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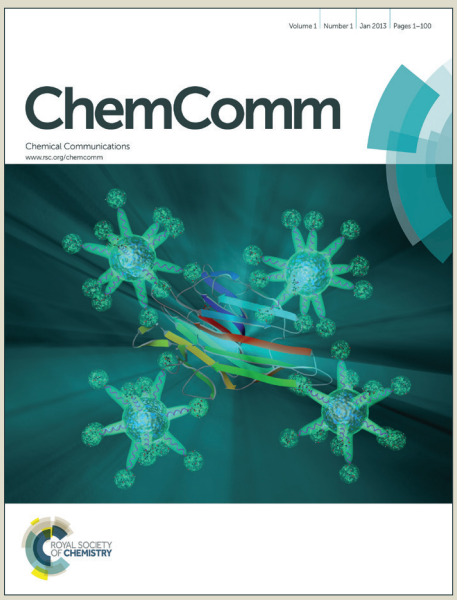

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Copper-promoted Oxidative–Fluorination of Arylphosphine under Mild Conditions

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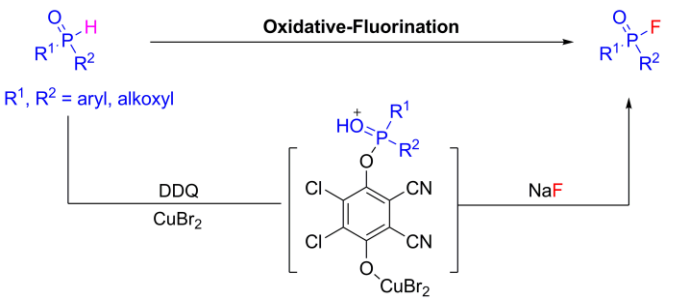
An efficient method for the synthesis of phosphoric fluoride via oxidative coupling between hydrophosphine oxide and NaF is reported. DDQ serves as the oxidizing reagent as well as hydrogen acceptor. The process involves a Cu(II) catalysis and exhibits great functional group tolerance in mild reaction conditions.

Organophosphorus-fluorine compounds have special importance, and been extensively used as mechanistic probes and potent inhibitors of enzymatic reactions, i.e. acetyl cholinesterasea.[1-5] As a consequent, the synthesis of the organophosphorus-fluorine compounds has stimulated tremendous research efforts, and tradition methods mainly rely on the use of pre-functionalized substrates such as chlorophosphates or trimethylsilyl-phosphites with particular fluorinating reagents. [6-12] As an alternative, Dubey and Kaushik reported an example of synthesis dialkyl fluorophosphates via in situ generation of dialkyl chlorophosphates from dialkylphosphites in the presence of excess trichloroacetonitrile (TCA) and DCDMH-KF (hybrid of organic and inorganic reagent).[13] Recently, Lermontov and Wozniak used XeF_2 and AgF respectively as fluoride source combined with diphenylphosphine oxide to synthesis dialkylphosphites.[14] These above methods, however elegantly, usually required multistep preparation of substrates, harsh reaction conditions, or expensive and toxic reagents, which restricted their applications enormously. As a result, the exploration for simple and high-efficiency catalytic system which can promote cheap fluoride source reacting directly with phosphorus reagents to synthesis phosphoric fluoride in mild reaction conditions is highly desirable. 2,3-dichloro-5,6-dicyano-4-benzoquinone (DDQ) is a common used oxidizing reagent in organic chemistry,[15] herein, we use DDQ as the oxidant as well as the hydrogen acceptor to prompt oxidative-fluoration reaction directly from diphenylphosphine oxides with NaF to synthesis phosphoric fluorides. In this reaction, copper salt as auxiliary is indispensable to improve the yield of product. Furthermore, it is worthy to note that this reaction system exhibits good functional group tolerance and wide applicability. A lot of nucleophilic reagents such as alcohol, phenol and thiophenol are successfully applied in this oxidative coupling reaction combined with diphenylphosphine oxide under the mild reaction conditions.

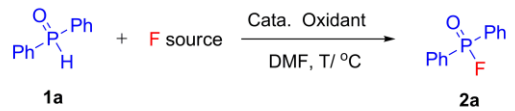


Scheme 1. $CuBr_2$-prompted Oxidative–Fluorination.

In the initial study, we chose diphenylphosphine oxide (**1a**) as substrate, KF as fluoride source and 1.5 eq of DDQ as oxidant, different metal catalysts, including cooper salts, palladium salts, iron salts and silver salts were tested in DMF at 80 °C. To our delighted, the desire product **2a** was formed in many systems, and $CuBr_2$ gave the 80% highest yield (Table 1, entry 4). Without metal salts, the product was only obtained in 47% yield (Table 1, entry 11). Other different oxidants were also evaluated using $CuBr_2$ as catalyst, when BQ and Oxone as oxidants, no desired product was obtained for their oxidizability maybe not strong enough to lead the phosphorus intermediate formation (Table 1, entries 12-13). By using $PhI(OAc)_2$ as oxidant, **2a** afforded a lower yield of 38% (Table 1, entry 14). When we reduced the reaction temperature to room temperature, the product was obtained in a higher yield of 88% (Table 1, entry 15). Then, different the fluorine source was screened, and

the results indicated that the NaF was the best choice and desired compound **2a** was obtained in a yield of 90% (Table 1, entry 16). When decreasing the loading of $CuBr_2$ to 5 mol%, the yield of **2a** was not distinctive changes (Table 1, entry 20). Furthermore, copper salts maybe act as the Lewis acid to prompt the reaction. In order to confirm this assumption, the non-oxidative $ZnBr_2$ was also examined and the **2a** was obtained with relative lower yield (Table 1, entry 21). Finally we obtained the optimized reaction conditions using 5.0 mol % $CuBr_2$ as catalyst, 1.5 equiv DDQ as oxidant and 1.5 equiv NaF as fluoride source in 1.0 mL DMF for 0.3 mmol diphenylphosphine oxide at room temperature.

Table 1. Screening of the Reaction Conditions. [a,b]



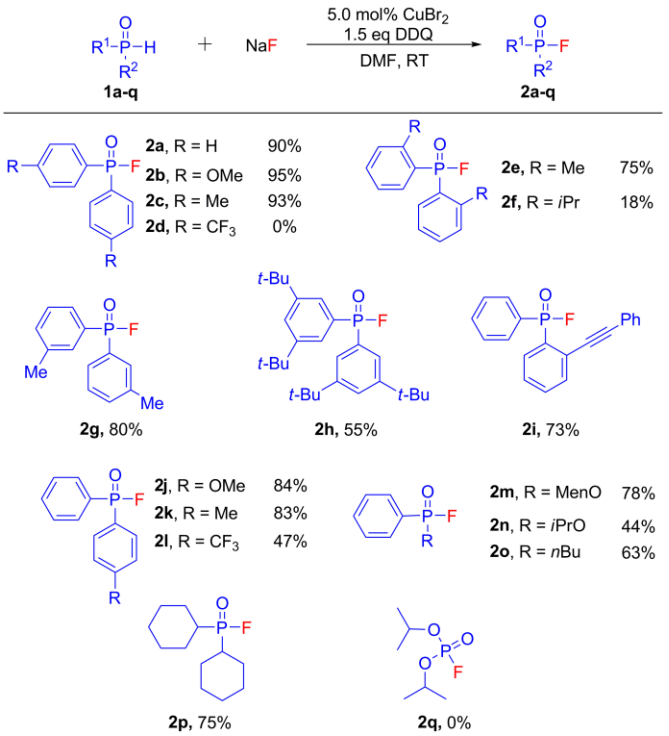
1a 2a

entry	cata. (mol%)	F source (equiv)	oxidant (equiv)	yield (%)
1	Cu_2O (10)	KF (1.5)	DDQ (1.5)	44
2	CuI (10)	KF (1.5)	DDQ (1.5)	69
3	$CuCl_2$ (10)	KF (1.5)	DDQ (1.5)	75
4	$CuBr_2$ (10)	KF (1.5)	DDQ (1.5)	80
5	$Cu(OAc)_2$ (10)	KF (1.5)	DDQ (1.5)	64
6	$Pd(OAc)_2$ (10)	KF (1.5)	DDQ (1.5)	65
7	$Pd(acac)_2$ (10)	KF (1.5)	DDQ (1.5)	56
8	$FeCl_3$ (10)	KF (1.5)	DDQ (1.5)	52
9	AgOAc (10)	KF (1.5)	DDQ (1.5)	58
10	AgOTf (10)	KF (1.5)	DDQ (1.5)	60
11	----	KF (1.5)	DDQ (1.5)	47[e]
12	$CuBr_2$ (10)	KF (1.5)	BQ(1.5)	n.d.[f]
13	$CuBr_2$ (10)	KF (1.5)	Oxone (1.5)	n.d.[f]
14	$CuBr_2$ (10)	KF (1.5)	$PhI(OAc)_2$ (1.5)	38
15[c]	$CuBr_2$ (10)	KF (1.5)	DDQ (1.5)	88
16[c]	$CuBr_2$ (10)	NaF (1.5)	DDQ (1.5)	90
17[c]	$CuBr_2$ (10)	CsF (1.5)	DDQ (1.5)	78
18[c]	$CuBr_2$ (10)	CuF_2 (1.5)	DDQ (1.5)	86
19[cd]	$CuBr_2$ (1.0)	NaF (1.5)	DDQ (1.5)	85
20[c]	$CuBr_2$ (5.0)	NaF (1.5)	DDQ (1.5)	90
21	$ZnBr_2$ (5.0)	NaF (1.5)	DDQ (1.5)	57

[a] All the reactions were carried out with catalyst in the presence of **1a** (0.3 mmol), F source and DDQ in 1.0 mL DMF at 80 °C under argon for 4 h. [b] Isolated yield. [c] RT. [d] 0.6 mmol $Ph_2P(O)H$. [e] only DDQ was added. [f] n.d. means not detected the product.

With the optimized reaction conditions in hand, we turned our attention to the scope of the substrates, as shown in Table 2. First, a series of substituted diphenylphosphine oxide with various substituents on the aromatic ring were investigated. Electron-donating groups, such as methoxyl, methyl and tert-butyl were bearded at different positions of the aromatic ring; the reactions usually proceeded smoothly to afford corresponding products in high yields (**2b**, **2c**, **2e**, **2g**, **2h, 2j, 2k**). However, when tert-butyl at ortho-position, the product only obtained in a low yields of 18% (**2h**). Substrates bearing electron-withdrawing groups on the aromatic rings, the corresponding products afforded in lower yield, when one CF_3 group at aromatic ring, only 47% desire product was formed (**2l**), no desired product was obtained when two CF_3 groups at aromatic rings (**2d**). These results indicated that the electronic effect and the steric effect played important roles in the reaction. When the one aromatic ring was replaced by alkyl groups, to our delight, the products were obtained in moderate yields (**2m-20**). If two aromatic rings of diphenylphosphine oxide were both replaced by cyclohexane, the desire product could obtain in a good yield of 75% (**2p**). But diisopropyl phosphonite failed to give the corresponding product (**2q**).

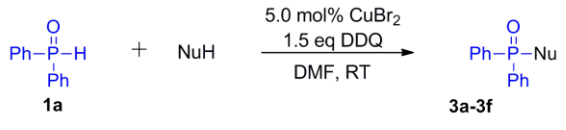
Table 2. Fluorination of the Different Substrates. [a,b]

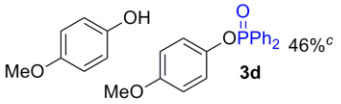


[a] the reactions were carried out in the presence of 0.3 mmol of **1a-1r**, DDQ (1.5eq) in 1mL DMF at room temperature. [b] Isolated yield.

Then a lot of different nucleophiles were also applied in the reaction system to expand the applicability of our method. Using methanol or benzyl alcohol as nucleophile to react with diphenylphosphine oxide **(1a)**, methyl diphenylphosphinate and benzyl diphenylphosphinate were obtained in 88% (**3a**) and 85% (**2b**) yields respectively. When 4-methoxyphenol was selected as nucleophile, the desired product has afforded in a moderate yield of 46% at 60 °C in dioxane (**3d**). *S*-phenyl diphenylphosphinothioate was formed in 81% yield using PhSH as solvent (**3e**). However, nucleophiles such as *N*-methyl aniline and $NaSO_2CF_3$ failed to give the desire products under the reaction conditions (**3c**, **3f**).

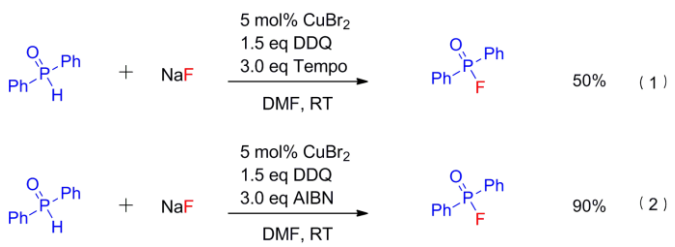
Table 3. Different Nucleophiles.[a,b]



Nucleophile	Product	Yield (%)	Nucleophile	Product	Yield (%)
MeOH	Ph–P(=O)(OMe)–Ph **3a**	88%		**3d**	46%[c]
$PhCH_2OH$	Ph–P(=O)(OBn)–Ph **3b**	81%	PhSH	Ph–P(=O)(SPh)–Ph **3e**	81%[d]
PhNHMe	Ph–P(=O)(N(Me)Ph)–Ph **3c**	0	$NaSO_2CF_3$	Ph–P(=O)(CF_3)–Ph **3f**	0

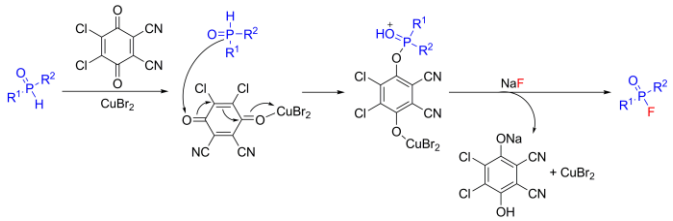
[a] All the reactions were carried out in the presence of 0.3 mmol of 1a with other nucleophilic reagents, and DDQ (1.5eq) at room temperature. [b] Isolated yield. [c] Dioxane as solvent. [d] PhSH as solvent

To elucidate the reaction mechanism and gain insight into this reaction, we used ESI/MS to capture the intermediate of the reaction. Fortunately, we got the signal of 2,3-dichloro-5,6-dicyano-4-hydroxyphenyl diphenylphosphinate in the reaction mixture. When we used $[Ph_2P(O)]_2O$ as the substrate and in the absence of DDQ, only 11% yield of the product was observed (seeing the Supporting Information), so that $[Ph_2P(O)]_2O$ was not the intermediate. Chemical trapping of radicals using 1-Oxyl-2,2,6,6-tetramethylpiperidine (TEMPO) and 2,2'-Dimethyl-2,2'-azodipropionitrile (AIBN) were operated under the reaction conditions. As illustrated in Scheme 2, the addition of AIBN did not affect the reaction at all (Scheme 2, eq 1) and TEMPO only decreased the yield of the product from 90% to 50% (Scheme 2, eq 2), it illustrated that the reaction did not go through the radical pathway.



Scheme 2. Trapping of Radicals Experiments.

According to the literature[16] and the observations of our experiments, we proposed a tentative pathway for this reaction (Scheme 3). First, with the assist of $CuBr_2$, diphenylphosphine oxide as nucleophile attack DDQ to form the phenol phosphinate as an intermediate **A**, then NaF as the fluorinating reagents reacts with intermediate **A** through a S_N2 pathway to give the fluorinated product **2a**, and regenerate the $CuBr_2$ to restart the reaction.



Scheme 3. The Proposed Mechanisms of Oxidative–Fluorination.

In summary, we have developed a new and simple oxidative coupling reaction to synthesis organophosphorus fluoride compounds via oxidative coupling using NaF as fluorinating reagents. In this reaction, DDQ is used not only as the oxidant, but also as the hydrogen acceptor. A lot of other nucleophiles, such as alcohols, phenol and thiols are successfully applied in the reaction system.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/ c3cc

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