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Two Scalable Syntheses of 3-(Trifluoromethyl)cyclobutane-1-carboxylic Acid

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ABSTRACT: Two efficient synthetic methods for preparation of 3-(trifluoromethyl)cyclobutane-1-carboxylic acid are reported starting from readily available 4-oxocyclobutane precursors. These cyclobutanones can be converted to their CF_3 carbinols upon treatment with $TMSCF_3$ and a fluoride source. The bis-carboxylate system **9** was deoxygenated by treatment of Bu_3SnH and provided desired compound **1** upon decarboxylation. In the monocarboxylate system **15**, the triflate could be efficiently eliminated; subsequent hydrogenation afforded *cis*-**1**.

KEYWORDS: *3-(trifluoromethyl)cyclobutane-1-carboxylic acid, cyclobutane isostere of benzene, medicinal chemistry building blocks, base-mediated elimination of sterically hindered, electronically deactivated tert-CF_3 carbinol triflate*

TWO SCALABLE SYNTHESES OF 3-(TRIFLUOROMETHYL)CYCLOBUTANE-1-CARBOXYLIC ACID

Cyclobutane derivatives have long been recognized as lower ClogP analogs of the phenyl isostere in medicinal chemistry,[1,2] leading to their prevalence in biologically active structures in drug discovery efforts. One such structural feature, the 3-(trifluoromethyl)cyclobutyl moiety, is a substructure commonly represented in pharmaceutical patents (e.g., **1a**−**1g**; Figure 1)[3−13] and likely incorporated through the derivatization of the building block 3-(trifluoromethyl)cyclobutane-1-carboxylic acid (**1**). However, the limited commercial availability of **1** restricts its extensive applications, in particular for larger-scale syntheses. In the context of a recent program, we needed to access significant quantities of building block **1** for structure−activity relationship (SAR) exploration and to de-risk toxicological side effects of the resulting compounds. Thus, we set out to develop a scalable and robust synthesis of **1**.

Recently, the only known formal synthesis of compound **1** was reported to proceed through a direct photomediated C−H trifluoromethylation of cyclobutane dicarboxylic acid to afford di-acid analog **1h**, which upon decarboxylation, yielded **1** (Scheme 1).[14] Although conceptually simple, the large-scale use of the Togni II reagent and MeCN-D_3 as a reaction solvent is prohibitive due to the cost and the potentially explosive nature of the I(III) reagent.

From the viewpoint of synthetic planning, two general strategies were pursued: (i) construction of the cyclobutyl ring *via de novo* synthesis or (ii) synthetic modifications of cyclobutyl precursors. The first strategy is detailed in Scheme 2: we reasoned that the readily available CF_3-containing starting material 2-CF_3-acrylic acid **2** could be elaborated to construct a cyclobutane ring *via* alkylation of a malonate building block. To this end, 2-CF_3-acrylic acid **2** was first hydrated to obtain hydroxy acid **3**[15] followed by reduction to diol **4a** (R = H). Unfortunately, assembling the cyclobutyl moiety by reacting **4a** (R = H) or its sulfonate derivatives **4b**/**4c** (R = OTs or OTf) under Mitsunobu or base-promoted alkylation conditions with diethyl or diisopropylmalonate building blocks uniformly failed. Under a variety of conditions, no desired cyclobutane **5** was observed. Instead, alkene **6** was the only product identified from a complex mixture. It is plausible that the increased acidity of C−H in the α-position to the CF_3 group is a key factor in favoring elimination over substitution in this case as analogous substrates without a CF_3 moiety cyclize readily to the corresponding cyclobutyl products.[16]

Therefore, the second synthetic strategy was adopted: introducing the CF_3 group into a commercially available cyclobutane precursor. After an extensive search for suitable starting materials, we focused on developing syntheses by employing readily available 3-oxocyclobutane-1-carboxylic acid derivatives as starting materials.

Readily available diisopropyl 3-oxocyclobutane-1,1-dicarboxylate (**7**; Scheme 3), for example, is an attractive building block, which has previously been used for constructing biologically and medicinally active molecules with cyclobutane substructures.[17] In our case, a CF_3 group can be introduced by reaction with $CsF/TMSCF_3$,[17a] resulting in efficient conversion to the CF_3 carbinol **8**. However, removal of the hydroxyl group in **8** proved to be challenging. We were able to convert the alcohol **8** to the corresponding mesylate or triflate under typical conditions; however, our attempts to convert the sulfonates to make the corresponding olefin under elimination

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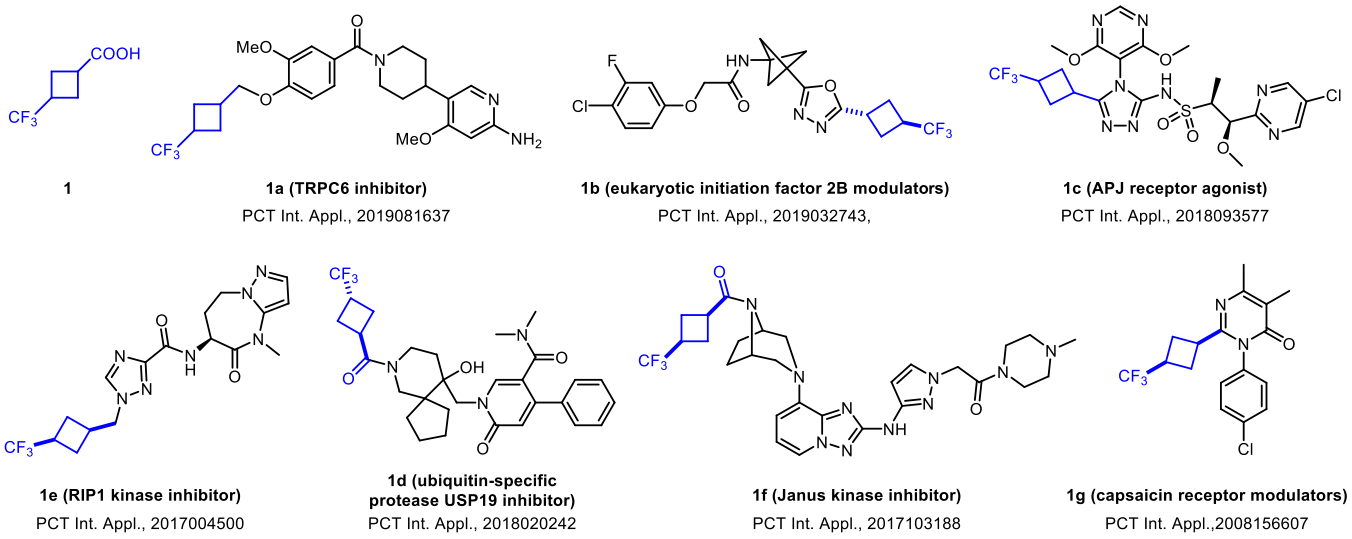
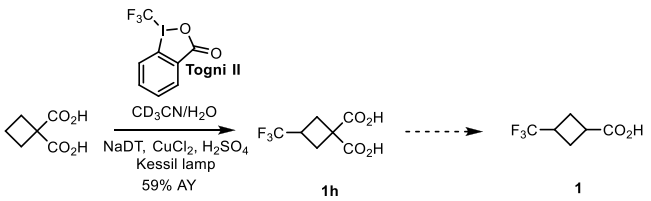


Figure 1. 3-(Trifluoromethyl)cyclobutane-1-carboxylic acid and its derivatives in recent pharmaceutical patents.

Scheme 1. Previously reported Trifluoromethylation of Cyclobutane Dicarboxylic Acid



conditions in the presence of bases only led to decomposition of the sulfonates. Other deoxygenating conditions such as the palladium-catalyzed hydrogenation of the corresponding mesylate also gave no reaction.

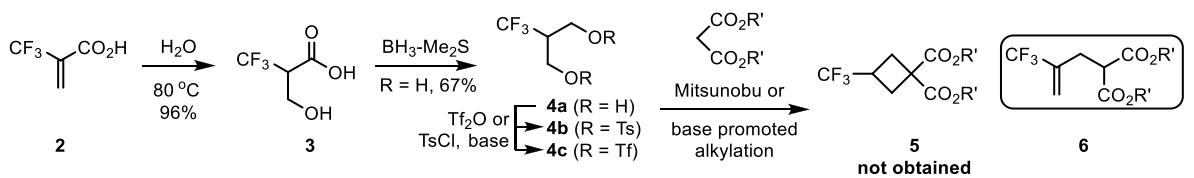
Gratifyingly, investigation of radical deoxygenation approaches proved to be overall more fruitful. Even though initial efforts found that commonly used thiocarbonyl radical precursors of **8** could not be synthesized efficiently, the oxalate **9** could be readily synthesized in high yields (91%). Subsequent reduction of **9** with tributyltin hydride[18] afforded **10** in a 66% isolated yield. Further hydrolysis and decarboxylation completed the synthesis of **1** (*cis*:*trans* = 1.4:1) with high efficiency. This five-step approach afforded a 40% overall yield and has been scaled up to produce the desired 3-(trifluoromethyl)cyclobutane-1-carboxylic acid **1** in >100 g quantities.

Despite the *de novo* synthesis in Scheme 3 being capable of delivering appreciable quantities of **1**, additional efforts were made to improve process practicality, safety, and greenness by eliminating the expensive and toxic reagent Bu_3SnH. Several Sn-free procedures to deoxygenate oxalate **9** by substituting Bu_3SnH with phenylsilane[19] or Hantzsch ester under photoredox conditions[20] were tested but all failed to deliver the desired product **10** cleanly.

To circumvent this drawback, we decided to reexamine hydroxyl elimination with a less-hindered monocarboxylate system (Scheme 4). Conversion of the benzyl ester of readily available compound **12** to the corresponding CF_3-substituted carbinol **14** proceeded in 20:1 diastereoselectivity. The monoester carbinol **14** can be activated as triflate **15** in a 77% yield. The subsequent elimination of triflate **15**, however, posed significant challenges. A base screen including DBU, KOtBu, LDA, NaH, and KOH generally afforded the bicyclic compound **16** in modest yields (e.g., 31% yield with KOtBu, as shown in Scheme 4). Attempted hydrogenation of **16** using a variety of conditions, including Ni(Ra), PtO_2, and Pd catalysts, not only afforded a mixture of reduced products, among them, the desired target compound **1**, but also the C−C bond-hydrogenated cyclopropyl products **17** and **18**.

To improve the last two steps of the process, we first conducted a screen of weaker bases for the elimination reaction of **15** to **16**. We hypothesized that weak bases would be less likely to deprotonate the benzyl ester but should still be able to enable triflate elimination (Table 1); this would be expected to result in the formation of an olefin instead of a bicyclic product. Indeed, our screen revealed that elimination could be achieved efficiently providing 95% LCAP (liquid chromatography area percent) of the desired product using tetramethyl ethylenediamine (TMEDA) as a base at 80 °C, albeit with concomitant partial migration of the double bond. The reaction was generally clean, with only trace amounts of bicycle **16** observed as a side product. A subsequent solvent screen revealed that the elimination proceeds well in DMF, while less polar solvent systems, such as MeCN, MeCN-H_2O, THF, and toluene, only show partial conversion and/or some

Scheme 2. Unsuccessful Attempt of *De Novo* Cyclobutane Synthesis



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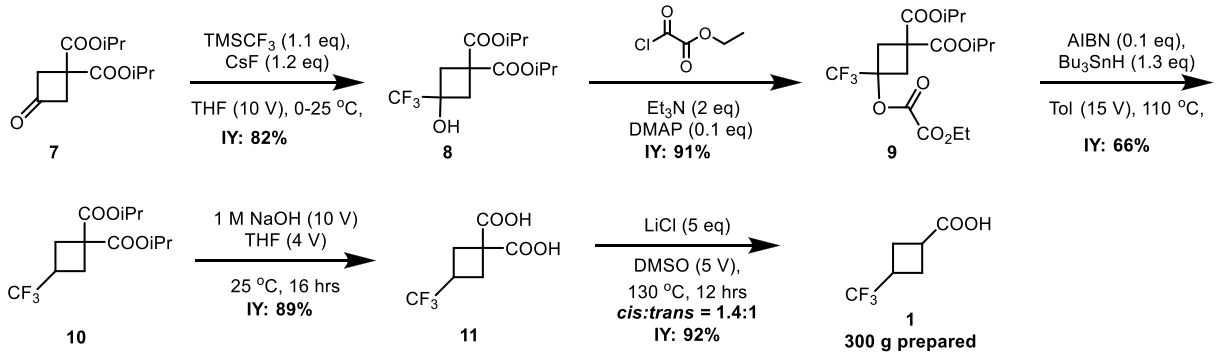
Scheme 3. First Successful Route *via* Tin Hydride Deoxygenation of CF_3 Carbinol



Scheme 4. Alternative Approach toward the Synthesis of 3-(Trifluoromethyl)cyclobutane-1-carboxylic Acid

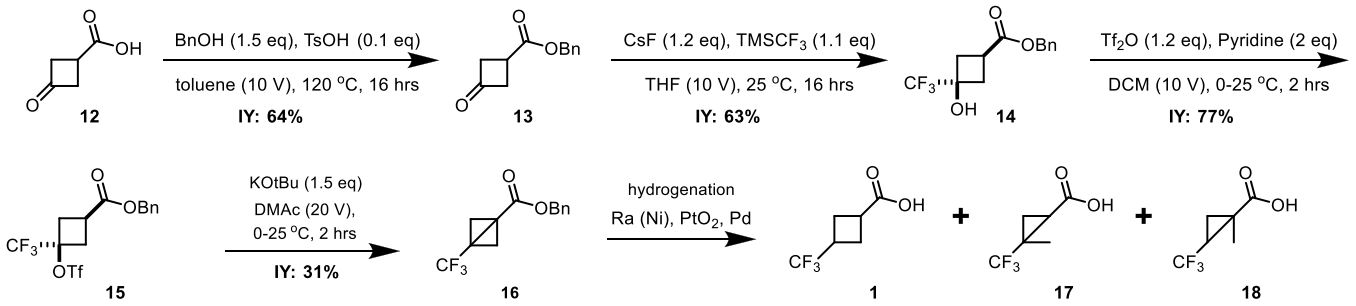


Table 1. Compound 15 Elimination Condition Screen

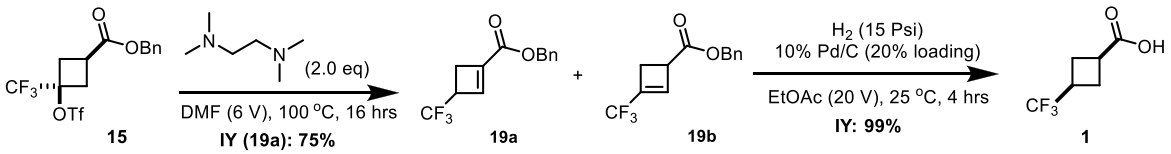
solvent	LCAP ratio of 15:19 after 16 h at 80 °C					
10 V	DIEA (2 equiv)	Et_3N (2 equiv)	TMEDA (2 equiv)	DIPA (2 equiv)	piperidine (2 equiv)	TMP (2 equiv)
DMF	68:13	34:65	3:95	53:44	12:1	59:39
MeCN	94:3	57:38	23:67	77:21	10:2	81:10
THF	94:1	88:9	30:65	93:4	7:3	95:1
Tol	88:2	84:12	55:42	88:8	25:7	88:8
MeCN/ H_2Ov/v = 10/1	69:6	37:38	10:70	49:15	25:4	52:10
THF/ H_2Ov/v = 10/1	80:1	98:0	15:50	43:10	15:0	44:8

decomposition of the product and substrate. Other weak bases such as $^{i}Pr_2NEt$ (DIPEA), NEt_3, $^{i}Pr_2NH$ (DIPA), piperidine, or 2,2,6,6-tetramethylpiperidine (TMP) did not work nearly as well, resulting in less conversion and decomposition.

The ideal base/solvent combination (TMEDA/DMF) was validated on a 20 g scale, affording a mixture of the **19a** in a 75% isolated yield with trace amounts of **19b** (Scheme 5). Compound **19a** was then hydrogenated to complete the synthesis of 3-(trifluoromethyl)cyclobutane-1-carboxylic acid **1**. Interestingly, this route only produces the *cis*-isomer of **1**. We reasoned that the steric hindrance created by the CF_3 group makes the opposite face of the cyclobutene ring more accessible for hydrogenation. This is consistent with other reported results that similarly substituted cyclobutene compounds were hydrogenated to give the 1,3-*cis* product, whereas zinc reduction gave mostly the trans products.[21] Overall, this five-step route, starting from commercially available compound **12**, delivered a 23% yield without the need to use stoichiometric Bu_3SnH as a reductant in the deoxygenation step.

In summary, two scalable routes have been developed to provide efficient access to 3-(trifluoromethyl)cyclobutane-1-carboxylic acid (**1**) on a multigram scale. Both presented routes relying on a key deoxygenation step, which is achieved either by Bu_3SnH-mediated radical deoxygenation or *via* a sulfonation/elimination sequence. Both routes employ readily available starting materials (**12** or **7**) and were completed with a 40 and 23% overall yield, respectively. Key to the success of the sulfonation/elimination sequence was establishing the efficient elimination of the sterically hindered and electronically deactivated *tert*-CF_3 carbinol triflate **15**, which is promoted using TMEDA as the base. These conditions circumvent the formation of bicyclic intermediate **16** in favor of the olefin products **19a**/**19b**, which is key to selective reduction in the final hydrogenation step.

Scheme 5. Efficient Elimination of *tert*-CF_3 Carbinol Triflate and Completion of an Alternative Synthesis of 1



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EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial sources and used without further purification. All experiments were conducted under an inert atmosphere. NMR spectra were obtained on a Bruker 400 MHz and a Varian 400 MHz spectrometer. Liquid chromatography−mass spectrometry (LCMS) analyses were carried out on a Shimadzu LCMS-2020 system, SPD-M20A detector, and LC-20 AD pump system, and gas chromatography−mass spectrometry (GCMS) analyses were carried out on a Shimadzu GCMS-QP2020 system and CMS-QP2020 EI detector. GC analyses were carried out on a Shimadzu Nexis GC-2030 system and flame ionization detector (FID). High-resolution mass spectrometry (HRMS) spectra were collected using a Waters Acquity UPLC I class system, binary solvent manager pump system, and Xevo G2-XS QT of a mass spectrometer system.

Diisopropyl 3-Hydroxy-3-(trifluoromethyl)-cyclobutane-1,1-dicarboxylate (8). Diisopropyl 3-oxocyclobutane-1,1-dicarboxylate **7** (160 g, 660 mmol) was charged into a 3 L three-necked round-bottom flask followed by THF (1.6 L) and CsF (120 g, 793 mmol). The system was degassed, purged with N_2 three times, and was cooled to 5 °C. The above flask was charged dropwise with a solution of $TMSCF_3$ (103 g, 726 mmol) in THF (160 mL), and the reaction was stirred at 25 °C for 12 h. TLC (petroleum ether:ethyl acetate = 5:1, R_f = 0.3) indicated that the starting material was consumed completely. The reaction mixture was filtered through a pad Celite. The filtrate was concentrated in vacuum, and the residue was redissolved in 2 L of ethyl acetate. The organic phase was washed with brine (500 mL × 2) and separated. It was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuum. The crude product was purified by a silica gel column chromatograph eluted with petroleum ether/ethyl acetate = 30/1 to 5/1 to obtain compound **8** (169 g, 541 mmol, 82% yield) as a colorless oil. Spectroscopic data of **8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00−5.16 (m, 2H), 3.52 (s, 1H), 3.05 (d, J = 14.68 Hz, 2H), 2.64 (br d, J = 14.43 Hz, 2H), 1.25 (t, J = 6.34 Hz, 12H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −84.44 (s, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.46 (s, 1C), 169.33 (s, 1C), 124.45 (q, J = 280.97 Hz, 1C), 70.35−70.50 (m, 1C), 68.48−71.73 (m, 2C), 45.67 (s, 1C), 37.34 (s, 2C), 21.41 (s, 4C) ppm; HRMS calcd for $C_{13}H_{19}F_3O_5$ 313.1185, found 313.1254.

Diisopropyl 3-(2-Ethoxy-2-oxoacetoxy)-3-(trifluoromethyl)cyclobutane-1,1-dicarboxylate (9). Ethyl 2-chloro-2-oxoacetate (169 g, 1236 mmol) was added to a stirred, cooled (0 °C) mixture of compound **8** (193 g, 618 mmol), Et_3N (172 mL, 1236 mmol), and DMAP (7.55 g, 61.8 mmol) in DCM (1.9 L), and the mixture was stirred at 25 °C for 16 h. TLC (petroleum ether:EtOAc = 5:1, R_f = 0.5) showed that the starting material was consumed completely. DCM (1 L) was added to the reaction mixture, which was washed with brine (500 mL × 2) and concentrated under vacuum to give a residue. The crude was purified by column chromatography on a silica gel (petroleum ether:ethyl acetate = 100:1 to 0:1) to give compound **9** (233 g, 565 mmol, 91% yield) as a colorless oil. Spectroscopic data of **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99−5.17 (m, 2H), 4.38 (q, J = 7.15 Hz, 2H), 3.26 (s, 4H), 1.40 (t, J = 7.15 Hz, 3H), 1.25 (dd, J = 6.27, 3.64 Hz, 12H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −80.32 (s, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.00 (d, J = 93.90 Hz, 2C), 155.78 (d, J = 146.72 Hz, 2C), 123.45 (q, J = 281.70 Hz, 1C), 76.75 (q, J = 331.75 Hz, 1C), 70.05 (d, J = 37.41 Hz, 2C), 63.66 (s, 1C), 46.29 (s, 1C), 35.33 (s, 2C), 21.43 (d, J = 3.67 Hz, 4C), 13.87 (s, 1C) ppm; HRMS calcd for $C_{17}H_{23}F_3O_8$ 413.1345, found 413.1427.

Diisopropyl 3-(Trifluoromethyl)cyclobutane-1,1-dicarboxylate (10). A mixture of compound **9** (223 g, 541 mmol) in anhydrous toluene (2.2 L) was added dropwise with AIBN (8.88 g, 54.1 mmol) and Bu_3SnH (205 g, 703 mmol) dissolved in anhydrous toluene (1.1 L) at 110 °C over 15 mins. The mixture was stirred at 110 °C for 0.5 h. TLC (petroleum ether:EtOAc = 5:1) showed that the reaction was complete. The mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (2 L) and aqueous KF solution (800 mL) and was filtered. The organic layer was separated. The aqueous phase was extracted with ethyl acetate (500 mL × 2). The combined organic layers were washed with brine (800 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluting with petroleum ether:ethyl acetate = 100:1 to 5:1) to give Compound **10** (105 g, 354 mmol, 65.5% yield) as an oil.

Spectroscopic data of **10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99−5.15 (m, 2H), 2.92−3.12 (m, 1H), 2.58−2.74 (m, 4H), 1.25 (dd, J = 6.14, 3.51 Hz, 12H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.28 (d, J = 8.17 Hz, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.13 (d, J = 89.80 Hz, 2C), 126.57 (q, J = 275.76 Hz, 1C), 69.38 (d, J = 36.16 Hz, 2C), 48.48 (s, 1C), 31.58 (q, J = 31.79 Hz, 1C), 27.29−28.63 (m, 2C), 21.49 (s, 4C) ppm; HRMS calcd for $C_{13}H_{19}F_3O_4$ 297.1235, found 297.1283.

3-(Trifluoromethyl)cyclobutane-1,1-dicarboxylic Acid (11). A solution of compound **10** (105 g, 354 mmol) in THF (420 mL) was added with NaOH (1050 mL, 1050 mmol, 1 M), and the mixture was stirred at 25 °C for 16 h. TLC (petroleum ether:EtOAc = 20:1, SM R_f = 0.6) showed that the starting material was consumed completely. Water (1 L) was added, which afforded a solution with pH 10−11. The mixture was washed with ethyl acetate (500 mL × 2). Then, an aqueous layer was acidified with HCl (6 M) to pH 2−3. The aqueous phase was extracted with ethyl acetate (800 mL × 2). The combined organic layers were washed with brine (700 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give compound **11** (67.0 g, 316 mmol, 89% yield) as a white solid. Spectroscopic data of **11**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (br s, 2H), 3.10−3.26 (m, 1H), 2.58−2.68 (m, 2H), 2.53 (s, 1H), 2.47 (s, 1 H) ppm; ^{19}F NMR (376 MHz, DMSO-d_6) δ −72.71 (s, 3F) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.18 (d, J = 44.02 Hz, 2C), 127.64 (q, J = 275.83 Hz, 1C), 48.36 (s, 1 C), 30.72 (q, J = 30.81 Hz, 1C), 27.97 (br d, J = 3.67 Hz, 2C) ppm; HRMS calcd for $C_7H_7F_3O_4$ 211.0296, found 211.0244.

3-(Trifluoromethyl)cyclobutane-1-carboxylic Acid (1). A mixture of compound **11** (67.0 g, 316 mmol) and LiCl (67.0 g, 1579 mmol) in DMSO (335 mL) was stirred at 130 °C for 12 h. TLC (DCM:MeOH = 10:1, SM R_f = 0.3) showed that the reaction was complete. Water (400 mL) was added, and the aqueous phase was extracted with ethyl acetate (200 mL × 3). The combined organic layers were washed with water (100 mL × 7), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to afford **1** (49.0 g, 291 mmol, 92% yield) as a yellow oil. Spectroscopic data of **1** (*cis*:*trans* = 1.4:1): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (br s, 1H), 3.00−3.21 (m, 2H), 2.30−2.46 (m, 2H), 2.13−2.30

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(m, 2H) ppm; ^{19}F NMR (376 MHz, DMSO-d_6) δ −72.88 (s, 3F), −72.55 (s, 3F) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 173.62−176.95 (m, 2C), 128.60 (q, J = 274.53 Hz, 1C), 127.47 (q, J = 274.25 Hz, 1C), 34.23 (s, 1C), 33.45 (q, J = 29.80 Hz, 1C), 32.63 (s, 1C), 32.02 (q, J = 30.60 Hz, 1C), 24.36−24.75 (m, 1C), 24.01 (br d, J = 3.58 Hz, 1C) ppm; HRMS calcd for $C_6H_7F_3O_2$ 167.0398, found 167.0368.

Benzyl 3-Oxocyclobutane-1-carboxylate (13). The solution of 3-oxocyclobutane-1-carboxylic acid **12** (100 g, 876 mmol), TsOH (10 g, 58.1 mmol), and BnOH (100 g, 920 mmol) in toluene (1.0 L) was stirred at 120 °C for 16 h. The solution was cooled to ambient temperature and was washed with water (300 mL × 3) and brine (200 mL × 1). The organic phase was separated and was dried over Na_2SO_4, filtered, and concentrated in vacuum (30 mmHg, 45 °C). The crude product was purified by a silica gel column (petroleum ether/ethyl acetate = 100/1 to 10/1) to afford an oil (114 g, 558 mmol, 63.7% yield). Spectroscopic data of **13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.44 (m, 5H), 5.20 (s, 2H), 3.38−3.52 (m, 2H), 3.22−3.36 (m, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.48 (s, 1C), 173.81 (s, 1C), 135.42 (s, 1C), 127.60−129.14 (m, 5C), 67.09 (s, 1C), 51.62 (s, 2C), 27.41 (s, 1C) ppm; GCMS calcd for $C_{12}H_{12}O_3$ 204.1, found 204.1; HRMS calcd for $C_{12}H_{12}O_3$ 203.0768, found 203.0648.

Benzyl 3-Hydroxy-3-(trifluoromethyl)cyclobutane-1-carboxylate (14). $TMSCF_3$ (87 g, 614 mmol) was added dropwise into the solution of compound **13** (114 g, 558 mmol) and CsF (102 g, 670 mmol) in THF (1.14 L) at 0 °C during 30 min. The solution was then stirred at 25 °C for 16 h. TLC (petroleum ether:ethyl acetate = 5:1) showed that the SM (R_f = 0.56) was consumed, and one main spot (R_f = 0.2) was detected. The solution was filtered and concentrated in vacuum at 30 mmHg, 45 °C. The crude product was purified by a silica gel column (eluent: petroleum ether/ethyl acetate = 100/1 to 10/1) to afford an oil **14** (96.0 g, 350 mmol, 62.7% yield). Spectroscopic data of **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.44 (m, 5H), 5.17 (s, 2H), 3.30 (br s, 1H), 2.92−3.07 (m, 1H), 2.74−2.84 (m, 2H), 2.41−2.55 (m, 2H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −84.90 (s, 3F) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.67 (br d, J = 16.87 Hz, 1C), 135.43 (s, 1C), 128.03−128.93 (m, 5C), 125.31 (q, J = 279.63 Hz, 1C), 70.87 (br dd, J = 31.91, 13.57 Hz, 1C), 67.04 (d, J = 2.93 Hz, 1C), 34.15 (br s, 2C), 28.85 (d, J = 2.93 Hz, 1C) ppm; GCMS calcd for $C_{13}H_{13}F_3O_3$ 274.1, found 274.1; HRMS calcd for $C_{13}H_{13}F_3O_3$ 273.0817, found 273.0728.

Benzyl 3-(Trifluoromethyl)-3-((trifluoromethyl)-sulfonyl)oxy)cyclobutane-1-carboxylate (15). A solution of compound **14** (96.0 g, 350 mmol) and pyridine (55.4 g, 700 mmol) in CH_2Cl_2 (960 mL) at 0 °C was added dropwise with Tf_2O (119 g, 420 mmol). The solution was stirred at 25 °C for 2 h. TLC (petroleum ether:ethyl acetate = 5:1, SM R_f = 0.2) showed that the SM was consumed, and one main spot was detected. The solution was poured into ice water (200 mL) and extracted with EtOAc (300 mL × 3). The combined organic phase was washed with brine (200 mL × 1), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by a silica gel column (eluent: petroleum ether/ethyl acetate = 100/1 to 10/1) to yield **15** as a light yellow oil (110 g, 271 mmol, 77.0% yield). Spectroscopic data of **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.64 (m, 5H), 5.19 (s, 2H), 2.89−3.27 (m, 5H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −82.55 (s, 3F), −75.30 (s, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.83 (s, 1C), 135.09 (s, 1C), 128.11−129.74 (m, 5C), 120.98 (q, J = 542.98 Hz, 1C), 120.31 (q, J = 149.28 Hz, 1C), 83.75 (q, J = 34.72 Hz, 1C), 67.44 (s, 1C), 33.40 (br s, 2C), 29.73 (s, 1C) ppm; GCMS calcd for $C_{14}H_{12}F_6O_5S$ 406.0, found 406.0.

Benzyl 3-(Trifluoromethyl)bicyclo[1.1.0]butane-1-carboxylate (16). A solution of compound **15** (60 g, 148 mmol) in DMAc (1.2 L) at 0 °C was added with tBuOK (24.8 g, 222 mmol). The solution was stirred for 1 h at 0−10 °C. TLC (petroleum ether:ethyl acetate = 5:1) showed that the starting material (R_f = 0.7) was consumed, and one main spot (R_f = 0.8) was detected. Water (1.2 L) was added, and the mixture was extracted with MTBE (400 mL × 3). The organic layer was washed with brine (300 mL) and concentrated in vacuum. The crude product was purified by silica gel chromatography (eluting with petroleum ether/ethyl acetate = 100/1 to 4/1) to afford **16** as an oil (11.7 g, 46 mmol, 31% yield). Spectroscopic data of **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.54 (m, 5H), 5.11−5.29 (m, 2H), 2.77 (s, 2H), 1.43−1.52 (m, 2H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.39 (s, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.37 (s, 1C), 135.43 (s, 1C), 128.32−128.58 (m, 5C), 120.55−128.58 (m, 1C), 67.39 (s, 2C), 35.15 (s, 1C), 23.43 (q, J = 46.46 Hz, 1C), 17.17 (s, 1C) ppm; GCMS calcd for C13H11F3O2 256.0, found 256.0.

Benzyl 3-(Trifluoromethyl)cyclobut-1-ene-1-carboxylate (19a). The solution of compound **15** (20.0 g, 46.8 mmol) and TMEDA (10.9 g, 94.0 mmol) in DMF (120 mL) was stirred at 80 °C for 16 h. TLC (petroleum ether:ethyl acetate = 5:1) showed that the SM (R_f = 0.5) was consumed, and one main spot (R_f = 0.6) was detected. The solution was poured into water (600 mL). The solution was extracted with MTBE (500 mL × 3). The combined organic phase was washed with brine (100 × 2 mL), dried over Na_2SO_4, filtered, and concentrated in vacuum (30 mmHg, 45 °C). The crude product was purified by a column (SiO_2, petroleum ether/ethyl acetate = 100/1 to 10/1) to afford **19a** (9.1 g, 35.4 mmol, 75.0% yield) as a yellow oil. Spectroscopic data of **19a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.43 (m, 5H), 6.63 (d, J = 1.13 Hz, 1H), 5.22 (s, 2H), 3.41 (qdt, J = 8.53, 8.53, 8.53, 4.85, 1.66, 1.66 Hz, 1H), 2.91−2.99 (m, 1H), 2.79−2.87 (m, 1H) ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −71.78 (s, 3F) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.11 (s, 1C), 141.84 (s, 1C), 139.04 (q, J = 3.67 Hz, 1C), 135.40 (s, 1C), 128.31−128.79 (m, 5C), 125.51 (q, J = 274.88 Hz, 1C), 121.26−127.02 (m, 1C), 66.48 (s, 1C), 40.85 (q, J = 32.28 Hz, 1C), 29.80 (q, J = 3.67 Hz, 1C) ppm; GCMS calcd for $C_{13}H_{11}F_3O_2$ 256.1, found 256.1; HRMS calcd for $C_{13}H_{11}F_3O_2$ 255.0711, found 255.2368.

(*cis*)-3-(Trifluoromethyl)cyclobutane-1-carboxylic Acid 1 (*cis*). A solution of compound **19a** (8.45 g, 33.0 mmol) in ethyl acetate (169 mL) was added with Pd-C (10%, 1.7 g) under N_2. The resulting suspension was degassed under vacuum and purged with H_2 three times. The mixture was stirred under H_2 (15 Psi) at 25 °C for 4 h. TLC showed (petroleum ether:ethyl acetate = 5:1) that the SM (R_f = 0.6) was consumed. The reaction slurry was filtered through a pad Celite to obtain a filtrate. The organic phase was washed with brine (20 mL × 2), dried over Na_2SO_4, filtered, and concentrated in vacuum (30 mm Hg, 45 °C). The crude product was purified by a column (SiO_2, DCM/MeOH = 100/1 to 30/1) to afford **1** (*cis*) (5.5 g, 32.7 mmol, 99.0% yield) as a yellow oil. Spectroscopic data of **1** (*cis*): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 2.98−3.22 (m, 2H), 2.26−2.41 (m, 2H), 2.11−2.25 (m, 2H) ppm; ^{19}F NMR (376 MHz,

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DMSO-d_6) δ −72.47 (s, 3F) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.77 (s, 1C), 126.96 (q, J = 275.34 Hz, 1C), 32.13 (s, 1C), 31.53 (q, J = 30.32 Hz, 1C), 24.03 (q, J = 3.67 Hz, 1C) ppm; HRMS calcd for $C_6H_7F_3O_2$ 167.0398, found 167.0345.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00422.

PDF file containing NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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