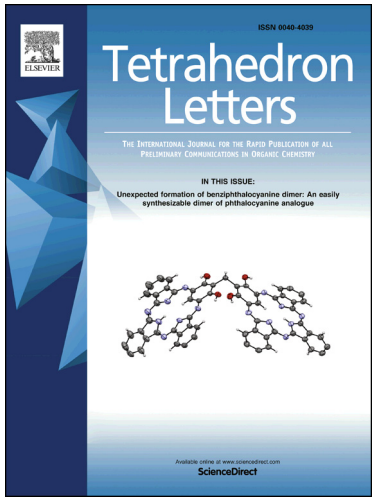

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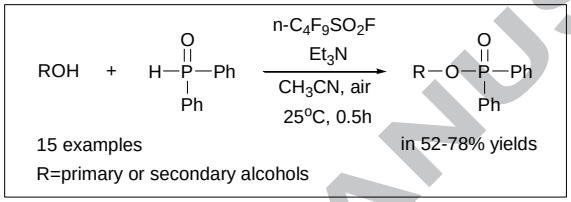

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ABSTRACT

An efficient method for the synthesis of diphenylphosphinate esters via the Atherton–Todd-like reaction of diphenylphosphine oxide with alcohols assisted by perfluoroalkanosulfonyl fluoride in the presence of triethylamine under air is achieved affording the corresponding diphenylphosphinate esters in moderate to good yields of 52-78%. The protocol features the use of non-toxic and stable perfluoroalkanosulfonyl fluoride and metal-free reaction conditions.

Introduction

Over the past decades, organophosphorus compounds have found widespread applications in medicinal chemistry[1], organic catalysis[2] and material sciences[3]. The conventional method for the preparation of organophosphorus compounds is the substitution reaction of phosphorus chlorides with a wide range of nucleophiles. The Atherton-Todd reaction provides a more efficient way to make phosphoramidates, phosphonate esters and other phosphorus-containing products, and it avoids the employment of moisture-sensitive and toxic phosphorus chlorides.[4] Recently, Zhao and Han systematically studied the stereochemistry at the phosphorus center under the Atherton-Todd reaction conditions leading to the smooth synthesis of optically active organophosphorus compounds.[5] However, the Atherton-Todd reaction requires the use of highly toxic carbon tetrachloride or bromotrichloromethane. To overcome this shortcoming, alternative methods have been recently developed to make organophosphorus products. In 2008, Hackenberger published a Lewis acid-catalyzed phosphorimidate rearrangement yielding secondary phosphoramidates,[6] which was subsequently applied in the site-specific PEGylation of proteins.[7] Hayes disclosed a straightforward synthesis of phosphoramidate starting from easily available amines and *H*-phosphonates using CuI as the catalyst and O_2 as the oxidant.[8] Yang also reported a copper-catalyzed oxidative reaction of hydrophosphine oxide with nucleophiles such as NaF, ROH and RSH for the synthesis of phosphoric fluorides, diphenylphosphinate esters and *S*-phenyl diphenylphosphinothioate esters.[9] Prabhu disclosed a I_2/H_2O_2-promoted phosphorylation of acohols and amines to synthesize phosphoramidates and phosphorus triesters.[10] In 2014, Yin reported Cs_2CO_3-promoted *O*-deprotonation/alkylation of diphenyl phosphinic acid with alkyl halides.[11] Generally speaking, the direct phosphorylation of hydrophosphine oxides or *H*-phosphonates with nucleophiles (such as alcohols and amines) possesses advantage of easily availability of substrates. In view that organophosphorus compounds play more and more important roles in both academic and industrial fields, the search for more convenient, straightforward and effective approaches to make them (such as phosphonate esters and phosphoramidates, etc) is still in highly demand.

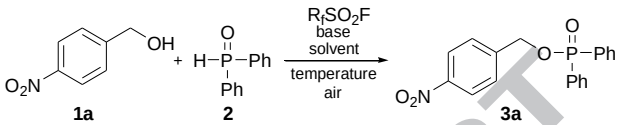
Perfluoroalkanosulfonyl fluoride (R_fSO_2F, such as *n*-$C_4F_9SO_2F$ and *n*-$C_8F_{17}SO_2F$) is a kind of commercially available and cost effective reagent. R_fSO_2F is non-toxic and moisture-tolerant compound. In industry, they have been widely applied as precusors for the synthesis of highly valued surfactants perfluoroalkanesulfonic acid salt $R_fSO_3^-M^+$. On the basis of the excellent leaving ability of perfluorosulfonate anion ($R_fSO_3^-$),[12] R_fSO_2F has been explored and used as an excellent hydroxyl group-activating reagent for fluorination of alcohols to synthesize fluorides,[13] and for cyclodehydration of chiral vicinal diols,[14] *N*-acylamino alcohols, *β*-hydroxy sulfonamides and *β*-hydroxy thioamides[15] for the synthesis of epoxides and other heterocyclic

compounds. When perfluoroalkanosulfonyl fluoride was used to activate hydroxyl group of *α,β*-unsaturated ketoximes, Beckmann rearrangement occurred leading to the smooth formation of acid-sensitive enamides.[16] The dehydration of aldoximes to nitriles[17] and esterification, amidation and anhydridization of carboxylic acids[18] induced by R_fSO_2F as an efficient condensing reagent have been achieved. R_fSO_2F shows its unique property in mediating the homoallylic carbocation rearrangement of 19-hydroxymethyl steroid[19] leading to the novel total synthesis of a naturally occurring (±)-Spiniferin.[20] However, to the best of our knowledge, the use of perfluoroalkanosulfonyl fluoride in the phosphorylation of alcohols with hydrophosphine oxides or *H*-phosphonates has not been investigated yet. In this work, we wish to report the Atherton–Todd-like reaction of diphenylphosphine oxide with alcohols under air assisted by perfluoroalkanosulfonyl fluoride resulting in the formation of diphenylphosphinate esters in moderate to good yields.

Results and discussion

Initially we chose *p*-nitrobenzyl alcohol (**1a**) as a model substrate and studied phosphorylation of **1a** (3.0 mmol) with diphenylphosphine oxide (**2**, 3.0 mmol) under air. The reaction was carried out in CH_2Cl_2 (10 mL) at 25°C using *n*-$C_4F_9SO_2F$ (6.0 mmol) as R_fSO_2F and Et_3N (9.0 mmol) as a base. Unfortunately, the desired product *p*-nitrobenzyl diphenylphosphinate (**3a**) was not detected and only *p*-nitrobenzyl fluoride was formed in 80% yield. However, when the amounts of *n*-$C_4F_9SO_2F$ and Et_3N were respectively increased to 6.0 equiv. and 6.0 equiv., to our delight, **3a** was smoothly obtained although in low yield of 20% (Table 1, entry 2). Thus optimization of reaction conditions was next undertaken. Solvent screening reactions revealed that CH_3CN was the best choice of solvent generating **3a** in 78% yield and the employment of THF, CH_3COCH_3, CH_3COOEt, $CHCl_3$, PhMe and DMF as solvents only resulted in the formation of **3a** in lower 5-57% yields (Table 1, entries 3-9). Among the different bases examined, Et_3N gave the best result (Table 1, entries 10-16). Then, the effect of reaction temperature was explored. The results showed that the incomplete reaction was observed at 0°C and *p*-nitrobenzyl fluoride was the major product at 50°C (Table 1, entries 17 and 18). When *n*-$C_4F_9SO_2F$ was replaced by a longer carbon-chain *n*-$C_8F_{17}SO_2F$, **3a** was produced in a slightly lower 73% yield (Table 1, entry 19). Finally, when the reaction of **1a** with **2** was run under nitrogen atmosphere, only trace of **3a** was detected (Table 1, entry 20), and this result disclosed that oxygen plays an important role in this phosphorylation. Further experiments confirmed that the amount of air has effects on yield of **3a**. The limited amount of air only resulted in the low yield of **3a**. when the reaction **1a** with **2** was run at 25°C for 30 min under air, the highest yield of **3a** was obtained, and longer reaction time or even bubbling of air into the reaction system did not improve the yield of **3a**. Therefore, the optimized reaction conditions are: *p*-nitrobenzyl alcohol (3.0 mmol), diphenylphosphine oxide (3.0 mmol), *n*-$C_4F_9SO_2F$ (18.0 mmol), Et_3N (18.0 mmol), 25°C, CH_3CN as solvent and under air.

Table 1 Optimization of reaction conditions[a]



1a **2** **3a**

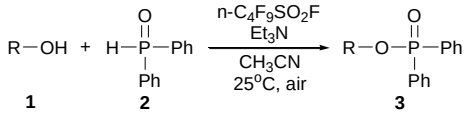
Entry	Solvent	Temp. (°C)	Base	Yield[b] (%)
1[c]	CH_2Cl_2	25	Et_3N	0
2	CH_2Cl_2	25	Et_3N	20
3	$CHCl_3$	25	Et_3N	5
4	CH_3COCH_3	25	Et_3N	57
5	$PhCH_3$	25	Et_3N	40
6	THF	25	Et_3N	45
7	DMF	25	Et_3N	23
8	CH_3CN	25	Et_3N	78
9	EtOAc	25	Et_3N	30
10	CH_3CN	25	Pyridine	0
11	CH_3CN	25	*i*-Pr_2NEt	0
12	CH_3CN	25	DBU	76
13	CH_3CN	25	NaH	trace
14	CH_3CN	25	KOH	43
15	CH_3CN	25	NaOH	58
16	CH_3CN	25	K_2CO_3	0
17	CH_3CN	0	Et_3N	40
18	CH_3CN	50	Et_3N	16
19[d]	CH_3CN	25	Et_3N	73
20[e]	CH_3CN	25	Et_3N	trace

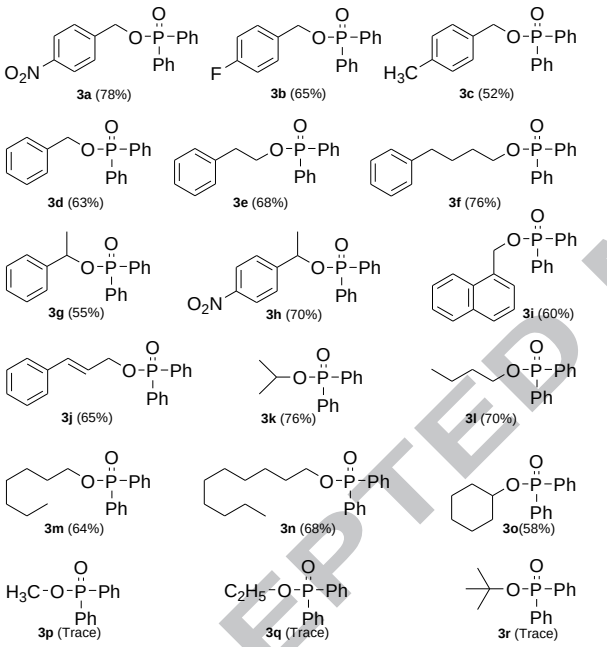
[a]Reaction conditions: **1a** (3.0 mmol), **2** (3.0 mmol), R_fSO_2F (18.0 mmol), base (18.0 mmol), solvent (20 mL), 25°C, 0.5-2 h, under air. [b]Isolated yields. [c]6.0 mmol of *n*-$C_4F_9SO_2F$ and 9.0 mmol of Et_3N were used. [d]18.0 mmol of *n*-$C_8F_{17}SO_2F$ was used. [e]The reaction was run under nitrogen atmosphere.

With the optimized conditions in hand, we continued to investigate the scope and generality of alcohol substrates for the phosphorylation with **2**. The results were summarized in Table 2. We are pleased to find that a wide range of alcohols underwent phosphorylation efficiently. The reactions of benzyl alcohols bearing electron-withdrawing groups on the benzene ring with **2** afford the corresponding esters in good yields of 78% and 65% (Table 2, **3a** and **3b**). However, for benzyl alcohol with electron-donating methyl group on the benzene ring, the corresponding product was obtained only in moderate 52% yield (Table 2, **3c**). 2-Phenylethanol and 4-phenylbutanol are suitable substrates giving **3e** and **3f** in 68% and 76% yields respectively (Table 2, **3e** and **3f**). For secondary benzylic alcohol substrates, the phosphorylation with **2** works well (Table2, **3g** and **3h**). In addition, when 1-hydroxymethylnaphthalene and cinnamyl alcohol were used as nucleophiles, the expected products were obtained in 60% and 65% yields (Table2, **3i** and **3j**). It is worth mentioning that when aliphatic primary and secondary alcohols,

such as isopropanol, *n*-butanol, *n*-heptanol, *n*-decanol, and cyclohexanol were subjected to phosphorylation with **2** under the optimized conditions, the corresponding products were offered in 58-76% yields (Table 2, **3k**-**3o**). However, when methanol, ethanol and *tert*-butyl alcohol were tested for the phosphorylation with **2**, only trace of diphenylphosphinate esters were detected. That the low sterically hindrance caused methanol and ethanol rather than **2** to prefer to directly react with *n*-$C_4F_9SO_2F$ generating the volatile fluorides can probably explain this result. On the contrary, the high sterically hindrance of *tert*-butyl alcohol might be the major reason that its phosphorylation with **2** almost did not work.

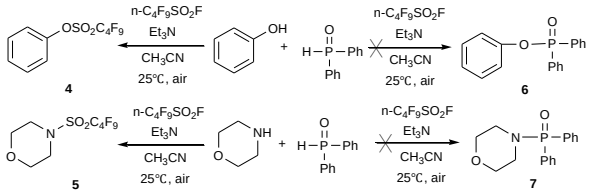
Table 2 Phosphorylation of different alcohols with **2**[a,b]





[a]The reaction conditions: alcohol (3.0 mmol), diphenylphosphine oxide (3.0 mmol), *n*-$C_4F_9SO_2F$ (18.0 mmol) and Et_3N (18.0 mmol), CH_3CN (20 mL), under air, 25°C, 0.5 h; [b]isolated yield.

Next, we explored the reactions of two other nucleophiles, phenol and morpholine, with diphenylphosphine oxide **2** under the above optimized conditions. Both reactions only provide undesired products **4** and **5** other than desired ones **6** and **7**, and the reason is due to the fact that the stronger nucleophilicity of phenol and morpholine results in their direct attack on R_fSO_2F preferentially (Scheme 1).

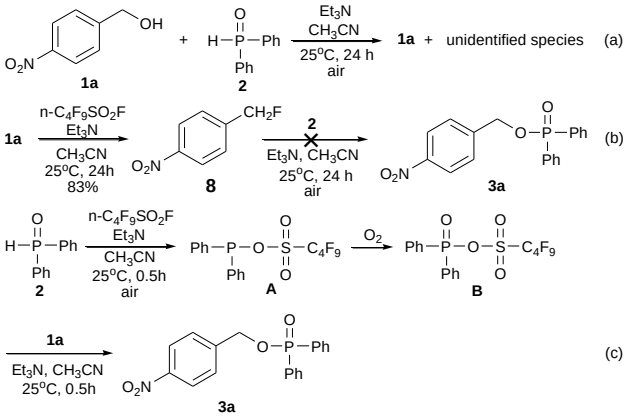


Scheme 1. The reactions of phenol and morpholine

Additionally, when the reactions of *p*-nitrobenzyl alcohol (**1a**) with two *H*-phosphonates (dimethyl phosphite and diethyl phosphite) instead of diphenylphosphine oxide (**2**) were evaluated, likewise, no desired phosphonate triesters products were detected.

Therefore, perfluoroalkanosulfonyl fluoride can neither be used to assist the phosphorylation of phenols and amines with hydrophosphine oxides or *H*-phosphonates, nor the phosphorylation of alcohols with *H*-phosphonates.

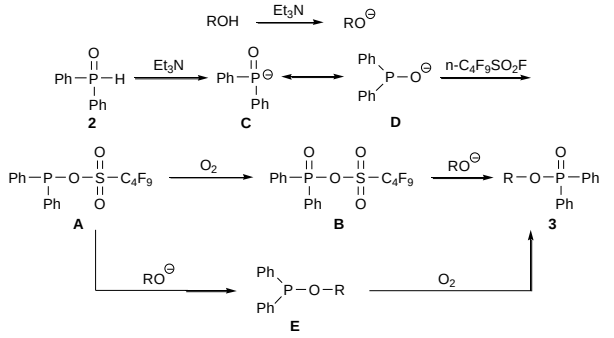
In order to put forward to a possible mechanism to interpret the phosphorylation of alcohols with diphenylphosphine oxide, a few of control experiments were conducted using *p*-nitrobenzyl alcohol (**1a**) as a model substrate (Scheme 2). When **1a** and diphenylphosphine oxide (**2**) were mixed in CH_3CN at room temperature in the presence of Et_3N without *n*-$C_4F_9SO_2F$, **1a** was found to keep unreacted accompanied by the formation of unidentified species probably originating from the oxidative dimerization of **2** (Scheme 2, Equation a). The oxidative dimerization of hydrophosphine oxides or *H*-phosphonate in the presence of organic base (such as Et_3N) and/or copper catalyst has been reported.[8,21] In the absence of **2**, the reaction of **1a** with *n*-$C_4F_9SO_2F$/Et_3N in CH_3CN gave the corresponding *p*-nitrobenzyl fluoride **8** which did not react with **1a** to give **3a** under the above optimized conditions (Scheme 2, Equation b). Without **1a**, the reaction of **2** with *n*-$C_4F_9SO_2F$/Et_3N in CH_3CN gave an unstable species **A** or **B** which was hard to isolate and not identified at this time and the subsequent reaction of species **B** with **1a** smoothly offered **3a** in 75% yield (Scheme 2, Equation c).



Scheme 2. Control experiments.

The results from the above control experiments and descriptions in literatures[21,22] bring us to propose a plausible mechanism for the phosphorylation of alcohols with diphenylphosphine oxide (Scheme 3). First, the reaction of **2** with Et_3N generated anion **D**. The subsequent attack of **D** on n-$C_4F_9SO_2F$ affords species **A** which was oxidized by oxygen providing unstable species **B**. Next, substitution of alkoxyl anion RO^- with **B** furnished product **3**. Meanwhile, species **A** may first react with alkoxyl anion RO^- to give species **E** which was subsequently oxidized by oxygen yielding **3**. However, at this time the exact structure of active and unstable species **A**, **B** and **E**

have not acturally confirmed yet, and further work is now underway in our laboratory.



Scheme3. The Plausible mechanism.

Conclusions

In summary, an efficient and convenient approach for the synthesis of diphenylphosphinate esters via the Atherton–Todd-like reaction of diphenylphosphine oxide with alcohols assisted by perfluoroalkanosulfonyl fluoride in the presence of triethylamine under air has been developed. The protocol features the use of non-toxic and stable perfluoroalkanosulfonyl fluoride and metal-free reaction conditions. The use of perfluoroalkanosulfonyl fluoride in organic synthesis has been further extended.

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Highlights:

- The use of non-toxic and stable reagent perfluoroalkanosulfonyl fluoride reagent.
- Mild and metal-free reaction conditions for synthesis of diphenylphosphinate ester.
- Perfluoroalkanosulfonyl fluoride-promoted formation of cationic phosphorus species.