ChemComm



View Article Online

COMMUNICATION



Cite this: Chem. Commun., 2014, 50, 10879

Received 25th June 2014, Accepted 25th July 2014

DOI: 10.1039/c4cc04830j

www.rsc.org/chemcomm

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 the hydrogen acceptor. The process involves a Cu(n) catalysis and exhibits great functional group tolerance under mild reaction conditions.

Organophosphorus-fluorine compounds have special importance, and have been extensively used as mechanistic probes and potent inhibitors of enzymatic reactions, *i.e.* acetyl cholinesterase.¹⁻⁵ As a consequence, 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 of dialkyl fluorophosphates via in situ generation of dialkyl chlorophosphates from dialkylphosphites in the presence of excess trichloroacetonitrile (TCA) and DCDMH-KF (a hybrid of organic and inorganic reagent).¹³ Recently, Lermontov and Wozniak used XeF2 and AgF, respectively, as a fluoride source combined with diphenylphosphine oxide to synthesise 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 a simple and highly efficient catalytic system which can promote a cheap fluoride source reacting directly with phosphorus reagents to synthesise phosphoric fluoride under mild reaction conditions is highly desirable. 2,3-Dichloro-5,6-dicyano-4-benzoquinone (DDQ) is a commonly used oxidizing reagent in organic chemistry,15 herein, we use DDQ as the oxidant as well as the hydrogen acceptor to promote the oxidative-fluorination reaction directly



Scheme 1 CuBr₂-promoted oxidative-fluorination.

from diphenylphosphine oxides with NaF to synthesise phosphoric fluorides. In this reaction, copper salt as auxiliary is indispensable to improve the yield of the product. Furthermore, it is worth noting that this reaction system exhibits good functional group tolerance and wide applicability. A lot of nucleophilic reagents such as alcohols, phenols and thiophenol are successfully applied in this oxidative coupling reaction combined with diphenylphosphine oxide under the mild reaction conditions (Scheme 1).

In the initial study, we chose diphenylphosphine oxide (1a) as the substrate, KF as the fluoride source and 1.5 equiv. of DDQ as the oxidant, different metal catalysts, including cooper salts, palladium salts, iron salts and silver salts were tested in DMF at 80 °C. To our delight, the desired product 2a was formed in many systems, and CuBr₂ gave the highest yield of 80% (Table 1, entry 4). Without metal salts, the product was obtained in only 47% yield (Table 1, entry 11). Other different oxidants were also evaluated using CuBr₂ as the catalyst, when BQ and oxone were used as oxidants, no desired product was obtained as their oxidizability maybe not strong enough to lead to the formation of the phosphorus intermediate (Table 1, entries 12 and 13). Upon using PhI(OAc)2 as the oxidant, 2a was obtained in 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 fluorine sources were screened, and the results indicated that NaF was the best choice and the desired compound 2a was obtained in a yield of 90% (Table 1, entry 16). When the loading of

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[†] Electronic supplementary information (ESI) available. See DOI: 10.1039/ c4cc04830j

 Table 1
 Screening of the reaction conditions^{a,b}

	O _N Ph	Cata. O	xidant O	O. Ph	
	Ph ⁻ R +	DMF,	T/°C Ph ⁻ P		
	1a		2a		
Entry	Cata. (mol%)	F source (equiv.)	Oxidant (equiv.)	Yield (%)	
1	Cu ₂ O (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	$\operatorname{FeCl}_{3}(10)$	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	
$19^{c,d}$	$CuBr_{2}(1.0)$	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 a 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 Ph₂P(O)H. ^e Only DDQ was added. ^f n.d. means not detected the product.

^{*a*} The reactions were carried out in the presence of 0.3 mmol of **1a-1r**, DDQ (1.5 equiv.) in 1 mL DMF at room temperature. ^{*b*} Isolated yield.

CuBr₂ was decreased to 5 mol%, no distinctive changes were observed in the yield of 2a (Table 1, entry 20). Furthermore, copper salts may act as the Lewis acid to promote the reaction. In order to confirm this assumption, the non-oxidative ZnBr₂ was also examined and 2a was obtained with a relatively low yield (Table 1, entry 21). Finally we obtained the optimized reaction conditions using 5.0 mol% CuBr₂ as the catalyst, 1.5 equiv. DDQ as the oxidant and 1.5 equiv. NaF as the fluoride source in 1.0 mL DMF for 0.3 mmol diphenylphosphine oxide at room temperature.

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 present 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 isopropyl was at the ortho-position, the product was obtained in a low yield of only 18% (2f). With substrates bearing electron-withdrawing groups on the aromatic rings, the corresponding products were obtained in lower yield; when one CF₃ group was at the aromatic ring, only 47% of the desired product was formed (21), no desired product was obtained when two CF_3 groups were at aromatic rings (2d). These results indicated that the electronic effect and the steric effect played important roles in the reaction. When one aromatic ring was replaced by alkyl groups, to our delight, the products were obtained in moderate yields (2m-2o). If two aromatic rings of diphenylphosphine oxide were both replaced by cyclohexane, the desired product could be obtained in a good yield of 75% (2p).

 Table 2
 Fluorination of the different substrates^{a,b}



But diisopropyl phosphonite failed to give the corresponding product (2q).

Then a lot of different nucleophiles were also applied in the reaction system to expand the applicability of our method. Upon using methanol or benzyl alcohol as the 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 the nucleophile, the desired product was obtained in a moderate yield of 46% at 60 °C in dioxane (3d). S-Phenyl diphenylphosphinothioate was produced in 81% yield using PhSH as the solvent (3e). However, nucleophiles such as N-methyl aniline and NaSO2CF3 failed to give the desired products under the reaction conditions (3c, 3f) (Table 3).

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 [Ph₂P(O)]₂O as the substrate and in the absence of DDQ, only 11% yield of the product was observed (see ESI⁺), so that [Ph₂P(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) was performed under the reaction conditions. As illustrated in Scheme 2, the addition of AIBN did not affect the reaction at all (Scheme 2, eqn (1)) and TEMPO only decreased the yield of the product from 90% to 50% (Scheme 2, eqn (2)); this illustrated that the reaction did not go through the radical pathway.

According to the literature¹⁶ and the observations of our experiments, we proposed a tentative pathway for this reaction

Table 3 Different nucleophiles^{a,b}



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



(Scheme 3). First, with the assistance of CuBr₂, diphenylphosphine oxide as the nucleophile attacks DDQ to form the phenol phosphinate as an intermediate **A**, then NaF as the fluorinating reagent reacts with intermediate **A** through a $S_N 2$ pathway to give the fluorinated product **2a**, and regenerate the CuBr₂ to restart the reaction.

In summary, we have developed a new and simple oxidative coupling reaction to synthesise organophosphorus fluoride compounds *via* oxidative coupling using NaF as the fluorinating reagent. 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, phenols and thiols, are successfully applied in the reaction system.

We are grateful to the NSFC (No. 21272100) and Program for New Century Excellent Talents in University (NCET-11-0215 and lzujbky-2013-k07) for financial support.



Scheme 3 The proposed mechanisms of oxidative-fluorination.

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