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Halogenation through Deoxygenation of Alcohols and Aldehydes

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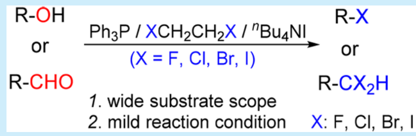
Supporting Information

ABSTRACT: An efficient reagent system, Ph_3P/XCH_2CH_2X (X = Cl, Br, or I), was very effective for the deoxygenative halogenation (including fluorination) of alcohols (including tertiary alcohols) and aldehydes. The easily available 1,2-dihaloethanes were used as key reagents and halogen sources. The use of $(EtO)_3P$ instead of Ph_3P could also realize deoxy-halogenation, allowing for a convenient purification process, as the byproduct $(EtO)_3P{=}O$ could be removed by aqueous washing. The mild reaction conditions, wide substrate scope, and wide availability of 1,2-dihaloethanes make this protocol attractive for the synthesis of halogenated compounds.



Naturally occurring organohalogenated molecules are being continuously discovered. Over 4700 molecules are now known, including 30 fluorinated, 2300 chlorinated, 2100 brominated, and 120 iodinated molecules.[1] Organohalogenated compounds are highly valuable intermediates in organic synthesis and are of increasing importance in pharmaceuticals,[2] agrochemicals,[3] and functional materials.[4] Therefore, significant efforts have been directed toward the development of mild approaches for halogen incorporation. A variety of efficient halogenation strategies have been devised, such as radical, electrophilic, nucleophilic, and decarboxylative halogenation.[5] Because alcohols and aldehydes are inexpensive and easily available materials, their deoxygenation and subsequent nucleophilic halogenation is apparently one of the most straightforward strategies for the incorporation of halogen atoms. However, efficient protocols for deoxygenative halogenation (including fluorination) are rather scarce.

Traditional deoxy-halogenation methods require the use of highly acidic agents such as hydrogen halides (HX), phosphorus halides (PX_5, POX_3, PX_3), and sulfur halides (SO_2X_2, SOX_2) (Figure 1, eq 1).[5b] These acidic agents are corrosive or moisture sensitive, and may lead to rearrangement or dehydration of alcohols. The Appel reaction, deoxy-halogenation of alcohols and aldehydes promoted by a trivalent phosphorus compound and an electrophilic halogen-containing agent, has proven to be one of the most successful strategies for halogen incorporation (Figure 1, eq 2).[6] However, the commonly used electrophilic halogen-containing agents,[6] including tetrahalomethanes, molecular halogens, and *N*-halo compounds, are highly toxic or may result in low functional group tolerance, owing to their high reactivity. Furthermore, Wittig-type dihalomethylenation products can sometimes be obtained as side products during the conversion of aldehydes.[6a,7] Recently, Denton reported an efficient method for a catalytic Appel reaction, in which a wide substrate scope was demonstrated.[8] To date, the Appel reaction conditions have been applied well for the halogenation of primary and secondary alcohols, but not for tertiary alcohols. Although many deoxy-halogenation approaches have been developed, a mild and general protocol that can be applied not only to deoxy-chlorination, -bromination, and -iodination, but also to deoxy-fluorination has not been developed. Usually, hazardous agents such as sulfur tetrafluoride (SF_4) or diethylaminosulfur trifluoride (DAST) have to be employed for deoxy-fluorination.[9] Recently, we found that a new reagent system, $Ph_3P/XCH_2CH_2X/^nBu_4NI$ (X = Cl, Br, or I), can be used for efficient and convenient halogenation reactions including fluorination (Figure 1, eq 3).

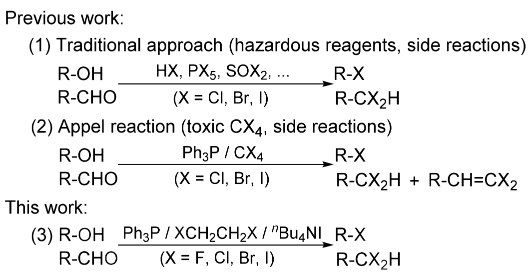


Figure 1. Halogenation through deoxygenation of alcohols and aldehydes.

Our interest in phosphonium chemistry[10] led us to discover that tetraarylphosphonium salts ($Ph_3P^+{-}Ar\ I^-$) can be applied to the nucleophilic arylation of aldehydes in the presence of cesium carbonate (Figure 2, eq 1).[10b] Here, the tetraarylphosphonium salts were prepared in advance from aryl iodide and triphenylphosphine. Therefore, our initial attempt was to combine this two-step reaction into a one-pot process, i.e., to perform the arylation directly with aryl iodide, triphenylphosphine, and aldehyde (Figure 2, eq 2). Although various reaction conditions were screened, the expected arylation product (**2a′**) was not obtained. Unexpectedly, a dichlorinated product (**2a**)

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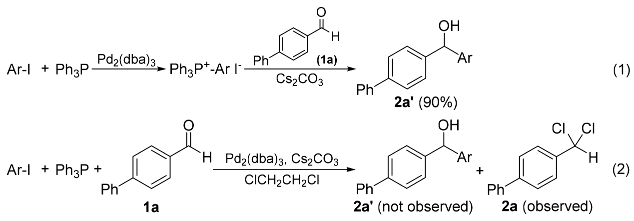
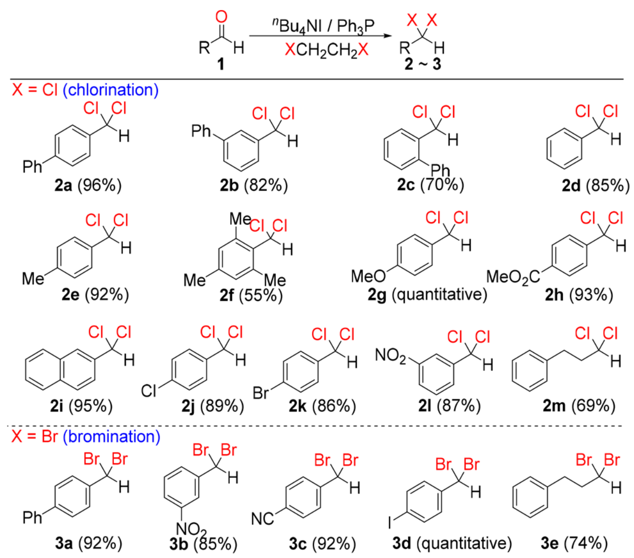


Figure 2. Unexpected chlorination through deoxygenation of an aldehyde.

was obtained when 1,2-dichloroethane was used as the reaction solvent.

The observation of product **2a** prompted us to screen the optimal reaction conditions for the unexpected deoxy-chlorination of aldehydes. A detailed survey of the conditions revealed the reaction with $ClCH_2CH_2Cl$ as the chlorination agent and reaction solvent proceeded smoothly to give the desired product in a high yield in the presence of a slight excess of Ph_3P and $^nBu_4NI$ (see Supporting Information (SI)). With the optimized reaction conditions in hand, we investigated the substrate scope for deoxy-halogenation of other carbonyls (Scheme 1). For deoxy-chlorination of aldehydes (**2a**−**2m**),

Scheme 1. Deoxy-chlorination and -bromination of Aldehydes[a]

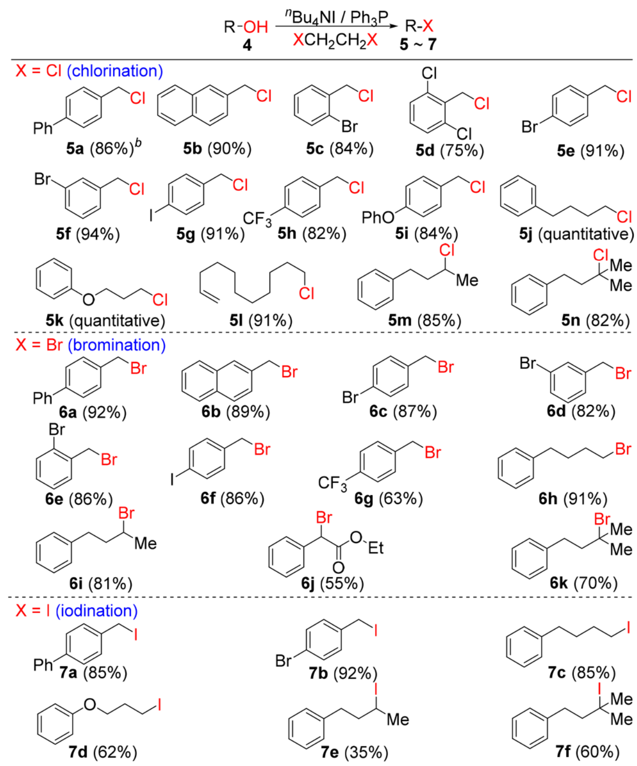


[a]Reaction conditions: for X = Cl, substrate 1 (0.5 mmol), Ph_3P (1.2 equiv (equiv)) and $^nBu_4NI$ (1.2 equiv) in $ClCH_2CH_2Cl$ (5 mL) at 80 °C for 10 h; for X = Br, substrate 1 (0.5 mmol), Ph_3P (2 equiv) and $^nBu_4NI$ (1 equiv) in $BrCH_2CH_2Br$ (5 mL) at 60 °C for 10 h. All the yields were isolated yields except for **2g**, which was determined by ^1H NMR.

electron-rich, -neutral, and -deficient aryl aldehydes were all converted smoothly into the desired products (**2a**−**2l**). Although a high conversion yield was obtained for the conversion of a substrate containing a strong electron-donating substituent, the desired product could not be isolated, owing to its instability (**2g**). Besides aryl aldehydes, an alkyl aldehyde was also transformed well (**2m**). Gratifyingly, the replacement of $ClCH_2CH_2Cl$ with $BrCH_2CH_2Br$ resulted in the deoxy-bromination of aldehydes (**3a**−**3e**). This deoxy-bromination reaction could be applied to both aryl- and alkyl-aldehydes. The deoxy-iodination of aldehydes was not fully investigated, as the desired products were highly unstable. For deoxy-chlorination of ketones such as 4′-nitroacetophenone, a dichlorinated product ($ArCCl_2CH_3$) was obtained as a minor product. Instead, a chlorinated olefin ($ArCHCl{=}CH_2$) was observed as the major product.

The successful deoxy-halogenation of carbonyls encouraged us to examine the dehydroxy-halogenation of alcohols. After determining the optimal reaction conditions (see SI), we investigated the substrate scope for dehydroxy-chlorination, -bromination, and -iodination of alcohols (Scheme 2). The use

Scheme 2. Dehydroxy-chlorination, -bromination, and -iodination of Alcohols[a]



[a]Reaction conditions: for X = Cl, alcohol **4** (0.5 mmol), Ph_3P (1.2 equiv), and $^nBu_4NI$ (1.2 equiv) in $ClCH_2CH_2Cl$ (5 mL) at 120 °C for 0.5 h; for X = Br, alcohol **4** (0.5 mmol), Ph_3P (1.2 equiv), and $^nBu_4NI$ (1.2 equiv) in $BrCH_2CH_2Br$ (5 mL) at 60 °C for 2 h; for X = I, alcohol **4** (0.5 mmol) and Ph_3P (1.2 equiv) in CH_3CN (5 mL) at 60 °C for 2 h. All the yields were isolated yields. [b]The reaction was performed on a 2 mmol scale (2 mmol of alcohol were used).

of $ClCH_2CH_2Cl$ as the chlorination agent and the reaction solvent also gave the desired chlorination products in moderate to high yields in the presence of Ph_3P and $^nBu_4NI$ (**5a**−**5n**). In contrast to deoxy-chlorination of aldehydes, dehydroxy-chlorination of alcohols occurred much faster (0.5 h versus 10 h), albeit at a higher reaction temperature (120 °C versus 80 °C). Various benzyl alcohols (**5a**−**5i**) and alkyl alcohols (**5j**−**5n**) were all suitable for this transformation. Compared with primary alcohols (**5a**−**5l**), a secondary alcohol (**5m**) and tertiary alcohol (**5n**) were converted into the desired products in slightly lower yields. Dehydroxy-bromination of alcohols by using $BrCH_2CH_2Br$ instead of $ClCH_2CH_2Cl$ also occurred very well at a lower temperature (**6a**−**6k**). A tertiary product (**6k**) could also be obtained in moderate yields. The use of DMF or CH_3CN as the reaction solvent allowed for the successful

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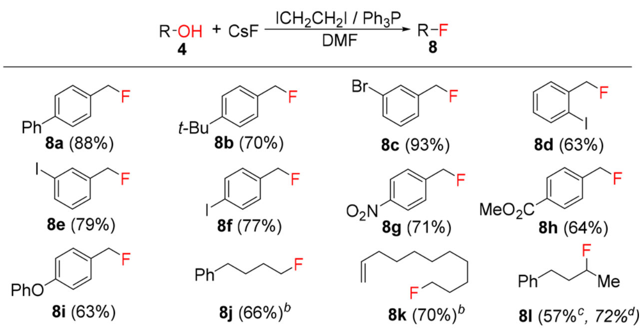
deoxy-iodination of alcohols (see the optimization of the reaction conditions in the SI) with only a slight excess of ICH_2CH_2I (1.2 equiv) (**7a**–**7f**). In contrast to the above chlorination and bromination, the iodination proceeded smoothly without the presence of $^nBu_4NI$.

Although the iodide anion was present during the chlorination and bromination, as shown in Scheme 2, no iodination product was observed, which may be because both chlorination and bromination were faster than iodination, owing to the stronger C–X (X = Cl, Br) bond. The successful iodination prompted us to speculate on the possibility of the challenging dehydroxy-fluorination of an alcohol when an external fluoride ion is added to the Ph_3P/ICH_2CH_2I system. To our delight, a brief survey of the reaction conditions (see SI) revealed that dehydroxy-fluorination could proceed well when CsF was used as the fluoride source. With the optimal reaction conditions in hand, we examined the substrate scope of the dehydroxy-fluorination of alcohols (Scheme 3). Benzyl alcohols

Scheme 3. Dehydroxy-fluorination of Alcohols



[a]Reaction conditions: alcohol **4** (0.5 mmol), Ph_3P (1.5 equiv), ICH_2CH_2I (1.5 equiv), and CsF (3 equiv) in DMF (5 mL) at 100 °C for 2 h. The yields were isolated yields. [b]2 equiv of 18-crown-6 were used, and the reaction temperature was 120 °C. [c]AgF (3 equiv) was used instead of CsF; the loadings of Ph_3P and ICH_2CH_2I were both decreased to 1.2 equiv. [d]The yield was determined by ^{19}F NMR spectroscopy.

were quite reactive, and the yields were not affected by the electronic effects of substituents (**8a**–**8i**). Besides benzyl alcohols, unactivated alcohols could also be smoothly converted into the desired products (**8j**–**8k**). Secondary alcohols displayed low reactivity under the optimal conditions. Fortunately, a moderate yield could be obtained by using AgF instead of CsF (**8l**). The high volatility of product **8l** led to a decrease in the isolated yield (57%) compared with the yield determined by ^{19}F NMR.

On the basis of the above results and the experimental evidence which has to be shown in SI due to length limits, we propose the plausible reaction mechanism, as shown in Figure 3. For the Ph_3P/XCH_2CH_2X (X = Cl or Br) system, substitution to provide ICH_2CH_2X followed by the release of ethylene produces molecular iodine, which reacts with triphenylphosphine to afford iodophosphonium salt **A**. For the Ph_3P/ICH_2CH_2I system, the halogen bonding drives the formation of intermediate **D**, which could be in equilibrium with salt **A**. The aldehyde substrate is activated by salt **A** via coordination to form complex **F**, the carbonyl carbon of which would be easily attacked by a halide anion to give intermediate **G**. The further halogenation of intermediate **G** affords the final product and releases triphenylphosphine oxide ($Ph_3P{=}O$) as

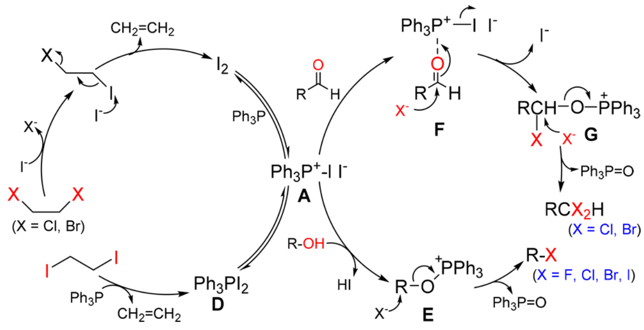


Figure 3. Proposed mechanism for deoxy-halogenation of aldehydes and alcohols.

the byproduct (determined by ^{31}P NMR; see SI). The alcohol could also be activated by salt **A** to form intermediate **E**. The nucleophilic attack of intermediate **E** by the halide via an S_N2 process affords the dehydroxy-halogenation product. For fluorination, the solvent DMF may attack intermediate **A** to produce a Vilsmeier–Haack-type intermediate $Me_2N^+{=}CHI$, which can also activate alcohols and thus allows for dehydroxy-fluorination.[11]

According to the proposed mechanism, a catalytic amount of iodide is enough for dehydroxy-chlorination and -bromination, and ethylene and Ph_3PO are produced as byproducts. Indeed, the presence of 0.2 equiv of iodide led to the chlorination of aldehyde **1a** to give product **2a**, albeit in 62% yield (Figure 4).

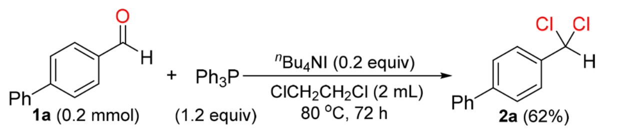


Figure 4. Dehydroxy-chlorination in the presence of a catalytic amount of $^nBu_4NI$.

However, a 72 h reaction time was required. Furthermore, owing to the slow chlorination process when using a catalytic amount of iodide, the quaternization of Ph_3P with $ClCH_2CH_2Cl$ occurred as a side reaction, resulting in a lower yield (62% versus 96%, as shown in Scheme 1). Therefore, a stoichiometric amount of $^nBu_4NI$ was employed to facilitate the dehydroxy-chlorination and -bromination reaction.

For the dehydroxy-fluorination, -chlorination, and -bromination reactions, no iodination product was observed even though an iodide anion was present. The question arose whether these products were formed from the substitution of an iodinated intermediate. If this is the dominant path, retention of configuration may be observed, owing to the double inversion. However, the transformation of enantiopure ***S*-4m** under the optimal reaction conditions led to the inversion of configuration (Figure 5). The inversion not only indicated that iodination to give ***R*-7e** followed by substitution was not the

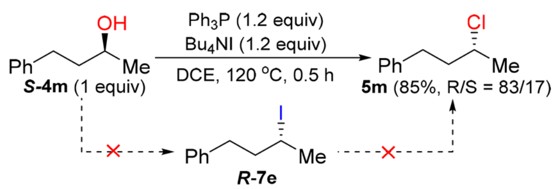


Figure 5. Inversion of configuration.

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probable path but also supported the S_N2 process for halogenation of intermediate **E** shown in Figure 3. Apparently, fluorination, chlorination, and bromination are faster than iodination, owing to the stronger C−X (X = F, Cl, Br) bond compared with the C−I bond.

In the above-mentioned reactions, the formation of by-product $Ph_3P{=}O$ could lead to a difficult purification process. However, the use of $(EtO)_3P$ instead of Ph_3P could also readily realize the dehydroxy-halogenation of alcohol (Figure 6). Like

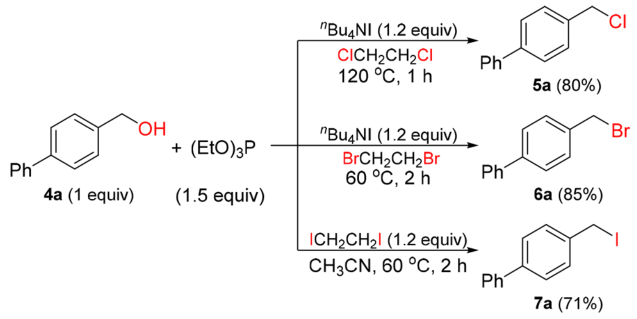

Figure 6. Use of $(EtO)_3P$ for dehydroxy-halogenation of alcohol.

Ph_3P, $(EtO)_3P$ was almost completely converted into an oxide, $(EtO)_3P{=}O$, which could be easily removed by washing with water, leading to a more convenient purification process for large-scale reaction.

In conclusion, we have described the dehydroxy-fluorination, -chlorination, -bromination, and -iodination of alcohols, and the deoxy-chlorination and -bromination of aldehydes with an R_3P/XCH_2CH_2X (X = Cl, Br, or I) system. This work represents the first protocol for a variety of efficient deoxygenative halogenation reactions, including challenging dehydroxyfluorination. The wide substrate scope and the availability of 1,2-dihaloethanes make this protocol attractive for the incorporation of halogens. The R_3P/XCH_2CH_2X (X = Cl, Br, or I) system may find synthetic utility in other research areas.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01058.

Experimental details; references and notes; copies of ^1H, ^{19}F, and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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