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Suzuki–Miyaura Cross-Coupling of Potassium Alkoxyethyltrifluoroborates: Access to Aryl/Heteroarylethyloxy Motifs

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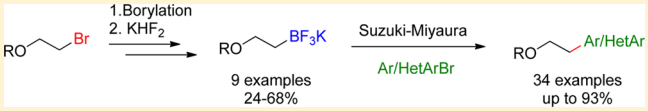
Supporting Information

ABSTRACT: The introduction of an alkoxyethyl moiety onto aromatic substructures has remained a long-standing challenge for synthetic organic chemists. The main reasons are the inherent instability of alkoxyethylmetallic species and the lack of general procedures to access them. A new method utilizing a cross-coupling strategy based on the exceptional properties of organotrifluoroborates has been developed, and the method allows an easy and efficient installation of this unit on a broad range of aryl and heteroaryl bromides.



INTRODUCTION

The Suzuki–Miyaura reaction has become a predominant asset in the toolbox of chemical transformations regularly employed by organic chemists.[1] Among the metal-catalyzed carbon–carbon bond forming reactions, this cross-coupling reaction between a boron species and an electrophile has gained dramatic interest owing to its robustness, versatility, and the relative lack of toxicity of its generated byproducts.

Our research group has devoted its efforts toward the development of organotrifluoroborates as new and efficient boron coupling partners.[2] Their tetracoordinate nature confers increased stability upon them, and when placed in specific reaction conditions, they slowly release *in situ* the reactive boron species that can undergo the desired cross-coupling reaction.[3] These unique features make them highly useful, functional group tolerant, bench-stable reagents that perform very well in the Suzuki–Miyaura reaction. Based on these properties, it has been possible to synthesize and cross-couple a large array of functionalized methyltrifluoroborates such as alkoxymethyl-, aminomethyl-, amidomethyl-, and carbamatomethyltrifluoroborates, providing new and useful methods to access those motifs.[2e,4]

To complement those useful synthons, our attention had been drawn to the development of alkoxyethyltrifluoroborates as an unprecedented way to synthesize alkoxyethylarenes. The current common methods to introduce the alkoxyethyl moiety are limited to reaction sequences such as the addition of an organometallic reagent to ethylene oxide or 2-haloethers, or hydroboration/oxidation/alkylation of a styrene derivative. Aside from requiring several steps, these routes suffer from harsh reaction conditions, low yields, and sensitivity/toxicity as well as poor availability of the reagents, all of which greatly limit their general application. A cross-coupling strategy would dramatically improve this situation and make the introduction of the alkoxyethyl group a very simple and straightforward process.

However, this concept is ultimately based on the ability to synthesize alkoxyethylboron coupling partners, several potential routes to which are depicted in Scheme 1. In general, these routes are fraught with challenges. Indeed, it is well documented that halogenoethylboron compounds are unstable.[5] For instance, β-bromoethylboronate species experience facile deboronobromination in the presence of weak nucleophiles such as potassium cyanate, aniline, pyridine, or even water.[5b] The mechanism of the decomposition, yielding ethylene and boron byproducts, transpires through a concerted *anti* elimination pathway that can be triggered by a Lewis base.[6] On the other hand, the hydroboration of vinyl ethers, the products of which are a bit more stable depending on the steric hindrance on the boron atom,[7] is not a suitable route either, as the intermediates are prone to transfer and elimination reactions.[8] Elimination can proceed through a *syn* or an *anti* mechanism depending on the presence or absence of a Lewis acid. Another synthetic pathway would employ the use of an alkoxyethylorganometallic species (such as organomagnesium or organolithium species) reacting with a borate, but unfortunately, such organometallic species are not stable and tend to decompose rapidly.[9]

RESULTS AND DISCUSSION

Given that the desired alkoxyethylboron compounds were not easily accessible, their use as reagents remained on hold until the development of metal-catalyzed borylation reactions. In

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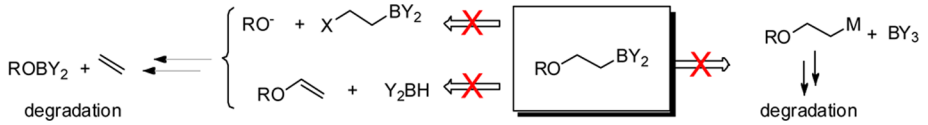
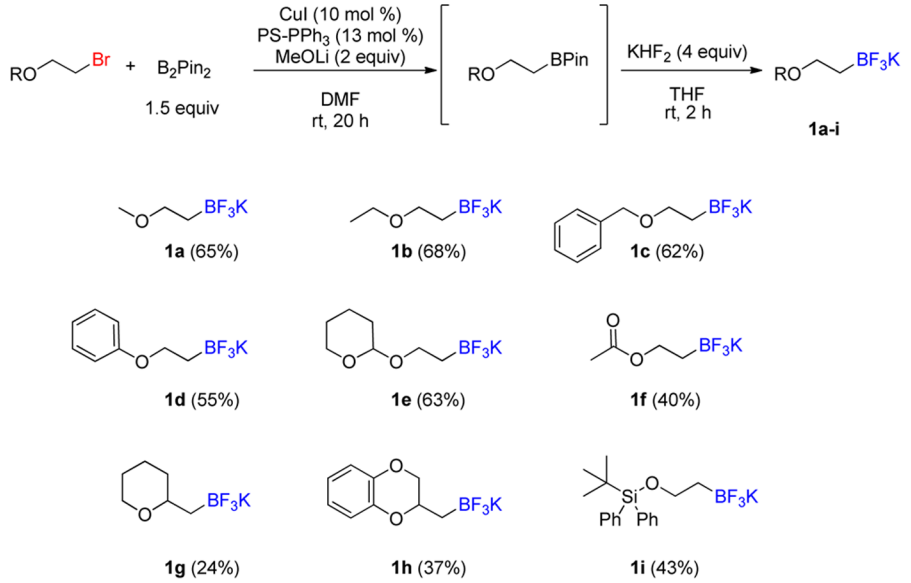
Scheme 1. Potential Synthetic Routes to Alkoxyethylboron Species



Scheme 2. Synthesis of Alkoxyethyltrifluoroborates *via* a Copper Catalyzed Borylation Procedure



2004, Hartwig reported the synthesis of an alkoxyethyl pinacolboronate *via* a Rh-catalyzed borylation of an ethyl ether with bis(pinacolato)diborane followed by its subsequent cross-coupling with an aryl bromide or hydrolysis of the boronate to a trifluoroborate.[10] Unfortunately, besides being run on a very small scale (0.14 mmol in NMR tubes) without isolation of the products (GC and NMR yields), the reaction conditions, which require a 10-fold excess of ethyl ether and heating the reaction mixture at 150 °C for 24 h, were not suitable for a large variety of substrates.

More recently, and in a very short time period, the borylation of nonactivated alkyl halides has attracted much interest in the chemical community.[11] Several research groups have developed reactions with mild conditions (rt to 60 °C) based on copper, nickel, or palladium catalysis. Although they all possess wide functional group tolerability, only two examples of alkoxyethylboron derivatives have been reported *via* one of these methods.[11a−c] Our attention was focused on the method developed by Marder and Liu, as it relies on the use of inexpensive PPh_3 and copper(I).[11a] A few modifications of the reaction conditions allowed us to synthesize various alkoxyethyltrifluoroborates. In particular, the use of polystyrene-supported triphenylphosphine (PS-PPh_3) as mentioned in the original report improved both the efficiency and the yield of the process, as various alkoxyethyltrifluoroborates could be prepared by the addition of KHF_2 to the reaction mixture after the borylation step, avoiding contamination by triphenylphosphine oxide.[12] The different alkoxyethyltrifluoroborates prepared in this manner are summarized in Scheme 2.

The desired alkoxyethyltrifluoroborates were obtained with moderate to good yields (24−68%), and are all white powders that showed no sign of decomposition after several months of being stored on the bench with no particular precautions. The borylation procedure tolerates a wide variety of functional groups on the oxygen such as alkyl, benzyl, or aryl substituents (yields of **1a−d** ranging from 55 to 68%). However, more sensitive substrates provided lower yields, as illustrated by the acetoxyethyltrifluoroborate **1f** and the silyl ether derivative **1i**, which were obtained in 40 and 43% yields, respectively. Cyclic secondary alkoxyethyl bromides did not react as well, and the corresponding trifluoroborates (**1g**, **1h**) were isolated in slightly lower yields. Attempts at using the Ni-based procedure reported by Fu et al.,[11d] which was developed for unactivated tertiary halides, did not provide better results. It is interesting to note that bromoethyl ethers bearing various easily removable protecting groups, such as benzyl, acetate, THP, or TBDPS could be utilized, and thus would easily provide access to a free hydroxyl group for further functionalization after the Suzuki−Miyaura coupling step.[13]

Direct conversion of the boronate esters to the corresponding potassium trifluoroborates helped to solve some stability issues of the alkoxyethylboron derivatives.[14] Even if the alkoxyethylpinacolatoborons are more stable than their boronic acid counterparts, they still remain sensitive and prone to decomposition. The benzyloxyethyltrifluoroborate **1c** could be recrystallized, and its X-ray structure was elucidated (Figure 1). Notably, the potassium cation can be seen bridging the oxygen and one of the fluorine atoms, rigidifying the structure of the molecule. A comparative study on the rate of degradation of an alkoxyethyltrifluoroborate has been conducted. It showed that, in the presence of 18-crown-6, the trifluoroborate degrades faster, suggesting an important role of the potassium ion in stabilizing the complexes.[15]

Extensive screening using High Throughput Experimentation (HTE) techniques allowed us to define efficient conditions to perform the Suzuki−Miyaura cross-coupling of the benzyloxyethyltrifluoroborate **1c** and various aryl bromides (Table 1). The best catalytic system was found to be $PdCl_2A^{ta}Phos_2$ in the

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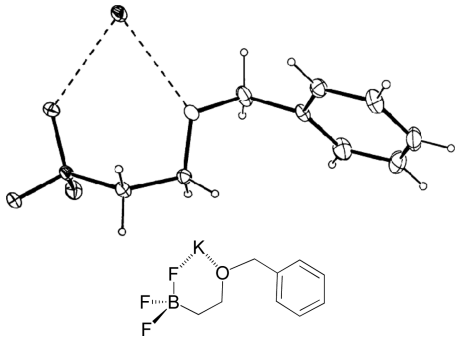

Figure 1. X-ray structure of potassium benzyloxyethyltrifluoroborate **1c**.

presence of cesium carbonate in toluene/water at 100 °C. This di-*tert*-butyl(4-dimethylamino)phenylphosphine was developed in 2006 by Guram et al.[16] and showed very interesting results in Suzuki–Miyaura cross-coupling reactions, especially when used as the air stable $PdCl_2L_2$ complex.[15,17] The steric and electronic properties of this ligand seem to help reduce β-hydride elimination when compared to P(*t*-Bu)$_3$,[18] and the ligand has been shown to provide very good results in the cross-coupling of alkyl α-cyanohydrin triflates with arylboronic acids.[16c]

As shown in Table 1, the substrate scope of the reaction between benzyloxyethyltrifluoroborate **1c** and aryl bromides is very broad. The reaction conditions seem to be extremely general, as they allow both electron-rich (entries 1–8) and electron-poor (entries 9–17, 19) bromides to be coupled with very good results. Electron-donating groups are tolerated on all positions of the aryl bromide, as illustrated by the *ortho*-, *meta*-, and *para*-bromoanisoles, affording the desired benzyloxyethylanisole derivatives with yields ranging from 82 to 93% (entries 1–3). Electron-withdrawing substituents at the *para* position seem to provide better results than at the *ortho* position (entries 9, 10 and 12, 13). Steric hindrance might not be the factor responsible for this observed trend, as other mono- or disubstituted electrophiles (entries 5, 6) cross-coupled efficiently with excellent yields (93 and 82%, respectively). The conditions are applicable to a large variety of functional groups such as aldehydes (entry 14), ketones (entry 15), esters (entry 16), nitriles (entries 12–13), nitro (entry 17), and even amides and sulfonamides (entries 18–19).

The robustness of the method was tested by performing the reaction on a larger scale (3 mmol of electrophile, entries 9 and 18). When using *ortho*-tolyl bromide, the cross-coupling product was obtained with an excellent 93% isolated yield, even after reducing the catalyst loading to 2.5 mol %. *para*-Acetamidobenzyl bromide was also tested on a larger scale and provided the expected cross-coupled product **2r** in a slightly lower yield (78%) after recrystallization (hexanes/ethyl acetate) when using only 1 mol % palladium and a 1:1 trifluoroborate/electrophile ratio. The reaction conditions were also tested with several aryl chlorides with less success. Electron-rich chlorides such as *para*-chloroanisole failed to react efficiently (30% conversion, entry 1), whereas electron-poor substrates cross-coupled smoothly, providing the desired benzyloxyethylbenzene derivatives with moderate to excellent yields (entries 12, 14).

The scope of the method was then further extended to heteroaryl bromides using the same set of optimized conditions. They proved to be effective, resulting in yields up to 89% for a wide array of heteroaryls. 3-Bromopyridines with or without substituents afforded the desired products in moderate to good yields (Table 2, entries 1–2). Quinoline and isoquinoline also responded well to the reaction conditions, coupling with yields up to 83% (entries 4–5). Indole-based electrophiles were also reactive; however, better yields were obtained when the nitrogen was protected (89% vs 55%, entries 6, 7). Pyrimidine, which is a particularly difficult substrate, was cross-coupled efficiently to give the corresponding product **3h** in 69% yield. Five-membered heterocycles were also tolerated; 3-bromothiophene gave the expected product **3i** in 88% yield (entry 9). 2-Halopyridines were also engaged in the reaction and could be cross-coupled, albeit in a much lower yield (entry 3). Interestingly, the chloropyridine reacted better than its bromo-counterpart owing to its lower tendency to undergo homocoupling.

The versatility of this new method was then demonstrated by employing different alkoxyethyltrifluoroborates as coupling partners under the same conditions (Table 3). Alkyl-substituted trifluoroborates provided the desired cross-coupled products in moderate to good yields (entries 1–3, 5–6), while the phenoxyethyl derivative **1d** afforded the expected product **4d** in only 31% yield. This substrate showed higher reactivity, as numerous byproducts were observed after the reaction (Heck, dimer, degradation...). It is interesting to note that for several substrates the yields could be improved by lowering the reaction temperature to 85 °C (entries 2, 6). Secondary alkoxyethyltrifluoroborates also proved to be suitable partners, providing yields up to 70% (entries 5–6). Trifluoroborates bearing more sensitive functional groups such as a silyl ether or an acetate moiety failed to give the cross-coupled products under the reaction conditions. When trifluoroborate **1i** (entry 7) was used, the corresponding silanol and bromoanisole were retrieved after the reaction, suggesting that the fluoride ions released during the hydrolysis of the trifluoroborate salt caused the cleavage of the silyl group and led to degradation before the cross-coupling could take place. The acetate group has been reported not to survive the reaction conditions;[19] however, the deprotected coupled product was not detected either, even when using milder reaction conditions.

■ CONCLUSIONS

In summary, a robust and efficient method for the introduction of ethyloxy motifs based on a Suzuki–Miyaura cross-coupling of the alkoxyethyltrifluoroborates has been developed. These coupling partners are synthesized using an inexpensive copper catalyzed borylation reaction. The scope of the method has been studied and includes aryl and heteroaryl bromides. Depending on the functional group on the alkoxyethyl unit, the resulting compounds can easily be deprotected to the corresponding alcohols.[20] This method is based on the unique properties offered by the trifluoroborates salts, as well as the versatility of the Suzuki–Miyaura reaction, and provides a novel, complementary means to generate alkoxyethylarenes that takes advantage of the wide availability of aryl halides as synthetic partners in the cross-coupling reaction.

■ EXPERIMENTAL SECTION

General Considerations. All commercially available reagents were used without purification. Both solvents and deionized water were degassed with N_2 each time prior to use. Standard benchtop techniques were employed for handling air-sensitive reagents. Melting points (°C) are uncorrected. NMR spectra were recorded on a 500, 400, or 300 MHz spectrometer. The resonance of the carbon center

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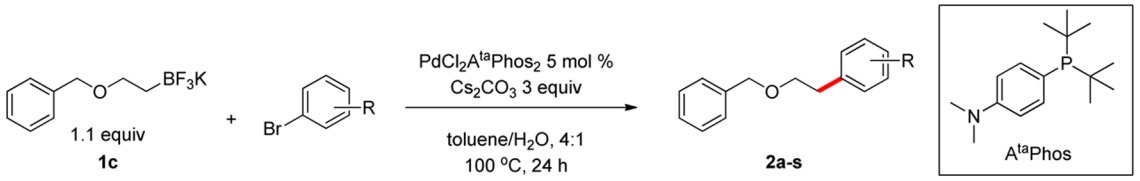
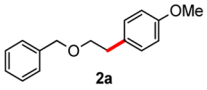
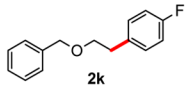
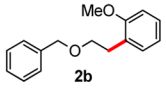
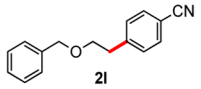
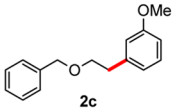
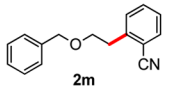
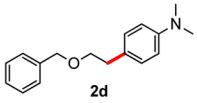
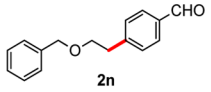
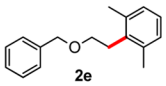
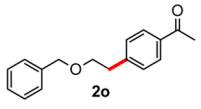
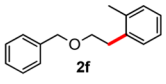
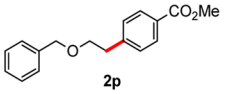
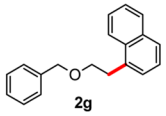
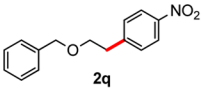
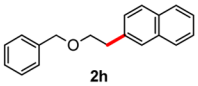
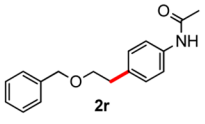
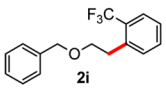
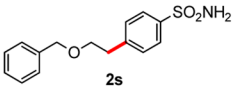
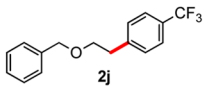
Table 1. Suzuki Cross-Coupling of Benzyloxyethyltrifluoroborate 1c and Various Aryl Bromides[a]



entry	product	isolated yield (%)[b]	entry	product	isolated yield (%)[b]
1	 **2a**	82 30% conv.(ArCl)	11	 **2k**	77
2	 **2b**	92	12	 **2l**	82 88 (ArCl)
3	 **2c**	93	13	 **2m**	67
4	 **2d**	51	14	 **2n**	74 57 (ArCl)
5	 **2e**	82	15	 **2o**	82
6	 **2f**	93[c]	16	 **2p**	92
7	 **2g**	74	17	 **2q**	93
8	 **2h**	89	18	 **2r**	87 72[e]
9	 **2i**	76[d]	19	 **2s**	34
10	 **2j**	89			

[a]General conditions: aryl bromide/chloride (0.25 mmol), trifluoroborate (0.275 mmol), $PdCl_2A^{ta}Phos_2$ (12.50 μmol), Cs_2CO_3 (0.75 mmol) in toluene (1 mL)/H_2O (0.25 mL) at 100 °C for 24 h. [b]Isolated yield after purification by flash chromatography on silica gel or recrystallization. [c]Reaction performed on a 3 mmol scale using 2.5 mol % catalyst. [d]Product contains up to 8% impurity. [e]Reaction performed on a 3 mmol scale using a 1:1 trifluoroborate/electrophile ratio and 1 mol % Pd.

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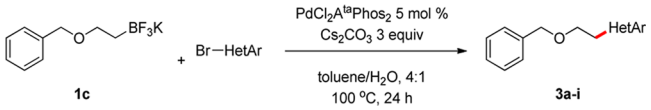
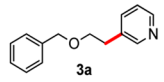
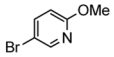
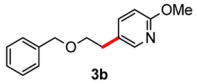
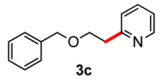
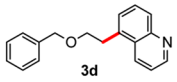
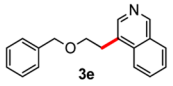
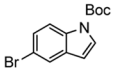
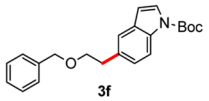
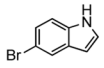
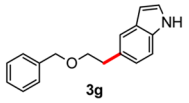
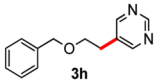
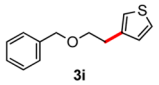
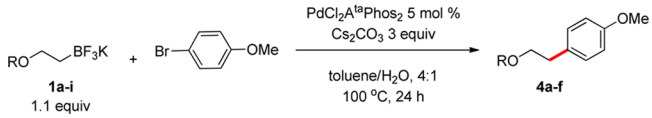
Table 2. Suzuki Cross-Coupling of Benzyloxyethyltrifluoroborate 1c and Various Heteroaryl Bromides[a]

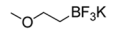
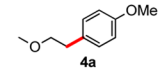
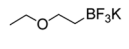
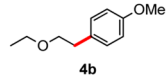
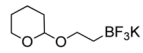
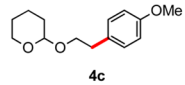
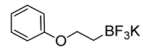
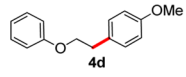
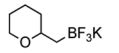
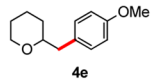
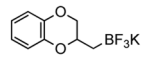
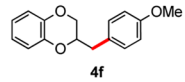
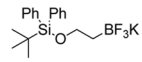
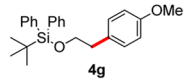
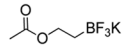
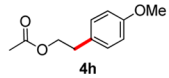


entry	electrophile	product	isolated yield (%)[b]
1		 3a	54
2		 3b	70
3		 3c	10 31 (ArCl)
4		 3d	83
5		 3e	77
6		 3f	89
7		 3g	55
8		 3h	69
9		 3i	88[c]

[a]General conditions: heteroaryl bromide/chloride (0.25 mmol), trifluoroborate (0.275 mmol), $PdCl_2A^{ta}Phos_2$ (12.50 μmol), Cs_2CO_3 (0.75 mmol) in toluene (1 mL)/H_2O (0.25 mL) at 100 °C for 24 h. [b]Isolated yield after purification by flash chromatography on silica gel. [c]Contaminated by up to 8% impurity.

Table 3. Suzuki Cross-Coupling of Various Alkoxyethyltrifluoroborates and *para*-Bromoanisole[a]



entry	trifluoroborate	product	isolated yield (%)[b]
1		 4a	63[c]
2		 4b	72 88[d]
3		 4c	77
4		 4d	31
5		 4e	70
6		 4f	49 60[d]
7		 4g	0
8		 4h	0[e]

[a]General conditions: 4-bromoanisole (0.25 mmol), trifluoroborate (0.275 mmol), $PdCl_2A^{ta}Phos_2$ (12.50 μmol), Cs_2CO_3 (0.75 mmol) in toluene (1 mL)/H_2O (0.25 mL) at 100 °C for 24 h. [b]Isolated yield after purification by flash chromatography on silica gel. [c]Contaminated by 7% impurity. [d]Reaction performed at 85 °C. [e]Reaction also performed at 85 °C in 10:1 toluene/H_2O and 2 equiv of base.

linked to the boron atom was not observed. ^{19}F NMR chemical shifts were referenced to external $CFCl_3$ (0.0 ppm). ^{11}B NMR spectra were obtained on a spectrometer equipped with the appropriate decoupling accessories. All ^{11}B NMR chemical shifts were referenced to external $BF_3{\cdot}OEt_2$ (0.0 ppm) with a negative sign indicating an upfield shift. Data are presented as follows: chemical shift (ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *br* = broad), coupling constant *J* (Hz), and integration. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Standard flash chromatography procedures were followed using 32−63 μm silica gel. Visualization was effected with ultraviolet light, $KMnO_4$, or ceric ammonium molybdate.

General Procedure for the Preparation of Potassium Alkoxyethyltrifluoroborates. This procedure was adapted from the borylation procedure reported by Marder and Liu:[11a] in air, bis(pinacolato)diboron (1.5 equiv), LiOMe (2.0 equiv), triphenylphosphine polymer-bound (13 mol %), and CuI (99.999%, 10 mol %) were weighed in a round-bottomed flask equipped with a stir bar. The flask was closed with a septum, evacuated, and backfilled with N_2. DMF (25 mL, *c* = 0.2 M) and alkoxyethyl bromide (1.0 equiv) were successively added by syringes (or, if the alkoxyethyl bromide was solid, it was added as a solution in DMF), and the resulting mixture was vigorously stirred at rt for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and filtered through a pad of Celite and then rinsed with CH_2Cl_2 (2 × 50 mL). The resulting solution was concentrated, poured into sat. aq NH_4Cl (50 mL), and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed successively with H_2O (300 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The residue was solubilized in THF (25 mL) in a

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round-bottomed flask equipped with a stir bar, and sat. aq KHF_2 (4.0 equiv) was added. The flask was closed with a septum, and the resulting mixture was stirred for 2 h at rt. The reaction mixture was evaporated to dryness, and the resulting salt was extracted several times with hot acetone (5 × 50 mL). The filtrate was concentrated to ~5 mL, and precipitation was achieved by dropwise addition of Et_2O (60 mL) at 0 °C. The resulting product was collected by gravity filtration on a fritted funnel and dried to the corresponding potassium alkoxyethyltrifluoroborate as a white solid.

Potassium (2-Methoxyethyl)trifluoroborate ***1a.*** Following the general procedure, the reaction performed with 2-bromoethyl methyl ether (730 mg, 5.32 mmol) afforded 576 mg (68%) of the title compound. Mp = 123−125 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 3.40−3.36 (*m*, 2H), 3.18 (*s*, 3H), 0.62−0.43 (*m*, 2H).^{13}C NMR (acetone-d^6, 100 MHz): δ 73.7, 57.6. ^{11}B NMR (acetone-d^6, 128 MHz): 4.90 (*br* s). ^{19}F NMR (acetone-d^6, 377 MHz): δ −139.8. IR: ν 2904, 1105, 1060, 1009, 984, 916, 608 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_3H_7BOF_3$ (M − K)$^-$ 127.0542, found 127.0547.

Potassium (2-Ethoxyethyl)trifluoroborate ***1b.*** Following the general procedure, the reaction performed with 2-bromoethyl ethyl ether (678 mg, 3.99 mmol) afforded 488 mg (68%) of the title compound. Mp = 112−114 °C.^{1}H NMR (acetone-d^6, 400 MHz): δ 3.44−3.38 (*m*, 2H), 3.34 (*q*, *J* = 7.0 Hz, 2H), 1.08 (*t*, *J* = 7.0 Hz, 3H), 0.59−0.46 (*m*, 2H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 71.1, 65.5, 15.8. ^{11}B NMR (acetone-d^6, 128 MHz) δ 4.91 (*br* s). ^{19}F NMR (acetone-d^6, 377 MHz): δ −139.9. IR: ν 2872, 1251, 1069, 1041, 938, 884, 732 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_4H_9BOF_3$ (M − K)$^-$ 141.0699, found 141.0704.

Potassium (2-Benzyloxyethyl)trifluoroborate ***1c.*** Following the general procedure, the reaction performed with 2-bromoethyl benzyl ether (1.09 g, 5.06 mmol) afforded 755 mg (62%) of the title compound. Mp = 180−184 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 7.35−7.27 (*m*, 4H), 7.22 (*tt*, *J* = 6.4, 1.8 Hz, 1H), 4.41 (*s*, 2H), 3.55−3.51 (*m*, 2H), 0.65−0.59 (*m*, 2H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 141.3, 128.9, 128.2, 127.7, 72.4, 71.6. ^{11}B NMR (acetone-d^6, 128 MHz) δ 4.81 (*br* s). ^{19}F NMR (acetone-d^6, 377 MHz): δ −139.8. IR: ν 2867, 1328, 1076, 977, 914, 692 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_9H_{11}BOF_3$ (M − K)$^-$ 203.0855, found 203.0863.

Potassium (2-Phenyloxyethyl)trifluoroborate ***1d.*** Following the general procedure, the reaction performed with 2-phenoxyethyl bromide (1.00 g, 4.97 mmol) afforded 621 mg (55%) of the title compound. Mp > 200 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 7.22−7.18 (*m*, 2H), 6.85−6.83 (*m*, 2H), 6.79 (*tt*, *J* = 7.3, 1.0 Hz, 1H), 4.03−3.99 (*m*, 2H), 0.76−0.71 (*m*, 2H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 161.1, 130.0, 120.1, 115.4, 69.3. ^{11}B NMR (acetone-d^6, 128 MHz): δ 4.51 (*br* s). ^{19}F NMR (acetone-d^6, 377 MHz): δ −140.2. IR: ν 1491, 1224, 1082, 1006, 940, 762 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_8H_9BOF_3$ (M − K)$^-$ 189.0699, found 189.0701.

Potassium (2-(Tetrahydro-2H-pyran-2-yloxy)ethyl)trifluoroborate ***1e.*** Following the general procedure, the reaction performed with 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (2.77 g, 13.2 mmol) afforded 1.96 g (63%) of the title compound. Mp = 182−185 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 4.45−4.43 (*m*, 1H), 3.75−3.72 (*m*, 1H), 3.60−3.55 (*m*, 1H), 3.36−3.34 (*m*, 1H), 3.28−3.22 (*m*, 1H), 1.72−1.68 (*m*, 1H), 1.58−1.54 (*m*, 1H), 1.43−1.35 (*m*, 4H), 0.43−0.26 (*m*, 2H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 97.5, 67.7, 61.3, 30.8, 25.3, 19.7. ^{11}B NMR (DMSO-d^6, 128 MHz): δ 4.28 (*br* s). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −136.0. IR: ν 2938, 1250, 1070, 1026, 945, 878, 648 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_7H_{13}BO_2F_3$ (M − K)$^-$ 197.0961, found 197.0960.

Potassium 2-(Trifluoroborato)ethyl Acetate ***1f.*** Following the general procedure, the reaction performed with 2-bromoethyl acetate (756 mg, 4.53 mmol) afforded 348 mg (40%) of the title compound. Mp = 165−167 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 4.09−4.05 (*m*, 2H), 1.89 (*s*, 3H), 0.57−0.54 (*m*, 2H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 171.5, 67.1, 21.4. ^{11}B NMR (acetone-d^6, 128 MHz): δ 4.35 (*q*, *J* = 63 Hz). ^{19}F NMR (acetone-d^6, 377 MHz): δ −140.4. IR: ν 1728, 1244, 1065, 1038, 975, 901, 835 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_4H_7BO_2F_3$ (M − K)$^-$ 155.0491, found 155.0494.

Potassium ((Tetrahydro-2H-pyran-2-yl)methyl)trifluoroborate ***1g.*** Following the general procedure, the reaction performed with 2-(bromomethyl)tetrahydro-2*H*-pyran (2.79 g, 15.60 mmol) afforded 759 mg (24%) of the title compound, using a Soxhlet apparatus overnight for the hot acetone extraction. Mp > 200 °C. ^{1}H NMR (DMSO-d^6, 400 MHz): δ 3.73−3.69 (*m*, 1H), 3.25−3.11 (*m*, 2H), 1.82−1.79 (*m*, 1H), 1.66−1.62 (*m*, 1H), 1.36−1.29 (*m*, 3H), 0.93−0.90 (*m*, 1H), 0.35−0.33 (*m*, 1H), 0.16−0.11 (*m*, 1H). ^{13}C NMR (DMSO-d^6, 100 MHz): δ 78.4, 67.0, 33.3, 26.3, 23.8. ^{11}B NMR (DMSO-d^6, 128 MHz): δ = 4.13 (*br* s). ^{19}F NMR (DMSO-d^6, 377 MHz): δ −134.4. IR: ν 2925, 1266, 1077, 1031, 950, 880, 722 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_6H_{11}BOF_3$ (M − K)$^-$ 167.0855, found 167.0856.

Potassium 2-Trifluoroboratomethyl-1,4-benzodioxane ***1h.*** Following the general procedure, the reaction performed with 2-bromomethyl-1,4-benzodioxane (3.06 g, 13.38 mmol) afforded 1.26 g (37%) of the title compound. Mp > 200 °C. ^{1}H NMR (acetone-d^6, 400 MHz): δ 6.75−6.69 (*m*, 4H), 4.48 (*dd*, *J* = 11.3, 2.1 Hz, 1H), 4.16−4.09 (*m*, 1H), 3.64 (*dd*, *J* = 11.3, 8.5 Hz, 1H), 0.87−0.81 (*m*, 1H), 0.53−0.42 (*m*, 1H). ^{13}C NMR (acetone-d^6, 100 MHz): δ 146.0, 144.9, 121.5, 120.9, 117.9, 117.4, 75.5, 70.9. ^{11}B NMR (acetone-d^6, 128 MHz): δ 4.30 (*br* s). ^{19}F NMR (acetone-d^6, 377 MHz): δ −138.6. IR: ν 1594, 1495, 1255, 1036, 939, 897, 751 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_9H_9BO_2F_3$ (M − K)$^-$ 217.0648, found 217.0648.

Synthesis of Potassium {2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl}trifluoroborate. *(2-Bromoethoxy)(tert-butyl)diphenylsilane.*[21] Freshly distilled 2-bromoethanol (881 mg, 7.05 mmol, 1 equiv) was added to a solution of imidazole (1.2 g, 2.5 equiv) and *tert*-butyldiphenylsilyl chloride (2.3 g, 1.2 equiv) in DMF (5 mL) according to Corey's procedure.[22] The resulting solution was stirred at rt for 24 h, treated with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under vacuum. The crude material was then purified by flash column chromatography on silica gel using hexanes/EtOAc as the eluent to give 1.53 g of a colorless oil (60%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70−7.68 (*m*, 4H), 7.45−7.39 (*m*, 6H), 3.94 (*t*, *J* = 6.5 Hz, 2H), 3.44 (*t*, *J* = 6.5 Hz, 2H), 1.09 (*s*, 9H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 135.5, 133.2, 129.7, 127.7, 63.9, 33.0, 26.7, 19.2. IR: ν 2921, 2857, 2358, 1428, 823, 700 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{24}OSiBr$ (M + H) 363.0780, found 363.0770.

Potassium {2-[(tert-Butyldiphenylsilyl)oxy]ethyl}trifluoroborate ***1i.*** The synthesis was adapted from the borylation procedure reported by Marder and Liu:[11a] a 20 mL vial was charged with CuI (55 mg, 10 mol %) and PPh_3 (99 mg, 13 mol %). Inside the glovebox, MeOLi (220 mg, 2 equiv) and B_2Pin_2 (1.1 g, 1.5 equiv) were then added. The vial was then sealed and removed from the glovebox. (2-Bromoethoxy)(*tert*-butyl)diphenylsilane (1.05 g, 2.89 mmol, 1 equiv) in dry DMF (15 mL) was added, and the resulting mixture was stirred at rt overnight. The color of the solution rapidly changed from cloudy white to dark black. The reaction mixture was then diluted with EtOAc (20 mL), filtered through silica gel with copious washings (EtOAc, 20 mL), and concentrated. The crude mixture was then dissolved in MeOH (5 mL), and aqueous KHF_2 (4.5 M, 3 mL) was added dropwise at 0 °C. After 30 min of stirring, the solvents were removed using a lyophilizer. The resulting white solid was dissolved in hot MeCN (10 mL) and sonicated, and the solution was filtered. The volume of the solution was reduced to ~2 mL, and the trifluoroborate was precipitated by addition of hexanes (10 mL) and Et_2O (5 mL), filtration, and drying under vacuum to give 484 mg of the desired product as a white solid (43%). Mp > 200 °C. ^{1}H NMR (DMSO-d^6, 500 MHz): δ 7.62 (*m*, 4H), 7.40 (*m*, 6H), 3.66−3.62 (*m*, 2H), 0.95 (*s*, 9H), 0.51 (*m*, 2H). ^{13}C NMR (DMSO-d^6, 125.8 MHz): δ 135.4, 135.0, 129.7, 128.0, 65.3, 27.2, 19.1. ^{11}B NMR (DMSO-d^6, 128.38 MHz): δ 5.16 (*m*). ^{19}F NMR (DMSO-d^6, 470.84 MHz): δ −135.8. IR: ν 2929, 1472, 1428, 1247, 1061, 1031, 940, 706 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{18}H_{23}OSiF_3B$ (M − K)$^-$ 351.1563, found 351.1564.

General Procedure for the Cross-Coupling of Alkoxyethyltrifluoroborates and Aryl or Heteroaryl Halides. In an oven-dried 8 mL microwave vial were introduced bis(di-*tert*-butyl(4-

dimethylaminophenyl)phosphine)dichloropalladium(II) (9 mg, 5 mol %), the alkoxyethyltrifluoroborate (0.275 mmol, 1.1 equiv), and Cs_2CO_3 (244 mg, 3 equiv). The vial was sealed with a cap lined with a disposable PTFE septum and evacuated under vacuum and purged with N_2 (×3). Degassed toluene (1 mL) and H_2O (0.25 mL) were added by syringe, followed by the desired electrophile (1 equiv). (When the aryl or heteroaryl halide was a solid, it was added after the base.) The reaction mixture was then placed in an oil bath preheated at 100 °C and stirred for 24 h at this temperature. After cooling to rt, the vial was uncapped and diluted with H_2O (3 mL) and EtOAc (5 mL × 2). The combined organics were dried ($MgSO_4$) and filtered through Celite and concentrated *in vacuo*. Purification of the crude was performed by flash chromatography with hexanes/EtOAc: 100/0 to 80/20 with 1% Et_3N.

1-(2-(Benzyloxy)ethyl)-4-methoxybenzene **2a**.[23] Obtained as a colorless oil (49.5 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.30 (*m*, 5H), 7.18 (*d*, *J* = 8.5 Hz, 2H), 6.87 (*dd*, *J* = 7.0, 2.5 Hz, 2H), 4.56 (*s*, 2H), 3.82 (*s*, 3H), 3.69 (*t*, *J* = 7.0 Hz, 2H), 2.91 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 158.0, 138.4, 131.0, 129.8, 128.3, 127.5, 127.4, 113.7, 72.9, 71.4, 55.2, 35.4. IR: ν 2931, 2855, 1512, 1246, 1100, 1036, 739 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{18}O_2Na$ (M + Na) 265.1204, found 265.1194.

1-(2-(Benzyloxy)ethyl)-2-methoxybenzene **2b**. Obtained as a colorless oil (56.0 mg, 92%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.35 (*m*, 4H), 7.32−7.30 (*m*, 1H), 7.24 (*t*, *J* = 7.0 Hz, 2H), 6.93 (*td*, *J* = 7.5, 1.0 Hz, 1H), 6.88 (*d*, *J* = 8.0 Hz, 1H), 4.58 (*s*, 2H), 3.83 (*s*, 3H), 3.73 (*t*, *J* = 7.0 Hz, 2H), 3.02 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 157.6, 138.6, 130.6, 128.2, 127.5, 127.4, 127.3, 127.1, 120.3, 110.2, 72.7, 69.8, 55.2, 30.8. IR: ν 2360, 1494, 1243, 1099, 1028, 751 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{18}O_2Na$ (M + Na) 265.1204, found 265.1212.

1-(2-(Benzyloxy)ethyl)-3-methoxybenzene **2c**. Obtained as a yellow oil (56.4 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40−7.30 (*m*, 5H), 7.26 (*t*, *J* = 7.0 Hz, 1H), 6.87 (*d*, *J* = 7.5 Hz, 1H), 6.83 (*br s*, 1H), 6.81 (*dd*, *J* = 8.5, 2.0 Hz, 1H), 4.57 (*s*, 2H), 3.82 (*s*, 3H), 3.74 (*t*, *J* = 7.0 Hz, 2H), 2.96 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 159.6, 140.5, 138.4, 129.2, 128.3, 127.6, 127.5, 121.3, 114.6, 111.6, 72.9, 71.1, 55.1, 36.4. IR: ν 2855, 1602, 1488, 1259, 1100, 737, 696 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{18}O_2$ (M+) 242.1307, found 242.1311.

4-(2-(Benzyloxy)ethyl)-N,N-dimethylaniline **2d**. Obtained as a yellow oil (32.4 mg, 51%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.34 (*m*, 4H), 7.31−7.30 (*m*, 1H), 7.14 (*d*, *J* = 8.5 Hz, 2H), 6.73 (*d*, *J* = 8.5 Hz, 2H), 4.57 (*s*, 2H), 3.69 (*t*, *J* = 7.0 Hz, 2H), 2.95 (*s*, 6H), 2.89 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 149.3, 138.5, 129.5, 128.3, 127.6, 127.4, 126.8, 112.9, 72.9, 71.8, 40.8, 35.3. IR: ν 2852, 1615, 1522, 1345, 1099, 947, 810, 644 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{22}NO$ (M + H) 256.1701, found 256.1689.

2-(2-(Benzyloxy)ethyl)-1,3-dimethylbenzene **2e**. Obtained as a yellow oil (49.6 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40−7.38 (*m*, 4H), 7.35−7.33 (*m*, 1H), 7.08−7.04 (*m*, 3H), 4.60 (*s*, 2H), 3.62 (*t*, *J* = 7.0 Hz, 2H), 3.08 (*t*, *J* = 7.0 Hz, 2H), 2.39 (*s*, 6H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.4, 136.7, 135.0, 128.3, 128.1, 127.5, 126.1, 72.9, 68.8, 30.2, 19.9. IR: ν 2855, 1453, 1361, 1100, 1028, 770, 644 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{19}O$ (M − H) 239.1436, found 239.1439.

1-(2-(Benzyloxy)ethyl)-2-methylbenzene **2f**. Obtained as a colorless oil (630.5 mg, 93%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.36 (*m*, 4H), 7.31−7.29 (*m*, 1H), 7.20−7.16 (*m*, 4H), 4.58 (*s*, 2H), 3.70 (*t*, *J* = 7.0 Hz, 2H), 2.99 (*t*, *J* = 7.0 Hz, 2H), 2.35 (*s*, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.4, 136.8, 136.3, 130.1, 129.3, 128.3, 127.5, 127.4, 126.3, 125.9, 72.9, 70.2, 33.5, 19.3. IR: ν = 2857, 1494, 1454, 1361, 1099, 1028, 740 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{18}O$ (M+) 226.1358, found 226.1367.

1-(2-(Benzyloxy)ethyl)naphthalene **2g**. Obtained as a colorless oil (48.3 mg, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 (*d*, *J* = 8.0 Hz, 1H), 7.91 (*d*, *J* = 7.5 Hz, 1H), 7.79 (*d*, *J* = 7.5 Hz, 1H), 7.57−7.51 (*m*, 2H), 7.47−7.43 (*m*, 2H), 7.39−7.33 (*m*, 5H), 4.60 (*s*, 2H), 3.89 (*t*, *J* = 7.0 Hz, 2H), 3.48 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.3, 134.8, 133.8, 132.1, 128.7, 128.3, 127.6, 127.5, 127.0, 126.8, 125.9, 125.5, 125.4, 123.7, 73.0, 70.6, 33.4. IR: ν 2856, 1454, 1361, 1100, 1027, 776, 608 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{18}ONa$ (M + Na) 285.1255, found 285.1250.

2-(2-(Benzyloxy)ethyl)naphthalene **2h**. Obtained as a yellow solid (58.5 mg, 89%). Mp = 35−36 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.88 (*d*, *J* = 7.5 Hz, 1H), 7.85 (*d*, *J* = 8.5 Hz, 2H), 7.75 (br s, 1H), 7.54−7.49 (*m*, 2H), 7.45 (*dd*, *J* = 8.5, 1.2 Hz, 1H), 7.42−7.38 (m, 4H), 7.34−7.37 (m, 1H), 4.62 (*s*, 2H), 3.86 (*t*, *J* = 7.0 Hz, 2H), 3.18 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.4, 136.6, 133.6, 132.2, 28.4, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 125.9, 125.3, 73.0, 71.1, 36.5. IR: ν 2866, 1368, 1098, 1074, 821, 740 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{19}H_{18}O$ (M+) 262.1358, found 262.1353.

1-(2-(Benzyloxy)ethyl)-2-(trifluoromethyl)benzene **2i**. Obtained as a colorless oil (53.6 mg, 76%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65−7.67 (*m*, 1H), 7.50−7.46 (*m*, 1H), 7.45−7.42 (*m*, 1H), 7.40−7.28 (*m*, 6H), 4.56 (*s*, 2H), 3.75 (*t*, *J* = 7.0 Hz, 2H), 3.17 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.2, 137.4, 131.8, 131.5, 128.6 (*q*, *J* = 29.5 Hz), 128.3, 127.5, 127.4, 126.2, 125.8 (*q*, *J* = 5.7 Hz), 124.5 (*d*, *J* = 273.9 Hz), 72.8, 70.5, 32.9. ^{19}F NMR ($CDCl_3$, 470.84 MHz): δ −59.6. IR: ν = 2980, 1313, 1114, 769, 741 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{15}OF_3$ (M+) 280.1075, found 280.1071.

1-(2-(Benzyloxy)ethyl)-4-(trifluoromethyl)benzene **2j**. Obtained as a white solid (62.1 mg, 89%). Mp = 44−46 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (*d*, *J* = 8.0 Hz, 2H), 7.38−7.35 (*m*, 3H), 7.33−7.30 (*m*, 4H), 4.56 (*s*, 2H), 3.75 (*t*, *J* = 7.0 Hz, 2H), 3.01 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 143.3, 138.1, 129.2, 128.5 (*q*, *J* = 32.0 Hz), 128.3, 127.6, 127.5, 125.1 (*q*, *J* = 3.9 Hz), 124.3 (*d*, *J* = 271.6 Hz), 73.0, 70.4, 36.1. ^{19}F NMR ($CDCl_3$, 470.84 MHz): δ −62.3. IR: ν 2868, 2362, 1322, 1114, 1066, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{14}OF_3$ (M − H) 279.0997, found 279.0994.

1-(2-(Benzyloxy)ethyl)-4-fluorobenzene **2k**. Obtained as a yellow oil (44.3 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37−7.31 (*m*, 5H), 7.24−7.20 (*m*, 2H), 7.19−6.98 (*m*, 2H), 4.56 (*s*, 2H), 3.71 (*t*, *J* = 7.0 Hz, 2H), 2.94 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 161.4 (*d*, *J* = 243.8 Hz), 138.3, 134.6 (*d*, *J* = 3.0 Hz), 130.2 (*d*, *J* = 8.3 Hz), 128.3, 127.5, 127.4, 115.0 (*d*, *J* = 21.1 Hz), 72.9, 71.0, 35.5. ^{19}F NMR ($CDCl_3$, 282.40 MHz): δ −117.3. IR: ν = 2861, 1509, 1221, 1098, 834, 825, 736 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{15}OF$ (M+) 230.1107, found 230.1100.

4-(2-(Benzyloxy)ethyl)benzonitrile **2l**. Obtained as a white solid [52.3 mg, 88% (from X = Cl)]. Mp = 45−47 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.58 (*d*, *J* = 8.0 Hz, 2H), 7.36−7.33 (*m*, 4H), 7.31 (*m*, 1H), 7.30−7.27 (*m*, 2H), 4.52 (*s*, 2H), 3.72 (*t*, *J* = 7.0 Hz, 2H), 2.99 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 144.9, 138.0, 132.0, 129.7, 128.3, 127.6, 127.5, 119.0, 110.0, 73.0, 69.9, 36.4. IR: ν 2866, 2224, 1608, 1364, 1096, 1077, 847, 746 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{15}NO$ (M+) 237.1154, found 237.1165.

4-(2-(Benzyloxy)ethyl)benzonitrile **2m**. Obtained as a yellow oil (39.7 mg, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (*d*, *J* = 7.5 Hz, 1H), 7.53 (*t*, *J* = 8.0 Hz, 1H), 7.42 (*d*, *J* = 7.5 Hz, 1H), 7.35−7.31 (*m*, 3H), 7.30−7.27 (*m*, 3H), 4.55 (*s*, 2H), 3.79 (*t*, *J* = 7.0 Hz, 2H), 3.18 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 143.0, 138.0, 132.7, 132.5, 130.3, 128.3, 127.5, 127.4, 126.8, 118.0, 112.7, 72.8, 69.5, 34.8. IR: ν 2861, 2224, 1452, 1361, 1099, 762, 738 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{16}NO$ (M + H) 238.1232, found 238.1229.

4-(2-(Benzyloxy)ethyl)benzaldehyde **2n**. Obtained as a yellow oil (44.7 mg, 74%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.00 (*s*, 1H), 7.82 (*d*, *J* = 8.0 Hz, 2H), 7.41 (*d*, *J* = 8.0 Hz, 2H), 7.33 (*d*, *J* = 7.0 Hz, 2H), 7.30−7.28 (*m*, 3H), 4.54 (*s*, 2H), 3.75 (*t*, *J* = 7.0 Hz, 2H), 3.02 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 191.9, 146.6, 138.1, 134.7, 129.8, 129.5, 128.3, 127.6, 127.5, 73.0, 70.2, 36.5. IR: ν 2856, 1698, 1607, 1212, 1169, 1099, 741 cm^{-1}. HRMS (ESI-TOF) *m*/*z* calcd for $C_{16}H_{17}O_2$ (M + H) 241.1229, found 241.1222.

1-(4-(2-(Benzyloxy)ethyl)phenyl)ethanone **2o**. Obtained as a yellow oil (52.4 mg, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (*d*, *J* = 8.0 Hz, 2H), 7.35−7.33 (*m*, 4H), 7.33−7.29 (*m*, 3H), 4.54 (*s*, 2H), 3.73 (*t*, *J* = 7.0 Hz, 2H), 3.00 (*t*, *J* = 7.0 Hz, 2H), 2.60 (*s*, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 197.7, 144.9, 138.1, 135.3, 129.1, 128.4, 128.3, 127.6, 127.5, 72.9, 70.4, 36.3, 26.5. IR: ν 2863, 2363, 1681,

1607, 1359, 1267, 1100, 956, 644 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{19}O_2$ (M + H) 255.1385, found 255.1383.

Methyl 4-(2-(Benzyloxy)ethyl)benzoate ***2p***. Obtained as a yellow solid (62.2 mg, 92%). Mp = 27−29 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.98 (*d*, *J* = 8.0 Hz, 2H), 7.36−7.29 (*m*, 7H), 4.53 (*s*, 2H), 3.92 (*s*, 3H), 3.73 (*t*, *J* = 7.0 Hz, 2H), 2.99 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 167.0, 144.6, 138.1, 129.6, 128.9, 128.3, 128.1, 127.6, 127.5, 72.9, 70.4, 51.9, 36.3. IR: ν 2862, 1719, 1610, 1278, 1105, 645 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{19}O_3$ (M + H) 271.1334, found 271.1336.

1-(2-(Benzyloxy)ethyl)-4-nitrobenzene ***2q***. Obtained as an orange solid (60.0 mg, 93%). Mp = 45−46 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.15 (*d*, *J* = 8.5 Hz, 2H), 7.40 (*d*, *J* = 8.5 Hz, 2H), 7.35−7.33 (*m*, 2H), 7.31−7.27 (*m*, 3H), 4.53 (*s*, 2H), 3.75 (*t*, *J* = 7.0 Hz, 2H), 3.03 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 147.2, 146.6, 137.9, 129.7, 128.3, 127.6, 127.5, 123.4, 73.0, 69.8, 36.1. IR: ν 2862, 1598, 1508, 1341, 1123, 856, 739 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{16}NO_3$ (M + H) 258.1130, found 258.1138.

N-(4-(2-(Benzyloxy)ethyl)phenyl)acetamide ***2r***. Obtained as a white solid (59.0 mg, 87%). Mp = 102−104 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.42 (*d*, *J* = 8.5 Hz, 2H), 7.34−7.28 (*m*, 6H), 7.18 (*d*, *J* = 8.5 Hz, 2H), 4.53 (*s*, 2H), 3.68 (*t*, *J* = 7.0 Hz, 2H), 2.90 (*t*, *J* = 7.0 Hz, 2H), 2.16 (*s*, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 168.2, 138.3, 136.0, 135.0, 129.3, 128.3, 127.5, 127.4, 119.9, 72.9, 71.1, 35.7, 24.4. IR: ν 3310, 1660, 1607, 1322, 1114, 834, 738 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{20}NO_2$ (M + H) 270.1494, found 270.1487.

4-(2-(Benzyloxy)ethyl)benzenesulfonamide ***2s***. Obtained as a white solid (25.0 mg, 34%). Mp = 114−115 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.85 (*d*, *J* = 7.5 Hz, 2H), 7.39 (*d*, *J* = 8.0 Hz, 2H), 7.36−7.33 (*m*, 2H), 7.30−7.27 (*m*, 3H), 4.89 (*br s*, 2H) 4.52 (*s*, 2H), 3.72 (*t*, *J* = 7.0 Hz, 2H), 3.00 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 144.8, 139.7, 137.9, 129.6, 128.3, 127.6, 127.5, 126.4, 73.0, 70.1, 36.1. IR: ν 3335, 3263, 2868, 2360, 2342, 1307, 1160, 903, 686 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{16}NO_3S$ (M − H) 290.0851, found 290.0864.

3-(2-(Benzyloxy)ethyl)pyridine ***3a***. Obtained as a yellow oil (28.8 mg, 54%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.51 (*s*, 1H), 7.48 (*d*, *J* = 5.0 Hz, 1H), 7.57 (*d*, *J* = 8.0 Hz, 1H), 7.40−7.33 (*m*, 2H), 7.32−7.28 (*m*, 3H), 7.21 (*dd*, *J* = 5.0, 7.5 Hz, 1H), 4.52 (*s*, 2H), 3.70 (*t*, *J* = 7.0 Hz, 2H), 2.92 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 150.2, 147.6, 138.0, 136.3, 134.5, 128.3, 127.6, 127.5, 123.1, 73.0, 70.3, 33.4. IR: ν 2858, 2362, 1361, 1100, 1028, 699 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{16}NO$ (M + H) 214.1232, found 214.1223.

5-(2-(Benzyloxy)ethyl)-2-methoxypyridine ***3b***. Obtained as a yellow oil (42.6 mg, 70%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.18 (*d*, *J* = 2.5 Hz, 1H), 8.12 (*s*, 1H), 7.35−7.27 (m, 5H), 7.10 (*s*, 1H), 4.52 (*s*, 2H), 3.83 (*s*, 3H), 3.71 (*t*, *J* = 7.0 Hz, 2H), 2.91 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 155.4, 142.5, 138.0, 135.3, 128.3, 127.6, 127.5, 127.4, 121.1, 73.0, 70.3, 55.4, 33.3. IR: ν 2852, 2362, 1588, 1283, 1100, 868, 699 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{18}NO_2$ (M + H) 244.1338, found 244.1328.

2-(2-(Benzyloxy)ethyl)pyridine ***3c***. Obtained as a colorless oil [16.5 mg, 31% (from X = Cl)]. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.54 (*d*, *J* = 5.0 Hz, 1H), 7.60 (*t*, *J* = 7.5 Hz, 1H), 7.34−7.27 (*m*, 5H), 7.23 (*m*, 1H), 7.13 (*t*, *J* = 7.5 Hz, 1H), 4.54 (*s*, 2H), 3.88 (*t*, *J* = 7.0 Hz, 2H), 3.12 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 159.2, 149.2, 138.3, 136.1, 128.2, 127.5, 127.4, 123.5, 121.2, 72.9, 69.5, 38.6. IR: ν 2851, 2362, 1592, 1093, 749, 698 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{16}NO$ (M + H) 214.1232, found 214.1225.

5-(2-(Benzyloxy)ethyl)quinoline ***3d***. Obtained as a yellow oil (55.0 mg, 83%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.91 (*d*, *J* = 1.5 Hz, 1H), 8.38 (*d*, *J* = 8.5 Hz, 1H), 8.02 (*d*, *J* = 8.5 Hz, 1H), 7.64 (*dd*, *J* = 8.5, 7.5 Hz, 1H), 7.44 (*d*, *J* = 7.0 Hz, 1H), 7.39 (*dd*, *J* = 7.5, 4.5 Hz, 1H), 7.33−7.26 (*m*, 5H), 4.53 (*s*, 2H), 3.81 (*t*, *J* = 7.0 Hz, 2H), 3.39 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 149.9, 148.6, 138.1, 135.5, 132.2, 129.0, 128.3, 127.6, 127.5, 127.2, 127.1, 120.7, 73.0, 70.4, 32.6. IR: ν = 2855, 2362, 1500, 1362, 1100, 802 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}NO$ (M + H) 264.1388, found 264.1380.

4-(2-(Benzyloxy)ethyl)isoquinoline ***3e***. Obtained as a yellow oil (50.5 mg, 77%). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.16 (*s*, 1H), 8.44 (*s*, 1H), 8.0 (*d*, *J* = 8.5 Hz, 1H), 7.98 (*d*, *J* = 8.5 Hz, 1H), 7.71 (*m*, 1H), 7.61 (*m*, 1H), 7.34−7.27 (*m*, 5H), 4.55 (*s*, 2H), 3.84 (*t*, *J* = 7.0 Hz, 2H), 3.36 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 151.5, 143.3, 138.1, 134.8, 130.2, 128.4, 128.3, 128.2, 128.1, 127.6, 127.5, 126.8, 122.8, 73.0, 70.0, 30.5. IR: ν 2918, 2362, 1622, 1100, 896, 748 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{18}H_{18}NO$ (M + H) 264.1388, found 264.1380.

tert-Butyl 5-(2-(Benzyloxy)ethyl)-1H-indole-1-carboxylate ***3f***. Obtained as a yellow solid (78.4 mg, 89%). Mp = 28−30 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.08 (m, 1H), 7.60 (*d*, *J* = 3.5 Hz, 1H), 7.44 (*d*, *J* = 1.0 Hz, 1H), 7.38−7.34 (*m*, 4H), 7.32−7.30 (*m*, 1H), 7.22 (*dd*, *J* = 8.5, 1.5 Hz, 1H), 6.54 (*d*, *J* = 3.5 Hz, 1H), 4.57 (*s*, 2H), 3.76 (*t*, *J* = 7.0 Hz, 2H), 3.06 (*t*, *J* = 7.0 Hz, 2H), 1.70 (*s*, 9H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 149.7, 138.4, 133.8, 133.2, 130.7, 128.3, 127.6, 127.4, 126.0, 125.3, 120.9, 114.9, 107.1, 83.4, 72.9, 71.7, 36.2, 28.1. IR: ν 2851, 1729, 1470, 1372, 1352, 1163, 1091, 1026, 648 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{22}H_{25}NO_3Na$ (M + Na) 374.1732, found 374.1727.

5-(2-(Benzyloxy)ethyl)-1H-indole ***3g***. Obtained as a yellow oil (34.4 mg, 55%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.14 (*br s*, 1H), 7.53 (*s*, 1H), 7.38 (*m*, 4H), 7.32 (*m*, 2H), 7.17 (*t*, *J* = 2.5 Hz, 1H), 7.11 (*d*, *J* = 8.5 Hz, 1H), 6.53 (*m*, 1H), 4.60 (*s*, 2H), 3.79 (*t*, *J* = 7.0 Hz, 2H), 3.09 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 138.5, 134.6, 130.0, 128.3, 128.1, 127.6, 127.4, 124.3, 123.3, 120.5, 110.8, 102.2, 72.9, 72.2, 36.4. IR: ν 3414, 1477, 1332, 1093, 726, 648 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{17}H_{18}NO$ (M + H) 252.1388, found 252.1379.

5-(2-(Benzyloxy)ethyl)pyrimidine ***3h***. Obtained as an orange oil (36.8 mg, 69%). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.09 (*s*, 1H), 8.64 (*s*, 2H), 7.34−7.29 (*m*, 2H), 7.29−7.23 (*m*, 3H), 4.51 (*s*, 2H), 3.70 (*t*, *J* = 7.0 Hz, 2H), 2.89 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 157.1, 157.0, 137.7, 132.6, 128.4, 127.7, 127.5, 73.1, 69.3, 30.9. IR: ν 2853, 2359, 1560, 1409, 1097, 728 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{14}N_2O$ (M+) 214.1106, found 214.1099.

3-(2-(Benzyloxy)ethyl)thiophene ***3i***:[24] Obtained as a colorless oil (48.1 mg, 88%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.33 (*m*, 4H), 7.32 (*m*, 1H), 7.28 (*m*, 1H), 7.06 (*m*, 1H), 7.03 (*m*, 1H), 4.58 (*s*, 2H), 3.74 (*t*, *J* = 7.0 Hz, 2H), 3.00 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 139.2, 138.3, 128.5, 128.3, 127.6, 127.5, 125.1, 121.1, 72.9, 70.4, 30.7. IR: ν 2360, 2341, 1453, 1099, 737, 648 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{14}OS$ (M+) 218.0765, found 218.0766.

1-Methoxy-4-(2-methoxyethyl)benzene ***4a***.[25] Obtained as a colorless oil (26.3 mg, 63%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.15 (*d*, *J* = 8.5 Hz, 2H), 6.85 (*dd*, *J* = 7.0, 2.0 Hz, 2H), 3.80 (*s*, 3H), 3.58 (*t*, *J* = 7.0 Hz, 2H), 3.37 (*s*, 3H), 2.84 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 158.0, 130.9, 129.7, 127.3, 114.0, 113.7, 73.8, 58.5, 55.1, 35.2. IR: ν 2833, 1513, 1246, 1114, 1034, 833 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{10}H_{15}O_2$ (M + H) 167.1072, found 167.1069.

1-(2-Ethoxyethyl)-4-methoxybenzene ***4b***. Obtained as a colorless oil (32.5 mg, 72%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.16 (*d*, *J* = 8.5 Hz, 2H), 6.85 (*dd*, *J* = 7.0, 2.0 Hz, 2H), 3.80 (*s*, 3H), 3.61 (*t*, *J* = 7.5 Hz, 2H), 3.52 (*q*, *J* = 7.0 Hz, 2H), 2.85 (*t*, *J* = 7.5 Hz, 2H), 1.22 (*t*, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 158.0, 131.0, 129.7, 127.3, 113.7, 71.8, 66.1, 55.1, 35.4, 15.1. IR: ν 2854, 1612, 1513, 1245, 1109, 1037, 830 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{11}H_{16}O_2$ (M +) 180.1150, found 180.1152.

2-(4-Methoxyphenethoxy)tetrahydro-2H-pyran ***4c***.[26] Obtained as a colorless oil (45.5 mg, 77%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.17 (*d*, *J* = 8.5 Hz, 2H), 6.84 (*dd*, *J* = 7.0, 2.0 Hz, 2H), 4.60 (*t*, *J* = 3.5 Hz, 1H), 3.95−3.90 (m, 1H), 3.85−3.77 (*m*, 1H), 3.79 (*s*, 3H), 3.62−3.57 (*m*, 1H), 3.48−3.46 (*m*, 1H), 2.87 (*t*, *J* = 7.0 Hz, 2H), 1.89−1.79 (*m*, 1H), 1.74−1.68 (*m*, 1H), 1.63−1.47 (*m*, 4H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 158.0, 131.1, 129.8, 113.6, 98.6, 68.4, 62.1, 55.1, 35.4, 30.6, 25.4, 19.4. IR: ν 2939, 1513, 1246, 1120, 1030, 824 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{14}H_{20}O_3$ (M+) 236.1412, found 236.1406.

1-Methoxy-4-(2-phenoxyethyl)benzene ***4d***.[27] Obtained as a colorless oil (18.0 mg, 31%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31−7.28 (*m*, 2H), 7.23 (*d*, *J* = 8.5 Hz, 2H), 6.96 (*t*, *J* = 7.5 Hz, 1H), 6.93 (*d*, *J* = 8.0 Hz, 2H), 6.88 (*d*, *J* = 8.5 Hz, 2H), 4.16 (*t*, *J* = 7.0 Hz, 2H), 3.82 (*s*, 3H), 3.06 (*t*, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ

158.7, 158.2, 130.2, 129.9, 129.3, 120.6, 114.5, 113.8, 68.7, 55.2, 34.8. IR: ν 2360, 1513, 1243, 1176, 1034, 825, 754 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{15}H_{16}O_2$ (M+) 228.1150, found 228.1144.

2-(4-Methoxybenzyl)tetrahydro-2H-pyran ***4e***. Obtained as a colorless oil (36.3 mg, 70%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.14 (*d*, *J* = 8.5 Hz, 2H), 6.84 (*d*, *J* = 8.5 Hz, 2H), 4.00−3.98 (m, 1H), 3.80 (*s*, 3H), 3.46−3.39 (*m*, 2H), 2.83 (*dd*, *J* = 14.0, 7.0 Hz, 1H), 2.60 (*dd*, *J* = 14.0, 7.0 Hz, 1H), 1.82 (*dd*, *J* = 13.0, 2.0 Hz, 1H), 1.63−1.55 (*m*, 2H), 1.52−1.47 (*m*, 1H), 1.46−1.41 (*m*, 1H), 1.32−1.24 (*m*, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 157.9, 130.8, 130.2, 113.5, 78.9, 68.5, 55.1, 42.2, 31.3, 26.0, 23.4. IR: ν 2934, 1512, 1245, 1090, 1039, 648 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{13}H_{19}O_2$ (M + H) 207.1385, found 207.1385.

2-((4-Methoxyphenethoxy)methyl)-2,3-dihydrobenzo[b][1,4]-dioxine ***4f***. Obtained as a white solid (31.2 mg, 49%). Mp = 68−71 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.20 (*d*, *J* = 8.0 Hz, 2H), 6.91−6.84 (*m*, 4H), 6.89 (*d*, *J* = 8.0 Hz, 2H), 4.33 (*qd*, *J* = 7.2, 2.0 Hz, 1H), 4.19 (*dd*, J = 11.2, 2.2 Hz, 1H), 3.91 (*dd*, *J* = 11.2, 7.0 Hz, 1H), 3.83 (*s*, 3H), 3.07 (*dd*, *J* = 14.0, 7.0 Hz, 1H), 2.85 (*dd*, *J* = 14.0, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 158.4, 143.2, 143.1, 130.3, 128.3, 121.4, 121.1, 117.3, 116.9, 114.0, 73.8, 66.9, 55.2, 36.6. IR: ν 1610, 1592, 1514, 1493, 1268, 1243, 1036, 754 cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{16}H_{16}O_3$ (M+) 256.1099, found 256.1104.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H, ^{13}C, ^{11}B, and ^{19}F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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