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Ph_3P═O-Catalyzed Reductive Deoxygenation of Alcohols

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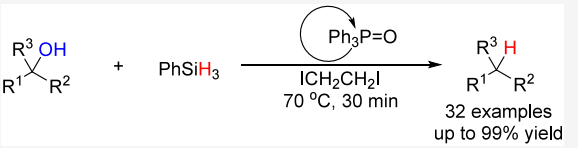
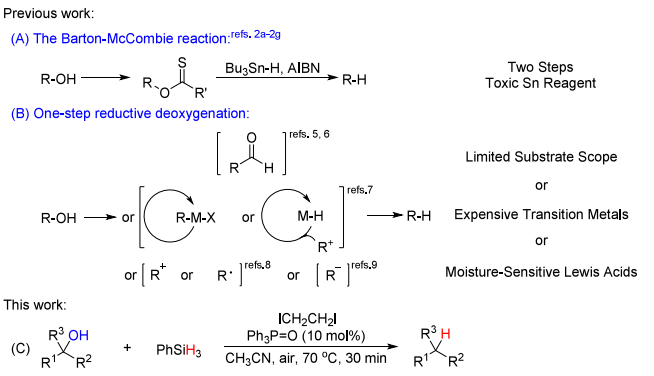
ABSTRACT: Reductive deoxygenation of alcohols is particularly challenging because of the high bond dissociation energy of the C−OH bond and the poor leaving ability of the hydroxyl group. Herein we describe a Ph_3P═O-catalyzed reductive deoxygenation of benzyl alcohols with $PhSiH_3$ under an air atmosphere within 30 min of reaction time. The use of catalytic loading of Ph_3P═O enhances the practicality of this protocol.



The hydroxyl group is ubiquitous and can be found in many drugs, natural products, and synthetic intermediates. Owing to the ubiquity of the hydroxyl group, dehydroxylative functionalization of alcohols have received substantial attention.[1] Of special interest is reductive deoxygenation of alcohols, which can readily provide alkanes.[2] However, reductive deoxygenation is quite challenging because of the high bond dissociation energy of the C−OH bond and the poor leaving ability of the hydroxyl group. The Barton−McCombie reaction is a classic method, requiring a two-step process, the transformation of OH into a good leaving group and the subsequent reduction by a highly toxic tin hydride reagent, which has to be used in a stoichiometric amount (Scheme 1A).[2a−g] Although the classic Barton−McCombie reaction has been modified to lower the loading of tin hydrides[3] or even to eliminate the use of tin reagents,[2f,4] the tedious two-step procedure may limit the wide applicability of this approach.

Scheme 1. Reductive Deoxygenation of Alcohols



One-step reduction is straightforward and is thus highly desirable. Some one-step reduction approaches have been developed (Scheme 1B). The Li group disclosed a Ir- or Ru-catalyzed reductive deoxygenation of alcohols through a combination of the oxidation of alcohols to aldehydes and the Wolff−Kishner reduction,[5] a strategy which was later modified by the Milstein group by replacing the Ir or Ru catalysts with a Mn catalyst.[6] Although efficient, the approach can only be applicable to primary alcohols. Alcohols can be activated by transition metal complexes through oxidative addition to form R-M-X species or activated by an acid to form carbocation that can be reduced by a transition metal hydride species generated in situ, which makes transition metal catalysis a highly effective method for reductive deoxygenation of alcohols with excellent functional group compatibility.[7] This approach can be applied to primary, secondary and tertiary alcohols, demonstrating a wide substrate scope, but it suffers from the use of an expensive transition metal catalyst. Although the hydroxyl group is a poor leaving group, its coordination to a Lewis acid may facilitate the cleavage of the C−OH bond to form a carbocation R^+ or a R· radical intermediate, both of which would be readily captured by a suitable hydrogen source to provide alkanes.[8] The used Lewis acids are quite sensitive to moisture, which may be a limitation of this strategy. The combination of first reduction to a R^- anion and the subsequent protonation would also deliver alkanes.[9] The R^- anion intermediate can function as a strong base or an active nucleophile, potentially leading to restricted functional group compatibility.

We have demonstrated in previous studies that the hydroxyl group can be effectively activated by a R_3P/ICH_2CH_2I system, enabling convenient dehydroxylative functionalization of alcohols,[10] such as halogenation,[10a] fluorination,[10d] and sulfonylation.[10f] The dehydroxylation protocol was successfully applied to a halogenation of alcohols in a total synthesis

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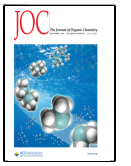

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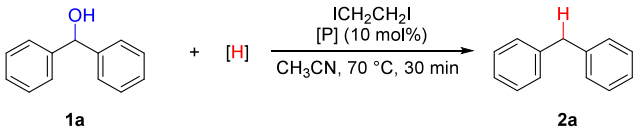
described by the Zhang group, a step which cannot be achieved by using commonly halogenation reagents.[11] We have found that the R_3P/ICH_2CH_2I system can also promote the reductive deoxygenation of alcohols.[10h] However, an apparent shortcoming of this dehydroxylation protocol is that the trivalent phosphine R_3P has to be used in an excessive amount, which is an issue in terms of atom economy. Furthermore, R_3P is converted into $R_3P{=}O$ in this process, causing inconveniences for the product isolation. Therefore, we have been interested in lowering the loading of the phosphorus species. Herein we describe a $Ph_3P{=}O$-catalyzed reductive deoxygenation of alcohols with $PhSiH_3$ (Scheme 1C). The reactions proceeded smoothly under an air atmosphere without the need for an inert atmosphere. The striking features of this protocol include convenient operations, catalytic loading of $Ph_3P{=}O$, and the use of cheap reagents.

Initially, we hypothesized that a hydrogen source could serve a dual function as both a hydride source to attack the C−OH unit and a reducing agent to reduce the in situ generated $Ph_3P{=}O$ for the catalytic cycle. Therefore, we screened various hydrogen sources for the $Ph_3P{=}O$-catalyzed reduction (Table 1, entries 1−5). $LiAlH_4$ and $NaBH_4$ may be too reactive and thus no desired product was detected (entries 1−2). Although Si−H reagents have proved to be excellent reducing agents,[12] neither $(EtO)_3SiH$ nor Ph_2MeSiH can effectively convert the alcohol into the desired alkane (entries 3−4). To our delight, a 95% yield was obtained by using $PhSiH_3$ as a hydrogen source. Trivalent phosphorus reagents instead of $Ph_3P{=}O$ were briefly examined (entries 6−8). Surprisingly, the reactions occurred well to provide the desired product in good yields. $Ph_3P{=}O$, $PhSiH_3$ and ICH_2CH_2I are all essential for this reaction, as demonstrated by the results that the absence of any one of them led to the complete suppression of the desired conversion (entries 9−11). The loadings of $PhSiH_3$ and ICH_2CH_2I were investigated (entries 12−16). For ICH_2CH_2I, 0.6 equiv. is a superior choice (entry 5 vs entries 12−13). Increasing the loading of $PhSiH_3$ to 2 equiv resulted in a lower yield (entry 16 vs entry 5). The reaction solvent is also crucial for this process. No desired product was produced or a dramatically lower yield was obtained in other solvents (entries 17−20). All of the above reactions were performed under an air atmosphere. In order to determine the necessity of oxygen gas in the process, a reaction was conducted under an inert atmosphere. Notably, a robust yield was achieved (entry 21), clearly indicating that oxygen gas is not necessary for the reaction.

With the optical reaction conditions in hand (Table 1, entry 5), we then investigated the substrate scope of the $Ph_3P{=}O$-catalyzed reductive deoxygenation of alcohols. As shown in Scheme 2, the process could be extended to a wide range of secondary and tertiary benzyl alcohols, and 30 min of reaction time gave the expected products in moderate to high yields. Electron-rich and -neutral secondary alcohols could all be

Table 1. Optimization of Reaction Conditions[a]

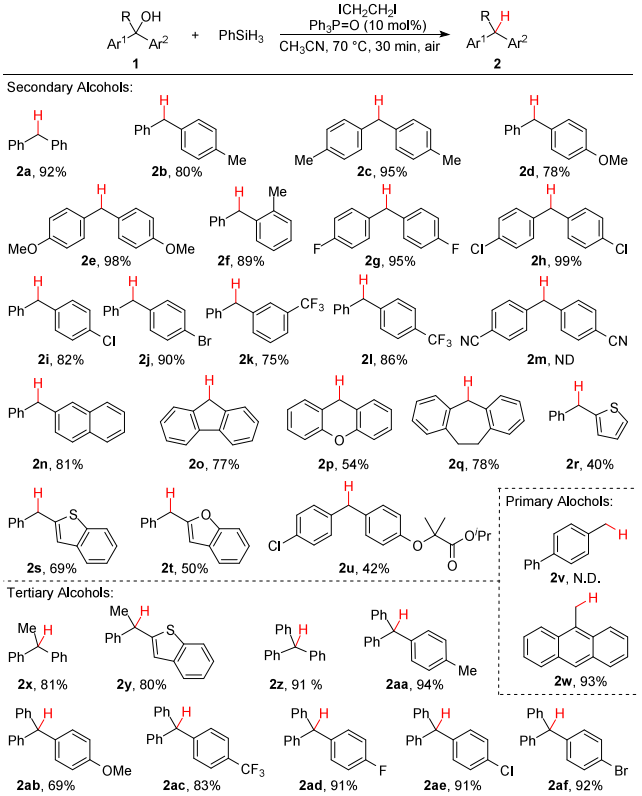


1a 2a

Entry	[P]	[H]	Solvent	Yields (%)[b]
1	$Ph_3P{=}O$	$LiAlH_4$	MeCN	ND
2	$Ph_3P{=}O$	$NaBH_4$	MeCN	ND
3	$Ph_3P{=}O$	$(EtO)_3SiH$	MeCN	ND
4	$Ph_3P{=}O$	Ph_2MeSiH	MeCN	trace
5	$Ph_3P{=}O$	$PhSiH_3$	MeCN	95
6	Ph_3P	$PhSiH_3$	MeCN	75
7	$(p\text{-}MePh)_3P$	$PhSiH_3$	MeCN	81
8	$(p\text{-}MeOPh)_3P$	$PhSiH_3$	MeCN	75
9	–	$PhSiH_3$	MeCN	ND
10	$Ph_3P{=}O$	–	MeCN	ND
11	$Ph_3P{=}O$	$PhSiH_3$	MeCN	ND
12[c]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	trace
13[d]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	80
14[e]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	34
15[f]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	55
16[g]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	78
17	$Ph_3P{=}O$	$PhSiH_3$	EtOAc	ND
18	$Ph_3P{=}O$	$PhSiH_3$	THF	ND
19	$Ph_3P{=}O$	$PhSiH_3$	DMF	ND
20	$Ph_3P{=}O$	$PhSiH_3$	$CHCl_3$	44
21[h]	$Ph_3P{=}O$	$PhSiH_3$	MeCN	93

[a]Reaction conditions: **1a** (0.1 mmol), $Ph_3P{=}O$ (10 mol %), ICH_2CH_2I (0.6 equiv), $PhSiH_3$ (1.5 equiv) and MeCN (1.0 mL) at 70 °C for 30 min under an air atmosphere. ND = not detected. [b]The yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard. [c]0.3 equiv of ICH_2CH_2I was used. [d]0.5 equiv of ICH_2CH_2I was used. [e]1.0 equiv of $PhSiH_3$ was used. [f]1.2 equiv of $PhSiH_3$ was used. [g]2.0 equiv of $PhSiH_3$ was used. [h]The reaction was performed under an Ar atmosphere.

Scheme 2. Substrate Scope Investigation[a]



[a]Isolated yields are shown. ND = not detected. Reaction conditions: **1** (0.5 mmol), $Ph_3P{=}O$ (10 mol %), ICH_2CH_2I (0.6 equiv), $PhSiH_3$ (1.5 equiv) and MeCN (5.0 mL) at 70 °C for 30 min under an air atmosphere.

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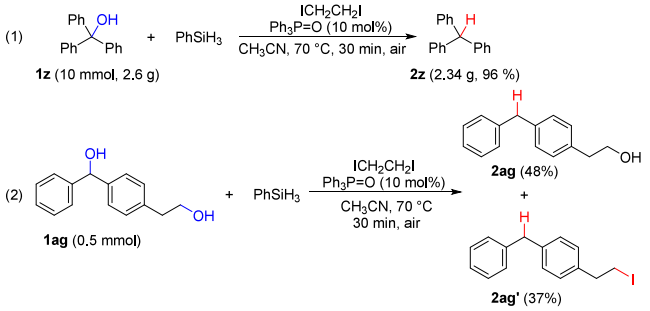
converted smoothly into the desired products in high yields. Substrates containing weak electron-withdrawing groups (**2g**–**2j**) or only one strong electron-withdrawing group are quite reactive under these conditions. However, if each phenyl ring contains a strong electron-withdrawing group, no desired product was produced (**2m**), reflecting the sensitivity to the substituent electron effects. In the cases of heteroaryl alcohols, only moderate yields were obtained (**2r**–**2t**). A derivative of Fenofibrate, which is an oral medication of the fibrate class used to treat abnormal blood lipid levels,[13] can be synthesized by this reductive deoxygenation protocol (**2u**). Primary benzyl alcohols cannot be converted into alkanes (**2v**), and undergo a different reaction pathway, resulting in the formation of benzyl iodides ($ArCH_2I$) instead of alkanes. Surprisingly, 9-anthracenemethanol was transformed into the desired product in a high yield (**2w**), probably because the benzyl cation generated in situ can be well stabilized by the extended π-conjugated system of the anthracene ring. Tertiary alcohols presented high reactivity in this process and high yields were achieved (**2x**–**2af**). In the case of ordinary alkyl alcohols, such as $PhCH_2CH_2CH_2OH$, no expected reductive deoxygenation product was observed.

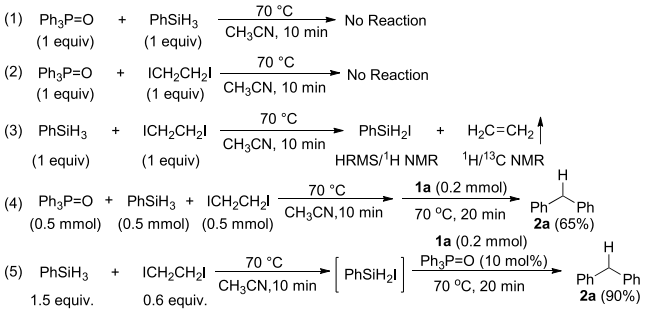
To further demonstrate the practicality and utility of this protocol, a gram-scale reaction was conducted and the chemoselectivity was investigated (Scheme 3). The gram-scale reaction can also occur rapidly, and a 96% yield was obtained within 30 min of reaction time (Scheme 3, eq 1). Substrate **1ag**, containing a secondary benzyl hydroxyl and a primary alkyl hydroxyl groups, can be converted into an alkane product (**2ag**) while leaving the primary hydroxyl group untouched, demonstrating the regioselectivity of the process. It should be noted that the iodination byproduct (**2ag′**) was also produced (eq 2).

Scheme 3. Gram-Scale Reaction and the Chemoselectivity



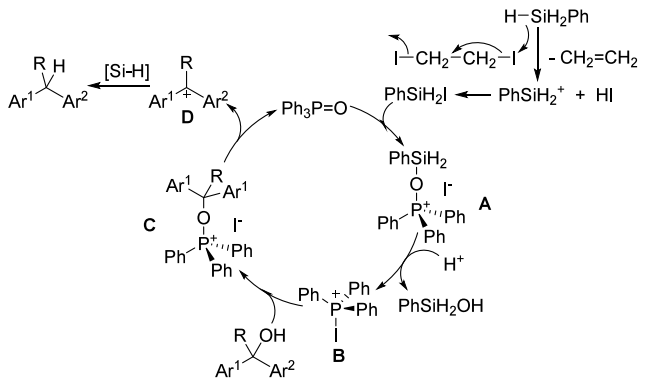
To gain more insights into the reaction mechanism, the role of $Ph_3P{=}O/ICH_2CH_2I/PhSiH_3$ system was investigated through three paired reactions. No reaction was observed between $Ph_3P{=}O$ and ICH_2CH_2I (Scheme 4, eq 1), and between $Ph_3P{=}O$ and $PhSiH_3$ (Scheme 4, eq 2). The reaction of $PhSiH_3$ with ICH_2CH_2I occurred rapidly to generate $PhSiH_2I$, which was confirmed by HR-MS (EI) and ^1H NMR spectroscopy,[14] and $CH_2{=}CH_2$, a gas which was collected and analyzed by $^1H/^{13}C$ NMR spectroscopy to determine its structure (Scheme 4, eq 3) (See Supporting Information). Apparently, the deoxygenation process starts from the reaction of $PhSiH_3$ with ICH_2CH_2I. $PhSiH_2I$ is a strong Lewis acid which may activate $Ph_3P{=}O$. Indeed, mixing $Ph_3P{=}O$, ICH_2CH_2I, $PhSiH_3$ together resulted in the complete conversion of $Ph_3P{=}O$ into an unknown species, whose ^{31}P NMR resonance appears at 47.2 ppm. Adding the substrate into the resulting mixture could also produce the desired product in a 65% yield (Scheme 4, eq 4). Instead, after $PhSiH_2I$ was produced, the addition of substrate **1a** and the catalytic amount of $Ph_3P{=}O$ could also deliver product **2a** in a high yield (Scheme 4, eq 5), further suggesting that $PhSiH_2I$ is a key intermediate and it could activate $Ph_3P{=}O$ for the subsequent deoxygenation.

Scheme 4. Paired Reactions To Determine the Role of $Ph_3P{=}O/ICH_2CH_2I/PhSiH_3$



On the basis of the above results, we propose the reaction mechanism as shown in Scheme 5. The reaction of $PhSiH_3$ with ICH_2CH_2I generates $PhSiH_2I$, a strong Lewis acid which coordinate with $Ph_3P{=}O$ to form complex **A**. The acidic conditions would lead to the cleavage of the P–O bond to form $Ph_3P^+–I$ (**B**), which can effectively activate the hydroxyl group by forming intermediate **C**.[10] This intermediate would easily collapse to release the $Ph_3P{=}O$ catalyst and afford cation **D**. The reduction of cation **D** by a Si–H species affords the final product. Alternatively, intermediate **C** may also be directly reduced by a Si–H species to provide the final product and release the $Ph_3P{=}O$ catalyst. Even though only 0.6 equiv of ICH_2CH_2I is required, which is not enough for the stoichiometric formation of $PhSiH_2I$, the reaction still proceeds effectively. One possible explanation for this is that some uncertain silane species can also serve as a Lewis acid to activate alcohols. The trivalent phosphorus (R_3P), rather than $Ph_3P{=}O$, can also catalyze this reaction, as demonstrated in entries 6–8 of Table 1, likely because the phosphorus species rapidly reacts with ICH_2CH_2I to form intermediate **B**, a process described in our previous work.[10]

Scheme 5. Proposed Reaction Mechanism



Although $PhSiH_3$ is a hydrogen source, we believe that the hydrogen attacking at cation **D** is not from $PhSiH_3$, but from an unknown Si–H generated in situ. As shown in the proposed mechanism, two hydrogen atoms are needed from the Si–H

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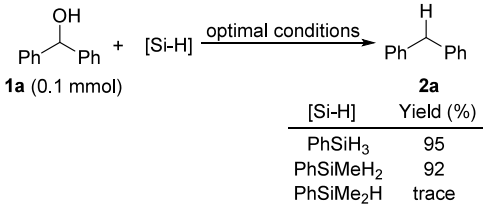
reagent. One is for the reduction of ICH_2CH_2I to form $PhSiH_2I$, and the other one is for the attack at cation **D**. Indeed, the use of $PhSiMeH_2$ as a hydrogen source can also give the desired product in a high yield, but almost no expected product was observed by using $PhSiMe_2H$, containing only one hydrogen atom, instead of $PhSiH_3$ (Scheme 6).

Scheme 6. Examination of Si−H Reagents



[Si-H]	Yield (%)
$PhSiH_3$	95
$PhSiMeH_2$	92
$PhSiMe_2H$	trace

In summary, we have described a $Ph_3P{=}O$-catalyzed reductive deoxygenation of alcohols with $PhSiH_3$. This protocol features convenient operations, catalytic loading of $Ph_3P{=}O$, and the use of cheap reagents. Secondary and tertiary aryl alcohols are quite reactive toward this reaction and can be transformed smoothly. All reactions occurred rapidly without the need of an inert atmosphere and 30 min of reaction time can give the expected products in moderate to high yields.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01847.

Materials and methods, experimental procedures, and ^1H NMR, ^{19}F NMR, ^{13}C NMR, IR, and MS data (PDF)

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Author Contributions

#Q.L. and Y.S. contributed equally.

Notes

The authors declare no competing financial interest.

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