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Synthesis of Alkyl Aryl Ethers by O-Arylation of Alcohols with Diaryliodonium Salts: Scope, Limitations, and Mechanism

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This manuscript is dedicated to the memory of Professor Keith Fagnou.

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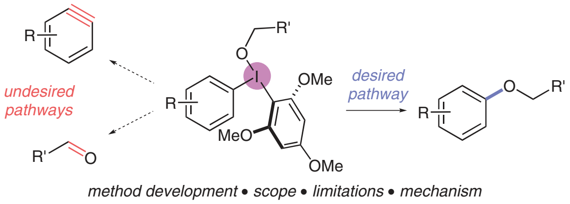

method development • scope • limitations • mechanism

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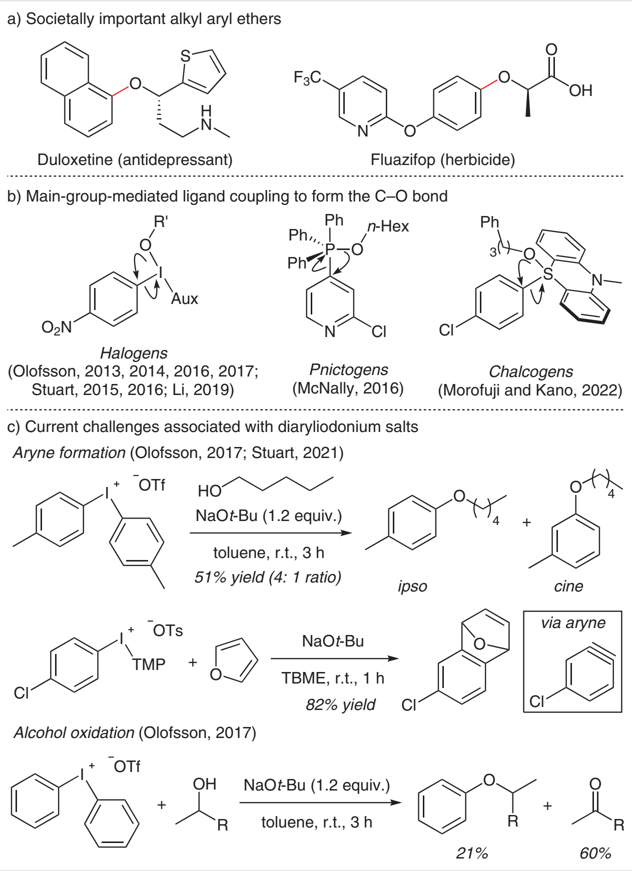
Abstract We describe the development of a C–O coupling reaction between aryl(2,4,6-trimethoxyphenyl)iodonium salts and aliphatic alcohols under weak base conditions. The scope of the reaction is presented, with 16 examples ranging in yield from moderate to high (54–96%). The limitations of the reaction are also presented. Mechanistic experiments reveal a complex network of reactions that include side reactions that generate arynes and oxidize the alcohol nucleophile.

Key words arylation, ethers, alcohols, diaryliodonium compounds, ligand coupling, C–O coupling

Alkyl aryl ethers are common motifs in pharmaceuticals, agrochemicals, and functional materials (Scheme 1a).[2] The reaction between an aryl electrophile and an alkoxide nucleophile is at the forefront of strategies to synthesize these scaffolds. Nucleophilic aromatic substitution (S_NAr) dominated early synthetic strategies,[3] though the advent of transition-metal-catalyzed reactions has greatly expanded the scope of these reactions.[4] Recent reports have also included the combination of transition-metal catalysts and either electrochemistry or photochemistry.[5] Notwithstanding the advances provided by these methods, they do have limitations: the S_NAr reaction is notably limited in substrate scope as a result of the Meisenheimer intermediate, copper- and palladium-catalyzed reactions often require designer ligands, and nickel/photocatalysis and nickel/electrochemistry are typically limited to electron-deficient (activated) aryl halides.

An alternative strategy for C–O coupling that has taken hold over the past decade involves the use of main-group mediators (Scheme 1b).[6–8] Mechanistically, these reactions are intriguing because the key C–O bond-forming step occurs through ligand coupling, which is the main-group equivalent of reductive elimination (Scheme 1b). Therefore, they have the potential for a substrate scope similar to that of transition-metal-catalyzed reactions, but using Earth-abundant materials.[9] Unlike S_NAr and transition-metal-catalyzed reactions that use commercially available aryl ha-



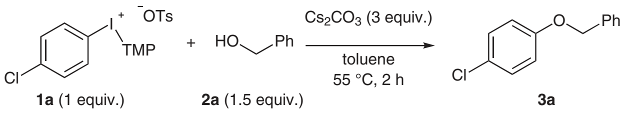
Scheme 1 Strategy and challenges in the synthesis of alkyl aryl ethers

lides, the iodonium, phosphonium, and sulfonium salt reagents that are needed in these reactions are typically not commercially available. However, the syntheses of these aryl main-group compounds are generally quite simple, and the products are isolated by filtration in high yields as bench-stable solids.

Our interest in the development of reactions with non-symmetrical aryl(TMP)iodonium salts (TMP = 2,4,6-trimethoxyphenyl)[10] and the success we have had in the arylation of phenols prompted us to develop a C–O coupling between aryl(TMP)iodonium salts and aliphatic alcohols. This area is well-trodden territory,[6] and several challenges have been identified.[10i,11] First, diaryliodonium salts are susceptible to aryne formation when treated with alkoxide bases: the Olofsson group reported that the reaction between ditolyliodonium triflate and pentanol with *t*-BuONa as a base resulted in a mixture of *ipso* and *cine* substitution products, consistent with an aryne intermediate (Scheme 1c).[11] Additionally, we have observed that treatment of 4-chlorophenyl(TMP)iodonium salts with *t*-BuONa in the presence of furan as an aryne trap resulted in an 82% yield of the aryne–furan cycloadduct (Scheme 1c).[10i] Secondly, oxidation of alcohols to carbonyl compounds has been observed in reactions involving diaryliodonium salts and strong bases. The Olofsson group observed that 1-phenylethanol was oxidized to acetophenone (60%) in the presence of diphenyliodonium triflate and *t*-BuONa (Scheme 1c).[11]

Our development of a method to couple diaryliodonium salts with aliphatic alcohols focused on substrates that are prone to undergo side reactions, so that we could address some of the challenges in this chemistry (Scheme 1c). We therefore used 4-chlorophenyl(TMP)iodonium tosylate (**1a**) as the aryl electrophile and benzyl alcohol (**2a**) as the alkoxide nucleophile source (Table 1). We found that 1.5 equivalents of alcohol **2a** and 3.0 equivalents of Cs_2CO_3 as the base in toluene as the solvent for two hours at 55 °C resulted in a 78% NMR yield of ether **3a**, and we consider these our 'standard conditions' (Table 1, entry 1). We tested other solvents that have been used for C–O coupling with diaryliodonium salts[6] but in all cases, a lower yield was observed for **3a** than with our standard conditions (entries 1–4). Temperatures that were lower or higher than 55 °C resulted in lower yields of **3a** (entries 5 and 6). Bases that have been successfully used in arylation of phenols with diaryliodonium salts, such as K_2CO_3 and *t*-BuONa, also provided lower yields of **3a** than did Cs_2CO_3 (entries 7 and 8). Triethylamine (NEt_3) was ineffective as a base in this reaction (entry 9). The mechanistic implications of our standard conditions are addressed later (see below).

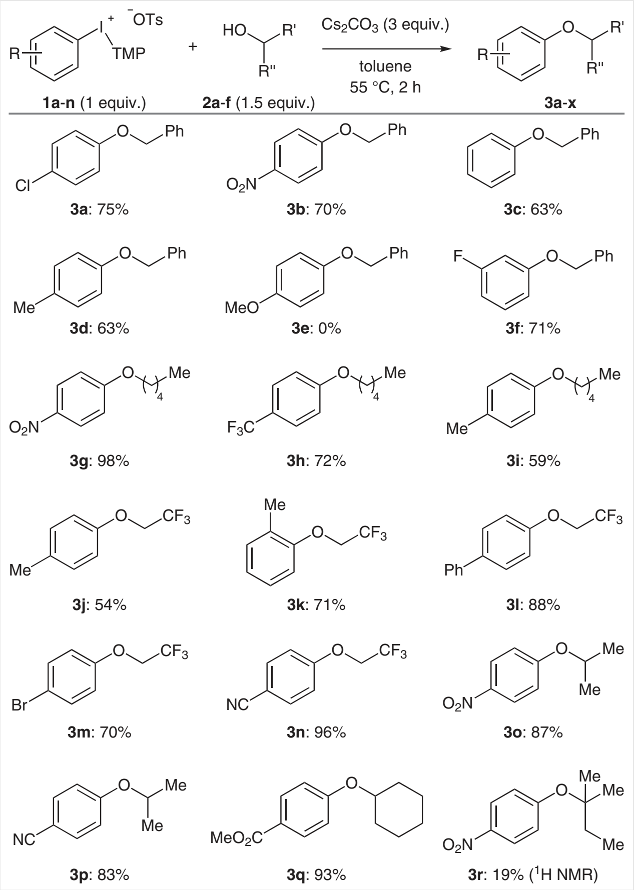
Table 1 Screening of Reaction Conditions[a]



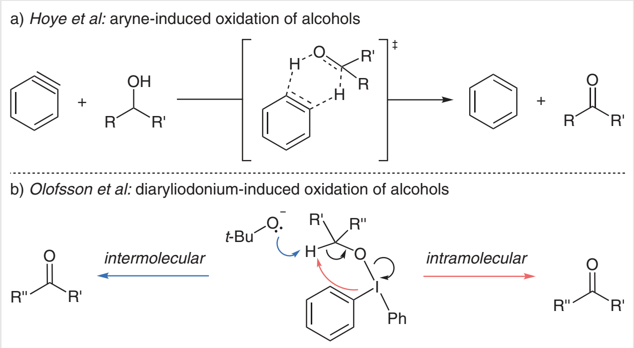
Entry	Deviation from standard conditions	Yield[b] (%) of 3a
1	–	78
2	THF as solvent	28
3	TBME as solvent	42
4	DCE as solvent	43
5	30 °C	43
6	80 °C	38
7	K_2CO_3 as the base	51
8	*t*-BuONa as the base	19
9	NEt_3 as the base	3
10	30 min	42

[a] Standard conditions: **1a** (0.1 mmol), **2a** (0.15 mmol, 1.5 equiv), Cs_2CO_3 (0.3 mmol, 3 equiv), toluene (0.5 mL), 55 °C, 2 h.
[b] Determined by ^1H NMR spectroscopy of the crude product with 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard.

The scope and limitations of this reaction are shown in Scheme 2. In the arylation of benzyl alcohol (**2a**), we obtained moderate to high yields (63–75%) of products **3a–d** from activated and moderately deactivated aryl(TMP)iodonium salts with substituents in the *para*-position to the iodonium leaving group. A limitation on this reaction is deactivated aryl(TMP)iodonium salts: the use of compound **1e**, bearing a 4-methoxy group, did not lead to the alkyl aryl ether product (Scheme 2). This is a distinct difference from our prior work on the arylation of phenols with aryl(TMP)iodonium salts.[10g] A substituent in the *meta*-position resulted in 71% yield of **3f**. Other primary alcohols were also compatible with this chemistry. Pentan-1-ol was arylated in high yields with aryl(TMP)iodonium salts bearing electron-withdrawing (NO_2 and CF_3) or electron-donating (Me) substituents in the *para*-position (**3g–i**). It is important to point out here that, in the case of the aryl(TMP)iodonium tosylate **1i** bearing a 4-methyl substituent, a small amount of an aryne was formed.[11] The ratio of *ipso*/*cine* substitution previously observed by Olofsson for a related substrate was 4:1,[11] and here we observed a ~19:1 ratio (Scheme 2). Additionally, the relatively weak nucleophile 2,2,2-trifluoroethanol was arylated under these conditions in moderate to high yields of 54–96% (**3j–n**).[12] The *ortho*-effect is operative in this reaction, and a competition experiment between **1k** and **1j** gave **3k** and **3j** in a 1.2:1 ratio, which is consistent with the yields observed for these two products (Scheme 2).[13,14] Secondary alcohols were arylated in high yield by activated aryl(TMP)iodonium salts (**3o–q**). Tertiary alcohols are another limitation of the reaction. Although we and others have observed C–O coupling of diaryliodonium salts with sodium *tert*-butoxide,[6d,10i] the use of *tert*-amyl alcohol under these conditions resulted in a very low yield of **3r**, even with the activated aryl(TMP)iodonium salt **1b**.



Scheme 2 Scope and limitations of C–O coupling

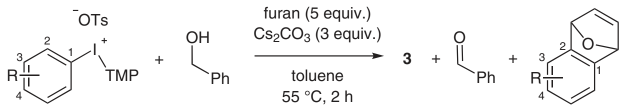


Scheme 3 Previous mechanistic proposals for alcohol oxidation involving arynes and diaryliodonium salts

Diaryliodonium salts, arynes, and the oxidation of alcohols can mechanistically intersect in several ways. First, we and others[11,15] have shown that diaryliodonium salts generate arynes under basic conditions. Even the relatively mild base used here, cesium carbonate, has been shown to be effective.[15j,m] Additionally, Hoye and co-workers have shown that arynes dehydrogenate alcohols in a concerted process to generate the simple arene and a carbonyl compound (Scheme 3a).[16] The Olofsson group has shown that the combination of a diaryliodonium salt, a benzylic alcohol, and a strong base (*t*-BuONa) resulted in alcohol oxidation (~60%).[11] Alcohol oxidation occurred even in the presence of a diaryliodonium salt that could not produce an aryne; this was key evidence supporting the view that arynes are not involved in alcohol oxidation.[11] The group proposed that alcohol oxidation occurs either by intramolecular deprotonation of the benzylic proton by an aryl group or by intermolecular deprotonation with *tert*-butoxide base (Scheme 3b).[11]

In light of the literature precedents, we conducted several experiments to identify potential reaction pathways in addition to C–O coupling under our optimal condition (Table 2). We also conducted two sets of control experiments to rule out background reactions. First, in the absence of the diaryliodonium salt, benzyl alcohol (**2a**) was not oxidized under our standard conditions (Cs_2CO_3, toluene, 55 °C, 2 h); therefore, the ambient atmosphere cannot lead to any benzaldehyde. Secondly, when benzyl alcohol was replaced by furan, we did not observe any aryne–furan cycloadduct and, therefore, Cs_2CO_3 is not sufficiently basic to generate arynes in toluene at 55 °C for two hours. We added furan as an aryne trap to a reaction of **1f** and **2a**, and analyzed the crude ^{1}H NMR spectrum. We observed a low 8% yield of the C–O coupling product **3f** and a high 73% yield of the aryne–furan cycloadduct **5a** (Table 2, entry 1). Consistent with our prior work, we also observed no benzaldehyde (entry 1).[6e] We have previously shown that *meta*-substituents activate aryl(TMP)iodonium salts toward aryne formation in the presence of alkoxides,[10i] so we turned our attention to *para*-substituted aryl(TMP)iodonium salts, which are less prone to aryne formation. The reaction of **1b**, bearing a strongly electron-withdrawing 4-nitro substituent, with **2a** in the presence of furan as an aryne trap resulted in a high yield of **3b** (96%) and no benzaldehyde or aryne–furan cycloadduct, based on an analysis of the crude ^{1}H NMR spectrum (entry 2). When we used **1a**, which has a less-electron-withdrawing 4-chloro substituent, the yield of the C–O coupling product was lower (58%), and we observed both benzaldehyde (14%) and the aryne–furan cycloadduct (10%) in the crude ^{1}H NMR spectrum (entry 3). The use of moderately electron-rich **1d**, bearing a 4-methyl substituent, again resulted in a slightly lower yield of the C–O coupling product **3d** (48%), a higher yield of benzaldehyde (23%), and a slightly lower yield of the aryne–furan cycloadduct (6%), based on the crude ^{1}H NMR spectrum. Collectively, these results point to a complex reaction system in which competitive reaction rates are controlled by the aryl substituent's position and electronic effects. Moreover, although arynes are formed in some reactions, consistent with Olofsson's observations,[11] it is unlikely that they are responsible for alcohol oxidation under these conditions.

Table 2 Experimental Evidence for the Formation of Arynes and Oxidation of Alcohols

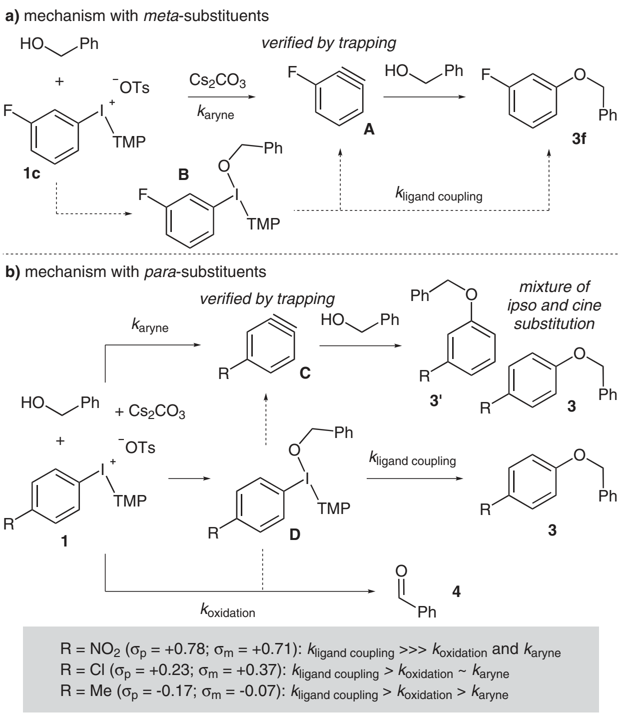


1 **2a** (1.5 equiv.) **4** **5**

Entry	Substrate	Yield (%) of **3**	Yield (%) of **4**	Yield (%) of **5**
1	**1f** (R = 3-F)	8	–	73
2	**1b** (R = 4-NO_2)	96	–	–
3	**1a** (R = 4-Cl)	58	14	10
4	**1d** (R = 4-Me)	48	23	6

[a] Reaction conditions: **1** (0.1 mmol, 1 equiv), **2a** (0.15 mmol, 1.5 equiv), furan (0.5 mmol, 5 equiv), Cs_2CO_3 (0.3 mmol, 3 equiv), toluene (0.5 mL), 55 °C, 2 h.

Our mechanistic interpretation is separated into substrates with *meta*- or *para*-substituents (Scheme 4). In the case of *meta*-substituents (i.e., compound **1f**), we observed a C–O coupling product (**3f**) and the aryne intermediate **A**, but no benzaldehyde was formed (Table 2, entry 1; Scheme 4a). The combination of Cs_2CO_3 and benzyl alcohol (**2a**) probably generates a sufficient quantity of alkoxide to deprotonate **1f** and generate the aryne intermediate **A** (Scheme 4a). The presence of **A** was confirmed by trapping experiments in which furan was introduced into reaction mixtures, and the yield of the aryne–furan cycloadduct **5a** was similar to that of **3f** in the absence of furan (Scheme 2; Table 2, entry 1). We can neither confirm nor rule out the presence of λ^3-iodane **B**, which might be a precursor to aryne **A** (Scheme 4a). However, given the high yield of aryne confirmed in these reactions, we posit that $k_{\text{aryne}} \ggg k_{\text{ligand coupling}}$ and that the vast majority of **3f** is derived from aryne **A** (Scheme 4a). We measured the arynophilicity of benzyl alcohol based on our previously reported scale,[10j,14] and we obtained a value of –1 (compared with 0 for furan), which agrees well with the ratio of **5a** and **3f** in Table 2, entry 1. We cannot rule out the possibility that a small amount of alkoxide also reacts with aryne **A**. In this case, the formation of aryne **A** is inconsequential to the product distribution because the major product of nucleophilic addition of benzyl alcohol (**2a**) to aryne **A** is the same as that produced by ligand coupling from **B**, that is *ipso*-substitution of the iodonium leaving group.[17] Moreover, given that we observe no benzaldehyde in the reaction of **1f** and **2a**, a combination that would generate substantial amounts of aryne, we speculate that under these conditions, arynes do not mediate the oxidation of benzyl alcohol.



R = NO_2 (σ_p = +0.78; σ_m = +0.71): $k_{\text{ligand coupling}} \ggg k_{\text{oxidation}}$ and k_{aryne}
R = Cl (σ_p = +0.23; σ_m = +0.37): $k_{\text{ligand coupling}} > k_{\text{oxidation}} \sim k_{\text{aryne}}$
R = Me (σ_p = -0.17; σ_m = -0.07): $k_{\text{ligand coupling}} > k_{\text{oxidation}} > k_{\text{aryne}}$

Scheme 4 Mechanistic interpretation

In the case of *para*-substituents, we observed C–O coupling products **3**, benzaldehyde (**4**), and arynes, though their ratios depend on the electronic effects of the substituent (Scheme 4b). In all three cases studied, the C–O coupling products **3b**, **3a**, and **3d** were the major product and, therefore, we suggest that λ^3-iodane **D** is a key intermediate in this case, unlike the case with *meta*-substituents (Schemes 4a and 4b). Compound **1b** with a *para*-nitro substituent gave a high yield of the C–O coupling product **3b** and no benzaldehyde (**4**) or aryne–furan cycloadduct **5b** when the reaction was conducted in the presence of furan (Table 2, entry 2). Therefore, we interpret these results as suggesting that when strongly electron-withdrawing substituents are present (i.e., NO_2), $k_{\text{ligand coupling}} \ggg k_{\text{oxidation}}$ and k_{aryne} (Scheme 4b). The 4-chloro substituent in compound **1a** is less electron withdrawing than the 4-nitro substituent in **1d** and, consequently, both alcohol oxidation and aryne formation were observed (Table 2, entry 3; Scheme 4b). The chloro substituent is inductively withdrawing and slightly activates the *meta*-position to deprotonation and aryne formation. Overall, the relative order of competitive rates for compound **1a** is $k_{\text{ligand coupling}} > k_{\text{oxidation}} \approx k_{\text{aryne}}$ (Scheme 4b). As the transferring aryl group becomes more electron rich, based on the substituent (4-NO_2 to 4-Cl to 4-Me), the yield of C–O coupling decreases and the yield of side reactions increases. The reaction of compound **1d** with an electron-donating 4-methyl substituent produces more benzaldehyde (**4**) than was observed with compound **1a** bearing a 4-chloro substituent. However, the amount aryne intermediate **C** is reduced relative to that observed for **1a** due to the inductively donating character of methyl, based on its σ_m value (Scheme 4b). Therefore, the relative order of competitive rates with compound **1d** is $k_{\text{ligand coupling}} > k_{\text{oxidation}} > k_{\text{aryne}}$ (Scheme 4b). In this case, the C–O coupling product is produced in a higher yield than the alcohol oxidation product, which is opposite to the result previously observed by Olofsson.[11] However, there are several differences between these two systems: (a) aryl(TMP)iodonium salts versus diphenyliodonium salt, (2) benzyl alcohol versus phenethyl alcohol, (3) 55 °C versus r.t., and (4) Cs_2CO_3 versus *t*-BuONa. Although the spectator ligand might be an important factor, and both systems employ benzylic alcohols, we suspect that the temperature and, especially, the nature of the base have greater impacts on the relative product distribution.

In conclusion, we have developed a method for O-arylation of aliphatic alcohols with aryl(TMP)iodonium salts.[18,19] The method is compatible with primary and secondary alcohols and with aryl groups bearing electron-withdrawing substituents or moderately electron-donating substituents. The mechanisms of O-arylation and alcohol oxidation (as a side reaction) are dependent on the position and electronic effects of the aryl substituent.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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(18) **C–O Coupling; General Procedure**
The appropriate aryl(TMP)iodonium tosylate **1a–l** (0.5 mmol, 1 equiv), Cs_2CO_3 (1.5 mmol, 3 equiv), alcohol **2a–f** (0.75 mmol, 1.5 equiv), and toluene (2.5 mL) were added to an 8 mL vial, equipped with a magnetic stirrer bar and sealed with a cap. The vial was placed in a preheated aluminum block set to 55 °C, and the mixture was stirred vigorously for 2 h. The vial was removed from the block and the mixture was partitioned between CH_2Cl_2 and sat. aq NH_4Cl. The resulting organic solution was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 0–3% EtOAc–hexane).

(19) **Benzyl 4-Chlorophenyl Ether** (**3a**)
White solid; yield 82.3 mg (75%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.32 (m, 5 H), 7.22 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.02 (s, 2 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 157.4, 136.6, 129.4, 128.7, 128.1, 127.5, 125.8, 116.2, 70.3.

4-Nitrophenyl Pentyl Ether (3g)
Yellow oil; yield: 102.8 mg (98%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19–8.15 (m, 2 H), 6.96–6.92 (m, 2 H), 4.04 (t, *J* = 6.5 Hz, 2 H), 1.86–1.79 (m, 2 H), 1.49–1.35 (m, 4 H), 0.94 (t, *J* = 7.1 Hz, 3 H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ = 164.3, 141.2, 125.8, 114.4, 68.9, 28.7, 28.0, 22.4, 14.0.

4-Bromophenyl 2,2,2-Trifluoroethyl Ether (**3m**)
Off-white solid; yield: 89.8 mg (70%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 8.9 Hz, 2 H), 4.31 (q, *J* = 8.1 Hz, 2 H). $^{13}C\{1 H\}$ NMR (101 MHz, $CDCl_3$): δ = 156.5, 132.6, 123.2 (q, *J* = 278.1 Hz), 116.8, 115.0, 66.0 (q, *J* = 35.8 Hz).