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Article

# Direct Deoxygenation of Free Alcohols and Ketones

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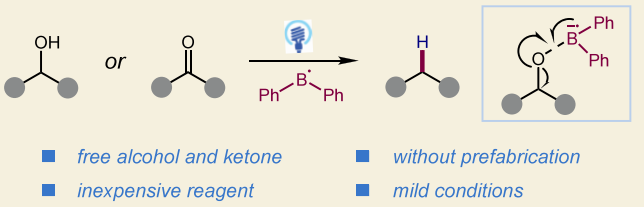
**ABSTRACT:** This work presents a feasible method for the elimination of alcohol hydroxyls through the direct activation of typical alkyl alcohols using neutral boron radicals. This transformation necessitates a proficient reagent capable of swiftly activating the alcohol hydroxyl group to produce radicals, thereby circumventing numerous alternative side reactions associated with the alcohol hydroxyl group. To implement this method, we have created an innovative photocatalytic reaction system that oxidizes sodium tetraphenylboron to produce neutral boron radicals, which subsequently enable the direct homolytic conversion of alcohol hydroxyl groups. This deoxygenation technique necessitates no additional preactivation of the alcohol and yields favorable outcomes for the majority of alcohol substrates. The technique facilitates the direct methylene reduction of aldehydes and ketones. Mechanistic studies have established that the reaction likely initiates with the production of alcohols, thereafter undergoing dehydroxylation to yield methylene-reduced products.




**KEYWORDS:** *Deoxygenation, free alcohols, ketone, boron radical, photocatalytic*

Organic synthesis fundamentally involves the formation of intricate molecules from basic precursors. Chemical reactions that diminish overall complexity by selectively eliminating specific functional groups are highly valuable. For instance, late-stage defunctionalization of biologically active compounds, reduction of biomass-derived precursors, and removal of protecting or orienting groups can be significantly advantageous in certain scenarios.[1] Specifically, reactions for the reductive cleavage of C−O bonds possess numerous uses. In complete synthesis research, it is frequently essential to modify the oxidation state of the product multiple times to facilitate a seamless transformation of the product's functional group.[2] The hydroxyl group (−OH) is a prevalent functional group that frequently serves a bridging function in the transformation processes of organic synthesis.[3] In the synthesis of a compound, certain groups are typically introduced initially based on synthetic strategies to mitigate the complexity of the synthesis and enhance the yield. In organic synthesis chemistry, it is occasionally essential to directly eliminate the hydroxyl group at a specific position to achieve the desired intermediate or target product, necessitating the use of suitable chemical techniques for its removal.[4] Consequently, the targeted elimination of prevalent hydroxyl functional groups from compounds has garnered significant interest among chemists. These approaches have also been extensively employed for the late alteration of intricate substrates. Prior research has shown that alcohol deoxygenation might be accomplished through the respective xanthate intermediate in the Barton-McCombie reaction[5] (Scheme 1A). Regrettably, the existing Barton-McCombie dehydroxylation reaction depends on stoichiometric trialkyltinhydrogen and thiocarbonyl activation of functional groups, with the chemicals being exceedingly toxic. Consequently, the advancement of an alternate deoxygenation technique continues to pose a considerable difficulty.

In recent years, the prefunctionalization of alcohols to carboxylic acid esters, including oxalates, tolylates, and benzoates, has garnered interest as a method for deoxygenation transition in a free radical milieu.[6] Likewise, the in situ synthesis of reactive alcohol derivatives utilizing N-heterocyclic carbenes (NHC) and phosphines, among other agents, is an efficient approach for cleaving carbon−oxygen bonds.[7] Doyle and Rovis documented the photoredox-catalyzed deoxygenation of benzyl alcohols through in situ generated phosphinylidene radicals,[8] Wickens delineated an effective method for the elimination of alcohol functional groups via reductive cleavage of their benzoate counterparts,[9] and Schuppe outlined a strategy for the hydrodeoxygenation of alcohols utilizing isonitrile intermediates[10] (Scheme 1B). While stoichiometric derivatization of hydroxyl groups yields a selective approach for numerous reactions, this strategy is suboptimal regarding atom and step economy. Catalytic methods for the deoxygenation of nonderivatized alcohols are a significant focus of synthetic research to resolve this issue. However, the elevated dissociation energy of the carbon−oxygen bond, along with

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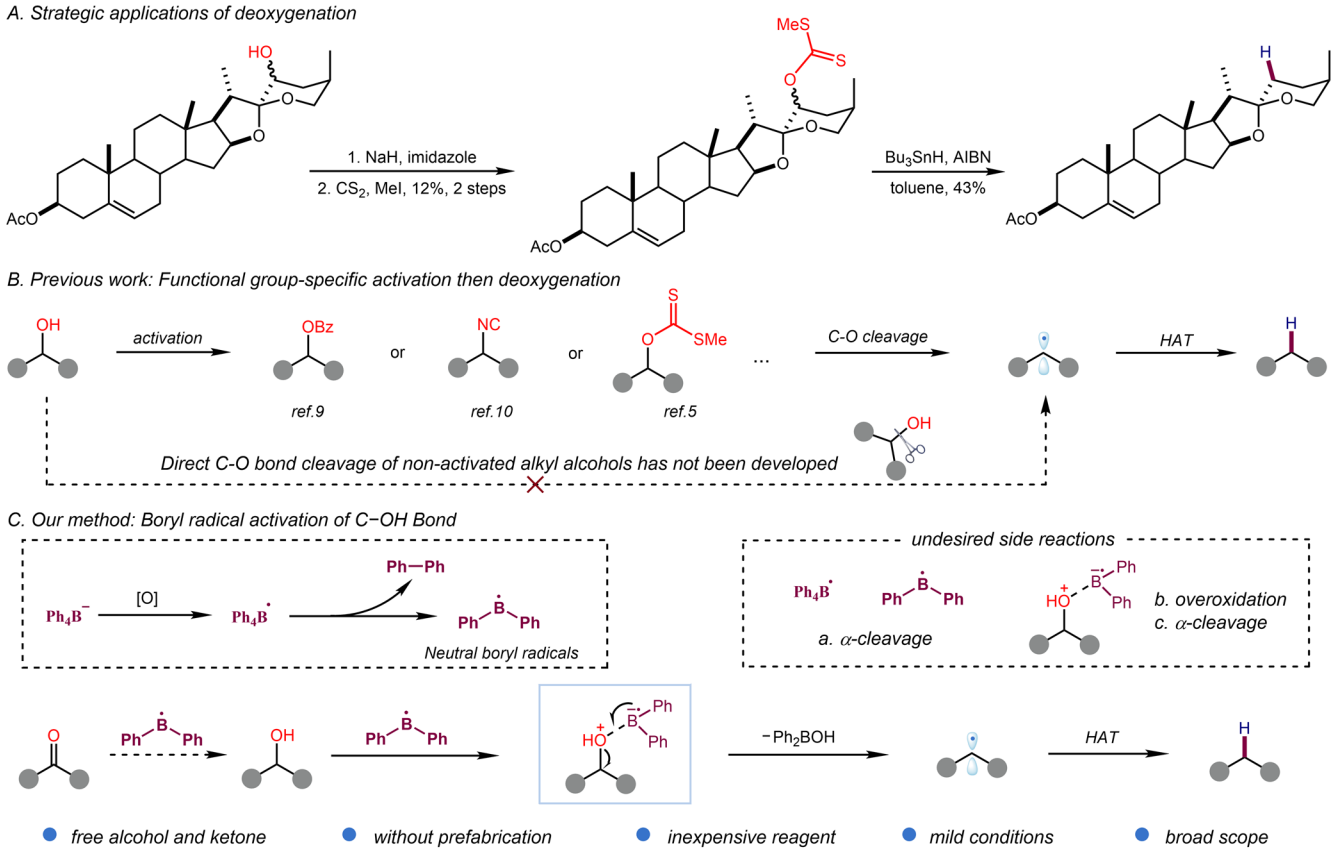
**Scheme 1. Deoxygenation of Free Alcohols**[a]




[a](A) Strategic applications of deoxygenation. (B) Reported strategies for deoxygenation. (C) Direct deoxygenation reaction of the non-activated alkyl alcohols.

the limited capacity of the hydroxyl group to depart and the extremely reactive and acidic characteristics of the hydrogen in the alcohol hydroxyl group, can lead to several side reactions.[11]

To accomplish the difficult breaking of carbon−oxygen bonds, we have sought to activate alcohol hydroxyl groups in situ by boron radicals produced in situ via photoredox catalysis. While numerous boron radical species have been documented,[12] diphenylboron radicals can be synthesized directly from inexpensive and accessible $NaBPh_4$. These radicals have been noted to activate benzyl alcohols[13] and bromine substituents,[14] however, the cleavage activation of the more challenging nonactivated alkyl alcohols remains unreported. We anticipate that this boron radical can easily attach to the hydroxyl group and thereafter undergo quick $\beta$-cleavage of the carbon−oxygen bond to generate the alkyl radical, resulting in the product following hydrogen atom transfer (HAT). While this scheme is theoretically viable, several challenges exist: 1) diaryl boron radicals are prone to $\alpha$-cleavage, resulting in aryl radicals,[15] 2) the intermediate boron oxygen radicals undergo oxidation before activation through $\beta$-cleavage, and 3) the intermediate boron oxygen radicals are also highly susceptible to $\alpha$-cleavage. By manipulating the boron radicals, we anticipate that this method will facilitate the direct conversion to the equivalent alkyl radical species. This approach necessitates no additional preactivation of the alcohol and represents the inaugural direct deoxygenation reaction of a nonactivated alkyl alcohol (Scheme 1C).

We first examined the deoxygenation of alcohol substrates using phenylbutanol 1 as a model molecule (Table 1). Utilizing commercially available $NaBPh_4$ alongside catalytic quantities of $Ph_3N$, phenylthiophenol, and 400 nm LEDs irradiation resulted in significant yields of the deoxygenation product. Subsequently, we evaluated several commercially accessible or easily synthesizable boron reagents and saw a reduction in efficiency when $NaBPh_4$ was transformed into either lithium or sodium salts. Subsequently, we synthesized various sodium tetraarylborates exhibiting distinct electrical characteristics and evaluated them in this process. The usage of sodium tetraphenylborates with electron-donating groups on the benzene ring yielded greater yields than those with electron-absorbing groups. No reaction occurred when $BPh_3$, $NaBF_4$, or $PPh_3$ were utilized in place of $NaBPh_4$. The use of dichloromethane, akin to the employed solvent, led to a minor decrease in the reaction yield. The essential role of triphenylamine in the reaction was thoroughly examined by a detailed analysis of its structural properties.[16] The simplest and most cost-effective triphenylamine molecule demonstrated significant efficacy in the reaction. After modifying its electrical characteristics by structural alterations of the aromatic substituents, it was found that the methoxy-substituted triphenylamines, which are more electron-rich, had less favorable outcomes. Moreover, $Ph_3N$ containing electron-withdrawing groups (-CN, $-NO_2$) showed no capacity to yield any compounds. Diphenylamine demonstrated superior efficacy, but aniline and alkylamines failed to produce the


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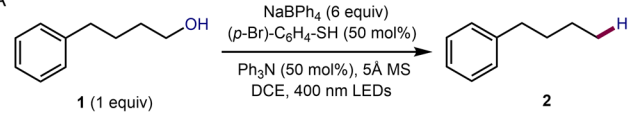
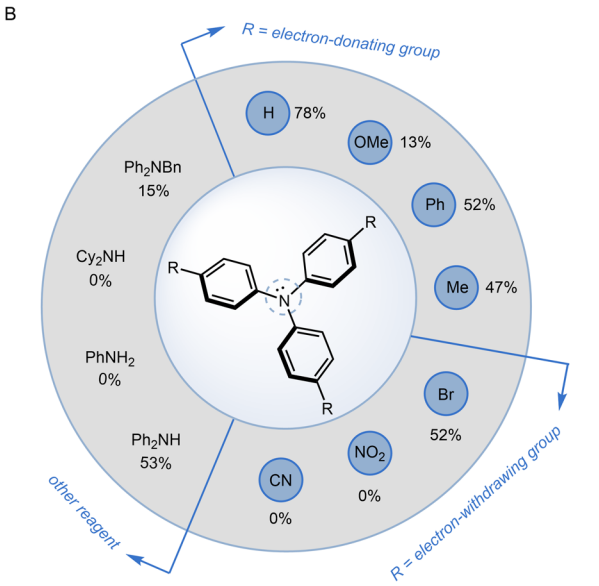
**Table 1. Reaction Development**[a,b]

A

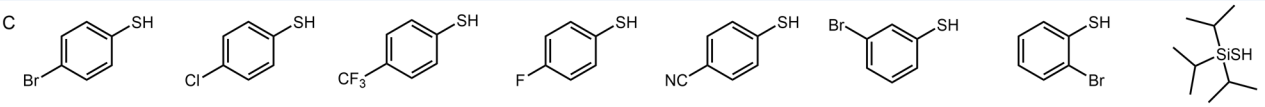



| Entry | variations from the standard condition | Yield [%] |
|---|---|---|
| 1 | none | 78 |
| 2 | $LiBPh_4$ instead of $NaBPh_4$ | 71 |
| 3 | $KBPh_4$ instead of $NaBPh_4$ | 49 |
| 4 | $NaB(4\text{-}Ph\text{-}C_6H_4)_4$ instead of $NaBPh_4$ | 0 |
| 5 | $NaB(4\text{-}Me\text{-}C_6H_4)_4$ instead of $NaBPh_4$ | 58 |
| 6 | $NaB[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_4$ instead of $NaBPh_4$ | 0 |
| 7 | $BPh_3$, $NaBF_4$, $PPh_3$ instead of $NaBPh_4$ | 0 |
| 8 | DCM instead of DCE | 61 |
| 9 | no $NaBPh_4$, no light, or no (p-Br)-$C_6H_4$-SH | 0 |
| 10 | no $Ph_3N$ | 2 |
| 11 | no molecular sieve | 44 |

B




C




[a]Reaction conditions: **1** (0.2 mmol), $NaBPh_4$ (6 equiv), (p-Br)-$C_6H_4$-SH (50 mol %), $Ph_3N$ (50 mol %), 5 Å MS (30 mg), DCE (5 mL), 400 nm blue LEDs, 36 h. [b]Determined by gas chromatography with anisole as an internal standard.

intended products, highlighting the importance of polyarylamine structure. Moreover, the inclusion of electron-withdrawing groups in benzenethiols was seen to increase product yield, but silanethiols (S8), frequently utilized as a reagent in HAT reactions, were discovered to hinder the reaction's progression. Ultimately, controlled investigations demonstrated that the process does not transpire without the presence of boron reagent, benzenethiol, or visible light irradiation. Conditions lacking $Ph_3N$ produced only minimal quantities of product. Moreover, the lack of molecular sieves led to a swift decrease in yield, likely attributable to trace quantities of water molecules that may compete with the alcohol substrate.

Upon establishing the optimal reaction conditions, the applicability of this transformation was examined utilizing various free alcohols (Table 2). Initially, challenging primary alcohols (**2**–**14**) demonstrated significant reactivity, despite the formation of unstable primary carbon radicals. Compounds such as phenyl ethers (**4**), benzyl ethers (**6**), silyl ethers (**7**), and anisole (**8**) were found to be prone to C–O bond cleavage; however, these compounds remained unaltered in the presence of elemental boron. Moreover, the existence of ester groups (**5**), chlorine atoms (**9**, **11**, **14**), and bromine atoms (**10** and **12**), known to readily interact with boron radicals, was determined to have no impact on the reaction, thereby affirming the nonexistence of the typical XAT reaction.[14] Furthermore, unactivated secondary and tertiary alcohols were effectively deoxygenated, yielding satisfactory results (**15**–**21**). Secondary and tertiary alcohols featuring an adamantane framework also produced favorable yields (**15** and **20**). The deoxygenation of cyclic secondary alcohols, including cyclooctanol (**18**) and cyclododecanol (**19**), proved to be effective. Additionally, the benzyl alcohol deoxygenation reaction, which has been thoroughly examined in the literature,[17] was shown to perform well in the current system (**22**–**24**). Moreover, the selective deoxygenation of some hydroxyl-containing natural compounds and their derivatives has been evidenced, underscoring the considerable utility of this innovative deoxygenation method (**25**–**29**).

The reductive deoxygenation of ketones to their corresponding saturated compounds is recognized as a topic of considerable interest, primarily due to its extensive application in the conversion of biomass feedstocks and petrochemicals.[18] This process is particularly crucial in the synthesis of diverse structural units in pharmaceuticals. In this context, the Clemmensen reduction[19] and the Wolff–Kishner-Huang reaction[20] are established and effective synthetic methodologies. Both methods depend on stoichiometrically toxic reagents and require stringent reaction conditions, which can be difficult to apply in practical scenarios. In this study, we have shown that efficient deoxygenation reduction of carbonyl compounds, including aldehydes and ketones, can be achieved under more favorable conditions. Initially, we determined that the less reactive ketones produced the desired products with satisfactory reaction yields (**30**–**37**). The reaction of cyclic ketones (**30**, **33**–**37**) and chain ketones (**31** and **32**) demonstrated compatibility with this approach, with no detrimental effects on other functional groups, including methoxy (**32**) and bromine atoms (**34** and **35**). Moreover, the reaction conditions proved suitable for the deoxygenation and reduction of aldehydes (**38**–**41**), so illustrating the method's versatility.



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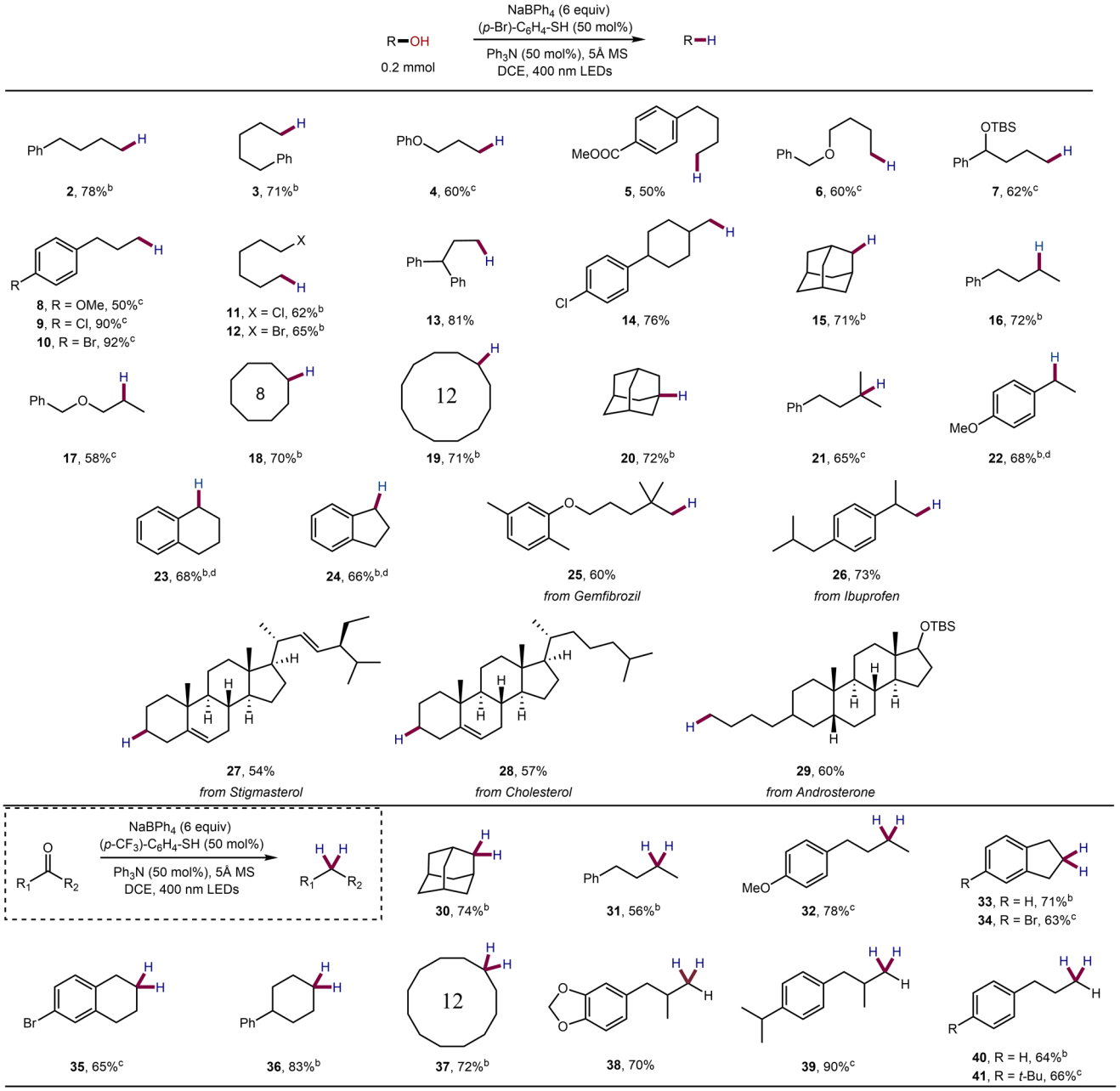
**Table 2. Scope of the Deoxygenation of Alcohols**[a]




[a]Reaction conditions: substrate (0.2 mmol), $NaBPh_4$ (6 equiv), (*p*-Br)-$C_6H_4$-SH (50 mol %), $Ph_3N$ (50 mol %), 5 Å MS (30 mg), DCE (5 mL), 400 nm blue LEDs, 36 h. Isolated yields unless otherwise noted. [b]GC yield. [c]NMR yield. [d]DCM instead of DCE.

This study elucidates the fundamental mechanistic characteristics of a unique direct deoxygenation reaction involving nonactivated alcohols. First, the reaction rates of this reaction system for primary, secondary, and tertiary alcohols with varying site resistances were studied. The one-pot reaction was conducted using equal equivalents of the three alcohols (Figure 1A), revealing that the reaction rates of the main and secondary alcohols were similar, however the tertiary alcohol reacted at a significantly slower pace. This discovery demonstrates that the site resistance of the alcohols significantly affects the reaction rate. In addition, stoichiometric TEMPO was introduced into the process (Figure 1B), leading to its inhibition. HRMS analysis was utilized to determine the exact molecular weight of the radical adduct. Moreover, free radical clock studies resulted in the effective synthesis of ring-opening olefination products (Figure 1C). The findings indicate that the reaction likely proceeded via a free radical mechanism, as opposed to an ionic dehydroxylation process.[21] The function of triphenylamine in the process was further examined. It was observed that triphenylamine was deteriorating during the process, with just 4% recovery measurable from the model reaction, and 25% of *N*-phenylcarbazole (CabZ) produced (Figure 1D). This indicates that, within the reaction system, $Ph_3N$ experiences photochemical cyclization, deprotonation, and subsequent SET oxidation processes to yield CabZ,[22] a reactivity documented in the literature, albeit under more intricate or rigorous reaction conditions. Given that CabZ has been identified as an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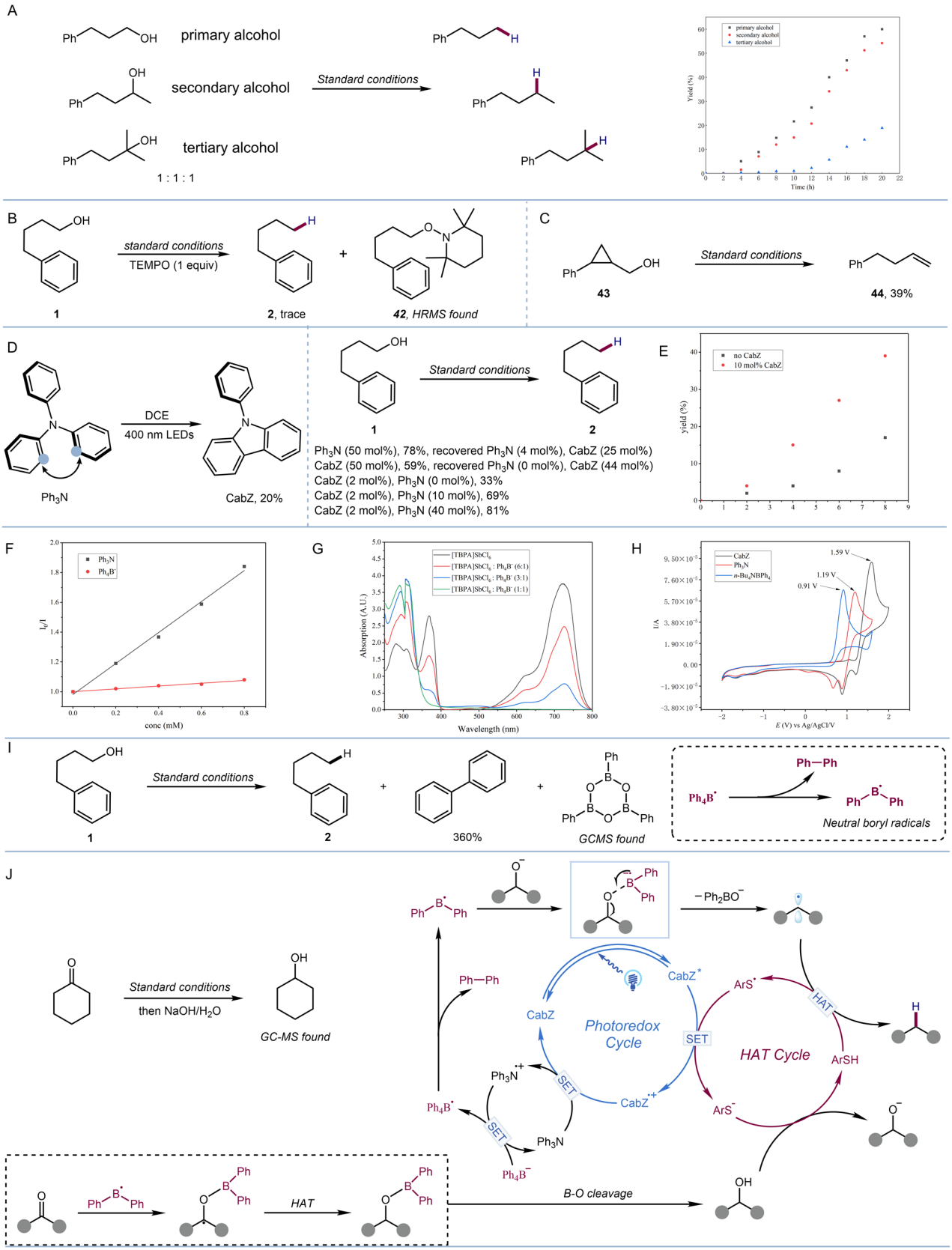


**Figure 1.** Mechanistic investigations. (A) Competition experiment of primary, secondary, and tertiary alcohols. (B) Radical trapping experiment. (C) Radical clock experiment. (D) Studies on the role of $Ph_3N$. (E) Reaction rate experiment. (F) Stern−Volmer quenching experiments. (G) UV−visible spectroscopy. (H) Cyclic voltammetry measurements. (I) Study of reaction byproducts. (J) Plausible mechanism.

efficient photocatalyst, it was postulated that $Ph_3N$ could function as a precatalyst for CabZ as a primary photocatalyst. A realistic model reaction was developed and evaluated, with CabZ as the catalyst. This reaction produced product **2** with a



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yield of 59%, while CabZ was recovered in significant amounts. Subsequently, the reaction was evaluated using 2 mol % CabZ, and it was noted that the incorporation of 10 mol % $Ph_3N$ resulted in a significant enhancement of the reaction yield. Moreover, when the quantity of $Ph_3N$ was elevated to 40 mol %, the yield rose to 81%. In the template reaction, the reaction rate was also found to be relatively faster with the addition of 10 mol % CabZ (Figure 1E). Furthermore, it was noted that the template reaction demonstrated slow advancement during the first 2 h, with the reaction initiating only after the system changed from white to brown (the color of CabZ), indicating a structural alteration in the photocatalyst. By correlating these experimental results with the reaction dynamics, it was postulated that CabZ acted as a true catalyst in the reaction and that $Ph_3N$ also contributed to an increase in the reaction yield. Stern−Volmer quenching experiments showed that the excited state of CabZ was mainly quenched by the $Ph_3N$ (Figure 1F), indicating that this process involves triphenylamine radical cation intermediate via a SET process. UV−visible spectroscopy was performed, and it was found that the tetraphenylboron anion can rapidly quench the triphenylamine radical cation (Figure 1G). As a result, we proposed a new mechanism in which CabZ ($E^{ox}$ = 1.59 V vs $Ag/Ag^+$, in DCE) (Figure 1H) first undergoes a one-electron transfer with $Ph_3N$ ($E^{ox}$ = 1.19 V vs $Ag/Ag^+$, in DCE) to generate the triphenylamine radical cation, and then oxidizes the tetraphenylboron anion ($E^{ox}$ = 0.91 V vs $Ag/Ag^+$, in DCE) to generate the tetraphenylboron radical. Additionally, a significant quantity of biphenyl byproducts was identified in the template reaction (Figure 1I), alongside the formation of triphenylboronic acid ester, which validated the proposed mechanism of alcohol hydroxyl activation by $NaBPh_4$.[13]

A provisional hypothesis on the general reaction mechanism is proposed based on the prior controlled studies and existing literature (Figure 1J). This hypothesis asserts that $Ph_3N$ generates the photocatalyst CabZ, whose excitation leads to the development of an excited state CabZ*, which subsequently undergoes electron loss to produce a radical cation, which is quenched by $Ph_3N$, forming a triphenylamine radical cation. The radical cation is quenched by a tetraphenylboron anion, leading to the formation of the tetraphenylboron radical. Subsequently, diphenylboron radicals are produced in situ, resulting in the liberation of diphenyl molecules. The pronounced electron shortage of the diphenylboron radical promotes the coordination of the alcohol's oxygen atom with the boron atom, resulting in the formation of a complex intermediate. The coordination link formed between boron and oxygen activates the C−O bond in the alcohol, resulting in the formation of an alkyl radical from the C−O bond. The transfer of hydrogen atoms from phenylthiophenol to produce the target product is then commenced. Regarding the deoxygenation mechanism of ketones, the formation of cyclohexanol was seen when cyclohexanone served as the substrate, leading to the notion that the carbonyl group initially formed an adduct with diphenylborane. The initial step is thought to produce a carbon radical intermediate, which then experiences a transfer of hydrogen atoms, resulting in the development of a borate intermediate. The concluding phase of this cycle entails the cleavage of the B−O bond, leading to the synthesis of the alcohol. The alcohol subsequently enters the catalytic cycle, where it is reduced to the required deoxygenated reduction product.

In conclusion, a new deoxygenation method has been established, characterized by mild conditions and the use of commercially accessible, cost-effective chemicals. The reaction occurs in a single step, eliminating the need for preactivation of the substrate alcohol. This signifies a groundbreaking progress in the radical deoxygenation of nonactivated alkyl alcohols. Moreover, this deoxygenation approach includes aldehydes and ketones, so avoiding the considerable difficulties typically faced in traditional synthesis. This deoxygenation scheme is expected to become a significant strategic tool in synthetic chemistry, providing several prospects for advanced deoxygenation reactions in sustainable synthesis.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.5c00154.

$^1H$ NMR, $^{13}C$ NMR spectra for all compounds, experimental procedure, compound characterization data, and additional materials and methods, including photographs of the experimental setup (PDF)

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### Author Contributions

H.Z. initiated and conducted the primary experiments, analyzed data, and contributed to the drafting of the manuscript; S.G., H.C., and G.Z. did some experiments and characterization of products; Y.C. contributed to conceptualization, funding acquisition, project administration, supervision, validation, and writing−review and editing. All authors contributed to this research project through in-depth discussions, data analysis, and result interpretation.

### Notes

The authors declare no competing financial interest.



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