Homologative Trifluoromethylation of Acetals

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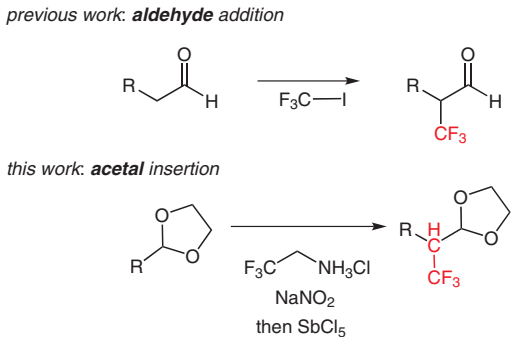
We dedicate this manuscript to Prof. Dr. Scott E. Denmark in honor of his 60th birthday.

Abstract: Trifluoroethyl α-insertion of acetals has been developed. Aromatic, heteroaromatic, and alkenyl acetals react with in situ generated (trifluoromethyl)diazomethane in the presence of antimony(V) chloride to furnish α-trifluoromethyl acetals. A stereoselective version of this transformation exploiting the acetal as a chiral auxiliary is also presented.

Key words: antimony, acetals, insertion, diazo compounds, trifluoromethyl group

Unique properties of fluorinated compounds in pharmaceutical, agrochemical, and materials industry[2] have stimulated recent development of methods to incorporate fluorine into organic scaffolds.[3] Despite the many impressive advances in this discipline, the introduction of trifluoromethyl groups onto aliphatic chains remains challenging. Previously reported approaches to access this moiety rely mainly on reactions of enolates via pathways involving organic halides, as electrophiles, or precursors to radical or organometallic intermediates.[4–6] The use of diazoalkane intermediates provides an alternative means to access these valuable compounds, yet relatively little has appeared involving these reactive species. Herein, we report a method for the introduction of trifluoroethyl groups into aromatic, heteroaromatic, and alkenyl acetals with in situ generated (trifluoromethyl)diazomethane (F_3CCHN_2), circumventing its handling and isolation (Scheme 1). A key feature of our protocol is the use of a strong Lewis acid, under conditions compatible with F_3CCHN_2 formation and the aqueous medium. This enables, for the first time, the direct synthesis of homologated trifluoromethyl-substituted acetals from acetals precursors.



Scheme 1 Comparison of work herein with prior tactics

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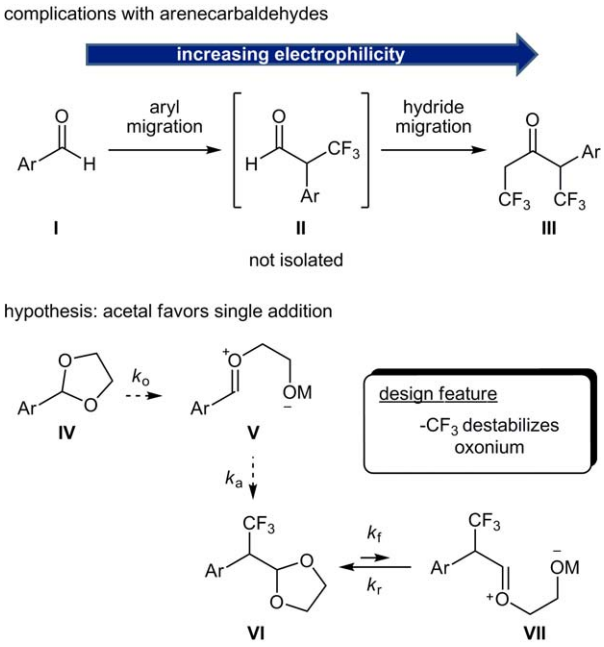
We have recently described the use of F_3CCHN_2 for the generation of synthetically useful building blocks via metal-catalyzed (Fe, Rh, Co) cyclopropanation and cyclopropenation,[7] as well as Lewis acid mediated processes.[8] As a part of this ongoing effort, we recently disclosed a strategy for aldehyde homologation/trifluoromethylation and cyclic ketone insertion to provide access to α-trifluoromethyl ketones.[9] Although aliphatic aldehydes may be converted into the homologated ketones cleanly, difficulties were encountered when aromatic aldehydes were employed as substrates (Scheme 2). In this respect, the fact that arenes display greater migratory aptitude than hydrides leads to a homologated trifluoromethylated aldehyde product which in turn participates in a second homologation, giving hexafluorinated ketones.



Scheme 2 Problem formulation and proposed solution

The observation of uncontrolled sequential migration for aromatic aldehydes prompted us to investigate other synthetic equivalents for the insertion reaction. Attributing the uncontrolled second homologation (Scheme 2, **II** → **III**) to the increased electrophilicity of trifluoromethylated aldehyde **II**, we envisioned that employment of acetals as synthetic equivalents of aldehydes could prevent the undesired second reaction. It was postulated that after the first insertion reaction of aromatic acetals (Scheme 2, **IV** → **VI**), subsequent formation of oxonium

VII would be disfavored due to the destabilizing effect of the trifluoromethyl group ($k_f < k_r$). Accordingly, we set out to investigate whether acetals would be suitable substrates for the homologative trifluoromethylation insertion reaction.

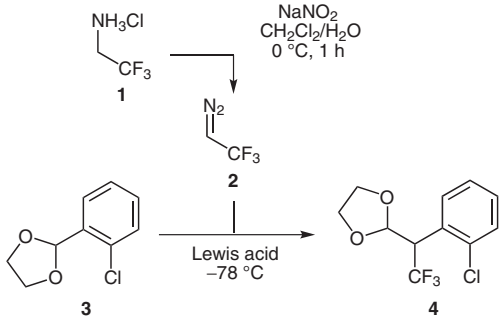
To our surprise, despite the rich chemistry of diazoalkanes, there is a single report by Doyle and co-workers of homologation of acetals with ethyl diazoacetate in the presence of $BF_3{\cdot}OEt_2$,[10] in which for all but two aldehydes examined mixtures of C–C and C–H migration products were observed, as well as cyclopropane products. Moreover, to the best of our knowledge, there are no examples involving fluorinated diazoalkanes.

We began by examining 2-phenyl-1,3-dioxolane with F_3CCHN_2, generated in situ, and $BF_3{\cdot}OEt_2$. Although the initial experimentation proved fruitful with electron-rich acetals, the procedure did not prove general, especially with more electron-deficient substrates.

A second screening was conducted with 2-(2-chlorophenyl)-1,3-dioxolane (**3**) with several Lewis acids, which led to the identification of $SbCl_5$ as optimal (Table 1). A control experiment with HCl was also conducted, as HCl could arise from a hydrolytic decomposition of $SbCl_5$, but no product formation was observed (Table 1, entry 7).

With a convenient protocol[11] in hand, the substrate scope of this reaction was next examined (Table 2). Both electron-rich and electron-poor aryl acetals smoothly afforded

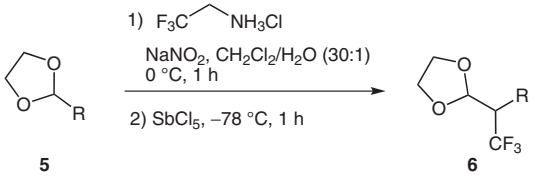
Table 1 Lewis Acid Screening[a]

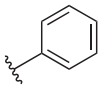
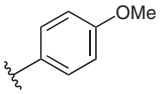
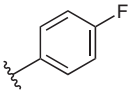
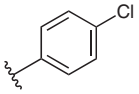
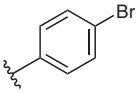
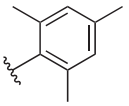
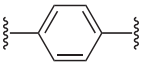
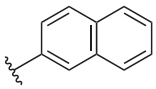
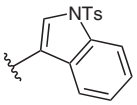
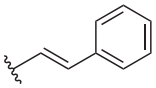


Entry	Lewis acid	Yield[b] (%)
1	$BF_3{\cdot}OEt_2$	n.r.[c]
2	$AlCl_3$	26
3	$ZrCl_4$	
4	$SnCl_4$	28
5	$SbCl_5$	76
6	$TiCl_4$	64
7	HCl	n.r.[c]

[a] Reaction conditions: $F_3CCH_2NH_3Cl$ (3.0 equiv), $NaNO_2$ (3.6 equiv), CH_2Cl_2–H_2O (30:1), stirring, 0 °C, 1 h; then, substrate (0.22 mmol, 1.0 equiv), Lewis acid (1.8 equiv), –78 °C.
[b] Yield determined by ^{19}F NMR integration relative to (trifluoromethyl)benzene as the internal standard.
[c] n.r. = no reaction.

Table 2 Substrate Scope[a]



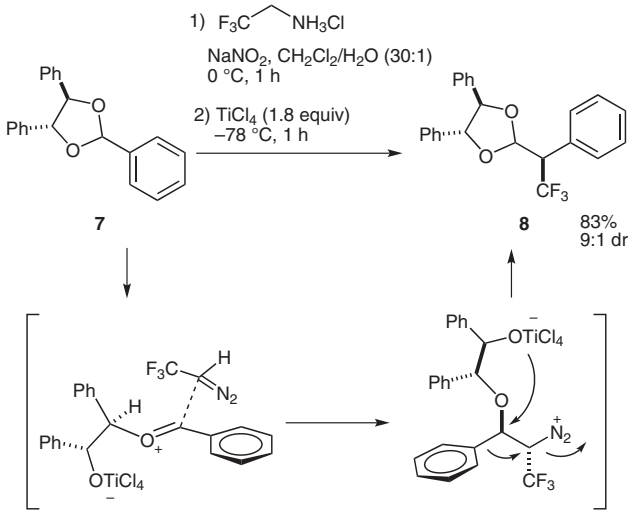
Entry	6	R	Yield[b] (%)
1	**6a**		69
2	**6b**		76
3	**6c**		62
4	**6d**		65
5	**6e**		57
6	**6f**		63
7	**6g**		51[c]
8	**6h**		82
9	**6i**		76
10	**6j**		70
11	**6k**		81
12	**6l**		52[d]

[a] Reaction conditions: $F_3CCH_2NH_3Cl$ (3.0 equiv), $NaNO_2$ (3.6 equiv), CH_2Cl_2–H_2O (30:1), stirring, 0 °C, 1 h; then, substrate (0.22 mmol, 1.0 equiv), $SbCl_5$ (1.0 equiv), –78 °C.
[b] Isolated yield after purification by flash chromatography.
[c] Performed with $SbCl_5$ (1.5 equiv).
[d] Lower yield due to product volatility.

the α-insertion products in good yields (Table 2, entries 1–5). Sterically hindered phenyl groups were also tolerated as substrates (Table 2, entry 6). We were pleased to find

that the reaction could be extended to heteroaromatics, with reactions of 2-pyrrole and 3-indole acetals proceeding well under the standard reaction conditions (Table 2, entries 9 and 10). The method was also applicable to alkenyl acetals, where alkene migration took place to furnish the α-trifluoromethyl-substituted β,γ-unsaturated acetals (Table 2, entries 11 and 12). These results were particularly interesting since convenient methods to construct an allylic trifluoromethyl functionality are scarce.[12]

Application of this strategy to introduce the trifluoromethyl group in a stereoselective manner exploiting a chiral acetal auxiliary was envisioned (Scheme 3).[13] In this respect, we disclose our preliminary observations toward this endeavor. Acetal **7**, derived from optically active stilbene diol and benzaldehyde, was prepared and investigated. For this case, $TiCl_4$ proved to be a superior Lewis acid, yielding the desired product **8** in good diastereoselectivity (dr 9:1) and yield (83%). Hydrogenolytic cleavage of **8** furnished enantioenriched α-trifluoromethyl aldehyde without racemization, which was immediately reduced for the purpose of isolation and characterization.[14]



Scheme 3 Formal enantioselective trifluoroethyl α-insertion

In summary, we have disclosed an insertion strategy using in situ generated F_3CCHN_2 to furnish α-trifluoromethyl acetals, which can be readily cleaved to yield the corresponding aldehydes. This methodology is complementary to other existing strategies to access these useful compounds, as it employs $F_3CCH_2NH_2$ instead of CF_3I. Importantly, the observations we describe represent the first example of the use of acetals as starting materials for the introduction of fluorinated fragments. The ability to use heteroaromatic and alkenyl substrates has important implications in medicinal chemistry. A preliminary result to obtain enantioenriched α-trifluoromethyl aldehydes using a chiral acetal has also been presented. Further investigation along this front will be reported in due course.

Unless otherwise noted, reagents were purchased from commercial suppliers and used without further purification, and all reactions were carried out under an atmosphere of argon. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} TLC glass plates which were visualized with 254 nm light and $KMnO_4$ staining solutions followed by heating. Purification of reaction products was carried out by flash chromatography using Brunschwig silica gel 32–63, 60 Å and technical grade pentane–Et_2O, which were distilled prior to use, as eluent with 0.3–0.5 bar pressure. Acetals were prepared by the reaction of the corresponding aldehyde with ethylene glycol and catalytic *p*-toluenesulfonic acid monohydrate in benzene with azeotropic removal of water. Analytical data were in accordance with previously reported values.[15] ^{1}H NMR spectra were recorded at r.t. on a Varian Mercury 300 MHz or a Bruker AV 400 MHz spectrometer and are reported in ppm with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm). ^{13}C NMR spectra were recorded with ^{1}H decoupling on a Varian Mercury 300 or a Bruker AV 400 spectrometer (at 75 MHz and 100 MHz, respectively) with the solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm). Infrared spectra were measured neat on a Perkin-Elmer Spectrum BX FT-IR spectrometer. The peaks are reported as absorption maxima (ν, cm^{-1}). Mass spectral data were obtained at the mass spectrometry service operated by the Laboratory of Organic Chemistry at the ETHZ on a VG-TRIBRID instrument for electron impact ionization (EI). The enantiomeric excess was determined by supercritical-fluid chromatography (SFC) on a Jasco 2080 Plus system. The optical rotation was measured with a Jasco DID-1000 Polarimeter (10 cm, 2 mL cell). The absolute configuration was determined by comparison with a reported $[\alpha]_D$ value.

Lewis Acid Screen (Table 1); General Procedure

To a stirred soln of $F_3CCH_2NH_3Cl$ (3.0 equiv), CH_2Cl_2 (3 mL), and H_2O (0.1 mL) in a sealed Schlenk tube at 0 °C was added $NaNO_2$ (3.6 equiv), and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then cooled to –78 °C by stirring in a dry ice–acetone bath for 10 min, which was followed by addition of the substrate (0.22 mmol, 1.0 equiv) and the Lewis acid (1.8 equiv). The mixture was stirred for 3 h, then the reaction was quenched by the addition of MeOH (3 mL) and then sat. aq $NaHCO_3$ (10 mL). The mixture was warmed to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The yield was determined by ^{19}F NMR analysis with (trifluoromethyl)benzene as the internal standard.

Trifluoroethyl α-Insertion (Table 2); General Procedure

To a stirred soln of $F_3CCH_2NH_3Cl$ (3.0 equiv), CH_2Cl_2 (3 mL), and H_2O (0.1 mL) in a sealed Schlenk tube at 0 °C was added $NaNO_2$ (3.6 equiv), and the resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was then cooled to –78 °C by stirring in a dry ice–acetone bath for 10 min, which was followed by addition of the substrate (0.22 mmol, 1.0 equiv) and $SbCl_5$ (1.0 equiv). The mixture was stirred for 1 h, then the reaction was quenched by the addition of MeOH (3 mL) and then sat. aq $NaHCO_3$ (10 mL). The mixture was warmed to r.t. and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via the respective described method.

2-(2,2,2-Trifluoro-1-phenylethyl)-1,3-dioxolane (6a)

The crude product was purified via flash chromatography (pentane–Et_2O, 29:1) to afford **6a** as a colorless oil; yield: 35 mg (69%).

IR (neat): 2956, 2895, 1498, 1457, 1401, 1365, 1251, 1163, 1145, 1106, 1048, 1032, 943, 875, 805 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 5.44 (d, *J* = 4.3 Hz, 1 H), 3.89–3.76 (m, 4 H), 3.58 (qd, *J* = 9.8, 4.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.0 (q, *J* = 1.9 Hz), 130.1, 128.5, 128.4, 127.4 (q, *J* = 280.7 Hz), 101.8 (q, *J* = 2.5 Hz), 65.3, 65.2, 54.2 (q, *J* = 25.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.2 (d, *J* = 9.7 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_{10}F_3O_2$: 231.0627; found: 231.0621.

2-(2,2,2-Trifluoro-1-(4-methoxyphenyl)ethyl)-1,3-dioxolane (6b)
The crude product was purified via flash chromatography (pentane–Et_2O, 14:1) to afford **6b** as a white solid; yield: 44 mg (76%).

IR (neat): 3007, 2962, 2929, 2902, 2837, 2361, 1883, 1616, 1519, 1305, 1273, 1244, 1162, 1118, 1031, 997, 939, 871, 816, 682 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (dm, *J* = 8.7 Hz, 2 H), 6.90 (dm, *J* = 8.8 Hz, 2 H), 5.41 (d, *J* = 4.2 Hz, 1 H), 3.90–3.76 (m, 7 H), 3.54 (qd, *J* = 9.8, 4.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.2, 130.9, 125.2 (q, *J* = 279.4 Hz), 122.7, 113.7, 101.6, 65.3, 55.2, 53.4 (q, *J* = 25.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –65.4 (d, *J* = 9.8 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{13}F_3O_3$: 262.0812; found: 262.0810.

2-(2,2,2-Trifluoro-1-(4-fluorophenyl)ethyl)-1,3-dioxolane (6c)
The crude product was purified via flash chromatography (pentane–Et_2O, 39:1) to afford **6c** as a colorless oil; yield: 34 mg (62%).

IR (neat): 2956, 2895, 2360, 2335, 1609, 1513, 1262, 1227, 1165, 1145, 1110, 1046, 944, 825 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (dd, *J* = 8.7, 5.4 Hz, 2 H), 7.05 (tm, *J* = 8.7 Hz, 2 H), 5.41 (d, *J* = 3.9 Hz, 1 H), 3.92–3.71 (m, 4 H), 3.60 (qd, *J* = 9.8, 3.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 247.4 Hz), 131.9 (d, *J* = 8.1 Hz), 126.6, 125.2 (q, *J* = 279.9 Hz), 115.4 (d, *J* = 21.5 Hz), 101.5 (q, *J* = 2.1 Hz), 65.3, 65.2, 53.3 (q, *J* = 25.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.5 (d, *J* = 9.7 Hz), –113.6.

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_9F_4O_2$: 249.0533; found: 249.0497.

2-(1-(4-Chlorophenyl)-2,2,2-trifluoroethyl)-1,3-dioxolane (6d)
The crude product was purified via flash chromatography (pentane–Et_2O, 39:1) to afford **6d** as a colorless oil; yield: 38 mg (65%).

IR (neat): 2961, 2894, 2359, 2335, 1599, 1495, 1254, 1164, 1145, 1114, 1104, 1093, 1039, 1016, 943, 876, 819, 806, 728, 678 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 4 H), 5.41 (d, *J* = 3.8 Hz, 1 H), 3.91–3.72 (m, 4 H), 3.59 (qd, *J* = 9.7, 3.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6, 131.5, 129.3 (q, *J* = 1.7 Hz), 128.6, 125.1 (q, *J* = 280.6 Hz), 101.4 (q, *J* = 2.5 Hz), 65.4, 65.2, 53.5 (q, *J* = 25.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.4 (d, *J* = 9.6 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_9ClF_3O_2$: 265.0238; found: 265.0243.

2-(1-(4-Bromophenyl)-2,2,2-trifluoroethyl)-1,3-dioxolane (6e)
The crude product was purified via flash chromatography (pentane–Et_2O, 49:1) to afford **6e** as a colorless oil; yield: 39 mg (57%).

IR (neat): 2956, 2892, 2359, 2335, 1594, 1492, 1252, 1163, 1145, 1114, 1104, 1037, 1012, 943, 814, 724, 674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dm, *J* = 8.6 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 5.41 (d, *J* = 3.8 Hz, 1 H), 3.90–3.73 (m, 4 H), 3.58 (qd, *J* = 9.7, 3.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.8, 131.6, 129.8 (q, *J* = 1.9 Hz), 125.0 (q, *J* = 280.5 Hz), 122.8, 101.3 (q, *J* = 2.5 Hz), 65.4, 65.2, 53.5 (q, *J* = 25.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.4 (d, *J* = 9.7 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{11}H_9BrF_3O_2$: 308.9733; found: 308.9739.

2-(2,2,2-Trifluoro-1-mesitylethyl)-1,3-dioxolane (6f)
The crude product was purified via flash chromatography (pentane–Et_2O, 49:1) to afford **6f** as a white, amorphous solid; yield: 38 mg (63%).

IR (neat): 2971, 2950, 2895, 2356, 2323, 1613, 1575, 1485, 1453, 1247, 1169, 1133, 1103, 1059, 1020, 943, 850, 823, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, *J* = 3.3 Hz, 2 H), 5.70 (d, *J* = 6.8 Hz, 1 H), 4.20–3.98 (m, 3 H), 3.96–3.88 (m, 1 H), 3.87–3.78 (m, 1 H), 2.43 (s, 3 H), 2.37 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 137.7, 137.3, 131.2, 129.5, 126.4 (q, *J* = 2.0 Hz), 126.0 (q, *J* = 281.5 Hz), 101.0 (q, *J* = 2.0 Hz), 65.3, 64.9, 51.2 (q, *J* = 26.4 Hz), 21.8, 21.6 (q, *J* = 3.5 Hz), 20.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.1 (d, *J* = 10.5 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{17}F_3O_2$: 274.1181; found: 274.1169.

1,4-Bis(1-(1,3-dioxolan-2-yl)-2,2,2-trifluoroethyl)benzene (6g)
Following the general procedure using $SbCl_5$ (1.5 equiv), the crude product was purified via flash chromatography (pentane–Et_2O, 4:1) to afford **6g** as a white, amorphous solid; yield: 44 mg (51%).

IR (neat): 2956, 2902, 2847, 2359, 1522, 1401, 1321, 1245, 1127, 1100, 1055, 1025, 943, 853, 814 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (s, 4 H), 5.43 (d, *J* = 3.9 Hz, 1 H), 5.42 (d, *J* = 3.9 Hz, 1 H), 3.92–3.71 (m, 8 H), 3.60 (qd, *J* = 9.8, 3.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.1, 130.2, 125.2 (q, *J* = 280.8 Hz), 101.6 (q, *J* = 2.4 Hz), 65.3, 65.3, 53.7 (q, *J* = 25.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –65.1 (d, *J* = 9.8 Hz), –65.1 (d, *J* = 9.8 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{16}H_{15}F_6O_4$: 385.0869; found: 385.0873.

2-(2,2,2-Trifluoro-1-(naphthalen-2-yl)ethyl)-1,3-dioxolane (6h)
The crude product was purified via flash chromatography (hexane–Et_2O, 9:1) to afford **6h** as a pale yellow, amorphous solid; yield: 51 mg (82%).

IR (neat): 3064, 2956, 2893, 1601, 1510, 1408, 1372, 1326, 1265, 1102, 1039, 1016, 822, 749, 675 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.83 (m, 4 H), 7.55–7.48 (m, 3 H), 5.55 (d, *J* = 4.1 Hz, 1 H), 3.90–3.73 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 132.9, 129.7, 128.2, 127.9, 127.5, 127.2, 126.3, 126.2, 125.3 (q, *J* = 280.3 Hz), 101.7, 65.3, 54.3 (q, *J* = 25.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –64.9 (d, *J* = 9.7 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}F_3O_2$: 282.0868; found: 282.0861.

2-(1-(1,3-Dioxolan-2-yl)-2,2,2-trifluoroethyl)-1-tosyl-1*H*-pyrrole (6i)
The crude product was purified via flash chromatography (pentane–Et_2O, 9:1) to afford **6i** as a white, amorphous solid; yield: 63 mg (76%).

IR (neat): 3128, 2996, 2891, 1595, 1469, 1402, 1366, 1359, 1303, 1251, 1143, 1049, 881, 810, 750, 701, 669 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 2 H), 7.38 (dd, *J* = 3.4, 1.7 Hz, 1 H), 7.28 (d, *J* = 8.0 Hz, 2 H), 6.47 (br, 1 H), 6.30 (t, *J* = 3.4 Hz, 1 H), 5.32 (d, *J* = 4.2 Hz, 1 H), 4.70 (qd, *J* = 9.2, 4.2 Hz, 1 H), 3.83–3.73 (m, 3 H), 3.71–3.61 (m, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 136.3, 129.8, 126.9, 124.4 (q, *J* = 280.4 Hz), 124.0, 123.9 (q, *J* = 2.3 Hz), 116.5, 111.8, 101.6 (q, *J* = 2.2 Hz), 65.3, 65.2, 44.7 (q, *J* = 26.5 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.3 (d, *J* = 9.2 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}F_3NO_4S$: 375.0752; found: 375.0751.

3-(1-(1,3-Dioxolan-2-yl)-2,2,2-trifluoroethyl)-1-tosyl-1*H*-indole (6j)

The crude product was purified via flash chromatography (pentane–Et_2O, 4:1) to afford **6j** as a white, amorphous solid; yield: 66 mg (70%).

IR (neat): 2976, 2899, 1596, 1444, 1370, 1258, 1165, 1112, 1090, 1073, 1038, 812, 736, 665 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.2 Hz, 1 H), 7.79–7.73 (m, 3 H), 7.56 (d, *J* = 7.8 Hz, 1 H), 7.38–7.19 (m, 4 H), 5.50 (d, *J* = 2.9 Hz, 1 H), 3.98 (qd, *J* = 9.6, 2.8 Hz, 1 H), 3.91–3.75 (m, 3 H), 3.64–3.55 (m, 1 H), 2.34 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 135.1, 134.5, 130.8, 129.8, 126.8, 126.5, 125.1 (q, *J* = 280.4 Hz), 124.9, 123.5, 119.5, 113.6, 111.5, 101.0 (q, *J* = 2.5 Hz), 65.7, 65.1, 45.2 (q, *J* = 26.6 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.3 (d, *J* = 9.7 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{18}F_3NO_4S$: 425.0909; found: 425.0900.

2-((*E*)-1,1,1-Trifluoro-4-phenylbut-3-en-2-yl)-1,3-dioxolane (6k)

The crude product was purified via flash chromatography (pentane–Et_2O, 19:1) to afford **6k** as a white, amorphous solid; yield: 46 mg (81%).

IR (neat): 2959, 2895, 1450, 1394, 1325, 1257, 1149, 1100, 1039, 972, 948, 870, 748, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.39 (m, 2 H), 7.38–7.24 (m, 3 H), 6.67 (d, *J* = 16.0 Hz, 1 H), 6.14 (dd, *J* = 16.0, 9.4 Hz, 1 H), 5.29 (d, *J* = 2.8 Hz, 1 H), 4.22–3.64 (m, 4 H), 3.33–3.17 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.8, 136.0, 128.5, 128.1, 126.5, 125.2 (q, *J* = 280.0 Hz), 116.8 (q, *J* = 2.3 Hz), 101.0 (q, *J* = 2.7 Hz), 65.8, 65.2, 52.0 (q, *J* = 25.4 Hz).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –67.3 (d, *J* = 9.2 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{13}H_{12}F_3O_2$: 257.0784; found: 257.0777.

2-(1,1,1-Trifluoro-4-methylpent-3-en-2-yl)-1,3-dioxolane (6l)

The crude product was purified via flash chromatography (pentane–Et_2O, 79:1) to afford **6l** as a colorless oil; yield: 24 mg (52%).

IR (neat): 2971, 2892, 2359, 1679, 1446, 1402, 1326, 1256, 1160, 1149, 1103, 1051, 1037, 1018, 876 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.18–5.13 (m, 1 H), 5.15 (d, *J* = 3.5 Hz, 1 H), 4.00–3.84 (m, 4 H), 3.37–3.25 (m, 1 H), 1.80 (d, *J* = 1.4 Hz, 3 H), 1.69 (d, *J* = 1.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 125.7 (q, *J* = 280.5 Hz), 112.4 (q, *J* = 2.3 Hz), 101.6 (q, *J* = 2.8 Hz), 65.5, 65.2, 47.1 (q, *J* = 25.1 Hz), 26.1, 18.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.5 (d, *J* = 9.2 Hz).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_9H_{12}F_3O_2$: 209.0784; found: 209.0776.

(4*R*,5*R*)-2,4,5-Triphenyl-1,3-dioxolane (7)

Compound **7** was obtained by following a reported procedure.[16] Analytical data were in accordance with reported values.

(4*R*,5*R*)-4,5-Diphenyl-2-((*R*)-2,2,2-trifluoro-1-phenylethyl)-1,3-dioxolane (8)

Following the general procedure using $TiCl_4$ (1.8 equiv), the crude product was purified via flash chromatography (pentane–Et_2O, 4:1) to afford **8** as a viscous oil; yield: 70 mg (83%). The product was obtained as an inseparable mixture of diastereomers (dr 9:1).

IR (neat): 3033, 2894, 2361, 2335, 1496, 1454, 1351, 1315, 1265, 1167, 1137, 1115, 1046, 1026, 761 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.52 (m, 2 H), 7.45–7.38 (m, 3 H), 7.33–7.19 (m, 6 H), 7.17–7.09 (m, 2 H), 7.04* (dd, *J* = 7.5, 2.0 Hz, 0.2 H), 6.90 (dd, *J* = 8.0, 1.4 Hz, 1.8 H), 6.02 (d, *J* = 2.4 Hz, 0.9 H), 5.99* (d, *J* = 3.2 Hz, 0.1 H), 4.72* (d, *J* = 8.3 Hz, 0.1 H), 4.68 (d, *J* = 8.3 Hz, 0.9 H), 4.43* (d, *J* = 8.2 Hz, 0.1 H), 4.38 (d, *J* = 8.3 Hz, 0.9 H), 3.86 (qd, *J* = 10.0, 2.5 Hz, 1 H); assignable peaks of the minor isomer are marked with asterisks.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2*, 137.1, 135.4, 135.3*, 130.7 (q, *J* = 1.7 Hz), 130.6, 128.6, 128.6, 128.5, 128.5, 128.5, 128.3, 126.8, 126.3, 125.45 (q, *J* = 280.7 Hz), 102.4 (q, *J* = 2.4 Hz), 102.2* (q, *J* = 2.4 Hz), 87.0*, 86.6, 85.4, 84.9*, 54.3 (q, *J* = 25.5 Hz); assignable peaks of the minor isomer are marked with asterisks.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –64.4* (d, *J* = 9.9 Hz, 0.3 F), –64.8 (d, *J* = 10.0 Hz, 2.7 F).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{23}H_{18}F_3O_2$: 383.1253; found: 383.1252.

(*R*)-3,3,3-Trifluoro-2-phenylpropan-1-ol

To a stirred soln of (4*R*,5*R*)-4,5-diphenyl-2-((*R*)-2,2,2-trifluoro-1-phenylethyl)-1,3-dioxolane (**8**; 70 mg, 0.18 mmol) in MeOH (1.6 mL) was added 10% Pd/C (95 mg, 0.090 mmol), and the mixture was stirred for 12 h under an atmosphere of H_2. The reaction mixture was then filtered, with MeOH (2.0 mL) washing. The filtrate was cooled to –78 °C, $NaBH_4$ (140 mg, 3.6 mmol) was added, and the mixture was stirred at –78 °C for 1 h. Then, the reaction was quenched by the addition of sat. aq NH_4Cl (2 mL). The resulting mixture was warmed to r.t. and diluted with sat. aq $NaHCO_3$ (10 mL), which was followed by extraction with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified via flash chromatography (pentane–Et_2O, 9:1) to afford the product as a white, amorphous solid; yield: 24 mg (69%). Analytical data were in accordance with reported values[14] and the absolute stereochemistry was determined as *R* by a comparison of $[\alpha]_D$ values.

$[\alpha]_D^{21}$ +29.5 (*c* 0.50, $CHCl_3$) [Lit.[14] $[\alpha]_D^{28}$ +33.3 (*c* 0.6, $CHCl_3$)].

SFC [Daicel Chiralcel OJ-H, CO_2–MeOH (98:2), 2 mL·min^{-1}, 25 °C, 200 nm]: 83% ee [t_R = 7.5 min (minor), 8.2 min (major)].

IR (neat): 3359, 2956, 2360, 2335, 1493, 1454, 1361, 1318, 1254, 1156, 1112, 1028, 873, 795, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.31 (m, 5 H), 4.20 (ddd, *J* = 11.5, 7.6, 5.8 Hz, 1 H), 4.04 (ddd, *J* = 11.5, 7.7, 5.6 Hz, 1 H), 3.62–3.50 (m, 1 H), 1.54 (dd, *J* = 7.6, 5.6 Hz, 1 H, OH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.5 (q, *J* = 2.1 Hz), 129.1, 129.0, 128.7, 126.1 (q, *J* = 280.4 Hz), 61.4 (q, *J* = 2.8 Hz), 52.6 (q, *J* = 25.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.4 (d, *J* = 9.4 Hz).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_9F_3O$: 190.0605; found: 190.0597.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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