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Boryl radical-mediated halogen-atom transfer (XAT) enables the Sonogashira-like alkylation of alkyl halides†

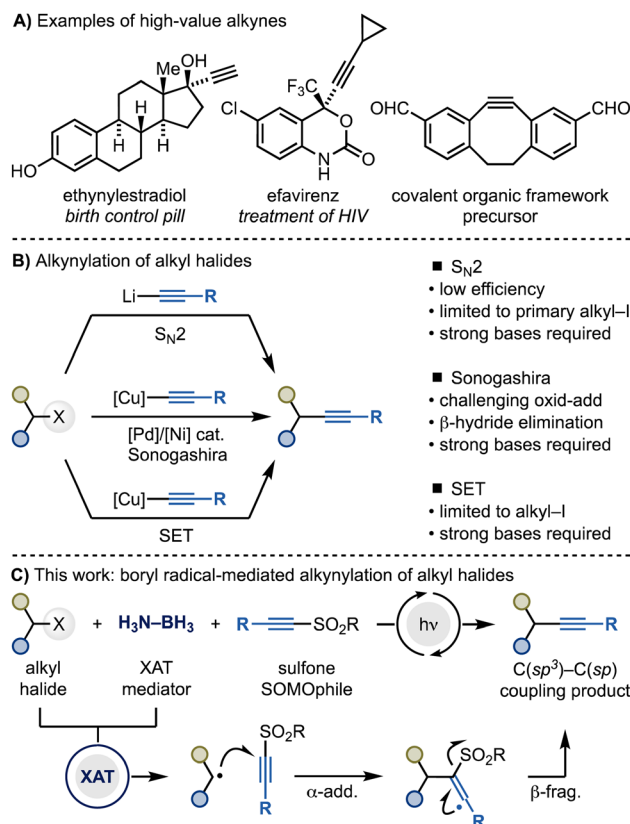
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Alkynes are a crucial class of materials with application across the wide range of chemical disciplines. The alkylation of alkyl halides presents an ideal strategy for assembling these materials. Current methods rely on the intrinsic electrophilic nature of alkyl halides to couple with nucleophilic acetylenic systems, but these methods face limitations in terms of applicability and generality. Herein, we introduce a different approach to alkylation of alkyl halides that proceeds via radical intermediates and uses alkynyl sulfones as coupling partners. This strategy exploits the ability of amine-ligated boryl radicals to activate alkyl iodides and bromides through halogen-atom transfer (XAT). The resulting radicals then undergo a cascade of α -addition and β -fragmentation with the sulfone reagent, leading to the construction of $C(sp^3)$ - $C(sp)$ bonds. The generality of the methodology has been demonstrated by its successful application in the alkylation of complex and high-value molecules.

Introduction

Alkynes play key roles in chemical synthesis, medicinal chemistry and materials science (Scheme 1A).^{1,2} For instance, alkynes are widely used as dipolarophiles in [3 + 2] cycloadditions, a pivotal transformation within the bioconjugation toolbox.³ Additionally, they are often employed as bioisosteres for various functionalities, such as carbonyls, 1,4-disubstituted phenyls, and cyclopropyl groups.⁴ Consequently, the development of methods for the modular introduction of alkyne functionalities onto organic molecules is still a highly sought-after goal in synthesis and catalysis.

Within this context, the alkylation of alkyl halides would be particularly useful considering the large amounts of derivatives commercially available (Scheme 1B). However, engaging these species in $C(sp^3)$ - $C(sp)$ bond formations is still synthetically challenging. Current methods match the intrinsic electrophilic nature of alkyl halides with nucleophilic acetylene sources for S_N2 reactivity (e.g. alkynyl organolithiums), Sonogashira cross-couplings (e.g. alkynyl organocoppers) and radical manifolds (also alkynyl organocoppers). However, these strategies are often synthetically restricted to primary alkyl iodides due to challenges in either substitution reactivity (S_N2 methods),⁵ oxidative addition and β -hydride

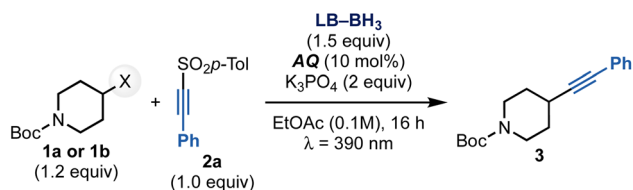


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Scheme 1 (A) Examples of high-value alkyne-containing materials. (B) General methods for the alkylation of alkyl halides and their limitations. (C) This work demonstrates a radical approach based on XAT for the alkylation of alkyl halides (iodides and bromides).





entry	X	LB-BH ₃	T (°C)	yield 3 (%)
1	I	Me ₃ N-BH ₃	r.t.	86
2	I	H ₃ N-BH ₃	r.t.	40
3	I	Me ₂ HN-BH ₃	r.t.	55
4	I	Et ₂ PhN-BH ₃	r.t.	12
5	I	pyr-BH ₃	r.t.	25
6	I	Ph ₃ P-BH ₃	r.t.	39
7	Br	Me ₃ N-BH ₃	r.t.	24
8	Br	Me ₃ N-BH ₃	55–60	61
9 ^a	I	Me ₃ N-BH ₃	r.t.	–
10 ^b	I	Me ₃ N-BH ₃	r.t.	–
11 ^c	I	Me ₃ N-BH ₃	r.t.	26

Scheme 3 Optimization for the alkylation of **1a** with **2a**. ^aReaction run in the dark. ^bReaction run without AQ. ^cReaction run without K₃PO₄.

the desired product **3** and a sulfinate radical, which could close the photocatalytic cycle by SET and deprotonation with the ketyl radical (KR).

Reaction development

To validate this mechanistic hypothesis, we evaluated the reaction of alkyl iodide **1a** and sulfone **2a** (Scheme 3). Pleasingly, the use of Me₃N-BH₃ as XAT mediator in the presence of K₃PO₄ as the base and anthraquinone (AQ) as the photocatalyst under purple LEDs ($\lambda = 390$ nm) irradiation in EtOAc gave **3** in 86% yield (entry 1, see the ESI† for further optimization studies). Other amine-ligated boranes as well as pyr-BH₃ and Ph₃P-BH₃ could be used in the process but they were all significantly less effective (entries 2–6). This can be mostly rationalized with their lower nucleophilic character that might retard the XAT process. Control experiments confirmed that all components as well as light irradiation are essential for reactivity (entries 9–10), while the base is mostly important to achieve high yields (entry 11). When the same reaction conditions were applied to the alkylation of bromide **1b**, the desired product **3** was obtained in poor conversion (entry 7, see the ESI†). However, conducting the reactions at 55–60 °C restored reactivity, providing **3** in 61% yield (entry 8). We believe the higher temperature might be necessary to facilitate the XAT on the stronger C(sp³)-Br bond.²²

Reaction scope

With a method for radical alkylation of alkyl halides in hand, we proceeded to explore the scope of the process. We initially examined a series of aryl-substituted alkynyl sulfones using **1a** and **1b** as the coupling partners (Scheme 4). This investigation

demonstrated the methodology's compatibility with aromatic units substituted with both electron-donating and electron-withdrawing substituents at the *para* (**4–9**), *meta* (**10–12**) and *ortho* (**13**) positions. Notably, the reactions tolerated ester (**5**), CF₃ (**6**), aryl chloride and fluoride (**7** and **12**) as well as free alcohol (**9**) and free aniline (**11**) functionalities.

Next, we valued reagents based on (hetero)aromatic systems and successfully extended the reactivity to sulfones containing 1-naphthyl (**14**), 9-phenanthrenyl (**15**) and 3-thienyl (**16**) groups.

The scope of alkyl halides was then explored using **2a** as the sulfone coupling partner. Pleasingly, we successfully engaged a range of saturated heterocyclic fragments commonly found in medicinal chemistry libraries.²³ These included 3-tetrahydropyran (**17**), 3-*N*-Boc-pyrrolidine (**18**) as well as 2-*N*-Boc-azetidine (**19**), 2-oxetane (**20**) and 2-indenol (**23**) derivatives. Complex alkyl halides can be conveniently accessed through halo-lactonization processes, which upon alkylation yielded tricyclic systems **21** and **22** in high diastereoselectivity (dr *exo* : *endo* > 20 : 1).

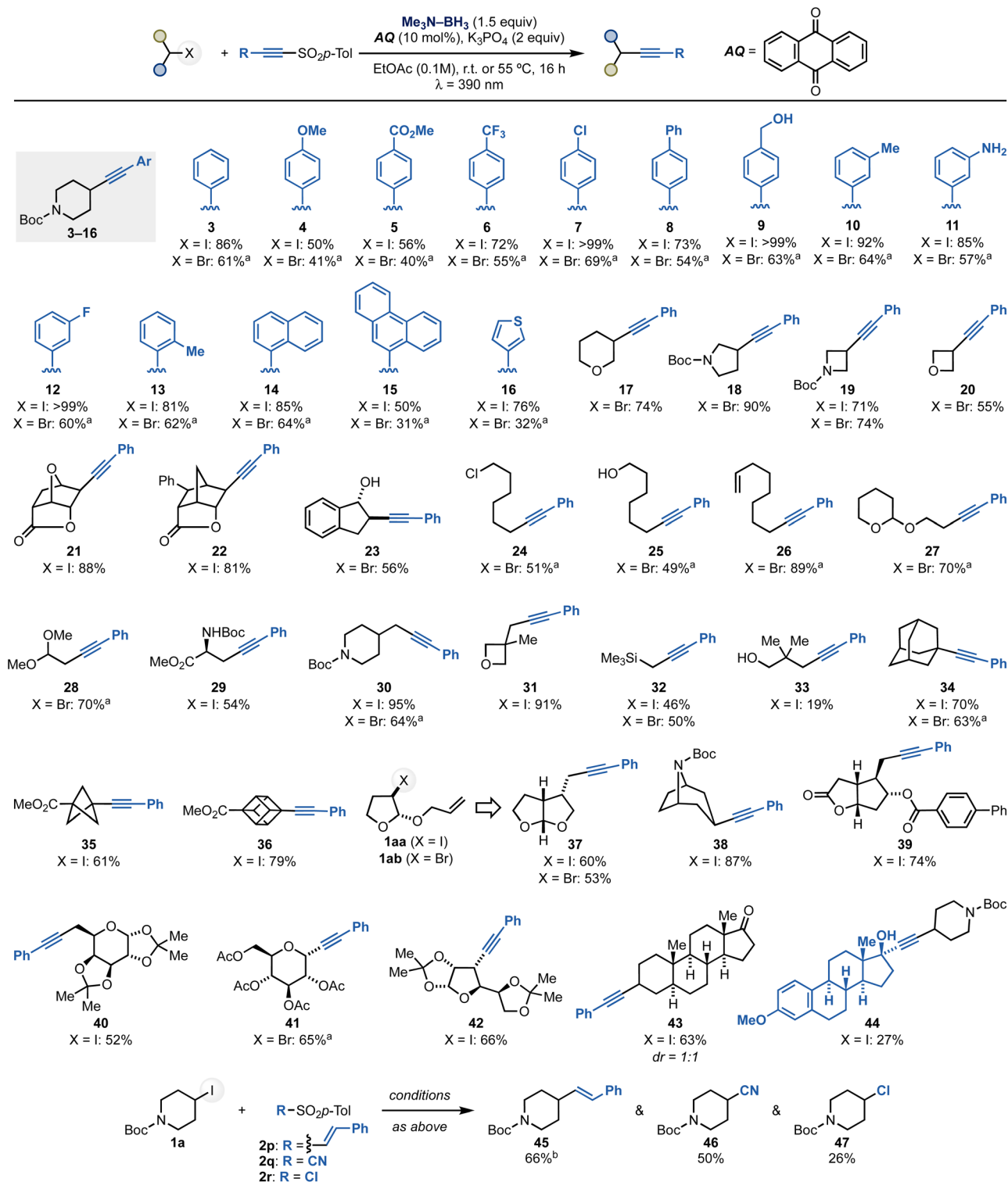
We then screened primary alkyl halides and demonstrated the chemistry's compatibility with alkyl chloride (**24**), free alcohol (**25**), olefin (**26**) as well as acetal (**27–28**) and amino acid (**29**) functionalities. We were then keen on determining if the method could be used for the functionalization of hindered halides. This was demonstrated by engaging a series of derivatives of neo-pentyl nature (**31**, **33**). Moreover, we showcased the reactivity on a series of tertiary halides featuring adamantyl (**34**), bicyclo[1.1.0]pentyl (**35**) and cubyl (**36**) units. The formation of **35** and **36** is particularly noteworthy, given the growing importance of these scaffolds as bioisosteric replacement units in modern medicinal chemistry campaigns.²⁴

The radical nature of the transformation was also harnessed as part of radical 5-*exo*-trig cyclization-alkynylation sequences using alkyl halides with tethered alkene functionalities (**37**). These processes took place in good yield and high diastereoselectivity (see the ESI†).

As a final element of substrate scope, we attempted the functionalization of complex alkyl halides. These species were obtained from the corresponding alcohol in one step by Appel reaction. Pleasingly, we successfully applied this method to the alkylation of carbohydrate derivatives based on α -D-galactopyranose (**40**), D-glucose (**41**) and α -D-glucopyranose (**42**) moieties. The chemistry was also applied to a derivative of Corey's lactone (**39**), the alkaloid nortropine (**38**) and the neurosteroid androsterone (**43**). Finally, we prepared a sulfonylated ethynylestradiol reagent that was successfully coupled with **1a** to give **44**. These examples highlight the ability of the method to engage alkyl-substituted acetylenic sulfones as reactive coupling partners.

Notably, this boryl radical-mediated XAT approach can also be used with other sulfone reagents for the transfer of additional functional groups. A preliminary demonstration of this potential is demonstrated by the reaction of **1a** with **2p–r** under identical reaction conditions to give products of olefination (**45**), cyanation (**46**) and chlorination (**47**).





Scheme 4 Scope of the process. Unless otherwise noted, reactions were carried out at room temperature using a fan. ^aReaction run at 55 °C. ^bReaction run using the SO₂Ph instead of SO₂p-Tol reagent.

Conclusions

The alkylation of alkyl halides remains a challenging transformation. The results presented here demonstrate that by converting alkyl halides into the corresponding radicals,

efficient C(sp³)-C(sp) bond formation can be achieved using alkynyl sulfones as the coupling partners. This method leverages amine-ligated boron radicals for halide activation by halogen-atom transfer (XAT), enabling effective functionalization of primary, secondary and tertiary sites. The broad



applicability of this approach has been showcased with the successful alkynylation of alkyl bromides, as well as the functionalization of complex and high-value molecules. We anticipate that this strategy will find utility in the preparation of alkyne-containing materials and further stimulate the development of novel methodologies employing boryl radical-mediated XAT.

Data availability

The data that support the findings of this study are available in the ESI† of this article.

Author contributions

J. C.: conceptualization, investigation, writing – original draft. M. A.: investigation. D. L.: conceptualization, supervision, funding, writing – review & editing.

Conflicts of interest

There are no conflicts to declare.

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