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Direct, Oxidative Halogenation of Diaryl- or Dialkylphosphine oxides with (Dihaloiodo)arenes

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ABSTRACT

The oxidative halogenation of diaryl- or dialkylphosphine oxides with the hypervalent iodine reagents (difluoroiodo)toluene (TolIF_2, **1**) and (dichloroiodo)benzene (PhICl_2, **2**) is reported. Phosphoric fluorides could be recovered in 32-75% yield, or they could be trapped with EtOH to give the corresponding phosphinate in typically good yield. Phosphoric chlorides were not readily isolable, and were trapped with alcohol and amine nucleophiles, giving diaryl- or dialkylphos-phinates and phosphinamides in up to 90% yield.

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Organophosphorus compounds that possess P(O)-F bonding are a class of biologically-active compound that has received considerable attention over the last century. The biological activity displayed by these synthetic fluorine-containing organophosphorus compounds is highly structure dependent:[1] whereas sarin and soman are highly toxic nerve agents, diisopropyl fluorophosphate (DPF)[2] is a therapeutic agent used in the treatment of chronic glaucoma (Figure 1). Phosphoric fluorides are selective mechanistic probes, as well as potent cholinesterase enzyme inhibitors, and both the fluorides and chlorides are powerful phosphorylating reagents, serving as precursors to other organophosphorus compounds. [3,4]

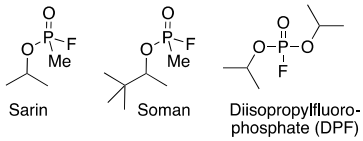


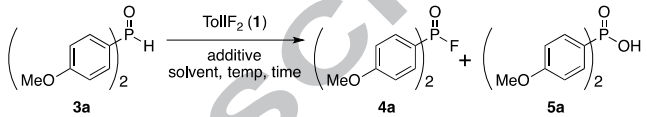
Figure 1. Examples of biologically active phosphoric fluorides.

Oxidative halogenation of P(O)-H compounds is a well-established approach to phosphoric halides. For example, their chlorination has been prepared with chlorine gas,[5] with sulfuryl chloride[6] or $CuCl_2$,[7] or with chloramines,[8] TCICA[9] or NCS.[10] These chlorination reactions can also be employed in strategies for the synthesis of phosphoric fluorides by simply adding a fluoride source. For example, in reactions with TCICA–KF,[11] trichloroacetonitrile–KF[12] or $CuCl_2$–CsF,[13] the initially-formed chlorides are intercepted by the fluoride. Electrophilic fluorination of a phosphine oxide is achieved with reagents such as XeF_2,[14] Selectfluor®[15] or DDQ/$CuBr_2$/NaF.[16] Drawbacks of these methods include harsh reaction conditions, the need for excess reagent, or use of reagents that are corrosive, toxic, costly or moisture sensitive, therefore the continued development of synthetic strategies remains important.

Phosphines and phosphine oxides react with hypervalent iodine reagents to undergo oxidative arylation,[17] alkynylation,[18] vinylation[19] and trifluoromethylation[20] of P-H bonds.[21] Hypervalent iodine reagents commonly effect oxidative halogenation reactions,[22] and so they are an attractive strategy for the synthesis of phosphoric halides from secondary phosphine oxides. As part of our ongoing interest in oxidative halogenation reactions of phosphines,[23] we were intrigued by the potential for generating phosphoric fluorides and chlorides from secondary phosphine oxides and TolIF$_2$ (**1**)[24] and PhICl$_2$ (**2**),[25] respectively. As oxidants and sources of halide nucleophiles, these reagents offer a facile and eco-friendly approach to the derivatization of organophosphorus compounds.[26] We report here that phosphoric fluorides and chlorides could be rapidly prepared by reacting secondary phosphine oxides with either **1** or **2**, and furthermore that the intermediates could be trapped in situ with nucleophiles to give phosphinate and phosphinamide products.

Our investigation into the synthesis of phosphoric fluorides began by reacting bis(4-methoxyphenyl)phosphine oxide (**3a**), prepared via double Grignard addition into diethyl phosphite, and TolIF$_2$ (**1**) in CH_2Cl_2 at room temperature. After 1 h, ^{31}P NMR indicated the consumption of **3a**, and phosphoric fluoride **4a** was recovered in 50% yield (Table 1, entry 1). Various other solvents were screened, and while the reaction proceeded in chlorinated, ethereal and even highly polar solvents, we found chlorobenzene to give **4a** in 58% yield (entries 2-6; see Supporting information for complete optimization table). The reaction temperature was then gradually increased from room temperature to 110 °C, and we found 60 °C to be optimal, giving **4a** in 69% yield (entries 7-9). Increasing the loading of TolIF$_2$ (**1**) failed to increase the yield of **4a** (entry 10), whereas lowering it to nearly equimolar caused a significant decrease in yield (entry 11). The addition of Lewis acidic activating agents[23b, 27] failed to improve the reaction (entries 12-15), presumably because the phosphine oxides are sufficiently nucleophilic to engage the iodane without prior activation. Throughout these trials, we consistently observed diaryl phosphinic acid **5a**, and ^{31}P NMR analysis of the reaction mixture showed this to be present prior to reaction workup. Using recrystallized reagents and conducting the reaction in a glovebox or with activated molecular sieves failed to prevent its formation. Nonetheless, the desired oxidative fluorination proved to be a viable strategy for phosphoric fluoride synthesis from secondary phosphine oxide precursors.

Table 1. Optimization of the phosphoric fluoride synthesis.[a]

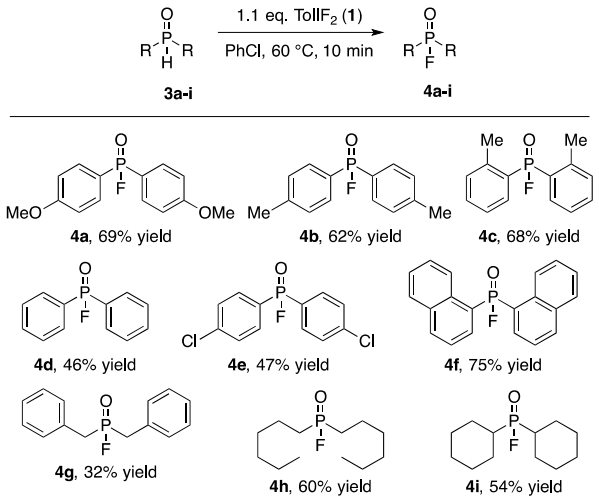


entry	solvent	temp (°C)	TolIF$_2$ (equiv)	additive (mol%)	time	**4a** %yield
1	CH_2Cl_2	rt	1.1	-	1 h	50
2	$CHCl_3$	rt	1.1	-	1 h	46
3	DCE	rt	1.1	-	1 h	53
4	PhCl	rt	1.1	-	1 h	58
5	THF	rt	1.1	-	1 h	51
6	CH_3CN	rt	1.1	-	1 h	38
7	PhCl	40	1.1	-	10 min	64
8	PhCl	60	1.1	-	10 min	69
9	PhCl	110	1.1	-	10 min	60
10	PhCl	60	1.4	-	10 min	67
11	PhCl	60	1.02	-	10 min	55
12	PhCl	60	1.1	BF_3•OEt_2 (10)	10 min	67
13	PhCl	60	1.1	TiF_3 (10)	10 min	57
14	PhCl	60	1.1	TiF_4 (10)	10 min	52
15	PhCl	60	1.1	FeF_3 (10)	10 min	57

[a] Reaction conditions: To **1** in solvent (0.25 mL) at temp (°C) was added **3a** and stirred. Isolated yields.

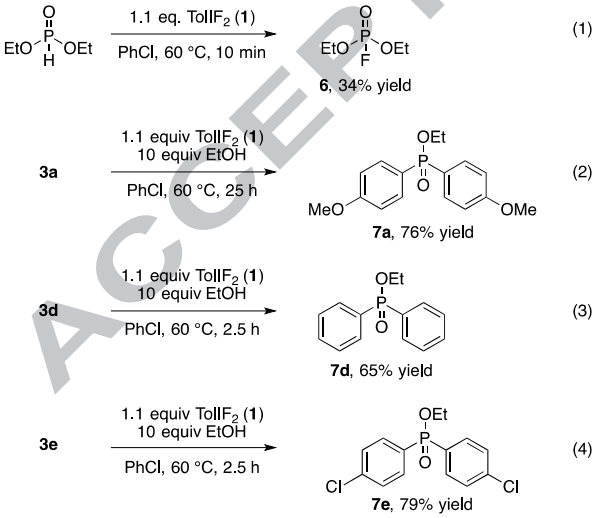
With the optimized conditions in hand, we tested a variety of substituted diarylphosphine oxides (**3b-i**) in the fluorination reaction (Scheme 1). Substrates possessing strongly (**3a**, *p*-OMe) or moderately electron-donating (**3b**, *p*-Me and **3c**, *o*-Me) substituents were all viable, and gave the corresponding phosphoric fluorides **4a-c** in higher yield than did diphenylphosphine oxide **3d**, which gave **4d** in 46% yield. The moderately electron-poor *para*-chloro substrate **3e** gave **4e** in a similarly low yield of 47%, whereas the di(naphthalen-1-yl)phosphine oxide (**3f**) gave **4f** in 75% yield. We also employed dialkylphosphine oxides in this process, and while the dibenzyl derivative **3g** only gave **4g** in 32% yield, the di-*n*-hexyl- and dicyclohexyl- derivatives (**3h** and **3i**) were converted to the corresponding phosphoric fluorides **4h** and **4i** in 60% and 54% yield, respectively.

We attempted to fluorinate diethylphosphite under these reaction conditions, and though consumption of the phosphite was rapid, diethyl phosphorofluoridate (**6**) was only recovered in 34% yield (eq 1). Throughout these



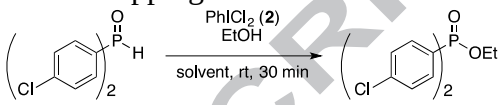
Scheme 1. Oxidative fluorination of diaryl- and dialkylphosphine oxides.

studies, the missing mass balance consisted predominantly of phosphinic acids **5a-i**, where its recovery increased with substrates where the phosphoric fluoride was poorly stabilized by the arene's substituents (eg. **4e**/**4g**). This undesired reactivity indicated that these phosphoric fluorides might be easily trapped by an alcoholic nucleophile like ethanol, resulting in a one-pot synthesis of ethyl diarylphosphinates. To test this hypothesis, we repeated the reaction with substrates **3a**, **3d** and **3e** in the presence of excess ethanol (eq 2-4). The yield of phosphinate **7a** was only moderately higher than the isolated yield of phosphoric fluoride **4a** (76%), but the esterification required 25 h to consume the fluoride. The yield of phosphinates **7d** and **7e** (65% and 79%, respectively) was significantly higher than those observed for **4d** and **4e**, requiring significantly less time to consume the phosphoric fluoride. This demonstrated that in cases where lower yields were observed for phosphoric fluorides, efficient trapping the fluoride with an alcoholic nucleophile was viable.



The oxidative chlorination of secondary phosphine oxides with $PhICl_2$ (**2**) was next investigated, using *para*-chloro derivative **3e** as the model substrate. And as the high reactivity of phosphoric chlorides was anticipated to preclude their isolation, we attempted to trap the initially-formed product in situ with ethanol. We discovered that the oxidative chlorination/trapping reaction proceeded in over 80% yield in nearly all chlorinated, ethereal, polar and non-polar solvents (Table 2, entries 1-5). We observed a slight decrease in product yield when conducting the reaction in DMF (68% yield, entry 6); however, conducting the reaction in EtOH as solvent have **7e** in 83% yield (entry 7), even though alcohol oxidation by **2** is a possible competing process.[28] Decreasing the loading of EtOH threefold had a slight effect on the yield (entry 9), and further decreasing the loading **2** from 1.1 to 1.02 equivalents had no adverse effect on the reaction outcome. The high chemoselectivity observed in this reaction, even when run in ethanol, comes from the increased nucleophilicity of the phosphine oxide starting material over ethanol, leading to the diarylphosphinate in high yield.[29]

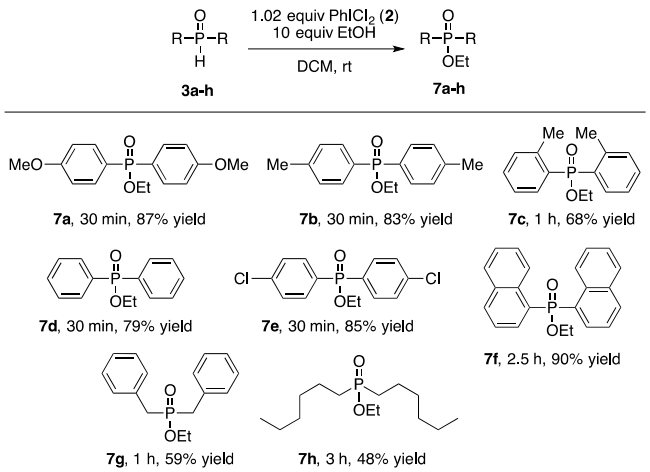
Table 2. Optimization of the phosphoric chloride synthesis and trapping with EtOH.[a]



entry	solvent	$PhICl_2$ (**2**) (equiv)	EtOH (equiv)	yield %
1	CH_2Cl_2	1.1	30	92
2	DCE	1.1	30	85
3	toluene	1.1	30	85
4	THF	1.1	30	81
5	CH_3CN	1.1	30	83
6	DMF	1.1	30	68
7	EtOH	1.1	-	83
8	PhCl	1.1	30	83
9	CH_2Cl_2	1.1	10	85
10	CH_2Cl_2	1.02	10	85

[a] Reaction conditions: To **2** in solvent was added EtOH then **3b**, and the reaction stirred for 30 minutes. Isolated yields.

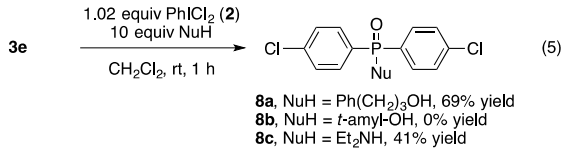
We then subjected the diaryl- and dialkylphosphine oxides to the optimized reaction conditions and found the process to be generally high yielding for all diaryl substrates, regardless of their substituents. Electron-rich, -neutral or -poor substrates all resulted in the corresponding diarylphosphinates in 68-90% yield (Scheme 2). The yield was significantly lower for the dibenzyl (**3g**) and di-*n*-hexyl (**3h**) derivatives, which gave **7g** and **7h** in 59% and 48% yield.



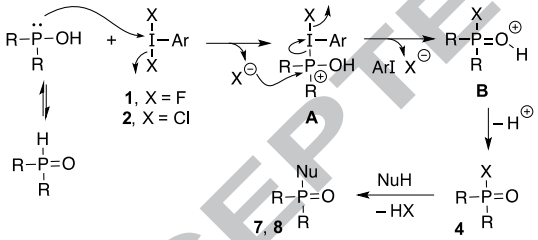
Scheme 2. Oxidative chlorination of diaryl- and dialkylphosphine oxides, followed by EtOH trap.

Given the ease with which the diarylphosphinates could be prepared by this tandem process, we investigated various other nucleophiles as trapping agents (eq 5). Employing the primary

alcohol 3-phenylpropanol gave **8a** 69% yield, but the reaction failed with the very hindered alcohol *t*-amyl alcohol (8b), and gave 41% yield of phosphinamide **8c** when trapping with diethylamine.



We were intrigued about why the diaryl phosphinic acids (**5**) were not significant byproducts in the tandem chlorination/ trapping reactions. Our observation of phosphoric chloride esterification being significantly more rapid than that of the analogous fluorides suggested that were hydrolysis due to residual water, these products should have been forming. A ^{31}P NMR control experiment was carried out with slow-reacting phosphine oxide **3f**, and while its consumption was complete within 15 minutes, little-to-no phosphinic acid was observed over the course of 150 minutes (See Supporting Information). As the same care and attention was given to both the chlorination and fluorination reactions, the occurrence of hydrolysis products **5** in the fluorination reactions remains unclear. Mechanistically, we envision these reactions initiating by attack of the phosphine on the electrophilic iodanes **1** or **2**, giving phosphonium adduct **A** (Scheme 3). Subsequent attack by the expelled halide on the phosphonium gives **B**, whose deprotonation results in the phosphoric halides. These could then be isolated as phosphoric fluorides (**C**, X = F), or intercepted with external nucleophiles (**C**, X = F or Cl) to give phosphinate or phosphinamide products **7** or **8**.



Scheme 3. Proposed mechanism of the oxidative halogenation reaction.

In conclusion, we have developed a mild and efficient synthesis of diaryl- and dialkylphosphoric fluorides and chlorides from secondary phosphine oxides. The hypervalent iodine reagents TolIF$_2$ (**1**) and PhICl$_2$ (**2**) served as both oxidants and sources of chloride and fluoride ions, which resulted in a chemoselective and operationally-simple process. Yields of the phosphoric fluorides were variable due to the formation of phosphinic acid byproducts; however, this could be overcome by trapping the intermediates with external nucleophiles.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

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(29) We did not observe significant quantities of the phosphinic acids in these reactions, even though the phosphoryl chlorides are more susceptible to hydrolysis by residual water than the phosphoryl fluorides. The increased occurrence of the phosphinic acid byproducts in the fluorination reactions might result from attack by oxygen nucleophiles that are generated in situ via glass etching by fluoride.

Highlights of this manuscript:

- New oxidative halogenation of secondary diaryl- or dialkyl phosphine oxides
- Phosphoric chlorides and fluorides are made with hypervalent iodine reagents
- One-pot esterification and amidation reactions of secondary phosphine oxides
- Typically mild, rapid and chemoselective reactions with yields up to 90%

Graphical Abstract

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