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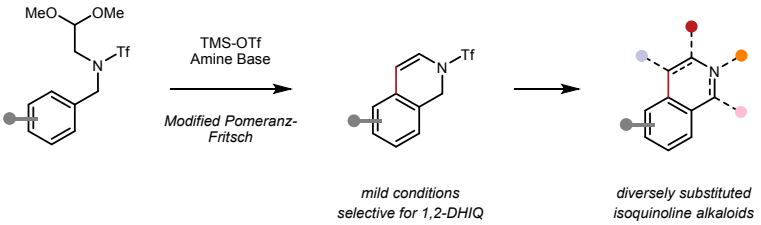
Supporting Information Placeholder

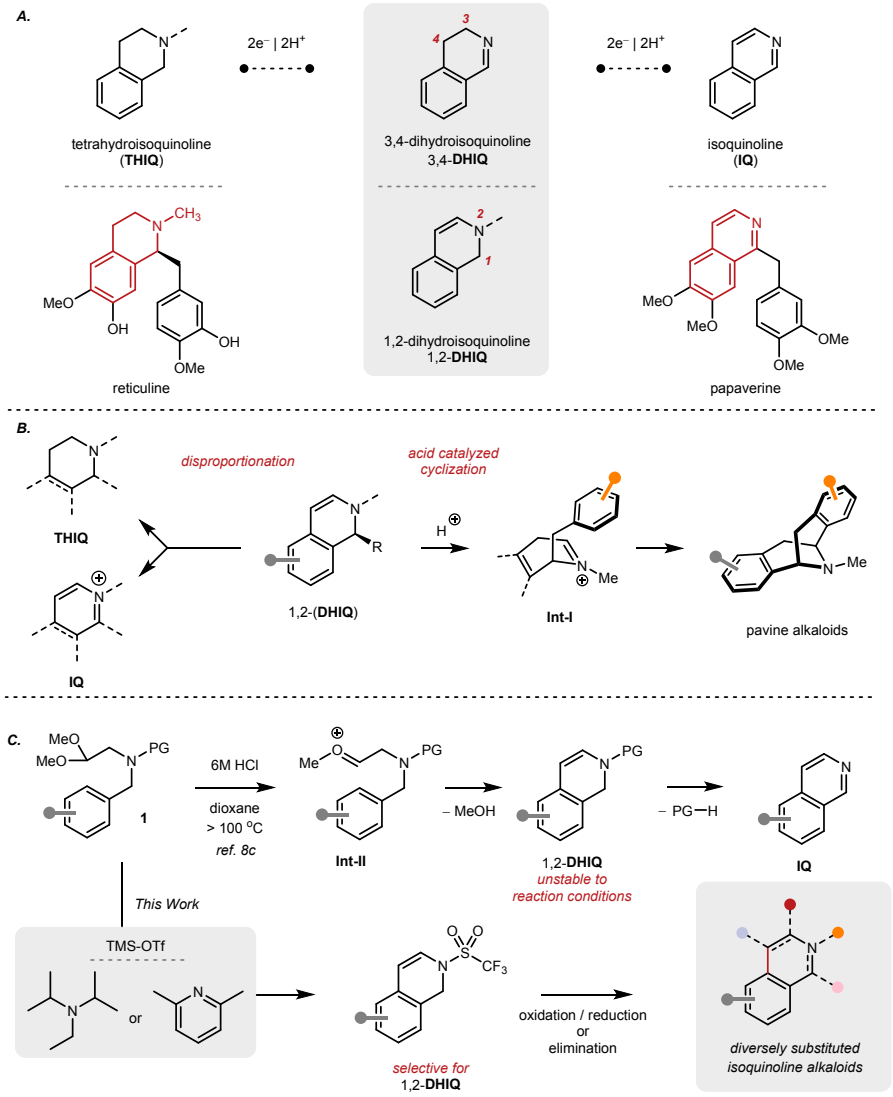


ABSTRACT: Isoquinolines (**IQs**) and their derivatives are present in many natural products and biologically active small molecules. Herein, we report a modified procedure for the classical Pomeranz-Fritsch protocol, which expands the scope of 1,2-dihydroisoquinoline (**DHIQs**) products. 1,2-**DHIQs** are an attractive branch point for the synthesis of **IQs**, but because of their innate reactivity, they have remained difficult to prepare. We demonstrate that the Fujioka/Kita conditions, combining trimethylsiyltriflate (TMSOTf) and an amine base, activate dimethylacetals required for Pomeranz-Fritsch cyclization under sufficiently mild conditions to prepare a broad range of 1,2-**DHIQ** products. We also demonstrate the synthetic value of these **DHIQs** by further functionalization to either reduced tetrahydroisoquinoline (**THIQ**) or fully aromatized **IQ** natural products.

INTRODUCTION

Isoquinoline alkaloids contain heterocyclic motifs that are commonly found in biologically active small molecules (Scheme 1A).[1] The scaffold appears most commonly in two discrete redox tautomeric forms that constitute a formal $4e^- \mid 4H^+$ redox couple. These are the fully saturated 1,2,3,4-tetrahydroisoquinolines (**THIQs**) or the aromatized isoquinonlines (**IQs**) (Scheme 1A).[2] The intermediary dihydroisoquinonlines (**DHIQs**) can exist as either 1,2- or 3,4-dihydro-isomers, and while they are less commonly encountered as natural products, both isomers have been the targets of previous synthetic studies.[3] 3,4-**DHIQs** are immediate products from the classic Bischler-Napieralski synthesis,[4] and are well-known synthetic precursors to enantiomerically pure 1-substituted **THIQ**s by asymmetric hydrogenation.[5] By comparison, the synthesis and isolation of 1,2-**DHIQs** is less well-developed,[6] despite their importance as intermediates in the synthesis of alkaloid natural products, including the pavines (Scheme 1B, right).[7] Classical methods for their preparation include the Pomeranz-Fritsch cyclization of benzylamine dimethyl acetals (Scheme 1C).[3,8] However, the enamine of the 1,2-**DHIQ** product can be unstable under these conditions, and it is common for either acid-mediated elimination[8c] or disproportionation[6] to lead to mixtures of **IQ** and **THIQ** (Scheme 1B, left). This has limited the scope of the Pomeranz-Fritsch, which typically requires strong aqueous acid (6M) and reaction temperatures in excess of 100 °C under Jackson's typical conditions.[8c] Modifications have been reported, including Perchonock's[9] use of excess aluminum trichloride ($AlCl_3$, >4 equiv.) at room temperature, and Miranda's[10] use of triflouoroacetic acid as a solvent at 50 °C. However, in spite of these adjustments, Pomeranz-Fritsch reactions remain capricious, and 1,2-**DHIQs** are more commonly prepared by partial dearomatization of **IQs**,[11,12] or transition-metal mediated annulation reactions.[13] Each comes with its own set of limitations, including the need for a previously constructed **IQ** core, the potential for over-reduction to the **THIQ**, or a carbonyl at C1 that leads to isoquinolinones.[14]

Despite its limitations, the Pomeranz-Fritsch cyclization provides an attractive disconnection for preparing 1,2-**DHIQs** from readily available acyclic starting materials.[3] Recognizing that the use of strong acids presents challenges of chemoselectivity, we questioned whether conditions developed by Fujioka and Kita,[15] combining a silyl triflate and a sterically encumbered pyridine base, could be used in their place, to allow acetal activation under milder, more chemoselective conditions (**Scheme 1c**). Herein, we report the success of this hypothesis, and demonstrate the synthetic value of the resulting 1,2-**DHIQs** for the preparation of either **IQ** or **THIQ** derivatives.[2,6]



Scheme 1. A) Redox States of Isoquinoline Compounds. B) Unique properties of 1,2-**DHIQ**. C) This Work: An Improved Pomeranz-Fritsch Synthesis of 1,2-**DHIQ** and other isoquinoline compounds.

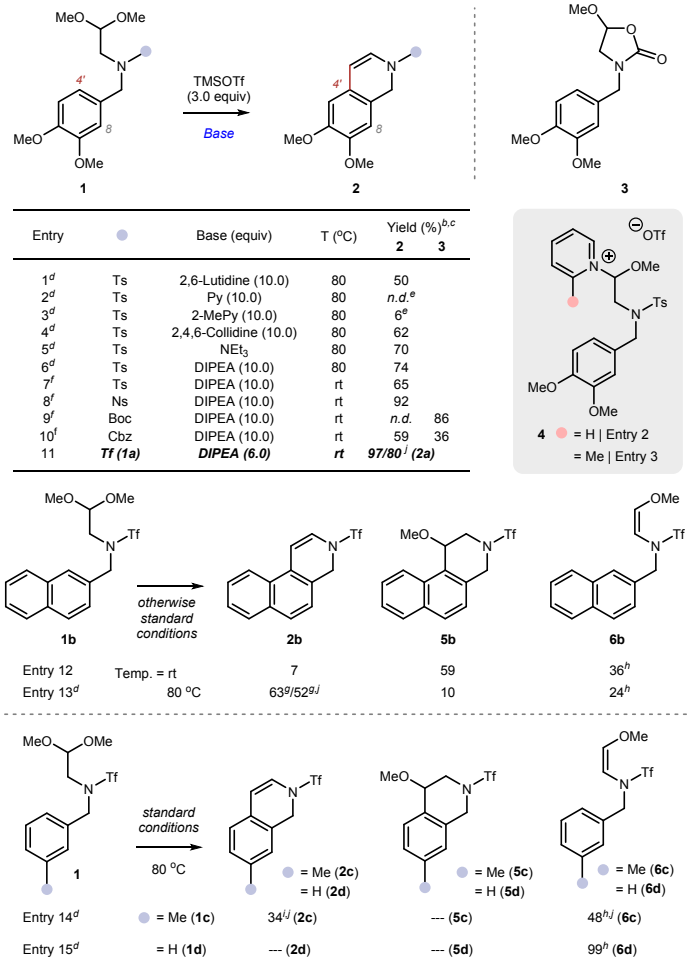
RESULTS AND DISCUSSION

As a point of departure, we selected substrate **1a** for our optimization studies, anticipating a regioselective cyclization at C4′ (isoquinoline numbering) based upon steric effects (Table 1). The desired 1,2-**DHIQ** product **2a** would possess a 5,6-dimethoxy substitution pattern that is widely found in isoquinoline alkaloid natural products.[3] Under Fujioka and Kita's[15] previously reported conditions, consisting of TMSOTf (3 equiv.) and 2,6-lutidine (10 equiv.) in 1,2-DCE at 80 °C, we obtained an encouraging yield of 50%, along with the formation of a complex mixture (Entry 1). The nature of the amine base has a profound impact on the course of the reaction, and using less sterically demanding pyridines resulted in the formation of non-cyclized pyridinium salts **4** (Entries 2 and 3), which have been observed previously.[15] While the use of 2,4,6-collidine provided some improvement (Entry 4), it was not until we evaluated sterically encumbered tertiary amines that we observed yields of 70% or higher (Entries 5 and 6). This stands in contrast to the literature, where pyridine bases have typically outperformed aliphatic amines in Fujioka/Kita protocols.[15-16] When using diisopropylethylamine (DIPEA), we also observed a dramatic increase in rate (4h to 15 min), allowing us to reduce the reaction temperature from 80 °C to room temperature (Entry 7). Next, we explored the effects of the substituent on nitrogen, and observed an improved yield of 92% for the *N*-nosyl derivative (Entry 8).[17] More Lewis-basic carbonate groups, including Boc or Cbz, were incompatible with the reaction conditions, and led instead to competitive formation of cyclic carbamate **3** (Entries 9 and 10). While both tosyl- and nosyl-groups performed well, the resulting products were difficult to purify by standard chromatography, leading to diminished isolated yields. This complication was addressed by using the corresponding triflate and lowering the quantity of DIPEA to 6 equivalents (Entry 11), which allowed us to maintain NMR yields in excess of 95% with more straightforward purification (1.0 mmol scale, 80% isolated yield, 259.4 mg).

Since the Pomeranz-Fritsch cyclization follows well-established trends for electrophilic aromatic substitution

(**$E_{Ar}S$**), less electron-rich aromatic rings were more reluctant to undergo cyclization under our standard conditions. For example, naphthyl substrate **1b** afforded only 7% yield of **2b**, along with a mixture of the intermediate **5b** and the elimination byproduct **6b** (Entry 12). Notably, **6b** is formed as a 5:1 mixture of olefin isomers in favor of the (*Z*)-configured vinyl ether.[18] Nevertheless, synthetically useful reactivity for this more recalcitrant substrate could be recovered by heating the reaction to 80 °C in 1,2-DCE, to provide the desired product in an improved yield of 63% (Entry 13). We observed similar amounts of premature elimination in both cases, suggesting that vinyl ethers **6b** are not reaction intermediates, but rather products of an irreversible shunt that decreases selectivity. Benzylic ether **5b** is a constructive intermediate that could be productively converted to the product at elevated temperatures.[19] As the aromatic nucleophile became less electron rich, we observed decreasing yields of the 1,2-**DHIQ** product, such that 3-methylphenyl substrate **1c** afforded only a 34% yield of **2c** under our more forcing conditions, and phenyl substrate **1d** did not undergo cyclization at all. In both cases, elimination to the vinyl ether **6** was competitive, and accounted for the majority of the reaction's mass balance.

Table 1. Reaction Optimization and Substituent Effects.[a]



Entry		Base (equiv)	T (°C)	Yield (%)[b,c] 2	3
1[d]	Ts	2,6-Lutidine (10.0)	80	50	
2[d]	Ts	Py (10.0)	80	*n.d.*[e]	
3[d]	Ts	2-MePy (10.0)	80	6[e]	
4[d]	Ts	2,4,6-Collidine (10.0)	80	62	
5[d]	Ts	NEt_3	80	70	
6[d]	Ts	DIPEA (10.0)	80	74	
7[f]	Ts	DIPEA (10.0)	rt	65	
8[f]	Ns	DIPEA (10.0)	rt	92	
9[f]	Boc	DIPEA (10.0)	rt	*n.d.*	86
10[f]	Cbz	DIPEA (10.0)	rt	59	36
11	***Tf (1a)***	***DIPEA (6.0)***	***rt***	***97/80[j] (2a)***	

Entry 12	Temp. = rt	7	59	36[h]
Entry 13[d]	80 °C	63[g]/52[g,i]	10	24[h]

Entry 14[d]	= Me (**1c**)	34[i,j] (**2c**)	--- (**5c**)	48[h,j] (**6c**)
Entry 15[d]	= H (**1d**)	--- (**2d**)	--- (**5d**)	99[h] (**6d**)

[a] Unless otherwise noted, reactions were performed using 0.2 mmol of **1,** CH_2Cl_2 as solvent and a 4h reaction time; [b] Yield determined by ^{1}H-NMR using hexamethylbenzene as internal standard; [c] Complete consumption of **1** was detected in all entries; [d] reaction performed in 1,2-dichloroethane; [e] uncyclized pyridinium salts **4** were formed as the major products; [f] 15 min reaction time; [g] An inseparable 20:1 regio-isomeric mixture was obtained; [h] A 5:1 ratio of Z/E olefin isomers was observed; [i] An inseparable 5:1 regio-isomeric mixture was obtained. [j] Isolated yield.

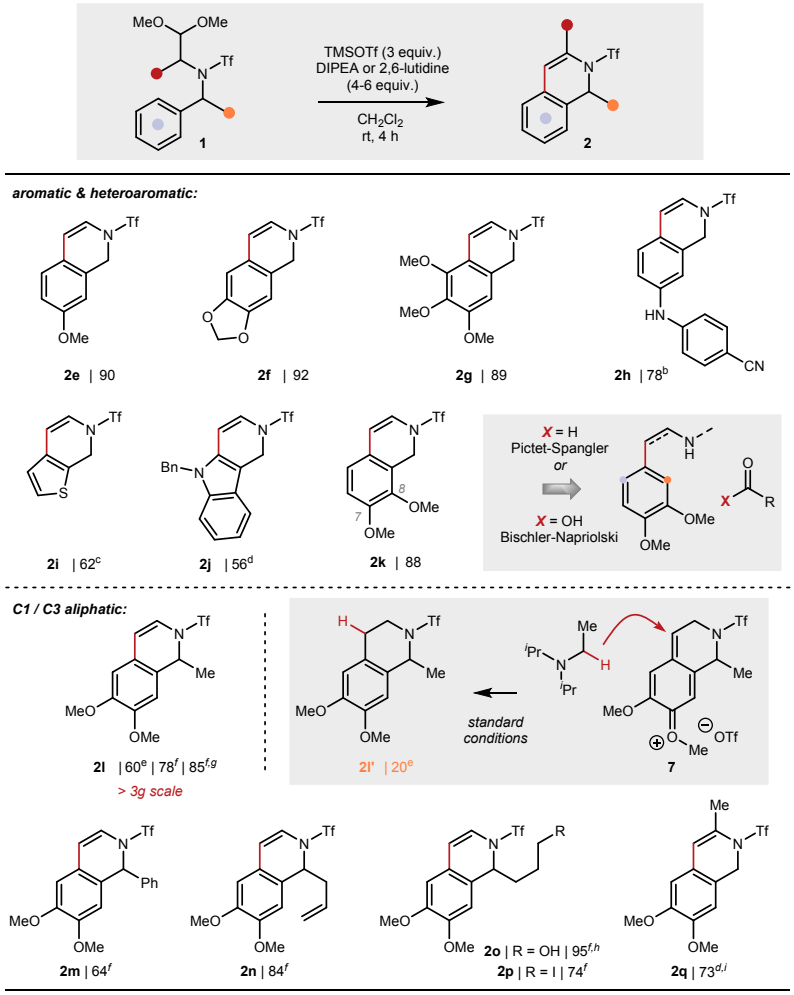
Our modified conditions demonstrated good functional group compatibility (Table 2). This included aromatic rings with electron donating groups (**2e-2g**, **2k**), as well as a diaryl amine (**2h**). In addition to classical 1,2-**DHIQ** substructures, heterocyclic analogues could also be prepared from the corresponding thiophene (**1i**) or indole (**1j**) starting materials, demonstrating compatibility with these more acid sensitive functionalities. Finally, 7,8-substituted-1,2-**DHIQ 2k**, representative of the cularine alkaloids,[20] could be synthesized in 88% yield with complete regioselectivity. This has been a difficult substitution pattern to prepare by more conventional Pictet-Spengler or Bischler-Napieralski syntheses, since they preferentially cyclize to the undesired 6,7-isomers (not shown).[21]

While the preparation of 1- or 3-substituted-1,2-**DHIQs** was also possible, these substrates were prone to competitive reduction to the corresponding **THIQ** under our standard reaction conditions. For example, using 3 equiv. of TMSOTf and 6 equiv. of DIPEA, 1-methyl-**DHIQ 2l** was obtained in only 60% yield, along with 20% of **THIQ 2l'**. The formation of **2l'** was consistent with hydride transfer from DIPEA to *para*-quinone methide **7**, which is not observed when using substrates lacking a C1-substituent. We speculate that the C1-substituent may increase the rate of cyclization, and thus the concentration of *para*-quinone methide **7**, allowing hydride transfer to compete with the elimination. Therefore, to avoid this complication, we replaced DIPEA with the non-reducing amine base 2,6-lutidine, and were pleased to see the yield of **2l** improve to 78% on 1.0 mmol scale, and 85% on 10 mmol scale. This allowed us to prepare >3 g of **2l** in a single pass. A range of synthetically useful functional handles are tolerated at C1, including a terminal alkene (**2n**), a 1° alcohol (**2o**) and a primary alkyl iodide (**2p**). Additionally, 3-methyl-**DHIQ 2q** could also be prepared in 73% yield, although more forc*ing conditions, including a prolonged reaction time (18 h)* and elevated reaction temperature (80 °C), were required. We attribute these changes to the increased steric demands of elimination, which involves deprotonation of a 3° C-H bond.

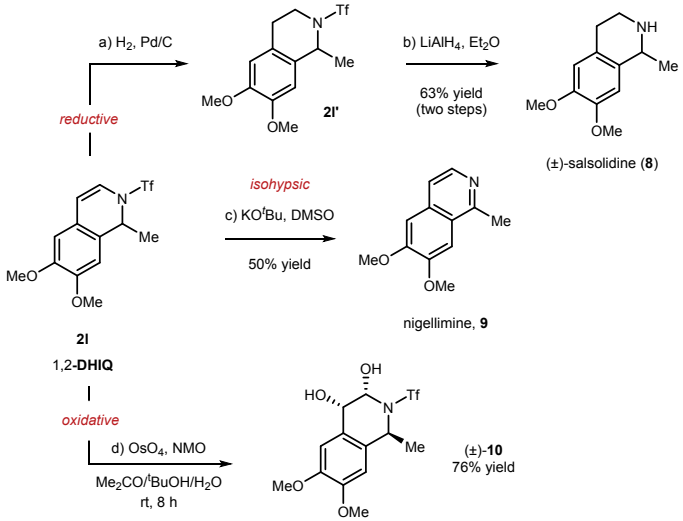
Since 1,2-**DHIQs** are attractive synthetic intermediates, our modified Pomeranz-Fritsch conditions provide entry into **IQ** and **THIQ** derivatives (**Scheme 2**). For example, reduction of the double bond by hydrogenation over Pd/C followed by reductive removal of the triflate with lithium aluminum hydride ($LiAlH_4$) provided **THIQ** (±)-salsolidine (**8**) in a 63% yield over two steps.[22] Alternatively, isohypsic elimination mediated by KO^{t}Bu in DMSO afforded the aromatized **IQ** natural product nigellimine (**9**) in a 50% yield.[23] Finally, oxidation using standard Upjohn conditions for dihydroxylation provided the 3,4-**THIQ** diol **10** in 70% yield and > 20:1 *d.r.*[24] Taken together, these

transformations demonstrate the synthetic value of 1,2-**DHIQs** for

Table 2. Substrate Scope with Aromatic and Aliphatic Substitutions.[a]



[a] Unless otherwise noted, reactions were performed using 1.0 mmol of **1** in the presence of TMSOTf (3 equiv.), DIPEA (6 equiv.) in CH_2Cl_2 (0.2 M) for 4 h at rt; [b] TMSOTf (4 equiv.) and DIPEA (8 equiv.) was used; [c] Reaction performed at 80 °C in 1,2-DCE; [d] 2,6-Lutidine (6 equiv.) was used instead of DIPEA; [e] **2l'** was also obtained in 20% yield; [f] 2,6-Lutidine (4 equiv.) was used instead of DIPEA; [g] Reaction performed on 10 mmol scale; [h] TMSOTf (4 equiv.) and 2,6-Lutidine (6 equiv.) was used; [i] Reaction performed at 80 °C in 1,2-DCE for 18 h.



Scheme 2. Synthetic Derivatization. Conditions and reagents: a) 10 wt% Pd/C, H_2 (10 psi), MeOH; b) $LiAlH_4$ (3 equiv.), Et_2O, reflux, 63% over 2 steps; c) KO^{t}Bu (3 equiv.), DMSO, rt, 50%; d) OsO_4 (2 mol%), NMO (1.5 equiv.), Me_2CO/^{t}BuOH/H_2O, rt, 76%, > 20:1 *dr*.

the synthesis of isoquinolines with complementary oxidation states and substitution patterns.

In conclusion, we have developed a new isoquinoline synthesis by modifying the classical Pomeranz-Fritsch protocol.[25] We have shown that the strong acids and elevated temperatures used previously can be replaced by a combination of TMSOTf with a sterically encumbered amine, following the precedent of Fujioka and Kita.[15] This modification tolerates acid-sensitive functional groups and heterocycles, and should facilitate the synthesis of diverse 1,2-**DHIQ** family members. Given their synthetic utility for the preparation of downstream isoquinoline products, we anticipate a number of opportunities for their future implementation.

EXPERIMENTAL SECTION

General Information. Chemicals and solvents were purchased from Sigma Aldrich, Alfa Aesar, Strem Chemicals, TCI or Oakwood, and used as received without further purification. Solvents were dried and purified using a PureSolv MD 7 (from Innovative Technology) or MB SPS 800 (from MBraun). We have not observed differences in the reaction outcome using either of these solvent purifiers. Proton nuclear magnetic resonance (^{1}H NMR) spectra were acquired using Bruker Ascend 500 MHz or 400 MHz spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak. Coupling constants (*J*) are reported in Hz. Multiplicities are reported using the following abbreviations: *s* = singlet; *d* = doublet; *t* = triplet; *q* = quartet; *m* = multiplet (range of multiplet is given); *br* = broad. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were acquired using Bruker Ascend 125 MHz or 100 MHz spectrometers. Fluorine nuclear magnetic resonance (^{19}F NMR) spectra were acquired using a Bruker Ascend 470 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak. High resolution mass spectra (HRMS) were recorded using a Bruker maXis Impact TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Fourier-transform infrared (FT-IR) spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR spectrometer. Analytical thin-layer chromatography was performed on pre-coated 250 mm layer thickness silica gel 60 F_{254} plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and/or by staining with potassium permanganate or cerium molybdate. Purifications by column chromatography were performed using standard column chromatography using silica gel (40-63 μm, 230-400 mesh).

General procedure for the synthesis of 2a-2q, 3 and 6c. A flame-dried, 10 mL test tube equipped with a Teflon-coated stir bar and a rubber septum was charged with the triflamide (1.0 mmol, 1.0 equiv). It was purged with N_2 for 5 min prior to the addition of dry and degassed CH_2Cl_2 or 1,2-DCE (5 mL, 2M). DIPEA or 2,6-lutidine (4.0 – 6.0 equiv) was added via syringe followed by dropwise addition of TMSOTf (3.0 equiv). The reaction was then stirred for 4 h at the indicated temperature and then quenched with 1M HCl (10 mL). The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate as eluent to afford the dihydroisoquinoline product.

*3-(3,4-dimethoxybenzyl)-5-methoxyoxazolidin-2-one (**3**)*. R_f = (hexanes/ethyl acetate 2:1): 0.11; IR (neat) ν = 2938, 2838, 1743, 1515, 1418, 1258, 1235, 1138, 1123 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 – 6.75 (m, 3H), 5.32 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.50 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.49 (s, 3H), 3.18 (dd, *J* = 10.1, 2.3 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.7, 149.5, 148.9, 128.0, 120.6, 111.21, 111.15, 98.1, 56.3, 56.04, 56.02, 50.2, 47.7; HRMS (ESI-TOF): Calcd. for $C_{13}H_{17}NO_5Na$ $[M+Na]^+$ = 290.0999 m/z, found = 290.0992 m/z.

*6,7-dimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2a**)*. White solid, 259.4 mg, yield = 80%. R_f = (hexanes/ethyl acetate 2:1): 0.60; IR (neat) ν = 2940, 2840, 1634, 1608, 1519, 1465, 1455, 1417, 1223, 1186, 1142 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1H), 6.62 (s, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.79 (s, 2H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.3, 149.1, 122.5, 122.4, 120.0 (q, J_F = 324.3 Hz), 119.9, 115.0, 109.0, 109.0, 56.3, 56.2, 48.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{12}H_{12}F_3NO_4SNa$ $[M+Na]^+$ = 346.0331 m/z, found = 346.0328 m/z. *We attributed the decreased isolated yield of **2a** (80%) compared to the NMR yield (97%) to the instability of the 1,2-dihydroisoquinoline to silica gel.*

*3-((trifluoromethyl)sulfonyl)-3,4-dihydrobenzo[f]isoquinoline (**2b**)*. White solid, 163.5 mg, yield = 52%, 20:1 mixture of inseparable regio-isomers. R_f = (hexanes/ethyl acetate 20:1): 0.46; IR (neat) ν = 3103, 1632, 1566, 1412, 1397, 1286, 1270, 1193, 1145 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *major regio-isomer*: δ 8.05 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.56 – 7.51 (m, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 5.01 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) *major regio-isomer*: δ 133.6, 129.0, 128.8, 128.4, 127.2, 126.4, 125.3, 124.8, 124.7, 123.5, 122.5, 120.0 (q, J_F = 324.1 Hz), 111.0, 49.2; ^{19}F NMR (470 MHz, $CDCl_3$) *major regio-isomer*: δ -75.3 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{14}H_{10}F_3NO_2SNa$ $[M+Na]^+$ = 336.0277 m/z, found = 336.0268 m/z. *We attributed the decreased isolated yield of **2b** (52%) compared to the NMR yield (63%) to the instability of the 1,2-dihydroisoquinoline to silica gel.*

*7-methyl-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2c**)*. Brown oil, 93.1 mg, yield = 34%, 5:1 mixture of inseparable regio-isomers. R_f = (hexanes/ethyl acetate 1:10): 0.68; IR (neat) ν = 2925, 1621, 1392, 1224, 1186, 1150, 1108 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *major regio-isomer*: δ 7.10 (d, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.92 (s, 1H), 6.55 (d, *J* = 7.6 Hz, 1H), 6.16 (d, *J* = 7.6 Hz, 1H), 4.82 (s, 2H), 2.35 (s, 3H); *minor regio-isomer*: δ 7.16 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 6.36 (d, *J* = 7.8 Hz, 1H), 4.82 (s, 2H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) *mixture of two regio-isomers*: δ 138.8, 133.3, 130.4, 129.3, 128.3, 128.0, 127.6, 127.4, 126.9, 126.3, 125.5, 124.0, 123.4, 123.2, 120.0 (q, J_F = 324.2 Hz), 115.0, 112.2, 49.0, 48.7, 21.4, 18.8; ^{19}F NMR (470 MHz, $CDCl_3$) *major regio-isomer:* δ -75.38 (s, 3F); *minor regio-isomer:* δ -75.41 (s, 3F); HRMS (APCI-TOF): Calcd. for $C_{11}H_{10}F_3NO_2S$ $[M]^+$ = 277.0379 m/z, found = 277.0381 m/z.

*(Z/E)-1,1,1-trifluoro-N-(2-methoxyvinyl)-N-(3-methylbenzyl)methanesulfonamide (**6c**)*. Colorless oil, 149.9 mg, yield = 48%, 4:1 mixture of inseparable diastereomers. R_f = (hexanes/ethyl acetate 1:10): 0.43; IR (neat) ν = 3021, 2942, 2859, 1670, 1386, 1183, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) *major diastereomer:* δ 7.28 – 7.22 (m, 1H), 7.18 – 7.08 (m, 3H), 5.86 (d, *J* = 4.4 Hz, 1H), 5.04 (d, *J* = 4.4 Hz, 1H), 4.74 (s, 2H), 3.70 (s, 3H), 2.36 (s, 3H); *minor diastereomer*: δ 7.28 – 7.21 (m, 1H), 7.17 – 7.08 (m, 3H), 6.48 (d, *J* = 11.3 Hz, 1H), 5.33 (d, *J* = 11.3 Hz, 1H),

4.55 (s, 2H), 3.52 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *mixture of diastereomers:* δ 154.7, 146.9, 138.7, 138.4, 135.4, 134.4, 129.5, 129.3, 129.2, 129.0, 128.7, 128.5, 126.0, 125.6, 120.5 (q, J_F = 324.9 Hz), 120.4 (q, J_F = 324.3 Hz), 102.9, 101.7, 61.0, 57.4, 56.4, 53.5, 21.52, 21.50; ^{19}F NMR (470 MHz, $CDCl_3$) *major diastereomer:* δ -75.2 (s, 3F); *minor diastereomer:* δ -73.8 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{12}H_{14}F_3NO_3SNa$ $[M+Na]^+$ = 332.0539 m/z, found = 332.0542 m/z.

*7-methoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2e**)*. White solid, 263.9 mg, yield = 90%. R_f = (hexanes/ethyl acetate 10:1): 0.32; IR (neat) v = 3102, 3016, 2942, 2916, 2845, 1608, 1566, 1500, 1388, 1305, 1279, 1253, 1185, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.4 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.48 (d, *J* = 7.6 Hz, 1H), 6.15 (d, *J* = 7.6 Hz, 1H), 4.81 (s, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.0, 129.1, 126.9, 122.5, 121.8, 120.0 (q, J_F = 324.2 Hz), 115.0, 113.6, 111.7, 55.5, 48.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.3 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{11}H_{10}F_3NO_3SNa$ $[M+Na]^+$ = 316.0217 m/z, found = 316.0226 m/z.

*6-((trifluoromethyl)sulfonyl)-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**2f**)*. White solid, 281.7 mg, yield = 92%. R_f = (hexanes/ethyl acetate 10:1): 0.53; IR (neat) v = 2971, 1641, 1506, 1485, 1390, 1375, 1286, 1257, 1187, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.60 (s, 1H), 6.50 (d, *J* = 7.6 Hz, 1H), 6.08 (d, *J* = 7.6 Hz, 1H), 5.97 (s, 2H), 4.74 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.9, 147.8, 123.9, 122.6, 121.2, 120.0 (q, J_F = 324.3 Hz), 115.4, 106.5, 106.2, 101.6, 48.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{11}H_9F_3NO_4S$ $[M+H]^+$ = 308.0199 m/z, found = 308.0191 m/z.

*6,7,8-trimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2g**)*. White solid, 314.6 mg, yield = 89%. R_f = (hexanes/ethyl acetate 4:1): 0.42; IR (neat) v = 2995, 2939, 2847, 1569, 1497, 1416, 1389, 1332, 1224, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (d, *J* = 7.7 Hz, 1H), 6.43 (d, *J* = 7.4 Hz, 1H), 6.43 (s, 1H), 4.74 (s, 2H), 3.89 (s, 3H), 3.86 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.9, 149.3, 142.0, 123.4, 121.9, 120.0 (q, J_F = 324.2 Hz), 116.7, 110.0, 105.1, 61.6, 61.1, 56.3, 48.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{14}F_3NO_5SNa$ $[M+Na]^+$ = 376.0437 m/z, found = 376.0426 m/z.

*4-((2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-7-yl)amino)benzonitrile (**2h**)*. Pale-yellow solid, 295.6 mg, yield = 78%. R_f = (hexanes/ethyl acetate 3:1): 0.45; IR (neat) v = 3400, 3331, 2216, 1596, 1515, 1441, 1390, 1274, 1188, 1128 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.07 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.27 (br s, 1H), 6.17 (d, *J* = 7.6 Hz, 1H), 4.81 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.0, 140.7, 134.0, 129.1, 126.9, 125.1, 123.1, 120.1, 119.9 (q, J_F = 332.5 Hz), 119.7, 117.3, 115.9, 114.6, 102.9, 48.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.2 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{17}H_{12}F_3N_3O_2SNa$ $[M+Na]^+$ = 402.0495 m/z, found = 402.0476 m/z.

*6-((trifluoromethyl)sulfonyl)-6,7-dihydrothieno[2,3-c]pyridine (**2i**)*. Pale-orange oil, 166.4 mg, yield = 62%. R_f = (hexanes/ethyl acetate 20:1): 0.39; IR (neat) v = 3109, 2859, 1624, 1395, 1333, 1276, 1225, 1186, 1152, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 5.1 Hz, 1H), 6.89 (d, *J* = 5.1 Hz, 1H), 6.49 (d, *J* = 7.6 Hz, 1H), 6.19 (d, *J* = 7.6 Hz, 1H), 5.04 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 131.8, 125.6, 124.6, 124.5, 121.8, 119.9 (q, J_F = 324.2 Hz), 110.6, 46.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.3 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_8H_7F_3NO_2S_2$ $[M+H]^+$ = 269.9865 m/z, found = 269.9857 m/z.

*5-benzyl-2-((trifluoromethyl)sulfonyl)-2,5-dihydro-1H-pyrido[4,3-b]indole (**2j**)*. Dark-red solid, 217.9 mg, yield = 56%. R_f = (hexanes/ethyl acetate 10:1): 0.49; IR (neat) v = 3120, 3057, 3031, 2923, 1740, 1453, 1330, 1199, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.38 – 7.29 (m, 4H), 7.26 – 7.19 (m, 2H), 7.10 (d, *J* = 6.8 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.06 (d, *J* = 8.0 Hz, 1H), 5.35 (s, 2H), 5.33 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 137.8, 137.2, 130.2, 129.0, 127.9, 126.3, 124.4, 124.3, 122.7, 120.8, 120.0 (q, J_F = 324.5 Hz), 118.1, 110.1, 103.1, 102.1, 46.9, 46.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.9 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{19}H_{15}F_3N_2O_2SNa$ $[M+Na]^+$ = 415.0699 m/z, found = 415.0685 m/z.

*7,8-dimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2k**)*. Pale-orange oil, 284.4 mg, yield = 88%. R_f = (hexanes/ethyl acetate 4:1): 0.45; IR (neat) v = 3104, 2944, 2840, 1636, 1605, 1495, 1273, 1186,1146 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 1H), 6.10 (d, *J* = 7.6 Hz, 1H), 4.91 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.1, 144.8, 123.0, 122.0, 122.0, 121.3, 120.0 (q, J_F = 324.3 Hz), 114.8, 111.8, 60.9, 55.9, 43.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{12}H_{12}F_3NO_4SNa$ $[M+Na]^+$ = 346.0331 m/z, found = 346.0332 m/z.

*6,7-dimethoxy-1-methyl-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2l**)*. White solid, 264.5 mg, yield = 78% on 1.0 mmol scale, 2.87 g, yield = 85% on 10.0 mmol scale. R_f = (hexanes/ethyl acetate 5:1): 0.26; IR (neat) v = 3006, 2982, 2960, 2936, 1636, 1515, 1384, 1268, 1137 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.59 (s, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 6.14 (d, *J* = 7.5 Hz, 1H), 5.17 (q, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.41 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.4, 148.8, 126.1, 120.9, 119.9 (q, J_F = 324.3 Hz), 119.6, 114.9, 109.1, 108.5, 56.2, 56.1, 55.7, 22.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -76.0 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{15}F_3NO_4S$ $[M+H]^+$ = 338.0668 m/z, found = 338.0666 m/z.

*6,7-dimethoxy-1-phenyl-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2m**)*. Off-white solid, 256.7 mg, yield = 64%. R_f = (hexanes/ethyl acetate 5:1): 0.36; IR (neat) v = 3007, 2939, 2839, 1634, 1576, 1495, 1452, 1349, 1144, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 3H), 7.19 (dd, *J* = 6.7, 2.7 Hz, 2H), 6.77 (s, 1H), 6.66 (s, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 6.25 (d, *J* = 7.4 Hz, 1H), 6.18 (s, 1H), 3.93 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.6, 149.2, 139.0, 128.7, 128.6, 127.5, 122.9, 122.2, 120.4, 120.1 (q, J_F = 324.9 Hz), 116.9, 109.9, 109.0, 61.1, 56.2, 56.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.2 (s, 3F); HRMS

(ESI-TOF): Calcd. for $C_{18}H_{17}F_3NO_4S$ $[M+H]^+$ = 400.0845 m/z, found = 400.0821 m/z.

*1-allyl-6,7-dimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2n**)*. White solid, 304.4 mg, yield = 84%. R_f = (hexanes/ethyl acetate 5:1): 0.30; IR (neat) v = 3076, 3019, 2979, 2903, 1573, 1466, 1414, 1350, 1270, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.57 (s, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 6.18 (d, *J* = 7.4 Hz, 1H), 5.78 – 5.65 (m, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 5.04 – 4.98 (m, 2H), 3.860 (s, 3H), 3.855 (s, 3H), 2.55 – 2.29 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.1, 148.9, 132.8, 124.2, 121.3, 119.9 (q, J_F = 324.6 Hz), 119.9, 119.2, 116.1, 109.3, 109.0, 59.3, 56.1, 56.0, 40.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.8 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{17}F_3NO_4S$ $[M+H]^+$ = 364.0825 m/z, found = 364.0825 m/z.

*3-(6,7-dimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinolin-1-yl)propan-1-ol (**2o**)*. Colorless oil, 362.3 mg, yield = 95%. R_f = (hexanes/ethyl acetate 1:1): 0.25; IR (neat) v = 2942, 2873, 1633, 1515, 1391, 1221, 1187, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.60 (s, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 6.20 (d, *J* = 7.4 Hz, 1H), 5.05 – 4.98 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.69 – 3.57 (m, 2H), 1.92 – 1.78 (m, 1H), 1.75 – 1.57 (m, 3H), 1.55 (br s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.3, 148.8, 125.0, 121.2, 120.0 (q, J_F = 325.0 Hz), 119.8, 116.6, 109.12, 109.10, 62.4, 59.6, 56.2, 56.1, 32.1, 28.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.5 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{18}F_3NO_5SNa$ $[M+Na]^+$ = 404.0750 m/z, found = 404.0750 m/z.

*1-(3-iodopropyl)-6,7-dimethoxy-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2p**)*. Pale-yellow oil, 365.9 mg, yield = 74%. R_f = (hexanes/ethyl acetate 5:1): 0.34; IR (neat) v = 3003, 2939, 2839, 1633, 1575, 1464, 1416, 1220, 1141 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.59 (s, 1H), 6.42 (d, *J* = 7.4 Hz, 1H), 6.23 (d, *J* = 7.4 Hz, 1H), 4.99 (t, *J* = 6.3 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.24 – 3.12 (m, 2H), 1.96 – 1.84 (m, 3H), 1.75 – 1.65 (m, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.5, 149.0, 124.6, 121.2, 120.0 (q, J_F = 324.9 Hz), 119.8, 116.8, 109.2, 108.9, 58.7, 56.3, 56.2, 36.2, 29.1, 5.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{18}F_3NIO_4S$ $[M+H]^+$ = 491.9948 m/z, found = 491.9950 m/z.

*6,7-dimethoxy-3-methyl-2-((trifluoromethyl)sulfonyl)-1,2-dihydroisoquinoline (**2q**)*. Off-white solid, 245.7 mg, yield = 73%. R_f = (hexanes/ethyl acetate 5:1): 0.21; IR (neat) v = 2939, 2838, 1648, 1509, 1380, 1277, 1121 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.63 (s, 1H), 6.24 (s, 1H), 4.68 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.25 (d, *J* = 1.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.99, 148.96, 133.0, 123.9, 121.7, 119.8 (q, J_F = 324.0 Hz), 119.7, 108.28, 108.26, 56.2, 56.1, 50.9, 20.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.9 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{15}F_3NO_4S$ $[M+H]^+$ = 338.0668 m/z, found = 338.0669 m/z.

*(±)-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**8**)*. A flame-dried, 50 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with **2l** (168.7 mg, 0.5 mmol), 10 wt% Pd/C (33.0 mg, 20 wt%) and purged with N_2 for 5 min, and dissolved in dry and degassed MeOH (5 mL, 0.1 M). The resulting mixture was then purged with H_2 for 5 min, and then pressurize to 10 psi, and stirred at rt for 4 h. The mixture was then filtered through celite. The filtrate was then concentrated *in vacuo* to afford the crude hydrogenation product, which was used for the next step directly. To the crude product was added $LiAlH_4$ (56.9 mg, 1.5 mmol, 3 equiv) and purged with N_2 for 5 min, prior to the addition of dry and degassed Et_2O (5 mL, 0.1 M). The resulting mixture was then refluxed for 12 h, and cooled to 0 °C in an ice bath. Water (0.3 mL), 15% NaOH solution (0.1 mL) was then added dropwise. The mixture was then warmed to rt and stirred for 30 min, and filtered through celite. The filtrate was poured on 10 mL 15% NaOH and extracted with EtOAc (3 × 20 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel (25% EtOAc in hexanes to 20% MeOH in EtOAc) to afford **(±)-8** (65.2 mg, 0.31 mmol, 63%) as a brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.55 (s, 1H), 4.05 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.24 (dt, *J* = 12.5, 5.1 Hz, 1H), 2.99 (ddd, *J* = 13.0, 8.4, 4.6 Hz, 1H), 2.84 (br s, 1H), 2.79 (ddd, *J* = 15.1, 9.0, 6.1 Hz, 1H), 2.65 (dt, *J* = 16.1, 4.8 Hz, 1H), 1.44 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.5, 147.4, 132.1, 126.7, 111.8, 109.1, 56.1, 55.9, 51.2, 41.7, 29.3, 22.8. The characterization data matches the data that has been reported previously.[26]

*6,7-dimethoxy-1-methylisoquinoline (**9**)*. A flame-dried, 5 mL microwave vial equipped with a Teflon-coated stir bar and a rubber septum was charged with **2l** (168.7 mg, 0.5 mmol), KO^{t}Bu (168.3 mg) and purged with N_2 for 5 min, and dissolved in dry and degassed DMSO (0.5 mL, 1 M). The resulting mixture was stirred at rt for 4 h. The solution was then poured on 10 mL 15% NaOH and extracted with EtOAc (3 × 20 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using EtOAc/MeOH (5:1) as eluent to afford **9** (50.9 mg, 0.25 mmol, 50%) as a brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 5.7 Hz, 1H), 7.39 (d, *J* = 5.7 Hz, 1H), 7.24 (s, 1H), 7.04 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 2.88 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 155.7, 153.0, 150.1, 140.1, 133.0, 123.3, 118.6, 105.4, 103.9, 56.2, 56.1, 22.0. The characterization data matches the data that has been reported previously.[23]

*(±)-(1S,3S,4S)-6,7-dimethoxy-1-methyl-2-((trifluoromethyl)sulfonyl)-1,2,3,4-tetrahydroisoquinoline-3,4-diol (**10**)*. The literature procedure was followed:[24] A flame-dried, 25 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with **2l** (168.7 mg, 0.5 mmol), NMO (87.9 mg, 0.75 mmol) and dissolved in Me_2CO/ H_2O (2 mL/0.5 mL). A solution of OsO_4 (2.54 mg, 0.01 mmol) in ^{t}BuOH (1 mL) was added. The mixture was stirred at rt for 8 h. It was then quenched by the addition of $Na_2S_2O_3$ (satd., 20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel (30% EtOAc in hexanes) to afford **(±)-10** (140.6 mg, 0.38 mmol, 76%, > 20:1 *d.r.*) as a white solid. The relative

stereochemistry was assigned based on literature precedent.[24] R_f = (ethyl acetate/hexane 1:2): 0.13; IR (neat) v = 3512, 3442, 3328, 1615, 1518, 1469, 1445, 1383, 1370, 1351, 1330, 1296, 1258, 1225, 1198, 1183, 1160, 1102 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.57 (s, 1H), 5.74 (br s, 1H), 4.99 (br s, 1H), 4.79 (br s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.49 (br s, 1H), 2.64 (br s, 1H), 1.81 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.2, 149.1, 127.2, 124.3, 119.7 (q, J_F = 322.1 Hz), 109.5, 108.4, 78.5, 67.6, 56.2, 56.2, 54.0, 27.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ -77.0 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{15}F_3NO_6S$ $[M-H]^-$ = 370.0578 m/z, found = 370.0577 m/z.

General procedure for the synthesis of 1a-1q. *Step 1: Reductive amination.* A flame-dried, 250 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with the aldehyde (20.0 mmol, 1.0 equiv) and dissolved in MeOH (40 mL, 0.5 M). Then AcOH (10 mmol, 0.5 equiv) and the amine (20.0 mmol, 1.0 equiv) were added via a syringe. The resulting mixture was stirred at room temperature for 2h, and cooled to 0 °C in an ice bath, prior to the portion-wise addition of $NaBH_4$ (30.0 mmol, 1.5 equiv). The resulting solution was then warmed to room temperature and stirred for 12h. The solution was then concentrated *in vacuo* and diluted with sat. $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was directly used for the next step. *Step 2: N-triflation.* A 250 mL round bottom flask containing the crude amine product was equipped with a Teflon-coated stir bar and a rubber septum. It was dissolved in CH_2Cl_2 (0.2 – 0.5 M), followed by the addition of DIPEA (1.5 equiv). The solution was cooled to -78 °C in a dry ice/acetone bath. Tf_2O (1.0 – 1.2 equiv) was added to the solution dropwise. The reaction was then stirred for 30 min at -78 °C, warmed to rt and stir for another 30 min and then quenched with H_2O and 1M HCl (10 mL / mmol). The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL / mmol). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate as eluent to afford the triflamide product.

*N-(3,4-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1a**)*. Off-white solid, 2.48 g, yield = 64%. R_f = (EtOAc : Hexanes 1:3): 0.23; IR (neat) v = 2940, 2838, 1608, 1517, 1421, 1259, 1184, 1137, 1119 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.91 – 6.87 (m, 1H), 6.84 (d, *J* = 8.7 Hz, 1H), 4.58 (br s, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.88 (s, 3H), 3.88 (s, 3H), 3.38 (s, 6H), 3.30 (br s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.5, 149.4, 126.6, 122.1, 120.2 (q, J_F = 325.1 Hz), 111.9, 111.1, 104.0, 56.1, 56.0, 55.2, 53.2, 47.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.5 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{14}H_{20}F_3NO_6SNa$ $[M+Na]^+$ = 410.0856 m/z, found = 410.0845 m/z.

*N-(3,4-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-4-methylbenzenesulfonamide (**1a-Ts**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with *N*-(3,4-dimethoxybenzyl)-2,2-dimethoxyethan-1-amine (used as crude, 5.0 mmol, 1.28 g, 1.0 equiv) and dissolved in CH_2Cl_2 (20 mL, 0.25 M). Then NEt_3 (15 mmol, 2.08 mL, 3.0 equiv), DMAP (0.5 mmol, 61.1 mg, 10 mol%) and TsCl (7.5 mmol, 1.43 g, 1.5 equiv) were added. The resulting mixture was stirred at room temperature for 12h and quenched by the addition of HCl (50 mL, 1M). The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate (2:1) as eluent to afford **1a-Ts** (1.96 g, 4.79 mmol, 96%) as a brown solid. R_f = (ethyl acetate/hexane 1:2): 0.26; ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.75 – 6.70 (m, 2H), 6.66 (d, *J* = 1.3 Hz, 1H), 4.39 (s, 2H), 4.34 (t, *J* = 5.3 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.23 (s, 6H), 3.19 (d, *J* = 5.3 Hz, 2H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.1, 148.7, 143.3, 137.8, 129.7, 128.6, 127.2, 121.2, 111.4, 110.8, 104.0, 55.9, 55.8, 54.7, 52.4, 48.4, 21.5. The characterization data matches the data that has been reported previously.[27]

*N-(3,4-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-2-nitrobenzenesulfonamide (**1a-Ns**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with *N*-(3,4-dimethoxybenzyl)-2,2-dimethoxyethan-1-amine (used as crude, 10.0 mmol, 2.55 g, 1.0 equiv) and dissolved in CH_2Cl_2 (20 mL, 0.5 M). Then NEt_3 (30 mmol, 4.16 mL, 3.0 equiv) and nosyl chloride (12 mmol, 2.66 g, 1.2 equiv) were added. The resulting mixture was stirred at room temperature for 12h and quenched by the addition of HCl (50 mL, 1M). The phases were then separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate (2:1) as eluent to afford **1a-Ns** (3.88 g, 8.80 mmol, 88%) as a pale-yellow oil. R_f = (ethyl acetate/hexane 1:2): 0.18; IR (neat) v = 2938, 2836, 1541, 1515, 1464, 1441, 1421, 1369, 1343, 1257, 1238, 1191, 1159, 1140, 1121 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.96 (m, 1H), 7.70 – 7.59 (m, 3H), 6.79 – 6.72 (m, 3H), 4.59 (s, 2H), 4.36 (t, *J* = 5.2 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.36 (d, *J* = 5.2 Hz, 2H), 3.28 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.3, 148.9, 148.0, 134.5, 133.4, 131.7, 131.2, 128.0, 124.2, 121.2, 111.3, 111.0, 104.0, 56.0, 55.9, 55.0, 52.4, 48.2; HRMS (ESI-TOF): Calcd. for $C_{19}H_{24}N_2O_8SNa$ $[M+Na]^+$ = 463.1146 m/z, found = 463.1136 m/z.

*tert-butyl (3,4-dimethoxybenzyl)(2,2-dimethoxyethyl)carbamate (**1a-Boc**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with *N*-(3,4-dimethoxybenzyl)-2,2-dimethoxyethan-1-amine (used as crude, 5.0 mmol, 1.28 g, 1.0 equiv) and dissolved in THF (10 mL, 0.5 M). Then Boc_2O (6.0 mmol, 1.31 g, 1.2 equiv) was added. The resulting mixture was stirred at room temperature for 12h and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate (2:1) as eluent to afford **1a-Boc** (1.29 g, 3.63 mmol, 73%) as a colorless oil. R_f = (ethyl acetate/hexane 1:2): 0.31; IR (neat) v = 2935, 2834, 1687, 1514, 1460, 1407,

1318, 1260, 1234, 1158, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *mixture of rotamers* δ 6.87 – 6.67 (m, 3H), 4.56 – 4.36 (m, 3H), 3.84 (s, 6H), 3.37 (s, 3H), 3.35 (s, 3H), 3.26 (br s, 1H), 3.17 (br s, 1H), 1.49 and 1.45 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *mixture of rotamers* δ 155.9, 149.1, 148.2, 131.2, 131.0, 120.4, 119.7, 111.3, 111.0, 110.6, 104.4, 103.7, 80.0, 56.0, 55.9, 54.8, 51.5, 50.6, 48.2, 48.0, 28.5; HRMS (ESI-TOF): Calcd. for $C_{18}H_{29}NO_6Na$ $[M+Na]^+$ = 378.1887 m/z, found = 378.1882 m/z.

*benzyl (3,4-dimethoxybenzyl)(2,2-dimethoxyethyl)carbamate (**1a-Cbz**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with *N*-(3,4-dimethoxybenzyl)-2,2-dimethoxyethan-1-amine (used as crude, 5.0 mmol, 1.28 g, 1.0 equiv), K_2CO_3 (1.38 g, 10 mmol, 2.0 equiv) and dissolved in MeCN (10 mL, 0.5 M). Then CbzCl (7.5 mmol, 1.07 mL, 1.5 equiv) was added. The resulting mixture was stirred at room temperature for 4h and diluted with H_2O (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then purified on silica gel using hexanes/ethyl acetate (2:1) as eluent to afford **1a-Cbz** (1.09 g, 2.80 mmol, 56%) as a colorless oil. R_f = (ethyl acetate/hexane 1:2): 0.27; IR (neat) v = 2938, 2834, 1695, 1514, 1462, 1412, 1364, 1319, 1298, 1260, 1231, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *mixture of rotamers* δ 7.46 – 7.26 (m, 5H), 6.85 – 6.63 (m, 3H), 5.20 (d, *J* = 4.9 Hz, 2H), 4.60 – 4.34 (m, 3H), 3.86 (s, 3H), 3.81 and 3.68 (s, 3H), 3.40 (s, 3H), 3.34 (d, *J* = 5.0 Hz, 1H), 3.30 (s, 3H), 3.26 (d, *J* = 4.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *mixture of rotamers* δ 149.2, 130.4, 128.6, 128.2, 128.1, 120.0, 111.4, 111.1, 110.8, 104.2, 103.6, 67.5, 56.0, 55.8, 54.8, 51.3, 48.6, 47.8; HRMS (ESI-TOF): Calcd. for $C_{21}H_{27}NO_6Na$ $[M+Na]^+$ = 412.1731 m/z, found = 412.1725 m/z.

*N-(2,2-dimethoxyethyl)-1,1,1-trifluoro-N-(naphthalen-2-ylmethyl)methanesulfonamide (**1b**)*. Pale-yellow oil, 3.12 g, yield = 83%. R_f = (EtOAc : Hexanes 1:5): 0.46; IR (neat) v = 2940, 2838, 1510, 1445, 1384, 1223, 1184, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 3H), 7.79 (s, 1H), 7.55 – 7.45 (m, 3H), 4.82 (br s, 2H), 4.49 (t, *J* = 5.4 Hz, 1H), 3.36 (s, 8H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 133.3, 131.7, 129.0, 128.5, 128.1, 127.9, 126.7, 126.1, 120.2 (q, J_F = 323.1 Hz), 103.9, 55.2, 53.6, 48.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.3 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{16}H_{18}F_3NO_4SNa$ $[M+Na]^+$ = 400.0801 m/z, found = 400.0790 m/z.

*N-(2,2-dimethoxyethyl)-1,1,1-trifluoro-N-(3-methylbenzyl)methanesulfonamide (**1c**)*. Colorless oil, 1.31 g, yield = 77%. R_f = (EtOAc : Hexanes 1:3): 0.59; IR (neat) v = 2941, 2839, 1610, 1491, 1384, 1259, 1183, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.7 Hz, 1H), 7.17 – 7.13 (m, 3H), 4.61 (s, 2H), 4.45 (t, *J* = 5.5 Hz, 1H), 3.37 (s, 6H), 3.31 (s, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 138.8, 134.2, 129.6, 129.4, 128.9, 126.1, 120.2 (q, J_F = 323.1 Hz), 103.8, 55.2, 53.3, 48.3, 21.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{18}F_3NO_4SNa$ $[M+Na]^+$ = 364.0801 m/z, found = 364.0790 m/z.

*N-benzyl-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1d**)*. Colorless oil, 1.37 g, yield = 84%. R_f = (EtOAc : Hexanes 1:3): 0.59; IR (neat) v = 2942, 2839, 1456, 1384, 1224, 1184, 1143, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 4.65 (br s, 2H), 4.45 (t, *J* = 5.5 Hz, 1H), 3.36 (s, 6H), 3.31 (br s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 134.4, 129.0, 128.6, 120.1 (q, J_F = 323.0 Hz), 103.9, 55.2, 53.4, 48.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{12}H_{16}F_3NO_4SNa$ $[M+Na]^+$ = 350.0644 m/z, found = 350.0630 m/z.

*N-(2,2-dimethoxyethyl)-1,1,1-trifluoro-N-(3-methoxybenzyl)methanesulfonamide (**1e**)*. Pale-yellow oil, 2.53 g, yield = 71%. R_f = (EtOAc : Hexanes 1:3): 0.48; IR (neat) v = 2942, 2839, 1602, 1491, 1458, 1384, 1223, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.90 – 6.85 (m, 2H), 4.62 (s, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.81 (s, 3H), 3.37 (s, 6H), 3.32 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.2, 135.9, 130.0, 121.2, 120.1 (q, J_F = 323.0 Hz), 114.4, 114.1, 103.8, 55.4, 55.1, 53.3, 48.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{18}F_3NO_5SNa$ $[M+Na]^+$ = 380.0750 m/z, found = 380.0736 m/z.

*N-(benzo[d][1,3]dioxol-5-ylmethyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1f**)*. White solid, 2.96 g, yield = 80%. R_f = (EtOAc : Hexanes 1:3): 0.38; IR (neat) v = 2945, 2844, 1503, 1491, 1334, 1245, 1146, 1116 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (d, *J* = 1.4 Hz, 1H), 6.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 5.97 (s, 2H), 4.54 (s, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.39 (s, 6H), 3.30 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 148.3, 148.0, 127.9, 123.2, 120.1 (q, J_F = 323.0 Hz), 109.4, 108.5, 104.0, 101.4, 55.3, 53.1, 47.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.6 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{13}H_{16}F_3NO_6SNa$ $[M+Na]^+$ = 394.0543 m/z, found = 394.0542 m/z.

*N-(2,2-dimethoxyethyl)-1,1,1-trifluoro-N-(3,4,5-trimethoxybenzyl)methanesulfonamide (**1g**)*. Pale-yellow oil, 3.08 g, yield = 74%. R_f = (EtOAc : Hexanes 1:3): 0.17; IR (neat) v = 2942, 2839, 1593, 1383, 1239, 1183cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 2H), 4.57 (s, 2H), 4.46 (t, *J* = 5.4 Hz, 1H), 3.85 (s, 6H), 3.84 (s, 3H),3.39 (s, 6H), 3.33 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 153.6, 138.2, 129.8, 120.1 (q, J_F = 323.1 Hz), 106.1, 104.0, 61.0, 56.3, 55.3, 53.6, 48.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{22}F_3NO_7SNa$ $[M+Na]^+$ = 440.0961 m/z, found = 440.0954 m/z.

N-(3-bromobenzyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide. Dark-red oil, 9.26 g, yield = 76%. R_f = (EtOAc : Hexanes 1:2): 0.76; IR (neat) v = 2941, 2838, 1597, 1431, 1224, 1185, 1143, 1120 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53 – 7.44 (m, 2H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 4.61 (s, 2H), 4.44 (t, *J* = 5.4 Hz, 1H), 3.37 (s, 6H), 3.32 (s, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 136.9, 131.9, 131.7, 130.5, 127.4, 123.0, 120.1 (q, J_F = 323.1 Hz), 103.9, 55.3, 52.8, 48.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{12}H_{15}BrF_3NO_4SNa$ $[M+Na]^+$ = 427.9749 m/z, found = 427.9732 m/z.

*N-(3-((4-cyanophenyl)amino)benzyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1h**)*. The literature procedure was followed:[28] A flame-dried, 25 mL Schlenk flask equipped with a Teflon-coated stir bar and a glass stopper was charged with XPhos-Pd-G1 (22.16 mg, 0.03 mmol), 4-aminobenzenitrile (425.3 mg, 3.6 mmol) and K_2CO_3 (580.5 mg, 4.2 mmol). The mixture was then evacuated and filled with N_2 (this process was repeated three times). Under a positive pressure of nitrogen, the stopper was opened, at which point a solution of *N*-(3-bromobenzyl)-*N*-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (1.22 g, 3.0 mmol) in ^{t}BuOH (6 mL) was added via a syringe. The stopper was then capped under N_2, and the resulting mixture was stirred at 110 °C in a pre-heated oil bath for 4 h. The mixture was then cooled to RT and poured on water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (5:1) as eluent to afford **1h** (888.3 mg, 2.0 mmol, 67%) as a white solid. R_f = (EtOAc : Hexanes 1:5): 0.20; IR (neat) ν = 3339, 2937, 2840, 2218, 1613, 1588, 1480, 1452, 1410, 1366, 1226, 1187 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.7 Hz, 2H), 7.34 (dd, *J* = 8.5, 7.8 Hz, 1H), 7.34 (dd, *J* = 8.5, 7.8 Hz, 1H), 7.17 – 7.12 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.32 (s, 1H), 4.62 (br s, 2H), 4.46 (t, *J* = 5.4 Hz, 1H), 3.38 (s, 6H), 3.34 (br s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.5, 140.9, 136.1, 133.9, 130.2, 123.8, 120.7, 120.4, 120.0 (q, J_F = 323.0 Hz), 119.9, 115.4, 103.9, 102.0, 55.3, 53.1, 48.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{19}H_{20}F_3N_3O_4SNa$ [M+Na]$^+$ = 466.1019 m/z, found = 466.0997 m/z.

*N-(2,2-dimethoxyethyl)-1,1,1-trifluoro-N-(thiophen-2-ylmethyl)methanesulfonamide (**1i**)*. Pale-orange oil, 2.70 g, yield = 81%. R_f = (EtOAc : Hexanes 1:5): 0.46; IR (neat) ν = 2941, 2839, 1385, 1278, 1224, 1185, 1117 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.08 (d, *J* = 3.4 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.5 Hz, 1H), 4.84 (s, 2H), 4.50 (t, *J* = 5.4 Hz, 1H), 3.42 (s, 6H), 3.37 (d, *J* = 5.2 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.6, 129.4, 127.2, 127.1, 120.0 (q, J_F = 322.7 Hz), 104.2, 55.4, 47.85, 47.81; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.8 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{10}H_{14}F_3NO_4S_2Na$ [M+Na]$^+$ = 356.0209 m/z, found = 356.0206 m/z.

*N-((1-benzyl-1H-indol-3-yl)methyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1j**)*. Dark-red oil, 8.67 g, yield = 70%. R_f = (EtOAc : Hexanes 1:10): 0.17; IR (neat) ν = 2940, 2838, 1736, 1550, 1468, 1270, 1129 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.2 Hz, 1H), 7.41 – 7.28 (m, 4H), 7.28 – 7.20 (m, 3H), 7.15 (d, *J* = 6.7 Hz, 2H), 5.34 (s, 2H), 4.92 (br s, 2H), 4.53 (t, *J* = 5.5 Hz, 1H), 3.43 (br s, 1H), 3.40 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.1, 136.8, 129.8, 128.9, 127.9, 127.7, 126.9, 122.5, 120.4, 120.2 (q, J_F = 323.4 Hz), 119.4, 110.1, 108.0, 104.1, 55.1, 50.2, 47.7, 45.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.4 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{21}H_{23}F_3N_2O_4SNa$ [M+Na]$^+$ = 479.1223 m/z, found = 479.1206 m/z.

*N-(2,3-dimethoxybenzyl)-N-(2,2-dimethoxyethyl)-1,1,1-trifluoromethanesulfonamide (**1k**)*. Pale-orange oil, 3.40 g, yield = 87%. R_f = (EtOAc : Hexanes 1:3): 0.38; IR (neat) ν = 2941, 2838, 1589, 1483, 1384, 1183, 1144, 1122 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (t, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.1, 1.3 Hz, 1H), 4.70 (s, 2H), 4.46 (t, *J* = 5.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.40 (s, 2H), 3.33 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.8, 147.5, 128.4, 124.4, 121.3, 120.1 (q, J_F = 323.8 Hz), 112.6, 103.2, 60.8, 56.0, 54.9, 49.4, 48.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.2 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{14}H_{20}F_3NO_6SNa$ [M+Na]$^+$ = 410.0856 m/z, found = 410.0857 m/z.

N-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-methanimine. A flame-dried, 250 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with 3,4-dimethoxybenzaldehyde (8.31 g, 50.0 mmol) and $MgSO_4$ (18.05 g, 150.0 mmol). Dry CH_2Cl_2 (100 mL) was added via syringe followed by 2-aminoacetaldehyde dimethylacetal (5.45 mL, 50.0 mmol). The resulting mixture was stirred at room temperature overnight and filtered through celite. The filtrate was then concentrated *in vacuo* and dried under high vacuum to provide the imine product (12.38 g, 98%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.16 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 4.67 (t, *J* = 5.3 Hz, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.75 (dt, *J* = 5.3, 2.6 Hz, 2H), 3.42 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.2, 151.6, 149.4, 129.5, 123.4, 110.5, 109.0, 104.1, 63.6, 56.1, 56.1, 54.3. The characterization data matches the data that has been reported previously.[27]

N-(1-(3,4-dimethoxyphenyl)ethyl)-2,2-dimethoxyethan-1-amine. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with (*E*)-*N*-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-methanimine (1.27 g, 5.0 mmol), purged with N_2 for 5 min, and dissolved in dry and degassed THF (25 mL, 0.2 M). The resulting mixture was stirred and cooled to -78 °C in a dry ice bath, prior to the dropwise addition of MeLi (2.42 mL, 7.5 mmol, 3.1 M). The resulting solution was stirred for 30 min and the dry ice bath was removed and the solution was stirred for another 5 mins and then quenched with H_2O (10 mL) and sat. NH_4Cl (10 mL). The solution was then extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (1:1) as eluent to afford the amine product (899.7 mg, 59%) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.4 Hz, 1H), 6.83 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.71 (q, *J* = 6.6 Hz, 1H), 3.36 (s, 3H), 3.31 (s, 3H), 2.63 (dd, *J* = 12.1, 5.6 Hz, 1H), 2.56 (dd, *J* = 12.1, 5.3 Hz, 1H), 1.63 (br s, 1H), 1.35 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.2, 148.1, 138.1, 118.9, 111.1, 109.6, 104.0, 58.2, 56.0, 56.0, 54.2, 53.8, 49.2, 24.6. The characterization data matches the data that has been reported previously.[29]

N-(2,2-dimethoxyethyl)-N-(1-(3,4-dimethoxyphenyl)ethyl)-1,1,1-trifluoromethanesulfonamide

*(**1l**)*. The general procedure for the *N*-triflation was followed. White solid, 3.38 g, yield = 64%. R_f = (EtOAc : Hexanes 1:3): 0.27; IR (neat) v = 2992, 2960, 2941, 2841, 1605, 1446, 1345, 1241, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (br s, 1H), 6.94 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.84 (d, *J* = 8.3 Hz, 1H), 5.17 (d, *J* = 6.3 Hz, 1H), 4.22 (br s, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 3.31 (s, 3H), 3.21 (s, 3H), 3.25 – 3.16 (m, 1H), 3.15 – 3.01 (m, 1H), 1.67 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.3, 149.2, 130.3, 120.20 (q, J_F = 319.5 Hz), 120.19, 111.6, 110.8, 103.4, 58.9, 56.0, 55.9, 55.4, 54.7, 47.1, 17.4; ^{19}F NMR (470 MHz, $CDCl_3$) *mixture of rotamers:* δ -74.4 & -76.0 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{22}F_3NO_6SNa$ $[M+Na]^+$ = 424.1012 m/z, found = 424.1007 m/z.

N-((3,4-dimethoxyphenyl)(phenyl)methyl)-2,2-dimethoxyethan-1-amine. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with (*E*)-*N*-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-methanimine (1.27 g, 5.0 mmol), purged with N_2 for 5 min, and dissolved in dry and degassed THF (25 mL, 0.2 M). The resulting mixture was stirred and cooled to -78 °C in a dry ice bath, prior to the dropwise addition of PhLi (5 mL, 9.5 mmol, 1.9 M). The resulting solution was stirred for 2 h with the temperature ramping from -78 °C to -40 °C and then quenched with H_2O (10 mL) and sat. NH_4Cl (10 mL). The solution was then extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (1:1) as eluent to afford the amine product (1.19 g, 72%) as a pale-yellow oil. R_f = (EtOAc : Hexanes 1:1): 0.40; IR (neat) v = 2996, 2935, 2905, 2831, 1592, 1451, 1345, 1129, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 1H), 6.99 – 6.91 (m, 2H), 6.80 (d, *J* = 8.1 Hz, 1H), 4.78 (s, 1H), 4.53 (t, *J* = 5.4 Hz, 1H), 3.84 (d, *J* = 10.4 Hz, 6H), 3.35 (s, 6H), 2.72 (d, *J* = 5.5 Hz, 2H), 1.78 (br s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.0, 148.0, 144.1, 136.6, 128.5, 127.2, 127.0, 119.4, 111.1, 110.3, 103.8, 67.0, 55.9, 55.9, 53.8, 53.7, 49.4; HRMS (ESI-TOF): Calcd. for $C_{19}H_{26}NO_4$ $[M+H]^+$ = 332.1856 m/z, found = 332.1857 m/z.

*N-(2,2-dimethoxyethyl)-N-((3,4-dimethoxyphenyl)(phenyl)methyl)-1,1,1-trifluoromethanesulfonamide (**1m**)*. The general procedure for the *N*-triflation was followed. Pale-yellow oil, 700.1 mg, yield = 30%. R_f = (EtOAc : Hexanes 1:5): 0.17; IR (neat) v = 2938, 2837, 1594, 1515, 1418, 1222, 1182, 1140 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 3H), 7.29 (d, *J* = 7.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 6.34 (s, 1H), 3.93 (br s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.44 (d, *J* = 5.0 Hz, 2H), 3.16 (s, 3H), 3.13 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.2, 149.0, 138.1, 128.5, 128.2, 122.3, 120.1 (q, *J* = 324.5 Hz), 112.9, 110.9, 102.4, 67.5, 56.0, 55.9, 54.2, 54.0, 48.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ -74.0 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{20}H_{24}F_3NO_6SNa$ $[M+Na]^+$ = 486.1169 m/z, found = 486.1157 m/z.

N-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)but-3-en-1-amine. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with (*E*)-*N*-(2,2-dimethoxyethyl)-1-(3,4-dimethoxyphenyl)-methanimine (1.27 g, 5.0 mmol), Zn powder (653.8 mg, 10 mmol) and purged with N_2 for 5 min, and dissolved in dry and degassed THF (10 mL, 0.5 M). The resulting mixture was stirred and cooled to 0 °C in an ice bath, prior to the dropwise addition of allyl bromide (649.1 μL, 7.5 mmol). The resulting mixture was stirred overnight at rt. The solution was then extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (1:1) as eluent to afford the amine product (1.40 g, 95%) as a pale-yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.4 Hz, 1H), 6.83 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 5.78 – 5.66 (m, 1H), 5.09 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.07 – 5.03 (m, 1H), 4.41 (t, *J* = 5.5 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 (t, *J* = 6.9 Hz, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 2.58 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.55 (dd, *J* = 11.4, 4.4 Hz, 1H), 2.43 – 2.36 (m, 2H), 1.63 (br s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.2, 148.2, 136.4, 135.5, 119.6, 117.6, 111.1, 109.9, 103.9, 62.6, 56.04, 56.02, 54.0, 53.7, 49.0, 43.2. The characterization data matches the data that has been reported previously.[30]

*N-(2,2-dimethoxyethyl)-N-(1-(3,4-dimethoxyphenyl)but-3-en-1-yl)-1,1,1-trifluoromethanesulfonamide (**1n**)*. The general procedure for the *N*-triflation was followed. Pale-yellow, 6.55 g, yield = 56%. R_f = (EtOAc : Hexanes 1:3): 0.23; IR (neat) v = 2939, 2838, 1606, 1518, 1260, 1222, 1183, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.1 Hz, 1H), 6.96 (br s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 5.66 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.13 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 4.99 (dd, *J* = 9.8, 5.6 Hz, 1H), 4.32 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.39 (br s, 3H), 3.27 (s, 3H), 3.23 (d, *J* = 15.8 Hz, 1H), 3.13 (dd, *J* = 12.5, 5.4 Hz, 1H), 3.04 (ddd, *J* = 15.3, 9.4, 6.2 Hz, 1H), 2.77 (br s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.4, 149.2, 134.00, 121.5, 118.3, 112.7, 110.9, 104.2, 63.8, 56.0, 55.9, 55.7, 54.9, 47.6; ^{19}F NMR (470 MHz, $CDCl_3$) *mixture of rotamers:* δ -74.1 & -75.7 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{17}H_{24}F_3NO_6SNa$ $[M+Na]^+$ = 450.1169 m/z, found = 450.1154 m/z.

*N-(2,2-dimethoxyethyl)-N-(1-(3,4-dimethoxyphenyl)-4-hydroxybutyl)-1,1,1-trifluoromethanesulfonamide (**1o**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with **1n** (2.14 g, 5.0 mmol) and purged with N_2 for 5 min, and dissolved in dry and degassed THF (10 mL, 0.5 M). Borane (2.5 mL, 2.5 mmol, 1 M in THF) was added dropwise via the syringe. The resulting solution was stirred at RT for 4 h, prior to the addition of H_2O_2 (2 mL, 20.0 mmol) and NaOH (10 mL, 1M aq.) and stirred for another 1 h. The solution was then extracted with EtOAc (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (1:1) as eluent to afford **1o** (1.21 g, 77%) as a colorless oil. R_f = (EtOAc : Hexanes 1:1): 0.14; IR (neat) v = 3511, 2941, 2839, 1737, 1518, 1379, 1221, 1184, 1108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.1 Hz, 1H), 6.96 (br s, 1 H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.95 (dd, *J* = 9.4, 6.1 Hz, 1H), 4.32 (br s, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.67 (t, *J* = 5.4

Hz, 2H), 3.37 (br s, 3H), 3.28 (s, 3H), 3.22 (d, *J* = 15.2 Hz, 1H), 3.13 (dd, *J* = 15.1, 6.2 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.09 (br s, 1H), 1.61 – 1.51 (m, 2H), 1.46 (br s, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.5, 149.3, 121.4, 112.6, 111.0, 104.1, 63.9, 62.3, 56.02, 55.96, 55.7, 54.8, 47.4, 29.8; ^{19}F NMR (470 MHz, $CDCl_3$) *mixture of rotamers:* δ -74.0 & -75.7 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{17}H_{26}F_3NO_7SNa$ $[M+Na]^+$ = 468.1274 m/z, found = 468.1257 m/z.

*N-(2,2-dimethoxyethyl)-N-(1-(3,4-dimethoxyphenyl)-4-iodobutyl)-1,1,1-trifluoromethanesulfonamide (**1p**)*. A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with **1o** (1.34 g, 3.0 mmol) in dry CH_2Cl_2 (15 mL, 0.2 M). I_2 (913.7 mg, 3.6 mmol), imidazole (306.4 mg, 4.5 mmol) and triphenylphosphine (944.2 mg, 3.6 mmol) was added. The resulting mixture was stirred at rt for 12 h. Hexanes (15 mL) was added to the mixture to allow the precipitation of the triphenylphosphine oxide byproduct. The mixture was then filtered, and the filtrate was concentrated *in vacuo*. The crude product was then purified on silica gel using hexanes/ethyl acetate (3:1) as eluent to afford **1p** (1.60 g, 96%) as a white solid. R_f = (EtOAc : Hexanes 1:3): 0.38; IR (neat) v = 2938, 2837, 1606, 1517, 1421, 1383, 1221, 1127 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (d, *J* = 8.6 Hz, 1H), 6.94 (s, 1H), 6.87 (d, *J* = 8.6 Hz, 1H), 4.93 (dd, *J* = 9.9, 5.6 Hz, 1H), 4.36 (br s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.44 (br s, 3H), 3.31 (s, 3H), 3.29 – 3.02 (m, 4H), 2.48 (br d, *J* = 9.5 Hz, 1H), 2.06 (br s, 1H), 1.88 – 1.63 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.6, 149.3, 121.6, 112.5, 111.1, 104.6, 63.5, 56.0, 55.0, 47.4, 30.4; ^{19}F NMR (470 MHz, $CDCl_3$) *mixture of rotamers:* δ -74.0 & -75.8 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{17}H_{25}F_3NIO_6SNa$ $[M+Na]^+$ = 578.0292 m/z, found = 578.0304 m/z.

*N-(3,4-dimethoxybenzyl)-N-(1,1-dimethoxypropan-2-yl)-1,1,1-trifluoromethanesulfonamide (**1q**)*. The literature procedure was followed:[31] A flame-dried, 100 mL round bottom flask equipped with a Teflon-coated stir bar and a rubber septum was charged with $NaBH(OAc)_3$ (3.0 g, 14.0 mmol) and dissolved in 1,2-DCE (35 mL). Then AcOH (572 µL, 10 mmol), 3,4-dimethoxybenzylamine (1.51 mL, 10 mmol) and 1,1-dimethoxypropan-2-one (1.21 mL, 10 mmol) were added via a syringe. The resulting mixture was stirred at room temperature overnight. The resulting solution was quenched with sat. $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic fractions were then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used directly for the next step following the general procedure for the *N*-triflate. Pale-orange solid, 2.49 g, yield = 62%. R_f = (EtOAc : Hexanes 1:5): 0.17; IR (neat) v = 3007, 2942, 2842, 1737, 1593, 1421, 1259, 1222, 1155, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.2 Hz, 1H), 4.96 – 4.06 (m, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.22 (br s, 6H), 1.21 (br s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.3, 149.1, 128.6, 121.0, δ 120.2 (q, J_F = 327.5 Hz), 111.7, 110.9, 105.4, 57.0, 56.0, 56.0, 54.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ -75.5 (s, 3F); HRMS (ESI-TOF): Calcd. for $C_{15}H_{22}F_3NO_6SNa$ $[M+Na]^+$ = 424.1012 m/z, found = 424.1008 m/z.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Optimization tables and copies of ^1H and ^{13}C NMR spectra (PDF)

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The authors declare no competing financial interest.

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