Direct Benzylic C–H Etherification Enabled by Base-Promoted Halogen Transfer

Kendelyn I. Bone†, Thomas R. Puleo†, Michael D. Delost, Yuka Shimizu and Jeffrey S. Bandar*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

ABSTRACT: We disclose a benzylic C–H oxidative coupling reaction with alcohols that proceeds through a synergistic deprotonation, halogenation and substitution sequence. The combination of *tert*-butoxide bases with 2-halothiophene halogen oxidants enables the first general protocol for generating and using benzyl halides through a deprotonative pathway. In contrast to existing radical-based pathways for C–H functionalization, this process is guided by C–H acidity trends. This gives rise to new synthetic capabilities, including the ability to functionalize diverse methyl(hetero)arenes, tolerance of oxidizable and nucleophilic functional groups, precision regioselectivity for polyalkylarenes and use of a double C–H etherification process to controllably oxidize methylarenes to benzaldehydes.

The widely valued benzyl ether motif is commonly produced by alcohol substitution reactions of benzylic electrophiles, especially benzyl halides.[1,2] As such, benzylic C–H radical halogenation methods are widely relied upon for the net coupling of alkylarenes with alcohols as a two-step route to benzyl ethers (Figure 1a).[3] In addition to the use of hazardous initiators, these routes require independent preparation and handling of toxic benzyl halides.[4] Furthermore, the C–H halogenation step is prone to undesired dihalogenation, is not site-selective for compounds with multiple weak C–H bonds and can be incompatible with nucleophilic or oxidizable functional groups.[5] While some of these concerns have been addressed through modern approaches to C–H radical halogenation[6], direct oxidative coupling of abundantly available alkylarenes with alcohols represents a more efficient and modular approach to benzyl ethers.[7,8] These advantages have motivated developments, led by the Doyle, Lei, Musacchio, Stahl and Yu groups, in benzylic C–H etherification reactions that proceed *via* initial alkylarene activation by single electron oxidation or hydrogen atom abstraction (Figure 1a).[9-11] In these reactions, C–O bond formation is ultimately accomplished by alcohol addition to benzylic carbocations or metal-mediated coupling of benzylic radicals. We herein describe a new approach to benzylic oxidative coupling reactions that proceeds *via* a base-promoted C–H halogenation/substitution sequence with unique scope, selectivity and utility that are distinct from existing C–H functionalization routes (Figure 1b).

Although seemingly simple, deprotonative benzylic C–H halogenation is undeveloped due to the incompatibility of strong bases and halogen oxidants. For example, the deprotonative halogenation of weakly acidic benzylic C–H bonds would require a two-step protocol consisting of metalation followed by electrophilic halogenation.[12] In practice, however, the benzyl halide generated upon addition of the halogen electrophile reacts with the pregenerated metalated alkylarene, causing benzylic dimerization (Figure 2a).[13,14] We note these challenges can be overcome for the C–H fluorination and chlorination of relatively acidic alkyl-*N*-heteroarenes (e.g., 4-alkylpyridines) using weak bases in conjunction with *N*-atom activation, as developed by the Britton and Stahl groups.[15] We realized that the key to productively leverage deprotonative benzylic halogenation more generally is to devise a process wherein the base, halogen oxidant and desired benzyl halide functionalization event (e.g., substitution) are all compatible.

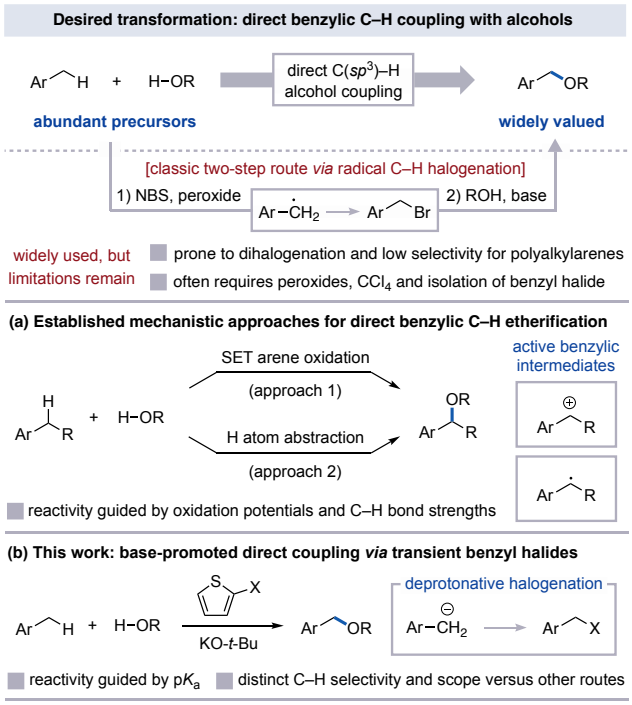


Figure 1. Motivation and summary of benzylic C–H etherification methods.

Our lab recently disclosed methods for direct (*N*-hetero)aryl C–H etherification and hydroxylation wherein KO-*t*-Bu catalyzes halogen transfer from 2-halothiophene oxidants to generate (*N*-hetero)aryl halide intermediates that undergo S_NAr reactions.[16] This approach is distinct from traditional metalation as it enables deprotonation, halogenation and substitution steps to

operate as compatible processes, allowing for an alkoxide base (pK_a ~32 in DMSO) to promote arene functionalization (pK_a up to ~38) with distinct regioselectivity trends.[17,18] These methods were inspired by "halogen dance" methodology developed decades ago where halogens migrate between aryl carbanion species.[19] We recently questioned if halogen transfer (X-transfer) could be applied to other types of weakly acidic C–H bonds, including C(sp^3)–H variants. We reasoned that if X-transfer to benzylic C–H bonds is possible, the compatibility of deprotonation, oxidation and substitution processes could enable a new means for benzylic C–H coupling with heteroatom pronucleophiles (Figure 2c).[20] Specifically, use of an alkoxide base would generate low concentrations of a benzylic carbanion such that, upon halogenation, rapid S_N2 with an anionic heteronucleophile would provide the coupled product and avoid benzylic dimerization.[21] Given that the pK_a of primary and secondary alcohols is lower than *t*-BuOH, we anticipated large concentrations of the desired alkoxide nucleophile would be generated to selectively capture the benzyl halide when *tert*-butoxide bases are used.[22-24]

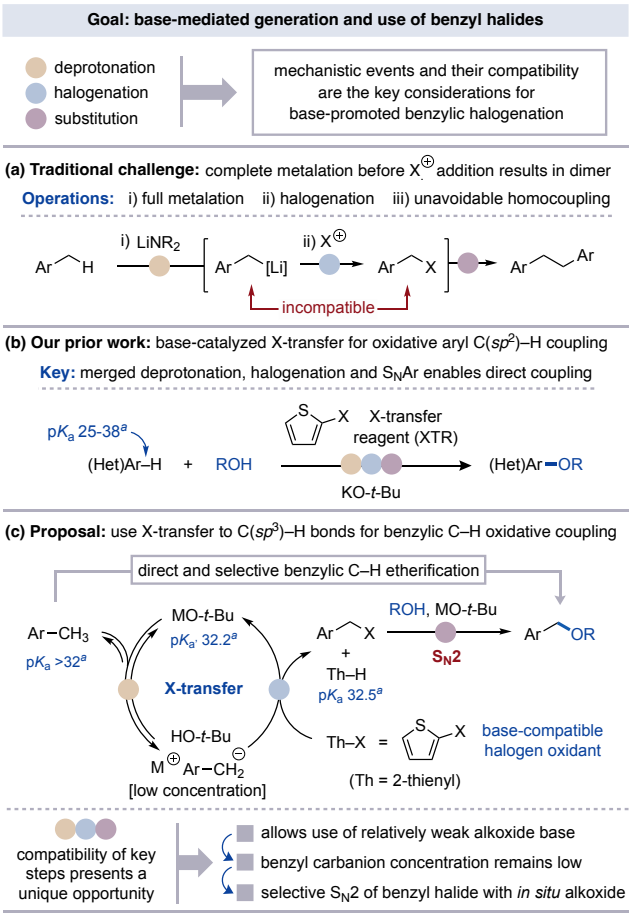


Figure 2. Considerations and outline of a deprotonative approach to the generation and use of benzyl halides. [a] pK_a values in DMSO.[18,21]

We tested this proposal for the C–H etherification of 2,6-dichlorotoluene (Figure 3a), a precursor to benzyl ether pharmaceuticals that has been studied for radical benzylic halogenation improvement.[25] We found the desired coupling occurs readily with KO-*t*-Bu and 2-iodothiophene (**XTR 1**, XTR = X-transfer reagent) under numerous conditions (e.g., 62% yield in DMPU and 97% in THF).[26] We next investigated 1-methylnaphthalene, a less acidic and potentially more challenging substrate (Figure 3b).[21] Use of KO-*t*-Bu and 2-iodothiophene (**XTR 1**) for this substrate gives 39% yield and could not be increased using other bases or conditions, suggesting improvement would need to come through X-transfer reagent modification.

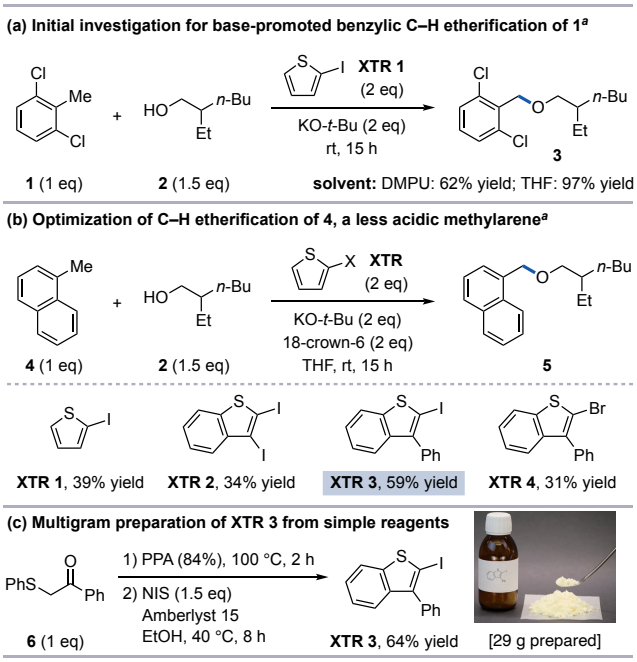
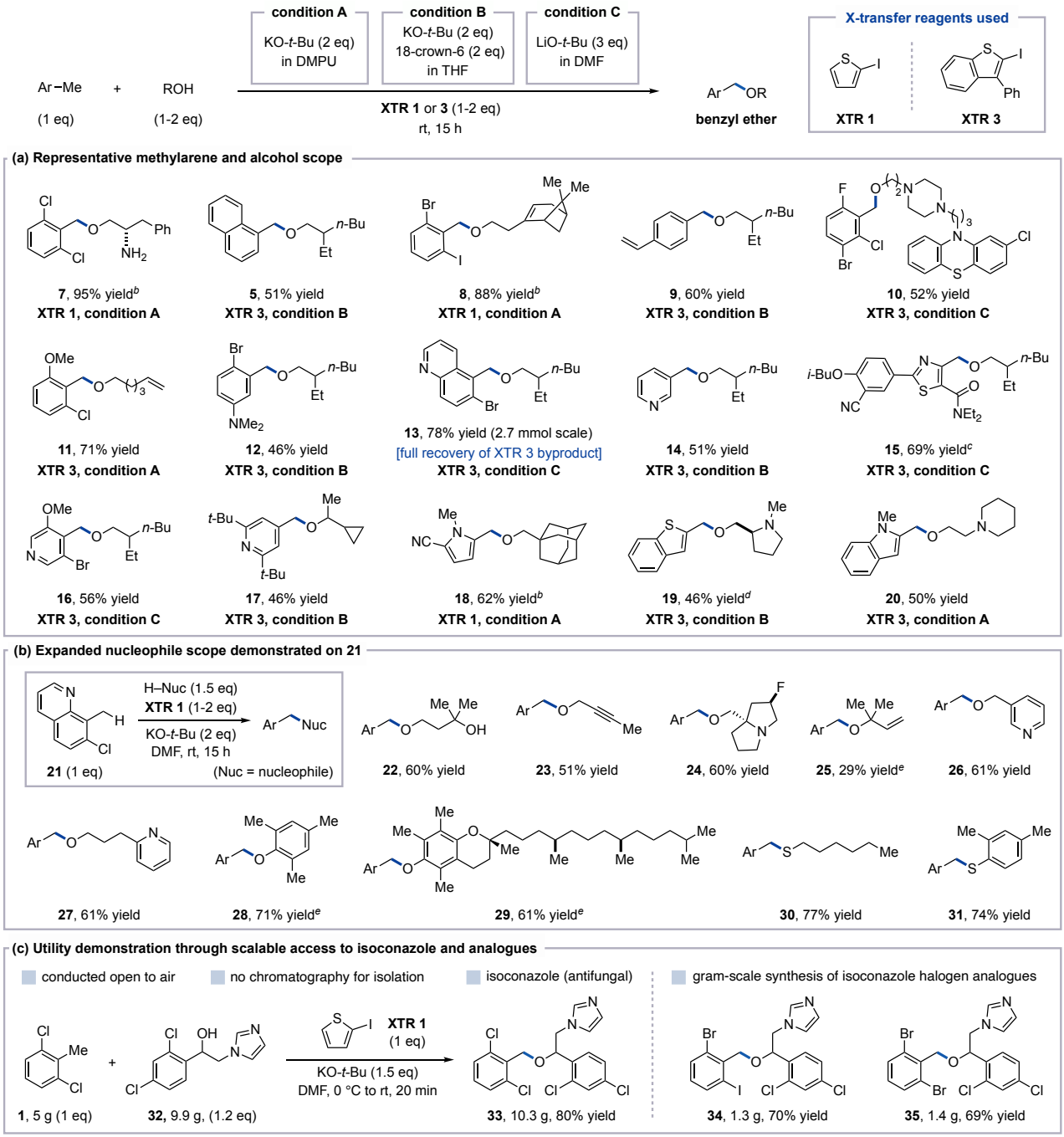


Figure 3. Benzylic C–H etherification optimization and the scalable synthesis of **XTR 3**. [a] ^{1}H NMR yields reported.

In our aryl C(sp^2)–H functionalization work, we found 2-iodothiophene undergoes base-promoted disproportionation to form 2,3-diiodothiophene that can act as an oxidant or rearrange further to inactive 3-iodothiophenes.[16,27] This previously led us to create 2,3-dihalobenzothiophenes as more effective X-transfer reagents that cannot rearrange. However, use of 2,3-diiodobenzothiophene (**XTR 2**) gives only 34% C–H etherification of 1-methylnaphthalene (**4**), indicating the 2,3-diiodothiophene motif is not an improved oxidant for this reaction. We therefore investigated 2-halobenzothiophenes with non-halogen 3-substituents, including 2-iodo-3-phenylbenzothiophene (**XTR 3**) which gives an improved 59% yield. Structural variations did not increase the yield further, including 3-aryl substituent derivatives or replacement of iodine with bromine (**XTR 4**). A summary of XTRs examined and additional condition variations for substrates **1** and **4** are provided in the Supporting Information. 2-Iodo-3-phenylbenzothiophene (**XTR 3**) is accessible in large quantity from thiophenol substitution of bromoacetophenone to produce **6** followed by a cyclization/halogenation sequence (Figure 3c).[28]

A representative scope of benzyl ethers accessible *via* this method is shown in Table 1a. Our optimization studies indicated multiple metal *tert*-butoxide bases and solvents promote C–H etherification; during our substrate scope studies, we identified three combinations (Conditions A-C) to be the most general using **XTR 1** or **XTR 3**.[29] Methylarenes with diverse functional groups, including all halogens, ethers, amines, alkenes and nitriles provide 45-90% yield (**7**-**12**); here, *ortho*-substitution is well-tolerated but not necessary. A wide range of methylheteroarenes also engage in this process (**13**-**20**), including pyridines with methyl groups in all positions and methylpyrimidines, -pyrroles, -quinolines, -indoles and -thiophenes. Less

Table 1. Benzylic C–H Etherification and Thioetherification Substrate Scope[a]



[a] Isolated yields of 0.25-1 mmol scale reactions. [b] 10 min reaction time. [c] ^{1}H NMR yield reported due to coelution with methylarene; 32% isolated. [d] 18-crown-6 (0.5 eq) used. [e] KOH and 18-crown-6 (2.5 eq) used.

acidic methylarenes (e.g., toluene) and ethylarenes do not undergo C–H etherification under the current conditions, presumably due to a more challenging deprotonation step.[21] We note in Table 1a that primary and secondary alcohols perform well, including unprotected aminoalcohols (**7**), the pharmaceutical perphenazine (**10**), an alkenol (**11**) and other bulky alcohols (**17** and **18**). While use of benzothiophene **XTR 3** is not ideal from an atom economy perspective, we note that the 3-phenylbenzothiophene byproduct can be recovered and recycled as shown in its gram-scale use for **13**.

We reasoned this approach to oxidative coupling would be readily transferrable to a broader scope of *O*- and *S*-pronucleophiles. Using 7-chloro-8-methylquinoline (**21**) as a model substrate, we found that effective coupling occurs with a wide range of alcohols, phenols, thiols and thiophenols using **XTR 1** (Table 1b).[30] We also studied polyfunctionalized pronucleophiles to assess the coupling selectivity and found that desired etherification occurs for a variety of more complex substrates. This includes an unprotected diol where benzylation occurs at the primary alcohol (**22**), a tertiary alkenol (**25**), and pyridine-containing alcohols that have acidic C–H bonds (**26** and **27**).[31] Additionally, methyl-substituted phenols (**28**) and thiophenols

(**31**), including vitamin E (**29**), do not undergo competing functionalization at their benzylic positions. Amines are generally not effective pronucleophiles under the current reaction conditions, a limitation that is being addressed in ongoing work.

The scalability and utility of this protocol is further demonstrated in Table 1c where the antifungal isoconazole (**33**) was prepared on a 10-gram scale (80% yield) in 20 minutes using **XTR 1**.[32] This reaction was conducted open to air, an unusual capability for a process that proceeds *via* a benzyl carbanion intermediate.[33] Thus, the inclusion of inexpensive 2-iodothiophene (**XTR 1**) enables rapid C–H substitution under conditions that parallel traditional base-promoted alcohol alkylation reactions with benzyl halides. This obviates the need to prepare, purchase or handle benzyl halides and streamlines access to analogues where the benzyl halide is not commercial. These advantages are shown for the gram-scale production of isoconazole halogen analogues **34** and **35**.[34]

This oxidative coupling reaction is initiated by deprotonation and is thus guided by acidity trends.[35] This contrasts existing benzylic C–H etherification methods that are dependent on C–H bond strengths or substrate oxidation potentials as they proceed *via* hydrogen atom abstraction or arene oxidation, respectively. This distinction makes the X-transfer mechanistic approach complementary as it is well suited for methylarenes, a class of substrates that are not within the scope of alternative methods.[9,10,36] This includes electron-deficient methylarenes and *N*-heteroarenes (e.g., **8**-**10** and **13**-**18**) that possess high oxidation potentials or substrates with oxidatively-sensitive C–H bonds or functional groups (e.g., **8**-**11**, **26**, **30**, **31**).[37]

The regioselective functionalization of polyalkylarenes that contain multiple benzylic positions represents an important goal for selective synthesis.[38] This mechanistic and synthetic challenge is exemplified by radical C–H halogenation of polymethylarenes that routinely gives regioisomeric benzyl halide mixtures that are difficult to separate.[4,5,39] Although radical-based C–H etherification reactions provide selectivity in certain contexts (e.g., for a weaker ethyl over methyl C–H bond or functionalization *para* to an alkoxy group), no general solution to distinguish between C–H bonds of similar strength or substrates devoid of strong directing groups has been disclosed.[9,10,36] In this regard, we proposed that the unique reagent combination of an X-transfer approach could drive selectivity for the most acidic position of polyalkylarenes in a broadly transferrable manner.

The X-transfer protocol uses alkoxide bases that facilitate energetically uphill benzylic deprotonation and, consequently, is sensitive to subtle differences in substituent acidity.[18,21,40] We therefore reasoned if X-transfer is fast enough, oxidative coupling would occur at the most acidic position of polyalkylarenes. Figure 4 demonstrates the efficacy and generality of this principle where the standard coupling conditions promote >10:1 regioselective C–H etherification across a broad range of polyalkylarenes. For polymethyl systems, the position that can form an anion in conjugation with a stabilizing group is preferentially functionalized (**36**-**38**), although minor electronic disparities can also guide high selectivity (**39**-**41**).[41] Subtle structural differences are also sufficient for positional precision, as seen for 3,4'-dimethylbiphenyl (**42**) and etherification of a methyl over an ethyl group in **43**.

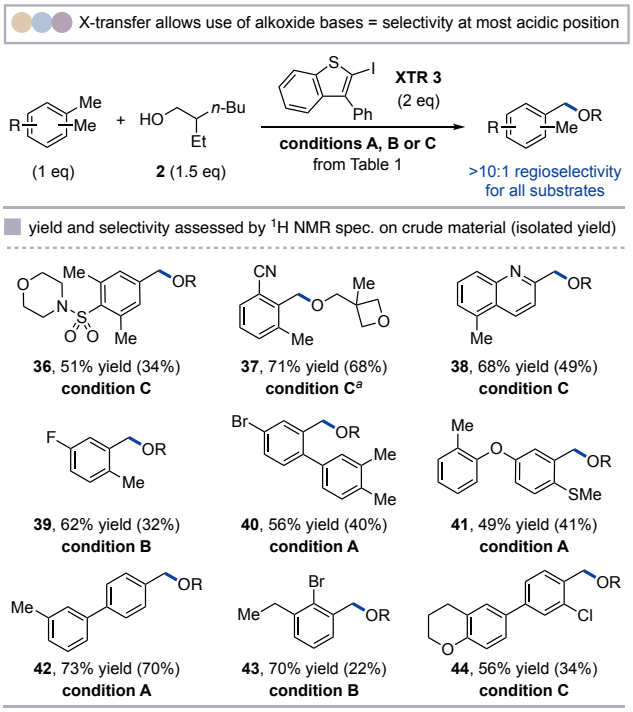


Figure 4. Regioselective polyalkylarene C–H etherification. ^{1}H NMR yields reported to assess selectivity on crude reaction material; isolated yields are lower due to coelution. [a] **XTR 1** used.

During our substrate studies, we found that several relatively acidic methylarenes could not be optimized above 50-65% etherification yield due to an X-transfer-promoted over-oxidation process. This is represented by 2-methylbenzotrifluoride (**45**) that readily undergoes C–H etherification (**46**) but with competing formation of an acetal (**47**). A reaction time profile revealed that the second oxidation does not occur to a substantial degree until about 60% ether forms (Figure 5a).[42] Thus, for substrates that engage in acetal formation, optimal yields may be obtained at shortened reaction times or through the use of LiO-*t*-Bu that is slower at promoting the second oxidation event (Condition C).[29]

The discovery of a double C–H etherification side process inspired us to apply this reactivity towards a controlled methylarene oxidation protocol.[43] Thus, under optimized conditions (excess base, **XTR 1** and *n*-propanol), high-yielding acetal formation provides aldehydes upon treatment with acid in a one-pot process (Figure 5b). This procedure can be applied to substrates previously shown in Table 1 and Figure 4 (e.g., **50**), as well as 2-methylpyridines (**51**) as a streamlined alternative to frequently used but tedious multistep oxidation routes.[44] Site- and oxidation-state selectivity is also observed for polyalkylarenes (**52**). This includes the 5-gram scale synthesis of benzaldehyde **53**, where aldehyde derivatization achieves site-selective methyl oxidations to all oxidation states (**57** and **58**), formal conversions of the methyl substituent to difluoromethyl (**54**) and vinyl (**55**) groups, or methyl removal to a hydrogen atom (**56**).

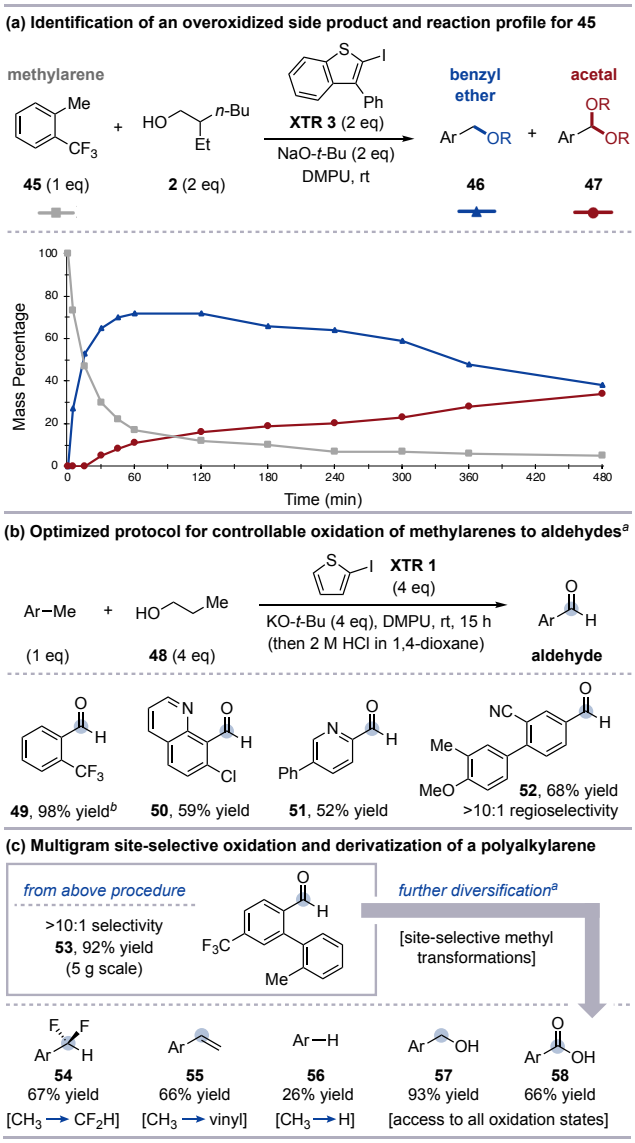


Figure 5. Acetal formation and its use for controllable methylarene oxidation. [a] Isolated yield from 0.25-1 mmol scale reactions. [b] ^{1}H NMR yield reported due to product volatility.

In summary, base-promoted X-transfer enables direct oxidative coupling reactions of benzylic C–H bonds with heteroatom pronucleophiles. The merger of deprotonation, halogenation and substitution steps is a critical design feature that enables *in situ* generation and use of benzyl halides under basic conditions. In turn, deprotonative activation provides new capabilities for benzylic C–H etherification, such as the ability to functionalize high-oxidation potential and oxidatively-sensitive substrates, to guide selectivity to the most acidic position and to regulate the number of oxidation events. We anticipate this mechanistic platform can bring similar advantages to other realms of C–H functionalization given that X-transfer is now shown to be general to both C(sp^3)–H and C(sp^2)–H bonds.[45]

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data of new compounds.

AUTHOR INFORMATION

Author Contributions

† K.I.B. and T.R.P. contributed equally to this work.

Corresponding Authors

*jeff.bandar@colostate.edu

Notes

The authors declare no competing financial interest.

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(39) Control studies for radical benzylic bromination were conducted on polyalkylarene starting materials for **36** and **40** in Figure 4; in both cases, more than four distinct products formed in significant quantities and could not be readily separate. See Supporting Information for details.

(40) Consistent with this proposal, control studies with deuterated alcohol showed that metal alkoxide bases promote regioselective deuterium exchange of polyalkylarene starting materials for **36** and **40** in Figure 4 under similar reaction conditions. See Supporting Information for details.

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