Development of an Imine Chaperone for Selective C-H Functionalization of Alcohols via Radical Relay

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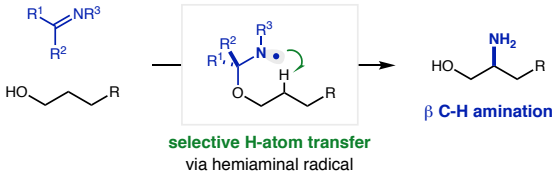
Supporting Information Placeholder

ABSTRACT: The design of a radical relay chaperone to promote selective C-H functionalizations is described. A saccharine-based imine was found to be uniquely suited to effect C-H amination of alcohols via an *in situ* generated hemiaminal. This radical chaperone facilitates the mild generation of an N-centered radical while also directing its regioselective H-atom transfer (HAT) to the β carbon of an alcohol. Upon β C-H halogenation, aminocyclization, and reductive cleavage, an NH_2 is formally added vicinal to an alcohol. The development, synthetic utility, and chemo-, regio-, and stereo-selectivity of this imine chaperone-mediated C-H amination is presented herein.



INTRODUCTION

Alcohols, ubiquitous motifs in synthesis, are ideal recognition elements for directing C-H functionalization within complex molecules.[1] In the metal-mediated realm, alcohols have been converted to carbamates, silyl ethers, and oximes, which serve as directing groups to facilitate Pd, Ru, or Ir-coordination and C-H functionalization via a metallocycle.[2,3] In the radical-mediated arena, pioneering efforts by Barton, Smith, Walling, and Čeković demonstrated the utility of O-centered radicals to effect regioselective C-H functionalization via 1,5-intramolecular H-atom transfer (HAT).[4-6] Complementarily, Breslow recognized the opportunity to append radical precursors, or chaperones, onto alcohols and demonstrated that remarkably selective, remote C-H halogenations and oxidations were possible.[7] In recent years, the labs of Baran, Gevorgyan, Kanai, Roizen, Chen, Kumar, and ours have made contributions towards the development of additional radical precursors that may be appended to alcohols to facilitate HAT.[8,9] Over the course of our own studies in this arena,[9] we wondered if a radical relay chaperone could *catalytically* (i) dock onto an alcohol, (ii) mediate HAT, and (iii) be released to engage another alcohol – in an enzyme-like fashion. Inspired by the transient hemiaminals independently developed by Tan and Beauchemin to promote regioselective functionalization of allyl alcohols and amines,[10] as well as complementary C-H functionalization strategies by others,[11] we proposed an imine catalyst might serve this role and facilitate selective HAT.

Our design, shown in Figure 1, entails the addition of an alcohol to imine catalyst **A** to generate transient hemiaminal **B**. We envisioned the exposed sp^3 N of **B** may then be chemoselectively oxidized to generate N-centered radical **C**, which should undergo regioselective 1,5-HAT[4] to afford β C-centered radical **D**. Upon

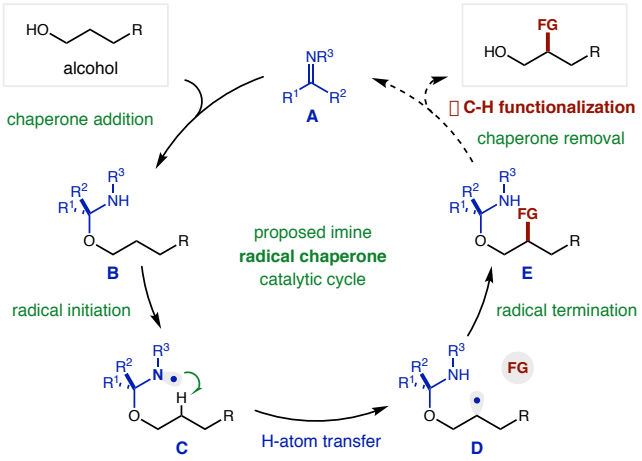


Figure 1. Design of an imine radical relay chaperone strategy for β C-H functionalization of alcohols via transient hemiaminals.

combination with a radical trap, the β C-H functionalized hemiaminal **E** may then collapse to provide a β substituted alcohol product, along with the regenerated imine catalyst **A**.

RESULTS AND DISCUSSION

To investigate our proposed strategy, a series of imines were designed, synthesized, and stoichiometrically evaluated in each of the proposed, elementary steps: (i) hemiaminal formation, (ii) C-H functionalization, (iii) and imine release (Figure 2). Based on our previous successful efforts effecting intramolecular HAT from Ts amides,[12] our initial imine design included Ts substituents (Figure 2b, **I**-**V**). Upon evaluation of aldehyde-derived Ts imines (**I**), we were pleased to find that they are readily converted to hemiaminals. However, these intermediates are highly prone to undergo β

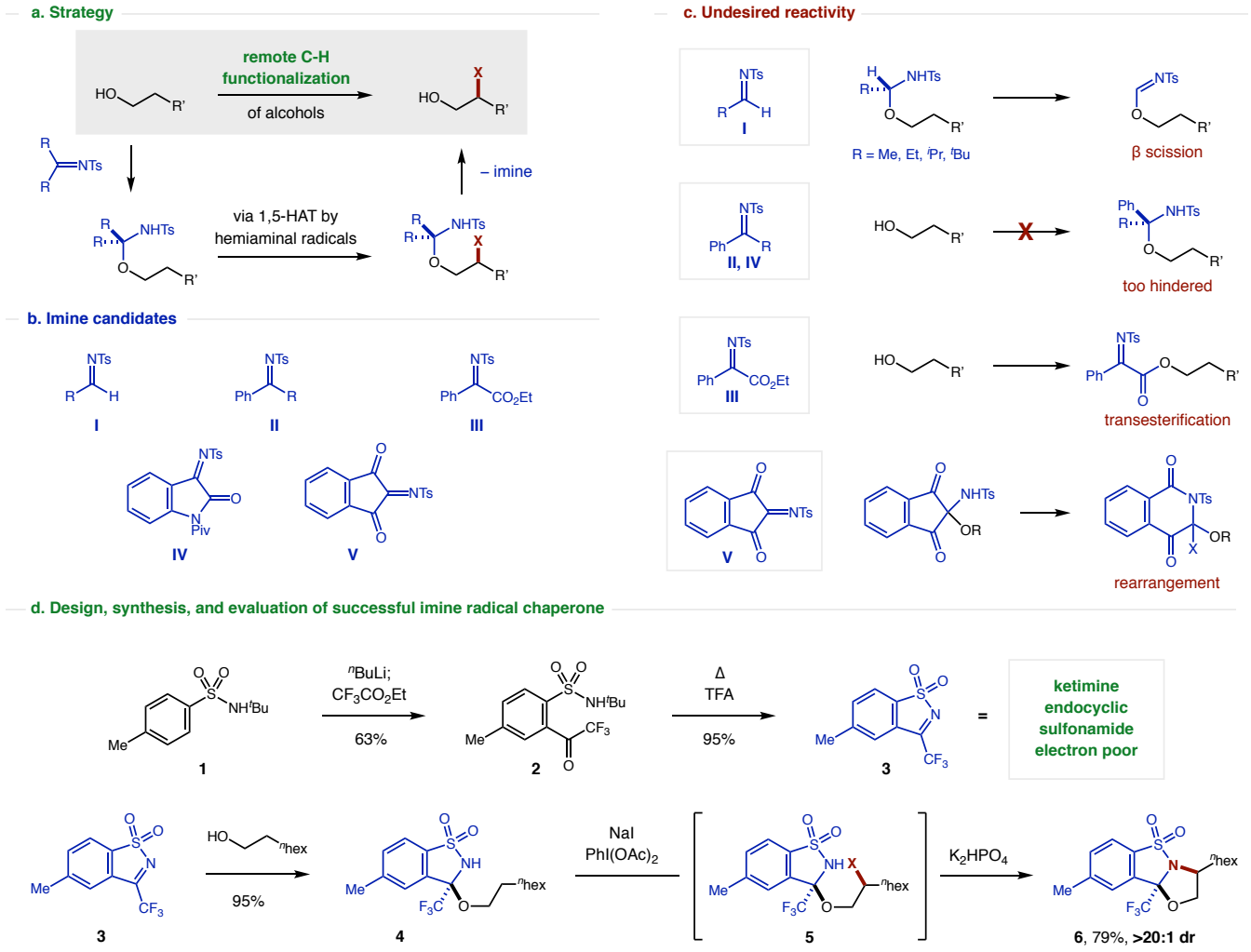


Figure 2. Development of an imine radical relay chaperone for β C-H functionalization of alcohols.

scission, rather than 1,5-HAT (Figure 2c).

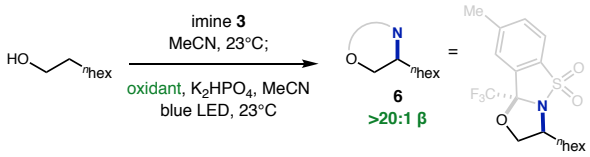
Interestingly, hemiaminals from each of the aldehydes that were prepared (**I**; R = Me, Et, ^{i}Pr, ^{t}Bu) resulted mainly in formation of imidate side products – even in cases that would formally furnish Me or Et radicals. We next turned to ketone derived imines (**II-V**) with the hopes of blocking the oxidizable carbon. Unfortunately, our attempts to convert these ketimines **II** to hemiaminals were unfruitful, likely due to attenuated electrophilicity. As a possible solution, we next incorporated a withdrawing ester substituent. However, α-imino ester **III** readily undergoes transesterification rather than hemiaminal formation. As our next design, we instead incorporated a withdrawing amide to prevent competitive attack of the imine at the adjacent carbonyl. However, hemiaminals of cyclic amide **IV**, derived from isatin, were highly prone to hydrolysis. Finally, we investigated ninhydrin-based imine **V**, bearing an imine with two flanking ketones. Yet, while **V** readily affords hemiaminals, these intermediates undergo undesired rearrangements.

In summarizing the necessary design elements of a suitable HAT chaperone from these studies, we proposed the imine should be ketone-derived, cyclic, substituted with an EWG, and non-enolizable (Figure 2d). As we brainstormed a molecule to meet these criteria, it occurred to us that an endocyclic Ts-imine may serve this purpose. To this end, we sought to use saccharin-type imine **3**.[13] The imine was readily prepared in a two-step synthesis from TsNH-^{t}Bu **1**. The first step entails a sulfonamide-directed *ortho*-lithiation, followed by quenching with ethyl trifluoroacetate to afford ketone **2** in 63% yield.[14] Upon treatment with TFA at 135 °C for 12 hours, this ketone was then cyclized, deprotected, and dehydrated in a single step to afford imine chaperone **3** as a crystalline, white solid in 95% yield. To our delight, alcohols readily add to this imine in MeCN at room temperature. Moreover, when subjected to NaI and $PhI(OAc)_2$,[12] the resulting hemiaminal **4** undergoes selective HAT to afford β C-H halide **5** (X = I), which is unstable and not isolated. To our surprise, however, when attempting to release the chaperone by treatment with base (K_2HPO_4), an intramolecular displacement instead occurs to afford aminated adduct **6**. Although net incorporation of the chaperone into the product via a covalent C-N bond prevents its use as a catalyst, the ongoing challenge and synthetic utility of C-H amination led us to continue developing this reaction.[15] Notably, when K_2HPO_4 is included in the direct C-H functionalization of **4**, the entire cascade directly results in efficient formation of the C-H aminated oxazolidine **6** (79% yield). Interestingly, along with exceptional regioselectivity (>20:1 β), this rigid,

polycyclic heterocycle is accessed as a single diastereomer (>20:1) via net, *cis* C-H amination.

We next turned to developing a one-pot protocol for directly converting alcohols to their β C-H aminated analogs (Table 1). After stirring octanol (0.1 mmol) and imine **3** (2 equiv) in MeCN (0.2 M) at 23 °C for 2 hours, hemiaminal **4** was formed quantitatively, as determined by crude ^{1}H NMR. Oxidant and K_2HPO_4 were then added, and the reaction was stirred under visible light irradiation (90W blue LED) at 23 °C until complete consumption of the *in situ* generated hemiaminal (2-24 hours). As illustrated in Table 1, this one-pot procedure for direct alcohol C-H functionalization affords either β iodide **5** (19% by NMR; without base), or oxazolidine **6** is formed in a slightly lower yield (52%, >20:1 dr; with base) than the stepwise procedure (entries 1-2). To improve this one-pot protocol, we also explored the Suárez method (I_2, $PhI(OAc)_2$)[16] for amidyl radical HAT. However, these conditions resulted in slightly diminished yields. On the other hand, employing N-halo succinimides as the oxidant afforded improved yields with either NIS (entries 5-6, up to 62% yield) or NBS (entries 7-8, up to 72% yield). Interestingly, although base is not necessary to promote cyclization with these reagents, its incorporation improves overall efficiency (entry 8, 67% isolated yield). To our delight, each of these C-H aminations of octanol are both exquisitely diastereoselective (>20:1 *syn*) and regioselective (>20:1 β).

Table 1. Development of a one-pot β C-H amination of alcohols.



entry	oxidant	base	product **6**
1	NaI, $PhI(OAc)_2$	–	19% **5** (X = I)
2	NaI, $PhI(OAc)_2$	+	52%, >20:1 dr
3	I_2, $PhI(OAc)_2$	–	13% **5** (X = I)
4	I_2, $PhI(OAc)_2$	+	41%, >20:1 dr
5	NIS	–	39%, >20:1 dr
6	NIS	+	62%, >20:1 dr
7	NBS	–	42%, >20:1 dr
8	NBS	+	72% (67%), >20:1 dr

Synthetic scope. In order to determine the synthetic utility of this new, imine-chaperone-mediated β C-H amination, we subjected a series of alcohols to this one-pot protocol. As shown in Figure 3, a wide range of alcohols undergo the radical relay mechanism to afford regioselective C-H amination (>20:1 β in all cases). For example, propanol, 4-^{t}Bu-cyclohexanol, and phenethyl alcohol each afford oxazolidine efficiently (**7-9**; 62-75% yield) and in high diastereoselectivity (>20:1). With the hopes of probing the synthetic utility of this HAT-mediated amination, we then investigated a range of stereoelectronically diverse 2-arylethanols. To our delight, *ortho* (**10-11**), *meta* (**12-13**), and *para* (**14-17**) substitution are all well-tolerated, including both electronically rich and deficient substituents (OMe, Me, Cl, F, CF_3). Notably, incorporation of a 2-pyridyl ethanol (**18**) also illustrates the applicability of this β C-H amination to alcohols with medicinal relevance. To this end, we also noted that β amino alcohol **16** is an interesting isomeric analog of the neurotransmitter, octopamine, wherein the N and O of the β amino alcohol are inverted.

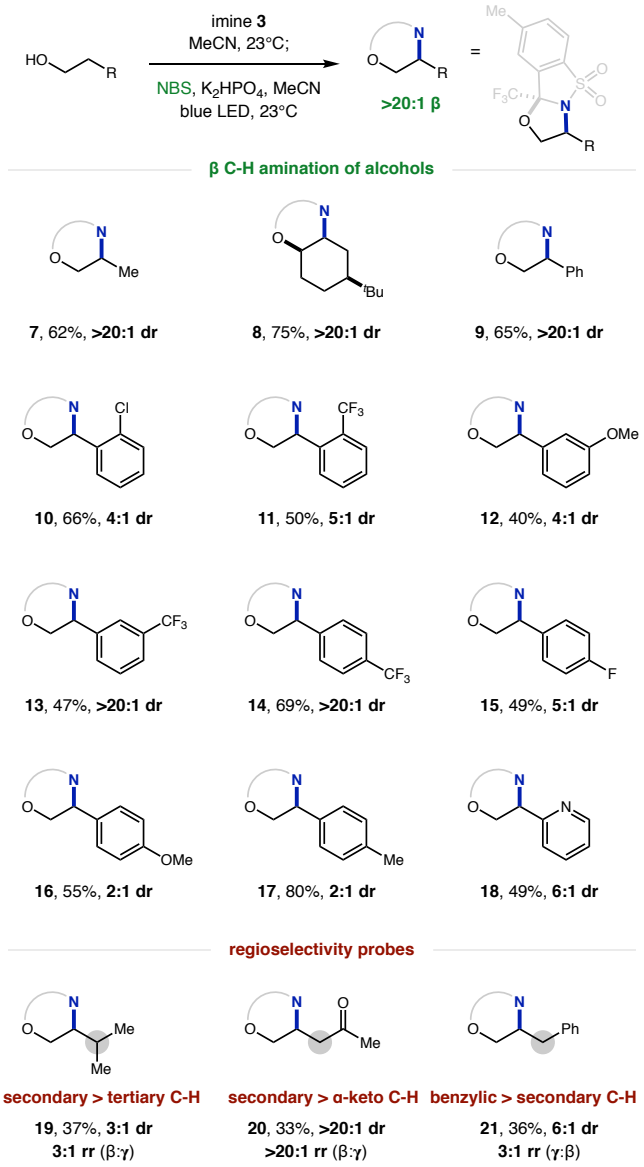


Figure 3. Synthetic evaluation of imine chaperone strategy for β C-H amination of alcohols.

Regioselectivity investigation. Motivated by the complete regioselectivity observed in all cases, but especially for 1-octanol, we sought to design and explore a series of regioselectivity probes to interrogate the HAT selectivity. To this end, we synthesized alcohols containing weaker C-H bonds at the γ positions, with the intention to quantify the tendency for 1,5-HAT versus the next most likely 1,6-HAT mechanism. In the case of a slightly weaker tertiary C-H (BDE: 96 kcal/mol vs secondary C-H, 98 kcal/mol),[17] a 3:1 regiomeric ratio (rr) was observed favoring the 1,5-HAT-mediated

β amine (**19**). However, when an even weaker α-keto C-H was used (BDE: 94 kcal/mol), complete β selectivity was instead observed (**20**, >20:1 rr), indicating that C-H polarity also plays an important role. Finally, when a much weaker benzylic C-H is incorporated (BDE: 90 kcal/mol), we observed a switch in regioselectivity to afford γ amine **21** instead (3:1 rr) – illustrating that 1,6-HAT may compete under strongly biased environments.

Stereoselectivity investigation. In addition to regioselectivity, we were also interested in investigating the diastereoselectivity of this HAT mechanism, especially for secondary alcohols (Figure 4). In this vein, we subjected both conformationally locked isomers of 4-ᵗBu-cyclohexanol, *cis*-**22** and *trans*-**22**, to the β C-H amination protocol. Surprisingly, whereas *cis*-**22** efficiently provides oxazolidine **8**, *trans*-**22** does not afford any C-H functionalized product. Since vicinal H-atoms are available for abstraction by either isomer, we interpret this divergent reactivity as evidence of a preference for amination by the axial oxygen-bound chaperone over the equatorial one.

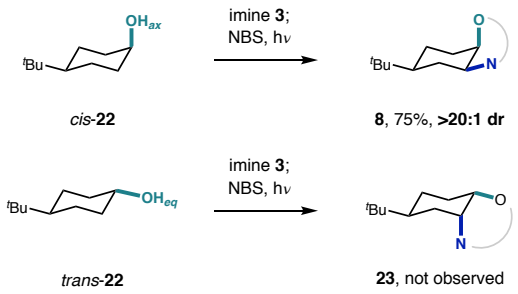


Figure 4. Diastereoselectivity probe.

Additionally, the *cis* stereochemical arrangement of the nitrogen and oxygen substituents on the central oxazolidine is supported by X-ray crystallography data (see SI for full details). Lastly, as shown in Figure 5, the imine chaperone may be removed by reduction with SmI_2. Acidic hydrolysis with TfOH furnishes the free β amino alcohol (50% yield).

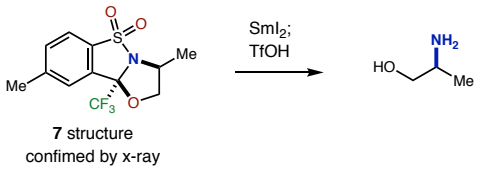


Figure 5. Removal of chaperone.

In summary, we have developed an imine chaperone, which is capable of transforming alcohols into β amino alcohols by a chemo, regio, and stereoselective HAT mechanism. We have interrogated the viability of various chaperone scaffolds in promoting this HAT, in addition to probing the synthetic utility and selectivity parameters of a saccharin-based imine. We expect the design principles observed for the discovery of this radical chaperone will allow the development of more C-H functionalization technologies using this strategy.

EXPERIMENTAL SECTION

Materials and Methods. All reagents, unless otherwise stated, were used as supplied from commercial sources without further purification. NBS, K_2HPO_4, and other solid reagents were dried under vacuum before use. Solvents were purified in the following manner. Acetonitrile (MeCN) was distilled over calcium hydride. CH_2Cl_2, THF, Et_2O and DMF were degassed with N_2 and dried by passing through columns containing alumina, copper, or molecular sieves. Flash column chromatography, or preparative thin-layer chromatography, was performed with Silicycle F60 (230-400 mesh) silica gel. Thin layer chromatography (TLC) analyses were performed using EMD 60 F254 TLC plates and visualized by fluorescence quenching or KMnO4 stain. All yields are averages of at least two experimental runs. All regioselectivity (rr) and diastereoselectivity (dr) values are measured by 1H NMR analysis of crude reaction materials.

Nuclear magnetic resonance (NMR) spectra (^1H, ^{13}C) were recorded using either a Bruker AVIII 400 or AVIII 600 MHz NMR spectrometer. ^1H and ^{13}C NMR chemical shifts are reported in parts per million and referenced to residual $CHCl_3$ signals in $CDCl_3$ (^1H: δ 7.26; ^{13}C: δ 77.16). ^1H NMR data are reported as follows: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad, ap = apparent), coupling constant (Hz), relative integral. Data for ^{13}C is reported in terms of chemical shift and multiplicity where appropriate. High-resolution Mass Spectrometry (HRMS) data were obtained using a Bruker MicrOTOF (ESI). Measured values are reported to 4 decimal places and are within ±5 ppm of the calculated value, which are based on the most abundant isotope. Infrared (IR) spectra were recorded using a Thermo Fisher Nicolet iS10 FT-IR and are reported in terms of frequency of absorption (cm^{-1}). Melting points were determined using an Electrotherman IA9000.

Photochemical reactions were performed by placing a 90 W Kessil blue LED lamp (λmax = 459 nm) approximately 5 cm from the reaction vessel (borosilicate glass, without an added filter), along with a fan behind the reaction vessel.

Synthesis of Imine Chaperone (3)

*N-(tert-butyl)-4-methylbenzenesulfonamide (**1**).* To a stirred suspension of tertbutylamine (27.3 ml, 260 mmol, 2.0 equiv.) and distilled triethylamine (54.4 mL, 390 mmol, 3.0 equiv.) in dry CH_2Cl_2 (100 mL) at 0°C was added 4-toluenesulfonyl chloride (24.8 g, 130 mmol, 1.0 equiv.) portion-wise at 0 °C. After complete addition, the resulting suspension was warmed to room temperature and stirred for 12 hours. The mixture was quenched with a 3M HCl aqueous solution (100 mL) at 0°C. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). Combined organic extracts were washed with brine (1 x 100 ml), dried over $MgSO_4$, and filtered. The combined organic layer was concentrated under reduced pressure to afford the title compound as a white solid (28.1 g, 95% yield), which was used without further purification. **TLC**: R_f= 0.21 in 20% EtOAc/hexanes; **MP**: 110.5 – 112.0 °C; IR (neat) ν (cm^{-1}): 3259, 2987, 2972, 1597, 1475, 1299, 1181, 1109, 995; **^{1}H NMR**

($CDCl_3$, 400 MHz) δ (ppm): 7.78 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.76 (br s, 1H), 2.41 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm): 142.9, 140.7, 129.6, 127.1, 54.7, 30.3, 21.6; **HRMS** (m/z ESI-TOF)**:** calculated for $C_9H_6F_3NO_2SH^+$ [M + H]$^+$ 250.0150, found 250.0141.

N-(tert-butyl)-4-methyl-2-(2,2,2-trifluoroacetyl)benzenesulfonamide (2). To a stirring solution of **1** (6.0 g, 26.4 mmol, 1.0 equiv.) and distilled TMEDA (11.8 mL, 79.1 mmol, 3.0 equiv.) at 0°C was added a solution of ^{n}BuLi (28.7 mL, 2.3 M in hexanes, 66.0 mmol, 2.5 equiv.) dropwise over 5 min. After complete addition, the resulting suspension was stirred at 0°C for 30 min. The reaction mixture was cooled to – 78°C. A solution of ethyl 2,2,2-trifluoroacetate (9.4 mL, 79.1 mmol, 3 equiv.) was added dropwise over 10 min. The resulting solution was then stirred for 3 hours, while slowly warming to room temperature. The mixture was cooled to 0°C and quenched with a 3M HCl aqueous solution (100 mL). The aqueous layer was extracted with Et_2O three times (3 x 50 mL). Combined organic extracts were washed with brine (1 x 100 mL), dried over $MgSO_4$, and filtered. The combined organic layer was concentrated under reduced pressure to afford a crude residue, which was purified on silica gel using hexanes/Et_2O as eluent (gradient from 100/0 to 30/70) to afford the title compound as a yellow oil (5.38g, 63% yield), which becomes a white solid. **TLC**: R_f = 0.21 in 20% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 3268, 2977, 1748, 1597, 1423, 1316, 1171, 1136, 1073, 970; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.98 (d, *J* = 8.2 Hz, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.40 (s, 1H), 4.88 (br s, 1H), 2.49 (s, 3H), 1.24 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 186.1 (q, J^2_{CF} = 37.4 Hz), 143.3, 140.5, 133.2, 131.5, 129.7, 128.5 (q, J^3_{CF} = 2.0 Hz), 115.8 (q, J^1_{CF} = 291.2 Hz), 55.5, 30.2, 21.5; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm)**:** – 73.8; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{13}H_{16}F_3NO_3SNa^+$ [M + Na]$^+$ 346.0695, found 346.0705. Data in accordance with those reported in the literature.[13]

5-methyl-3-(trifluoromethyl)benzo[d]isothiazole 1,1-dioxide (3). To a solution of **2** (2.0 g, 6.2 mmol, 1.0 equiv.) in degassed toluene (2 ml) in a pressure tube, trifluoromethyl acetic acid (2.4 ml, 31.0 mmol, 5.0 equiv.) was added under a flow of dry nitrogen. The reaction mixture was stirred for 12 hours at 135 °C. Then, toluene and acid was removed via azeotrope with dry CH_2Cl_2 (2 × 10 mL) under vacuo. The title compound was isolated as an oil, which solidified upon further drying (light brown solid, 1.5 g, 95% yield). Due to its hydrophilicity, this crude imine was used directly in the following reactions. **MP:** 127.1 – 128.9 °C; **TLC:** R_f = 0.26 in 40% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 3356, 3250, 2981, 2361, 2341, 1601, 1286, 1174, 1053; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.88 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.26 (s, 1H), 2.56 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 160.7 (q, J^2_{CF} = 40.0 Hz), 146.5, 138.0, 135.8, 133.7, 126.1, 123.5, 118.9 (q, J^1_{CF} = 278.4 Hz), 22.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm)**:** – 67.7; **HRMS** (m/z ESI-TOF)**:** calculated for $C_9H_6F_3NO_2SH^+$ [M + H]$^+$ 250.0105, found 250.0141. **HRMS** (m/z ESI-TOF)**:** calculated for $C_9H_6F_3NO_2SH^+$ [M + H]$^+$ 250.0105, found 250.0141.

General Procedure for one-pot β C-H amination of primary alcohols (GP1). To a stirred solution of **3** (49.8 mg, 0.2 mmol, 2.0 equiv.) in an oven-dried septa vial, the appropriate alcohol (0.1 mmol, 1.0 equiv.) in acetonitrile (0.5 mL, 0.2 M) was added. The reaction was stirred at room temperature (23 °C) for 2 hours. The solvent was removed and the mixture was dried under vacuum. In a glove box, recrystallized NBS (71.2 mg, 0.4 mmol, 4.0 equiv.) and oven-dried K_2HPO_4 (78.4 mg, 0.45 mmol, 4.5 equiv.) were added to the reaction vial. Freshly distilled and degassed acetonitrile (3 mL) was then added to the vial. The reaction was irradiated with a blue 90W LED for 24 hours, while being cooled with a fan to keep the temperature constant (vials were placed approximately 5 cm from the light). The resulting reaction mixture was concentrated first and diluted with CH_2Cl_2. Aqueous solution of 20 % $Na_2S_2O_3$ was added, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). Combined organic extracts were washed with brine, dried over $MgSO_4$ and filtered. The organic layer was concentrated under reduced pressure and purified on silica gel using Hexanes/EtOAc as eluent (gradient from 100/0 to 80/20).

General Procedure for one-pot β C-H amination of secondary alcohols (GP2). GP2 is the same as GP1 except for the following changes: **3** (74.7 mg, 0.3 mmol, 3.0 equiv.) was used, and the hemiaminal formation was let stir longer until disappearance of alcohol was observed by TLC (up to 24 hours).

3-hexyl-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (6). Following GP1, the compound was formed using 1-octanol (15.0 µL, 0.1 mmol. 1 equiv). The title compound was obtained as a white solid (25.3 mg, 67% yield, >20 : 1 dr). **MP** 67.7 – 68.5 °C; **TLC:** R_f = 0.53 in 20% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2963, 2923, 2893, 2859, 1600, 1469, 1385, 1335, 1250, 1182, 1169; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.68 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.49 (m, 2H), 4.30 (quint, *J* = 6.7 Hz, 1H), 4.24 – 4.20 (m, 1H), 4.10 – 4.06 (m, 1H), 2.50 (s, 3H), 1.89 – 1.81 (m, 1H), 1.57 – 1.29 (m, 8H), 0.90 (t, J = 7.0 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 145.6, 134.8, 133.7, 132.1, 125.9, 123.0 (q, J^1_{CF} = 287.3 Hz), 121.5, 97.5 (q, J^2_{CF} = 34.4 Hz), 74.7, 61.7, 33.9, 31.7, 29.1, 26.5, 22.7, 22.0, 14.2; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm)**:** -79.1; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{17}H_{22}F_3NO_3SNa^+$ [M + Na]$^+$ 400.1165, found 400.1171.

3,8-dimethyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (7). Following GP1, the compound was formed using 1-propanol (7.5 µL, 0.1 mmol. 1 equiv), but the amination proceeded in only 8 hours (rather than 24 hours). The title compound was obtained as a white solid (62% yield, >20 : 1 dr – NMR). **MP** 105.0 – 107.0 °C; **TLC:** R_f = 0.41 in 20% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2925, 2860, 1599, 1469, 1384, 1322, 1250, 1182, 1140; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.67 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.49 (m, 2H), 4.44 – 4.35 (m, 1H), 4.26 (ap t, *J* = 7.5 Hz, 1H), 4.04 (ap t, *J* = 7.7 Hz, 1H), 2.50 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 145.6, 134.7, 133.7, 132.1, 125.8, 123.1 (q, J^1_{CF} = 287.0 Hz), 121.5, 97.5 (q, J^2_{CF} = 34.1 Hz), 75.9, 57.5, 21.9, 19.3; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm)**:** -79.2; **HRMS** (m/z ESI-TOF)**:**

calculated for $C_{12}H_{12}F_3NO_3SNa^+$ $[M + Na]^+$ 330.0388, found 330.0375.

*8-(tert-butyl)-2-methyl-11a-(trifluoromethyl)-6a,7,8,9,10,10a-hexahydro-11aH-benzo[d]benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**8**).* Following GP2, the compound was formed using *cis*-4-terbutylcyclohexanol (15.6 mg, 0.1 mmol. 1 equiv). The title compound was obtained as a white solid (75% yield, >20 : 1 dr – NMR). **TLC:** R_f = 0.30 in 10% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2926, 1600, 1454, 1342, 1250, 1185, 1151; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.69 (d, *J* = 8.0 Hz, 1H), 7.52 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 4.35 – 4.29 (m, 1H), 3.74 – 3.72 (m, 1H), 2.51 (s, 3H), 2.25 – 2.20 (m, 1H), 2.10 – 2.04 (m, 1H), 1.63 – 1.52 (m, 4H), 1.04 – 0.97 (m, 1H), 0.89 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 145.5, 136.4, 133.6, 133.5, 126.0, 123.8, 122.5 (q, J^1_{CF} = 276.2 Hz), 121.8, 121.0, 97.0 (q, J^2_{CF} = 35.2 Hz), 76.5, 61.8, 45.8, 32.6, 30.1, 29.9, 27.8, 27.6, 27.5, 27.2, 22.0, 20.9; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -78.6. **HRMS** (m/z ESI-TOF)**:** calculated for $C_{19}H_{24}F_3N_2O_3SNa^+$ $([M + Na]^+)$ 426.1321 found 426.1309.

*8-methyl-3-phenyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**9**).* Following GP1, the compound was formed using 2-phenylethanol (12 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (26.3 mg, 66% yield, >20 : 1 dr). **MP** 126.0 – 128.0 °C; **TLC:** R_f = 0.15 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 3067, 3038, 2968, 2911, 1599, 1495, 1476, 1456, 1337, 1305, 1255, 1166, 1117, 974, 816; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 7.70 (d, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 23.7, 8.7 Hz, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.3 Hz, 1H), 5.26 (ap t, *J* = 8.3 Hz, 1H), 4.68 (ap t, *J* = 8.6 Hz, 1H), 4.38 (ap t, *J* = 8.6 Hz, 1H), 2.53 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 145.7, 136.1, 134.6, 133.9, 132.0, 129.2, 128.8, 128.1, 126.8, 125.9, 125.9, 123.4 (q, J^1_{CF} = 288.0 Hz), 121.7, 97.8 (q, J^2_{CF} = 34.1 Hz), 64.7, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -78.4; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{17}H_{14}F_3NO_3SNa$ $([M + Na]^+)$ 392.0544, found 392.0549.

*3-(2-chlorophenyl)-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-nenzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**10**).* Following GP1, the compound was formed using 2-(2-chlorophenyl)ethan-1-ol (13.2 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (66% yield, 4 : 1 dr – NMR). **MP** 150.0 – 151.0 °C. **TLC:** R_f = 0.13 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 2965, 2914, 1574, 1475, 1335, 1182, 1168, 1032, 996; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 7.92 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.57 – 7.55 (m, 2H), 7.41 – 7.38 (m, 2H), 7.31 – 7.29 (m, 1H), 5.65 (ap t, *J* = 8.3 Hz, 1H), 5.02 – 4.99 (m, 1H), 4.25 – 4.22 (m, 1H), 2.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 145.8, 134.8, 134.4, 134.0, 132.3, 131.7, 129.8, 129.7, 128.0, 127.7, 125.9, 123.4 (q, J^1_{CF} = 290.1 Hz), 121.8, 97.6 (q, J^2_{CF} = 33.9 Hz), 76.3, 62.2, 22.1; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -78.4; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{17}H_{13}ClF_3NO_3SNa^+$ $([M + Na]^+)$ 426.0154 found 426.0144.

*8-methyl-9b-(trifluoromethyl)-3-(2-(trifluoromethyl)phenyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**11**).* Following GP1, the compound was formed using 2-(2-(trifluoromethyl)phenyl)ethan-1-ol (15.2 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (21.9 mg, 50% yield, 5 : 1 dr). **MP** 138.0 – 140.0 °C; **TLC:** R_f = 0.15 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 2960, 2915, 1600, 1455, 1340, 1313, 1255, 1183, 1116, 975, 820; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 8.20 (d, *J* = 8.1 Hz, 1H), 7.72 – 7.68 (m, 3H), 7.52 – 7.55 (m, 2H), 7.48 (t, *J* = 7.7 Hz, 1H), 5.63 (ap t, *J* = 8.5 Hz, 1H), 4.80 (ap t, *J* = 7.9 Hz, 1H), 4.22 (ap t, *J* = 9.2 Hz, 1H), 2.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 145.9, 134.7, 134.4, 134.0, 133.3, 131.9, 128.8, 128.1 (J^2_{CF} = 30.2 Hz), 128.1, 126.4 (J^3_{CF} = 5.9 Hz), 125.9, 123.5 (J^1_{CF} = 288.5 Hz), 124.3 (J^1_{CF} = 270.9 Hz), 121.8, 97.5 (J^2_{CF} = 35.9 Hz), 77.8, 61.9, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -62.7, -78.4; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{13}F_6NO_3SNa^+$ $([M + Na]^+)$ 460.0418 found 460.0416.

*3-(3-methoxyphenyl)-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**12**).* Following GP1, the compound was formed using 2-(3-methoxyphenyl)ethan-1-ol (14.2 µL, 0.1 mmol. 1 equiv). The title compound was obtained as a white solid (40% yield, 4 : 1 dr – NMR). **MP** 129.0 – 131.0 °C; **TLC:** R_f = 0.36 in 20% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2923, 1604, 1494, 1470, 1437, 1371, 1336, 1307, 1276, 1256, 1224, 1184; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.71 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.34 – 7.30 (m, 1H), 7.09 – 7.06 (m, 2H), 6.90 – 6.87 (m, 1H), 5.24 (ap t, *J* = 9.0 Hz, 1H), 4.70 – 4.65 (m, 1H), 4.39 – 4.34 (m, 1H), 3.83 (s, 3H), 2.53 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 160.3, 145.7, 137.7, 134.6, 133.9, 131.9, 130.3, 129.8, 125.9, 123.3 (q, J^1_{CF} = 284.1 Hz), 121.7, 119.0, 114.3, 112.3, 97.8 (q, J^2_{CF} = 32.6 Hz), 64.5, 55.4, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** ***Major diastereomer*** -78.4, ***Minor diastereomer*** 78.9; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{16}F_3NO_4SNa^+$ $([M + Na]^+)$ 422.0650 found 422.0643.

*8-methyl-9b-(trifluoromethyl)-3-(3-(trifluoromethyl)phenyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide (**13**).* Following GP1, the compound was formed using 2-(3-(trifluoromethyl)phenyl)ethan-1-ol (15.2 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (20.7 mg, 47% yield, >20 : 1 dr). **MP** 141.0 – 142.0 °C; **TLC:** R_f = 0.31 in 20% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 2919, 2850, 1735, 1599, 1457, 1378, 1329, 1270, 1254, 1223; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 7.80 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.68 (s, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.55 (m, 3H), 5.32 (ap t, *J* = 8.2 Hz, 1H), 4.73 – 4.69 (m, 1H), 4.40 – 4.35 (m, 1H), 2.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 146.0, 137.4, 134.4, 134.1, 131.7, 131.6 (q, J^2_{CF} = 32.6 Hz), 130.2, 129.4, 125.9, 125.8 (J^3_{CF} = 3.7 Hz), 124.0 (q, J^1_{CF} = 272.5 Hz), 123.7 (q, J^3_{CF} = 3.7 Hz), 123.3 (q, J^1_{CF} = 287.8 Hz), 121.8, 97.9 (q, J^2_{CF} = 34.5 Hz), 76.9, 64.1, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -62.7, -78.4; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{13}F_6NO_3SNa^+$ $([M + Na]^+)$ 460.0418 found 460.0415.

8-methyl-9b-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide

(14). Following GP1, the compound was formed using 2-(4-(trifluoromethyl)phenyl)ethan-1-ol (15.2 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (30.2 mg, 69% yield, >20 : 1 dr). **MP** 138.0 – 140.0 °C; **TLC:** R_f = 0.38 in 20% EtOAc/pentane;**IR** (neat) **ν** (cm^{-1}): 2914, 1623, 1600, 1478, 1428, 1337, 1323, 1303, 1257, 1225, 1175, 1149, 1104; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.72 – 7.55 (m, 7H), 5.33 (ap t, *J* = 8.0 Hz, 1H), 4.72 (ap t, *J* = 8.0 Hz, 1H), 4.37 (ap t, *J* = 8.8 Hz, 1H), 2.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 160.3, 146.0, 140.3, 134.3, 134.1, 131.7, 131.1 (q, J^2_{CF} = 32.7 Hz), 127.2, 126.2 (q, J^3_{CF} = 3.9 Hz), 125.9, 125.9, 124.1 (q, J^1_{CF} = 272.8 Hz), 123.3 (q, J^1_{CF} = 288.5 Hz), 121.8, 97.9 (q, J^2_{CF} = 34.2 Hz), 64.0, 22.0; **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm)**:** -62.7, -78.4; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{13}F_6NO_3SNa^+$ ([M + Na]$^+$) 460.0418 found 460.0415.

*3-(4-fluorophenyl)-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide **(15)**.* Following GP1, the compound was formed using 2-(4-fluorophenyl)ethan-1-ol (12.5 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (34.8 mg, 49% yield, 5 : 1 dr – NMR). **MP** 136.0 – 138.0 °C; **TLC:** R_f = 0.13 in 10% EtOAc/pentane;**IR** (neat) **ν** (cm^{-1})**:** 2963, 2917, 2851, 1735, 1606, 1512, 1334, 1181, 1151, 976, 835. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 7.70 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.47 (m, 4H), 7.13 – 7.08 (m, 2H), 5.23 (ap t, *J* = 8.4 Hz, 1H), 4.68 – 4.63 (m, 1H), 4.37 – 4.32 (m, 1H), 2.53 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 163.9, 162.2, 145.8, 145.7, 135.5, 134.5, 134.0, 133.6, 132.3, 131.9, 131.6, 130.7, 130.0 (d, J^2_{CF} = 9.1 Hz), 128.7 (d, J^2_{CF} = 8.6 Hz), 125.9, 125.8, 123.4 (q, J^1_{CF} = 287.8 Hz), 123.1 (q, J^1_{CF} = 289.2 Hz), 121.8, 121.5, 121.1, 116.2 (d, J^1_{CF} = 21.1 Hz), 115.8 (d, J^1_{CF} = 21.3 Hz), 97.7 (q, J^2_{CF} = 34.1 Hz), 72.9, 67.8, 65.0, 64.1, 22.1, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** ***Major diastereomer*** -78.5, -113.3, ***Minor diastereomer*** -78.9 -112.3; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{17}H_{13}F_4NO_3SNa^+$ ([M + Na]$^+$) 410.0450 found 410.0437.

*3-(4-methoxyphenyl)-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo [3,2-b]oxazole 5,5-dioxide **(16)**.* Following GP1, the compound was formed using 2-(4-methoxyphenyl)ethan-1-ol (15.2 mg, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (55% yield, 1.5 : 1 dr – NMR). **MP** 110.0 – 112.0 °C; **TLC:** R_f = 0.15 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 2959, 2925, 2852, 1613, 1516, 1463, 1333, 1181, 1109, 828, 760; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** ***Major diastereomer*** 7.69 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.30 (dd, *J* = 8.9, 5.7 Hz, 1H), 4.64 – 4.60 (m, 1H), 4.41 (ap t, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 2.53 (s, 3H). ***Minor diastereomer*** 7.78 (d, *J* = 8.3 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.49 (d, *J* = 8.1Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 5.20 (ap t, *J* = 8.4 Hz, 1H), 4.64 – 4.60 (m, 1H), 4.36 (ap t, *J* = 8.7 Hz, 1H), 3.82 (s, 3H), 2.53 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 160.1, 160.0, 145.7, 145.5, 135.6, 134.7, 133.9, 133.5, 132.0, 130.7, 129.6, 128.3, 127.8, 125.9, 125.7, 123.6, 123.4 (J^1_{CF} = 289.7 Hz), 123.2 (J^1_{CF} = 287.1 Hz), 121.7, 121.0, 114.6, 114.1, 97.6 (J^2_{CF} = 34.4 Hz), 96.9 (J^2_{CF} = 34.4 Hz), 72.7, 65.4, 34.5, 55.5, 55.4, 22.0, 21.9; **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm)**:** ***Major diastereomer*** -78.9, ***Minor diastereomer*** -78.5; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{16}F_3NO_4SNa^+$ ([M + Na]$^+$) 422.0650 found 422.0637.

*(3R,9bR)-8-methyl-3-(p-tolyl)-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide **(17)**.* Following GP1, the compound was formed using 2-(*p*-tolyl)ethan-1-ol (13.8 µL, 0.1 mmol. 1 equiv). The title compound was obtained as off-white solid (80% yield, 2 : 1 dr – NMR). **MP** 130.0 – 132.0 °C; **TLC:** R_f = 0.18 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 2961, 2924, 1514, 1334, 1224, 1181, 992, 816; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** ***Major diastereomer*** 7.69 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 5.22 (ap t, *J* = 8.5 Hz, 1H), 4.67 – 4.61 (m, 1H), 4.43 – 4.33 (m, 1H), 2.53 (s, 3H), 2.37 (s, 3H); ***Minor diastereomer*** 7.61 (bs, 1H), 7.56 – 7.47 (m, 2H), 7.27 (d, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.31 (dd, *J* = 8.6, 5.8 Hz, 1H), 4.67 – 4.61 (m, 1H), 2.53 (s, 3H), 2.35 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 145.7, 145.6, 138.8, 138.6, 135.5, 134.7, 133.5, 133.0, 132.0, 130.7, 129.9, 129.4, 129.0, 128.0, 126.8, 125.9, 125.7, 123.4 (J^1_{CF} = 289.3 Hz), 123.2 (J^1_{CF} = 286.2 Hz), 121.7, 121.0, 97.7 (J^2_{CF} = 34.4 Hz), 96.9 (J^2_{CF} = 32.9 Hz), 72.7, 65.5, 64.7, 22.0, 21.9, 21.4, 21.3; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** ***Major diastereomer*** -78.4, ***Minor diastereomer*** -78.9; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{16}F_3NO_3SNa^+$ ([M + Na]$^+$) 406.0701 found 406.0688.

*8-methyl-3-(pyridin-2-yl)-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b] oxazole 5,5-dioxide **(18)**.* Following GP1, the compound was formed using 2-pyridineethanol (11.3 µL, 0.1 mmol. 1 equiv), but the amination proceeded in only 8 hours (rather than 24 hours). The title compound was obtained as an off-white solid (49% yield, 6 :1 dr – NMR). **MP** 125.0 – 127.0 °C; **TLC:** R_f = 0.08 in 10% EtOAc/pentane; **IR** (neat) **ν** (cm^{-1})**:** 3022, 2963, 2926, 2854, 1598, 1475, 1355, 1215, 1183, 748; **^{1}H NMR** ($CDCl_3$, 600 MHz) δ (ppm)**:** 8.57 – 8.55 (m, 1H), 7.82 – 7.78 (m, 2H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.31 (d, *J* = 7.3 Hz, 1H), 5.52 (ap t, *J* = 7.4 Hz, 1H), 4.80 – 4.72 (m, 2H), 2.54 (s, 3H); **^{13}C NMR** ($CDCl_3$, 150 MHz) δ (ppm)**:** 157.3, 149.4, 146.0, 137.6, 134.4, 133.9, 131.8, 125.9, 123.1 (q, J^1_{CF} = 287.1 Hz), 123.1, 121.7, 121.0, 96.1 (J^2_{CF} = 32.7 Hz), 75.5, 64.1, 22.0; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** -78.7; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{16}H_{14}F_3N_2O_3S^+$ ([M + H]$^+$) 371.0672 found 371.0674.

*3-isopropyl-8-methyl-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazole 5,5-dioxide **(19)**.* Following GP1, the compound was formed using 3-methyl-1-butanol (11.0 µL, 0.1 mmol. 1 equiv). The title compound was obtained as a white solid (37% yield, 2.3 : 1, β : γ – NMR). **MP** 97.0 – 99.0 °C. **TLC:** R_f = 0.44 in 20% EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2968, 2923, 2851, 1598, 1467, 1341, 1322, 1304, 1256, 1173, 1158; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.70 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 4.25 – 4.20 (m, 2H), 4.01 – 3.96 (m, 1H), 2.50 (s, 3H), 1.97 – 1.91 (m, 1H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 145.6, 134.6, 133.7, 131.9, 125.7, 123.1 (q, J^1_{CF} = 287.2 Hz), 121.6,

97.7 (q, J^2_{CF} = 34.0 Hz), 73.6, 67.5, 31.8, 29.9, 22.0, 20.5, 19.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ (ppm)**:** – 79.0; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{14}H_{16}F_3NO_3SNa^+$ $[M + Na]^+$ 358.0695, found 358.0678.

*1-(8-methyl-5,5-dioxido-9b-(trifluoromethyl)-2,3-dihydro-9bH-benzo[4,5]isothiazolo[3,2-b]oxazol-3-yl)propan-2-one (**20**).* Following GP1, the compound was formed using 3-Acetyl-1-propanol (10 µL, 0.1 mmol. 1 equiv). The title compound was obtained as an off-white solid (33% yield, >20 : 1 dr, – NMR), **TLC:** R_f = 0.21 in 20% in EtOAc/hexanes; **IR** (neat) **ν** (cm^{-1})**:** 2923, 1716, 1600, 1417, 1358, 1282, 1249, 1179, 1160, 1118, 1057; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** 7.68 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.50 (m, 2H), 4.69 – 4.63 (m, 1H), 4.41 – 4.37 (m, 1H), 4.04 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.24 (dd, *J* = 18.4, 4.5 Hz, 1H), 2.91 (dd, *J* = 18.4, 9.9 Hz, 1H), 2.54 (s, 3H), 2.22 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 205.8, 146.2, 145.8, 134.6, 133.8, 133.2, 131.8, 129.9, 129.7, 125.9 (q, J^3_{CF} = 1.8 Hz), 125.7 (q, J^1_{CF} = 276.7 Hz), 124.9 (q, J^3_{CF} = 1.6 Hz), 122.3 121.9 (q, J^1_{CF} = 282.0 Hz), 121.5, 97.1 (q, J^2_{CF} = 34.2 Hz), 74.6, 57.0, 47.9, 30.3, 22.0, 21.9; **^{19}F NMR** ($CDCl_3$, 377 MHz) δ (ppm)**:** -79.3; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{14}H_{14}F_3NO_4SNa^+$ $[M + Na]^+$ 372.0488, found 372.0474.

*(4S,10bR)-9-methyl-4-phenyl-10b-(trifluoromethyl)-3,4-dihydro-2H,10bH-benzo[4,5]isothiazolo[3,2-b][1,3]oxazine 6,6-dioxide (**21**).* Following GP1, the compound was formed using 3-phenylpropanol (13.6 µL, 0.1 mmol. 1 equiv). The title compound was obtained as a white solid (36% yield, 1 : 2.6, β : γ – NMR). **TLC:** R_f = 0.51 in 10% EtOAc/hexanes**; IR** (neat) **ν** (cm^{-1})**:** 2923, 2852, 1696, 1602, 1458, 1336, 1253, 1185, 1150, 1115, 1081; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ (ppm)**:** ***β-amination*** 7.78 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.52 (m, 1H), 7.50 – 7.45 (m, 2H), 7.42 – 7.34 (m, 3H), 5.39 (ap t, *J* = 8.4 Hz, 1H), 4.19 – 4.14 (m, 1H), 3.90 – 3.80 (m, 1H), 2.52 (s, 3H), 2.47 – 2.42 (m, 1H); ***γ-amination*** 7.76 (d, *J* = 7.9 Hz, 1H), 7.56 – 7.54 (m, 1H), 7.50 – 7.45 (m, 3H), 7.42 – 7.34 (m, 3H), 5.11 – 5.06 (m, 2H), 3.90 – 3.80 (m, 2H), 2.54 – 2.52 (m, 1H), 2.51 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ (ppm)**:** 145.6, 134.8, 133.7, 132.1, 125.9, 123.0 (q, J^1_{CF} = 287.3 Hz), 121.5, 97.5 (q, J^2_{CF} = 34.4 Hz), 74.7, 61.7, 33.9, 31.7, 29.1, 26.5, 22.7, 22.0, 14.2; **^{19}F NMR** ($CDCl_3$, 565 MHz) δ (ppm)**:** ***β-amination*** -77.7, ***γ-amination*** -79.3; **HRMS** (m/z ESI-TOF)**:** calculated for $C_{18}H_{16}F_3NO_3SNa^+$ ($[M + Na]^+$) 406.0695 found 406.0682.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI:
^{1}H, ^{13}C, and ^{19}F NMR spectral data (PDF)
X-ray crystallographic data (CIF) can also be found at The Cambridge Crystallographic Data Centre (CCDC 1943557).

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