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Copper-catalyzed benzylic C–H coupling with alcohols via radical relay

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Abstract

Cross coupling reactions enable rapid convergent synthesis of diverse molecules and provide the foundation for modern chemical synthesis. The most widely used methods employ sp^2 -hybridized coupling partners, such as aryl halides or related pre-functionalized substrates. Here, we demonstrate copper-catalyzed oxidative cross coupling of benzylic C–H bonds with alcohols to afford benzyl ethers, enabled by mechanistic insights that led to a novel reductant-based strategy for in situ regeneration of the active copper catalyst. The reactions employ the C–H substrate as the limiting reagent and exhibit broad scope with respect to both substrate partners. This approach to direct site-selective functionalization of sp^3 C–H bonds provides the basis for efficient three-dimensional diversification of organic molecules and should find widespread utility in organic synthesis, particularly for medicinal chemistry applications.

Medicinal chemistry efforts in the pharmaceutical industry rely on efficient synthetic methods to prepare molecules with diverse chemical structures and compositions. Coupling methods that unite molecular fragments from two large pools of substrates, such as amide coupling and palladium catalyzed cross coupling, are among the most important and widely used reaction classes in this domain.^{1,2} The prevalent use of sp^2 -hybridized coupling partners (i.e., aryl, vinyl, acyl electrophiles), however, constrains the topological diversity of molecules that may be accessed and, in many cases, leads to molecules with less desirable physicochemical and other pharmaceutical properties. These limitations have contributed to a growing demand for cross coupling methods involving sp^3 -hybridized carbon atoms to access molecules with more three-dimensional character.^{3,4} $C(sp^3)$ -H bonds adjacent to aromatic and heteroaromatic rings are ubiquitous in key pharmacophores, and methods for selective cross coupling of benzylic C-H bonds and other versatile substrate partners (e.g., arylboronic acids, amines, alcohols, Figure 1a) could have a transformative influence on drug discovery. Such reactions would present a wealth of opportunities for elaboration of simple building blocks and pharmaceutical intermediates, as well as late stage functionalization of drug molecules.⁵ The comparatively low bond strength of benzylic C-H bonds makes them intrinsically reactive and provides a potential basis for high site selectivity in complex molecules bearing many other C-H bonds. Benzylic sites are also notorious metabolic "hot spots" in pharmaceuticals, and their selective substitution has important pharmacological implications.⁶ Here, we report a method for the preparation of benzyl ethers, a prominent motif in pharmaceuticals and bioactive molecules (Figure 1b), via direct oxidative cross coupling of benzylic C-H bonds with alcohols. A unique strategy for in situ reductive activation of the catalyst provides the basis for successful reactivity in the present reactions and sets the stage for development of other benzylic C-H cross coupling methods.

a. Cross-coupling reactions

Existing methods, e.g., aryl halides

Target: Benzylic C-H substrates

b. Benzylic ethers in pharmaceuticals

c. Radical relay strategy for cross-coupling of alcohols and benzylic C-H substrates

Figure 1. Cross coupling reactions of benzylic C-H bonds and alcohols via a radical relay pathway. **a**, Conceptual similarity between traditional cross coupling reactions of aryl halides and the targeted benzylic C-H functionalization reactions. **b**, Important examples of existing drug molecules containing benzylic ether moieties. **c**, Proposed radical relay mechanism for benzylic C-H etherification enabling the coupling of two diverse pools of substrates.

In recent years, a number of methods have been developed for intermolecular functionalization of sp^3 C-H bonds that show good site-selectivity, even in the absence of a directing group. Some of the most effective are those that replace the hydrogen atom of a C-H bond with a small fragment, for example, oxygenation,⁷ amination,⁸⁻¹⁰ carbene insertion,¹¹ halogenation,^{12,13} and various

pseudohalogenation reactions.¹⁴⁻¹⁷ Complementary advances have been made in methods for site-selective functionalization of low-cost feedstock molecules, such as alkylarenes,^{18, 19} tetrahydrofuran,^{20,21} or simple hydrocarbons²²⁻²⁴ that use excess C–H substrate relative to the oxidant and/or functionalization reagent. Collectively, these precedents do not incorporate the characteristics typically associated with "cross coupling" reactions. The most effective cross coupling methods, such as the Suzuki-Miyaura²⁵ and Buchwald-Hartwig^{26,27} reactions, have a number of common traits: (a) the most valuable coupling partner is used as the limiting reagent, in ideal cases employing a 1:1 stoichiometry of the two coupling partners, (b) both coupling partners draw from a diverse pool of readily (ideally commercially) available reagents, and (c) the reactions exhibit broad tolerance of the steric, electronic and functional-group properties of both coupling partners.

Alcohols represent an abundant class of building blocks that are widely used as partners in other coupling reactions, including classical methods, such as the Williamson ether synthesis,²⁸ in addition to modern catalytic methods.^{26,29} Precedents for the direct oxidative coupling of benzylic C–H bonds and alcohols, however, are confined to electron-rich arenes that stabilize benzylic cation intermediates, such as those capable of undergoing hydride transfer to DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).^{30,31} C–H cleavage via hydrogen-atom transfer (HAT) should be much less sensitive to electronic effects relative to pathways initiated by electron or hydride transfer,³² which generate cationic intermediates. Thus, we postulated that a "radical relay" strategy¹⁴ could provide the basis for selective, broad scope cross coupling of benzylic C–H bonds and alcohols, using the C–H substrate as the limiting reagent (Figure 1c). This reaction could be initiated by Cu^I-mediated activation of an oxidant, such as *N*-fluorobenzenesulfonimide (NFSI), which generates an N-centered radical capable of promoting HAT from the benzylic C–H bond.

The resulting Cu^{II} species is then available to mediate coupling of the benzylic radical with the alcohol coupling partner (Figure 1c).

Recent examples of radical relay cyanation,¹⁴ arylation,³³ and related functionalization of benzylic C–H bonds^{34–36} provided a starting point for this investigation, and we anticipated that reaction conditions similar to these precedents could lead to effective benzylic etherification (Figure 2a). Attempted coupling of 4-ethylbiphenyl and methanol, however, led to negligible yield of the benzylic ether **4** with little conversion of the substrate or NFSI (Figure 2a). The good product yields observed from analogous cyanation and arylation reactions suggested that the coupling partner may play an important role in activating the Cu catalyst. Stoichiometric experiments probing the reaction of Cu^{II} with the coupling partners showed that TMSCN and $\text{ArB}(\text{OH})_2$ induce rapid reduction of Cu^{II} to Cu^{I} , resulting in the formation of cyanogen³⁷ and biaryl.³⁸ In contrast, MeOH does not reduce Cu^{II} under these conditions (Figure 2b).

These observations indicate that the mechanism in Figure 1c is overly simplified and needs to be modified to explain successful reaction with certain coupling partners but not with others. The modified mechanism in Figure 2c retains reaction of Cu^{I} (**A**) with NFSI to initiate the reaction. This step generates Cu^{II} (**B**) and an N-centered radical (Fig 2c, left cycle). The nitrogen radical can undergo productive reaction with the benzylic C–H bond, but it can also react readily with a second equivalent of Cu^{I} , thereby quenching the radical and converting Cu^{I} into a second Cu^{II} species (**B'**; Fig 2c, right cycle). We postulate that NFSI rapidly oxidizes all of the Cu^{I} to Cu^{II} when the reaction is initiated, but that certain coupling partners, such as TMSCN or $\text{ArB}(\text{OH})_2$, are capable of reducing Cu^{II} to regenerate Cu^{I} during the course of the reaction (right cycle, red arrow). In these cases, the Cu^{I} will react with NFSI to generate an N-centered radical in the absence of a large pool of Cu^{I} , thereby enabling productive HAT from the benzylic substrate. MeOH does not readily

Figure 2 Cu-catalyzed benzylic C–H functionalization with NFSI as the oxidant. a, Cu-catalyzed benzylic C–H functionalization reactions^{14,33}. **b,** Changes in the Cu redox state between +1 (brown) and +2 (blue-green) upon addition of NFSI to a solution of the Cu^I catalyst precursor, followed by addition of cross coupling partners. **c,** Modified radical relay mechanism (cf. Figure 1d) to account for quenching of the N-centered radical by Cu^I and regeneration of Cu^I by a reducing substrate or additive. **d,** Reaction time course for benzylic etherification conducted in the absence (red) and presence of 0.5 equiv of dimethylphosphite. Reaction conditions: 4-phenylethylbenzene (0.2 mmol), NFSI (0.4 mmol), MeOH (1.0 mmol), CuCl (0.02 mmol), 2,2'-bioxazoline (0.02 mmol), DCM (1 ml), room temperature.

reduce Cu^{II}, and the Cu catalyst will accumulate as Cu^{II} (e.g., **B** or **B'**). The inability of Cu^{II} to react with NFSI under such conditions will cause the reaction to stall. These mechanistic considerations raised the possibility that a reductant could be identified to rescue the catalyst via slow generation of Cu^I during the reaction. To test this hypothesis, several reductants were tested

as additives in the etherification reaction with MeOH, including phosphites, silanes, hydrazines, and sodium ascorbate (see Table S3 and S4 in the Supplementary Information for details). Promising reactivity was observed with dimethylphosphite [(MeO)₂P(O)H], and a representative time course of the reaction in Figure 2d illustrates the effect of this additive. In the absence of phosphite, the reaction proceeds to <10% conversion of 4-ethylbiphenyl, while inclusion of 0.5 equiv of (MeO)₂P(O)H leads to high conversion within 5 h at room temperature, generating the benzyl methyl ether in 52% yield (unoptimized). The latter reaction mixture exhibits a blue-green color (cf. Figure 2b), implicating a Cu^{II} catalyst resting state, but the phosphite is proposed to serve as a "redox buffer", capable of slowly generating small quantities of reactive Cu^I to support productive turnover (Figure 2c).

This preliminary result provided the basis for further reaction optimization, and the oxidative coupling of ethylbenzene and methanol was tested with different solvents, ancillary ligands, Cu sources, and reaction temperatures (see the Supplementary Information for details). A number of monodentate and bidentate ligands were evaluated, and the unsubstituted 2,2'-bioxazoline (biox) ligand led to the best product yields. Use of chiral ligand derivatives did not lead to enantioselectivity under these conditions, but the effectiveness of this ligand class raises prospects for pursuit of this goal in future studies.^{14,39} Inclusion of hexafluoroisopropanol (HFIP) as a co-solvent with dichloromethane (DCM:HFIP = 4:1) led to higher yields and significantly increased the reaction rate, allowing the reaction to proceed at lower temperature (40 °C).⁴⁰ Under these conditions, reactions of ethylbenzene and 4-ethylbiphenyl, which are electronically similar, generated the 1-methoxyethylbenzene and 4-(1-methoxyethyl)biphenyl in 80% and 88% yield, respectively (Figure 3). Use of ethylarenes bearing electron-donating and electron-withdrawing substituents exhibited variable results, with yields ranging from 10–67% (Figure 3, red bars);

however, the modular nature of the reaction conditions enabled straightforward optimization of these yields by applying intuitive principles. For example, the electron-rich 4-methoxyethylbenzene is more reactive under the standard conditions and undergoes full conversion with the generation of considerable unidentified side products. Use of more gentle conditions, including removing the co-solvent HFIP, which enhances reactivity, and lowering the temperature from 40 °C to room temperature, led to formation of the desired product in 80% yield. Substrates bearing electron-withdrawing substituents are somewhat less reactive, as evident from incomplete conversion of the starting material under the original conditions. In these cases, the product yield was improved by raising the reaction temperature to 50 °C and/or increasing the Cu catalyst loading to 20 mol %. After applying these variations, the product yields ranged from 66–88%. Only the 4-cyano derivative, which is very electron deficient, retained a low yield (10%) after attempted optimization.

Figure 3 Electronic effects and site selectivity observed in the oxidative coupling of ethylarenes and methanol. a, Results observed from the reaction under standard (red) and individually optimized (blue) conditions (^1H NMR yields with CH_2Br_2 as the internal standard). ^a Optimized conditions: X = OMe: 20 mol % Cu/biox in DCM at r.t.; X = Br: 5 mol % Cu/biox; X = OAc: 20 mol % Cu/biox at 50 °C. **b,** Analysis of benzylic versus tertiary site selectivity observed in reaction of isobutylbenzene and ibuprofen methyl ester (see Figure 4 for reaction conditions).

The broad tolerance of arene electronic properties is complemented by nearly exclusive site selectivity. Isobutylbenzene and the ibuprofen methyl ester have been used previously to probe selectivity for benzylic versus tertiary C–H activation in photoredox-based azidation¹³ and nitrene insertion^{9,41} reactions. Approximately 1:1 product ratios were observed in the reported reactions with these substrates (Figure 3b). Anticipating that the selectivity depends on the mechanism and reagent involved in the C–H cleavage step, we tested these substrates in the present oxidative coupling conditions with methanol. Exclusive reaction at the benzylic position was observed with both substrates (Figure 3b), affording 72% and 67% yield of the two methyl ethers, respectively.

Benzylic methoxylation is a valuable transformation in medicinal chemistry, particularly in late-stage functionalization applications, because the introduction of small molecular fragments can significantly influence the activity and pharmacological properties of pharmaceuticals.^{4,5} For example, these groups can modulate the physicochemical characteristics and conformational dynamics of the molecule, introduce hydrogen bond donors/acceptors that can lead to enhanced ligand-target binding interactions, and block reactive sites to slow metabolism and excretion. The methoxy group is an appealing fragment because it has minimal impact on the mass or lipophilicity (i.e., LogP) of the molecule and introduces a potential hydrogen bond acceptor site.⁵

Examination of the substrate scope for benzylic methoxylation began with a number of small molecules and pharmaceutical building blocks as coupling partners (Figure 4). Longer alkyl chains, including those bearing primary alkyl halide substituents are tolerated by the reaction conditions (**10-12**, **14**), and good reactivity was also observed with a phenylacetic ester derivative (**13**).

Figure 4. Assessment of different benzylic C–H substrates in oxidative cross coupling reactions with methanol. ^a Isolated yields. ^b ¹H NMR yield; isolated yield unavailable due to compound volatility. ^c See Figure 3a for optimized conditions. ^d 15 mol % Cu/biox. ^e Reaction yield at 4 h. ^f At room temperature. ^g DCM as the solvent. ^h 20 mol % Cu/biox. ⁱ Only one regioisomer was observed. ^j At 30 °C. ^k 30 mol % Cu/biox. ^l Two regioisomers were observed with a ratio of 9:1.

Tetralin (**14**), a substructure present in numerous drugs such as sertraline, treprostinil and rotigotine, underwent effective methoxylation at room temperature. Benzhydryl ethers, including benztropine and ebastine (cf. Figure 1a) represent an important class of antihistamines.⁴² Methyl ethers were obtained in good yield with a series of benzhydryls (**15–19**) via oxidative cross coupling with methanol. Substrates included the benzhydryl fragment present in dapagliflozin, an approved drug for treatment of type 2 diabetes (cf. **19**). This promising reactivity was extended to C–H bonds adjacent to medicinally relevant sulfur-, oxygen- and nitrogen-containing heterocycles (**20–29**). Noteworthy features among these examples include tolerance of (hetero)aryl bromides (**20, 23, 24**) and a formyl group (**22**), which are versatile functional groups that permit further elaboration of the products. The thiophenylarylmethane core in **24** is a key fragment in canagliflozin, another commercial drug for type 2 diabetes. Chromans and azoles, which represent important pharmacophores⁴³ undergo effective coupling with methanol (**25, 26** and **27–29**). Some substrates, such as those with pyridine and indole heterocycles, led to lower yields or failed to afford the desired product (see summary provided in Table S5 of the Supplementary Information).

The methoxylation reaction also proceeded effectively in the late-stage functionalization of a number of pharmaceuticals and related bioactive molecules, including the immunosuppressant desoxyanisoin (**30**);⁴⁴ the natural product celestolide (**33**); a precursor to a GnRH antagonist (**35**);⁴⁵ a cyclopentapyrazolyl anti-inflammatory and anti-allergy agent (**36**);⁴⁶ and the insecticide, tebufenpyrad (**37**). Each of these underwent effective coupling with methanol and exhibited excellent selectivity for reaction at the benzylic position. For example, no products were obtained from methoxylation of the aliphatic C–H bond next to the nitrogen atom in **35** or adjacent to the alkoxy oxygen atoms in **30**. Good selectivity was also observed between the two similar cyclopentyl C–H positions in **36**. The 9:1 ratio favoring the product shown over the alternate

regioisomer probably arises from higher reactivity at the more electron-rich site. Free -OH groups, such as those present in a sugar fragment of dapagliflozin (anti-diabetic), a carboxylic acid of ibuprofen (anti-inflammatory), and a phenol in benzbromarone (xanthine oxidase inhibitor⁴⁷) interfere with the etherification reaction, but successful reactivity proceeds when these groups are suitably protected (**31**, **32**, **34**).

The potential utility of this method for medicinal chemistry library synthesis is especially evident from assessment of the C–H cross coupling reaction with diverse alcohols. The thiophene-containing fragment of canagliflozin was selected as a representative, moderately complex core structure for these studies (Figure 5). Initial tests employing 2-chloroethanol as the coupling partner led to two products, the desired 2-chloroethyl ether in addition to the methyl ether product in 64% and 18% yields, respectively. The latter product derives from participation of the methoxy group from the (MeO)₂P(O)H reductant in the reaction. Reevaluation of other phosphites showed that this side product formation could be nearly eliminated (<2%) by using diisopropyl phosphite (see Table S6 in the Supplementary Information for details). This insight was then implemented in reactions with numerous other alcohol coupling partners. Several 2-substituted ethanol derivatives, including those bearing chloro, methoxy, BocNH (Boc = *tert*-butyloxycarbonyl), alkynyl, vinyl, naphthyl, and benzyl ether substituents (**38–44**), were effective in the reaction, in most cases affording product in good-to-excellent yields. Only the alkene-containing substrate **42** led to a relatively low yield, possibly reflecting competitive reaction with the allylic C–H bonds. The presence of benzylic C–H bonds in the alcohols **43** and **44** did not interfere with successful reactivity. Both afforded the desired product in good yield. Expanding on this compatibility, a series of *ortho*-, *meta*-, and *para*-substituted benzyl alcohols with different electronic and steric

properties proved to be excellent coupling partners in these reactions (**45–49**, 73–91% yields). Only small amounts of benzaldehyde by-product were observed in these reactions.

Figure 5. Assessment of different alcohols in benzylic C–H etherification reactions. ^a Calibrated ^1H NMR yields using dibromomethane as the internal standard (isolated yields in parentheses). ^b 30 mol % Cu/biox . ^c Conducted with 3.0 equiv. alcohol. ^d Conducted with 1.1 equiv. alcohol.

Other aliphatic alcohols were also successful, including trimethylsilylmethanol, cyclopropylmethanol (**50**, **51**), and several oxetane and azetidine analogs (**52–54**). Small groups such as these are increasingly featured in preclinical and clinical drug candidates,^{48,49} and the cross coupling of benzylic C–H bonds and alcohols provides a compelling strategy to introduce these units. The effectiveness of adamantanol and (–)-borneol (**55**, **56**) showed that sterically hindered alcohols can serve as effective coupling partners. Finally, the method proved effective with complex alcohols, including cholesterol (**57**) and a pyrimidinylmethanol precursor to rosuvastatin

(**58**). The latter reaction was demonstrated on >1 g scale (91% yield, 1.3 g) and was also successful with only 1.1 equiv of **58** (88% yield).

Collectively, these results demonstrate a new class of highly selective, non-directed C–H cross coupling reactions that create opportunities for efficient synthesis of novel molecules and diversification of chemical structures, ranging from simple aromatic and heteroaromatic building blocks to complex pharmacophores and existing drug molecules. Prominent features of these reactions include good product yields, ability to use the benzylic substrate as the limiting reagent, high benzylic site selectivity, and access to a broad substrate scope with respect to both reaction partners. Mechanistic insights set the stage for these results by revealing that traditional reaction conditions lead to accumulation of the catalyst in an inactive Cu^{II} state, and the key breakthrough arose from the discovery that the addition of phosphite allows for slow in situ reduction of Cu^{II} to Cu^I during the course of the reaction. We anticipate that this "redox buffering" strategy will not be unique to this reaction class, but it will lead to the discovery and development of other radical relay C–H cross coupling methods with potential for widespread impact in medicinal chemistry and organic synthesis.

Supplementary Information.

Experimental procedures for preparation, optimization conditions, characterization data and NMR spectra of compounds (pdf).

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Supplementary Information

Copper-catalyzed benzylic C–H coupling with alcohols via radical relay

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I. General Considerations

All reagents were purchased and used as received unless otherwise noted. Cu salts were purchased from Aldrich. Benzylic C–H substrates were purchased from Oakwood Chemicals, Combi-Blocks, Chem-Impex, Alfa Aesar, TCI America, Ark Pharm, Enamine, AstaTech or Aldrich. With the exception of ligand L8 (cf. Table S1), which was prepared by a literature protocol¹, ligands were purchased from Aldrich or TCI America. N-Fluorobenzenesulfonimide (NFSI) was purchased from Combi-Blocks and Ark Pharm. Methanol was purchased from Aldrich and Macron Fine Chemicals. Dialkyl phosphites were purchased from Aldrich, TCI America, Alfa Aesar and Oakwood Chemicals. All the reagents were used without further purification.

¹H and ¹³C NMR spectra were recorded on Bruker 400 MHz or Bruker 500 MHz spectrometers and chemical shifts are reported in parts per million (ppm). ¹H NMR spectra were referenced to tetramethylsilane at 0.00 ppm and ¹³C NMR spectra were referenced to CDCl₃ at 77.16 ppm. Chromatography was performed using either a Combi-flash® with reusable 24 g or 12 g Combi-flash gold® cartridges, or a Biotage Isolera One® with reusable 25 g SNAP Ultra® cartridges or standard silica cartridges. High-resolution mass spectra were obtained using a Thermo Q Exactive™ Plus (ESI or ASAP-MS) by the mass spectrometry facility at the University of Wisconsin (funded by NIH grant: 1S10OD020022-1).

II. Experimental Procedures for Preparations of Compounds

General Procedure (I) for Methoxylation of Benzylic C–H Substrates (pressure tube)

Copper(I) chloride (2.0 mg, 0.020 mmol, 10 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (2.8 mg, 0.020 mmol, 10 mol%), NFSI (126.1 mg, 0.40 mmol, 2.0 equiv.) and benzylic substrate (if solid, 0.20 mmol, 1.0 equiv.) were added to a pressure tube under air, and then the tube was moved to a glove box. Solvent (1.0 mL), benzylic substrate (if liquid, 0.20 mmol, 1.0 equiv.), methanol (42 μ L, 1.0 mmol, 5.0 equiv.) and dimethyl phosphonate (9.5 μ L, 0.10 mmol, 0.5 equiv.) were added to the tube. The tube was sealed in the glove box and taken out to a hot plate. The sealed tube was heated at 40 °C with stirring for 16 h. When the reaction finished, the mixture was cooled down to room temperature, poured into water and extracted with CHCl₃ (10 mL $\times$ 3). The organic layers were combined and washed by saturated sodium bicarbonate, brine and dried with Na₂SO₄ and filtered. Then the mixture was evaporated under vacuum and the crude mixture was purified by automated flash chromatography (silica gel, eluted by pentane:ethyl acetate = 20:1 to 4:1).

General Procedure (II) for Methoxylation of Benzylic C–H Substrates (glass vial)

Copper(I) chloride (2.0 mg, 0.020 mmol, 10 mol%), 4,4',5,5'-tetrahydro-2,2'-bioxazole (2.8 mg, 0.020 mmol, 10 mol%), NFSI (126.1 mg, 0.40 mmol, 2.0 equiv.) and benzylic substrate (if solid, 0.20 mmol, 1.0 equiv.) were added under air to a 4 ml vial containing a magnetic stir bar. Then the vial was capped with a pierceable Teflon cap. A needle was pierced through the cap to facilitate exchange of the vial headspace with the atmosphere. Then the vial was moved into a glove box,

through three vacuum-nitrogen-backfill cycles. The needle was removed, and the vial was taken out of the glove box (now sealed under an inert gas). Solvent (1.0 mL), benzylic substrate (if liquid, 0.20 mmol, 1.0 equiv.), methanol (42 μ L, 1.0 mmol, 5.0 equiv.) and dimethyl phosphonate (9.5 μ L, 0.10 mmol, 0.5 equiv.) were added into the vial by injection through the cap. The sealed vial was heated at 40 $^{\circ}$ C and stirred for 16 h. When the reaction finished, the mixture was cooled down to room temperature and triethylamine (140 μ L, 1.0 mmol, 5.0 equiv.) was added to quench any unreacted NFSI. Then the mixture was evaporated under vacuum and the crude mixture was purified by automated flash chromatography (silica gel, eluted by pentane:ethyl acetate = 20:1 to 4:1).

Procedure for the gram scale experiment.

Copper(I) chloride (15 mg, 0.30 mmol), 4,4',5,5'-tetrahydro-2,2'-bioxazole (42 mg, 0.30 mmol), NFSI (1261 mg, 4.0 mmol), 4-(4-Fluorophenyl)-6-isopropyl-2-[(N-methyl-N-methylsulfonyl)amino]pyrimidine-5-yl-methanol (1414 mg, 4.0 mmol) and 2-(5-Bromo-2-methylbenzyl)-5-(4-fluorophenyl)thiophene (723 mg, 2.0 mmol) were added under air to a 24 ml vial containing a magnetic stir bar. Then the vial was capped with a pierceable Teflon cap. A needle was pierced through the cap and kept in the cap facilitate the exchange of the vial headspace with the atmosphere. Then the vial was transferred to a glove box, through three vacuum-nitrogen-backfill cycles. The needle was then removed in the glove box. Dichloromethane (10 mL) and diisopropyl phosphite (163 μ L, 1.0 mmol) were added into the vial. The vial was capped, taken out of the glove box and stirred at room temperature for 16 h. When the reaction finished, triethylamine (1.4 mL, 10 mmol) was added. Then the mixture was evaporated under vacuum and the crude mixture was purified by flash chromatography (silica gel, eluted by pentane/ethyl acetate = 9:1). 1.30 g (91%) of pale-yellow liquid was obtained.

Procedure for the preparation of the substrate **59**.

The synthetic protocol for the preparation of **59** was adapted from a literature procedure². 6-ethyl-1,3-benzothiazol-2-amine (446 mg, 2.5 mmol) was weighed into 15 ml glass vial containing a

Teflon magnetic stir bar. Toluene (15 ml) and acetic anhydride (94.5 μ L, 10.0 equiv.) were added into the flask in sequence. The vial was then capped with a Teflon pierceable cap and the reaction mixture was stirred at 115 $^{\circ}$ C overnight. The reaction was concentrated under vacuum and the residue was triturated with 5 ml ethyl acetate and 50 ml pentane. The product was filtered out and dried. Trituration and filtration were repeated three times and 473 mg (86% isolated yield) of **59** (the substrate of **27**) was collected.

Procedure for the preparation of the substrate **60**.

The synthetic protocol for the preparation of **62** was adapted from a literature procedure³. 2-[3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]acetic acid (298 mg, 1.2 mmol) was weighed into 15 ml vial containing a Teflon magnetic stir bar. A mixture of acetonitrile and MeOH (9:1, 4.8 ml), followed diisopropylethylamine (0.43 ml, 1.5 equiv.) were added into the flask and the mixture was stirred for 10 min, and then trimethylsilyldiazoethane (2.0 M Hexane solution, 0.9 ml, 1.5 equiv.) was added dropwise into the reaction mixture. When no obvious bubbling was observed, the vial was capped with a pierceable Teflon cap and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography (pentane:ethyl acetate = 4:1). 255 mg white solid (82% isolated yield) of **60** (the substrate of **28**) was collected.

Procedure for the preparation of the substrate **61**.

The synthetic protocol for the preparation of **61** was adapted from a literature procedure³. Benzbromarone (1.70 g, 4.0 mmol) was weighed into a 50 ml round bottom flask containing a Teflon magnetic stir bar. A mixture of acetonitrile and MeOH (9:1, 16 ml), followed diisopropylethylamine (1.44 ml, 1.5 equiv.) was added into the flask and the mixture was stirred for 10 min, and then trimethylsilyldiazoethane (2.0 M Hexane solution, 3 ml, 1.5 equiv.) was added dropwise into the reaction mixture. A funnel was placed upside down on top of the flask to minimize the evaporation of the solvent and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue was purified by purified by column chromatography (pentane:ethyl acetate = 4:1). 1.67 g (95% isolated yield) of **61** (the substrate of **34**) was collected.

Table S1a. Ligand Optimization

Table S2. Optimization of the Reaction Conditions with Various Solvents, Cu Salts and Temperature

CC(O)c1ccccc1 + CO
 $\xrightarrow[\text{N}_2, T^\circ\text{C}]{\begin{smallmatrix} [\text{Cu}] (10 \text{ mol } \%) \\ \text{Ligand} (10 \text{ mol } \%) \\ \text{NFSI} (2.0 \text{ equiv.}) \\ \text{Solvent} (1.0 \text{ ml}), 16 \text{ h} \end{smallmatrix}}$
CC(OC)c1ccccc1

0.2 mmol (5.0 equiv.) % Yield

Entry	Cu Source	Solvent	T (°C)	Conv. of 1 (%)	Yield of 3 (%)
1	CuCl	DCE	80	56	44
2	CuBr	DCE	80	64	41
3	CuCl ₂	DCE	80	59	42
4	[Cu(MeCN) ₄]BF ₄	DCE	80	69	40
5	CuCl	DMC	80	56	33
6	CuCl	Benzene	80	59	35
7	CuCl	EtOAc	80	30	17
8	CuCl	DCM	80	67	49
9	CuCl	MeOH	80	16	16
10	CuCl	HFIP	80	85	2
11	CuCl	DCM:HFIP=4:1	40	81	72
12	CuCl	DCM	40	23	23
13^b	CuCl	DCM:HFIP=4:1	40	97	80

^aReactions were conducted with 0.02 mmol CuCl as the catalyst and dichloroethane (DCE) as the solvent at 80°C. ^b50 mol % of (MeO)₂P(O)H was added. DCE, 1,2-dichloroethane; DMC, dimethyl carbonate; DCM, dichloromethane; HFIP, hexafluoroisopropanol; T, temperature; Conv., conversion.

Table S3. Investigation of dimethylphosphite with 4-phenylethylbenzene as the substrate

0.2 mmol (5.0 equiv.) % Yield

Entry	Additive (0.5 equiv.)	Solvent	T (°C)	Conv. (%)	Yield (%)
1	—	Benzene	r. t.	5	4
2	—	DCM	r. t.	9	9
3	(MeO) ₂ POH	DCM	r. t.	88	57
4	—	DCM	40	52	26
5	(MeO) ₂ POH	DCM	40	100	70
6	—	DCM : HFIP = 4 : 1	r. t.	4	5
7	(MeO) ₂ POH	DCM : HFIP = 4 : 1	r. t.	49	45
8	—	DCM : HFIP = 4 : 1	40	25	23
9	(MeO) ₂ POH	DCM : HFIP = 4 : 1	40	85	77

Table S4. Investigation of various reductants with ethylbenzene as the substrate

0.2 mmol (5.0 equiv.) % Yield

Entry	Reductant	Conv. of 1 (%)	Yield of 3 (%)
1	(MeO)₂P(O)H	100	80
2	(EtO) ₂ P(O)H	91	77
3	(ⁱ PrO) ₂ P(O)H	88	73
4	(^t BuO) ₂ P(O)H	34	28
5	(ⁿ BuO) ₂ P(O)H	94	75
6	(MeO) ₂ MeSiH	79	70
7	(EtO) ₂ MeSiH	100	62
8	PhNHNHPh	7	0
9	EtCO ₂ NHNHCO ₂ Et	94	62
10	P(ⁿ Bu) ₃	37	22
11	Sodium Ascorbate	100	62

Unsuccessful Substrates.

Not all substrates tested were effective in the benzylic etherification reaction. The substrates in Table S5a afford methyl ethers in < 40% yield, based on analysis of the crude reaction mixture by ^1H NMR spectroscopy (Table S5a). An elimination product was observed in the case of splitomicin. Substrates in Table S5b generally underwent high conversion but led to low-to-negligible yields of the desired products. Pyridines, quinoline and pyrimidine derivatives have been reported to react directly with NFSI and no desirable methoxylated product was observed under all the reaction conditions tested⁴. Substrates in Table S5c are rather inactive, giving low conversions and low yields. Substrates with free phenols or acidic N-H groups suffered from low conversion, possibly reflecting inhibition by coordination to Cu. Sites adjacent to electron-deficient heterocycles were generally unreactive, and unreacted starting material was observed with the substrates in Table S5c.

Table S5. Unsuccessful substrates in benzylic C-H methoxylation

Table S6. Investigation of various phosphites with a canagliflozin precursor

Entry	Additive	Conv. of the substrate (%) ^a	Yield of 38' (%) ^a	Yield of 38 (%) ^a
1	(MeO) ₂ P(O)H	83	18	64
2	(EtO) ₂ P(O)H	92	8	81
3	(ⁱ Pr) ₂ P(O)H	95	2	92
4	(ⁿ Bu) ₂ P(O)H	94	8	84
5	(Bn) ₂ P(O)H	92	13	76
6	(CF ₃ CH ₂ O) ₂ P(O)H	69	3	59
7	(^t Bu) ₂ P(O)H	68	3	65
8	-	23	-	23

^aCalibrated ¹H NMR yields using dibromomethane as the internal standard. Conv., conversion.

IV. Characterization of Compounds

4-(1-methoxyethyl)-1,1'-biphenyl, **4**. Characterization data matched those previously reported⁵.

Reaction run at 0.4 mmol scale and 73.8 mg (87%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.62 – 7.55 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 4.35 (q, *J* = 6.5 Hz, 1H), 3.26 (s, 3H), 1.48 (d, *J* = 6.4 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 142.6, 141.0, 140.4, 128.8, 127.2 (2C), 127.1, 126.6, 79.4, 56.5, 23.9 ppm.

1-methoxy-4-(1-methoxyethyl)benzene, **6**. Characterization data matched those previously reported⁶.

Reaction run at 0.4 mmol scale and 45.9 mg (69%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.23 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 1H), 4.25 (q, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.19 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 159.0, 135.5, 127.4, 113.8, 79.1, 56.2, 55.3, 23.8 ppm.

1-bromo-4-(1-methoxyethyl)benzene, **7**. Characterization data matched those previously reported⁵.

Reaction run at 0.2 mmol scale and 28.4 mg (66%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.47 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 4.26 (q, *J* = 6.5 Hz, 1H), 3.21 (s, 3H), 1.40 (t, *J* = 6.5 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 142.6, 131.6, 127.9, 121.2, 79.0, 56.5, 23.8 ppm.

4-(1-methoxyethyl)phenyl acetate, **8**.

Reaction run at 0.4 mmol scale and 46.6 mg (60%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.31 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 4.29 (q, *J* = 6.5 Hz, 1H), 3.22 (s, 3H), 2.30 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 169.5, 149.9, 141.1, 127.2, 121.5, 79.1, 56.5, 23.9, 21.2 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{14}\text{O}_3+\text{NH}_4]^+$: 212.1281, Found: 212.1278.

(1-methoxyhexyl)benzene, **10**.

Reaction run at 0.4 mmol scale and 53.8 mg (70%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.38 – 7.31 (m, 2H), 7.31 – 7.24 (m, 3H), 4.07 (dd, $J = 7.3, 6.0$ Hz, 1H), 3.20 (s, 3H), 1.86 – 1.72 (m, 1H), 1.67 – 1.55 (m, 1H), 1.46 – 1.33 (m, 1H), 1.32 – 1.16 (m, 5H), 0.86 (t, $J = 6.9$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 142.6, 128.3, 127.4, 126.7, 84.2, 56.6, 38.2, 31.8, 25.5, 22.6, 14.1 ppm.

HRMS (ASAP-MS) Calculated for $[\text{C}_{13}\text{H}_{20}\text{O}-\text{OMe}]^+$: 161.1325, Found: 161.1323.

(3-chloro-1-methoxypropyl)benzene, **11**.

Reaction run at 0.4 mmol scale and 37.7 mg (51%) of colorless liquid isolated. Characterization data matched those previously reported⁷.

^1H NMR (CDCl_3 , 400 MHz): 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 4.37 (dd, $J = 8.5, 4.8$, 1H), 3.71 (ddd, $J = 10.8, 8.1, 5.6$, 1H), 3.50 (ddd, $J = 10.8, 5.9$, 1H), 3.23 (s, 3H), 2.23 (ddt, $J = 14.2, 8.4, 5.7$ Hz, 1H), 2.01 (dddd, $J = 14.3, 8.1, 6.0, 4.9$ Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 141.2, 128.6, 127.9, 126.6, 80.4, 56.8, 41.7, 40.9 ppm.

(3-bromo-1-methoxypropyl)benzene, **12**. Characterization data matched those previously reported⁸.

Reaction run at 0.4 mmol scale and 37.7 mg (41%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.40 – 7.34 (m, 2H), 7.33 – 7.27 (m, 3H), 4.35 (dd, $J = 8.4, 4.8$ Hz, 1H), 3.61 – 3.52 (m, 1H), 3.41 – 3.33 (m, 1H), 3.24 (s, 3H), 2.36 – 2.26 (m, 1H), 2.15 – 2.04 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 141.1, 128.6, 127.9, 126.6, 81.4, 56.9, 41.1, 30.3 ppm.

methyl 2-methoxy-2-(4-methoxyphenyl)acetate, **13**. Characterization data matched those previously reported⁹.

Reaction run at 0.4 mmol scale and 74.8 mg (89%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.36 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.72 (s, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.38 (s, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 171.4, 160.0, 128.6, 128.2, 114.1, 82.1, 57.1, 55.3, 52.3 ppm.

1-methoxy-1,2,3,4-tetrahydronaphthalene, **14**. Characterization data matched those previously reported¹⁰.

Reaction run at 0.4 mmol scale and 38.9 mg (60%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.38 – 7.31 (m, 1H), 7.22 – 7.14 (m, 1H), 7.12 – 7.06 (m, 1H), 4.31 (t, *J* = 4.7 Hz, 1H), 2.83 (dt, *J* = 16.8, 5.7 Hz, 1H), 2.71 (ddd, *J* = 16.7, 8.3, 6.0 Hz, 1H), 2.07 – 1.93 (m, 2H), 1.93 – 1.83 (m, 1H), 1.79 – 1.67 (m, 1H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 137.5, 136.6, 129.3, 129.0, 127.5, 125.7, 76.8, 56.2, 29.1, 27.4, 18.7 ppm.

(methoxymethylene)dibenzene, **15**. Characterization data matched those previously reported¹¹.

Reaction run at 0.4 mmol scale and 63.4 mg (80%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.37–7.28 (m, 8H), 7.26 – 7.21 (m, 2H), 5.24 (s, 1H), 3.38 (s, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 142.1, 128.4, 127.5, 126.9, 85.5, 57.1 ppm.

4,4'-(methoxymethylene)bis(fluorobenzene), **16**. Characterization data matched those previously reported¹².

Reaction run at 0.4 mmol scale and 71.2 mg (76%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.31 – 7.24 (m, 4H), 7.05 – 6.97 (m, 4H), 5.20 (s, 1H), 3.35 (s, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 162.2 (d, *J* = 244.3 Hz), 137.7 (d, *J* = 3.2 Hz), 128.5 (d, *J* = 8.1 Hz), 115.3 (d, *J* = 21.3 Hz), 84.0, 56.9 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.9 ppm.

1-bromo-4-(methoxy(phenyl)methyl)benzene, **17**. Characterization data matched those previously reported¹³.

Reaction run at 0.4 mmol scale and 84.3 mg (76%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.44 (d, $J = 8.4$ Hz, 2H), 7.35 – 7.24 (m, 5H), 7.22 (dd, $J = 8.6, 0.6$ Hz, 2H), 5.19 (s, 1H), 3.36 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 141.5, 141.3, 131.5, 128.6, 128.6, 127.8, 126.9, 121.4, 84.7, 57.0 ppm.

1-bromo-2-(methoxy(phenyl)methyl)benzene, **18**. Characterization data matched those previously reported¹⁴.

Reaction run at 0.4 mmol scale and 59.9 mg (54%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.56 – 7.50 (m, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.29 (m, 3H), 7.28 – 7.22 (m, 1H), 7.12 (td, $J = 7.6, 1.7$ Hz, 1H), 5.67 (s, 1H), 3.39 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 141.0, 140.5, 132.8, 129.0, 128.5, 128.4, 127.8, 127.7, 127.4, 123.6, 83.5, 57.2 ppm.

4-bromo-1-chloro-2-((4-ethoxyphenyl)(methoxy)methyl)benzene, **19**.

Reaction run at 0.2 mmol scale and 112 mg (79%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.75 (d, $J = 2.4$ Hz, 1H), 7.31 (dd, $J = 8.5, 2.5$ Hz, 1H), 7.25 (d, $J = 8.7$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 5.52 (s, 1H), 4.01 (q, $J = 7.0$ Hz, 2H), 3.36 (s, 3H), 1.39 (t, $J = 7.0$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 158.7, 142.0, 131.7, 131.5, 131.5, 130.9, 130.6, 128.8, 121.0, 114.4, 80.8, 63.4, 57.0, 14.8 ppm.

HRMS (ASAP-MS) Calculated for $[\text{C}_{16}\text{H}_{16}\text{BrClO}_2\text{-OMe}]^+$: 322.9833, Found: 322.9832.

2-bromo-5-(1-methoxyhexyl)thiophene, **20**.

Reaction run at 0.4 mmol scale and 72.1 mg (65%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 6.90 (d, $J = 3.7$ Hz, 1H), 6.70 (d, $J = 3.7$ Hz, 1H), 4.25 (t, $J = 6.8$ Hz, 1H), 3.26 (s, 3H), 1.91 – 1.78 (m, 1H), 1.67 (m, 1H), 1.46 – 1.17 (m, 6H), 0.87 (t, $J = 6.9$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 148.3, 129.0, 125.6, 111.6, 79.8, 56.5, 38.1, 31.6, 25.4, 22.5, 14.0 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{17}\text{BrOS}+\text{Na}]^+$: 299.0076, Found: 299.0074.

2-(1-methoxyhexyl)thiophene, **21**.

Reaction run at 0.4 mmol scale and 40.5 mg (51%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.30 – 7.23 (m, 1H), 7.01 – 6.92 (m, 2H), 4.35 (t, $J = 6.8$ Hz, 1H), 3.25 (s, 3H), 1.99 – 1.84 (m, 1H), 1.72 (m, 1H), 1.49 – 1.34 (m, 1H), 1.33 – 1.23 (m, 5H), 0.87 (t, $J = 6.7$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 146.4, 126.2, 125.2, 124.8, 79.5, 56.4, 38.3, 31.6, 25.5, 22.6, 14.0 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{18}\text{OS}+\text{Na}]^+$: 221.0971, Found: 221.0969.

5-(1-methoxyethyl)thiophene-2-carbaldehyde, **22**.

Reaction run at 0.4 mmol scale and 33.4 mg (49%) of yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 9.88 (s, 1H), 7.66 (d, $J = 3.8$ Hz, 1H), 7.07 (dd, $J = 3.8, 0.7$ Hz, 1H), 4.59 (qd, $J = 6.5, 0.7$ Hz, 1H), 3.33 (s, 3H), 1.55 (d, $J = 6.5$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 183.0, 158.0, 142.7, 136.3, 125.1, 75.2, 56.8, 23.6 ppm.

HRMS Calculated for $[\text{C}_8\text{H}_{10}\text{O}_2\text{S}+\text{H}]^+$: 171.0474, Found: 171.0473.

2,5-dibromo-3-(1-methoxyhexyl)thiophene, **23**.

Reaction run at 0.2 mmol scale and 52.6 mg (74%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 8.43 (d, *J* = 7.8 Hz, 1H), 8.24 (s, 1H), 6.88 (s, 1H), 4.23 (dd, *J* = 7.2, 6.4 Hz, 1H), 3.20 (s, 3H), 1.76 (dddd, *J* = 13.4, 9.8, 7.2, 5.2 Hz, 1H), 1.57 (dddd, *J* = 13.4, 10.0, 6.4, 5.3 Hz, 1H), 1.42 – 1.19 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 143.4, 128.8, 111.5, 109.4, 78.2, 56.8, 36.2, 31.6, 25.1, 22.6, 14.1 ppm.

HRMS Calculated for [C₁₁H₁₆Br₂OS+Na]⁺: 376.9181, Found: 376.9180.

2-((5-bromo-2-methylphenyl)(methoxy)methyl)-5-(4-fluorophenyl)thiophene, **24**.

Reaction run at 0.4 mmol scale and 65.7 mg (84%) of white solid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.72 (d, *J* = 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.07 – 6.99 (m, 4H), 6.75 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.51 (s, 1H), 3.41 (s, 3H), 2.24 (s, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 162.3 (d, *J* = 245.7 Hz), 143.8, 143.7, 141.2, 134.5, 132.3, 130.8, 130.5 (d, *J* = 3.4 Hz), 129.1, 127.4 (d, *J* = 8.0 Hz), 126.9, 122.3 (d, *J* = 1.2 Hz), 120.1, 115.8 (d, *J* = 21.7 Hz), 78.0, 57.0, 18.8 ppm.

¹⁹F NMR (377 MHz, CDCl₃): -114.5 ppm.

HRMS Calculated for [C₁₉H₁₆BrFOS+Na]⁺: 412.9982, Found: 412.9980.

4-methoxychromane, **25**.

Reaction run at 0.4 mmol scale and 30.2 mg (46%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.24 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28 (td, *J* = 7.7, 1.7 Hz, 1H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H), 6.84 (dd, *J* = 8.2, 1.2 Hz, 1H), 4.32 – 4.21 (m, 3H), 3.44 (s, 3H), 2.18 – 2.10 (m, 1H), 2.09 – 1.98 (m, 1H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 154.8, 130.6, 129.7, 121.6, 119.9, 117.0, 71.8, 62.0, 55.8, 27.2 ppm.

HRMS (ASAP-MS) Calculated for [C₁₀H₁₂O₂-OMe]⁺: 133.0648, Found: 133.0646.

6-bromo-4-methoxychromane, **26**.

Reaction run at 0.4 mmol scale and 50.6 mg (52%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.37 (d, $J = 2.4$ Hz, 1H), 7.28 (dd, $J = 8.8, 3.2$ Hz, 1H), 6.72 (d, $J = 8.7$ Hz, 1H), 4.29 – 4.19 (m, 3H), 3.44 (s, 3H), 2.16 – 2.08 (m, 1H), 2.01 (dddd, $J = 14.2, 9.6, 5.4, 3.8$ Hz, 1H) ppm.
 ^{13}C NMR (CDCl_3 , 100 MHz): 153.9, 132.9, 132.5, 123.7, 118.9, 111.9, 71.5, 62.3, 56.0, 26.8 ppm.
 HRMS (ASAP-MS) Calculated for $[\text{C}_{10}\text{H}_{11}\text{BrO}_2\text{-OMe}]^+$: 210.9753, Found: 210.9752.

N-[6-(1-methoxyethyl)-1,3-benzothiazol-2-yl]acetamide, **27**.

Reaction run at 0.4 mmol scale and 40.3 mg (40%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 11.77 (s, 1H), 7.80 (d, $J = 1.7$ Hz, 2H), 7.74 (d, $J = 8.3$ Hz, 1H), 7.41 (dd, $J = 8.4$ Hz, $J = 1.7$ Hz, 1H), 4.43 (q, $J = 6.4$ Hz, 1H), 3.27 (s, 3H), 2.30 (s, 3H), 1.50 (d, $J = 6.4$ Hz, 3H) ppm.
 ^{13}C NMR (CDCl_3 , 100 MHz): 168.89, 159.91, 147.17, 139.91, 132.07, 124.80, 120.28, 119.22, 79.52, 56.59, 24.00, 23.57 ppm.

HRMS Calculated for $[\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_2\text{S+H}]^+$: 251.0849, Found: 251.0846

N-[6-(1-methoxyethyl)-1,3-benzothiazol-2-yl]acetamide, **28**.

Reaction run at 0.4 mmol scale and 72.9 mg (62%) of yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 4.88 (d, $J = 17.5$ Hz, 1H), 4.78 (d, $J = 17.5$ Hz, 1H), 4.43 (t, $J = 3.4$ Hz, 1H), 3.77 (s, 3H), 3.42 (s, 3H), 2.61 (ddd, $J = 16.3$ Hz, $J = 5.8$ Hz, $J = 3.0$ Hz, 1H), 2.46 (ddd, $J = 16.5$ Hz, $J = 10.7$ Hz, $J = 6.1$ Hz, 1H), 2.14 (ddd, $J = 14.1$ Hz, $J = 5.4$ Hz, $J = 2.8$ Hz, 1H), 2.00 (tdd, $J = 10.5$ Hz, $J = 8.1$ Hz, $J = 5.3$ Hz, 1H), 1.95-1.79 (m, 1H), 1.68-1.54 (m, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 167.3, 142.7, 140.0 (q, $J = 37.3$ Hz), 121.6 (q, $J = 269.4$ Hz), 116.2, 69.3, 56.5, 52.8, 50.5, 26.5, 21.0, 17.0 ppm.

^{19}F NMR (377 MHz, CDCl_3): -61.5 ppm.

HRMS Calculated for $[\text{C}_{12}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3\text{+H}]^+$: 293.1108, Found: 293.1102

methoxy(1-methyl-1H-indazol-3-yl)acetonitrile, **29**.

Reaction run at 0.4 mmol scale and 30.5 mg (38%) of orange to green liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.90 (d, $J = 8.2$ Hz, 1H), 7.43 (m, 2H), 7.24 (m, 1H), 5.63 (s, 1H), 4.08 (s,

3H), 3.57 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 141.3, 136.5, 127.1, 121.7, 121.3, 120.2, 116.2, 189.5, 66.6, 57.1, 35.8 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2+\text{H}]^+$: 202.0975, Found: 202.0975

{2-methoxy-1, 2-bis(4-methoxyphenyl) ethenone}, **30**. Characterization data matched those previously reported¹⁵.

Reaction run at 0.4 mmol scale and 66.6 mg (58%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.99 (d, $J = 8.96$ Hz, 2H), 7.38 (d, $J = 8.62$ Hz, 2H), 6.87 (d, $J = 2.85$ Hz, 2H), 6.85 (d, $J = 3.03$ Hz, 2H), 5.45 (s, 3H), 3.81 (s, 3H), 3.76 (s, 3H), 3.42 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 195.5, 163.5, 159.7, 131.3, 129.0, 128.5, 127.9, 114.3, 113.7, 85.8, 57.2, 55.4, 55.2 ppm.

HRMS Calculated for $[\text{C}_{17}\text{H}_{18}\text{O}_4+\text{Na}]^+$: 309.1097, Found: 309.1092.

(2*R*,3*R*,4*R*,5*S*,6*S*)-2-(acetoxymethyl)-6-(4-chloro-3-((4-ethoxyphenyl)(methoxy)methyl)phenyl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate, **31**.

Reaction run at 0.4 mmol scale and 233 mg (91%) of white solid was isolated. (a mixture of two diastereomers): d. r. = 1.1:1 (by ^1H NMR spectroscopy. Reported spectral values are of the mixture).

Major diastereomer: ^1H NMR (CDCl_3 , 400 MHz): 7.54 (d, $J = 2.1$ Hz, 1H, major diastereomer), 7.48 (d, $J = 2.1$ Hz, 1H, minor diastereomer), 7.34 (dd, $J = 10.1$, 1H, minor diastereomer), 7.32 (dd, $J = 10.1$, 1H, major diastereomer), 7.28 – 7.17 (m, 3H), 6.88 – 6.77 (m, 2H), 5.61 (s, 1H, minor diastereomer), 5.55 (s, 1H, major diastereomer), 5.32 (t, $J = 9.3$ Hz, 1H, minor diastereomer), 5.31 (t, $J = 9.3$ Hz, 1H, major diastereomer), 5.23 (t, $J = 9.7$, 1H), 5.11 (t, 9.6 Hz, 1H, major diastereomer), 5.06 (t, 9.6 Hz, 1H), 4.40 (d, $J = 9.8$ Hz, 1H), 4.27 (dd, $J = 12.4$, 4.9, 1H), 4.18 (dd, $J = 12.4$, 2.4 Hz, 1H), 4.00 (q, $J = 7.0$ Hz, 2H, major diastereomer), 3.98 (q, $J = 7.0$ Hz, 2H), 3.82 (ddd, $J = 9.9$, 4.8, 2.1 Hz, 1H), 3.37 (s, 3H, minor diastereomer), 3.32 (s, 3H, major diastereomer), 2.09 (s, 3H), 2.06 (s, 3H), 2.01 (s, 3H, minor diastereomer), 1.99 (s, 3H, major diastereomer), 1.87 (s, 3H, major diastereomer), 1.61 (s, 3H, minor diastereomer), 1.38 (t, $J = 7.0$, 3H).

^{13}C NMR (CDCl_3 , 100 MHz): 170.73, 170.36, 170.34, 169.51, 168.90, 168.81, 158.53, 158.47, 139.85, 139.61, 135.57, 135.37, 133.43, 133.20, 132.42, 131.94, 129.90, 129.79, 128.81, 128.33, 126.95, 126.79,

126.72, 126.68, 114.50, 114.30, 114.24, 80.81, 80.63, 79.43, 76.15, 76.11, 74.17, 74.14, 72.66, 72.56, 68.54, 63.40, 63.38, 62.29, 57.12, 56.74, 20.79, 20.67, 20.66, 20.43, 20.19, 14.84, 14.81.

HRMS Calculated for $[C_{30}H_{35}ClO_{11}+NH_4]^+$: 624.2206, Found: 624.2203.

Methyl 2-[4-(1-methoxy-2-methylpropyl)phenyl]propanoate, **32**.

Reaction run at 0.4 mmol scale and 33.5 mg (67%) of colorless liquid was isolated.

1H NMR ($CDCl_3$, 400 MHz): 7.26 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 3.73 (m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 1.89 (doublet of septets, J = 6.8 Hz, 1H), 1.50 (d, J = 7.2 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 175.1, 140.0, 139.4, 127.7, 127.1, 89.4, 57.0, 52.0, 45.1, 34.7, 19.0, 18.9, 18.6 ppm.

HRMS Calculated for $[C_{15}H_{22}O_3+NH_4]^+$: 268.1907, Found: 268.1904.

1-(6-tert-butyl-3-methoxy-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan-1-one, **33**.

Reaction run at 0.4 mmol scale and 84.1 mg (77%) of colorless liquid isolated.

1H NMR ($CDCl_3$, 400 MHz): 7.66 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 1.8 Hz, 1H), 5.21 (dd, J = 5.7, 3.1 Hz, 1H), 3.42 (s, 3H), 2.62 (s, 3H), 2.18 – 1.99 (m, 2H), 1.34 (s, 9H), 1.35 (s, 3H), 1.30 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 100 MHz): 200.77, 154.23, 152.59, 137.84, 135.24, 125.05, 123.18, 81.61, 57.16, 46.12, 42.63, 34.94, 31.42, 31.19, 29.77, 28.77 ppm.

HRMS Calculated for $[C_{17}H_{23}O_2-OCH_3]^+$: 243.1743, Found: 243.1740.

1-(6-tert-butyl-3-methoxy-1,1-dimethyl-2,3-dihydro-1H-inden-4-yl)ethan-1-one, **34**.

Reaction run at 0.4 mmol scale and 61.0 mg (65%) of white solid isolated.

1H NMR ($CDCl_3$, 400 MHz): 8.03 (s, 2H), 7.71-7.48 (m, 1H), 7.43-7.33 (m, 2H), 7.32-7.24 (m, 1H), 4.73

(q, $J = 6.6$ Hz, 1H), 3.99 (s, 3H), 3.29 (s, 3H), 1.63 (d, $J = 6.6$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 187.6, 162.5, 158.1, 154.0, 136.6, 133.8, 125.7, 125.67, 124.1, 121.3, 118.7, 117.6, 111.9, 71.3, 60.9, 57.0, 19.4 ppm.

HRMS Calculated for $[\text{C}_{19}\text{H}_{16}\text{Br}_2\text{O}_4+\text{H}]^+$: 466.9488, Found: 466.9484.

1-(4-chloro-3-nitrobenzene-1-sulfonyl)-4-methoxy-1,2,3,4-tetrahydroquinoline, **35**.

Reaction run at 0.4 mmol scale and 36.8 mg (48%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 8.02 (d, $J = 2.1$ Hz, 2H), 7.89 (d, $J = 8.3$ Hz, 2H), 7.65 (dd, $J = 8.5$ Hz, $J = 2.1$ Hz, 2H), 7.56 (d, $J = 8.5$ Hz, 2H), 7.36 (ddd, $J = 8.4$ Hz, $J = 5.6$ Hz, $J = 2.8$ Hz, 3H), 7.16 (m, 2H), 4.04 (t, $J = 6.8$ Hz, 1H), 3.96 (ddd, $J = 12.3$ Hz, $J = 5.9$ Hz, $J = 3.0$ Hz, 1H), 3.72 (td, $J = 12.3$ Hz, $J = 4.9$ Hz, 1H), 2.94 (s, 3H), 2.16 (m, 1H), 1.75 (dddd, $J = 14.0$ Hz, $J = 12.3$ Hz, $J = 5.9$ Hz, $J = 2.9$ Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 147.6, 138.1, 135.3, 132.3, 131.4, 131.2, 129.9, 129.6, 129.5, 125.2, 124.4, 124.3, 73.8, 55.7, 42.3, 27.9 ppm.

HRMS Calculated for $[\text{C}_{16}\text{H}_{15}\text{ClN}_2\text{O}_5\text{S}+\text{NH}_4]^+$: 400.0729, Found: 400.0721.

Ethyl-1-(4-fluorophenyl)-4-methoxy-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazole-3-carboxylate, **36a**.

Reaction run at 0.4 mmol scale and 97.7 mg (80%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.65 (dd, $J = 8.4$ Hz, $J = 4.3$ Hz, 2H), 7.14 (t, $J = 8.2$ Hz, 2H), 4.84 (d, $J = 5.7$ Hz, 1H), 4.43 (q, $J = 7.1$ Hz, 2H), 3.22 (m, 1H), 2.83 (m, 2H), 2.63 (m, 1H), 1.40 (t, $J = 7.0$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.1, 161.5 (d, $J = 247.4$ Hz), 152.2, 138.8, 135.7 (d, $J = 3.0$ Hz), 131.3, 122.3 (d, $J = 8.5$ Hz), 116.2 (d, $J = 23.1$ Hz), 76.1, 61.1, 56.6, 38.9, 24.6, 14.3 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.3 ppm.

HRMS Calculated for $[\text{C}_{16}\text{H}_{17}\text{FN}_2\text{O}_3+\text{H}]^+$: 305.1296, Found: 305.1290.

Ethyl-1-(4-fluorophenyl)-6-methoxy-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrazole-3-carboxylate, **36b**.

Reaction run at 0.4 mmol scale and 11.0 mg (9%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.84 (m, 2H), 7.14 (m, 2H), 4.95 (m, 1H), 4.41 (q, $J = 7.1$ Hz, 2H), 3.00 (m, 1H), 2.82 (m, 2H), 2.63 (m, 1H), 1.40 (t, $J = 7.1$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3, 161.6 (d, $J = 247.0$ Hz), 148.5, 138.0, 135.9 (d, $J = 3.0$ Hz), 134.7, 122.5 (d, $J = 8.4$ Hz), 116.1 (d, $J = 22.9$ Hz), 75.7, 61.0, 54.6, 36.9, 22.4, 14.4 ppm.

HRMS Calculated for $[\text{C}_{16}\text{H}_{17}\text{FN}_2\text{O}_3 + \text{H}]^+$: 305.1296, Found: 305.1291.

4-chloro-3-ethyl-N-[methoxy(4-tert-butylphenyl)methyl]-1-methyl-1H-pyrazole-5-carboxamide, **37**.

Reaction run at 0.2 mmol scale and 32.7 mg (45%) of white solid isolated.

^1H NMR (CDCl_3 , 500 MHz) δ 7.42 (s, 4H), 7.22 (d, $J = 9.0$ Hz, 1H), 6.28 (d, $J = 9.1$ Hz, 1H), 4.15 (s, 3H), 3.53 (s, 3H), 2.63 (q, $J = 7.6$ Hz, 2H), 1.32 (s, 9H), 1.23 (t, $J = 7.6$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz): 158.55, 151.86, 149.71, 135.66, 130.52, 125.75, 125.70, 125.62, 125.58, 108.16, 81.63, 56.21, 40.79, 34.65, 31.30, 19.23, 12.84 ppm.

HRMS Calculated for $[\text{C}_{19}\text{H}_{26}\text{ClN}_3\text{O}_2 + \text{H}]^+$: 364.1786, Found: 364.1782.

2-((5-bromo-2-methylphenyl)(2-chloroethoxy)methyl)-5-(4-fluorophenyl)thiophene, **38**.

Reaction run at 0.2 mmol scale and 75.6 mg (86%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.74 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, $J = 8.0, 2.2$ Hz, 1H), 7.07 – 6.99 (m, 4H), 6.77 (dd, $J = 3.8, 0.8$ Hz, 1H), 5.71 (s, 1H), 3.81 – 3.72 (m, 2H), 3.69 (td, $J = 5.8, 1.0$ Hz, 1H), 2.24 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.8$ Hz), 144.1, 143.2, 140.9, 134.5, 132.3, 131.0, 130.5 (d, $J = 3.4$ Hz), 129.3, 127.4 (d, $J = 8.0$ Hz), 127.1, 122.4 (d, $J = 1.2$ Hz), 120.2, 115.8 (d, $J = 21.7$ Hz), 76.9, 69.2, 42.8, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.3 ppm.

HRMS Calculated for $[\text{C}_{20}\text{H}_{18}\text{BrClFOS} + \text{Na}]^+$: 460.9748, Found: 460.9744.

2-((5-bromo-2-methylphenyl)(2-methoxyethoxy)methyl)-5-(4-fluorophenyl)thiophene, **39**.

Reaction run at 0.2 mmol scale and 62.7 mg (72%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.75 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.07 – 6.99 (m, 4H), 6.76 (dd, $J = 3.7, 0.8$ Hz, 1H), 5.72 (s, 1H), 3.73 – 3.59 (m, 4H), 3.40 (s, 3H), 2.24 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.7$ Hz), 143.8, 141.4, 134.5, 132.2, 130.8, 130.6 (d, $J = 3.4$ Hz), 129.3, 127.4 (d, $J = 8.0$ Hz), 127.0, 122.32, 122.30, 120.1, 115.8 (d, $J = 21.7$ Hz), 76.6, 72.1, 68.5, 59.1, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.6 ppm.

HRMS Calculated for $[\text{C}_{21}\text{H}_{20}\text{BrFNO}_2\text{S}+\text{Na}]^+$: 457.0244, Found: 457.0242.

tert-butyl(2-((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)ethyl)carbamate, **40**.

Reaction run at 0.2 mmol scale and 72.7 mg (70%) of yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.70 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.08 – 6.99 (m, 4H), 6.76 (dd, $J = 3.6, 0.8$ Hz, 1H), 5.63 (s, 1H), 5.03 – 4.83 (m, 1H), 3.60 (dt, $J = 9.5, 5.1$ Hz, 1H), 3.55 (dt, $J = 9.5, 4.9$ Hz, 1H), 3.40 (d, $J = 5.5$ Hz, 1H), 3.38 (d, $J = 5.5$ Hz, 1H), 2.24 (s, 3H), 1.43 (s, 9H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.8$ Hz), 156.0, 144.0, 143.6, 141.2, 134.4, 132.3, 130.9, 130.5 (d, $J = 3.4$ Hz), 129.0, 127.4 (d, $J = 8.0$ Hz), 127.0, 122.3 (d, $J = 1.2$ Hz), 120.1, 115.8 (d, $J = 21.6$ Hz), 79.4, 76.5, 68.5, 40.5, 28.4, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.4 ppm.

HRMS Calculated for $[\text{C}_{25}\text{H}_{27}\text{BrFNO}_3\text{S}+\text{Na}]^+$: 542.0771, Found: 542.0768.

2-((5-bromo-2-methylphenyl)(pent-3-yn-1-yloxy)methyl)-5-(4-fluorophenyl)thiophene, **41**.

Reaction run at 0.2 mmol scale and 45.2 mg (51%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.75 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, $J = 8.0, 2.2$ Hz, 1H), 7.07 – 6.99 (m, 4H), 6.73 (dd, $J = 3.6, 0.9$ Hz, 1H), 5.69 (s, 1H), 3.60 (qt, $J = 9.0, 6.9$ Hz, 1H), 2.50 (tq, J

= 7.2, 2.5 Hz, 1H), 2.24 (s, 3H), 1.79 (t, $J = 2.5$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.8$ Hz), 143.8, 143.8, 141.2, 134.5, 132.2, 130.8, 130.6 (d, $J = 3.3$ Hz), 129.3, 127.4 (d, $J = 8.0$ Hz), 126.9, 122.3 (d, $J = 1.2$ Hz), 120.1, 115.8 (d, $J = 21.7$ Hz), 77.0, 76.4, 75.7, 67.9, 20.3, 18.8, 3.6 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.5 ppm.

HRMS Calculated for $[\text{C}_{23}\text{H}_{20}\text{BrFOS}+\text{Na}]^+$: 465.0295, Found: 465.0294.

2-((5-bromo-2-methylphenyl)(2-((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethoxy)methyl)-5-(4-fluorophenyl)thiophene, **42**.

Reaction run at 0.2 mmol scale and 35.7 mg (34%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.73 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.34 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.07 – 6.99 (m, 4H), 6.71 (dd, $J = 3.6, 0.8$ Hz, 1H), 5.60 (d, $J = 2.0$ Hz, 1H), 5.27 (ddq, $J = 4.7, 3.2, 1.6$ Hz, 1H), 3.58 – 3.45 (m, 2H), 2.42 – 2.14 (m, 8H), 2.10 – 2.02 (m, 2H), 1.26 (d, $J = 3.7$ Hz, 3H), 1.17 (d, $J = 8.5$ Hz, 1H), 0.82 (d, $J = 1.5$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.5$ Hz), 144.9, 144.3, 143.6, 141.7, 134.4, 132.2, 130.7, 130.6 (d, $J = 3.4$ Hz), 129.3, 127.3 (d, $J = 8.0$ Hz), 126.6, 122.3, 120.1, 118.1, 115.8 (d, $J = 21.6$ Hz), 76.3, 67.9, 46.0, 40.8, 38.0, 37.2, 31.7, 31.4, 26.3, 21.2, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.6 ppm.

HRMS Calculated for $[\text{C}_{29}\text{H}_{30}\text{BrFOS}+\text{Na}]^+$: 547.1077, Found: 547.1071.

2-((5-bromo-2-methylphenyl)(2-(naphthalen-1-yl)ethoxy)methyl)-5-(4-fluorophenyl)thiophene, **43**.

Reaction run at 0.2 mmol scale and 95.7 mg (90%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 8.02 (d, $J = 8.6$ Hz, 1H), 7.84 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.75 – 7.70 (m, 2H), 7.53 – 7.43 (m, 4H), 7.43 – 7.36 (m, 2H), 7.32 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.08 – 6.95 (m, 4H), 6.67 (dd, $J = 3.7, 0.8$ Hz, 1H), 5.58 (s, 1H), 3.90 – 3.78 (m, 2H), 3.46 (t, $J = 7.3$ Hz, 2H), 2.14 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.7$ Hz), 144.0, 143.7, 141.5, 134.7, 134.4, 133.9, 132.2, 132.1, 130.8, 130.6 (d, $J = 3.4$ Hz), 129.2, 128.8, 127.4 (d, $J = 8.0$ Hz), 127.2, 127.1, 126.8, 126.1, 125.6 (d, $J = 1.5$ Hz), 123.8, 122.3, 122.3, 120.1, 115.8 (d, $J = 21.6$ Hz), 76.5, 69.5, 33.6, 18.7 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.4 ppm.

HRMS Calculated for $[\text{C}_{30}\text{H}_{24}\text{BrFOS}+\text{Na}]^+$: 553.0608, Found: 553.0606.

2-((3-(benzyloxy)propoxy)(5-bromo-2-methylphenyl)methyl)-5-(4-fluorophenyl)thiophene, **44**.

Reaction run at 0.2 mmol scale and 73.7 mg (70%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.71 (d, $J = 2.1$ Hz, 1H), 7.51 – 7.45 (m, 2H), 7.33 (dd, $J = 8.0, 2.2$ Hz, 1H), 7.32 – 7.22 (m, 5H), 7.06 – 6.99 (m, 4H), 6.70 (dd, $J = 3.7, 0.9$ Hz, 1H), 5.60 (s, 1H), 4.51 (d, $J = 11.8$ Hz, 1H), 4.49 (d, $J = 11.8$ Hz, 1H), 3.69 – 3.55 (m, 4H), 2.23 (s, 3H), 1.96 (p, $J = 6.2$ Hz, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.5$ Hz), 144.3, 143.6, 141.6, 138.5, 134.5, 132.2, 130.8, 130.6 (d, $J = 3.4$ Hz), 129.3, 128.4, 127.7, 127.6, 127.4 (d, $J = 8.0$ Hz), 126.7, 122.3 (d, $J = 1.2$ Hz), 120.1, 115.8 (d, $J = 21.6$ Hz), 76.5, 73.1, 67.2, 66.3, 30.2, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.5 ppm.

HRMS Calculated for $[\text{C}_{28}\text{H}_{26}\text{BrFO}_2\text{S}+\text{Na}]^+$: 547.0713, Found: 547.0709.

2-((5-bromo-2-methylphenyl)((4-chlorobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **45**.

Reaction run at 0.2 mmol scale and 90.3 mg (90%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.77 (d, $J = 2.2$ Hz, 1H), 7.54 – 7.46 (m, 2H), 7.39 – 7.27 (m, 5H), 7.07 – 6.99 (m, 4H), 6.72 (dd, $J = 3.8, 0.9$ Hz, 1H), 5.67 (s, 1H), 4.57 (d, $J = 12.1$ Hz, 1H), 4.51 (d, $J = 12.1$ Hz, 1H), 2.18 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.8$ Hz), 144.0, 143.7, 140.9, 136.2, 134.6, 133.6, 132.4, 131.0, 130.9, 130.5 (d, $J = 3.4$ Hz), 129.5, 129.4, 129.2, 128.7, 127.4 (d, $J = 8.0$ Hz), 127.0, 122.4 (d, $J = 1.2$ Hz), 120.2, 115.8 (d, $J = 21.7$ Hz), 75.2, 69.9, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.3 ppm.

HRMS Calculated for $[\text{C}_{25}\text{H}_{19}\text{BrClFOS}+\text{Na}]^+$: 522.9905, Found: 522.9899.

2-((5-bromo-2-methylphenyl)((4-methoxybenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **46**.

Reaction run at 0.2 mmol scale and 72.6 mg (73%) of yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.78 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.29 (d, $J = 8.6$ Hz, 2H), 7.07 – 6.98 (m, 4H), 6.69 (dd, $J = 3.6, 0.9$ Hz, 1H), 5.66 (s, 1H), 4.56 (d, $J = 11.6$ Hz, 1H), 4.46 (d, $J = 11.6$ Hz, 1H), 3.81 (s, 3H), 2.17 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.7$ Hz), 159.4, 144.1, 143.7, 141.2, 134.7, 132.3, 130.9, 130.6 (d, $J = 3.4$ Hz), 129.7, 129.6, 129.6, 127.4 (d, $J = 8.0$ Hz), 126.8, 122.3 (d, $J = 1.2$ Hz), 120.1, 115.8 (d, $J = 21.6$ Hz), 113.9, 74.5, 70.3, 55.3, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.5 ppm.

HRMS Calculated for $[\text{C}_{26}\text{H}_{22}\text{BrFO}_2\text{S}+\text{Na}]^+$: 519.0400, Found: 519.0397.

2-((5-bromo-2-methylphenyl)((4-nitrobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **47**.

Reaction run at 0.2 mmol scale and 81.9 mg (79%) of yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 8.23 (d, $J = 8.7$ Hz, 2H), 7.78 (d, $J = 2.2$ Hz, 1H), 7.55 (d, $J = 8.6$ Hz, 2H), 7.54 – 7.48 (m, 2H), 7.38 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.09 – 7.01 (m, 4H), 6.77 (dd, $J = 3.6, 0.9$ Hz, 1H), 5.73 (s, 1H), 4.69 (d, $J = 13.1$ Hz, 1H), 4.67 (d, $J = 13.1$ Hz, 1H), 2.21 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.7$ Hz), 147.5, 145.3, 144.2, 143.1, 140.6, 134.6, 132.5, 131.2, 130.4 (d, $J = 3.4$ Hz), 129.2, 127.9, 127.4 (d, $J = 8.0$ Hz), 127.2, 123.8, 122.4 (d, $J = 1.2$ Hz), 120.2, 115.9 (d, $J = 21.7$ Hz), 76.2, 69.6, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.1 ppm.

HRMS Calculated for $[\text{C}_{25}\text{H}_{19}\text{BrFNO}_3\text{S}+\text{Na}]^+$: 534.0145, Found: 534.0144.

2-((5-bromo-2-methylphenyl)((2-bromobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **48**.

Reaction run at 0.2 mmol scale and 89.6 mg (82%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.81 (d, $J = 2.2$ Hz, 1H), 7.59 – 7.46 (m, 4H), 7.39 – 7.31 (m, 2H), 7.16 (td, $J = 7.7, 1.7$ Hz, 1H), 7.06 – 6.99 (m, 4H), 6.75 (dd, $J = 3.8, 0.9$ Hz, 1H), 5.76 (s, 1H), 4.642 (d, $J = 13.3$ Hz, 1H), 4.639 (d, $J = 13.3$ Hz, 1H), 2.22 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.8$ Hz), 144.0, 143.7, 141.0, 137.1, 134.7, 132.6, 132.4, 131.0, 130.6 (d, $J = 3.4$ Hz), 129.5, 129.4, 129.2, 127.6, 127.4 (d, $J = 8.0$ Hz), 127.0, 122.9, 122.4 (d, $J = 1.2$ Hz), 120.2, 115.8 (d, $J = 21.6$ Hz), 76.1, 70.4, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.4 ppm.

HRMS Calculated for $[\text{C}_{25}\text{H}_{19}\text{Br}_2\text{FOS}+\text{Na}]^+$: 566.9400, Found: 566.9396.

2-((5-bromo-2-methylphenyl)((3-bromobenzyl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **49**.

Reaction run at 0.2 mmol scale and 99.4 mg (91%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.77 (d, $J = 2.2$ Hz, 1H), 7.54 – 7.48 (m, 3H), 7.44 (dt, $J = 7.9, 1.6$ Hz, 1H), 7.36 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.30 (dt, $J = 7.7, 1.4$ Hz, 1H), 7.24 (t, $J = 7.7$ Hz, 1H), 7.08 – 7.00 (m, 4H), 6.73 (dd, $J = 3.7, 0.9$ Hz, 1H), 5.68 (s, 1H), 4.57 (d, $J = 12.2$ Hz, 1H), 4.51 (d, $J = 12.2$ Hz, 1H), 2.19 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.4 (d, $J = 245.9$ Hz), 144.0, 143.5, 140.8, 140.0, 134.6, 132.4, 131.0, 130.9, 130.8, 130.5 (d, $J = 3.4$ Hz), 130.1, 129.4, 127.4 (d, $J = 8.0$ Hz), 127.0, 126.3, 122.6, 122.4 (d, $J = 1.2$ Hz), 120.2, 115.8 (d, $J = 21.7$ Hz), 75.5, 69.9, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.4 ppm.

HRMS Calculated for $[\text{C}_{25}\text{H}_{19}\text{Br}_2\text{FNOS}+\text{Na}]^+$: 566.9400, Found: 566.9399.

(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)trimethylsilane, **50**.

Reaction run at 0.2 mmol scale and 76.9 mg (83%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.63 (d, $J = 2.1$ Hz, 1H), 7.55 – 7.48 (m, 2H), 7.34 (dd, $J = 8.1$, 2.2 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.66 (dd, $J = 3.6$, 1.0 Hz, 1H), 5.45 (s, 1H), 3.17 (d, $J = 12.4$ Hz, 1H), 3.10 (d, $J = 12.4$ Hz, 1H), 2.24 (s, 3H), 0.10 (s, 9H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.2 (d, $J = 245.5$ Hz), 144.8, 143.4, 141.7, 134.9, 132.2, 130.7 (d, $J = 3.3$ Hz), 130.6, 129.7, 127.4 (d, $J = 8.0$ Hz), 126.3, 122.2 (d, $J = 1.2$ Hz), 119.9, 115.7 (d, $J = 21.6$ Hz), 80.4, 63.0, 18.7, -3.0 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.7 ppm.

HRMS Calculated for $[\text{C}_{22}\text{H}_{24}\text{BrFOSSi}+\text{Na}]^+$: 485.0377, Found: 485.0377.

2-((5-bromo-2-methylphenyl)(cyclopropylmethoxy)methyl)-5-(4-fluorophenyl)thiophene, **51**.

Reaction run at 0.2 mmol scale and 75.1 mg (87%) of colorless liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.76 (d, $J = 2.2$ Hz, 1H), 7.55 – 7.48 (m, 2H), 7.35 (dd, $J = 8.1$, 2.2 Hz, 1H), 7.08 – 7.00 (m, 4H), 6.74 (dd, $J = 3.7$, 0.8 Hz, 1H), 5.71 (s, 1H), 3.42 (dd, $J = 10.1$, 6.8 Hz, 1H), 3.34 (dd, $J = 10.1$, 6.9 Hz, 1H), 2.27 (s, 3H), 1.15 (dddd, $J = 13.2$, 6.8, 5.0, 2.6 Hz, 1H), 0.65 – 0.51 (m, 2H), 0.30 – 0.17 (m, 2H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 245.6$ Hz), 144.2, 143.6, 141.5, 134.6, 132.2, 130.7, 130.6 (d, $J = 3.3$ Hz), 129.4, 127.4 (d, $J = 8.0$ Hz), 126.7, 122.3 (d, $J = 1.2$ Hz), 120.1, 115.8 (d, $J = 21.6$ Hz), 75.7, 73.9, 18.8, 10.7, 3.25, 3.24 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.6 ppm.

HRMS Calculated for $[\text{C}_{22}\text{H}_{20}\text{BrFOS}+\text{Na}]^+$: 453.0295, Found: 453.0288.

tert-butyl 3-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)azetidine-1-carboxylate, **52**.

Reaction run at 0.2 mmol scale and 78.7 mg (72%) of yellow liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.67 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.36 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 – 7.01 (m, 4H), 6.73 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.62 (s, 1H), 4.02 (td, *J* = 8.5, 2.1 Hz, 2H), 3.75 – 3.58 (m, 4H), 2.89 – 2.77 (m, 1H), 2.24 (s, 3H), 1.43 (s, 9H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 162.3 (d, *J* = 197.0 Hz), 156.4, 143.9, 143.6, 141.1, 134.5, 132.3, 132.2, 130.4 (d, *J* = 3.0 Hz), 129.2, 127.4 (d, *J* = 12.0 Hz), 126.8, 122.3 (d, *J* = 2.0 Hz), 120.1, 115.8 (d, *J* = 17.0 Hz), 79.4, 77.2, 76.9, 71.2, 64.6, 64.8, 28.4, 18.8 ppm.

¹⁹F NMR (377 MHz, CDCl₃): -114.4 ppm.

HRMS Calculated for [C₂₇H₂₉BrFO₃S+Na]⁺: 568.0928, Found: 568.0921.

tert-butyl 3-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)azetidine-1-carboxylate, **53**.

Reaction run at 0.2 mmol scale and 91.6 mg (86%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.76 (d, *J* = 2.1 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.36 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 – 7.00 (m, 4H), 6.78 (dd, *J* = 3.7, 0.8 Hz, 1H), 5.59 (s, 1H), 4.37 (tt, *J* = 6.6, 4.5 Hz, 1H), 4.04 (dddd, *J* = 14.3, 9.4, 6.6, 1.0 Hz, 2H), 3.92 (ddd, *J* = 14.3, 9.3, 4.6 Hz, 2H), 2.20 (s, 3H), 1.43 (s, 9H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 162.4 (d, *J* = 246.1 Hz), 156.3, 144.5, 142.8, 140.7, 134.2, 132.3, 131.1, 130.3 (d, *J* = 3.5 Hz), 129.1, 127.4 (d, *J* = 8.0 Hz), 127.3, 122.4 (d, *J* = 1.2 Hz), 120.1, 115.9 (d, *J* = 21.7 Hz), 79.7, 75.0, 66.4, 57.2 – 56.3 (m), 28.4, 18.8 ppm.

¹⁹F NMR (377 MHz, CDCl₃): -114.2 ppm.

HRMS Calculated for [C₂₆H₂₇BrFO₃S+Na]⁺: 554.0771, Found: 554.0767.

3-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)oxetane, **54**.

Reaction run at 0.2 mmol scale and 39.9 mg (46%) of colorless liquid isolated.

¹H NMR (CDCl₃, 400 MHz): 7.78 (d, *J* = 2.1 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.36 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.08 – 6.99 (m, 4H), 6.77 (dd, *J* = 3.6, 0.8 Hz, 1H), 5.58 (s, 1H), 4.76 – 4.62 (m, 5H), 2.20 (s, 3H) ppm.

¹³C NMR (CDCl₃, 100 MHz): 162.4 (d, *J* = 246.2 Hz), 144.4, 143.0, 140.8, 134.1, 132.3, 131.1, 130.3 (d, *J* = 3.4 Hz), 129.1, 127.4 (d, *J* = 8.0 Hz), 127.3, 122.4 (d, *J* = 1.2 Hz), 120.1, 115.9 (d, *J* = 21.8 Hz), 79.1,

75.3, 71.2, 18.8 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.1 ppm.

HRMS Calculated for $[\text{C}_{21}\text{H}_{18}\text{BrFO}_2\text{S}+\text{Na}]^+$: 455.0087, Found: 455.0083.

2-(((3*S*,5*S*,7*S*)-adamantan-1-yl)oxy)(5-bromo-2-methylphenyl)methyl)-5-(4-fluorophenyl)thiophene, **55**.

Reaction run at 0.2 mmol scale and 75.7 mg (74%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.83 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.32 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.07 – 6.98 (m, 3H), 6.95 (d, $J = 3.6$ Hz, 1H), 6.42 (dd, $J = 3.7, 1.0$ Hz, 1H), 5.96 (s, 1H), 2.27 (s, 3H), 2.14 (q, $J = 3.2$ Hz, 3H), 1.83 (d, $J = 11.3$ Hz, 3H), 1.76 (d, $J = 11.3$ Hz, 3H), 1.63 (d, $J = 13.9$ Hz, 3H), 1.60 (d, $J = 13.9$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.2 (d, $J = 245.4$ Hz), 147.3, 144.5, 143.1, 133.2, 131.9, 130.4 (d, $J = 3.4$ Hz), 130.3, 130.2, 127.3 (d, $J = 8.0$ Hz), 125.8, 122.4 (d, $J = 0.9$ Hz), 119.8, 115.7 (d, $J = 21.6$ Hz), 75.0, 66.8, 42.6, 36.3, 30.7, 18.9 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.9 ppm.

HRMS Calculated for $[\text{C}_{28}\text{H}_{28}\text{BrFNOS}+\text{Na}]^+$: 533.0921, Found: 533.0916.

2-((*S*)-(5-bromo-2-methylphenyl)(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **56a**.

Reaction run at 0.2 mmol scale and 49.3 mg (48%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.69 (d, $J = 2.2$ Hz, 1H), 7.55 – 7.47 (m, 2H), 7.35 (dd, $J = 8.0, 2.2$ Hz, 1H), 7.08 – 7.01 (m, 3H), 6.99 (d, $J = 3.6$ Hz, 1H), 6.50 (dd, $J = 3.7, 1.1$ Hz, 1H), 5.62 (d, $J = 1.1$ Hz, 1H), 3.64 (ddd, $J = 9.1, 3.3, 1.8$ Hz, 1H), 2.29 – 2.20 (m, 4H), 2.17 – 2.07 (m, 1H), 1.78 (tq, $J = 11.8, 4.1$ Hz, 1H), 1.70 (t, $J = 4.6$ Hz, 1H), 1.38 (ddd, $J = 11.9, 9.4, 4.4$ Hz, 1H), 1.34 – 1.25 (m, 1H), 1.22 (dd, $J = 12.8, 3.2$ Hz, 1H), 0.86 (s, 3H), 0.85 (s, 3H), 0.76 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.2 (d, $J = 245.3$ Hz), 146.2, 143.1, 141.5, 134.9, 132.2, 130.8 (d, $J = 3.4$ Hz), 130.7, 130.2, 127.4 (d, $J = 7.9$ Hz), 125.5, 122.3 (d, $J = 1.2$ Hz), 119.9, 115.7 (d, $J = 21.7$ Hz), 82.5, 74.6, 49.4, 47.9, 45.2, 36.0, 28.3, 26.9, 19.8, 19.0, 18.8, 13.7 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.8 ppm.

HRMS Calculated for $[\text{C}_{28}\text{H}_{30}\text{BrFNOS}+\text{Na}]^+$: 535.1077, Found: 535.1081.

2-((*R*)-(5-bromo-2-methylphenyl)(((1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **56b**.

Reaction run at 0.2 mmol scale and 38.0 mg (37%) of white solid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.76 (d, $J = 2.2$ Hz, 1H), 7.54 – 7.48 (m, 2H), 7.33 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.07 – 6.98 (m, 4H), 6.64 (dd, $J = 3.7, 0.9$ Hz, 1H), 5.61 (s, 1H), 3.79 (ddd, $J = 9.5, 3.5, 1.8$ Hz, 1H), 2.23 (s, 3H), 2.22 – 2.16 (m, 1H), 2.02 (ddd, $J = 13.1, 9.3, 4.1$ Hz, 1H), 1.71 (tt, $J = 12.2, 4.1$ Hz, 1H), 1.61 (t, $J = 4.6$ Hz, 1H), 1.36 – 1.19 (m, 1H), 1.03 (dd, $J = 13.1, 3.4$ Hz, 1H), 0.95 (s, 3H), 0.85 (s, 3H), 0.79 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 162.3 (d, $J = 196.5$ Hz), 145.2, 143.4, 142.8, 134.2, 132.1, 130.7 (d, $J = 2.7$ Hz), 130.5, 129.8, 127.3 (d, $J = 6.4$ Hz), 126.2 (d, $J = 1.4$ Hz), 122.1 (d, $J = 2.4$ Hz), 119.8, 115.7 (d, $J = 17.3$ Hz), 83.6, 76.0, 49.7, 47.7, 45.1, 35.9, 28.2, 27.1, 19.8, 19.0, 18.9, 14.1 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.8 ppm.

HRMS Calculated for $[\text{C}_{28}\text{H}_{30}\text{BrFNOS} + \text{Na}]^+$: 535.1077, Found: 535.1077.

2-((5-bromo-2-methylphenyl)(((3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)methyl)-5-(4-fluorophenyl)thiophene, **57**.

Reaction run at 0.2 mmol scale and 58.2 mg (39%) of pale yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.77 (d, $J = 2.2$ Hz, 1H), 7.53 – 7.46 (m, 2H), 7.33 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.07 – 6.98 (m, 4H), 6.66 (dd, $J = 4.6, 0.8$ Hz, 1H), 5.81 (s, 1H), 5.33 (dd, $J = 12.1, 5.0$ Hz, 1H), 3.31 (td, $J = 10.2, 5.0$ Hz, 1H), 2.50 – 2.30 (m, 2H), 2.25 (s, 3H), 2.05 – 1.75 (m, 4H), 1.70 – 0.93 (m, 22H), 1.02 (s, 3H), 0.91 (d, $J = 6.5$ Hz, 3H), 0.862 (d, $J = 6.6$ Hz, 3H), 0.857 (d, $J = 6.6$ Hz, 3H), 0.67 (s, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 163.3 (d, $J = 245.4$ Hz), 145.0, 143.5, 142.2, 140.7, 134.3, 132.2, 130.6 (d, $J = 3.2$ Hz), 129.6, 127.4 (d, $J = 7.9$ Hz), 126.4, 122.3, 121.88, 121.86, 120.1, 115.7 (d, $J = 21.6$ Hz), 73.1, 56.8, 56.1, 50.2, 42.3, 39.8, 39.5, 39.4, 39.2, 37.2, 36.9, 36.2, 35.8, 31.9, 28.8, 28.5, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.1, 19.4, 18.9, 18.7, 11.9 ppm.

^{19}F NMR (377 MHz, CDCl_3): -114.6 ppm.

HRMS Calculated for $[\text{C}_{45}\text{H}_{58}\text{BrFOS-OC}_{27}\text{H}_{45}]^+$ (ASAP-MS): 358.9900, Found: 358.9895.

N-(5-(((5-bromo-2-methylphenyl)(5-(4-fluorophenyl)thiophen-2-yl)methoxy)methyl)-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl)-*N*-methylmethanesulfonamide, **58**.

Reaction run at 0.2 mmol scale and 133 mg (93%) of pale yellow liquid isolated.

^1H NMR (CDCl_3 , 400 MHz): 7.83 (d, $J = 2.1$ Hz, 1H), 7.77 – 7.70 (m, 2H), 7.54 – 7.47 (m, 2H), 7.39 (dd, $J = 8.1, 2.2$ Hz, 1H), 7.11 – 7.02 (m, 6H), 6.74 (dd, $J = 3.6, 0.8$ Hz, 1H), 5.68 (s, 1H), 4.46 (d, $J = 10.2$ Hz, 1H), 4.41 (d, $J = 10.2$ Hz, 1H), 3.58 (s, 3H), 3.51 (s, 3H), 3.34 (sept., $J = 6.6$ Hz, 1H), 2.22 (s, 3H), 1.34 (d, $J = 6.6$ Hz, 3H), 1.31 (d, $J = 6.6$ Hz, 3H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 178.3, 166.6, 163.7 (d, $J = 248.4$ Hz), 162.5 (d, $J = 246.1$ Hz), 158.2, 144.3, 143.1, 140.8, 134.3, 134.0 (d, $J = 3.2$ Hz), 132.4, 131.4 (d, $J = 8.4$ Hz), 131.2, 130.3 (d, $J = 3.4$ Hz), 129.2, 127.44 (d, $J = 8.0$ Hz), 127.37, 122.5 (d, $J = 1.2$ Hz), 120.1, 118.3, 115.9 (d, $J = 21.7$ Hz), 115.4 (d, $J = 21.5$ Hz), 76.6, 64.6, 42.4, 33.1, 31.7, 22.4, 22.2, 18.9 ppm.

^{19}F NMR (377 MHz, CDCl_3): -111.1, -114.0 ppm.

HRMS Calculated for $[\text{C}_{34}\text{H}_{32}\text{BrF}_2\text{O}_3\text{S}_2+\text{Na}]^+$: 712.1109, Found: 712.1112.

N-(6-ethyl-1,3-benzothiazol-2-yl)acetamide, **59**.

Reaction run at 2.5 mmol scale and 473 mg (86%) of off white solid was isolated.

^1H NMR (CDCl_3 , 400 MHz): 10.01 (s, 1H), 7.69 (m, 2H), 7.31 (m, 1H), 2.80 (q, $J = 7.5$ Hz, 2H), 2.32 (s, 3H), 1.32 (t, 3H) ppm.

^{13}C NMR (CDCl_3 , 126 MHz): 168.8, 159.4, 145.7, 140.6, 132.0, 126.8, 120.3, 120.0, 28.9, 23.5, 15.9 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{12}\text{N}_2\text{OS}+\text{H}]^+$: 221.0743, Found: 221.0737.

methyl [3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl]acetate, **60**.

Reaction run at 2.0 mmol scale and 347 mg (66%) of white solid was isolated.

^1H NMR (CDCl_3 , 400 MHz): 4.82 (s, 2H), 3.76 (s, 3H), 2.56 (m, 4H), 1.80 (m, 4H) ppm.

^{13}C NMR (CDCl_3 , 100 MHz): 167.6, 141.3, 139.2 (q, $J = 36.7$ Hz), 121.9 (q, $J = 269.1$ Hz), 115.5 (q, $J = 1.5$ Hz), 52.7, 50.5, 22.2, 22.0, 21.1, 19.9 ppm.

^{19}F NMR (377 MHz, CDCl_3): -61.7 ppm.

HRMS Calculated for $[\text{C}_{11}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_2 + \text{H}]^+$: 263.1002, Found: 263.0999.

(3,5-dibromo-4-methoxyphenyl)(2-ethyl-1-benzofuran-3-yl)methanone, **61**.

Reaction run at 4.0 mmol scale and 1.67 g (95%) of white solid was isolated.

^1H NMR (CDCl_3 , 400 MHz): 8.01 (s, 2H), 7.53 (dt, $J = 8.2$ Hz, $J = 0.9$ Hz, 1H), 7.44 (dt, $J = 7.6$ Hz, $J = 0.9$ Hz, 1H), 7.34 (ddd, $J = 8.3$ Hz, $J = 7.3$ Hz, $J = 1.5$ Hz, 1H), 7.27 (td, $J = 7.5$ Hz, $J = 1.1$ Hz, 1H), 4.01 (s, 3H), 2.92 (q, $J = 7.5$ Hz, 2H), 1.38 (t, $J = 7.5$ Hz, 3H)

^{13}C NMR (CDCl_3 , 100 MHz): 188.1, 166.9, 157.7, 153.7, 137.2, 133.6, 126.4, 124.7, 123.9, 121.0, 118.5, 115.3, 111.2, 60.9, 22.1, 12.2.

HRMS Calculated for $[\text{C}_{19}\text{H}_{16}\text{Br}_2\text{O}_4 + \text{H}]^+$: 436.9383, Found: 436.9380.

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VI. NMR spectral Data

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