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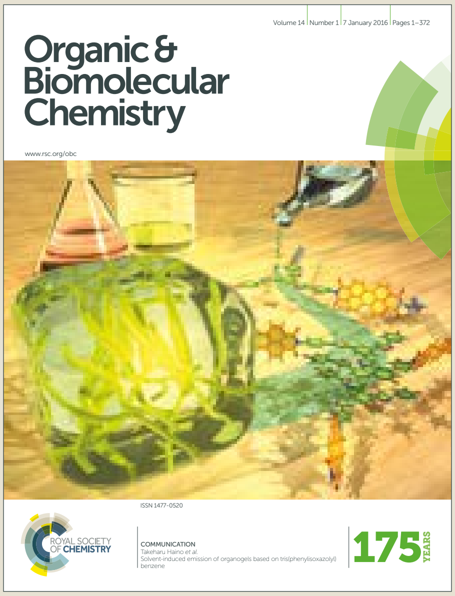

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ARTICLE

A Highly Efficient Nucleophilic Substitution Reaction Between $R_2P(O)H$ and Triarylmethanols to Phosphorus-Substituted Triarylmethanes

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A highly efficient and general nucleophilic substitution reaction between dialkyl H-phosphonates or diarylphosphine oxides and triarylmethanols catalyzed by HOTf (trifluoromethanesulfonic acid) has been developed. It provides an atom-economical protocol for the synthesis of various symmetrical and unsymmetrical phosphorus-substituted triarylmethanes that constitute an emerging family of potent anticancer agents in rich diversity with 40 to 96% yield. The synthetic applicability of this protocol is demonstrated by the gram-scale preparations.

Introduction

Triarylmethanes and related compounds have attracted significant attention as a result of their distinctive structural and physical properties and diverse applications as leuco dye precursors,[1] fluorescent probes,[2] and photochromic agents.[3] In addition, they also show powerful value in medicinal chemistry (Figure 1).[4] On the other hand, organophosphorus compounds play an important role in organic synthesis, catalysis, biochemistry.[5-9] Thus, it is suspected that phosphorus-substituted triarylmethanes, which combine the triarylmethyl group and $P(E)R_2$ (E = O or lone pair) moieties together at a tetrasubstituted carbon center, potentially have some unique bioactivities. For instance, Hergenrother *et al*. has demonstrated that triarylmethyl-containing phosphonates constituted an emerging family of potent anticancer agents, which potentially induce death of multiple cancer cell lines in culture (Figure 1).[10]

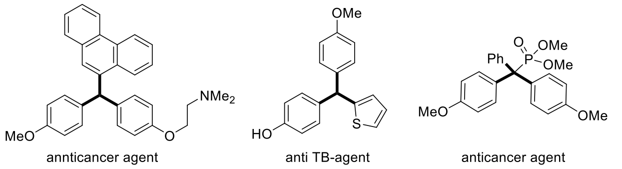
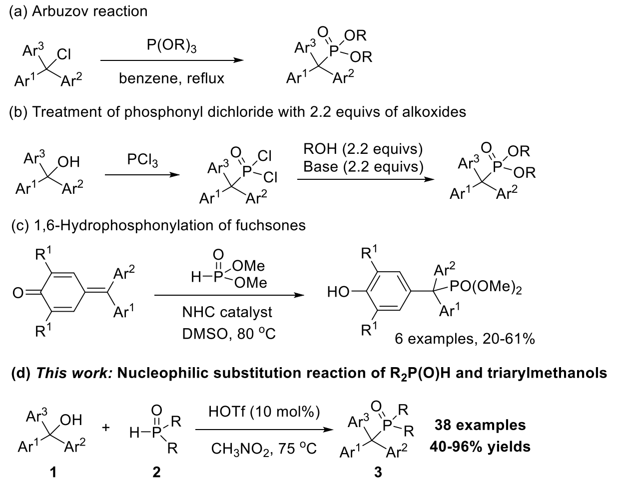


Figure 1 Some biologically important triarylmethanes.

However, the synthesis of phosphorus-substituted triarylmethanes has been scarcely investigated. The classical approach to these compounds involves the Arbuzov reaction between trialkyl- or triarylphosphite and triarylmethyl chlorides (Scheme 1a).[11] However, this transformation generally suffers from harsh reaction conditions and the limited unavailability of trialkylphosphites or triarylmethanols. Displacement of the chlorines of triarylmethyl phosphonyl dichloride (prepared from triarylmethanols and phosphorus trichloride) with alkoxides was another choice to gain access to α-triarylsubstituted phosphonates (Scheme 1b).[10] Although the reaction condition of this method is relatively mild, the easy hydrolysis of phosphorus trichloride and triarylmethyl phosphonyl dichloride limits its application. Recently, Anand and co-workers developed an attractive protocol for accessing these compounds via NHC catalyzed 1,6-hydrophosphonation of fuchsones (Scheme 1c).[12] Nevertheless, the substrate scope and diversity of the products are limited, and the reaction yield is low to moderate. Therefore, the development of highly efficient method for synthesis of phosphorus-substituted triarylmethanes would be more attractive and highly desired.



Scheme 1 Synthetic approaches to phosphorus-substituted triarylmethanes.

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The catalytic nucleophilic substitution reaction of tertiary alcohols and carbon or heteroatom based nucleophiles is a versatile method for efficient, diverse and atom-economical synthesis of fully substituted carbon centers.[13] Up to now, *C*-, *O*-, *S*- and *N*-based nucleophiles have be well used. But to the best of our knowledge, phosphorus-containing nucleophiles have not been applied in this transformation, which could provide a quite useful methodology for accessing phosphorus-substituted tetrasubstituted carbon centers.[14] In addition, this strategy has two important advantages: (i) high atom-economy,[15] as only water is generated as the by-product; and (ii) excellent diversity, because different kinds of substituted tertiary alcohols could readily react with phosphorus-containing nucleophiles, enabling convenient construction of phosphorus-substituted tetrasubstituted carbon centers in sufficient structural diversity, which could be attractive in medicinal research.

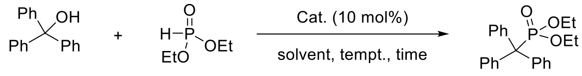
As continuous work directed at the catalytic construction of organophosphorus compounds using easily available starting materials,[16] we envisage the acid catalyzed nucleophilic substitution reaction between triarylmethanols and disubstituted phosphonates or phosphine oxides[17] would be a feasible protocol for synthesis of phosphorus-substituted triarylmethanes (Scheme 1d). Herein, we are pleased to find this reaction could proceed smoothly by using HOTf as Brønsted acid catalyst, affording the desired products in good to excellent yields.

Results and discussion

The reaction of α-triphenylmethanol **1a** and diethyl H-phosphonate **2a** was selected as the model reaction for condition optimization, and typical results were shown in Table 1. The reaction was run out in 1,2-dichloroethane (DCE) at 60 °C. We first screened a variety of inexpensive and easily to handle metal perchlorate hydrates, known as powerful Lewis acid catalysts.[18] Fe^{III}-, Cu^{II}-, Zn^{II}-, Hg^{II}- and Ag^{I}-derived perchlorates could catalyze the reaction smoothly, furnishing the desired product **3a** in moderate yields (Table 1, entries 1-5). Among them, $Hg(ClO_4)_2{\cdot}3H_2O$ proved to be the most efficient one, and afforded **3a** in 63% yield within 20 h (entry 4). And we found metal triflates[19] could also mediate the reaction. For example, under the catalysis of $Ga(OTf)_2$ and $Hg(OTf)_2$, product **3a** was obtained in 60% and 65% yield, respectively (Entries 6-7). However, lower yields were observed when $Sc(OTf)_3$ and AgOTf were used (entries 8-9). Finally, Brønsted acids[20] such as CF_3CO_2H, *p*-TsOH·H_2O, $HClO_4$ and HOTf were investigated, and only $HClO_4$ and HOTf could promote the reaction well, furnishing product **3a** in 64% and 75% yield (entries 9-10).

The catalyst screening indicated that HOTf was the optimal acid catalyst. On this basis, we further investigated the solvent effects. It was found that the solvent had a great effect on reaction outcome, but there is no obvious pattern. For example, the use of tetrahydrofuran (THF) and acetone as solvent resulted in trace product (entries 11 and 15), and low to moderate yields were obtained in 1,4-dioxane, ethyl acetate and toluene. (entries 12-14). When polar and aprotic solvent *N*,*N*-dimethylformamide (DMF) was used, no desired product was observed even raising the reaction temperaure (entry 16). To our delight, improved yields could be achieved by employing CH_3CN and CH_3NO_2 as solvent (entries 17-18). And CH_3NO_2 was found to be the best solvent in terms of reaction yield and time, which gave product **3a** in 80% yield within 14 h. (entry 18). We also tried raising the amount of **1a**, and found 85% yield could be obtained when using 1.5 equivs of **1a** (entry 19). However, no further improvement was observed even increasing the equivlents of **1a** to 2.0 (entry 20). Interestingly, when increasing the temperature from 60 to 75 °C, the reaction could proceed completely within 10 h, giving **3a** in 90% yield (entry 21). Reaction at 90 °C led to the formation of side products and lower yield of **3a** (entry 22). Based on these results, the optimal reaction conditions were at 75 °C under air using 10 mol% of HOTf as catalyst and CH_3NO_2 as solvent.

Table 1 Condition optimization



1a (1.0 eq) **2a** (1.0 eq) **3a**

entry[a]	catalyst	solvent	tempt. (°C)	time (h)	yield (%)[b]
1	$Fe(ClO_4)_3{\cdot}6H_2O$	$ClCH_2CH_2Cl$	60	24	55
2	$Cu(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	60	24	50
3	$Zn(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	60	24	44
4	$Hg(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	60	20	63
5	$AgClO_4{\cdot}H_2O$	$ClCH_2CH_2Cl$	60	24	43
6	$Ga(OTf)_2$	$ClCH_2CH_2Cl$	60	44	60
7	$Hg(OTf)_2$	$ClCH_2CH_2Cl$	60	18	65
8	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	60	18	51
9	AgOTf	$ClCH_2CH_2Cl$	60	44	46
9	$HClO_4$	$ClCH_2CH_2Cl$	60	24	64
10	CF_3SO_3H	$ClCH_2CH_2Cl$	60	18	75
11	CF_3SO_3H	THF	60	24	trace
12	CF_3SO_3H	1,4-dioxane	60	24	30
13	CF_3SO_3H	Ethyl acetate	60	12	32
14	CF_3SO_3H	Toluene	60	24	59
15	CF_3SO_3H	Acetone	60	24	trace
16	CF_3SO_3H	DMF	60	24	np
17	CF_3SO_3H	CH_3CN	60	22	72
18	CF_3SO_3H	CH_3NO_2	60	14	80
19[c]	CF_3SO_3H	CH_3NO_2	60	14	85
20[d]	CF_3SO_3H	CH_3NO_2	60	14	86
21[c]	**CF_3SO_3H**	**CH_3NO_2**	**75**	**10**	**90**
22[c]	CF_3SO_3H	CH_3NO_2	90	10	79

[a] On a 0.30 mmol scale; [b] Isolated yield, np means no product **3a**; [c] 0.45 mmol of **1a**; [d] 0.6 mmol of **1a**.

With the best conditions in hand, we next examined the substrate scope with respect to both triarylmethanols and $R_2P(O)H$. The reaction of a variety of symmetrical and unsymmetrical triarylmethanols and diethyl H-phosphonate **2a** were first checked as shown in Scheme 2. The substituents on the phenyl ring greatly influence the reaction rate and yield. For example, triarylmethanols

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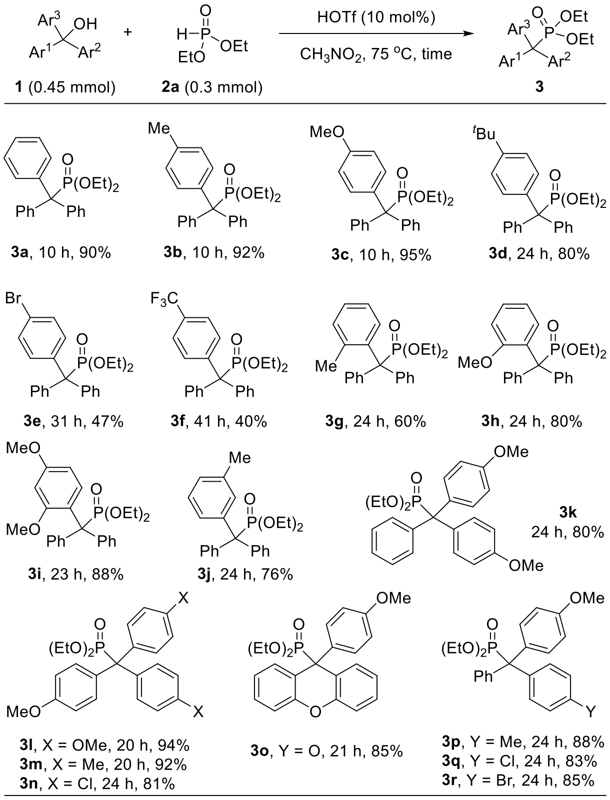
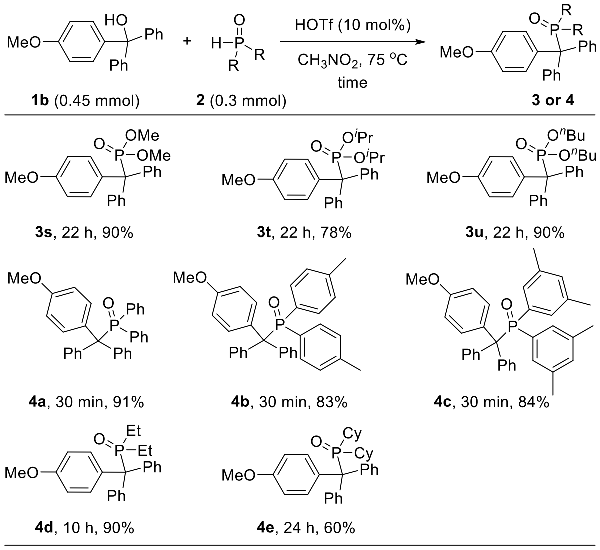
that have electron-donating group such as methyl, methoxyl and *tert*-butyl at the *para* position of the phenyl ring, afforded products **3b**, **3c** and **3d**, respectively, in 80-95% yields. While triarylmethanols, with electron-withdrawing group such as bromo, trifluomethyl, were much less reactive and longer reaction time (31-41 h) and low yields (only 40-47%) were observed for products **3e** and **3f**. Substituents on the *ortho* and *meta* position of phenyl ring also affect the reaction results. Lower yields were obtained for products **3g** and **3h** compared to **3b** and **3c**. Interestingly, triarylmethaol that bear two methoxyl groups on the *ortho* and *para* positon of phenyl ring could afford **3j** in 88% yield within 23 h. Other symmetrical triarylmethanols that prepared from (4-methoxyphenyl)magnesium bromide and the corresponding diaryl ketones could also participate in this reaction, furnishing products **3k**-**3o** in good to high yields. In addition, unsymmetrical triarylmethanols were also viable substrates under this reaction condition, thereby affording the desired unsymmetrical triarylmethanes bearing a diethyl H-phosphonate group **3p**-**3r** in 83-88% yield.



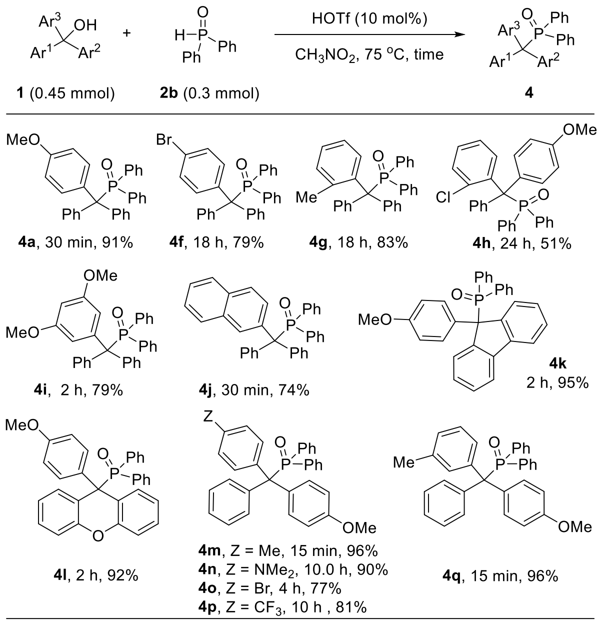
Scheme 2 Substrate scope of symmetrical and unsymmetrical triarylmethanols.

Triarylmethanol **1b** was then selected to evaluate the scope of phosphorus-containing nucleophiles (Scheme 3). Dialkyl H-phosphonates with methyl, isopropyl, and *n*-butyl as the ester functionality could also be tolerated and afforded products **3s**-**3u** in 78-90% yields. We also examined the reaction of **1b** and diaryl- and dialkyl substituted phosphine oxides, which provided a convenient route to the stable precursors of phosphine compounds containing a α-triarylmethyl group. Interestingly, the reactivity of diarylphosphine oxides was much higher than dialkyl H-phosphonates in this reaction, and products **4a**-**4c** were obtained in 84-91% yields within 30 mins. We supposed the higher reactivity of diarylphosphine oxides might be ascribed to the higher nucleophilicity of their corresponding phosphine tautomeric forms compared to that of dialkyl H-phoshonates.[21]



Scheme 3 Substrate scope of $R_2P(O)H$ compounds.

Considering the potential utility of phosphine oxides containing an α-triarylmethyl group, we further checked the reaction of diphenyl phosphine oxide **2b** with various symmetrical and unsymmetrical triarylmethanols (Scheme 4). Generally, the reaction could proceed completely in 15 mins to 18 h, and the corresponding products **4a**-**4q** were produced in good to high yields (up to 96%).



Scheme 4 Syntheis of α-triarylmethyl substituted phosphine oxides.

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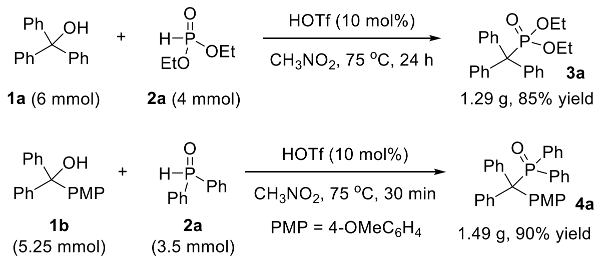
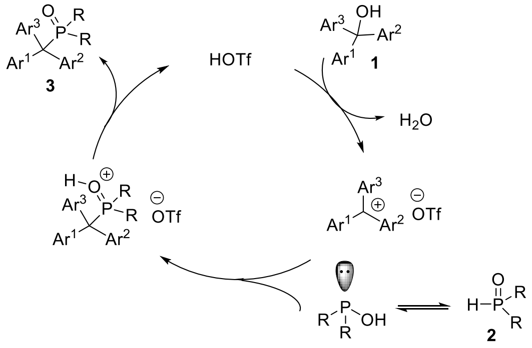
To demonstrate the synthetic applicability of this protocol, the nucleophilic substitution reaction between $R_2P(O)H$ and triarylmethanols was carried out on a gram scale under optimal conditions (Scheme 5). As anticipated, products **3a** and **4a** were obtained in 85% and 90% yields, respectively.



Scheme 5 Gram scale reaction.

Considering the fact that the electronic property of the substituents on the phenyl ring has great impact on the reaction efficiency (Scheme 2 and 4) and similar kinds of literature reports,[17] we proposed a plausible mechanism for this transformation (Scheme 6). In the presence of HOTf, triarylmethyl cation is generated from triarylmethanol **1**, while the equilibrium of $R_2P^{V}(O)H$ and $R_2P^{III}OH$ shifts to the more nucleophilic form $R_2P^{III}OH$. $R_2P^{III}OH$ then immediately reacts with triarylmethyl cation to produce the product **3** along with releasing the catalyst HOTf.



Scheme 6 Plausible mechanism.

Conclusions

In summary, we have reported in this article an atom-economical and highly efficient nucleophilic substitution reaction between $R_2P(O)H$ and triarylmethanols for efficient and diverse synthesis of symmetrical and unsymmetrical phosphorus-substituted triarylmethanes in good to excellent yields. This is the first example that demonstrates that phosphorus-containing nucleophiles could participate in the functionalization of tertiary alcohols to generate phosphorus-containing fully substituted carbon centres. The exploration of potential applications of the obtained products in medicinal research and the extension of this protocol in the construction of other useful phosphorus-containing compounds are now in progress in our laboratory.

Experimental Section

General information: Reactions were monitored by thin layer chromatography using UV light to visualize the reaction course. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. ^1H and ^{13}C NMR spectra were obtained using a Bruker DPX-400 spectrometer. The ^{31}P NMR spectra were recorded at 162 MHz with 85% H_3PO_4 as external standard. All reactions were run under an atmosphere of air. Anhydrous CH_3NO_2 was prepared by first drying with anhydrous Na_2SO_4 and then distilling under reduced pressure. Triarylmethanols **1** were prepared according to the literature report.[22] Commercially available HOTf (trifluoromethanesulfonic acid) was used as received.

General procedure for the nucleophilic substitution reaction between $R_2P(O)H$ and triarylmethanols

To a 5-mL vial were added triarylmethanols **1** (0.45 mmol, 1.5 equivs), $R_2P(O)H$ **2** (0.3 mmol, 1.0 equiv) and 1.0 mL of anhydrous CH_3NO_2. After adding HOTf (4.5 mg, 10 mol%) which was prepared as a solution in CH_3NO_2, the reaction mixture was stirred at 75 °C till almost full conversion of **2** by TLC analysis. The reaction mixture was directly subjected to column chromatography using petrol ether/ethyl acetate (generally 6:1 to 3:1, v:v) as the eluent to afford the desired products **3** or **4**. The representative products are listed here.

Diethyl tritylphosphonate (**3a**).[10] White solid, 102.6 mg, 90% yield; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.25 (m, 15H), 4.06-3.96 (m, 2H), 3.87-3.77 (m, 2H), 1.09 (t, J = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.6 (d, J_{C-P}= 5.0 Hz), 130.7 (d, J_{C-P} = 6.0 Hz), 127.8, 126.8 (d, J_{C-P} = 1.0 Hz), 63.3(d, J_{C-P} = 8.0 Hz), 63.0 (d, J_{C-P} = 135.0 Hz), 16.2, 16.1; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 25.9.

Diethyl (diphenyl(*p*-tolyl)methyl)phosphonate (**3b**). White solid, 108.7 mg, 92% yield; Mp: 126-128 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.35 (m, 4H), 7.32-7.27 (m, 6H), 7.24-7.22 (m, 2H), 7.12-7.10 (m, 2H), 4.08-3.98 (m, 2H), 3.89-3.79 (m, 2H), 2.36 (s, 3H), 1.11 (t, J = 7.2 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 141.6, 138.4, 136.4, 130.6 (d, J_{C-P} = 4.0 Hz), 130.5 (d, J_{C-P} = 4.0 Hz), 128.5, 127.7, 126.8, 63.3 (d, J_{C-P} = 5.0 Hz), 62.5 (d, J_{C-P} = 90.0 Hz), 20.9, 16.2, 16.1; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 26.2; IR (neat): 3756, 2920, 1493, 1241, 1046, 954, 700, 624 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{24}H_{27}O_3P$ $[M+H]^+$: 395.1771, Found: 395.1769.

((4-Methoxyphenyl)diphenylmethyl)diphenylphosphine oxide (**4a**). White powder, 129.4 mg, 91% yield; Mp: 181-183 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.39 (m, 2H), 7.28-7.21 (m, 16 H), 7.14-7.11 (m, 4H), 6.77-6.76 (m, 2H), 3.81 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 158.5, 133.5 (d, J_{C-P} = 5.0 Hz), 132.9, 132.7, 132.1, 131.7, 131.4, 127.9, 127.8, 127.7, 127.1, 113.0, 64.0 (d, J_{C-P} = 42.0 Hz), 55.2; $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 35.0; IR (neat): 3068, 2838, 1607, 1508, 1436, 1251, 1104, 1031, 932, 712 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{32}H_{27}O_2P$ $[M+H]^+$: 475.1821, Found: 475.1820.

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Conflicts of interest

There are no conflicts to declare.

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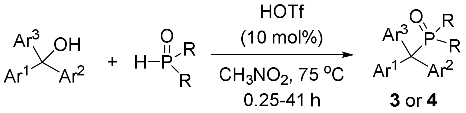

1 **2** **3** or **4**

38 examples, 40-96%

- Air-atmosphere
- Mild reaction conditions
- Good substrate scope
- Large-scale preparation

A highly efficient nucleophilic substitution reaction between $R_2P(O)H$ and triarylmethanols was reported, which provides phosphorous-substituted triarylmethanes in rich diversity with 40-96% yield .