

Hydroalkylation of styrenes enabled by boryl radical mediated halogen atom transfer

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ABSTRACT: Organohalides are a class of widely accessible synthetic synthons, but their high reduction potential has hampered their use in radical chemistry. However, recent advances in photoredox-catalyzed halogen atom transfer (XAT) strategies have introduced milder and more straightforward methods to achieve radical formation. In this work, we present a ligated boryl radical-mediated halogen abstraction from alkyl and aryl bromides, thus generating C-centered radicals. The generated radicals were further engaged in the anti-Markovnikov hydroalkylation of electronically diverse styrenes. The methodology proved to be applicable to the generation of (1°, 2°, 3°) alkyl radicals as well as aryl radicals, demonstrating high tolerance and robustness. The role of the ligated boryl radical in enabling hydrogen atom transfer (HAT) from H₂O was elucidated as well. Mechanistic investigations and density functional theory (DFT) calculations were performed to enlighten the overall reaction pathway.

Forging C-C bonds remains an evergreen objective in organic synthesis.^{1,2} This research area has greatly benefited from the interest and the advancement that photoredox catalysis has received and continues to receive.^{3,4} Considerable endeavor has been directed to find a wide array of alkyl radical precursors, in order to meet the need for easily synthesizable starting materials and broadly applicable reactivities.⁵ Nevertheless, easy accessibility often brings along substrate activation challenges. Radical generation from alkyl and aryl halides, being fundamental building blocks in the organic chemist's toolbox, represents a convenient approach, but their highly negative reduction potential ($E_{\text{red}} \ll -2\text{V}$) has hampered the development of mild strategies for the purpose.⁶⁻⁸ Besides the limited applications of UV-mediated homolytic break of the C-X bond, single electron transfer (SET) methods so far developed rely on the use of strong reductants, on the use of activated organohalides bearing electron-withdrawing groups that lower their reduction potential, or on electrochemical methods.^{9,10}

To overcome this inherent limitation, a different approach has been devised, where a halogen atom transfer (XAT) step rather than a SET step leads to radical formation. The feasibility of the XAT process relies on different parameters, but mostly on the bond dissociation energy (BDE) difference between the C-X bond and the abstractor-X bond, with the latter generally needing to be stronger than the broken C-X bond (**Figure 1**).⁹ The safety and selectivity concerns inherently linked to the first use of tin-containing reagents as halogen abstractors have been overcome by recent elegant photoredox-catalyzed halogen atom transfer (XAT) approaches, with silicon-based reagents¹¹⁻¹⁵ and α -amino radicals^{8,16,17} as halogen abstractors.

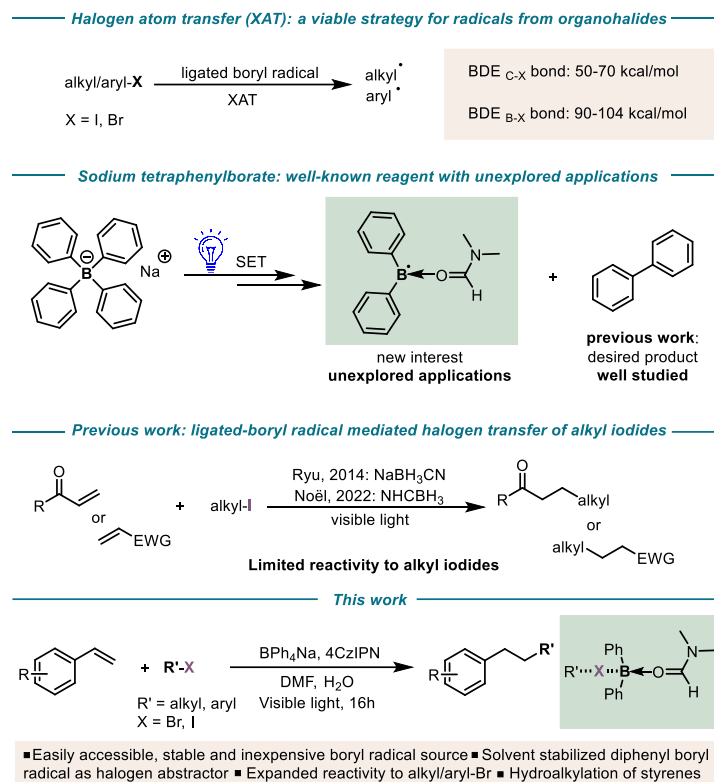


Figure 1: Boryl radical mediated Halogen Atom Transfer strategies.

Boron-based radicals, on the other hand, have received far less attention, despite their comparable performance in halogen atom abstraction.^{18,19} This is mainly due to the inherent instability of the transient neutral boryl radicals.²⁰ To tackle the issue, ligated boryl radical sources were introduced instead. In these species, the boron atom is coordinated to a Lewis base (mostly amines, phosphines and NHC carbenes) and the radical generated after oxidation (and deprotonation) becomes more stable and can be involved in different reaction pathways (direct addition to unsaturated bonds, HAT, XAT etc.).^{21–24} The use of ligated boryl radicals in this synthetic field has mostly resulted in the reduction of organic halides^{25,26} or CO insertion examples.²⁷ Scarce reports have appeared reporting C-C bond forming reactions, where often specific halogen-bearing starting materials were required to achieve halogen abstraction.²⁸ In addition to those, Roberts and co-workers²⁹, Ryu and co-workers³⁰ and, more recently, Noël's group³¹, succeeded in the alkylation of electron-poor alkenes through a Giese-type mechanism. In these examples, more reactive alkyl iodides were employed, while organobromides were found to be unreactive. Given their higher BDE¹¹, bromine abstraction was found to be thermodynamically unfavorable.

Consequently, we wondered if it would be possible to: a) introduce a bench stable, affordable and easily accessible source of boryl radicals; b) identify an alternative reaction platform that would effectively expand the generation of C-centered radicals to the more common and abundantly available organobromides; and c) extend the methodology to the hydroalkylation of styrenes. In this regard, we identified sodium tetraphenylborate (NaBPh₄, **B1**) as an intriguing candidate for the purpose. Tetraphenylborates have historically been used in the generation of biphenyls through electrochemical^{32–35}, thermal³⁶ or photoredox methodologies.³⁷ More recently, Lan, Xia and co-workers employed NaBPh₄ as a source of diphenylboryl radical rather than well documented biaryl synthesis to accomplish C-O bond homolytic cleavage.^{38,39} Aware of the central role of the solvent (dimethylformamide, DMF) in stabilizing the highly reactive diphenyl boryl radical, we wondered if it could be possible to explore the XAT ability of this reactive intermediate.

Results and discussion

To assess the feasibility of the devised transformation, we began the optimization studies employing 4-*tert*-butyl styrene **1** and cyclohexyl bromide **2** as model substrates. Upon initial screening (see SI for further details), we found that sodium tetraphenylborate (NaBPh₄, **B1**), in the presence of 4CzIPN (**PC1**) as the photocatalyst and employing *N,N*-dimethylformamide (DMF) as the solvent, was able to promote the desired hydroalkylation of **1**, affording product **3** in 65% yield (**Figure 2, Entry 1**) after 16 h of irradiation under blue light. Among the photocatalysts tested, only 4CzIPN-*t*Bu (**PC2**) afforded comparable results to 4CzIPN (**Entry 4**). Nonetheless, 4CzIPN was chosen for further studies due to its easier synthesis and economical price of starting materials.

Entry	PC	Boron source	Solvent	Equivalents (1/2/B)	Yield ^c
1	PC1 (5 mol%)	B1	DMF	1.5/1/1	65%
2	PC1 (5 mol%)	B1	DMF	2/1/2	68%
3	PC3 (2 mol%)	B1	DMF	1.5/1/1	38%
4	PC2 (5 mol%)	B1	DMF	2/1/2	68%
5	PC1 (5 mol%)	B1	DMA	1/1.5/1.5	35%
6	PC1 (5 mol%)	B1	MeOH	1/1.5/1.5	-
7	PC1 (5 mol%)	B1	1,4-dioxane	1/1.5/1.5	Traces
8	PC1 (5 mol%)	B1	DMF	2/1/2	83% ^b
9	PC1 (5 mol%)	B1	DMF, H ₂ O (5 equiv)	2/1/2	95% (85%) ^b
10	PC1 (5 mol%)	B2	DMF, H ₂ O (5 equiv)	2/1/2	- ^b
11	PC1 (5 mol%)	B3	DMF, H ₂ O (5 equiv)	2/1/2	75% ^b
12	PC1 (5 mol%)	B4	DMF, H ₂ O (5 equiv)	2/1/2	Traces ^b

^aAll reactions were carried out on a 0.2 mmol scale. The source of the 456 nm light employed was a 3D in-house printed photoreactor (14 W); ^bA 390 nm violet light (Kessil lamp, 52 W) was employed. ^cDetermined by crude NMR yield using 1,3,5-trimethoxybenzene as internal standard. Isolated yields are in parentheses.

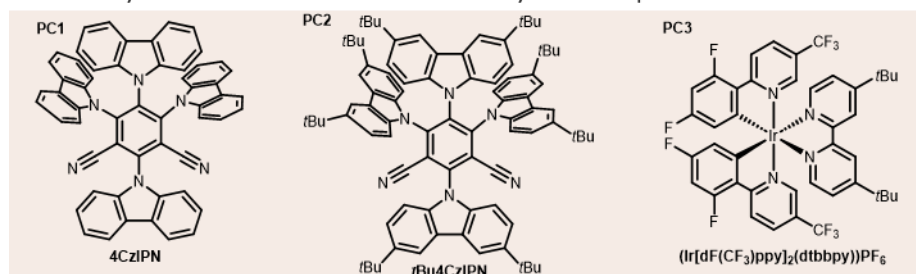


Figure 2: Optimization studies.

When analyzing the effect of different solvents on the reaction outcome, we noticed the need for DMF to stabilize the boryl radical intermediate (**Entry 5-7**).³⁸ Interestingly, a shift in the wavelength (violet light, 390 nm instead of blue light, 456 nm) helped to increase the yield to 83% (**Entry 8**). Being aware of the challenges associated to the reduction of benzylic radicals^{40,41}, we hypothesized a final HAT or a proton-coupled electron transfer step and we therefore evaluated the effect of water addition to the reaction mixture. To our delight, adding 5 equiv of water provided the desired product in high yield (**Entry 9**). A change in the boron source did not lead to any appreciable improvement (**Entry 10-12**).

Control experiments (see SI for further details) confirmed that light irradiation and PC are essential for the reaction, that was completely suppressed in their absence. Similarly, in the absence of BPh₄Na, product formation was not detected, suggesting the substantial role of the boryl radical source in C-radical generation. In addition, an oxygen-free atmosphere was found to be important for the reaction outcome, since without air exclusion a steep decline in the yield occurred. Encouraged by the results obtained, we sought to investigate the generality of the method by evaluating a broad variety of substrates. Cyclic alkyl bromides afforded the desired hydroalkylated product in good to excellent yields (**3-6**, **Figure 3**). Similarly, bridged alkyl bromides such as *exo*-2-bromonorborene (**7**) and 1-bromoadamantane (**16**) were successfully coupled, with the latter substrate demonstrating the feasible involvement of tertiary bromides in the reaction. An acyclic secondary alkyl bromide, 2-bromobutane (**8**), could also be coupled, despite the lower yield. We then focused on primary alkyl bromides, challenging substrates to engage in the desired reactivity because of their higher reduction potential compared to their secondary and tertiary counterpart (**9-15**).¹⁰ Pleasingly, despite the decreased yield in some cases, a broad variety of substrates was found to be

reactive. Non-functionalized alkyl chains, including the short ethyl chain (**9**), could be successfully incorporated. More importantly, the tolerance for common functionalities was observed, and terminal alkynes (**12**), esters (**13**), ethers (**15**), and silanes (**14**) could be successfully installed. Free hydroxyl groups could not be employed under our optimized conditions possibly due to their interaction with the boryl radical intermediate.³⁸ Following this hypothesis, the protection of the free hydroxyl group allowed us to obtain the desired product **14**. Remarkably, 1-bromo-2-chloroethane was selectively functionalized at the C-Br bond, affording product **11** in 51% yield, providing the pathway for orthogonal functionalization.

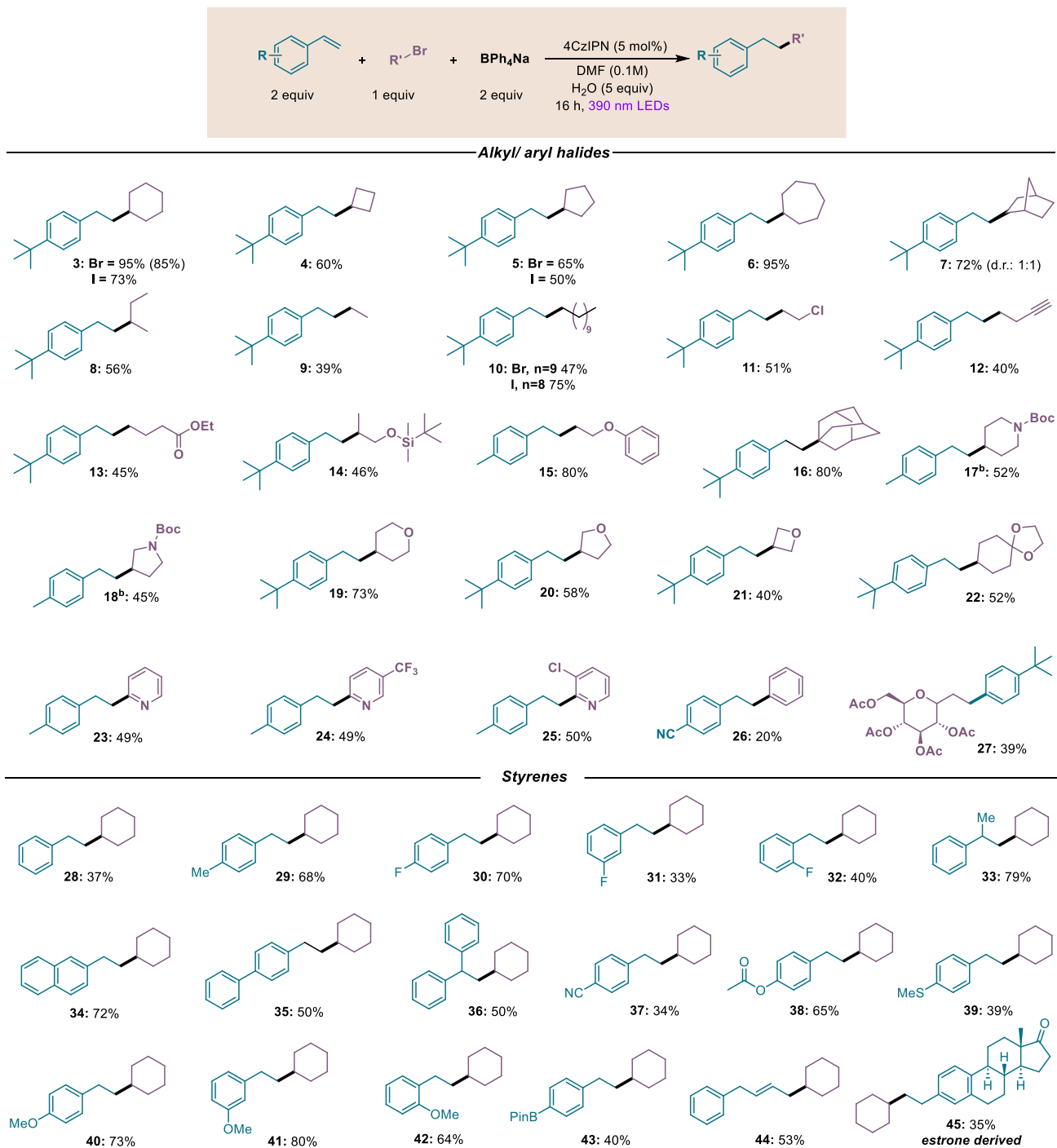


Figure 3: Scope of the developed transformation. Conditions unless otherwise noted: styrene (2 equiv), alkyl/aryl bromide (1 equiv, 0.3 mmol), BPh₄Na (2 equiv), 4CzIPN (5 mol%), H₂O (5 equiv), DMF (0.1 M). Irradiation with 390 nm Kessil light (54W), 16h. ^b1.5 equiv of DBU added.

The protocol was further extended to the installation of *O*-containing heterocyclic scaffolds (**19-21**), commonly present in medically relevant structures, that were successfully coupled in good to moderate yields, with lower yield observed for the strained oxetane ring (**21**). The acid-sensitive acetal **22** was also successfully employed, allowing further transformations. The

N-containing heterocyclic molecule *N*-*boc* piperidine **17** and *N*-*boc* pyrrolidine **18** were successfully employed as well. In these cases, the addition of a base was necessary to improve the yield. Pleasingly, acetobromo- α -D-galactose (**27**) was found to be a competent reaction partner, affording the desired product in 39% yield. The employment of aryl bromides was then also attempted. 2-Bromopyridines (**23–25**) reacted smoothly and led to the formation of interesting functionalized scaffolds. The selective reactivity of 2-bromo-5-chloropyridine (**25**) at the C-Br bond in particular forecasts further involvement in more transformations. Aryl bromides such as 1-bromo-4-cyanobenzene underwent the reaction as well, despite the lower yield obtained (**26**). Csp²-Csp³ bond forging could therefore be unlocked as well. Further studies to broaden the range of aryl halides are currently undergoing in our group.

We then sought to study the generality of the vinyl arene counterpart. Differently functionalized styrenes were efficiently alkylated. Despite the lower yield for styrene (**28**), which afforded the desired product in 37% yield, methyl (**29**), phenyl (**35**), acetoxy (**38**), -F (**30–32**), cyano (**37**), methylthio (**39**) and -BPin (**43**) substituents were tolerated. 2-Vinylnaphthalene (**34**) was functionalized as well. Remarkably, the presence of an electron donating group (-OMe, **40–42**) on the styrene scaffold was also tolerated. *Ortho*, *meta* and *para* substitutions, both in the case of electron-deficient and in the case of electron-rich substitutions, gave high to moderate yields. Interestingly, 1-phenyl-1,3-butadiene (**44**) was also alkylated in good yield, providing an alternative to metal-catalyzed functionalization of this scaffold.⁴² An estrone derivative also successfully engaged in the transformation. Surprisingly, *p*-Cl and *p*-CF₃ substituted styrenes were not compatible reaction partners, despite their electron withdrawing nature that should have facilitated the radical attack. In these cases, GC-MS analysis of a reaction mixture that did not contain cyclohexyl bromide revealed that these styrenes underwent decomposition. For such cases, a faster decomposition rate could hinder the desired radical attack. Nevertheless, this catalytic system enables the possibility to achieve the alkylation of a broad range of styrenes avoiding the use of Grignard or organometallic reagents, whose employment causes loss in selectivity and functional group tolerance.⁴¹

Mechanistic investigations

To gain more insights into the underlying mechanism of the reaction, a series of experimental and computational studies were performed. First, the addition of a radical scavenger (2,2,6,6-tetramethyl-1-piperidinyloxy, TEMPO) suppressed the reaction (only 4% of the product was detected through GC-MS). In addition, radical clock experiments were performed. In the presence of (bromomethyl)cyclopropane, the ring-opened product was formed in 40% yield. Similarly, 6-bromohex-1-ene led to the formation of a cyclopentyl ring in 39% yield. These experiments therefore confirmed the hypothesis of a radical-based mechanism (Figure 4, B3 and B4). We further confirmed by cyclic voltammetry that, among the participants in the described reaction, only NaBPh₄ is susceptible to oxidation in the redox window of the photocatalyst employed ($E^{1/2}_{ox} = +0.91$ V in ACN vs SCE, $E(P^*/P^{\cdot-}) = +1.35$ V and $E(P/P^{\cdot-}) = -1.21$ V vs SCE in ACN, see SI for further details). Fluorescence quenching experiments further confirmed that the borate initiates the reaction, since it was the only reactant able to quench the excited state of 4CzIPN (Figure 4, B5). Despite this evidence, we observed discoloration of the reaction mixture after continuous irradiation, implying photo-bleaching or a structural change of the PC. We therefore wondered if the need of a 390 nm light could be explained by considering a change in the catalyst structure. As thought, UV-Vis analysis of the reaction mixture showed the decrease of the absorbance at 456 nm, and a blue-shift that would explain the need of a different wavelength to reach the completion of the reaction. Though the catalyst fate was not analyzed in more details, the formation of a new, but still active photocatalytic species cannot be excluded (see SI for further details).⁴³

After determining the role of BPh₄Na in kickstarting the reaction, we used computational methods to analyse the halogen atom transfer step. It was found that the interaction between the biphenylboryl radical and cyclohexyl bromide leads to the generation of cyclohexyl radical through TS1 ($\Delta G_{R-Br} = +12.5$ kcal/mol, Figure 4C). Though slightly endergonic, the value is in accordance with the energetic profile calculated for α -amino radicals or NHC-boranes in similar halogen transfer steps.¹⁹ Interestingly, Noël *et al.* explained the lack of reactivity of alkyl bromides with a kinetically disfavored step compared to alkyl iodides ($\Delta G_{R-Br} = +17.9$ kcal/mol vs $\Delta G_{R-I} = +11.6$ kcal/mol).¹⁹ In our case instead, the energy required was found to be lower, thus enabling C-Br homolytic cleavage. Similarly, ΔG_{R-I} was found to be +10.13 kcal/mol. In light of this result, the use of alkyl iodides was also attempted (Figure 3, 3, 5, 10). A satisfactory yield was obtained, and the reaction platform proved to be equally effective for alkyl iodides.

Upon radical formation, an exergonic radical attack on 4-*tert*-butylstyrene then occurs ($\Delta G = -19.2$ kcal/mol), generating a benzylic radical intermediate (Figure 4A and 4C).^{40,41,44} At this stage, the reactivity observed for electronically diverse styrenes, including non-functionalized or electron-rich styrenes, urged us to investigate the last step of the mechanism. In the case of the latter group of styrenes especially, the reduction potential of the benzylic radical intermediate is high, leading us to hypothesize a hydrogen atom transfer (HAT) step, and not a SET-mediated anion formation, followed by protonation. In line with this hypothesis, we performed control experiments in the presence of DMF-*d*₇ and D₂O (Figure 4, B1 and B2). To our surprise, no appreciable deuteration from the solvent was observed, while the reaction in the presence of D₂O afforded the desired product with 80% deuterium enrichment. Given that HAT is a more likely step than anion formation *via* SET, we began investigating what in our system could promote HAT from H₂O or D₂O, with the aid of computational calculations as well. A recent work from Studer and co-workers demonstrated how water activation toward HAT is made possible through a phosphine-mediated radical process, by means of the formation of an adduct between H₂O and phosphine.⁴⁵ Similarly, the

effect of adduct formation between water and boranes for a homolytic O-H bond cleavage has also been demonstrated.^{46,46,47} As a result, we hypothesized the possible involvement of sodium tetraphenylborate (and thus boryl radical or side products) in the weakening of the O-H/ O-D bond, leading to homolytic cleavage.

To prove the hypothesis, we performed a control experiment where bromocyclohexane was not added to the reaction mixture. The reduction of 4-*tert*-butylstyrene was observed, in accordance to the HAT-mediated mechanism delineated by Studer and co-workers. Similarly, if instead of H₂O, D₂O was added, deuterium incorporation could be detected. DFT calculation also confirmed that adduct formation between a boryl radical and water would lead to a favorable exergonic HAT step which would bring to the generation of the desired product. Similarly, the involvement of borinic acid or HBr (side products of the reaction) as HAT mediators could not be excluded (**Figure 4A**). Nevertheless, as suggested by Hull *et al.*, a proton coupled electron transfer process cannot be ruled out as well, contributing to photocatalyst regeneration.⁴¹

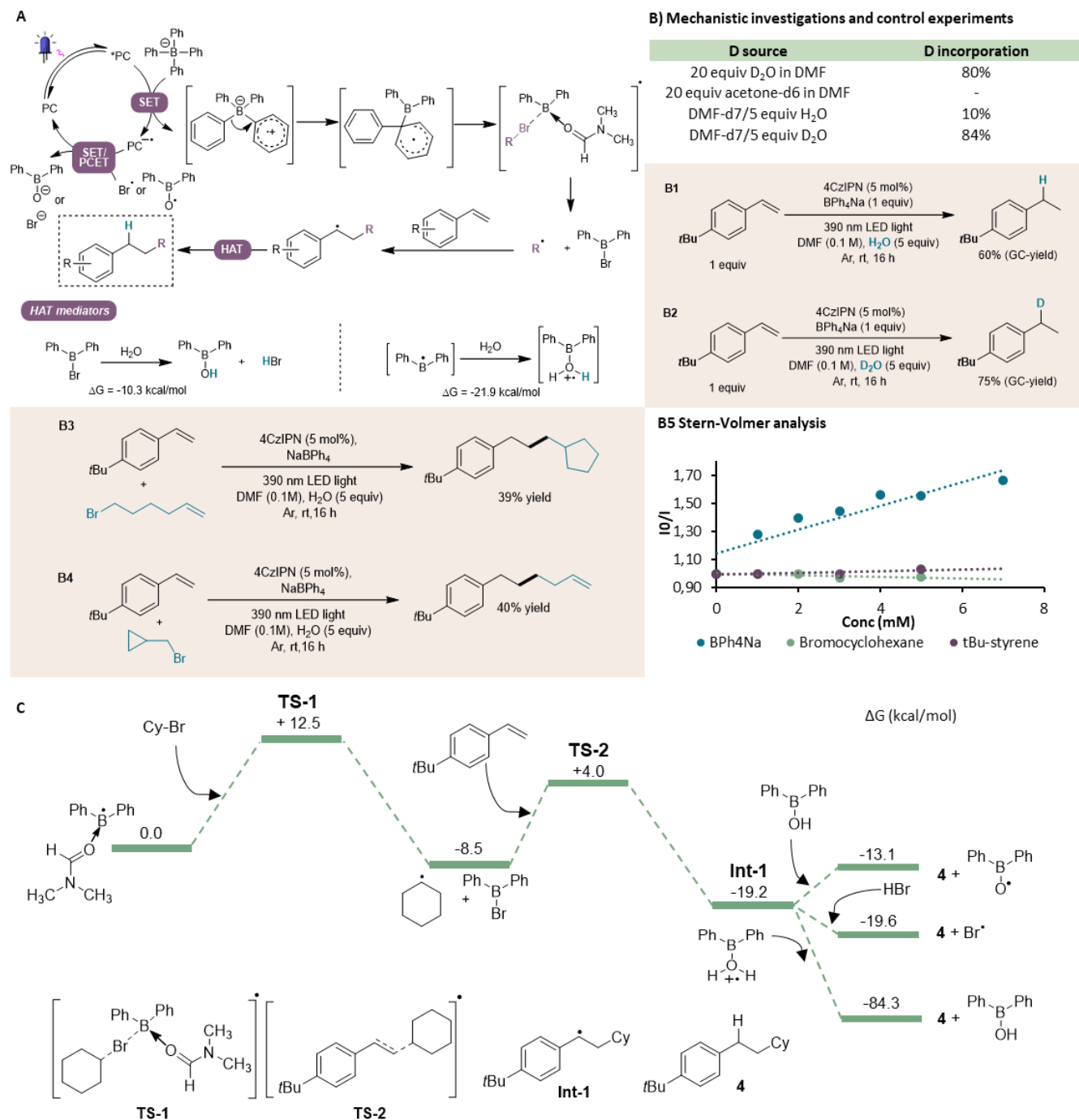


Figure 4: Mechanistic proposal and investigations. A) Proposed mechanism. B) Control experiments and deuteration studies. C) DFT calculations.

Conclusions

In conclusion, we have demonstrated the ability of an inexpensive and easily available boryl radical source like sodium tetraphenylborate to enable halogen atom transfer not only from alkyl iodides, but also from alkyl and aryl bromides, commercially available and stable precursors. The alkyl/aryl radicals thus generated were further involved in the anti-Markovnikov hydroalkylation of electronically diverse styrenes. A broad scope, including natural product-derived molecules, was subjected to these mild reaction conditions, achieving the formation of the hydroalkylated products in moderate to good yield. Moreover, sodium tetraphenylborate was also found to be fundamental in enabling a HAT step from H₂O, a transformation that would otherwise be unfavorable due to the high O-H bond strength. Overall, the methodology that we present here constitutes a valuable addition to the landscape of halogen atom transfer based methodologies. As a result, we are sure that our findings will serve as the foundation for further studies and development of reactivity patterns for boron centered radical species.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: S. P. and U. K.S.; methodology and experiments: S. P.; DFT calculations: R. W. draft manuscript preparation: S.P., R.W., U.K.S., E.VdE.

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