHz, CDCl}_3\text{)} \delta: & \quad -79.7; \quad \text{IR (neat, cm}^{-1}\text{)} \nu: & \quad 2961, 1739, 1646, 1190; \quad \text{LRMS (ESI): } m/z & \quad 430 [M+Na]^+; \quad \text{HRMS (ESI): } m/z & \quad \text{calcd for C}_{22}\text{H}_{24}\text{F}_3\text{NO}_3\text{Na [M+Na]^+ 430.1601, Found 430.1620.}
\end{align*}

\textit{N}-hydroxy-3-((2-methylpentan-2-yl)oxy)-3-trifluoromethyl-isoindolinone (1b)

\begin{align*}
\text{reddish solid; } ^1\text{H NMR (500 MHz, CDCl}_3\text{)} \delta: & \quad 9.95 (brs, 1H), 7.78 (d, 1H, J = 7.3 Hz), 7.66 (d, 1H, J = 7.3 Hz), 7.61 (dd, 1H, J = 7.3 Hz, 7.3 Hz), 7.57 (dd, 1H, J = 7.3 Hz, 7.3 Hz), 1.40-1.55 (m, 4H), 1.15 (s, 3H), 0.96 (s, 3H), 0.90 (t, 3H, J = 6.6 Hz); \quad \text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3\text{)} \delta: & \quad 165.4, 137.6, 132.5, 131.2, 129.8, 125.2, 123.7, 122.1 (q, J = 288.2 Hz), 89.9 (q, J = 32.3 Hz), 82.6, 46.2, 27.2, 26.2, 17.1, 14.4; \quad \text{\textsuperscript{19}F NMR (369 MHz, CDCl}_3\text{)} \delta: & \quad -79.5, -79.7 (rotamers); \quad \text{IR (KBr, cm}^{-1}\text{)} \nu: & \quad 3159, 2962, 1718, 1473, 1391, 1373, 1192; \quad \text{LRMS (ESI): } m/z & \quad 340 [M+Na]^+; \quad \text{HRMS (ESI): } m/z & \quad \text{calcd for C}_{15}\text{H}_{18}\text{F}_3\text{NO}_3\text{Na [M+Na]^+ 340.1131, Found 340.1117.}
\end{align*}

the mixture of

\textit{N}-hydroxy-3-((2-methyl-4-oxopentan-2-yl)oxy)-3-trifluoromethyl-isoindolinone (2b)

and

4-hydroxy-2,2,4-trimethyl-11b-(trifluoromethyl)-3,4-dihydro-2\textit{H}-[1,4,2]dioxazepino[3,2-\textit{a}]isoindol-7(11b\textit{H})-one (2b'); diastereomixture

Starting material 1b (31.7 mg, 0.1 mmol) was oxygenated under condition A of section 2, and 2b' (20.7 mg, 0.062 mmol) was isolated as described in the General method (62% yield).

2b easily cyclizes to form 2b' and the equilibrium position lies far to the right.
No peaks of \(2b\) were detected in NMR spectra when the solvent was CDCl\(_3\); the peaks of \(2b\) could be slightly detected when the solvent was acetone-\(d_6\) as shown below (CDCl\(_3\) should be avoided to take a \(^{13}\)C NMR spectrum because \(2b'\) doesn’t dissolve in CDCl\(_3\) very much).

white solid; \(^1\)H NMR (500 MHz, acetone-\(d_6\); underlined chemical shifts for \(2b\)) \(\delta\): 9.47 (s, 1H), 7.68-7.86 (m, 4H), 5.68-5.71 (m, 1H), 2.81 (d, 1H, \(J = 14.9\) Hz), 2.72 (d, 1H, \(J = 14.9\) Hz), 2.23 (d, 1H, \(J = 14.9\) Hz), 2.10 (d, 1H, \(J = 14.9\) Hz), 1.60 (s, 3H), 1.31 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); \(^{13}\)C NMR (126 MHz, acetone-\(d_6\); underlined chemical shifts for \(2b\); wavy-lined shifts for \(2b\) or \(2b'\); dashed-lined shifts for both \(2b\) and \(2b'\); two shifts in brackets derived from "the same" carbon of the diastereomers) \(\delta\): 207.4, 164.0, 163.5, 139.8, 134.1, 132.6, 132.0, 131.5, 130.4, 126.6, 124.7, 124.2, 124.1, 123.6 (q, \(J = 288.5\) Hz), 90.3 (q, \(J = 31.7\) Hz), 56.1, 52.8, 33.9, 32.1, 28.2, 27.6, 27.5, 26.1, 25.6; \(^{19}\)F NMR (369 MHz, CDCl\(_3\); underlined chemical shifts for \(2b\)) \(\delta\): –79.1, –79.7; IR (KBr, cm\(^{-1}\)) \(\nu\): 3460, 2985, 1730, 1469, 1250, 1191; LRMS (ESI): \(m/z\) 35 4 \([\text{M+Na}]+\); HRMS (ESI): \(m/z\) calcd for C\(_{15}\)H\(_{16}\)F\(_3\)NO\(_4\)Na \([\text{M+Na}]+\) 354.0924, Found 354.0924.

\(N\)-benzyloxy-3-(2,2-dimethylbutoxy)-3-trifluoromethyl-isoindolinone (S4c)

colorless liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.91 (d, 1H, \(J = 7.4\) Hz), 7.70 (dd, 1H, \(J = 7.4\) Hz, 7.4 Hz), 7.65 (dd, 1H, \(J = 7.4\) Hz, 7.4 Hz), 7.60 (d, 1H, \(J = 7.4\) Hz), 7.55 (dd, 2H, \(J = 7.4\) Hz), 7.35-7.43 (m, 3H), 5.34 (d, 1H, \(J = 9.2\) Hz), 5.14 (d, 1H, \(J = 9.2\) Hz), 3.05 (d, 1H, \(J = 8.3\) Hz), 2.58 (d, 1H, \(J = 8.3\) Hz), 1.29 (q, 2H, \(J = 7.5\) Hz), 0.84 (s, 3H), 0.82 (s, 3H), 0.73 (t, 3H, \(J = 7.5\) Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 165.7, 135.4, 134.6, 133.2, 131.4, 130.1, 129.2, 128.7, 128.4, 124.15, 124.13, 122.3 (q, \(J = 86.3\) Hz), 90.8 (q, \(J = 32.3\) Hz), 79.0, 71.7, 34.1, 31.1, 23.8, 23.7, 8.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.6; IR (KBr, cm\(^{-1}\)) \(\nu\): 2965, 1747, 1468, 1294, 1190; LRMS (ESI): \(m/z\) 340 \([\text{M+Na}]+\); HRMS (ESI): \(m/z\) cacled for C\(_{22}\)H\(_{24}\)F\(_3\)NO\(_3\)Na \([\text{M+Na}]+\) 340.1601, Found 340.1614.

white solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 9.89 (brs, 1H), 7.79 (d, 1H, \(J = 7.4\) Hz), 7.66 (dd, 1H, \(J = 7.4\) Hz, 7.4 Hz), 7.56-7.62 (m, 2H), 3.16 (d, 1H, \(J = 8.0\) Hz), 2.61 (d, 1H, \(J = 8.0\) Hz), 1.29-1.40 (m, 2H), 0.91 (s, 3H), 0.88 (s, 3H), 0.81 (t, 3H, \(J = 7.4\) Hz); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 165.8, 135.3, 133.2, 131.4, 130.0, 124.0, 123.8, 122.0 (q, \(J = 287.1\) Hz), 90.9 (q, \(J = 32.8\) Hz), 71.8, 34.1, 31.2, 23.8, 23.7, 8.1; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.6; IR (KBr, cm\(^{-1}\)) \(\nu\): 3168, 2964, 2883, 1721, 1525, 1473, 1382, 1311, 1203; LRMS (ESI): \(m/z\) 340 \([\text{M+Na}]+\); HRMS (ESI): \(m/z\) cacled for C\(_{15}\)H\(_{18}\)F\(_3\)NO\(_3\)Na \([\text{M+Na}]+\) 340.1131, Found 340.1117.
3-(2,2-dimethyl-3-oxobutoxy)-N-hydroxy-3-trifluoromethyl-isoindolinone (2c)

Starting material 1c (31.7 mg, 0.1 mmol) was oxygenated under condition A of section 2, and 2c (17.7 mg, 0.053 mmol) was isolated as described in the General method (53% yield). White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.17 (brs, 1H), 7.84 (d, 1H, $J = 7.2$ Hz), 7.54-7.70 (m, 3H), 3.49 (d, 1H, $J = 8.7$ Hz), 2.87 (d, 1H, $J = 8.7$ Hz), 2.23 (s, 3H), 1.23 (s, 3H), 1.11 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 213.4, 164.6, 134.2, 133.2, 131.7, 130.2, 124.1, 121.7 (q, $J = 286.1$ Hz), 90.5 (q, $J = 34.1$ Hz), 69.0, 47.9, 25.8, 22.0, 21.7; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.4; IR (KBr, cm$^{-1}$) ν: 3138, 2941, 1709, 1471, 1304, 1199; LRMS (ESI): m/z 354 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{15}$H$_{16}$F$_3$NO$_4$Na [M+Na]$^+$ 354.0924, Found 354.0924.

N-benzyloxy-3-hexoxy-3-trifluoromethyl-isoindolinone (S4d)

Light yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.90 (d, 1H, $J = 6.7$ Hz), 7.59-7.72 (m, 3H), 7.53-7.58 (m, 2H), 7.35-7.43 (m, 3H), 5.31 (d, 1H, $J = 9.9$ Hz), 5.14 (d, 1H, $J = 9.9$ Hz), 3.25 (dt, 1H, $J = 8.7$ Hz, 6.5 Hz), 2.93 (dt, 1H, $J = 8.7$ Hz, 6.5 Hz), 1.47-1.57 (m, 2H), 1.13-1.34 (m, 6H), 0.82 (t, 3H, $J = 7.0$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.6, 135.3, 134.6, 133.4, 131.6, 130.0, 129.3, 128.8, 128.4, 124.2, 124.1, 122.2 (q, $J = 285.9$ Hz), 91.0 (q, $J = 32.8$ Hz), 79.1, 64.2, 31.3, 28.9, 25.4, 22.4, 13.9; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.1; IR (neat, cm$^{-1}$) ν: 2934, 1746, 1468, 1294, 1188; LRMS (ESI): m/z 430 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{22}$H$_{24}$F$_3$NO$_3$Na [M+Na]$^+$ 430.1604, Found 430.1604.

3-hexoxy-N-hydroxy-3-trifluoromethyl-isoindolinone (1d)

Light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.88 (brs, 1H), 7.79 (d, 1H, $J = 6.9$ Hz), 7.60 (d, 1H, $J = 6.9$ Hz), 7.59 (dd, 1H, $J = 6.9$ Hz, 7.5 Hz), 7.59 (dd, 1H, $J = 6.9$ Hz, 7.5 Hz), 3.42 (dt, 1H, $J = 8.6$ Hz, 6.3 Hz), 2.97 (dt, 1H, $J = 8.6$ Hz, 6.3 Hz), 1.56-1.67 (m, 2H), 1.19-1.41 (m, 6H), 0.86 (t, 3H, $J = 6.9$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.9, 135.3, 133.2, 131.4, 130.0, 124.0, 123.8, 121.9 (q, $J = 286.7$ Hz), 91.0 (q, $J = 32.4$ Hz), 64.4, 31.4, 29.0, 25.4, 22.5, 13.9; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.5; IR (neat, cm$^{-1}$) ν: 3141, 2935, 1718, 1470, 1200; LRMS (ESI): m/z 340 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{15}$H$_{18}$F$_3$NO$_3$Na [M+Na]$^+$ 340.1131, Found 340.1117.
**N-hydroxy-3-((3-oxohexyl)oxy)-3-trifluoromethyl-isoindolinone (2d)**

Starting material 1d (95.2 mg, 0.3 mmol) was oxygenated under condition A of section 2, and regiomixture of 2d + 2d' (41.0 mg, 0.12 mmol) was obtained according to the procedure described in the General method (41% combined yield).

HPLC purification was required for the separation of the oxygenation products of 1-hexanol, γ-oxo- (2d) and δ-oxo-1-hexanol (2d'), which were not separable by normal silica gel column chromatography.

- Column: Inertsil® Diol φ 20 mm x 250 mm
- Eluent: hexane/CHCl₃ = 2/1
- Flow rate: 9.5 mL/min
- RT: 46 min (2d), 83 min (2d')

light yellow liquid; ¹H NMR (400 MHz, CDCl₃) δ: 8.99 (brs, 1H), 7.85 (d, 1H, J = 7.2 Hz), 7.56-7.67 (m, 3H), 3.52-3.60 (m, 1H), 3.21-3.28 (m, 1H), 2.81-2.91 (m, 1H), 2.61-2.69 (m, 1H), 2.44 (t, 2H, J = 7.2 Hz), 1.54-1.65 (m, 2H), 0.89 (t, 3H, J = 7.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ: 210.7, 163.9, 133.9, 133.0, 131.6, 130.4, 124.1, 121.7 (q, J = 286.3 Hz), 90.5 (q, J = 34.1 Hz), 57.9, 45.1, 41.1, 17.0, 13.4; ¹⁹F NMR (369 MHz, CDCl₃) δ: -78.2; IR (neat, cm⁻¹) ν: 3219, 2964, 1717, 1469, 1302, 1198; LRMS (ESI): m/z 354 [M+Na]⁺; HRMS (ESI): m/z calcd for C₁₅H₁₆F₃NO₄Na [M+Na]⁺ 354.0924, Found 354.0929.

**N-hydroxy-3-((4-oxohexyl)oxy)-3-trifluoromethyl-isoindolinone (2d')**

light yellow liquid; ¹H NMR (400 MHz, CDCl₃) δ: 9.50 (brs, 1H), 7.83 (d, 1H, J = 7.6 Hz), 7.55-7.68 (m, 3H), 3.25-3.32 (m, 1H), 3.07-3.14 (m, 1H), 2.54-2.69 (m, 2H), 2.48 (q, 2H, J = 7.3 Hz), 1.80-2.00 (m, 2H), 1.04 (t, 3H, J = 7.3 Hz); ¹³C NMR (126 MHz, CDCl₃) δ: 212.5, 165.2, 134.8, 133.2, 131.6, 130.1, 124.1, 124.0, 121.9 (q, J = 286.7 Hz), 90.8 (q, J = 33.2 Hz), 62.8, 38.3, 35.9, 23.4, 7.7; ¹⁹F NMR (369 MHz, CDCl₃) δ: -78.3; IR (neat, cm⁻¹) ν: 3218, 2925, 1716, 1469, 1190; LRMS (ESI): m/z 354 [M+Na]⁺; HRMS (ESI): m/z calcd for C₁₅H₁₆F₃NO₄Na [M+Na]⁺ 354.0924, Found 354.0929.

**5-((N-benzyloxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)pentyl acetate (S4e)**

light yellow liquid; ¹H NMR (500 MHz, CDCl₃) δ: 7.89 (d, 1H, J = 7.5 Hz), 7.69 (ddd, 1H, 1.2 Hz, 7.5 Hz, 7.5 Hz), 7.63 (ddd, 1H, J = 1.2 Hz, 7.5 Hz, 7.5 Hz), 7.60 (d, 2H, J = 7.5 Hz), 7.52-7.56 (m, 2H), 7.34-7.41
(m, 3H), 5.31 (d, 1H, J = 9.8 Hz), 5.12 (d, 1H, J = 9.8 Hz), 3.96 (t, 2H, J = 6.3 Hz), 3.23 (dt, 1H, J = 8.6 Hz, 6.3 Hz), 2.93 (dt, 1H, J = 8.6 Hz, 6.3 Hz), 1.50-1.57 (m, 4H), 1.30-1.38 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta:\) 171.0, 165.6, 135.2, 134.5, 133.5, 131.6, 130.0, 129.3, 128.8, 128.4, 124.1, 122.2 (q, J = 285.5 Hz), 90.8 (q, J = 33.6 Hz), 79.1, 64.1, 63.7, 28.5, 28.0, 22.2, 20.8; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta:\) -78.1; IR (neat, cm\(^{-1}\)) \(\nu:\) 2951, 1741, 1469, 1367, 1244, 1189; LRMS (ESI): \(m/z\) 474 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{23}\)H\(_{24}\)F\(_{3}\)NO\(_{5}\)Na [M+Na]\(^+\) 474.1499, Found 474.1496.

5-((N-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)pentyl acetate (1e)

light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:\) 9.76 (brs, 1H), 7.80 (d, 1H, J = 7.5 Hz), 7.66 (dd, 1H, J = 1.2 Hz, 7.5 Hz, 7.5 Hz), 7.60 (dd, 2H, J = 7.5 Hz, 7.5 Hz), 4.06 (t, 2H, J = 6.9 Hz), 3.40 (dt, 1H, J = 9.2 Hz, 6.3 Hz), 2.98 (dt, 1H, J = 9.2 Hz, 6.3 Hz), 2.02 (s, 3H), 1.57-1.67 (m, 4H), 1.34-1.50 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta:\) 171.5, 165.7, 135.1, 133.2, 131.5, 131.0, 124.0, 123.9, 121.9 (q, J = 285.5 Hz), 90.9 (q, J = 33.6 Hz), 64.3, 63.9, 28.5, 28.1, 22.2, 20.9; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta:\) -78.5; IR (neat, cm\(^{-1}\)) \(\nu:\) 3175, 2955, 1736, 1470, 1241, 1198; LRMS (ESI): \(m/z\) 384 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{18}\)F\(_{3}\)NO\(_{6}\)Na [M+Na]\(^+\) 384.1029, Found 384.1039.

5-((N-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-3-oxopentyl acetate (2e)

Starting material 1e (36.1 mg, 0.1 mmol) was oxygenated under condition A of section 2, and 2e (13.8 mg, 0.037 mmol) was isolated as described in the General method (37% yield).

light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:\) 8.58 (brs, 1H), 7.88 (d, 1H, J = 7.4 Hz), 7.58-7.69 (m, 3H), 4.34 (t, 2H, J = 6.0 Hz), 3.59 (dt, 1H, J = 3.4 Hz, 9.5 Hz), 3.26-3.30 (m, 1H), 2.93 (ddd, 1H, J = 18.3 Hz, 3.4 Hz, 1.8 Hz), 2.83 (t, 2H, J = 6.0 Hz), 2.70 (dd, 1H, J = 18.3 Hz, 3.4 Hz, 1.8 Hz), 2.02 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta:\) 207.4, 170.9, 163.9, 133.9, 133.0, 131.8, 130.4, 124.2, 124.1, 121.7 (q, J = 286.7 Hz), 90.5 (q, J = 33.6 Hz), 58.8, 57.7, 41.9, 41.6, 20.7; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta:\) -78.2; IR (neat, cm\(^{-1}\)) \(\nu:\) 3302, 2955, 1738, 1469, 1370, 1191; LRMS (ESI): \(m/z\) 398 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{16}\)F\(_{3}\)NO\(_{6}\)Na [M+Na]\(^+\) 398.0822, Found 398.0808.

2-(5-((2-(benzyloxy)-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)pentyl)isoindoline-1,3-dione (S4f)
light yellow solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.88 (d, 1H, \(J = 7.4\) Hz), 7.78-7.83 (m, 2H), 7.66-7.72 (m, 3H), 7.58-7.65 (m, 2H), 7.54 (d, 2H, \(J = 6.9\) Hz), 7.31-7.40 (m, 3H), 5.29 (d, 1H, \(J = 9.7\) Hz), 5.12 (d, 1H, \(J = 9.7\) Hz), 3.60 (t, 2H, \(J = 7.2\) Hz), 3.20-3.26 (m, 1H), 2.88-2.94 (m, 1H), 1.48-1.64 (m, 4H), 1.23-1.39 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 168.3, 165.6, 135.2, 134.6, 133.4, 133.8, 133.5, 132.0, 131.6, 129.9, 129.3, 128.8, 128.4, 124.1, 124.1, 123.1, 122.1 (q, \(J = 286.0\) Hz), 90.9 (q, \(J = 32.9\) Hz), 79.1, 63.7, 37.6, 28.4, 28.1, 23.1; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.0; IR (KBr, cm\(^{-1}\)) \(\nu\): 3463, 3038, 2948, 2893, 1742, 1707, 1607, 1194; LRMS (ESI): \(m/z\) 561 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{29}\)H\(_{25}\)F\(_3\)N\(_2\)O\(_5\)Na [M+Na]\(^+\) 561.1608, Found 561.1587.

2-(5-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)pentyl)isoindoline-1,3-dione (1f)

Starting material 1f (89.7 mg, 0.2 mmol) was oxygenated under condition A of section 2, and 2f (30.9 mg, 0.067 mmol) was isolated as described in the General method (33% yield).

light yellow liquid; \(^1\)H NMR (500 MHz, acetone-\(d_6\)) \(\delta\): 9.55 (brs, 1H), 7.66-7.84 (m, 8H), 3.61 (t, 2H, \(J = 7.2\) Hz), 3.36-3.44 (m, 1H), 2.95-3.04 (m, 1H), 1.55-1.71 (m, 4H), 1.28-1.48 (m, 2H); \(^{13}\)C NMR (100 MHz, acetone-\(d_6\)) \(\delta\): 168.7, 164.6, 135.7, 134.9, 134.1, 132.9, 132.6, 131.5, 125.1, 124.2, 123.6, 123.3 (q, \(J = 286.6\) Hz), 91.4 (q, \(J = 31.9\) Hz), 64.2, 38.1, 29.2, 28.7, 23.8; \(^{19}\)F NMR (369 MHz, acetone-\(d_6\)) \(\delta\): –78.7; IR (KBr, cm\(^{-1}\)) \(\nu\): 3524, 3368, 2940, 2889, 2712, 1731, 1699, 1200; LRMS (ESI): \(m/z\) 471 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{22}\)H\(_{19}\)F\(_3\)N\(_2\)O\(_5\)Na [M+Na]\(^+\) 471.1138, Found 471.1119.

methyl 6-((2-(benzyloxy)-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)hexanoate (S4g)
colorless liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.89 (d, 1H, $J = 7.4$ Hz), 7.58-7.71 (m, 3H), 7.52-7.57 (m, 2H), 7.34-7.42 (m, 3H), 5.31 (d, 1H, $J = 9.5$ Hz), 5.13 (d, 1H, $J = 9.5$ Hz), 3.63 (s, 3H), 3.20-3.26 (m, 1H), 2.90-2.96 (m, 1H), 2.22 (t, 2H, $J = 7.4$ Hz), 1.47-1.58 (m, 4H), 1.24-1.36 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 173.9, 165.6, 135.2, 134.6, 133.5, 131.6, 130.0, 129.3, 128.8, 128.4, 124.2, 124.1, 121.1 (q, $J = 286.0$ Hz), 90.1 (q, $J = 32.9$ Hz), 79.1, 63.8, 51.4, 33.7, 28.6, 25.3, 24.4; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.1; IR (neat, cm$^{-1}$) $\nu$: 2950, 1741, 1468, 1194; LRMS (ESI): $m/z$ 474 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{23}$H$_{24}$F$_3$NO$_5$Na [M+Na]$^+$ 474.1499, Found 474.1515.

methyl 6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)hexanoate (1g)

red liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.71 (s, 1H), 7.81 (d, 1H, $J = 7.4$ Hz), 7.63-7.68 (m, 1H), 7.56-7.62 (m, 2H), 3.64 (s, 3H), 3.36-3.42 (m, 1H), 2.95-3.01 (m, 1H), 2.29 (t, 2H, $J = 7.4$ Hz), 1.55-1.66 (m, 4H), 1.30-1.46 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 174.4, 165.6, 135.0, 133.2, 131.5, 130.0, 124.0, 123.9, 121.9 (q, $J = 286.7$ Hz), 90.9 (q, $J = 32.8$ Hz), 63.8, 51.6, 33.8, 28.5, 25.2, 24.3; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.4; IR (neat, cm$^{-1}$) $\nu$: 3177, 2951, 1719, 1469, 1303, 1199; LRMS (ESI): $m/z$ 384 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{16}$H$_{18}$F$_3$NO$_5$Na [M+Na]$^+$ 384.1029, Found 384.1029.

methyl 6-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-4-oxohexanoate (2g)

Starting material 1g (72.3mg, 0.2 mmol) was oxygenated under condition A of section 2, and 2g (22.2 mg, 0.059 mmol) was isolated as described in the General method (30% yield).

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.60 (s, 1H), 7.88 (d, 1H, $J = 8.0$ Hz), 7.57-7.68 (m, 3H), 3.67 (dt, 1H, $J = 6.9$ Hz), 3.24-3.29 (m, 1H), 2.97 (ddd, 1H, $J = 18.3$ Hz, 10.0 Hz, 3.7 Hz), 2.62-2.87 (m, 4H), 2.55-2.62 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 208.8, 173.1, 163.7, 133.8, 132.9, 131.7, 130.5, 124.2, 124.1, 121.2 (q, $J = 286.6$ Hz), 90.5 (q, $J = 33.6$ Hz), 57.8, 52.0, 41.4, 37.5, 27.6; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.1; IR (neat, cm$^{-1}$) $\nu$: 3222, 2954, 1719, 1469, 1303, 1199; LRMS (ESI): $m/z$ 398 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{16}$H$_{18}$F$_3$NO$_6$Na [M+Na]$^+$ 398.0822, Found 398.0804.

$N$-benzyloxy-3-(2-cyclohexylethoxy)-3-trifluoromethyl-isoindolinone (S4i)
light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.90 (d, 1H, 7.5 Hz), 7.67-7.72 (m, 1H), 7.60-7.66 (m, 2H), 7.57 (dd, $J = 1.2$ Hz 8.1 Hz), 7.35-7.43 (m, 3H), 5.33 (d, 1H, $J = 9.7$ Hz), 5.15 (d, 1H, $J = 9.7$ Hz), 3.31 (dd, 1H, $J = 8.6$ Hz, 6.9 Hz), 2.99 (dd, 1H, $J = 8.6$ Hz, 6.9 Hz), 1.50-1.65 (m, 5H), 1.40-1.45 (m, 2H), 1.26-1.38 (m, 1H), 1.02-1.20 (m, 3H), 0.74-0.83 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.6, 135.3, 134.6, 133.4, 131.6, 130.0, 129.3, 128.8, 128.4, 124.13, 124.10, 122.2 (q, $J = 287.6$ Hz), 90.9 (q, $J = 33.6$ Hz), 79.1, 62.1, 36.4, 34.1, 33.2, 33.05, 33.02, 26.3, 26.05, 25.96; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.1; IR (neat, cm$^{-1}$) $\nu$: 2924, 1746, 1664, 1468, 1295, 1189; LRMS (ESI): $m/z$ 456 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{24}$H$_{26}$F$_3$NO$_3$Na [M+Na]$^+$ 456.1757, Found 456.1754.

3-(2-cyclohexylethoxy)-$N$-hydroxy-3-trifluoromethyl-isoindolinone (1i)

white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.87 (s, 1H), 7.79 (d, 1H, $J = 8.0$ Hz), 7.66 (dd, 1H, $J = 8.0$ Hz, 7.4 Hz), 7.57-7.62 (m, 2H), 3.47 (dt, 1H, $J = 8.0$ Hz, 6.9 Hz), 3.00 (dt, 1H, $J = 8.0$ Hz, 6.9 Hz), 1.47-1.69 (m, 6H), 1.32-1.43 (m, 1H), 1.05-1.28 (m, 4H), 0.88-0.90 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.9, 135.3, 133.2, 131.4, 130.0, 124.0, 123.9, 121.9 (q, $J = 286.7$ Hz), 91.0 (q, $J = 32.4$ Hz), 62.4, 36.4, 34.2, 33.2, 33.0, 26.4, 26.2, 26.1; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.5; IR (KBr, cm$^{-1}$) $\nu$: 3176, 3114, 2933, 2854, 1721, 1452, 1309, 1185; LRMS (ESI): $m/z$ 366 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{17}$H$_{20}$F$_3$NO$_3$Na [M+Na]$^+$ 366.1288, Found 366.1277.

$N$-hydroxy-3-(2-(1-hydroxycyclohexyl)ethoxy)-3-trifluoromethyl-isoindolinone (2i)

Starting material 1i (1.02 g, 2.97 mmol) was oxygenated under condition B of section 2, and 2i (597 mg, 1.66 mmol) was isolated as described in the General method (56% yield).

white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.42 (s, 1H), 7.88 (d, 1H, $J = 7.5$ Hz), 7.58-7.68 (m, 3H), 3.53 (dt, 1H, $J = 3.4$ Hz, 9.8 Hz), 3.27-3.33 (m, 1H), 1.96 (ddd, 1H, $J = 4.6$ Hz, 5.7 Hz, 14.9 Hz), 1.84-1.91 (m, 1H), 1.22-1.66 (m, 10H); $^{13}$C NMR (126 MHz, acetone-$d_6$) $\delta$: 164.2, 135.6, 133.9, 132.7, 131.8, 125.2, 124.3, 123.3 (q, $J = 285.5$ Hz), 91.4 (q, $J = 32.4$ Hz), 70.7, 61.0, 41.4, 38.6, 38.5, 26.4, 22.7; $^{19}$F NMR (369 MHz, acetone-$d_6$) $\delta$: –78.8; IR (KBr, cm$^{-1}$) $\nu$: 3321, 2933, 2857, 2771, 1720, 1473, 1193; LRMS (ESI): $m/z$ 382 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{17}$H$_{20}$F$_3$NO$_4$Na [M+Na]$^+$ 382.1237, Found 382.1249.

$N$-benzyloxy-3-cyclohexylmethoxy-3-trifluoromethyl-isoindolinone (S4j)
light yellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.90 (d, 1H, $J = 7.6$ Hz), 7.69 (dd, 1H, $J = 1.3$ Hz, 7.6 Hz, 7.6 Hz), 7.64 (dd, 1H, $J = 7.6$ Hz, 7.6 Hz), 7.54-7.62 (m, 3H), 7.35-7.44 (m, 3H), 5.32 (d, 1H, $J = 9.9$ Hz), 5.26 (d, 1H, $J = 9.9$ Hz), 3.11 (dd, 1H, $J = 6.3$ Hz, 8.5 Hz), 2.71 (dd, 1H, $J = 6.7$ Hz, 8.5 Hz), 1.71-1.82 (m, 1H), 1.50-1.71 (m, 5H), 1.02-1.28 (m, 3H), 0.76-0.89 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.6, 135.3, 134.6, 133.4, 131.6, 130.0, 129.3, 128.7, 128.4, 124.2, 124.1, 122.2 (q, $J = 285.6$ Hz), 90.9 (q, $J = 32.0$ Hz), 79.0, 69.2, 37.3, 29.7, 29.4, 26.3, 25.6, 25.5; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 2927, 1746, 1648, 1291, 1187; LRMS (ESI): m/z 442 [M+Na]$^+$; HRMS (ESI): m/z calcld for C$_{23}$H$_{24}$F$_3$NO$_3$Na [M+Na]$^+$ 442.1601, Found 442.1620.

3-cyclohexylmethoxy-N-hydroxy-3-trifluoromethyl-isoindolinone (1j)

white solid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.86 (brs, 1H), 7.89 (d, 1H, $J = 7.5$ Hz), 7.66 (dd, 1H, $J = 7.5$ Hz, 7.5 Hz), 7.60 (dd, 2H, $J = 7.5$ Hz, 7.5 Hz), 3.24 (dd, 1H, $J = 6.3$ Hz, 8.1 Hz), 2.73 (dd, 1H, $J = 7.5$ Hz, 7.5 Hz), 1.62-1.82 (m, 6H), 1.18-1.30 (m, 2H), 1.07-1.18 (m, 1H), 0.81-0.98 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.8, 135.3, 133.2, 131.4, 130.0, 124.1, 123.8, 121.9 (q, $J = 285.5$ Hz), 91.0 (q, $J = 33.6$ Hz), 69.5, 37.3, 29.7, 29.4, 26.4, 25.7, 25.6; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.5; IR (KBr, cm$^{-1}$) ν: 3117, 2925, 2856, 1708, 1473, 13990, 1309, 1184; LRMS (ESI): m/z 352 [M+Na]$^+$; HRMS (ESI): m/z calcld for C$_{16}$H$_{18}$F$_3$NO$_3$Na [M+Na]$^+$ 352.1131, Found 352.1118.

N-hydroxy-3-((1-hydroxycyclohexyl)methoxy)-3-trifluoromethyl-isoindolinone (2j)

white solid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.97 (brs, 1H), 7.84 (d, 1H, $J = 6.9$ Hz), 7.61-7.70 (m, 3H), 3.33 (d, 1H, $J = 11.5$ Hz), 2.99 (d, 1H, $J = 11.5$ Hz), 1.89-1.97 (m, 1H), 1.48-1.70 (m, 5H), 1.39-1.48 (m, 2H), 1.24-1.34 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 163.9, 134.7, 133.0, 131.6, 130.8, 124.0, 123.8, 121.9 (q, $J = 286.6$ Hz), 91.0 (q, $J = 33.2$ Hz), 73.4, 71.6, 34.1, 32.7, 25.6, 21.5; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 3318, 2936, 2861, 1723, 1469, 1298, 1191; LRMS (ESI): m/z 368 [M+Na]$^+$; HRMS (ESI): m/z calcld for C$_{18}$H$_{18}$F$_3$NO$_4$Na [M+Na]$^+$ 368.1080, Found 368.1092.
(R)-N-benzyl oxy-3-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-3-trifluoromethyl-isoindoline ((R)-S4k)

white solid; 1H NMR (500 MHz, CDCl3): δ: 7.88 (dd, 1H, J = 1.7 Hz, 6.3 Hz), 7.67-7.71 (m, 1H), 7.59-7.67 (m, 2H), 7.55 (dd, 2H, J = 1.7 Hz, 7.4 Hz), 7.36-7.42 (m, 3H), 5.46 (d, 1H, J = 8.6 Hz), 5.01 (d, 1H, J = 8.6 Hz), 3.40 (dt, 1H, J = 4.6 Hz 10.4 Hz), 2.31-2.41 (m, 1H), 1.43-1.55 (m, 2H), 1.22-1.29 (m, 1H), 0.90-1.01 (m, 1H), 0.75-0.84 (m, 2H), 0.79 (d, 3H, J = 6.9 Hz), 0.58-0.71 (m, 2H), 0.54 (d, 1H, J = 6.9 Hz), 0.33 (d, 3H, J = 6.9 Hz); 13C NMR (126 MHz, CDCl3): δ: 164.7, 138.1, 134.0, 132.9, 131.3, 130.0, 129.0, 128.9, 128.3, 124.7, 123.8, 122.7 (q, J = 286.7 Hz), 89.1 (q, J = 33.6 Hz), 78.6, 76.0, 48.6, 42.5, 33.7, 31.1, 24.4, 22.8, 22.0, 21.4, 16.0; 19F NMR (369 MHz, CDCl3) δ: –78.3; IR (KBr, cm⁻¹) ν: 3037, 2954, 2931, 2863, 1740, 1616, 1187; LRMS (ESI): m/z 484 [M+Na]+; HRMS (ESI): m/z calcd for C26H30F3NO3Na [M+Na]+ 484.2070, Found 484.2088.

(R)-N-hydroxy-3-(((1S,2R,5S)-2-isopropyl-5-methylcyclohexyl)oxy)-3-trifluoromethyl-isoindolinone ((R)-1k)

reddish solid; 1H NMR (400 MHz, CDCl3): δ: 9.74 (brs, 1H), 7.76 (d, 1H, J = 6.7 Hz), 7.53-7.67 (m, 3H), 3.64 (dt, 1H, J = 4.3 Hz, 10.4 Hz), 2.45-2.57 (m, 1H), 1.58-1.68 (m, 1H), 1.49-1.58 (m, 1H), 1.28-1.43 (m, 1H), 0.87-1.15 (m, 3H), 0.95 (d, 3H, J = 7.2 Hz), 0.83 (d, 3H, J = 6.7 Hz), 0.59 (d, 3H, J = 6.7 Hz); 13C NMR (100 MHz, CDCl3): δ: 165.7, 138.0, 132.8, 131.2, 128.9, 124.7, 123.6, 122.2 (q, J = 287.5 Hz), 90.1 (q, J = 32.6 Hz), 76.7, 48.6, 42.8, 33.9, 31.2, 24.9, 23.0, 22.0, 21.4, 15.9; 19F NMR (369 MHz, CDCl3) δ: –78.5; IR (KBr, cm⁻¹) ν: 3198, 2959, 2871, 1719, 1472, 1375, 1290, 1192; LRMS (ESI): m/z 394 [M+Na]+; HRMS (ESI): m/z calcd for C19H24F3NO3Na [M+Na]+ 394.1601, Found 394.1611.

(R)-N-hydroxy-3-(((1S,2S,5S)-2-(2-hydroxypropan-2-yl)-5-methylcyclohexyl)oxy)-3-trifluoromethyl -isoindolinone ((R)-2k)

Starting material (R)-1k (37.1 mg, 0.1 mmol) was oxygenated under condition B of section 2, and (R)-2k (36.2 mg, 0.093 mmol) was isolated as described in the General method (93% yield).
white solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 10.4 (brs, 1H), 7.80-7.87 (m, 1H), 7.66-7.73 (m, 1H), 7.57-7.64 (m, 2H), 4.26 (brs, 1H), 3.75-3.83 (m, 1H), 1.57-1.67 (m, 1H), 1.51-1.60 (m, 1H), 1.44 (s, 3H), 1.32-1.39 (m, 1H), 1.27 (s, 3H), 0.93-1.13 (m, 2H), 0.72-0.87 (m, 1H), 0.66 (d, 3H, \(J = 6.3\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 163.6, 135.9, 132.0, 131.5, 130.6, 125.6, 123.8, 122.1 (q, \(J = 285.6\) Hz), 90.6 (q, \(J = 32.0\) Hz), 74.5, 52.0, 43.1, 33.7, 31.0, 30.9, 27.2, 25.7, 21.9; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –77.3; IR (KBr, cm\(^{-1}\)) \(\nu\): 3366, 2974, 2928, 2866, 1726, 1191; LRMS (ESI): \(m/z\) 410 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{19}\)H\(_{24}\)F\(_3\)NO\(_4\)Na [M+Na]\(^+\) 410.1550, Found 410.1551.

\(N\)-benzyloxy-3-(((S,3,7-dimethyloct-6-en-1-yl)oxy)-3-trifluoromethyl-isoinodolinone (S4l)

light yellow liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.91 (d, 1H + 1H, \(J = 7.4\) Hz), 7.60-7.72 (m, 3H + 3H), 7.55-7.59 (m, 2H + 2H), 7.35-7.43 (m, 3H + 3H), 5.31-5.35 (m, 1H + 1H), 2.96-3.03 (m, 1H + 1H), 1.83-2.00 (m, 1H + 1H), 1.68 (s, 3H), 1.67 (s, 3H), 1.48-1.68 (m, 2H + 2H), 1.59 (s, 3H), 1.58 (s, 3H), 1.19-1.40 (m, 2H + 2H), 1.01-1.14 (m, 1H + 1H), 0.75-0.79 (m, 3H + 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 165.6, 165.5, 135.31, 135.26, 134.6, 133.4, 131.6, 131.2, 131.1, 130.04, 130.02, 129.30, 129.28, 128.8, 128.39, 128.37, 124.5, 124.1, 122.2 (q, \(J = 285.1\) Hz), 90.93 (q, \(J = 33.2\) Hz), 90.90 (q, \(J = 32.8\) Hz), 79.1, 77.2, 62.43, 62.40, 36.9, 36.7, 35.9, 35.8, 29.1, 29.0, 25.6, 25.2, 19.4, 19.2, 17.5; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.0, –78.1; IR (neat, cm\(^{-1}\)) \(\nu\): 2925, 1746, 1469, 1306, 1201; LRMS (ESI): \(m/z\) 484 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{22}\)H\(_{26}\)N\(_2\)O\(_2\)Na [M+Na]\(^+\) 484.2070, Found 484.2062.

3-(((S,3,7-dimethyloctyl)oxy)-N-hydroxy-3-trifluoromethyl-isoinodolinone (1l)

light yellow liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 10.1 (brs, 1H + 1H), 7.80 (d, 1H + 1H, \(J = 7.5\) Hz), 7.65-7.70 (m, 1H + 1H), 7.58-7.63 (m, 2H + 2H), 3.47-3.55 (m, 1H + 1H), 2.98-3.06 (m, 1H + 1H), 1.61-1.75 (m, 1H + 1H), 1.53-1.61 (m, 1H + 1H), 1.37-1.53 (m, 2H + 2H), 1.15-1.33 (m, 3H + 3H), 1.00-1.15 (m, 3H + 3H), 0.78-0.86 (m, 9H + 9H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 165.93, 165.92, 135.3, 133.2, 131.5, 130.0, 124.0, 123.9, 121.9 (q, \(J = 286.3\) Hz), 91.1 (q, \(J = 33.2\) Hz), 62.8, 62.7, 39.2, 39.1, 37.3, 37.0, 36.1, 36.0, 29.61, 29.58, 27.9, 24.6, 24.5, 22.63, 22.61, 22.5, 19.5, 19.3; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.5; IR (neat, cm\(^{-1}\)) \(\nu\): 3154, 2954, 1718, 1469, 1306, 1201; LRMS (ESI): \(m/z\) 396 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{19}\)H\(_{25}\)F\(_3\)NO\(_3\)Na [M+Na]\(^+\) 396.1757, Found 396.1768.

\(N\)-hydroxy-3-(((3-hydroxy-3,7-dimethyloctyl)oxy)-3-trifluoromethyl-isoinodolinone (2l)
Starting material 11 (37.3 mg, 0.1 mmol) was oxygenated under condition B of section 2, and 21 (21.5 mg, 0.055 mmol) was obtained as a diastereomixture according to the procedure as described in the General method (55% yield).

light yellow liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 9.65-9.86 (brs, 1H + 1H), 7.83-7.88 (m, 1H + 1H), 7.58-7.68 (m, 3H + 3H), 3.52-3.60 (m, 1H + 1H), 3.42 (brs, 1H + 1H), 3.24-3.32 (m, 1H + 1H), 1.95-2.03 (m, 1H), 1.87-1.95 (m, 1H), 1.57-1.74 (m, 2H + 2H), 1.40-1.57 (m, 2H + 2H), 1.36 (s, 3H), 1.23-1.38 (m, 2H), 1.18 (s, 3H), 1.07-1.20 (m, 2H + 2H), 0.82-0.88 (m, 6H + 6H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 164.8, 134.44, 134.41, 133.0, 131.6, 130.4, 124.15, 124.13, 124.0, 121.8 (q, \(J = 284.9\) Hz), 90.9 (q, \(J = 34.0\) Hz), 72.7, 72.6, 60.7, 60.6, 43.4, 43.0, 39.28, 39.26, 39.1, 27.8, 27.2, 26.8, 22.54, 22.52, 22.5, 21.8, 21.6; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): -78.2; IR (neat, cm\(^{-1}\)) \(\nu\): 3406, 3161, 2954, 1721, 1469, 1383, 1306, 1200; LRMS (ESI): \(m/z\) 412 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{19}\)H\(_{26}\)F\(_3\)NO\(_4\)Na [M+Na]+ 412.1706, Found 412.1701.

\(N\)-benzyloxy-3-((5-hydroxy-3-methylpentyl)oxy)-3-trifluoromethyl-isoindolinone (S4m)

colorless liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.90 (d, 1H + 1H, \(J = 6.9\) Hz), 7.59-7.72 (m, 3H + 3H), 7.53-7.58 (m, 2H + 2H), 7.35-7.43 (m, 3H + 3H), 7.53-7.58 (m, 2H + 2H), 7.35-7.43 (m, 3H + 3H), 5.30-5.35 (m, 1H), 5.10-5.14 (m, 1H), 3.49-3.65 (m, 2H), 3.25-3.33 (m, 1H + 1H), 2.94-3.03 (m, 1H + 1H), 1.63-1.73 (m, 1H + 1H), 1.45-1.60 (m, 2H + 2H), 1.24-1.43 (m, 2H + 2H), 0.76-0.80 (m, 3H + 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 165.7, 165.6, 135.25, 135.21, 134.535, 134.525, 133.52, 133.50, 131.7, 130.0, 129.5, 129.45, 129.37, 128.9, 128.8, 128.5, 128.4, 124.2, 124.1, 122.2 (q, \(J = 286.1\) Hz), 90.80 (q, \(J = 32.9\) Hz), 90.78 (q, \(J = 32.9\) Hz), 79.1, 62.3, 62.1, 60.714, 60.705, 39.41, 39.40, 26.5, 26.2, 19.42, 19.35; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): -78.2; IR (neat, cm\(^{-1}\)) \(\nu\): 3417, 2929, 1742, 1468, 1295, 1189; LRMS (ESI): \(m/z\) 446 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{22}\)H\(_{24}\)F\(_3\)NO\(_4\)Na [M+Na]+ 446.1550, Found 446.1536.

\(N\)-hydroxy-3-((5-hydroxy-3-methylpentyl)oxy)-3-trifluoromethyl-isoindolinone (1m)

white solid (diastereomixture); \(^1\)H NMR (400 MHz, acetone-\(d_6\)) \(\delta\): 7.70-7.88 (m, 4H + 4H), 3.51-3.66 (m, 2H + 2H), 3.37-3.47 (m, 1H + 1H), 3.05-3.19 (m, 1H + 1H), 1.80-1.91 (m, 1H), 1.69-1.80 (m, 1H), 1.40-1.68 (m, 3H + 3H), 1.18-1.31 (m, 1H + 1H), 0.82-0.87 (m, 3H + 3H); \(^1^3\)C NMR (100 MHz, acetone-\(d_6\)) \(\delta\): 164.7, 135.8, 135.7, 134.1, 134.0, 132.6, 131.7, 131.6, 125.21, 125.19, 125.16, 125.14,
124.30, 124.25, 123.4 (q, J = 286.1 Hz), 123.3 (q, J = 286.1 Hz), 91.6 (q, J = 31.9 Hz), 91.5 (q, J = 32.4 Hz), 63.0, 62.6, 60.25, 60.19, 40.3, 39.9, 37.0, 36.9, 27.4, 26.5, 19.99, 19.98; \(^{19}\)F NMR (369 MHz, acetone-\(d_6\)) \(\delta:\) -78.6, -78.8; IR (KBr, cm\(^{-1}\)) \(\nu:\) 3374, 2955, 2775, 1724, 1470, 1304, 1200; LRMS (ESI): \(m/z\) 356 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{15}\)H\(_{18}\)F\(_3\)NO\(_4\)Na [M+Na]\(^+\) 356.1080, Found 356.1075.

3-((3,5-dihydroxy-3-methylpentyl)oxy)-N-hydroxy-3-trifluoromethyl-isoindolinone (2m)

Starting material 1m (100 mg, 0.3 mmol) was oxygenated under condition B of section 2, and 2m (51.6 mg, 0.15 mmol) was obtained as a diastereomixture according to the procedure described in the General method (49% yield).

colorless liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:\) 9.73 (brs, 1H), 9.67 (brs, 1H), 7.88 (d, 1H, J = 7.4 Hz), 7.58-7.69 (m, 3H + 3H), 3.84-4.03 (m, 2H + 2H), 3.50-3.60 (m, 1H + 1H), 3.25-3.33 (m, 1H + 1H), 2.02-2.10 (m, 1H), 1.88-2.01 (m, 1H + 1H), 1.76-1.83 (m, 1H), 1.64-1.76 (m, 2H + 2H), 1.44 (s, 3H), 1.61 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta:\) 164.9, 164.7, 134.4, 134.3, 133.1, 133.0, 131.67, 131.65, 130.4, 130.3, 124.1, 124.0, 121.9 (q, J = 286.7 Hz), 90.9 (q, J = 32.4 Hz), 90.8 (q, J = 32.4 Hz), 73.09, 73.06, 59.34, 59.28, 42.3, 40.3, 39.7, 29.1, 27.3, 26.4; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta:\) -78.2; IR (neat, cm\(^{-1}\)) \(\nu:\) 3391, 2930, 1720, 1469, 1191; LRMS (ESI): \(m/z\) 372 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{15}\)H\(_{18}\)F\(_3\)NO\(_5\)Na [M+Na]\(^+\) 372.1029, Found 372.1021.

N-benzyl-3-((5-(methoxymethoxy)-3-methylpentyl)oxy)-3-trifluoromethyl-isoindolinone (S4n)

colorless liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:\) 7.89 (d, 1H + 1H, J = 6.9 Hz), 7.59-7.71 (m, 3H + 3H), 7.53-7.57 (m, 2H + 2H), 7.33-7.43 (m, 3H + 3H), 5.29-5.33 (m, 1H + 1H), 5.11-5.15 (m, 1H + 1H), 4.56 (s, 2H), 4.55 (s, 2H), 3.42-3.53 (m, 2H + 2H), 3.32 (s, 3H), 3.31 (s, 3H), 3.27-3.35 (m, 1H + 1H), 2.94-3.02 (m, 1H + 1H), 1.47-1.76 (m, 3H + 3H), 1.28-1.42 (m, 2H + 2H), 0.77-0.80 (m, 3H + 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta:\) 165.6, 165.5, 135.3, 135.2, 134.58, 134.56, 133.44, 133.42, 131.6, 130.03, 130.01, 129.33, 129.30, 128.79, 128.77, 128.40, 128.38, 124.2, 124.1, 122.2 (q, J = 285.1 Hz), 122.1 (q, J = 286.7 Hz), 96.3, 90.9 (q, J = 32.8 Hz), 90.8 (q, J = 33.2 Hz), 79.1, 65.6, 65.5, 62.2, 55.0, 36.6, 36.4, 35.9, 35.8, 26.71, 26.68, 19.3, 19.2; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta:\) -78.08, -78.14; IR (neat, cm\(^{-1}\)) \(\nu:\) 2931, 1745, 1468, 1294, 1189; LRMS (ESI): \(m/z\) 490 [M+Na]\(^+\); HRMS (ESI): \(m/z\) calcd for C\(_{24}\)H\(_{28}\)F\(_3\)NO\(_5\)Na [M+Na]\(^+\) 490.1812, Found 490.1799.

N-hydroxy-3-((5-(methoxymethoxy)-3-methylpentyl)oxy)-3-trifluoromethyl-isoindolinone (1n)
N-hydroxy-3-((3-hydroxy-5-(methoxymethoxy)-3-methylpentyl)oxy)-3-trifluoromethyl-isoyindoline (2n)

Starting material 1n (37.7 mg, 0.1 mmol) was oxygenated under condition B of section 2, and 2n (25.1 mg, 0.064 mmol) was obtained as a diastereomixture according to the purification procedure described in the General method (64% yield).

colorless liquid (diastereomixture); $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.43 (brs, 1H + 1H), 7.85-7.90 (m, 1H + 1H), 7.56-7.73 (m, 3H + 3H), 4.61 (s, 2H), 4.58-4.60 (m, 2H), 4.44 (brs, 1H), 4.06 (brs, 1H), 3.66-3.87 (m, 2H + 2H), 3.43-3.60 (m, 1H + 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.24-3.40 (m, 1H + 1H), 1.56-2.13 (m, 4H + 4H), 1.46 (s, 3H), 1.19 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 164.0, 163.8, 134.4, 134.2, 132.8, 132.7, 131.6, 131.5, 130.8, 130.7, 124.12, 124.08, 124.0, 122.0 (q, $J = 286.6$ Hz), 121.9 (q, $J = 286.6$ Hz), 96.49, 96.47, 90.8 (q, $J = 286.6$ Hz), 90.6 (q, $J = 286.6$ Hz), 72.5, 72.4, 64.4, 60.2, 60.1, 55.7, 55.6, 41.1, 40.5, 39.8, 39.4, 27.4, 26.5; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.1, –78.2; IR (neat, cm$^{-1}$) ν: 3423, 2937, 1721, 1469, 1191; LRMS (ESI): m/z 416 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{17}$H$_{22}$F$_3$NO$_6$Na [M+Na]$^+$ 416.1291, Found 416.1301.

N-(4-methoxybenzyl)oxy-3-((3-methyl-5-(pent-4-yn-1-yl)oxy)pentyl)oxy)-3-trifluoromethyl-isoyindoline (S4'o)

colorless liquid (diastereomixture); $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.88 (d, 1H + 1H, $J = 7.4$ Hz), 7.58-7.70 (m, 3H + 3H), 7.45-7.50 (m, 2H + 2H), 6.91 (d, 2H + 2H, $J = 8.6$ Hz), 5.24 (d, 1H + 1H, $J = 9.7$ Hz), 5.03-5.08 (m, 1H + 1H), 3.81 (s, 3H + 3H), 3.26-3.46 (m, 5H + 5H), 2.93-3.01 (m, 1H + 1H),
2.21-2.26 (m, 2H + 2H), 1.93 (t, 1H + 1H, J = 2.6 Hz), 1.69-1.77 (m, 2H + 2H), 1.44-1.69 (m, 3H + 3H),
1.26-1.42 (m, 2H + 2H), 0.78 (d, 3H, J = 6.9 Hz), 0.76 (d, 3H, J = 6.9 Hz); 13C NMR (126 MHz, CDCl3) δ:
165.5, 165.4, 160.1, 135.30, 133.37, 133.35, 131.6, 131.12, 131.10, 130.1, 126.8, 124.2, 124.11,
124.07, 122.2 (q, J = 286.3 Hz), 113.8, 90.9 (q, J = 32.8 Hz), 90.8 (q, J = 32.8 Hz), 83.92, 83.91, 78.8, 69.0,
68.9, 68.8, 68.7, 68.35, 68.33, 62.29, 62.27, 55.2, 36.5, 36.3, 36.0, 35.9, 28.5, 26.83, 26.80, 19.4, 19.3,
15.1; 19F NMR (369 MHz, CDCl3) δ: –78.07, –78.13; IR (neat, cm⁻¹) ν: 3301, 2953, 2870, 1743, 1613,
1516, 1468, 1253, 1188, 1113; LRMS (ESI): m/z 542 [M+Na]⁺; HRMS (ESI): m/z calcd for C28H32F3NO5Na
[M+Na]⁺ 542.2125, Found 542.2121.

N-hydroxy-3-((3-methyl-5-(pent-4-yn-1-yloxy)pentyl)oxy)-3-trifluoromethyl-isoindolinone (1o)

yellow liquid (diastereomixture); ¹H NMR (500 MHz, CDCl3) δ: 9.46 (brs, 1H + 1H), 7.80-7.86 (m, 1H +
1H), 7.63-7.67 (m, 1H + 1H), 7.57-7.63 (m, 2H + 2H), 3.31-3.63 (m, 5H + 5H), 3.11-3.18 (m, 1H),
3.04-3.11 (m, 1H), 2.23-2.32 (m, 2H + 2H), 1.91-1.95 (m, 1H + 1H), 1.56-1.95 (m, 5H + 5H), 1.37-1.49 (m,
1H + 1H), 1.27-1.36 (m, 1H), 1.14-1.24 (m, 1H), 0.87 (d, 3H + 3H, J = 6.3 Hz); ¹³C NMR (126 MHz,
CDCl3) δ: 165.6, 165.4, 135.0, 134.9, 134.9, 133.1, 133.0, 131.47, 131.45, 131.0, 130.3, 130.1, 124.2, 124.1,
124.0, 123.9, 121.88 (q, J = 286.7 Hz), 121.85 (q, J = 286.7 Hz), 91.1 (q, J = 32.8 Hz), 91.0 (q, J = 33.6 Hz),
83.82, 83.75, 69.5, 69.2, 68.9, 68.6, 68.52, 68.46, 63.0, 61.7, 36.2, 36.1, 36.0, 35.4, 28.3, 28.0, 27.4, 25.4,
19.8, 19.7, 15.1, 15.0; ¹⁹F NMR (369 MHz, CDCl3) δ: –77.6, –78.0; IR (neat, cm⁻¹) ν: 3302, 2932, 2874,
1718, 1469, 1303, 1198; LRMS (ESI): m/z 422 [M+Na]⁺; HRMS (ESI): m/z calcd for C20H24F3NO4Na
[M+Na]⁺ 422.1550, Found 422.1564.

N-hydroxy-3-((3-hydroxy-3-methyl-5-(pent-4-yn-1-yloxy)pentyl)oxy)-3-trifluoromethyl-isoindolinon
e (2o)

Starting material 1o (32.0 mg, 0.08 mmol) was oxygenated under condition B of section 2, and 2o (13.7
mg, 0.033 mmol) was obtained as a diastereomixture according to the purification procedure described in
the General method (41% yield).

colorless liquid (diastereomixture); ¹H NMR (500 MHz, CDCl3) δ: 9.46 (s, 1H), 9.39 (s, 1H), 7.86-7.92 (m,
1H + 1H), 7.57-7.67 (m, 3H + 3H), 4.65 (s, 1H), 4.31 (s, 1H), 3.25-3.76 (m, 6H + 6H), 2.22-2.29 (m, 2H +
2H), 2.02-2.13 (m, 1H), 1.96 (t, 1H, J = 2.3 Hz), 1.86-1.96 (m, 1H + 1H), 1.67-1.82 (m, 3H + 4H),
1.55-1.65 (m, 1H + 1H), 1.47 (s, 3H), 1.17 (s, 3H); ¹³C NMR (126 MHz, CDCl3) δ: 163.7, 163.6, 134.3,
134.2, 132.7, 132.6, 131.54, 131.47, 130.9, 130.8, 124.11, 124.07, 124.0, 123.9, 122.0 (q, J = 286.6 Hz),
121.9 (q, J = 286.6 Hz), 90.5 (q, J = 32.9 Hz), 83.4, 83.2, 72.8, 72.5, 70.0, 69.9, 69.0, 68.8, 67.9, 67.8, 60.1,
60.0, 41.2, 40.4, 39.8, 39.2, 28.1, 28.0, 27.6, 26.2, 15.21, 15.18; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.1; IR (neat, cm\(^{-1}\)) \(\nu\): 3404, 3304, 2936, 2118, 1723, 1469, 1377, 1303, 1198; LRMS (ESI): \(m/z\) 438 [M+Na]+;
HRMS (ESI): \(m/z\) calcd for C\(_{20}\)H\(_{24}\)F\(_3\)NO\(_5\)Na [M+Na]+ 438.1499, Found 438.1499.

\(N\)-hydroxy-3-((3-hydroxy-3-methyl-7-en-1-yl)oxy)-3-trifluoromethyl-isooindolinone (2p)

Starting material 1p (14.3 mg, 0.04 mmol) was oxygenated under condition B of section 2, and 2p (2.8 mg, 0.0075 mmol) was obtained as a diastereomixture according to the purification procedure described in the General method (19% yield).

colorless liquid (diastereomixture); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 9.49 (brs, 1H), 9.43 (brs, 1H), 7.83-7.92 (m, 1H + 1H), 7.58-7.70 (m, 3H + 3H), 5.70-5.87 (m, 1H + 1H), 4.90-5.04 (m, 2H + 2H), 3.50-3.58 (m, 1H + 1H), 3.25-3.33 (m, 1H + 1H), 1.86-2.10 (m, 3H + 3H), 1.58-1.72 (m, 2H + 2H), 1.35-1.55 (m, 3H + 3H), 1.36 (s, 3H), 1.19 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 164.6, 138.6, 138.4, 134.4, 134.3, 133.0, 131.64, 131.63, 130.4, 124.20, 124.18, 124.1, 121.9 (q, \(J = 286.1\) Hz), 114.8, 114.7, 90.89 (q, \(J = 33.4\) Hz), 90.86 (q, \(J = 33.4\) Hz), 72.8, 72.7, 60.6, 60.5, 42.6, 42.3, 39.3, 39.1, 33.9, 27.3, 26.8, 23.4, 23.2; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.2; IR (neat, cm\(^{-1}\)) \(\nu\): 3377, 2937, 1719, 1469, 1303, 1190; LRMS (ESI): \(m/z\) 396 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{18}\)H\(_{22}\)F\(_3\)NO\(_4\)Na [M+Na]+ 396.1393, Found 396.1388.

\(N\)-benzylxoxy-3-((3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl)oxy)-3-trifluoromethyl-isooindolinone (S4q)

colorless liquid (diastereomixture); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.89 (d, 1H + 1H, \(J = 7.2\) Hz), 7.57-7.72 (m, 2H + 2H), 7.55 (d, 1H + 1H, \(J = 6.7\) Hz), 5.25-5.33 (m, 1H + 1H), 5.13 (d, 1H, \(J = 9.4\) Hz), 3.23-3.35 (m, 1H + 1H), 2.91-3.01 (m, 1H + 1H), 1.42-1.65 (m, 2H + 2H), 1.22-1.41 (m, 4H + 4H), 1.23 (s, 12H + 12H), 1.10-1.22 (m, 4H + 4H), 0.91-1.08 (m, 1H + 1H), 0.69-0.78 (m, 5H + 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 165.6, 165.5, 135.32, 135.27, 134.6, 133.4, 131.6, 130.05, 130.03, 129.30, 129.27, 128.77, 128.76, 128.40, 128.38, 124.2, 124.1, 122.2 (q, \(J = 285.6\) Hz), 91.0 (q, \(J = 32.9\) Hz), 90.9 (q, \(J = 32.9\) Hz), 82.8, 79.10, 79.07, 62.48, 62.46, 53.4, 36.8, 36.5, 36.0, 35.9, 32.56, 32.55, 29.47, 29.46, 26.53, 26.51, 24.7, 23.9, 19.4, 19.2; \(^{11}\)B NMR (126 MHz, CDCl\(_3\)) \(\delta\): 36.1; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.0, –78.1; IR (neat, cm\(^{-1}\)) \(\nu\): 2927, 1747, 1468, 1378, 1195; LRMS (ESI): \(m/z\) 598 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{31}\)H\(_{41}\)BF\(_3\)NO\(_5\)Na [M+Na]+ 598.2922, Found 598.2937.

\(N\)-hydroxy-3-((3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl)oxy)-3-trifluoromethyl-isooindolinone (1q)

S39
colorless liquid (diastereomixture); $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.70 (s, 1H), 9.69 (s, 1H), 7.75-7.82 (m, 1H + 1H), 7.55-7.68 (m, 3H + 3H), 3.39-3.50 (m, 1H + 1H), 2.91-3.03 (m, 1H + 1H), 1.47-1.69 (m, 2H + 2H), 1.33-1.47 (m, 3H + 3H), 1.17-1.30 (m, 5H + 5H), 1.23 (s, 12H + 12H), 1.05-1.10 (m, 1H + 1H), 0.70-0.83 (m, 5H + 5H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.8, 135.33, 135.32, 133.2, 131.4, 130.04, 130.01, 123.94, 123.85, 121.9 (q, $J = 285.6$ Hz), 90.92 (q, $J = 32.6$ Hz), 90.91 (q, $J = 32.6$ Hz), 82.93, 82.90, 62.7, 62.6, 36.51, 36.47, 36.1, 36.0, 32.5, 32.3, 29.6, 29.3, 26.5, 26.4, 24.72, 24.69, 23.9, 23.7, 19.5, 19.3; $^{11}$B NMR (126 MHz, CDCl$_3$) δ: 36.3; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.5; IR (neat, cm$^{-1}$) ν: 3423, 2927, 1720, 1469, 1378, 1315, 1200; LRMS (ESI): m/z 508 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{24}$H$_{35}$BF$_3$NO$_5$Na [M+Na]$^+$ 508.2453, Found 508.2443.

$N$-hydroxy-3-((3-hydroxy-3-methyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octyl)oxy)-3-trifluoromethyl-isoindolinone (2q)

Starting material 1q (38.8 mg, 0.08 mmol) was oxygenated under condition B of section 2, and 2q (18.2 mg, 0.036 mmol) was obtained as a diastereomixture according to the purification procedure described in the General method (45% yield).

colorless liquid (diastereomixture); $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.45 (brs, 1H), 9.40 (brs, 1H), 7.84-7.90 (m, 1H + 1H), 7.58-7.69 (m, 3H + 3H), 3.46-3.57 (m, 1H + 1H), 3.23-3.33 (m, 1H + 1H), 3.03 (brs, 1H), 2.94 (brs, 1H), 1.84-2.02 (m, 2H + 2H), 1.56-1.70 (m, 2H + 2H), 1.22-1.52 (m, 6H + 6H), 1.22 (s, 3H), 1.24 (s, 12H), 1.16 (s, 3H), 0.71-0.80 (m, 2H + 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 164.53, 164.48, 134.43, 134.41, 132.9, 131.6, 130.5, 124.2, 124.1, 124.0, 121.90 (q, $J = 286.7$ Hz), 121.86 (q, $J = 286.7$ Hz), 90.9 (q, $J = 32.4$ Hz), 90.8 (q, $J = 33.6$ Hz), 82.92, 82.90, 72.9, 72.7, 60.62, 60.59, 43.0, 42.8, 39.3, 39.2, 32.64, 32.59, 29.2, 27.3, 26.7, 24.8, 24.7, 23.8, 23.72, 23.70, 23.5; $^{11}$B NMR (126 MHz, CDCl$_3$) δ: 35.8; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.1; IR (neat, cm$^{-1}$) ν: 3423, 2927, 1723, 1469, 1374, 1315, 1199; LRMS (ESI): m/z 524 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{24}$H$_{35}$BF$_3$NO$_6$Na [M+Na]$^+$ 524.2402, Found 524.2407.

2-((2R)-1-((N-(benzyloxy)-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-3-methylbutan-2-yl)isoindoline-1,3-dione (S4r)
2-((2R)-1-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-3-methylbutan-2-yl)isoindoline-1,3-dione (1r)

white solid (diastereomixture); $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.04 (brs, 1H), 8.09 (brs, 1H), 7.82-7.89 (m, 3H + 3H), 7.72-7.79 (m, 2H + 2H), 7.57-7.72 (m, 2H + 2H), 7.52-7.57 (m, 1H), 7.30 (d, 1H, $J = 7.5$ Hz), 4.14-4.25 (m, 1H + 1H), 4.08 (dd, 1H, $J = 9.4$ Hz, 9.4 Hz), 3.73-3.77 (m, 1H + 1H), 3.35-3.39 (m, 1H), 2.16-2.33 (m, 1H + 1H), 0.80-0.95 (m, 6H + 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 169.2, 168.7, 165.4, 165.0, 134.4, 134.14, 134.07, 133.3, 133.2, 131.8, 131.7, 131.5, 130.0, 129.9, 124.2, 124.1, 124.0, 123.29, 123.26, 121.5 (q, $J = 286.3$ Hz), 90.8 (q, $J = 33.0$ Hz), 90.7 (q, $J = 33.6$ Hz), 62.3, 61.9, 57.1, 57.0, 28.0, 27.7, 20.0, 19.9, 19.7; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.3, −78.4; IR (KBr, cm$^{-1}$) ν: 3219, 2968, 1713, 1469, 1390, 1200; LRMS (ESI): $m/z$ 471 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{22}$H$_{12}$F$_3$N$_2$O$_5$Na [M+Na]$^+$ 471.1138, Found 471.1120.

2-((2S)-3-hydroxy-1-((N-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)-3-methylbutan-2-yl)isoindoline-1,3-dione (2r)
Starting material 1r (89.7 mg, 0.2 mmol) was oxygenated under condition B of section 2, and 2r (37.5 mg, 0.081 mmol) was obtained as a diastereomixture according to the purification procedure described in the General method (40% yield).

White solid (diastereomixture); \( ^1\)H NMR (500 MHz, CDCl\(_3\)); underlined chemical shifts for one isomer) \( \delta: 9.05\) (brs, 1H), 9.05 (brs, 1H), 7.90-7.95 (m, 2H), 7.83-7.88 (m, 1H), 7.83-7.88 (m, 3H), 7.76-7.80 (m, 2H), 7.61-7.69 (m, 3H), 7.52-7.61 (m, 2H), 7.37 (d, 1H, \( J = 7.5\) Hz), 4.66 (brs, 1H), 4.59 (dd, 1H, \( J = 7.5\) Hz, 7.5 Hz), 4.40 (dd, 1H, \( J = 3.7\) Hz, 8.5 Hz), 4.28 (brs, 1H), 3.94 (dd, 1H, \( J = 7.5\) Hz, 9.5 Hz), 3.91 (dd, 1H, \( J = 8.5\) Hz, 10.7 Hz), 3.85 (dd, 1H, \( J = 3.7\) Hz, 10.7 Hz), 3.45 (dd, 1H, \( J = 7.5\) Hz, 9.5 Hz), 1.55 (s, 3H), 1.25 (s, 3H), 1.18 (s, 3H), 1.16 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)); \( \delta: 164.6, 164.0, 134.8, 134.5, 134.2, 133.7, 133.2, 133.0, 131.9, 131.8, 131.5, 131.2, 130.1, 124.4, 121.5 (q, \( J = 287.1\) Hz), 121.5 (q, \( J = 286.7\) Hz), 90.8 (q, \( J = 33.6\) Hz), 90.7 (q, \( J = 33.2\) Hz), 72.0, 71.5, 60.8, 60.4, 59.6, 58.1, 28.4, 27.98, 27.96, 27.6; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)); \( \delta: -77.8, -78.3\); IR (KBr, cm\(^{-1}\)) \( \nu: 3449, 2979, 1704, 1396, 1199\); LRMS (ESI): \( m/z 487 [\text{M+Na}]^+\); HRMS (ESI): \( m/z \) calcd for C\(_{22}\)H\(_{19}\)F\(_3\)N\(_2\)O\(_6\)Na [M+Na]\(^+\) 487.1087, Found 487.1083.

**N-benzyloxy-3-(3-phenylpropoxy)-3-trifluoromethyl-isoindolinone (S4s)**

Light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)); \( \delta: 7.89\) (dd, 1H, \( J = 6.9\) Hz, 1.2 Hz), 7.62-7.68 (m, 2H), 7.56-7.59 (m, 3H), 7.36-7.44 (m, 3H), 7.19-7.25 (m, 2H), 7.09-7.12 (m, 2H), 3.29 (dt, \( J = 9.2\) Hz, 5.8 Hz), 2.96 (dt, \( J = 9.2\) Hz, 5.8 Hz), 2.60-2.71 (m, 2H), 1.78-1.92 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)); \( \delta: 165.6, 141.1, 135.2, 134.6, 133.4, 131.6, 130.0, 129.4, 128.9, 128.5, 128.4, 128.3, 125.9, 124.2, 121.4, 122.2 (q, \( J = 285.5\) Hz), 90.9 (q, \( J = 33.6\) Hz), 79.1, 63.1, 31.8, 30.5; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)); \( \delta: -78.0\); IR (neat, cm\(^{-1}\)) \( \nu: 2950, 1744, 1468, 1190\); LRMS (ESI): \( m/z 464 [\text{M+Na}]^+\); HRMS (ESI): \( m/z \) calcd for C\(_{25}\)H\(_{22}\)F\(_3\)NO\(_3\)Na [M+Na]\(^+\) 464.1444, Found 464.1450.

**N-hydroxy-3-(3-phenylpropoxy)-3-trifluoromethyl-isoindolinone (1s)**

Light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)); \( \delta: 10.12\) (brs, 1H), 7.80 (d, 1H, \( J = 7.5\) Hz), 7.67 (dd, 1H, \( J = 7.5\) Hz, 7.5 Hz), 7.59-7.63 (m, 2H), 7.30 (dd, 2H, \( J = 7.5\) Hz, 7.5 Hz), 7.19-7.23 (m, 3H), 3.35 (dt, 1H, \( J = 7.5\) Hz, 7.5 Hz).
= 8.6 Hz, 5.8 Hz), 2.95-3.05 (m, 1H), 2.67-2.77 (m, 2H), 1.90-1.98 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.9, 141.3, 135.0, 133.2, 131.5, 129.8, 128.4, 128.3, 125.8, 124.0, 123.8, 121.9 (q, $J = 285.5$ Hz), 91.0 (q, $J = 33.6$ Hz), 63.4, 31.3, 30.5; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.3; IR (neat, cm$^{-1}$) ν: 3144, 2948, 1717, 1469, 1305, 1200; LRMS (ESI): m/z 374 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{18}$H$_{16}$F$_3$NO$_3$Na [M+Na]$^+$ 374.0975, Found 374.0990.

$N$-hydroxy-3-(3-oxo-3-phenylpropoxy)-3-trifluoromethyl-isooindolinone (2s)

Starting material 1s (35.1 mg, 0.1 mmol) was oxygenated under condition B of section 2, and 2s (32.4 mg, 0.089 mmol) was isolated according to the purification procedure described in the General method (89% yield).

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.91 (brs, 1H), 7.98 (d, 2H, $J = 7.5$ Hz), 7.89 (d, 1H, $J = 8.0$ Hz), 7.66-7.70 (m, 1H), 7.59-7.66 (m, 3H), 7.49 (dd, 2H, $J = 7.5$ Hz), 3.77 (dt, 1H, $J = 3.1$ Hz, 9.6 Hz), 3.54 (dd, 1H, $J = 18.3$ Hz, 9.6 Hz, 3.1 Hz), 3.43 (dt, 1H, $J = 9.6$ Hz, 3.1 Hz), 3.16 (dt, 1H, $J = 18.3$ Hz, 3.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 198.8, 163.6, 135.9, 134.1, 133.9, 132.9, 131.7, 130.6, 128.8, 128.3, 124.2, 124.1, 121.8 (q, $J = 286.6$ Hz), 90.5 (q, $J = 32.9$ Hz), 57.9, 37.2, 29.2; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.1; IR (neat, cm$^{-1}$) ν: 3220, 2952, 1718, 1197; LRMS (ESI): m/z 388 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{18}$H$_{14}$F$_3$NO$_4$Na [M+Na]$^+$ 388.0767, Found 388.0759.

4-(3-((2-benzyloxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)propyl)phenyl acetate (S4t)

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.88 (d, 1H, $J = 7.4$ Hz), 7.60-7.70 (m, 2H), 7.54-7.58 (m, 3H), 7.34-7.44 (m, 3H), 7.09 (d, 2H, $J = 8.6$ Hz), 6.92 (d, 2H, $J = 8.6$ Hz), 5.32 (d, 1H, $J = 9.7$ Hz), 5.14 (d, 1H, $J = 9.7$ Hz), 3.27 (dt, 1H, $J = 8.6$ Hz, 6.3 Hz), 2.92-2.98 (m, 1H), 2.64 (t, 2H, $J = 7.7$ Hz), 2.28 (s, 3H), 1.76-1.89 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 169.5, 165.6, 148.8, 138.6, 135.1, 134.6, 133.5, 131.7, 129.9, 129.4, 128.9, 128.8, 128.4, 124.2, 124.1, 122.2 (q, $J = 285.5$ Hz), 121.3, 90.9 (q, $J = 33.2$ Hz), 79.1, 63.0, 31.1, 30.3, 21.0; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 2949, 1747, 1194; LRMS (ESI): m/z 522 [M+Na]$^+$; HRMS (ESI): m/z calcd for C$_{27}$H$_{24}$F$_3$NO$_5$Na [M+Na]$^+$ 522.1499, Found 522.1492.

4-(3-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)propyl)phenyl acetate (1t)
reddish sticky liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.78 (brs, 1H), 7.77 (d, 1H, $J = 7.4$ Hz), 7.62-7.66 (m, 1H), 7.53-7.60 (m, 2H), 7.17 (d, 2H, $J = 8.6$ Hz), 6.98 (d, 2H, $J = 8.6$ Hz), 3.40-3.46 (m, 1H), 2.97-3.05 (m, 1H), 2.68-2.78 (m, 2H), 2.28 (s, 3H), 1.85-2.01 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 169.7, 165.8, 148.8, 138.9, 135.0, 133.3, 131.5, 129.9, 129.3, 124.0, 123.9, 121.9 (q, $J = 286.7$ Hz), 121.3, 91.0 (q, $J = 32.8$ Hz), 63.2, 31.2, 30.4, 21.0; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: $-$78.4; IR (neat, cm$^{-1}$) $\nu$: 3425, 1719, 1645, 1196; LRMS (ESI): $m/z$ 432 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{18}$F$_3$NO$_5$Na [M+Na]$^+$ 432.1029, Found 432.1011.

$^4$-(3-((2-hydroxy-3-oxo-1-(trifluoromethyl)isoindolin-1-yl)oxy)propanoyl)phenyl acetate (2t)

Starting material 1t (53.8 mg, 0.13 mmol) was oxygenated under condition A of section 2, and 2t (30.0 mg, 0.071 mmol) was isolated according to the purification procedure described in the General method (54% yield).

white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.97 (brs, 1H), 8.00 (dd, 2H, $J = 8.6$ Hz, 1.1 Hz), 7.86 (d, 1H, $J = 8.0$ Hz), 7.60-7.69 (m, 3H), 7.21 (dd, 2H, $J = 8.6$ Hz, 1.1 Hz), 3.72-3.78 (m, 1H), 3.42-3.51 (m, 2H), 3.13-3.22 (m, 1H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 197.5, 168.7, 163.9, 134.7, 134.1, 133.6, 130.0, 121.7 (q, $J = 286.6$ Hz), 90.5 (q, $J = 33.2$ Hz), 62.9, 32.5, 28.3, 21.1; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: $-$78.1; IR (neat, cm$^{-1}$) $\nu$: 3243, 1719, 1195; LRMS (ESI): $m/z$ 446 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{20}$H$_{16}$F$_3$NO$_6$Na [M+Na]$^+$ 446.0822, Found 446.0825.

$N$-benzyloxy-3-(3-(4-methoxyphenyl)propoxy)-3-trifluoromethyl-isoindolinone (S4u)

colorless liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.89 (dd, 1H, $J = 6.3$ Hz, 1.1 Hz), 7.60-7.69 (m, 2H), 7.55-7.60 (m, 3H), 7.35-7.44 (m, 3H), 7.00-7.04 (m, 2H), 6.72-6.67 (m, 2H), 5.31 (d, 1H, $J = 9.7$ Hz), 5.13 (d, 1H, $J = 9.7$ Hz), 3.75 (s, 3H), 3.25-3.32 (m, 1H), 2.92-2.99 (m, 1H), 2.53-2.65 (m, 2H), 1.76-1.89 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.5, 157.8, 135.2, 134.6, 133.4, 133.1, 131.6, 130.0, 129.4, 129.2, 128.8, 128.4, 124.2, 124.1, 122.2 (q, $J = 285.9$ Hz), 113.7, 90.9 (q, $J = 32.8$ Hz), 79.1, 63.0, 55.1, 30.8, 30.7; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: $-$78.0; IR (neat, cm$^{-1}$) $\nu$: 2952, 1745, 1613, 1513, 1468, 1188; LRMS
(ESI): \( m/z \) 494 [M+Na]+; HRMS (ESI): \( m/z \) calcd for C\(_{26}H_{24}F_3NO_4Na\) [M+Na]+ 494.1550, Found 494.1547.

**N-hydroxy-3-(3-(4-methoxyphenyl)propoxy)-3-trifluoromethyl-isoindolinone (1u)**

![Structure of 1u](image1)

colorless liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 9.70 (brs, 1H), 7.74-7.79 (m, 1H), 7.55-7.67 (m, 3H), 7.05-7.12 (m, 2H), 6.78-6.85 (m, 2H), 3.78 (s, 3H), 3.40-3.47 (m, 1H), 2.97-3.05 (m, 1H), 2.60-2.74 (m, 2H), 1.83-2.01 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 165.8, 157.8, 135.1, 133.4, 133.2, 131.5, 129.9, 129.3, 124.1, 123.9, 121.9 (\( J = 286.7 \) Hz), 113.8, 91.0 (\( J = 32.8 \) Hz), 63.4, 55.2, 30.9, 30.8; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.4; IR (neat, cm\(^{-1}\)) \( \nu \): 3422, 3173, 2951, 1717, 1613, 1513, 1301, 1191; LRMS (ESI): \( m/z \) 404 [M+Na]+; HRMS (ESI): \( m/z \) calcd for C\(_{19}H_{18}F_3NO_4Na\) [M+Na]+ 404.1080, Found 404.1074.

**N-hydroxy-3-(3-(4-methoxyphenyl)-3-oxopropoxy)-3-trifluoromethyl-isoindolinone (2u)**

Starting material 1u (38.1 mg, 0.1 mmol) was oxygenated under condition B of section 2, and 2u (27.7 mg, 0.070 mmol) was isolated according to the purification procedure described in the General method (70% yield).

light yellow solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 9.03 (brs, 1H), 7.95 (d, 2H, \( J = 8.8 \) Hz), 7.90 (d, 1H, \( J = 6.9 \) Hz), 7.61-7.69 (m, 3H), 6.94 (d, 2H, \( J = 8.8 \) Hz), 3.87 (s, 3H), 3.74 (td, 1H, \( J = 9.7 \) Hz, 2.3 Hz), 3.43-3.52 (m, 1H), 3.37-3.43 (m, 1H), 3.04-3.11 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 197.3, 164.4, 163.8, 134.0, 132.8, 131.7, 130.8, 129.0, 128.4, 124.2, 124.0, 121.8 (\( q, J = 287.1 \) Hz), 114.0, 90.5 (\( q, J = 33.2 \) Hz), 57.8, 55.5, 36.7; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.1; IR (KBr, cm\(^{-1}\)) \( \nu \): 3152, 2967, 1739, 1659, 1600, 1184; LRMS (ESI): \( m/z \) 418 [M+Na]+; HRMS (ESI): \( m/z \) calcd for C\(_{19}H_{16}F_3NO_5Na\) [M+Na]+ 418.0873, Found 418.0874.

**3-(3-(4-bromophenyl)propoxy)-N-((4-methoxybenzyl)oxy)-3-trifluoromethyl-isoindolinone (S4'v)**

![Structure of S4'v](image2)

colorless liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 7.85-7.90 (m, 1H), 7.60-7.70 (m, 2H), 7.56 (d, 1H, \( J = 7.2 \) Hz, 4H), 7.41-7.45 (m, 2H), 7.30-7.35 (m, 3H), 6.92-6.99 (m, 2H), 3.77 (s, 3H), 3.35-3.40 (m, 1H), 3.00-3.05 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 165.8, 157.8, 135.1, 133.4, 133.2, 131.5, 129.8, 129.1, 124.1, 123.8, 121.8 (\( q, J = 286.7 \) Hz), 113.8, 90.5 (\( q, J = 32.8 \) Hz), 63.4, 55.2, 30.9, 30.8; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.4; IR (neat, cm\(^{-1}\)) \( \nu \): 3422, 3173, 2951, 1717, 1613, 1513, 1301, 1191; LRMS (ESI): \( m/z \) 404 [M+Na]+; HRMS (ESI): \( m/z \) calcd for C\(_{19}H_{18}F_3NO_4Na\) [M+Na]+ 404.1080, Found 404.1074.
Hz), 7.47-7.52 (m, 2H), 7.25-7.30 (m, 2H), 6.92-6.97 (m, 4H), 5.26 (d, 1H, \( J = 9.2 \) Hz), 5.04 (d, 1H, \( J = 9.2 \) Hz), 3.82 (s, 3H), 3.20-3.28 (m, 1H), 2.87-2.95 (m, 1H), 2.52-2.66 (m, 2H), 1.75-1.84 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 165.5, 160.1, 140.0, 135.1, 133.4, 131.7, 131.28, 131.25, 130.2, 130.0, 126.7, 124.11, 124.05, 122.2 (q, \( J = 285.6 \) Hz), 119.6, 113.8, 90.7 (q, \( J = 32.9 \) Hz), 78.8, 62.7, 55.2, 31.1, 30.2; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.1; IR (neat, cm\(^{-1}\)) \( \nu \): 2953, 1742, 1613, 1545, 1253, 1189; LRMS (ESI): \( m/z \) 572 [M+Na]\(^+\); HRMS (ESI): \( m/z \) calcd for C\(_{26}\)H\(_{23}\)BrF\(_3\)NO\(_4\)Na [M+Na]\(^+\) 572.0655, Found 572.0671.

3-(3-(4-bromophenyl)propoxy)-N-hydroxy-3-trifluoromethyl-isoindolinone (1v)

light orange gum; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 9.80 (s, 1H), 7.75 (d, 1H, \( J = 7.2 \) Hz), 7.53-7.68 (m, 3H), 7.37 (d, 2H, \( J = 8.1 \) Hz), 7.05 (d, 2H, \( J = 8.1 \) Hz), 3.37-3.46 (m, 1H), 2.94-3.04 (m, 1H), 2.63-2.76 (m, 2H), 1.83-2.00 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 165.8, 140.3, 135.0, 133.3, 131.6, 131.4, 130.2, 129.8, 124.0, 123.9, 121.9 (q, \( J = 286.6 \) Hz), 119.6, 90.9 (q, \( J = 33.2 \) Hz), 63.2, 31.3, 30.4; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.4; IR (neat, cm\(^{-1}\)) \( \nu \): 3144, 2950, 1717, 1488, 1305, 1200; LRMS (ESI): \( m/z \) 452 [M+Na]\(^+\); HRMS (ESI): \( m/z \) calcd for C\(_{18}\)H\(_{15}\)BrF\(_3\)NO\(_3\)Na [M+Na]\(^+\) 452.0080, Found 452.0098.

3-(3-(4-bromophenyl)-3-oxopropoxy)-N-hydroxy-3-trifluoromethyl-isoindolinone (2v)

Starting material 1v (17.2 mg, 0.04 mmol) was oxygenated under condition B of section 2, and 2v (8.3 mg, 0.019 mmol) was isolated according to the purification procedure described in the General method (47% yield).

light yellow solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 8.48 (brs, 1H), 7.93 (dd, 1H, \( J = 1.1 \) Hz, 6.3 Hz), 7.85 (d, 2H, \( J = 8.0 \) Hz), 7.61-7.70 (m, 5H), 3.72-3.79 (m, 1H), 3.47-3.56 (m, 1H), 3.28-3.43 (m, 1H), 3.04-3.11 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \): 197.7, 164.0, 134.8, 134.0, 133.0, 132.1, 131.7, 130.4, 129.8, 129.4, 124.2, 124.1, 121.7 (q, \( J = 285.9 \) Hz), 90.6 (q, \( J = 32.8 \) Hz), 58.1, 37.3; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \( \delta \): –78.1; IR (KBr, cm\(^{-1}\)) \( \nu \): 3220, 2950, 1720, 1678, 1586, 1469, 1398, 1278, 1120; LRMS (ESI): \( m/z \) 466 [M+Na]\(^+\); HRMS (ESI): \( m/z \) calcd for C\(_{18}\)H\(_{13}\)BrF\(_3\)NO\(_4\)Na [M+Na]\(^+\) 465.9872, Found 465.9855.

N-benzyloxy-3-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)-3-trifluoromethyl-isoindolinone (S4w)
colorless liquid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.89 (dd, 1H, $J = 6.5$ Hz, 1.6 Hz), 7.60-7.71 (m, 4H), 7.54-7.60 (m, 3H), 7.35-7.46 (m, 3H), 7.12 (d, 2H, $J = 8.1$ Hz), 5.31 (d, 1H, $J = 9.9$ Hz), 5.14 (d, 1H, $J = 9.9$ Hz), 3.24-3.33 (m, 1H), 2.92-3.00 (m, 1H), 2.58-2.73 (m, 2H), 1.74-1.95 (m, 2H), 1.35 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.6, 144.5, 135.1, 134.9, 134.6, 133.4, 133.4, 131.6, 130.0, 129.3, 128.8, 128.4, 127.8, 124.2, 124.1, 122.2 (q, $J = 286.1$ Hz), 90.9 (q, $J = 33.0$ Hz), 83.6, 79.1, 63.1, 32.0, 30.3, 24.8; $^{11}$B NMR (126 MHz, CDCl$_3$) δ: 32.8; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 2978, 1746, 1612, 1469, 1362, 1195; LRMS (ESI): $m/z$ 590 [M+Na]$^+$; HRMS (ESI): $m/z$ calecd for C$_{31}$H$_{33}$BF$_3$NO$_5$Na [M+Na]$^+$ 590.2296, Found 590.2293.

$N$-hydroxy-3-(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)-3-trifluoromethyl isoindolinone (1w)

white solid; $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.79 (s, 1H), 7.76 (d, 1H, $J = 6.7$ Hz), 7.73 (d, 2H, $J = 8.1$ Hz), 7.54-7.67 (m, 3H), 7.18 (d, 2H, $J = 8.1$ Hz), 3.40-3.49 (m, 1H), 2.96-3.06 (m, 1H), 2.67-2.82 (m, 2H), 1.85-2.05 (m, 2H), 1.35 (s, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 165.8, 144.8, 135.0, 134.9, 133.2, 131.5, 129.9, 127.9, 124.0, 123.9, 121.9 (q, $J = 286.6$ Hz), 91.0 (q, $J = 33.2$ Hz), 83.7, 63.4, 32.1, 30.4, 24.8; $^{11}$B NMR (126 MHz, CDCl$_3$) δ: 33.3; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.4; IR (KBr, cm$^{-1}$) ν: 3177, 2979, 1719, 1613, 1470, 1362, 1200; LRMS (ESI): $m/z$ 500 [M+Na]$^+$; HRMS (ESI): $m/z$ calecd for C$_{24}$H$_{27}$BF$_3$NO$_5$Na [M+Na]$^+$ 500.1827, Found 500.1802.

$N$-hydroxy-3-(3-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propoxy)-3-trifluoromethyl isoindolinone (2w)

Starting material 1w (19.1 mg, 0.04 mmol) was oxygenated under condition A of section 2, and 2w (4.9 mg, 0.010 mmol) was isolated according to the purification procedure described in the General method.

S47
(25% yield).
light yellow solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 8.60 (s, 1H), 7.89-7.97 (m, 5H), 7.61-7.70 (m, 3H), 3.74-3.80 (m, 1H), 3.53-3.61 (m, 1H), 3.38-3.43 (m, 1H), 3.08-3.16 (m, 1H), 1.36 (s, 12H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 199.1, 163.6, 137.8, 135.0, 133.9, 132.9, 131.7, 130.7, 127.3, 124.3, 124.1, 121.8 (q, \(J = 285.6\) Hz), 90.5 (q, \(J = 33.5\) Hz), 84.3, 57.8, 37.4, 24.8; \(^{11}\)B NMR (126 MHz, CDCl\(_3\)) \(\delta\): 32.9; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.1; IR (neat, cm\(^{-1}\)) v: 3426, 2979, 1722, 1508, 1469, 1360, 1199; LRMS (ESI): \(m/z\) 514 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{24}\)H\(_{25}\)BF\(_3\)NO\(_6\)Na [M+Na\(^+\)] 514.1619, Found 514.1621.

3-(3-(2-iodophenyl)propoxy)-N-((4-methoxybenzyl)oxy)-3-trifluoromethyl-isoindolinone (S4’x)

![Chemical Structure]

yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 7.89-7.76 (d, 1H, \(J = 7.4\) Hz), 7.61-7.71 (m, 3H), 7.48-7.53 (m, 2H), 7.11-7.18 (m, 2H), 6.90-6.94 (m, 2H), 6.82-6.87 (m, 1H), 5.26 (d, 1H, \(J = 9.2\) Hz), 5.06 (d, 1H, \(J = 9.2\) Hz), 3.81 (s, 3H), 3.29-3.36 (m, 1H), 2.96-3.02 (m, 1H), 2.67-2.78 (m, 2H), 1.78-1.87 (m, 2H), \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\): 165.5, 160.1, 143.7, 139.5, 135.2, 133.4, 131.7, 131.2, 130.1, 129.4, 128.2, 127.8, 126.8, 124.24, 124.16, 122.2 (q, \(J = 286.7\) Hz), 113.9, 100.4, 90.9 (q, \(J = 32.8\) Hz), 78.9, 63.1, 55.3, 36.9, 29.3; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.0; IR (neat, cm\(^{-1}\)) v: 1742, 1613, 1515, 1467, 1252, 1187; LRMS (ESI): \(m/z\) 620 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{26}\)H\(_{23}\)F\(_3\)INO\(_4\)Na [M+Na\(^+\)] 620.0516, Found 620.0514.

N-hydroxy-3-(3-(2-iodophenyl)propoxy)-3-trifluoromethyl-isoindolinone (1x)

![Chemical Structure]

light yellow liquid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.81 (brs, 1H), 7.79 (d, 2H, \(J = 7.6\) Hz), 7.56-7.69 (m, 3H), 7.23-7.29 (m, 2H), 6.83-6.91 (m, 1H), 3.45-3.54 (m, 1H), 3.02-3.10 (m, 1H), 2.76-2.90 (m, 2H), 1.87-2.02 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 165.7, 143.8, 139.5, 135.1, 133.3, 131.6, 129.9, 129.6, 128.4, 127.9, 124.1, 124.0, 121.9 (q, \(J = 286.6\) Hz), 100.4, 91.0 (q, \(J = 33.2\) Hz), 63.4, 37.0, 29.3; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta\): –78.4; IR (neat, cm\(^{-1}\)) v: 3143, 2943, 1716, 1468, 1304, 1192; LRMS (ESI): \(m/z\) 500 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{34}\)H\(_{32}\)F\(_3\)INO\(_4\)Na [M+Na\(^+\)] 500.0510, Found 500.0511.

N-hydroxy-3-(3-(2-iodophenyl)-3-oxopropyloxy)-3-trifluoromethyl-isoindolinone (2x)

![Chemical Structure]
Starting material 1x (23.9 mg, 0.05 mmol) was oxygenated under condition B of section 2, and 2x (13.0 mg, 0.026 mmol) was isolated according to the purification procedure described in the General method (53% yield).

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.77 (brs, 1H), 7.96 (d, 1H, $J = 7.7$ Hz), 7.88 (d, 1H, $J = 6.9$ Hz), 7.60-7.70 (m, 3H), 7.50 (dd, 1H, $J = 7.7$ Hz, 1.5 Hz), 7.44 (t, 1H, $J = 7.7$ Hz), 7.16 (td, 1H, $J = 7.7$ Hz, 1.5 Hz), 3.79 (td, 1H, $J = 8.9$ Hz, 4.0 Hz), 3.42-3.51 (m, 1H), 3.31-3.42 (m, 1H), 3.13-3.24 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 202.7, 164.3, 142.8, 141.1, 134.1, 133.1, 132.4, 131.8, 130.4, 128.4, 128.2, 124.2, 121.8 (q, $J = 286.7$ Hz), 91.1, 90.7 (q, $J = 33.6$ Hz), 58.4, 40.6; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 3166, 2926, 1715, 1468, 1192; LRMS (ESI): $m/z$ 514 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{13}$F$_3$INO$_4$Na [M+Na]$^+$ 513.9734, Found 513.9727.

$N$-benzyloxy-3-trifluoromethyl-3-(3-(2-(trimethylsilyl)phenyl)propoxy)-isoindolinone (S4y)

colorless liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.93 (d, 1H, $J = 7.4$ Hz), 7.63-7.74 (m, 3H), 7.57 (d, 2H, $J = 6.9$ Hz), 7.47 (dd, 1H, $J = 7.4$ Hz, 1.4 Hz), 7.35-7.43 (m, 3H), 7.26 (td, 1H, $J = 7.4$ Hz, 1.4 Hz), 7.17 (t, 1H, $J = 7.4$ Hz), 7.13 (d, 1H, $J = 7.4$ Hz), 5.35 (d, 1H, $J = 9.2$ Hz), 5.17 (d, 1H, $J = 9.2$ Hz), 3.37-3.43 (m, 1H), 3.03-3.10 (m, 1H), 2.72-2.85 (m, 2H), 1.77-1.90 (m, 2H), 0.31 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.6, 147.1, 138.1, 135.2, 134.57, 134.56, 133.5, 131.7, 130.1, 129.4, 129.2, 128.8, 128.4, 125.2, 124.2, 122.2 (q, $J = 285.9$ Hz), 90.9 (q, $J = 33.2$ Hz), 79.2, 63.8, 32.5, 31.7, 0.24; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: –78.0; IR (neat, cm$^{-1}$) ν: 1746, 1465, 1188; LRMS (ESI): $m/z$ 536 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{28}$H$_{30}$F$_3$NO$_4$SiNa [M+Na]$^+$ 536.1839, Found 536.1816.

$N$-hydroxy-3-trifluoromethyl-3-(3-(2-(trimethylsilyl)phenyl)propoxy)-isoindolinone (1y)

colorless liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 10.00 (brs, 1H), 7.84 (d, 1H, $J = 7.4$ Hz), 7.60-7.74 (m, 3H), 7.53 (d, 1H, $J = 7.4$ Hz), 7.34 (t, 1H, $J = 7.4$ Hz), 7.19-7.25 (m, 2H), 3.60-3.66 (m, 1H), 3.14-3.21 (m, 1H), 2.86-3.00 (m, 2H), 1.90-2.07 (m, 2H), 0.39 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.9, 147.3, 138.3, 135.2, 134.6, 133.3, 131.5, 130.0, 129.2, 128.5, 125.2, 124.0, 123.9, 121.9 (q, $J = 286.7$ Hz), 91.1 (q,
$J = 32.8 \text{ Hz}$, 64.0, 32.6, 31.6, 0.27; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: -78.4; IR (neat, cm$^{-1}$) $\nu$: 3152, 2953, 1718, 1469, 1200; LRMS (ESI): $m/z$ 446 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{21}$H$_{24}$F$_3$NO$_3$SiNa [M+Na]$^+$ 446.1370, Found 446.1351.

$N$-hydroxy-$3$-($3$-oxo-$3$-(2-(trimethylsilyl)phenyl)propoxy)-3-trifluoromethyl-isooindolinone ($2y$)

Starting material $1y$ (98.0 mg, 0.23 mmol) was oxygenated under condition B of section 2, and $2y$ (62.6 mg, 0.14 mmol) was isolated according to the purification procedure described in the General method (62% yield).

light yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.83 (brs, 1H), 7.88-7.93 (m, 2H), 7.77 (dd, 1H, $J = 7.4$ Hz, 1.1 Hz), 7.60-7.71 (m, 3H), 7.56 (td, 1H, $J = 7.5$ Hz, 1.3 Hz), 7.48 (td, 1H, $J = 7.5$ Hz, 1.3 Hz), 3.79 (td, 1H, $J = 9.4$ Hz, 2.7 Hz), 3.47-3.58 (m, 1H), 3.39-3.47 (m, 1H), 3.16-3.26 (m, 1H), 0.29 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 201.3, 163.4, 142.9, 141.5, 136.3, 133.9, 132.9, 132.5, 131.7, 130.7, 129.5, 128.9, 124.3, 124.1, 121.8 (q, $J = 286.6$ Hz), 90.5 (q, $J = 33.5$ Hz), 57.7, 37.9, 0.23; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: -78.0; IR (KBr, cm$^{-1}$) $\nu$: 3228, 2953, 1719, 1469, 1200; LRMS (ESI): $m/z$ 460 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{21}$H$_{22}$F$_3$NO$_4$SiNa [M+Na]$^+$ 460.1162, Found 460.1180.

3-(3-(4-ethylphenyl)propoxy)-$N$-benzyloxy-3-trifluoromethyl-isooindolinone (S4z)

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.89 (d, 1H, $J = 6.9$ Hz), 7.61-7.68 (m, 2H), 7.55-7.60 (m, 3H), 7.36-7.44 (m, 3H), 7.00-7.06 (m, 4H), 5.30 (d, 1H, $J = 9.5$ Hz), 5.13 (d, 1H, $J = 9.5$ Hz), 3.26-3.32 (m, 1H), 2.94-2.99 (m, 1H), 2.56-2.68 (m, 4H), 1.77-1.92 (m, 2H), 1.21 (t, 3H, $J = 7.7$ Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.6, 141.8, 138.3, 135.2, 134.6, 133.4, 131.6, 130.1, 129.4, 128.8, 128.5, 128.3, 127.8, 124.3, 124.1, 122.2 (q, $J = 285.5$ Hz), 91.0 (q, $J = 32.8$ Hz), 79.1, 63.2, 31.3, 30.5, 28.4, 15.6; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: -78.0; IR (neat, cm$^{-1}$) $\nu$: 2960, 1745, 1468, 1188; LRMS (ESI): $m/z$ 492 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{27}$H$_{26}$F$_3$NO$_4$Na [M+Na]$^+$ 492.1757, Found 492.1767.

3-(3-(4-ethylphenyl)propoxy)-$N$-hydroxy-3-trifluoromethyl-isooindolinone (1z)

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.80 (brs, 1H), 7.75 (d, 1H, $J = 6.9$ Hz), 7.59-7.64 (m, 1H), 7.53-7.58 (m, 2H), 7.05-7.12 (m, 4H), 3.41-3.47 (m, 1H), 2.96-3.04 (m, 1H), 2.63-2.75 (m, 2H), 2.60
(q, 2H, J = 7.7 Hz), 1.85-2.01 (m, 2H), 1.21 (t, 3H, J = 7.7 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 165.8, 141.7, 138.5, 135.1, 133.2, 131.5, 129.9, 128.3, 127.8, 124.1, 123.9, 121.9 (q, J = 286.7 Hz), 91.0 (q, J = 32.8 Hz), 63.5, 31.4, 30.6, 28.4, 15.6; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.4; IR (neat, cm$^{-1}$) ν: 3421, 2962, 1716, 1643, 1200; LRMS (ESI): m/z 402 [M+Na]$^{+}$; HRMS (ESI): m/z calcd for C$_{20}$H$_{20}$F$_3$NO$_3$Na [M+Na]$^{+}$ 402.1288, Found 402.1273.

3-(3-(4-ethylphenyl)-3-oxopropoxy)-N-hydroxy-3-trifluoromethyl-isoindolinone (2z)

Starting material 1z (15.2 mg, 0.04 mmol) was oxygenated under condition B of section 2, and 2z (8.6 mg, 0.022 mmol) was isolated according to the purification procedure described in the General method (55% yield).

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.82 (brs, 1H), 7.89-7.94 (m, 3H), 7.61-7.70 (m, 3H), 7.31 (d, 2H, J = 8.0 Hz), 3.73-3.80 (m, 1H), 3.50-3.58 (m, 1H), 3.37-3.43 (m, 1H), 3.05-3.12 (m, 1H), 2.72 (q, 2H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.5 Hz); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 198.6, 163.2, 151.5, 133.9, 133.7, 132.8, 131.7, 130.9, 128.7, 128.3, 124.3, 124.0, 121.8 (q, J = 286.7 Hz), 90.4 (q, J = 33.4 Hz), 57.6, 37.0, 29.0, 15.1; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.1; IR (neat, cm$^{-1}$) ν: 3433, 1644, 1190; LRMS (ESI): m/z 416 [M+Na]$^{+}$; HRMS (ESI): m/z calcd for C$_{20}$H$_{18}$F$_3$NO$_4$Na [M+Na]$^{+}$ 416.1080, Found 416.1088.

N-hydroxy-3-((3-oxooct-4-yn-1-yl)oxy)-3-trifluoromethyl-isoindolinone (2aa)

Starting material 1aa (13.7 mg, 0.04 mmol) was oxygenated under condition A of section 2, and 2aa (6.1 mg, 0.017 mmol) was isolated according to the purification procedure described in the General method (43% yield).

light yellow liquid (unstable); $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.87 (d, 1H, J = 6.7 Hz), 7.56-7.71 (m, 3H), 3.62 (dt, 1H, J = 3.6 Hz, 9.2 Hz), 3.26-3.34 (m, 1H), 2.97-3.08 (m, 1H), 2.79-2.88 (m, 1H), 2.36 (t, 2H, J = 7.0 Hz), 1.55-1.67 (m, 2H), 1.01 (t, 3H, J = 7.4 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 185.7, 164.1, 134.0, 133.1, 131.7, 130.4, 124.2, 121.7 (q, J = 286.7 Hz), 97.2, 90.6 (q, J = 33.2 Hz), 80.8, 57.7, 44.2, 21.1, 20.9, 13.4; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: −78.2; IR (neat, cm$^{-1}$) ν: 3215, 2967, 2213, 1720, 1674, 1470, 1191; LRMS (ESI): m/z 378 [M+Na]$^{+}$; HRMS (ESI): m/z calcd for C$_{17}$H$_{16}$F$_3$NO$_4$Na [M+Na]$^{+}$ 378.0924, Found 378.0929.

3-((6,6-dimethylhept-4-yn-1-yl)oxy)-N-((4-methoxybenzyl)oxy)-3-trifluoromethyl-isoindolinone (S4'ab)
light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.89 (d, 1H, $J = 6.9$ Hz), 7.59-7.71 (m, 3H), 7.49 (d, 2H, $J = 8.6$ Hz), 6.92 (d, 2H, $J = 8.6$ Hz), 5.25 (d, 1H, $J = 9.2$ Hz), 5.08 (d, 1H, $J = 9.2$ Hz), 3.81 (s, 3H), 3.33-3.39 (m, 1H), 3.05-3.12 (m, 1H), 2.15-2.26 (m, 2H), 1.62-1.78 (m, 2H), 1.07 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.4, 160.1, 135.2, 133.4, 131.6, 131.1, 130.2, 126.8, 124.3, 124.1, 122.1 (q, $J = 286.3$ Hz), 113.8, 91.0 (q, $J = 33.2$ Hz), 89.6, 78.9, 76.9, 62.6, 55.2, 31.2, 28.6, 27.1, 15.1; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.0; IR (neat, cm$^{-1}$) $\nu$: 2966, 1746, 1613, 1516, 1468, 1253, 1187; LRMS (ESI): $m/z$ 498 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{26}$H$_{28}$F$_{3}$NO$_{4}$Na [M+Na]$^+$ 498.1863, Found 498.1855.

3-((6,6-dimethylhept-4-yn-1-yl)oxy)-N-hydroxy-3-trifluoromethyl-isooindolinone (1ab)

yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.41 (brs, 1H), 7.82 (d, 1H, $J = 7.4$ Hz), 7.57-7.68 (m, 3H), 3.43-3.49 (m, 1H), 3.12-3.17 (m, 1H), 2.29 (t, 2H, $J = 6.9$ Hz), 1.71-1.84 (m, 2H), 1.10 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.4, 135.0, 133.2, 131.5, 130.0, 124.1, 123.9, 121.9 (q, $J = 285.5$ Hz), 90.9 (q, $J = 33.2$ Hz), 90.0, 77.1, 62.5, 31.2, 28.4, 27.2, 15.1; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.4; IR (neat, cm$^{-1}$) $\nu$: 3423, 2968, 1719, 1470, 1200; LRMS (ESI): $m/z$ 378 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{20}$F$_{3}$NO$_{3}$Na [M+Na]$^+$ 378.1288, Found 378.1280.

3-((6,6-dimethyl-3-oxohept-4-yn-1-yl)oxy)-N-hydroxy-3-trifluoromethyl-isooindolinone (2ab)

Starting material 1ab (18.2 mg, 0.04 mmol) was oxygenated under condition A of section 2, and 2ab (7.6 mg, 0.021 mmol) was isolated according to the purification procedure described in the General method (47% yield).

light yellow liquid (unstable); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 8.69 (brs, 1H), 7.85-7.88 (m, 1H), 7.59-7.69 (m, 3H), 3.62 (dt, 1H, $J = 4.0$ Hz, 9.2 Hz), 3.27-3.32 (m, 1H), 2.97-3.06 (m, 1H), 2.80-2.87 (m, 1H), 1.27 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 185.9, 164.2, 134.1, 133.1, 131.7, 130.4, 124.2, 123.9, 121.7 (q, $J = 286.3$ Hz), 104.3, 90.6 (q, $J = 33.6$ Hz), 79.2, 57.7, 44.2, 29.9, 27.8; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: –78.2; IR (neat, cm$^{-1}$) $\nu$: 3196, 2974, 2211, 1719, 1675, 1470, 1199; LRMS (ESI): $m/z$ 392 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{18}$H$_{18}$F$_{3}$NO$_{4}$Na [M+Na]$^+$ 392.1080, Found 392.1070.

$N$-((4-methoxybenzyl)oxy)-3-((8-methylnon-4-yn-1-yl)oxy)-3-(trifluoromethyl)-isoindolinone (S4'ac)
colorless liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.89 (dd, 1H, $J = 6.5$ Hz, 1.1 Hz), 7.60-7.71 (m, 3H), 7.46-7.52 (m, 2H), 6.90-6.95 (m, 2H), 5.25 (d, 1H, $J = 9.2$ Hz), 5.08 (d, 1H, $J = 9.2$ Hz), 3.82 (s, 3H), 3.34-3.41 (m, 1H), 3.04-3.12 (m, 1H), 2.19-2.26 (m, 2H), 1.96-2.04 (m, 2H), 1.61-1.80 (m, 2H), 1.50-1.60 (m, 1H), 1.24 (q, 2H, $J = 7.2$ Hz), 0.80-0.84 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 165.4, 160.1, 135.1, 133.3, 131.6, 131.1, 130.2, 126.8, 124.3, 124.1, 122.1 (q, $J = 285.9$ Hz), 113.8, 91.0 (q, $J = 32.9$ Hz), 81.0, 78.9, 78.4, 62.5, 55.2, 37.9, 28.5, 27.1, 22.10, 22.08, 16.6, 15.2; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: −78.0; IR (neat, cm$^{-1}$) $\nu$: 2956, 1744, 1613, 1515, 1468, 1253, 1187; LRMS (ESI): $m/z$ 512 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{27}$H$_{30}$F$_3$NO$_4$Na [M+Na]$^+$ 512.2019, Found 512.2003.

*N*-hydroxy-3-((8-methylnon-4-yn-1-yl)oxy)-3-(trifluoromethyl)-isoindolinone (1ac)

light yellow liquid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.30 (brs, 1H), 7.82 (d, 1H, $J = 7.4$ Hz), 7.58-7.68 (m, 3H), 3.44-3.50 (m, 1H), 3.12-3.18 (m, 1H), 2.29-2.35 (m, 2H), 2.04-2.10 (m, 2H), 1.71-1.85 (m, 2H), 1.53-1.63 (m, 1H), 1.29 (q, 2H, $J = 7.5$ Hz), 0.82-0.86 (m, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 165.4, 135.0, 133.1, 130.1, 124.2, 123.9, 121.9 (q, $J = 286.7$ Hz), 90.9 (q, $J = 33.2$ Hz), 81.5, 78.7, 62.5, 37.9, 28.2, 27.2, 22.1, 16.6, 15.2; $^{19}$F NMR (369 MHz, CDCl$_3$) $\delta$: −78.2; IR (neat, cm$^{-1}$) $\nu$: 3159, 2956, 1718, 1469, 1305, 1191; LRMS (ESI): $m/z$ 392 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{19}$H$_{22}$F$_3$NO$_3$Na [M+Na]$^+$ 392.1444, Found 392.1442.

*N*-hydroxy-3-((8-methyl-3-oxonon-4-yn-1-yl)oxy)-3-(trifluoromethyl)-isoindolinone (2ac)

Starting material 1ac (73.9 mg, 0.2 mmol) was oxygenated under condition A of section 2, and 2ac (26.0 mg, 0.068 mmol) was isolated according to the purification procedure described in the General method (34% yield).

eyellow liquid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.77 (brs, 1H), 7.86 (d, 1H, $J = 6.7$ Hz), 7.58-7.69 (m, 3H), 3.62 (td, 1H, $J = 9.0$ Hz, 4.0 Hz), 3.27-3.34 (m, 1H), 2.95-3.05 (m, 1H), 2.84 (td, 1H, $J = 4.7$ Hz, 18.5 Hz), 2.37 (t, 2H, $J = 7.3$ Hz), 1.60-1.73 (m, 1H), 1.47 (q, 2H, $J = 7.3$ Hz), 0.90 (d, 6H, $J = 6.7$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 185.6, 164.3, 134.1, 133.1, 131.7, 130.3, 124.19, 124.16, 121.7 (q, $J = 286.6$ Hz), 154.2; IR (neat, cm$^{-1}$) $\nu$: 3147, 2949, 1717, 1469, 1305, 1191; LRMS (ESI): $m/z$ 392 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{19}$H$_{22}$F$_3$NO$_3$Na [M+Na]$^+$ 392.1444, Found 392.1442.

S53
97.3, 90.6 (q, \(J = 33.5\) Hz), 80.6, 57.8, 44.2, 36.3, 27.3, 21.9, 17.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.2;\) IR (neat, cm\(^{-1}\)) \(\nu: 3182, 2958, 2212, 1721, 1675, 1469, 1149;\) LRMS (ESI): \(m/z\) 406 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{19}\)H\(_{20}\)F\(_3\)NO\(_4\)Na [M+Na]+ 406.1237, Found 406.1234.

\(N\)-((4-methoxybenzyl)oxy)-3-(3-(thiophen-2-yl)propoxy)-3-trifluoromethyl-isoindolinone (S\(_4\)ad)

![Image](image1)

light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta: 7.89 (d, 1H, J = 6.9 Hz), 7.61-7.69 (m, 2H), 7.58 (d, 1H, \(J = 7.4\) Hz), 7.50 (d, 2H, \(J = 8.6\) Hz), 7.07 (dd, 1H, \(J = 5.2\) Hz, 1.1 Hz), 6.92-6.96 (m, 2H), 6.84 (dd, 1H, \(J = 5.2\) Hz, 3.4 Hz), 6.69-6.71 (m, 1H), 5.25 (d, 1H, \(J = 9.5\) Hz), 5.06 (d, 1H, \(J = 9.5\) Hz), 3.82 (s, 3H), 3.28-3.35 (m, 1H), 2.96-3.03 (m, 1H), 2.87 (t, 2H, \(J = 7.4\) Hz), 1.83-1.97 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta: 165.5, 160.1, 143.8, 135.1, 133.4, 131.3, 131.2, 126.8, 126.7, 124.4, 124.2, 124.1, 123.1, 122.2 (q, \(J = 285.5\) Hz), 113.8, 90.8 (q, \(J = 32.8\) Hz), 78.8, 62.8, 55.2, 30.8, 26.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.0;\) IR (neat, cm\(^{-1}\)) \(\nu: 3437, 2953, 1742, 1613, 1515, 1253, 1188;\) LRMS (ESI): \(m/z\) 500 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{24}\)H\(_{22}\)F\(_3\)NO\(_4\)SNa [M+Na]+ 500.1114, Found 500.1136.

\(N\)-hydroxy-3-(3-(thiophen-2-yl)propoxy)-3-trifluoromethyl-isoindolinone (1ad)

![Image](image2)

light yellow liquid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta: 9.66 (brs, 1H), 7.76-7.80 (m, 1H), 7.62-7.67 (m, 1H), 7.56-7.61 (m, 2H), 7.08-7.10 (m, 1H), 6.90 (dd, 1H, \(J = 5.2\) Hz, 3.4 Hz), 3.42-3.49 (m, 1H), 3.03-3.09 (m, 1H), 2.97 (t, 2H, \(J = 7.4\) Hz), 1.93-2.09 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta: 165.8, 144.1, 135.0, 133.3, 131.5, 129.9, 126.7, 124.5, 124.1, 123.9, 123.1, 121.9 (q, \(J = 286.3\) Hz), 91.0 (q, \(J = 33.2\) Hz), 63.1, 30.9, 26.1; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.4;\) IR (neat, cm\(^{-1}\)) \(\nu: 3158, 2950, 1718, 1469, 1200;\) LRMS (ESI): \(m/z\) 380 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{14}\)F\(_3\)NO\(_3\)SNa [M+Na]+ 380.0539, Found 380.0547.

\(N\)-hydroxy-3-(3-oxo-3-(thiophen-2-yl)propoxy)-3-trifluoromethyl-isoindolinone (2ad)

![Image](image3)

Starting material \(1\)ad (35.7 mg, 0.1 mmol) was oxygenated under condition A of section 2, and \(2\)ad (19.4 mg, 0.052 mmol) was isolated according to the purification procedure described in the General method (52% yield).

light yellow solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta: 8.79 (brs, 1H), 7.88 (d, 1H, \(J = 7.4\) Hz), 7.79 (d, 1H, \(J = 4.0\) Hz), 7.72 (d, 1H, \(J = 5.2\) Hz), 7.60-7.69 (m, 3H), 7.14-7.17 (m, 1H), 3.75 (dt, 1H, \(J = 3.1\) Hz, 9.9 Hz), 3.39-3.49 (m, 2H), 3.10-3.37 (m, 1H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta: 191.3, 163.9, 143.1, 135.0, 134.0, 133.0, 129.9, 126.7, 124.5, 124.1, 123.9, 123.1, 121.9 (q, \(J = 286.3\) Hz), 91.0 (q, \(J = 33.2\) Hz), 63.1, 30.9, 26.1; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.4;\) IR (neat, cm\(^{-1}\)) \(\nu: 3158, 2950, 1718, 1469, 1200;\) LRMS (ESI): \(m/z\) 380 [M+Na]+; HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{14}\)F\(_3\)NO\(_3\)SNa [M+Na]+ 380.0539, Found 380.0547.
133.2, 133.0, 131.7, 130.5, 128.4, 124.2, 124.1, 121.8 (q, \(J = 286.7\) Hz), 90.6 (q, \(J = 33.6\) Hz), 58.0, 38.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.1\); IR (KBr, cm\(^{-1}\)) \(\nu\): 3178, 2959, 1741, 1637, 1418, 1197; LRMS (ESI): \(m/z\) 394 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{12}\)F\(_3\)NO\(_4\)SNa [M+Na\(^+\)] 394.0331, Found 394.0337.

\(N\)-benzyloxy-3-(3-(1-tosyl-1\(H\)-indol-3-yl)propoxy)-3-trifluoromethyl-isooindolinone (S4ae)

white solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta: 7.97\) (d, 1H, \(J = 8.5\) Hz), 7.88-7.93 (m, 1H), 7.71 (d, 2H, \(J = 8.5\) Hz), 7.53-7.70 (m, 5H), 7.34-7.43 (m, 4H), 7.27-7.33 (m, 1H), 7.25 (s, 1H), 7.15-7.22 (m, 3H), 5.35 (d, 1H, \(J = 9.7\) Hz), 5.14 (d, 1H, \(J = 9.7\) Hz), 3.26-3.35 (m, 1H), 2.96-3.04 (m, 1H), 2.63-2.79 (m, 2H), 2.31 (s, 3H), 1.81-2.00 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta: 165.6, 144.7, 135.2, 135.0, 134.5, 133.6, 131.7, 130.7, 129.8, 129.7, 129.3, 128.8, 128.4, 126.6, 124.6, 124.2, 124.1, 122.9, 122.6, 122.2 (q, \(J = 285.2\) Hz), 121.9, 119.3, 113.6, 90.8 (q, \(J = 32.9\) Hz), 79.1, 63.0, 28.1, 21.4, 20.9; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.0\); IR (KBr, cm\(^{-1}\)) \(\nu\): 3064, 2950, 1744, 1448, 1370, 1174; LRMS (ESI): \(m/z\) 657 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{34}\)H\(_{29}\)F\(_3\)N\(_2\)O\(_5\)SNa [M+Na\(^+\)] 657.1642, Found 657.1631.

\(N\)-hydroxy-3-(3-(1-tosyl-1\(H\)-indol-3-yl)propoxy)-3-trifluoromethyl-isooindolinone (1ae)

white solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta: 9.84\) (brs,1H), 7.97 (d, 1H, \(J = 8.0\) Hz), 7.73 (d, 3H, \(J = 8.0\) Hz), 7.50-7.65 (m, 3H), 7.47 (d, 1H, \(J = 8.0\) Hz), 7.28-7.34 (m, 2H), 7.16-7.23 (m, 3H), 3.44-3.50 (m, 1H), 3.02-3.09 (m, 1H), 2.80 (t, 2H, \(J = 7.4\) Hz), 2.30 (s, 3H), 1.93-2.10 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta: 165.8, 144.7, 135.3, 135.2, 135.0, 133.4, 131.6, 130.8, 129.8, 126.7, 124.6, 124.0, 123.9, 122.9, 122.8, 122.0, 121.9 (q, \(J = 286.7\) Hz), 119.4, 113.6, 91.0 (q, \(J = 33.6\) Hz), 63.2, 28.2, 21.4, 21.0; \(^{19}\)F NMR (369 MHz, CDCl\(_3\)) \(\delta: -78.3\); IR (KBr, cm\(^{-1}\)) \(\nu\): 3117, 2943, 1718, 1448, 1372, 1174; LRMS (ESI): \(m/z\) 567 [M+Na\(^+\)]; HRMS (ESI): \(m/z\) calcd for C\(_{27}\)H\(_{23}\)F\(_3\)N\(_2\)O\(_5\)SNa [M+Na\(^+\)] 567.1172, Found 567.1165.

\(N\)-hydroxy-3-(3-oxo-3-(1-tosyl-1\(H\)-indol-3-yl)propoxy)-3-trifluoromethyl-isooindolinone (2ae)

Starting material 1ae (27.2 mg, 0.05 mmol) was oxygenated under condition A of section 2, and 2ae (14.8 mg, 0.026 mmol) was isolated according to the purification procedure described in the General
method (53% yield).
light yellow solid; $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.04 (brs, 1H), 8.32 (s, 1H), 8.24 (d, 1H, $J = 8.0$ Hz), 7.86-7.92 (m, 2H), 7.83 (d, 2H, $J = 8.6$ Hz), 7.58-7.69 (m, 3H), 7.31-7.39 (m, 2H), 7.28 (d, 2H, $J = 8.6$ Hz), 3.76-3.83 (m, 1H), 3.41-3.49 (m, 2H), 3.11-3.20 (m, 1H), 2.35 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ: 194.5, 163.7, 146.2, 134.7, 134.2, 133.9, 132.91, 132.89, 131.7, 130.6, 130.3, 127.2, 127.1, 126.0, 125.1, 124.2, 124.1, 123.0, 121.8 (q, $J = 286.7$ Hz), 120.6, 113.0, 90.5 (q, $J = 32.4$ Hz), 57.8, 38.3, 21.6; $^{19}$F NMR (369 MHz, CDCl$_3$) δ: -78.0; IR (KBr, cm$^{-1}$) ν: 3135, 2952, 1736, 1656, 1536, 1382, 1178; LRMS (ESI): $m/z$ 581 [M+Na]$^+$; HRMS (ESI): $m/z$ calcd for C$_{27}$H$_{21}$F$_3$N$_2$O$_6$SNa [M+Na]$^+$ 581.0965, Found 581.0978.
S2, CF₃-OH

![N-OBn](image)

O

F₃C

OH

S2
N-OPMB

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BuOH, 02

[Chemical structure image]

2a

[1H NMR spectrum image]
1,1-dMe-BuOH, Bn

**S4b**
2,2-dMe-BuOH, Bn

DFILE ozawa04-142_1_13C.pdf
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SCANS 79
ACQTM 1.0420 sec
PD 3.0000 sec
FW1 3.40 ussec
IRNUC 1H
CTEMP 21.7 C
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 72

[Chemical structure diagram]
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

OAc, OH

DFILE ozawa04-024_1H.jdf
COMMNT OAc, OH
DATIM 2014-02-01 21:14:19
OBMNIC 1H
EXMOD proton.jsp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 16384
FRQUS 9384.38 Hz
SCANS 4
ACQTM 1.7459 sec
PD 5.0000 sec
FWH 5.55 usec
IRNUC 1H
CTEMP 21.2 c
SLNVT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 28

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}
DFILE: Ni_C5-CO2Me_1H.jdf
COMMNT: OH
DATIM: 2014-03-03 20:26:24
OBNUC: 1H
EXMCOD: proton.jkp
OBFREQ: 500.16 MHz
OBSTMR: 2.41 kHz
OBFIN: 6.01 Hz
POINT: 16384
FREQU: 9384.38 Hz
SCANS: 4
ACQTM: 1.7459 sec
PB: 5.0000 sec
FW: 5.55 usec
IRNUC: 1H
CTEMP: 21.1 C
SIVNT: CDCl3
EXREF: 7.26 ppm
BF: 0.12 Hz
RGAIN: 28
| MeBuOH, OH |
|----------|

- **DFILE**: ozawa04-063rsm_13C.jdf
- **COMNT**: MeBuOH, OH
- **DATIM**: 2014-01-21 12:35:34
- **GENUC**: 13C
- **EXMOD**: carbon.jxp

**OBFRQ**: 125.77 MHz
**OBSET**: 7.87 KHz
**OBFIN**: 4.21 Hz
**FOINT**: 32767
**FREQU**: 39300.18 Hz
**SCANS**: 100
**ACQTM**: 0.8336 sec
**PD**: 3.0000 sec
**FW1**: 3.40 usec
**IRNUC**: 1H
**CTEMP**: 21.7 °C
**SINVNT**: CDCl3
**EXREF**: 77.00 ppm
**BF**: 0.12 Hz
**RGAIN**: 60

![N-OH Me](image)

![F3C O 1h](image)
CyEtOH

DFILE ozawa04-050_13C.jdf
COMNT CyEtOH
DATIM 2013-11-25 17:16:21
OBNUC 13C
EXMOD carbon.jxp

OBRFRQ 125.77 MHz
OBSET 7.87 KHz
OBFIN 4.21 Hz
POINT 32767
FREQU 39308.18 Hz
SCANS 140
ACQTM 0.8336 sec
PD 3.0000 sec
FW1 3.40 usec
IRNUC 1H
CTEMP 23.0 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60

S4i
The image contains a spectroscopic chart with a peak at various chemical shifts and the molecular structure of compound S4 with the following annotations:

- The compound contains a benzene ring with a nitrogen atom and an oxygen substituent labeled as O-Bn.
- An oxygen atom is also present with a three fluorine substituent labeled as F₃C.
- The structure is labeled as S4 with an index i.
column, CyEtOH

[Chemical structure diagram]

DFILE ozawa04-056_1_1H.jdf
COMNT column, CyEtOH
DATIM 2013-11-29 14:27:28
OBNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 KHz
OBFIN 6.01 Hz
POINT 16384
FREQU 9384.38 Hz
SCANS 4
ACQTM 1.7459 sec
PD 5.0000 sec
FW1 5.55 usec
IRNUC 1H
CTEMP 22.7 c
SLVNT CDCl3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 30
S4j
CyMe3, Bu
citronellol, Bn
3-Me-5-OMOM, Bn

DFILE: ozawa07-022_i3C.als
COMMT: 3-Me-5-OMOM, Bn
DATIN: 2015-03-02 10:02:04
OSINUC: 13C
RQMOD: carbon.jsp
ORFREQ: 125.77 MHz
OSSET: 7.87 kHz
OBFIN: 4.21 Hz
POINT: 26214
FREQ: 31466.54 Hz
SCANS: 476
ACQTM: 0.8336 sec
PD: 2.0000 sec
PWL: 3.40 usec
IRNUNC: 1H
CTEMP: 24.0 c
SLVNT: CDCL3
EXREF: 77.00 ppm
BF: 0.12 Hz
RRAIN: 60

\[
\text{O} \\
\text{N-OBn Me} \\
\text{F}_3\text{C-O-} \\
\text{OMOM}
\]
3-Me-5-O(4-pentyne), OH
3-Me-5-O(4-pentyne), OH
O

N-OH

Me

OH

O

F₃C

O

OH

O

OH

20
3-Me-7-octenol
3-Me-7-octenol, OH

\[
\text{[Chemical Structure Image]}
\]
3-Me-7-octenol, [0]
alkyl boronic acid ester, OH

Chemical shift (δ) and coupling constants (J):

1. 7.09 ppm (s)
2. 7.34 ppm (s)
3. 4.37 ppm (s)
4. 3.08 ppm (s)
5. 1.00 ppm (s)

Coupling constants (J):

1. J1 = 9.5 Hz
2. J2 = 1.5 Hz
3. J3 = 2.0 Hz

NMR conditions:

Solvent: CDCl3
Temperature: 22.1 °C
Sample concentration: 7.26 ppm
Sample weight: 0.12 Hz
Gain: 22

Chemical structure:

[Chemical structure image]
alkyl boronic acid ester, ON
alkyl boronic acid ester, OH
alkyl Bpin, [0]
valinol, OH

1H NMR spectrum

Chemical shifts: 7.87, 7.61, 7.54, 7.47, 7.40, 7.33, 7.26, 7.19, 7.12, 7.05, 6.98, 6.91, 6.84, 6.77, 6.70, 6.63, 6.56, 6.49, 6.42, 6.35, 6.28, 6.21, 6.14, 6.07, 5.99, 5.92, 5.85, 5.78, 5.71, 5.64, 5.57, 5.50, 5.43, 5.36, 5.29, 5.22, 5.15, 5.08, 5.01, 4.94, 4.87, 4.80, 4.73, 4.66, 4.59, 4.52, 4.45, 4.38, 4.31, 4.24, 4.17, 4.10, 4.03, 3.96, 3.89, 3.82, 3.75, 3.68, 3.61, 3.54, 3.47, 3.40, 3.33, 3.26, 3.19, 3.12, 3.05, 2.98, 2.91, 2.84, 2.77, 2.70, 2.63, 2.56, 2.49, 2.42, 2.35, 2.28, 2.21, 2.14, 2.07, 2.00, 1.93, 1.86, 1.79, 1.72, 1.65, 1.58, 1.51, 1.44, 1.37, 1.30, 1.23, 1.16, 1.09, 1.02, 0.95, 0.88, 0.81, 0.74, 0.67, 0.60, 0.53, 0.46, 0.39, 0.32, 0.25, 0.18, 0.11, 0.04 ppm

Ozonolysis product

Structural formula:

```
O
\|\n\|\nN-OH
Me
\|\n\|\nF_3C
O
\|\n\|\nN
```

1r
PhOAc, Bn

DFILE ozawa05-048_13C.jdf
COMNT PhOAc, Bn
DATIM 2014-08-15 13:13:33
OBNUC 13C
EXMOD carbon.jp
OBFREQ 125.77 MHz
OBSF 7.87 KHz
OBFIN 4.21 Hz
POINT 32767
FREQU 39308.18 Hz
SCANS 180
ACQTM 0.8336 sec
PD 3.0000 sec
FWI 3.40 usec
IRNUC 1H
CTEMP 26.4 °C
SLVNT CDCl3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60
DFILE ozawa07-049_C13.jdf
COMMT 4-OMe-Ph, OH
DATTM 2015-03-20 17:28:55
OBNUC 13C
EXMOD carbon.jpg
OBFRQ 125.77 MHz
OBSET 7.87 kHz
OBFIN 4.21 Hz
POINT 32767
FREQQ 39308.18 Hz
SCANS 256
ACQTM 0.8336 sec
PD 2.0000 sec
PMI 3.40 usec
IRNUC 1H
CTEMP 26.7 c
SVNCT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 60

1u
Ph-Bpin, Bn

S4w
PTLC, 2-I-Ph, PMB
2-TMS-Ph [0]

![Chemical Structure Image]

2y
tBu-yne, OH

DFILE ozawa05-128_1_1H.jdf
COMNT tBu-yne, OH
DATIM 2014-08-15 18:35:12
BNUC 1H
EXMOD proton.jxp
OBFRQ 500.16 MHz
OBSET 2.41 kHz
OBFIN 6.01 Hz
POINT 16384
FREQU 9384.38 Hz
SCANS 4
ACQTM 1.7459 sec
PB 5.0000 sec
PW1 5.55 usec
IRNUC 1H
CTEMP 26.1 °C
SLVNT CDCL3
EXREF 7.26 ppm
BF 0.12 Hz
RGAIN 26
thiophene, PMB
thiophene, OH

1ad
thiophene, OH

1ad
thiophene, [6]

2ad
2ad
The given image contains a chemical structure labeled as 'S4ae' with a Ts group and an OBn group. The structure includes a benzene ring with a nitrogen atom and a trifluoromethyl group. The image also contains a spectrum with peaks, which are typically used to analyze the molecular structure and properties. The text and spectrum are related to the chemical identification and analysis of the compound.
