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Hypervalent Iodine-Based Activation of Triphenylphosphine for the Functionalization of Alcohols

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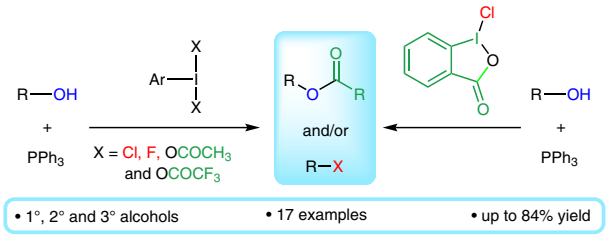
Dedicated to Professor Victor Snieckus on the occasion of his 80th birthday



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Abstract The use of hypervalent iodine reagents as a general tool for the activation of PPh_3 and its application to the functionalization of alcohols is reported. Combination of PPh_3 with $PhICl_2$ or $TolIF_2$ gives dihalophosphoranes that are characterized by ^{31}P NMR, however, with $PhIOAc_2$, $PhI(OTFA)_2$, or the cyclic chloro(benzoyloxy)iodane, no phosphoranes were observed. Reaction of these iodanes with PPh_3 in the presence of primary, secondary, or tertiary alcohols results in either halogenation or acyl-transfer products in moderate to high yield.

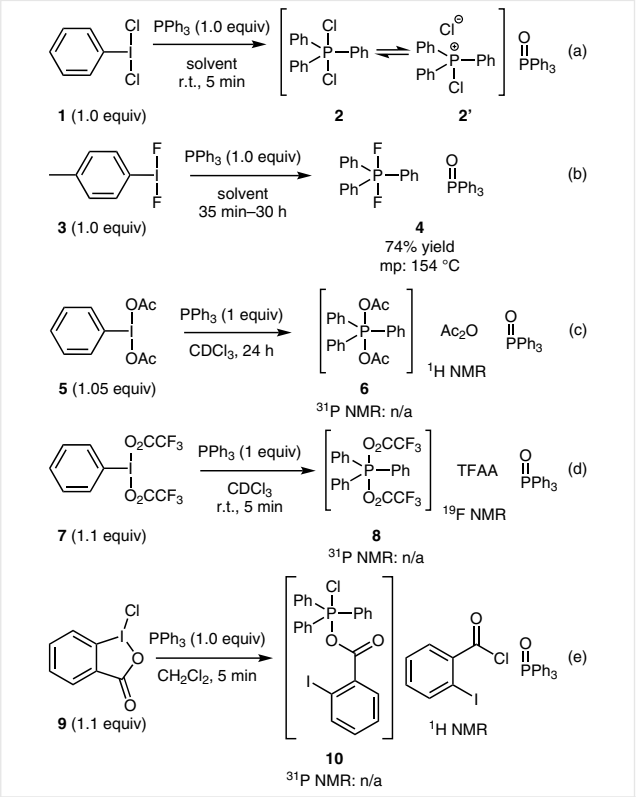
Key words Appel reaction, hypervalent iodine, halogenation, acylation, benzoylation

Disubstituted triphenylphosphoranes (Ph_3PX_2) are valuable reagents due to their ability to effect deoxygenative functionalization reactions. Recently, Zhang and co-workers disclosed a new strategy for effecting esterification and amidation reactions by activating triarylphosphines (e.g., PPh_3) with hypervalent iodine reagents.[1] We were very intrigued by their mechanistic proposal that the iodane's ligands were not being transferred to the activated phosphine, as might be expected with nucleophilic phosphines. This spurred us to investigate whether hypervalent iodine(III) reagents could transfer their ligands to phosphine, and whether such reagent combinations might be used to effect Appel-type reactivity[2] with alcohols. Given the breadth of these hypervalent iodine reagents, coupled with recent discoveries of catalytic, recyclable, and asymmetric reactions thereof,[3] this strategy might hold unexplored potential in the synthesis of novel phosphoranes and in alcohol functionalization.

As part of our interest in ligand-transfer reactions of hypervalent iodine reagents,[4] we assessed their reaction with PPh_3 using time-lapse NMR experiments to identify and characterize the resulting products (phosphorane, etc). We report here that PPh_3 can be made to react rapidly and quantitatively with both cyclic and acyclic hypervalent iodine reagents possessing various halide and acetate-type ligands, and that when phosphine activation is carried out in the presence of alcohols, halogenation, and/or acylation reactions ensue.

We began this study using time-lapse ^{31}P NMR experiments to determine if the synthesis of disubstituted triphenylphosphoranes was generalizable upon the combination of PPh_3 and iodane. Because $PhICl_2$ engages in ligand-transfer reactions with ease in many solvents,[5] we investigated the solvent scope for the synthesis of Ph_3PCl_2 (**2**) from $PhICl_2$ (**1**) and PPh_3(Scheme 1, a).[6] In nearly all solvents, the chlorine transfer from $PhICl_2$ (**1**) to PPh_3 was complete within five minutes, with covalent phosphorane **2** being observed in toluene, benzene, and THF, and the ionic phosphorane **2′** being observed in $CHCl_3$, CH_2Cl_2, DCE, and MeCN. Additionally, hydrolysis of phosphorane **2** was encountered in each instance, with a ^{31}P NMR signal for Ph_3PO being observed regardless of solvent employed (see Supporting Information).

Given the importance of fluorination processes in drug discovery, medical imaging, materials science, and so on,[7] we investigated the synthesis of the fluorinating agent difluorotriphenylphosphorane (Ph_3PF_2, **4**)[8] from $TolIF_2$ (**3**). Time-lapse ^{31}P NMR experiments using an equimolar ratio of **3** and PPh_3 in various solvents led to complete conversion into **4**, with reaction times varying between 35 minutes ($CHCl_3$) and 30 hours (Et_2O). In each reaction, a triplet at ca. δ = –55 ppm (J = ca. 660 Hz) was observed with no evidence of the ionic phosphorane.[9] The ligand-transfer reaction could be accelerated by increasing the loading of $TolIF_2$ to 1.1 equivalents, and because **4** proved resistant to hydrolysis,[10] even over lengthy reaction times, it could be isolated as a white solid in 74% yield (see Supporting Information).



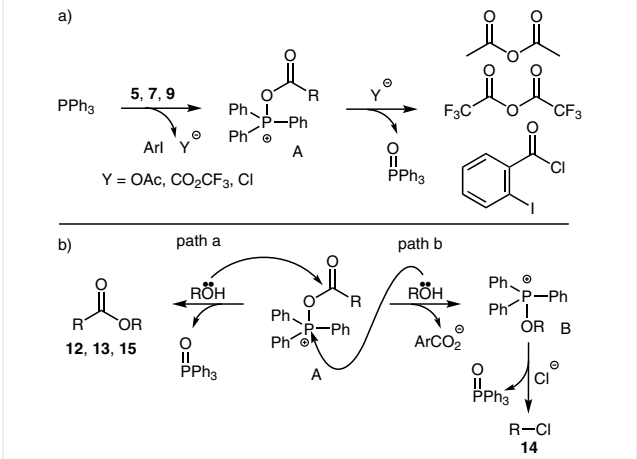
Scheme 1 Attempted synthesis of disubstituted triphenylphosphoranes by reacting PPh_3 with hypervalent iodine reagents

Diacetoxytriphenylphosphorane **6** was reported to be a good acetylating agent for alcohols, though its synthesis relied on in situ ligand metathesis on the iodane from bromide to acetate.[11] A direct synthesis from $PhI(OAc)_2$ (**5**) and PPh_3 would therefore offer a significant improvement in ease of reaction. The time-lapse ^{31}P NMR experiment at room temperature in $CDCl_3$ showed very little consumption of PPh_3 after five minutes, and phosphine remained even after 24 hours. Consumption of PPh_3 could be achieved more rapidly by heating to reflux in $CDCl_3$ for three hours. Though the ^{31}P NMR peak reported for $Ph_3P(OAc)_2$ (δ = 45 ppm in CD_3CN) was not observed in either investigation, ^1H NMR analysis of the reaction mixture confirmed acetic anhydride as the fate of the acetate ligands (see Supporting Information).[12]

We next reacted PPh_3 with a slight excess of the more electrophilic iodane $PhI(OTFA)_2$ (**7**), again using time-lapse NMR and looking for any peaks attributable to $Ph_3P(OTFA)_2$ (**8**). Complete consumption of the phosphine occurred within five minutes at room temperature (Scheme 1, d). However, ^{31}P NMR showed only triphenylphosphine oxide, and ^{19}F NMR analysis of the product mixture showed TFAA to be the fate of the trifluoroacetate ligands (see Supporting Information).[12]

Lastly, we reacted PPh_3 with the unsymmetrically substituted iodane **9** in CH_2Cl_2 at room temperature, and complete consumption of the phosphine occurred within five minutes (Scheme 1, e). Analysis of the mixture by ^{31}P NMR showed triphenylphosphine oxide and nothing attributable to the putative disubstituted phosphorane **10**, though ^1H NMR confirmed 2-iodobenzoyl chloride as the deoxygenated ligand coupling product (see Supporting Information).

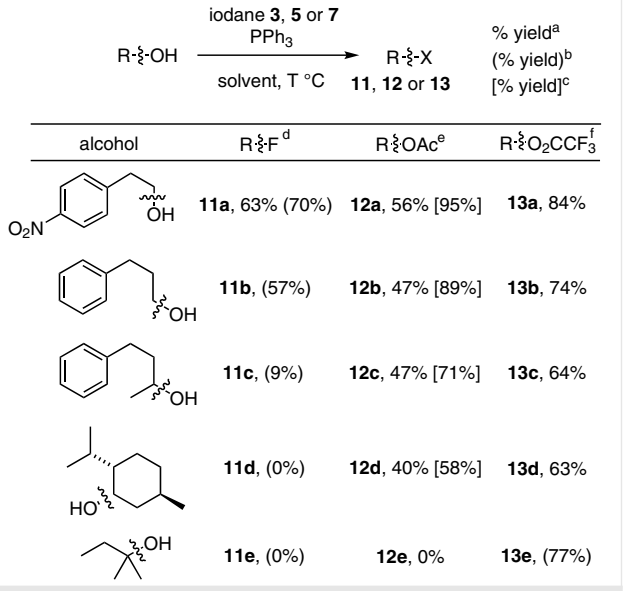
The Ac_2O, TFAA, and 2-iodobenzoyl chloride products observed in the reactions of iodanes **5**, **7**, and **9** with PPh_3, respectively, are consistent with previous investigations and mechanistic proposals (Scheme 2, a). Varvoglis[12] and others,[1,13] have suggested PPh_3 can displace a ligand (Y) on the iodane, from which an acyloxyphosphonium[14] intermediate (**A**) can be produced by reductive elimination, or by nucleophilic displacement of iodoarene. Attack by the displaced ligand (Y) on the activated carboxylate intermediate **A** would give triphenylphosphine oxide and the corresponding anhydride or benzoyl chloride products.



Scheme 2 a) Reaction of PPh_3 with iodanes **5**, **7**, and **9** gives anhydride and benzoyl chloride products, and b) how this might be useful in the functionalization of alcohols

Phosphoranes **2**[15] and **4**[16] are both known to effect deoxygenative halogenation of alcohols, but there are very limited examples of combining iodanes with phosphines to effect acylation reactions.[13] Given that PPh_3 is a strong nucleophile, and because little reaction is expected between iodanes and alcohols under these conditions,[13,17] intermediate **A** should still occur when phosphine activation by iodanes **5**, **7**, and **9** is carried out in the presence of alcohols (Scheme 2, b). Should an alcohol attack the acyloxyphosphonium intermediate **A** at the carboxyl (path a),[14,18] acylation would ensue. In the case of iodane **9**, attack could either occur at the activated carboxylate (path a), or at the phosphonium ion (path b) to generate intermediate **B**, which could terminate through nucleophilic chlorination.

Given the ease of alcohol chlorination previously reported for the mixture of PPh_3 and $PhICl_2$ (**1**),[19] we investigated the potential of iodanes **3**, **5**, **7**, or **9** and PPh_3 to also functionalize alcohols. We began by treating a small series of alcohols with $TolIF_2$ (**3**), PPh_3, and the activating agent TiF_3, aiming to convert them into the corresponding fluorides **11** (Scheme 3). The primary alkyl fluorides **11a**,**b** were observed in moderate yield, with alkyl fluoride **11a** isolated in 63% yield.[20] The secondary alcohols generally failed, with only 9% NMR yield observed for **11d**, and no **11e** observed by ^1H NMR or ^{19}F NMR spectroscopy. Fluorination of the sterically congested *tert*-amyl alcohol also failed, which we attribute to the poor rates of S_N2 reactions on tertiary substrates.[21]

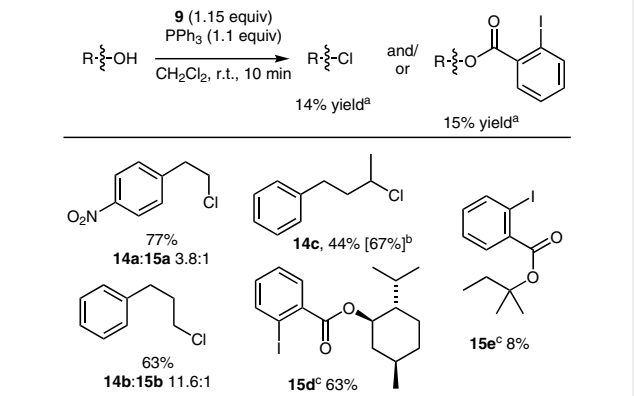


Scheme 3 Reactions of iodanes **3**, **5,** or **7** with PPh_3 and alcohols. [a]Isolated yield. [b]NMR yield. [c]Yield based on recovered alcohol. [d]*Reagents and conditions*: 1.6 equiv **3**, 1.5 equiv PPh_3, PhCl at 160 °C with 10 mol% TiF_3. [e]*Reagents and conditions*: 1.1 equiv **5**, 1.1 equiv PPh_3, CH_2Cl_2 at r.t. or $CHCl_3$ at reflux. [f]*Reagents and conditions*: 1.1 equiv **7**, 1.1 equiv PPh_3, CH_2Cl_2 at r.t.

Consistent with previous reports,[13,22] alcohol acetylation with **5** and PPh_3 was viable, though slow at room temperature, with incomplete conversion observed in every instance. However, after adjusting for recovered alcohol, the yield of primary acetates **12a**,**b** was high (Scheme 3). Acetylation of the secondary and tertiary alcohols was conducted over 12 hours at reflux in $CHCl_3$, and while the yield of acetates **12c**,**d** was moderate, no *tert*-amyl acetate (**12e**) was observed by ^1H NMR spectrosopy. While the acetylation reaction rates could be increased with heating, the most sterically hindered alcohol failed to intercept intermediate **A** (Scheme 2), leading to Ac_2O as the iodane-derived product.

The trifluoroacetylation reactions using iodane **7** and PPh_3 were all rapid at room temperature, showing complete conversion by ^1H NMR analyses within 30 minutes, and providing trifluoroacetates **13a–d** in 63–84% yield. Contrary to the acetylation of *tert*-amyl alcohol using **5**, the trifluoroacetylation was rapid and high yielding, giving **13e** in 77% NMR yield. We attribute this difference in reactivity to the increased electrophilicity of putative trifluoroacetylating intermediate **A** (Scheme 2) when using iodane **7**. The rapid consumption of PPh_3 by **7**, and the efficacy of this method (even with sterically demanding alcohols) suggests this could represent an expeditious, room temperature means to trifluoroacetylate alcohols under neutral conditions.[22]

Functionalizing alcohols with iodane **9** held the potential for forming two possible products: the alkyl chlorides **14** (via path b, Scheme 2) or 2-iodobenzoate esters **15** (via path a, Scheme 2). The primary alcohols were converted predominantly into the alkyl chlorides **14a**,**b** in good yield within ten minutes, though benzoates **15a**,**b** were also recovered as the minor products (Scheme 4).[23] The reaction of 4-phenyl-2-butanol with **9** also gave chloride **14c** as the major product, with only a trace of **15c** observed by NMR analysis of the crude reaction mixture. Conversely, the more sterically congested (–)-menthol and *tert*-amyl alcohol required heating to reflux in CH_2Cl_2, and gave benzoates **15d**,**e** as the sole products in 63% and 8% yield, respectively.[24] Therefore, reaction intermediates **A** or **B** (Scheme 2) could both be viable in alcohol functionalization when employing asymmetrically substituted iodanes, with the product distribution deriving from the steric hindrance of the alcohol employed.



Scheme 4 Reaction of iodane **9** with PPh_3 and alcohols. [a]Isolated yield. [b]Yield based on recovered alcohol. [c]Heated 13 h at reflux.

In conclusion, we have shown hypervalent iodine(III) reagents to be efficient activators for PPh_3, with the phosphorane intermediates Ph_3PCl_2 and Ph_3PF_2 observed and characterized by ^{31}P NMR spectroscopy in numerous solvents.[25] The putative phosphoranes derived from iodanes **5**, **7**, or **9** were not detected, with the reaction instead undergoing deoxygenative ligand coupling. Primary, secondary

and tertiary alcohols reacted with these iodanes and PPh_3 to give alkyl chlorides, fluorides, acetates, trifluoroacetates, or 2-iodobenzoates in moderate to good yield. Appel-type reactivity dominated with iodanes **1** and **3**, but acylation reactions dominated with iodanes **5** and **7**, consistent with an electrophilic acyloxyphosphonium intermediate serving as the active acylating agents. The chemoselectivity observed with iodane **9** was related to the steric hindrance and/or nucleophilicity of the alcohol, giving alkyl chlorides with unhindered alcohols and benzoates with hindered alcohols. This study shows various ligands can be transferred from hypervalent iodine reagents to alcohols and offers a facile approach to common alcohol derivatives.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589069.

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(20) Reacting Ph_3PF_2 (**4**, 1.6 equiv) with 4-nitrophenethyl alcohol for 45 min at 160 °C using 10 mol% TiF_3 as an activating agent produced alkyl fluoride **5a** in 66% yield.

(21) The major competing reaction pathway in these experiments was alcohol dimerization, giving the ether. It is proposed that this arises from the alcohol outcompeting fluoride as the nucleophile. See ref. 16.

(22) Zhang and co-workers reported phenethyl acetate to be the major byproduct of a reaction between **5**, phenethyl alcohol, hexanoic acid, DMAP, and PPh_3. No indication of phenethyl trifluoroacetate was reported for the analogous reaction using iodane **7**. See Table S1 in the supporting information of ref. 1a.

(23) Only trace amounts of **15a** or **15b** were visible by ^1H NMR analysis of the crude reaction mixtures after 10 min. Prolonging the reaction times to 2–3 h did not significantly change the product ratios, suggesting that the reaction pathways are competing, as opposed to **14** reacting with the benzoate byproduct of the reaction to give **15**. Concentrating the reaction mixtures before column chromatography appears to have increased the ratio of the benzoate products.

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(25) **Sample Experimental Procedure**
Into a conical flask was added the 4-phenyl-2-butanol (0.063 g, 0.42 mmol, 1 equiv) and CH_2Cl_2 (0.5 mL), and to this was added PPh_3 (1.1 equiv) and [bis(trifluoro-acetoxy)iodo]benzene (1.1

equiv). The reaction mixture was stirred at r.t. for 30 min, concentrated by rotary evaporation and subjected to column chromatography, where the stationary phase as acidified with 0.2% TFA in hexane. The crude reaction mixture was purified via column chromatography (10% EtOAc/hexane) to give **13c** (0.066 g, 64% yield) as a colorless oil.^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 5 H), 5.11 (m, 1 H), 2.74–2.60 (m, 2 H), 2.15–1.87 (m, 2 H), 1.39 (d, *J* = 6.3 Hz, 3 H);^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.1 (q, *J* = 41.5 Hz), 140.5, 128.6, 128.3, 126.3, 114.6 (q, *J* = 286.1 Hz), 75.8, 37.1, 31.4, 19.5.