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One-Pot Deoxygenation and Substitution of Alcohols Mediated by Sulfuryl Fluoride

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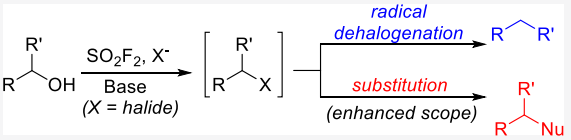
ABSTRACT: Sulfuryl fluoride is a valuable reagent for the one-pot activation and derivatization of aliphatic alcohols, but the highly reactive alkyl fluorosulfate intermediates limit both the types of reactions that can be accessed as well as the scope. Herein, we report the SO_2F_2-mediated alcohol substitution and deoxygenation method that relies on the conversion of fluorosulfates to alkyl halide intermediates. This strategy allows the expansion of SO_2F_2-mediated one-pot processes to include radical reactions, where the alkyl halides can also be exploited in the one-pot deoxygenation of primary alcohols under mild conditions (52−95% yield). This strategy can also enhance the scope of substitutions to nucleophiles that are previously incompatible with one-pot SO_2F_2-mediated alcohol activation and enables substitution of primary and secondary alcohols in 54−95% yield. Chiral secondary alcohols undergo a highly stereospecific (90−98% ee) double nucleophilic displacement with an overall retention of configuration.

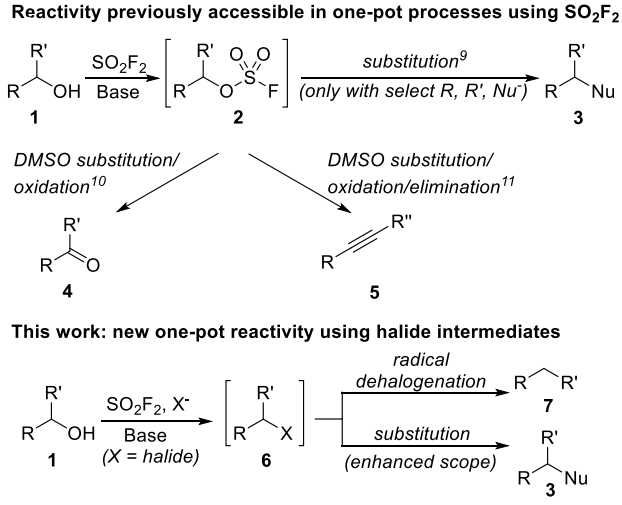


INTRODUCTION

One-pot synthesis, in which multiple chemical reactions are carried out in a single reaction vessel, is a powerful strategy as it leads to higher efficiency, minimization of reactor time, and a decrease in the amount of chemical waste.[1] From Robinson's one-pot synthesis of tropinone[2] to recent advances in multistep catalysis,[3] there has been a long history of the development of one-pot processes in synthetic organic chemistry. Despite the depth of research in this area, many simple transformations are still challenging to perform in a single step. This is exemplified in one-pot transformations involving aliphatic alcohols. Alcohol derivatizations, which make up a major proportion of U.S. pharmaceutical synthetic patents over the past 40 years,[4] are consistently identified by the industry as one of the top five transformations that require better one-pot processes.[5] While significant progress has been made in this area through the development of novel reagents and catalysts,[6] new versatile one-pot processes are still essential to meet the breadth of substrate scope needed for the chemical industry.[7]

Sulfuryl fluoride (SO_2F_2) is a promising candidate for promoting one-pot processes with alcohols as the reaction byproducts are relatively unreactive and are easy to remove.[8] Strategically, every one-pot method involving SO_2F_2 has relied upon alkyl fluorosulfate intermediate **2** as the key reactive intermediate (Scheme 1). This has limited the reactions that can be accessed to substitutions[9] and substitutions combined with subsequent oxidations[10] and/or eliminations.[11] Even for the successful one-pot methods, the high reactivity of fluorosulfate **2** places significant limitations on the scope with respect to both the alcohol and the nucleophile. A new approach is needed to increase both the synthetic utility and generality of these SO_2F_2-mediated processes.

Scheme 1. Strategies for SO_2F_2-Mediated Alcohol Activation Nucleophilic Substitution



We hypothesized that we may be able to develop a more general SO_2F_2-mediated one-pot alcohol activation strategy by first converting alkyl fluorosulfate **2** to a reactive intermediate, which would be more stable than fluorosulfate yet still sufficiently reactive to undergo a variety of subsequent

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transformations (Scheme 1). Alkyl halide **6** was identified as a potential candidate as it enables a subsequent radical or ionic transformation. Alkyl halides are commonly utilized as intermediates in one-pot transformations,[12] but there were no examples of using them as the intermediates in one-pot sulfuryl fluoride-mediated processes.

RESULTS AND DISCUSSION

To examine the synthetic utility of sulfuryl fluoride-mediate one-pot processes beyond nucleophilic substitutions and oxidations, we began our studies by investigating one-pot halodeoxygenation followed by dehalogenation, which achieves a net deoxygenation reaction. Primary alcohols were selected as they can be challenging to reduce using conventional Barton–McCombie reactions.[13] Recent one-pot approaches to primary alcohol deoxygenation include Lewis acid-catalyzed silane reduction,[14] dehydrogenation followed by Wolff–Kishner reduction,[15] and photoredox catalysis.[16] We began our investigations into a one-pot deoxygenation reaction by first focusing on the halodeoxygenation step.[17] A brief exploration found that alkyl chlorides, bromides, and iodides could be formed cleanly using the respective tetrabutylammonium halide salt in only 12 min (Scheme 2).[18,23] Notably,

Scheme 2. SO_2F_2-Mediated Conversion of Benzylic Alcohols to Alkyl Halides[a]

6a: X = I 70% (70%)
6b: X = Br 66% (87%)[b]
6c: X = Cl 52% (91%)[b]

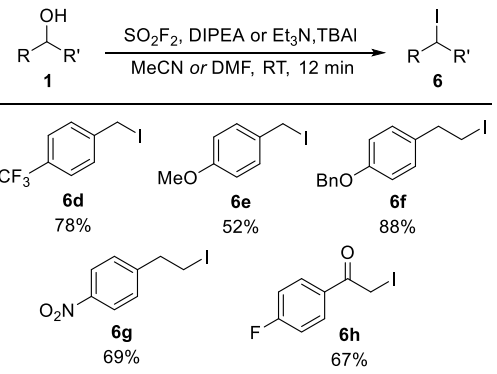
[a]Reaction conditions: SO_2F_2 (4.3 equiv; generated according to the procedure described in ref 18) was bubbled through a solution of **1a** (0.6 mmol), DIPEA (2.0 equiv), and TBAX (2.0 equiv) in DMF for 5 min; then, the reaction mixture was allowed to stir at room temperature for an additional 7 min. All reactions were run on 0.6 mmol scale. Isolated yields are reported with ^{19}F NMR yields in parentheses. [b]Isolated yields were lower than ^{19}F NMR yields due to the volatility of these compounds.

when tetrabutylammonium iodide (TBAI) was used as the halide source, the reaction mixture gradually changed color.[19] We suspected that this color change could have been caused by an undesired redox reaction between iodide and SO_2F_2. Control experiments demonstrated that iodine had indeed been formed but only in minor quantities (<5% of iodide oxidized in 15 min) suggesting that this redox process is considerably slower than alkyl iodide formation.

This halogenation protocol was then applied to representative primary alcohols (Scheme 3). Trifluoromethyl benzyl alcohol was an effective substrate, affording the desired iodide (**d**) in 78% yield. A slight decrease in yield was observed for electron-rich *para*-methoxy benzyl alcohol (**6e**). Phenethyl iodides **6f** and **6g** were successfully synthesized in good to excellent yields, with 10% elimination observed along with **6f** and no elimination observed with **6g**. Activated α-keto alcohol (**1h**) was also an effective substrate, giving **6h** in 68% yield.

Using the optimized halogenation procedure, we examined the one-pot deoxygenation of 3-phenyl-1-propanol.

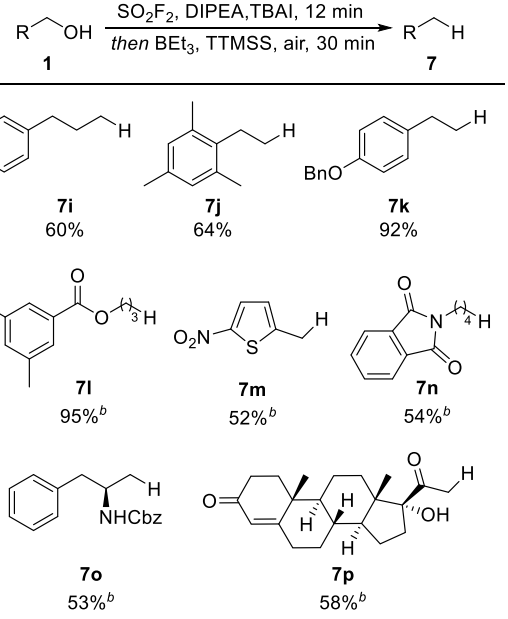
Scheme 3. Alcohol Scope for the SO_2F_2-Mediated Alkyl Halide Formation[a]



[a]Reaction conditions: SO_2F_2 (4.3 equiv; generated according to the procedure described in ref 18) was bubbled through a solution of **1** (0.6 mmol), DIPEA or Et_3N (2.0 equiv), and TBAI (2.0 equiv) in acetonitrile or DMF for ~5 min; then, the reaction mixture was allowed to stir at room temperature for an additional 7 min. All reactions were run on 0.6 mmol scale. Isolated yields are reported.

Treatment of 3-phenyl-1-propanol with SO_2F_2, *N*,*N*-diisopropylethyl-amine (DIPEA), and TBAI for 10 min, followed by triethylborane and tris(trimethylsilyl)silane (TTMSS),[19] readily produced dehalogenation product **7i** in 60% isolated yield (Scheme 4). Trimethylphenyl substrate **7j** was isolated in a comparable yield. The deoxygenation

Scheme 4. Primary Alcohol Scope for One-Pot Alcohol deoxygenation[a]



[a]Reaction conditions: SO_2F_2 (3.0 equiv; generated according to the procedure described in ref 18) was bubbled through a solution of alcohol (1.0 mmol), DIPEA (2.0 equiv), and TBAI (1.1 equiv) in DMF for 5 min; then, the reaction mixture was allowed to stir at room temperature for an additional 7 min. Subsequently, BEt_3 (1 M in THF, 0.2 equiv) and TTMSS (1.2 equiv) were added, and the mixture was allowed to stir at room temperature for 30 min to 2 h. All reactions were run on 1.0 mmol scale. All yields refer to isolated yields. [b]A second addition of SO_2F_2 was carried out; see the Experimental Section for details.

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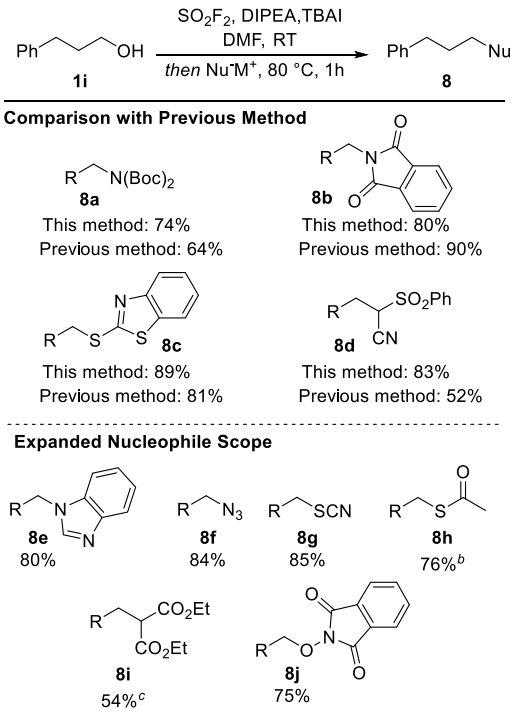
protocol also afforded a *O*-benzyl phenol derivative (**7k**) and 3,5-dimethyl benzoate (**7l**) in nearly quantitative yields. This method was tolerant of nitrogroups and thiophenes (**7m**), phthalimides (**7n**), and Cbz-protected amines (**7o**). A more complex substrate, cortexolone, successfully underwent deoxygenation to give **7p** in 58% yield.

With a new reaction class for one-pot SO_2F_2-mediated transformations established, we then explored if this halide-intermediate strategy is effective in one-pot substitution reactions. Substitution reactions make up the majority of alcohol functionalization reactions in the industry.[4] Classic methods for one-pot substitution typically use phosphorus-based reagents whose byproducts are often challenging to remove.[20] While there are many variants that address some of the fundamental challenges, none have the scope required by the industry.[6] Recent attention has focused on reagents that do not contain phosphorus, such as sulfuryl fluoride, but the scope of these methods is limited by the high reactivity of the alkyl fluorosulfate intermediate. Efficient reactivity can be achieved when the alkyl fluorosulfate intermediate is stabilized, but this approach limits the alcohol scope to deactivated 1,1-dihydrofluoroalcohols.[9c] Primary aliphatic alcohols could be used in select cases but the nucleophile scope was limited to reagents that do not readily react with SO_2F_2.[8] Of the successful nucleophiles, only aryl thiols could be used to displace secondary aliphatic alcohols.

We began our investigations into applying our new sulfuryl fluoride-mediated strategy in substitution reactions with the one-pot displacement of 3-phenyl-1-propanol. Using the same halide formation protocol, followed by adding 2 equiv of sodium di-*tert*-butyliminodicarboxylate ($Na^+(Boc)_2N^-$), afforded **8a** in 74% isolated yield (Scheme 5). This is a slightly better yield than what was achieved using 4 equiv of nucleophiles in our previously developed conditions.[8] Using this new protocol with nucleophiles that were competent in our previous method afforded **8b**, **8c**, and **8d** in 80, 89, and 83% isolated yields, respectively. We next explored nucleophiles that were unsuccessful in our previous methodology. Nitrogen nucleophiles, such as benzimidazole and azide, provided **8e** and **8f** in 80 and 84% yields, respectively. The success of **8f** is noteworthy as this protocol prevents the interaction of SO_2F_2 and azide, which can lead to the formation of fluorosulfuryl azide.[21] The scope with respect to sulfur nucleophiles can be expanded to thiocyanate and thioacetate to afford **8g** and **8h** in good yields. Diethyl malonate and *N*-hydroxyphthalimide were also effective nucleophiles, affording **8i** and **8j** in 54 and 75% yields, respectively.

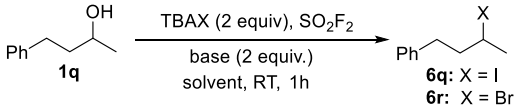
A significant limitation of previous SO_2F_2-mediated substitution reaction was that only aryl thiols could be used to displace enantiopure secondary aliphatic alcohols without deterioration of the enantiomeric excess (ee). Investigations began with examining the deoxyhalogenation step with secondary alcohol **1q** (Table 1). Under the previously developed conditions, alkyl halide **6q** was formed in 65% conversion (entry 1), along with 24% conversion to undesired byproducts.[22] Switching the solvent to acetonitrile led to a modest improvement in conversion (entry 2), and only 10% of the starting material was lost to byproduct formation. DBU was an ineffective base for this transformation as only 11% of **6q** was formed along with 33% of products resulting from elimination (entry 3). The conversion could be increased if triethylamine was used as a base with either TBAI (entry 4) or TBAB (entry 5), with the latter leading to less byproduct formation.

Scheme 5. Nucleophile Scope for SO_2F_2-Mediated Primary Alcohol Substitution[a]



[a]Reaction conditions: alkyl iodide was prepared as described in Scheme 2 using 2.0 equiv of TBAI (see the Experimental Section); then, the reaction mixture was degassed with N_2 for 1 min, charged with nucleophile (2.0 equiv; either prepared by reacting the corresponding nucleophile with NaH or purchased from commercial sources), and allowed to stir at 80 °C for 1 h. All reactions were run on 0.6 mmol scale. All yields refer to isolated yields. R = $PhCH_2CH_2$. [b]The reaction was carried out at room temperature. [c]Decarboxylation was a competing pathway at 80 °C; to minimize this, the reaction was carried out at room temperature.

Table 1. Reaction Condition Optimization for the SO_2F_2-Mediated Alcohol Conversion to the Corresponding Alkyl Halide[a]



entry	base	halide source	solvent	conv to **6q** or **6r** (%)	conv to byproducts[b] (%)
1	DIPEA	TBAI	DMF	65	24
2	DIPEA	TBAI	MeCN	73	10
3	DBU	TBAI	MeCN	11	33
4	NEt_3	TBAI	MeCN	82	12
5	NEt_3	TBAB	MeCN	90	4

[a]All reactions were run on 0.6 mmol scale. The ratio of products was determined by ^1H NMR analysis of the crude reaction mixture after 1 h. [b]See Supporting Information for details about the observed byproducts.

With the optimized conditions in hand, we explored the nucleophile scope for secondary alcohols. Unfortunately, chiral benzylic alcohols were not successful as poor enantioselectivities were observed using thioacetate.[23] Chiral aliphatic

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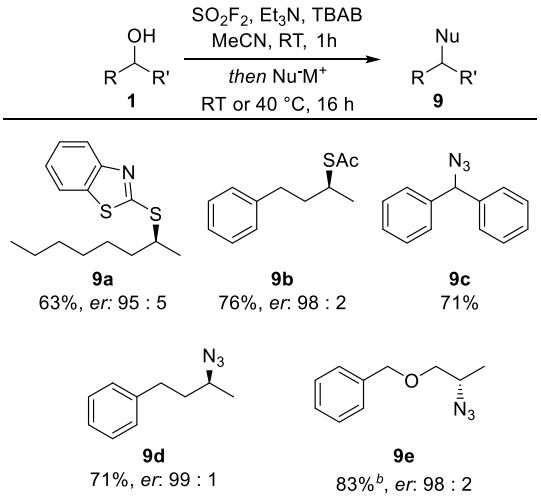
alcohols, such as (*S*)-2-octanol, could be converted to the corresponding aryl thiol **9a** in 63% yield with a net retention of configuration (Scheme 6). Unlike in our previous report, thioacetate was also an effective nucleophile, affording **9b** in 76% yield and 96% ee. Sodium azide could also be utilized for the formation of achiral product **9c** in 71% yield, as well as products **9d** and **9e** in 71% and 83% yield, respectively.

Scheme 6. Secondary Alcohol Scope for the One-Pot Halogenation Substitution[a]



[a]Reaction conditions: SO_2F_2 (4.3 equiv; generated according to the procedure described in ref 18) was bubbled through a solution of **1** (0.6 mmol), Et_3N (2.0 equiv), and TBAB (tetrabutylammonium bromide, 2.0 equiv) in acetonitrile for 3−5 min; then, the reaction mixture was allowed to stir at room temperature for 1 h. The mixture was degassed with N_2 for 1 min, charged with nucleophile (2.0 equiv), and allowed to stir at room temperature for 16 h. All reactions were run on 0.6 mmol scale. All yields refer to isolated yields. [b]The substitution step was carried out at 40 °C.

CONCLUSIONS

We have demonstrated a new strategy in one-pot, SO_2F_2-mediated alcohol derivatizations that exploit alkyl halides as the key reactive intermediates. This strategy was used to expand the reactions that can be promoted in one-pot sulfuryl fluoride-mediated processes to radical reactions. We have demonstrated that the radical dehalogenation of iodide intermediates can be utilized in the overall two-step, one-pot deoxygenation of primary alcohols under mild conditions. This protocol also provides the most general SO_2F_2-mediated, one-pot alcohol substitution process developed to date. In particular, the scope with respect to nucleophiles is now competitive with phosphorus-based methods. Our SO_2F_2 method also enables substitution of enantiopure alcohols to provide overall retention of configuration, which is consistent with two sequential nucleophilic displacements.

EXPERIMENTAL SECTION

General Information. All reactions were performed in 20 mL (28 × 61 mm) glass vials under air atmosphere unless otherwise noted. All chemicals and solvents were purchased from commercial sources and used as received unless otherwise noted. Sulfuryl diimidazole (SDI) was either prepared or purchased (Oakwood Product, Inc.) and used to generate sulfuryl fluoride (SO_2F_2) following a modified procedure from *Org. Lett.* **2017**, *19*, 5244−5247. Screw caps and polytetrafluoroethylene/silicon septa were purchased from Chemglass Life Sciences LLC. BD Intramedic polyethylene tubing (I.D. 1.57 mm, O.D. 2.08 mm) was used for the reactions. Infrared (IR) spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer or a PerkinElmer Frontier FT-IR. The spectra are reported in cm^{-1}. High-resolution electrospray ionization mass (HRMS-ESI) spectra were recorded on a Waters, Micromass LCT or Agilent 6550 iFunnel Q-TOF spectrometer. High-resolution electron ionization (HRMS-EI) spectra were recorded on a JEOL AccuTOF-GC spectrometer. The enantiomeric ratio was determined by HPLC analysis using a chiral column on an Agilent 1290 infinity LC system. Chiral HPLC: Chiralcel OJ-RH, 4.6 × 150 mm, multi UV−vis detector (210 or 230 nm), at 30 °C, eluent: (acetonitrile/1% formic acid in water), flow rate: 0.5 mL/min at 57−58 bar. Optical rotations were measured on a Jasco P-2000 polarimeter. The reported value was the average of five runs. Proton, carbon, and fluorine nuclear magnetic resonance (^1H, ^{13}C, and ^{19}F NMR) spectra were obtained using a Bruker AV-300 or AV-400 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and are referenced to the centerline of $CDCl_3$ (7.26 ppm ^1H NMR; 77.16 ppm ^{13}C NMR). ^{19}F NMR chemical shifts were referenced to $CFCl_3$. Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), br s (broad singlet), m (multiplet), dd (doublet of doublets), tq (triplet of quartets), and qt (quartet of triplets). Assignment of peaks was done based on the chemical shifts, multiplicities, and integrals of the peaks. NMR yields were determined by ^{19}F NMR using a relaxation delay (or recycle delay) of 40 s to ensure complete relaxation of all fluorine nuclei. α,α,α-Trifluorotoluene ($PhCF_3$, δ −63.72 ppm) was used as an internal standard, unless otherwise specified.

CAUTION: Sulfuryl fluoride is a toxic gas and must always be handled with care in a well-ventilated fumehood. Excess sulfuryl fluoride can be quenched by passing it through a basic aqueous medium.

General Procedure (A) for the SO_2F_2-Mediated Reaction of Alcohols with Tetrabutylammonium Halides. Two 20 mL vials equipped with magnetic stir-bars were capped with septum-fitted vial caps and then connected by a polyethylene tube. Vial A was charged with SDI (2.6 mmol, 4.3 equiv) and anhydrous KF (7.0 mmol, 11.7 equiv). To vial B were added alcohol (0.6 mmol, 1.0 equiv) and TBAI (1.2 mmol, 2.0 equiv) in MeCN (2.0 mL), followed by DIPEA (1.2 mmol, 2.0 equiv) to afford a homogenous solution. The polyethylene tube in vial B was immersed into the solution, and then, to vial A was added trifluoroacetic acid (TFA) (1.5 mL) in one portion. Vigorous bubbling of SO_2F_2 and fuming were observed in vial B for 2−3 min, and when the bubbling subsided, vial B was vented via a needle for 1−2 min (this triggered more bubbling of SO_2F_2 through the solution). The polyethylene tube and needle were then removed, and the reaction mixture in vial B was allowed to stir at room temperature for 10 min.

Workup and Purification. To the reaction mixture were added H_2O (20 mL) and Et_2O (20 mL); the layers were separated; then, the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine (40 mL), then dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography. Fractions containing the desired product were combined and concentrated under reduced pressure.

General Procedure (B) for the SO_2F_2-Mediated One-Pot Deoxygenation of Primary Alcohols. Two 20 mL vials equipped with magnetic stir-bars were capped with septum-fitted vial caps connected by a polyethylene tube. Vial A was charged with SDI (3 mmol, 3.0 equiv) and anhydrous KF (7.9 mmol, 7.9 equiv). Vial B was charged with TBAI (1.1 mmol, 1.1 equiv); then, the system was evacuated and filled with N_2 three times. To vial B were then added DIPEA (2 mmol, 2.0 equiv) and primary alcohol (1 mmol, 1.0 equiv) in dry dimethylformamide (DMF) (2.9 mL). The polyethylene tube in vial B was immersed into the solution, and then, to vial A was added TFA (1.6 mL). Vigorous bubbling of SO_2F_2 and fuming were observed in vial B for a few minutes, and when the bubbling subsided,

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vial B was vented via a needle for 1−2 min (this triggered more bubbling of SO_2F_2 through the solution). The tube and needle were then removed, and the mixture in vial B was allowed to stir at room temperature. The reaction progress was monitored by thin layer chromatography (TLC), and if unreacted starting materials were observed after 10 min, second addition of SO_2F_2 was carried out (see below). Otherwise, to the solution were added Et_3B (1 M in THF, 0.2 mmol, 0.2 equiv) and TTMSS (1.2 mmol, 1.2 equiv), and the mixture was left stirring at room temperature under air. The reaction progress was monitored by TLC and gas chromatography−mass spectrometry. Once all alkyl iodide had been consumed, TBAF quench, workup, and purification were carried out (see below).

Second Addition of SO_2F_2. To reaction vial B was added DIPEA (2 mmol, 2.0 equiv). A new vial A was prepared containing SDI (3 mmol, 3.0 equiv) and anhydrous KF (7.9 mmol, 7.9 equiv) and individually evacuated and filled with N_2 three times. As in the general procedure, the two vials were connected by a polyethylene tube and TFA (1.6 mL) was added to vial A. SO_2F_2 generated bubbles through the mixture in vial B for a few minutes; then, the vial was vented via a needle and allowed to stir at room temperature for another 10 min.

TBAF Quench, Workup, and Purification. To quench unreacted TTMSS and silane byproducts, 1 M TBAF in THF was added dropwise to the reaction mixture until evolution of gas (Me_3SiF) stopped. The solution was then diluted with 20 mL of 1 M aqueous HCl and 20 mL of organic solvent (pentanes, hexanes, or diethyl ether); the layers were separated; then, the aqueous layer was extracted with 3 × 20 mL of previously used organic solvent. The combined organics were washed with water (20 mL) and brine (20 mL) and then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography. Fractions containing the desired product were combined and concentrated under reduced pressure. The final product was occasionally contaminated with tetrakis-(trimethylsilyloxy)silane $Si(OSiMe_3)_4$. In such cases, the final yield was corrected for this impurity.

*1-Fluoro-4-(iodomethyl)benzene (**6a**).* The title compound was prepared on a 0.6 mmol scale following general procedure A using DMF as the solvent. The crude product was obtained (70%) based on quantitative ^{19}F NMR using trifluorotoluene as the internal standard. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as a pale orange solid (100 mg, 70% yield). The spectroscopic data match a literature report (Artaryan, A.; Mardyukov, A.; Kulbitski, K.; Avigdori, I.; Nisnevich, G. A.; Schreiner, P. R.; Gandelman, M. Aliphatic C−H Bond Iodination by a *N*-Iodoamide and Isolation of an Elusive *N*-Amidyl Radical. *J. Org. Chem.* **2017**, *82*, 7093−7100). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (dd, J = 8.6, 5.3 Hz, 2H), 6.98 (t, J = 8.6 Hz, 2H), 4.44 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.2 (d, $^1J_{C-F}$ = 247.7 Hz), 135.3 (d, $^4J_{C-F}$ = 3.4 Hz), 130.6 (d, $^3J_{C-F}$ = 8.4 Hz), 115.9 (d, $^2J_{C-F}$ = 21.7 Hz), 4.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.8 (t, J = 7.2 Hz). LRMS-El (m/z): 236.0 $[M]^+$.

*1-(Bromomethyl)-4-fluorobenzene (**6b**).* The title compound was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as the nucleophile and DMF as the solvent. The crude product was obtained (87%) based on quantitative ^{19}F NMR using trifluorotoluene as the internal standard. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as a colorless oil (75 mg, 66% yield). The spectroscopic data matched that of an authentic sample (Sigma-Aldrich). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, J = 8.6, 5.3 Hz, 2H), 7.03 (t, J = 8.6 Hz, 2H), 4.48 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.7 (d, $^1J_{C-F}$ = 248.0 Hz), 133.8 (d, $^4J_{C-F}$ = 3.3 Hz), 131.0 (d, $^3J_{C-F}$ = 8.4 Hz), 115.9 (d, $^2J_{C-F}$ = 21.8 Hz), 32.7. ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.2 (tt, J = 9.0, 5.3 Hz). LRMS-El (m/z): 188.0 $[M]^+$.

*1-(Chloromethyl)-4-fluorobenzene (**6c**).* The title compound was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium chloride as the nucleophile and DMF as a solvent. The crude product was obtained (91%) based on quantitative ^{19}F NMR using trifluorotoluene as the internal standard. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as a colorless oil (45 mg, 52% yield).The spectroscopic data match a literature report (Bayguzina, A. R.; Gallyamova, L. I.; Khalilov, L. M.; Khusnutdinov, R. I. Synthesis of Mono- and Difluorobenzyl Chlorides by Chlorination of Mono- and Difluorotoluenes with CCl_4 and *t*-BuOCl Induced by Iron-Containing Catalysts. *J. Fluorine Chem.* **2019**, *226*, 109346). ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 (dd, J = 8.6, 5.3 Hz, 2H), 7.05 (t, J = 8.7 Hz, 2H), 4.57 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 162.8 (d, $^1J_{C-F}$ = 247.5 Hz), 133.5 (d, $^4J_{C-F}$ = 3.3 Hz), 130.6 (d, $^3J_{C-F}$ = 8.4 Hz), 115.8 (d, $^2J_{C-F}$ = 21.8 Hz), 45.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.6 (tt, J = 8.9, 4.5 Hz). LRMS-El (m/z): 144.0 $[M]^+$.

*1-(Iodomethyl)-4-(trifluoromethyl)benzene (**6d**).* The title compound was prepared on a 0.6 mmol scale following general procedure A. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as an orange solid (134 mg, 78% yield). The spectroscopic data match a literature report (Combe, S. H.; Hosseini, A.; Song, L.; Hausmann, H.; Schreiner, P. R. Catalytic Halogen Bond Activation in the Benzylic C−H Bond Iodination with Iodohydantoins. *Org. Lett.* **2017**, *19*, 6156−6159). ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 4.46 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 143.5, 130.1 (q, $^2J_{C-F}$ = 32.7 Hz), 129.2, 125.9 (q, $^3J_{C-F}$ = 3.7 Hz), 124.1 (q, $^1J_{C-F}$ = 273.2 Hz), 3.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ −63.1. LRMS-El (m/z): 286.0 $[M]^+$.

*1-(Iodomethyl)-4-methoxybenzene (**6e**).* The title compound was prepared on a 0.6 mmol scale following general procedure A. The product was isolated via flash column chromatography (5% Et_2O/petroleum ether) as a yellow oil (77 mg, 52% yield). The spectroscopic data match a literature report (Krohn, K.; Steingröver, K.; Srinivasa Rao, M. Isolation and Synthesis of Chalcones with Different Degrees of Saturation. *Phytochemistry* **2002**, *61*, 931−936). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.26 (m, 2H), 6.85−6.79 (m, 2H), 4.48 (s, 2H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.3, 131.5, 130.2, 114.4, 55.5, 6.7. LRMS-El (m/z): 248.0 $[M]^+$.

*1-(Benzyloxy)-4-(2-iodoethyl)benzene (**6f**).* The title compound was prepared on a 0.6 mmol scale following general procedure A. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as an off-white solid (179 mg, 88% yield). The spectroscopic data match a literature report (Erdeljac, N.; Kehr, G.; Ahlqvist, M.; Knerr, L.; Gilmour, R. Exploring Physicochemical Space *via* a Bioisostere of the Trifluoromethyl and Ethyl Groups (BITE): Attenuating Lipophilicity in Fluorinated Analogues of Gilenya for Multiple Sclerosis. *Chem. Commun.* **2018**, *54*, 12002−12005). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48−7.27 (m, 5H), 7.15−7.07 (m, 2H), 6.97−6.89 (m, 2H), 5.05 (s, 2H), 3.32 (t, J = 8.3 Hz, 2H), 3.12 (t, J = 7.8 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 157.9, 137.1, 133.3, 129.5, 128.7, 128.1, 127.6, 115.1, 70.2, 39.7, 6.4. LRMS-El (m/z): 338.0 $[M]^+$.

*1-(2-Iodoethyl)-4-nitrobenzene (**6g**).* The title compound was prepared on a 0.6 mmol scale following general procedure A. The product was isolated via flash column chromatography (5% Et_2O/petroleum ether) as a white solid (115 mg, 69% yield). The spectroscopic data match a literature report (Ellwood, A. R.; Porter, M. J. Selective Conversion of Alcohols into Alkyl Iodides Using a Thioiminium Salt. *J. Org. Chem.* **2009**, *74*, 7982−7985). ^1H NMR (300 MHz, $CDCl_3$): δ 8.24−8.15 (m, 2H), 7.42−7.32 (m, 2H), 3.45−3.33 (m, 2H), 3.35−3.23 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 147.8, 147.1, 129.4, 124.1, 39.6, 3.8. LRMS-El (m/z): 277.0 $[M]^+$.

*1-(4-Fluorophenyl)-2-iodoethan-1-one (**6h**).* The title compound was prepared on a 0.6 mmol scale following general procedure A. The product was isolated via flash column chromatography (1% Et_2O/petroleum ether) as a pale yellow oil (108 mg, 67% yield). The spectroscopic data match a literature report (Zhang, J.; Li, S.; Deng, G.-J.; Gong, H. Metal-Free, Oxidant-Free, and Controllable Graphene Oxide Catalyzed Direct Iodination of Arenes and Ketones. *ChemCatChem* **2018**, *10*, 376−380). ^1H NMR (300 MHz, $CDCl_3$): δ 8.09−7.95 (m, 2H), 7.21−7.08 (m, 2H), 4.33 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 191.4, 166.1 (d, $^1J_{C-F}$ = 256.3 Hz), 131.9

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(d, $^3J_{C-F}$ = 9.4 Hz), 129.9 (d, $^4J_{C-F}$ = 3.0 Hz), 116.1 (d, $^2J_{C-F}$ = 22.1 Hz), 1.5. ^{19}F NMR (282 MHz, $CDCl_3$): δ −103.8 (tt, J = 8.4, 5.3 Hz). LRMS-El (m/z): 264.0 $[M]^+$.

*Propylbenzene (**7i**).* The title compound was synthesized on a 1 mmol scale according to general procedure B using pentanes for extraction. The product was isolated via flash column chromatography (100% pentanes) as a clear liquid (85 mg, 60% yield). The product yield has been corrected for $Si(OSiMe_3)_4$. The spectroscopic data match a literature report (Eisch, J. J.; Dutta, S. Carbon−Carbon Bond Formation in the Surprising Rearrangement of Diorganylzirconium Dialkoxides: Linear Dimerization of Terminal Olefins. *Organometallics* **2005,** *24,* 3355−3358). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.26 (m, 2H), 7.24−7.16 (m, 3H), 2.67−2.56 (m, 2H), 1.68 (sxt, J = 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 142.8, 128.6, 128.4, 125.7, 38.2, 24.7, 14.0. LRMS-El (m/z): 120.2 $[M^+]$.

*2-Ethyl-1,3,5-trimethylbenzene (**7j**).* The title compound was synthesized on a 1 mmol scale according to general procedure B using pentanes for extraction. The product was isolated via flash column chromatography (hexanes to 10% ethyl acetate/hexanes) as a clear liquid (125.2 mg, 64% yield). The product yield has been corrected for $Si(OSiMe_3)_4$. The spectroscopic data match a literature report (Kondolff, I.; Doucet, H.; Santelli, M. Palladium−Tetraphosphine as Catalyst Precursor for High-Turnover-Number Negishi Cross-Coupling of Alkyl- or Phenylzinc Derivatives with Aryl Bromides. *Organometallics* **2006,** *25,* 5219−5222). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (s, 2H), 2.70 (q, J = 7.5 Hz, 2H), 2.37 (s, 6H), 2.33 (s, 3H), 1.18 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 138.0, 135.8, 134.9, 129.0, 22.4, 20.9, 19.6, 13.6. LRMS-El (m/z): 148.2 $[M^+]$.

*1-(Benzyloxy)-4-ethylbenzene (**7k**).* The title compound was synthesized on a 1 mmol scale according to general procedure B. The second addition of SO_2F_2 was performed, and diethyl ether was used for extraction. The product was isolated via flash column chromatography (5% ethyl acetate/hexanes) as a clear oil (195 mg, 92% yield). The spectroscopic data match a literature report (Zhu, C.; Yukimura, N.; Yamane, M. Synthesis of Oxygen- and Sulfur-Bridged Dirhodium Complexes and Their Use As Catalysts in the Chemoselective Hydrogenation of Alkenes. *Organometallics* **2010,** *29,* 2098−2103). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47−7.29 (m, 5H), 7.13 (d, J = 8.2 Hz, 2H), 6.92 (d, J = 8.2 Hz, 2H), 5.05 (s, 2H), 2.60 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 157.0, 137.4, 136.8, 128.8, 128.6, 128.0, 127.6, 114.8, 70.1, 28.1, 16.0. LRMS-El (m/z): 212.2 $[M^+]$.

*3-Hydroxypropyl 3,5-Dimethylbenzoate (**Precursor to 7l**).* A solution of propane-1,3-diol (45 mmol, 3 equiv) and Et_3N (30 mmol, 2 equiv) in dichloromethane (DCM) (75 mL) was cooled down to 0 °C. To the mixture was added 3,5-dimethylbenzoyl chloride (15 mmol, 1 equiv) dropwise over 5 min. The mixture was warmed up to room temperature and allowed to stir for 17 h. The solution was transferred to a separatory funnel and diluted with 75 mL of water, and the layers were separated. The aqueous layer was extracted with DCM (3 × 50 mL), and the combined organics were washed with brine (75 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The product was isolated via flash column chromatography (50% ethyl acetate/hexanes) as a clear oil (1.73 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 2H), 7.15 (s, 1H), 4.43 (t, J = 6.2 Hz, 2H), 3.75 (t, J = 6.1 Hz, 2H), 2.89 (br s, 1H), 2.32 (s, 6H), 1.98 (p, J = 6.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.4, 138.0, 134.7, 129.9, 127.3, 61.8, 59.0, 31.9, 21.1. HRMS-ESI (m/z): calcd for $C_{12}H_{16}O_3Na$ ($[M + Na]^+$), 231.0997; found, 231.0991.

*Propyl 3,5-Dimethylbenzoate (**7l**).* The title compound was synthesized on a 1 mmol scale from the corresponding alcohol (preparation of which is described above) according to general procedure B. The second addition of SO_2F_2 was performed with an additional 0.55 equiv of TBAI added prior to it. Diethyl ether was used for extraction, and the product was isolated via flash column chromatography (5% ethyl acetate/hexanes) as a pale yellow solid (195 mg, 95% yield). The product yield has been corrected for $Si(OSiMe_3)_4$. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (s, 2H), 7.16 (s, 1H), 4.26 (t, J = 6.7 Hz, 2H), 1.79 (sxt, J = 7.2 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.0, 137.9, 134.4, 130.4, 127.3, 66.4, 22.2, 21.1, 10.5. IR (cm^{-1}) (neat): 2968, 2922, 1716, 1609, 1309, 1210. HRMS-EI (m/z): calcd for $C_{12}H_{16}O_2$ ($[M^+]$), 192.1150; found, 192.1149.

*(5-Nitrothiophen-2-yl)methanol (Precursor to **7m**).* 5-Nitrothiophene-2-carboxaldehyde (10 mmol, 1 equiv) was dissolved in methanol (32 mL) at 0 °C, and to the resulting solution was added sodium borohydride (11 mmol, 1.1 equiv). The mixture was warmed up to room temperature and allowed to stir for 2 h. The mixture was poured onto ice, acidified with 1 M aqueous HCl to pH 7, and extracted with ethyl acetate (5 × 20 mL). The combined organics were concentrated, and the product was isolated by flash column chromatography (50% ethyl acetate/hexane to 100% ethyl acetate) as a brown oil (1.33 g, 84% yield). The spectroscopic data match a literature report (Rivière, P.; Castel, A.; Cosledan, F. Etude de Nouvelles reactions par transfert monoelectronique: action d'organogermyllithiums sur le furfureal le thiophenaldehyde et les derives intres correspondants. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995,** *104,* 169−180). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J = 4.2 Hz, 1H), 6.88 (d, J = 4.2 Hz, 1H), 4.81 (d, J = 1.1 Hz, 2H), 3.67 (br s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 154.4, 150.4, 129.2, 123.5, 60.0. LRMS-ESl (m/z): 158.2 $[M-H]^-$.

*2-Methyl-5-nitrothiophene (**7m**).* The title compound was synthesized on a 1 mmol scale from the corresponding alcohol (preparation of which is described above) according to general procedure B. The second addition of SO_2F_2 was performed; TBAF quench was skipped, and diethyl ether was used for extraction. The product was isolated via flash column chromatography (10% ethyl acetate/hexanes) as a pale brown solid (73 mg, 52% yield). The spectroscopic data match a literature report (Katritzky, A.; Vakulenko, A.; Sivapackiam, J.; Draghici, B.; Damavarapu, R. Synthesis of Dinitro-Substituted Furans, Thiophenes, and Azoles. *Synthesis* **2008,** *2008,* 699−706). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, J = 4.1 Hz, 1H), 6.74 (dd, J = 4.1, 1.1 Hz, 1H), 2.54 (d, J = 1.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 149.6, 149.3, 129.3, 125.6, 16.4. LRMS-El (m/z): 143.0 $[M^+]$.

*2-(4-Hydroxybutyl)isoindoline-1,3-dione (**Precursor to 7n**).* 4-Amino-1-butanol (10 mmol, 1 equiv), phthalimide (20 mmol, 2 equiv), and iron(III) nitrate nonahydrate (0.5 mmol, 0.05 equiv) were suspended in toluene (10 mL). The resulting reaction mixture was stirred under reflux (heated in an oil bath) for 17 h, then allowed to cool down, diluted with ethyl acetate (20 mL), and filtered through Celite. The filtrate was concentrated under reduced pressure, and the resulting residue was diluted with 3% MeOH/DCM. The undissolved solid (phthalimide) was filtered off, and the product was isolated by flash column chromatography (3 to 5% MeOH/DCM) as a straw-colored solid (1.69 g, 76% yield). The product yield has been corrected for MeOH. The spectroscopic data match a literature report (Wappes, E. A.; Nakafuku, K. M.; Nagib, D. A. Directed β C−H Amination of Alcohols via Radical Relay Chaperones. *J. Am. Chem. Soc.* **2017,** *139,* 10204−10207). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86−7.77 (m, 2H), 7.73−7.65 (m, 2H), 3.74−3.62 (m, 4H), 1.93 (br s, 1H), 1.83−1.69 (m, 2H), 1.66−1.49 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.6, 134.0, 132.2, 123.3, 62.3, 37.8, 29.9, 25.2. LRMS-ESl (m/z): 220.3 $[M + H]^+$.

*2-Butylisoindoline-1,3-dione (**7n**).* The title compound was synthesized on a 1 mmol scale from the corresponding alcohol (preparation of which is described above) according to general procedure B with equivalents of SDI, KF, DIPEA, and TBAI doubled. Diethyl ether was used for extraction, and the product was isolated via flash column chromatography (8% ethyl acetate/hexanes) as a clear oil (110 mg, 54% yield). The spectroscopic data match a literature report (Hsieh, J.-C.; Cheng, C.-H. Nickel-Catalyzed Coupling of Isocyanates with 1,3-Iodoesters and Halobenzenes: A Novel Method for the Synthesis of Imide and Amide Derivatives. *Chem. Commun.* **2005,** 4554). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88−7.79 (m, 2H), 7.74−7.66 (m, 2H), 3.68 (t, J = 7.3 Hz, 2H), 1.72−1.60 (m, 2H), 1.44−1.29 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75

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MHz, $CDCl_3$): δ 168.5, 133.9, 132.3, 123.2, 37.9, 30.7, 20.2, 13.7. LRMS-ESI (*m*/*z*): 242.4 $[M + K]^+$.

*Benzyl (R)-(1-Phenylpropan-2-yl)carbamate (**7o**).* The title compound was synthesized on a 1 mmol scale according to general procedure B. The second addition of SO_2F_2 was performed with an additional 1.1 equiv of TBAI added prior to it. Diethyl ether was used for extraction, and the product was isolated via flash column chromatography (5 to 15% ethyl acetate/hexanes) as a white solid (143 mg, 53% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.39−7.30 (m, 5H), 7.29−7.21 (m, 3H), 7.19−7.12 (m, 2H), 5.08 (s, 2H), 4.63−4.53 (br s, 1H), 4.06−3.94 (m, 1H), 2.85 (dd, *J* = 13.6, 5.7 Hz, 1H), 2.70 (dd, *J* = 13.4, 7.2 Hz, 1H), 1.12 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 155.7, 138.0, 136.8, 129.6, 128.6, 128.5, 128.2, 126.6, 66.6, 48.13, 42.9, 20.3. IR (cm^{-1}) (neat): 3355, 2971, 2929, 1688, 1533, 1340, 1249. HRMS-ESI (*m*/*z*): calcd for $C_{17}H_{20}NO_2^+$ ($[M + H]^+$), 270.1494; found, 270.1488.

*(8R,9S,10R,13S,14S,17R)-17-Acetyl-17-hydroxy-10,13-dimethyl-1,2,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3H-cyclopenta[a]phenanthren-3-one (**7p**).* The title compound was synthesized on a 1 mmol scale according to general procedure B. The second addition of SO_2F_2 was performed with an additional 1.1 equiv of TBAI added prior to it. Diethyl ether was used for extraction, and the product was isolated via flash column chromatography (10 to 20% ethyl acetate/DCM) as a white solid (191 mg, 58% yield). The spectroscopic data match a literature report (Claudel, E.; Arbez-Gindre, C.; Berl, V.; Lepoittevin, J.-P. An Efficient Hemisynthesis of 20- and 21-[^{13}C]-Labeled Cortexolone: A Model for the Study of Skin Sensitization to Corticosteroids. *Synthesis* **2009,** *2009,* 3391−3398). ^1H NMR (300 MHz, $CDCl_3$): δ 5.73 (br s, 1H), 2.68 (ddd, *J* = 14.7, 11.4, 2.9 Hz, 1H), 2.51−2.34 (m, 4H), 2.28 (s, 3H), 2.09−1.96 (m, 1H), 1.93−1.52 (m, 9H), 1.50−1.33 (m, 3H), 1.19 (s, 3H), 1.15−0.93 (m, 2H), 0.77 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 211.7, 199.7, 171.3, 124.0, 89.9, 53.4, 50.1, 48.2, 38.7, 35.8, 35.6, 34.0, 33.6, 32.9, 32.1, 30.2, 27.9, 24.0, 20.6, 17.5, 15.5. LRMS-ESI (*m*/*z*): 353.2 $[M + Na]^+$.

*tert-Butyl (tert-Butoxycarbonyl)(3-phenylpropyl)carbamate (**8a**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting reaction mixture was degassed with nitrogen for 60 s and then was added to a solution of $NHBoc_2$ (2.0 equiv) and NaH (2.2 equiv) in DMF (1.0 mL) at room temperature. The solution of $NHBoc_2$, NaH, and DMF was prepared 30 min prior to the addition. The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (2% ethyl acetate/hexane) as a colorless oil (148 mg, 74% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−7.24 (m, 2H), 7.21−7.14 (m, 3H), 3.67−3.55 (m, 2H), 2.68−2.56 (m, 2H), 1.90 (p, *J* = 7.7 Hz, 2H), 1.48 (s, 18H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 152.8, 141.8, 128.5, 128.4, 126.0, 82.3, 46.4, 33.4, 30.8, 28.2. IR (cm^{-1}) (neat): 2978, 2930, 1694, 1366, 1134. HRMS-ESI (*m*/*z*): calcd for $C_{19}H_{29}NO_4Na^+$ ($[M + Na]^+$), 358.1994; found, 358.1991.

*2-(3-Phenylpropyl)isoindoline-1,3-dione (**8b**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following general procedure A using DMF as the solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was charged with potassium phthalimide (2.0 equiv). The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (20% ethyl acetate/hexane) as a white solid (124 mg, 80% yield). The spectroscopic data match a literature report (Tsui, G. C.; Menard, F.; Lautens, M. Regioselective Rhodium(I)-Catalyzed Hydroarylation of Protected Allylic Amines with Arylboronic Acids. *Org. Lett.* **2010,** *12,* 2456−2459). ^1H NMR (300 MHz, $CDCl_3$): δ 7.87−7.77 (m, 2H), 7.75−7.63 (m, 2H), 7.29−7.09 (m, 5H), 3.75 (t, *J* = 7.2 Hz, 2H), 2.73−2.66 (m, 2H), 2.04 (p, *J* = 7.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.57, 141.18, 134.02, 132.28, 128.52, 128.44, 126.08, 123.32, 37.96, 33.32, 30.02. LRMS-ESI (*m*/*z*): 288.3 $[M + Na]^+$.

*2-((3-Phenylpropyl)thio)benzo[d]thiazole (**8c**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following the general procedure A using DMF as the solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was charged with sodium 2-mercaptobenzothiazole (2.0 equiv). The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (5% Et_2O/hexane) as a colorless oil (152 mg, 89% yield). The spectroscopic data match a literature report (Yu, Y.; Li, Z.; Jiang, L. A Novel Synthesis of 2-Alkylthiobenzothiazoles and 2-Alkylthiobenzoxazoles. *Phosphorus, Sulfur Silicon Relat. Elem.* **2012,** *187,* 632−640). ^1H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.41 (td, *J* = 8.2, 7.8, 1.3 Hz, 1H), 7.34−7.25 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 3H), 3.36 (t, *J* = 7.2 Hz, 2H), 2.86−2.77 (m, 2H), 2.17 (p, *J* = 7.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 167.0, 153.4, 141.0, 135.3, 128.6, 128.6, 126.2, 126.1, 124.3, 121.6, 121.0, 34.8, 33.0, 30.9. LRMS-APCl (*m*/*z*): 286.3 $[M + H]^+$.

*5-Phenyl-2-(phenylsulfonyl)pentanenitrile (**8d**).* (3-Iodopropyl)benzene was prepared on a 0.57 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was added to a solution of (phenylsulfonyl)acetonitrile (2.0 equiv) and NaH (2.2 equiv) in DMF (1.0 mL) at room temperature. The solution of (phenylsulfonyl)acetonitrile, NaH, and DMF was prepared 30 min prior to the addition. The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (20% ethyl acetate/hexane) as a colorless oil (248 mg, 83% yield). The spectroscopic data match a literature report (Hirose, D.; Gazvoda, M.; Košmrlj, J.; Taniguchi, T. Systematic Evaluation of 2-Arylazocarboxylates and 2-Arylazocarboxamides as Mitsunobu Reagents. *J. Org. Chem.* **2018,** *83,* 4712−4729). ^1H NMR (300 MHz, $CDCl_3$): δ 8.03−7.93 (m, 2H), 7.83−7.71 (m, 1H), 7.70−7.58 (m, 2H), 7.33−7.10 (m, 5H), 3.88 (dd, *J* = 10.1, 4.6 Hz, 1H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.32−2.13 (m, 1H), 2.04−1.89 (m, 2H), 1.89−1.71 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 140.4, 135.7, 135.4, 129.8, 129.7, 128.8, 128.5, 126.5, 114.0, 57.5, 35.1, 28.4, 26.4. LRMS-APCl (*m*/*z*): 322.2 $[M + Na]^+$.

*1-(3-Phenylpropyl)-1H-benzo[d]imidazole (**8e**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was added to a solution of benzimidazole (2.0 equiv) and NaH (2.2 equiv) in DMF (1.0 mL) at room temperature. The solution of benzimidazole, NaH, and DMF was prepared 30 min prior to the addition. The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (50% ethyl acetate/DCM) as a white solid (113 mg, 80% yield). The spectroscopic data match a literature report (O'Connell, J.; Moriarty, E.; Aldabbagh, F. Access to Aromatic Ring-Fused Benzimidazoles Using Photochemical Substitutions of the Benzimidazol-2-Yl Radical. *Synthesis* **2012**, *44*, 3371−3377). ^1H NMR (300 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.90−7.79 (m, 1H), 7.40−7.26 (m, 5H), 7.27−7.12 (m, 3H), 4.21 (t, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.27 (p, *J* = 7.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.1, 143.1, 140.3, 133.9, 128.8, 128.5, 126.5, 123.0, 122.2, 120.6, 109.8, 44.4, 32.8, 31.1. LRMS-ESI (*m*/*z*): 237.4 $[M + H]^+$.

*(3-Azidopropyl)benzene (**8f**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was charged with sodium azide (2.0 equiv). The resulting reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A to afford the product as a yellow oil (83 mg, 84% yield). The spectroscopic data match a literature report (Benati, L.; Bencivenni, G.; Leardini, R.; Nanni, D.; Minozzi, M.; Spagnolo, P.; Scialpi, R.; Zanardi, G. Reaction of Azides with Dichloroindium Hydride: Very Mild Production of Amines and Pyrrolidin-2-Imines

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through Possible Indium−Aminyl Radicals. *Org. Lett.* **2006,** *8,* 2499−2502). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3−7.3 (m, 2H), 7.2−7.2 (m, 3H), 3.3 (t, J = 6.9 Hz, 2H), 2.7−2.7 (m, 2H), 2.0−1.9 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 141.0, 128.7, 128.6, 126.3, 50.8, 32.9, 30.6. HRMS-EI (m/z): calcd for $C_9H_{11}N_3$ ([M]$^+$), 161.0953; found, 161.0953.

*(3-Thiocyanatopropyl)benzene (**8g**).* (3-Iodopropyl)benzene was prepared on 0.58 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was charged with ammonium thiocyanate (2.0 equiv). The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (10% Et_2O/pentane) as a yellow oil (88 mg, 85% yield). The spectroscopic data match a literature report (Kiasat, A. R.; Fallah-Mehrjardi, M. Polyethylene Glycol: A Cheap and Efficient Medium for the Thiocyanation of Alkyl Halides. *Bull. Korean Chem. Soc.* **2008,** *29,* 2346−2348). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.27 (m, 2H), 7.25−7.13 (m, 3H), 2.93 (t, J = 7.2 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.17 (p, J = 7.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 139.9, 128.8, 128.6, 126.6, 112.2, 33.9, 33.2, 31.3. HRMS-EI (m/z): calcd for $C_{10}H_{11}NS$ ([M]$^+$), 177.0612; found, 177.0610.

*S-(3-Phenylpropyl) Ethanethioate (**8h**).* (3-Iodopropyl)benzene was prepared on a 0.59 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was charged with potassium thioacetate (2.0 equiv). The reaction mixture was stirred at room temperature for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (2% ethyl acetate/hexane) as a yellow oil (87 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.26 (m, 2H), 7.24−7.13 (m, 3H), 2.89 (t, J = 7.3 Hz, 2H), 2.75−2.63 (m, 2H), 2.34 (s, 3H), 1.98−1.82 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 196.0, 141.3, 128.6, 128.6, 126.2, 35.0, 31.3, 30.8, 28.7. IR (cm^{-1}) (neat): 3025, 2934, 2853, 1688, 1502, 1132. HRMS-ESI (m/z): calcd for $C_{11}H_{14}ONaS$ ([M + Na]$^+$), 217.0663; found, 217.0661.

*Diethyl 2-(3-Phenylpropyl)malonate (**8i**).* (3-Iodopropyl)benzene was prepared on a 0.6 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was added to a solution of diethyl malonate (2.0 equiv) and NaH (2.2 equiv) in DMF (1.0 mL) at room temperature. The solution of diethyl malonate, NaH, and DMF was prepared 30 min prior to the addition. The reaction mixture was stirred at room temperature for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (5% ethyl acetate/hexane) as a colorless oil (91 mg, 54% yield). The spectroscopic data match a literature report (Inés, B.; Palomas, D.; Holle, S.; Steinberg, S.; Nicasio, J. A.; Alcarazo, M. Metal-Free Hydrogenation of Electron-Poor Allenes and Alkenes. *Angew. Chem. Int. Ed.* **2012,** *51,* 12367−12369). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33−7.22 (m, 2H), 7.24−7.12 (m, 3H), 4.19 (q, J = 7.2 Hz, 4H), 3.34 (t, J = 7.5 Hz, 1H), 2.65 (t, J = 7.7 Hz, 2H), 2.02−1.88 (m, 2H), 1.66 (p, J = 8.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 169.6, 141.9, 128.5, 126.0, 61.5, 52.1, 35.6, 29.3, 28.5, 14.2. LRMS-ESI (m/z): 301.3 [M + Na]$^+$.

*2-(3-Phenylpropoxy)isoindoline-1,3-dione (**8j**).* (3-Iodopropyl)-benzene was prepared on a 0.58 mmol scale following general procedure A using DMF as a solvent. After stirring for 10 min, the resulting mixture was degassed with nitrogen for 60 s and then was added to a solution of PhthN-OH (2.0 equiv) and NaH (2.2 equiv) in DMF (1.0 mL) at room temperature. The solution of PhthN-OH, NaH, and DMF was prepared 30 min prior to the addition. The reaction mixture was heated in an oil bath to 80 °C for 1 h and then was worked up as per general procedure A. The product was isolated via flash column chromatography (20% ethyl acetate/hexane) as a pale yellow solid (122 mg, 75% yield). The spectroscopic data match a literature report (Hirose, D.; Taniguchi, T.; Ishibashi, H. Recyclable Mitsunobu Reagents: Catalytic Mitsunobu Reactions with an Iron Catalyst and Atmospheric Oxygen. *Angew. Chem. Int. Ed.* **2013,** *52,* 4613−4617). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91−7.78 (m, 2H), 7.81−7.69 (m, 2H), 7.36−7.26 (m, 4H), 7.23−7.14 (m, 1H), 4.23 (t, J = 6.4 Hz, 2H), 2.93−2.82 (m, 2H), 2.18−2.03 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 163.8, 141.3, 134.6, 129.1, 128.8, 128.6, 126.2, 123.7, 77.7, 31.9, 30.1. LRMS-ESI (m/z): 304.3 [M + Na]$^+$.

*(S)-2-(Octan-2-ylthio)benzo[d]thiazole (**9a**).* (R)-2-Bromooctane was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as the nucleophile and 4.0 mL of MeCN. After stirring for 1 h, the resulting mixture was degassed with nitrogen for 60 s and then was charged with sodium 2-mercaptobenzothiazole (2.0 equiv). The reaction mixture was stirred at room temperature overnight and then was worked up as per general procedure A. The product was isolated via flash column chromatography (4% Et_2O/petroleum ether) as a colorless oil (106 mg, 63% yield). The spectroscopic data match a literature report (Hirose, D.; Gazvoda, M.; Košmrlj, J.; Taniguchi, T. Systematic Evaluation of 2-Arylazocarboxylates and 2-Arylazocarboxamides as Mitsunobu Reagents. *J. Org. Chem.* **2018,** *83,* 4712−4729). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.46−7.36 (m, 1H), 7.32−7.26 (m, 1H), 3.97 (h, J = 6.8 Hz, 1H), 1.90−1.56 (m, 2H), 1.54−1.48 (m, 4H), 1.39−1.18 (m, 7H), 0.91−0.83 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.3, 153.2, 135.2, 126.2, 124.4, 121.6, 121.0, 44.8, 36.9, 31.8, 29.2, 27.1, 22.7, 21.6, 14.2. LRMS-ESI (m/z): 280.4 [M + H]$^+$. The enantiomeric ratio was determined by HPLC analysis using a chiral column to be 95:5, t_R = 31.2 (S), 32.6 (R); $[\alpha]_D$ = −10.8 (c = 1.33, $CHCl_3$), eluent: (acetonitrile/1% formic acid in water) 65:35.

*(S)-(4-Phenylbutan-2-yl) Ethanethioate (**9b**).* (R)-(3-Bromobutyl)benzene was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as the nucleophile and 4.0 mL of MeCN. After stirring for 1 h, the resulting mixture was degassed with nitrogen for 60 s and then charged with potassium thioacetate (2.0 equiv). The reaction mixture was stirred at room temperature overnight and then was worked up as per general procedure A. The product was isolated via flash column chromatography (2% Et_2O/petroleum ether) as a yellow oil (95 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.23 (m, 2H), 7.25−7.13 (m, 3H), 3.60 (h, J = 6.9 Hz, 1H), 2.81−2.60 (m, 2H), 2.33 (s, 3H), 1.95−1.80 (m, 2H), 1.35 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 196.0, 141.7, 128.5, 128.5, 126.1, 39.4, 38.4, 33.5, 30.9, 21.6. IR (cm^{-1}) (neat): 3029, 2927, 2860, 1685, 1495, 1111. HRMS-EI (m/z): calcd for $C_{12}H_{16}OS$ ([M]$^+$), 208.0922; found, 208.0925. The enantiomeric ratio was determined by HPLC analysis using a chiral column to be 98:2, t_R = 11.458 (R), 12.018 (S); $[\alpha]_D$ = −29.4 (c = 1.16, $CHCl_3$), eluent: (acetonitrile/1% formic acid in water) 65:35.

*(Azidomethylene)dibenzene (**9c**).* (Bromomethylene)dibenzene was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as nucleophile and 4.0 mL of MeCN. After stirring for 1 h, the resulting mixture was degassed with nitrogen for 60 s, and then, sodium azide (2.0 equiv) was added. The reaction mixture was stirred at room temperature overnight and then was worked up as per general procedure A. The product was isolated via flash column chromatography (2% Et_2O/petroleum ether) as a colorless oil (89 mg, 71% yield). The spectroscopic data match a literature report (Matoba, M.; Kajimoto, T.; Nishide, K.; Node, M. Preparation and Application of Odorless 1,3-Propanedithiol Reagents. *Chem. Pharm. Bull.* **2006,** *54,* 141−146). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.25 (m, 10H), 5.72 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 139.7, 128.9, 128.2, 127.5, 68.7. LRMS-APCI [M − N_2 + H]$^+$: 182.4.

*(S)-(3-Azidobutyl)benzene (**9d**).* (R)-(3-Bromobutyl)benzene was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as the nucleophile and 4.0 mL of MeCN. After stirring for 1 h, the resulting mixture was degassed with nitrogen for 60 s and then was charged with sodium azide (2.0 equiv). The reaction mixture was stirred at room temperature overnight and then was worked up as per general procedure A. The product was isolated via flash column chromatography (4% Et_2O/petroleum ether) as pale yellow oil (75 mg, 71% yield). The spectroscopic data match a literature report (Liu, C.; Wang, X.; Li, Z.; Cui, L.; Li, C.

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Silver-Catalyzed Decarboxylative Radical Azidation of Aliphatic Carboxylic Acids in Aqueous Solution. *J. Am. Chem. Soc.* **2015**, *137*, 9820−9823). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.24 (m, 2H), 7.26−7.15 (m, 3H), 3.44 (h, J = 6.5 Hz, 1H), 2.84−2.59 (m, 2H), 1.92−1.67 (m, 2H), 1.29 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 141.4, 128.6, 128.6, 126.2, 57.3, 38.0, 32.5, 19.6. LRMS-APCI (m/z): 148.3 $[M-N_2 + H]^+$. The enantiomeric ratio was determined by HPLC analysis using a chiral column to be 99:1, t_R = 26.2 (*R*), 27.3 (*S*); $[\alpha]_D$ = −53.6 (c = 1.18, $CHCl_3$), eluent: (acetonitrile/1% formic acid in water) 50:50.

*(S)-((2-Azidopropoxy)methyl)benzene (**9e**).* (*R*)-((2-Bromopropoxy)methyl)benzene was prepared on a 0.6 mmol scale following general procedure A using tetrabutylammonium bromide as the nucleophile and 4.0 mL of MeCN. After stirring for 1 h, the resulting mixture was degassed with nitrogen for 60 s and then charged with sodium azide (2.0 equiv). The reaction mixture was stirred at 40 °C overnight (heated in an oil bath) and then was worked up as per general procedure A. The product was isolated via flash column chromatography (2% Et_2O/petroleum ether) as a colorless oil (82 mg, 83% yield). The spectroscopic data match a literature report (Waser, J.; Nambu, H.; Carreira, E. M. Cobalt-Catalyzed Hydroazidation of Olefins: Convenient Access to Alkyl Azides. *J. Am. Chem. Soc.* **2005**, *127*, 8294−8295). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42−7.25 (m, 6H), 4.57 (s, 2H), 3.78−3.62 (m, 1H), 3.56−3.39 (m, 2H), 1.22 (d, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 138.0, 128.6, 127.9, 127.7, 74.0, 73.5, 57.1, 16.4. LRMS-APCI $[M-N_2 + H]^+$: 164.3. The enantiomeric ratio was determined by HPLC analysis using a chiral column to be 98:2, t_R = 40.4 (*S*), 41.9 (*R*); $[\alpha]_D$ = +6.6 (c = 1.80, $CHCl_3$), eluent: (acetonitrile/1% formic acid in water) 40:60.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02557.

Selected optimization studies; chiral HPLC chromatograms; and ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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