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Nucleophilic arylation with tetraarylphosphonium salts

Zuyong Deng¹, Jin-Hong Lin¹ & Ji-Chang Xiao¹

Organic phosphonium salts have served as important intermediates in synthetic chemistry. But the use of a substituent on the positive phosphorus as a nucleophile to construct C–C bond remains a significant challenge. Here we report an efficient transition-metal-free protocol for the direct nucleophilic arylation of carbonyls and imines with tetraarylphosphonium salts in the presence of caesium carbonate. The aryl nucleophile generated from phosphonium salt shows low basicity and good nucleophilicity, as evidenced by the successful conversion of enolizable aldehydes and ketones. The reaction is not particularly sensitive to water, shows wide substrate scope, and is compatible with a variety of functional groups including cyano and ester groups. Compared with the arylmetallic reagents that are usually moisture sensitive, the phosphonium salts are shelf-stable and can be easily handled.

¹Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. Correspondence and requests for materials should be addressed to J.-C.X. (email: jchxiao@sioc.ac.cn).

Significant advances in C-arylation have emerged in the past few decades because this reaction can effectively form C–C bonds to provide valuable molecules that are the core structures of natural products or pharmaceuticals^{1–5}. Recently, intensive studies have been devoted to the exploration of efficient methods for arylation of carbonyl and imino compounds, allowing access to α -aryl-alcohols and α -aryl-amines, which are abundant in biologically active molecules^{1,2}. Traditional arylmetallic reagents, which are usually generated *in situ* under Barbier-type conditions^{6–8} or prepared in advance like arylmagnesium reagents^{9–11}, have long been used for nucleophilic addition to carbonyl or imino groups. However, this approach often suffers from narrow substrate scope, or the high moisture sensitivity and the strong basicity of the reagents. Transition-metal-catalysed arylation of carbonyl or imino groups with aryl halides^{12,13}, arylboronic acid derivatives^{14–20} or other reactive reagents^{21–25} showed good functional group tolerance under mild reaction conditions. However, the high cost of noble transition metal complexes and possible contamination of the end products by trace amounts of heavy metals probably limit the wide application of this approach in industrial and pharmaceutical processes. Therefore, it is highly desirable to explore broadly applicable transition-metal-free methods for the arylation of carbonyl and imino compounds.

Our research interest in the chemistry of organic phosphonium salts^{26–29} prompted us to investigate their application in arylation reactions. Organic phosphonium salts have served as important intermediates in synthetic chemistry^{30–35}. Although phosphonium salts are electrophilic species and the positive phosphorus could enhance the electrophilicity³⁶ or acidity^{34,35,37} of its substituents because of the inductive effect, we speculated that the substituent on the phosphorus might be converted to a nucleophile initiated by another appropriate nucleophile, which may firstly attack the phosphorus and then result in the cleavage of a substituent with nucleophilic ability (Fig. 1).

Herein we report a nucleophilic arylation of carbonyl and imino compounds with tetraarylphosphonium salts in the presence of caesium carbonate (Fig. 1). The generated aryl nucleophiles exhibit low basicity and good nucleophilicity. The arylation protocol shows wide substrate scope and a high level of functional group tolerance. Mechanistic investigation reveals that the reaction is predominantly initiated by caesium carbonate.

Results

Optimization of reaction conditions. Considering the high affinity between phosphorus and oxygen, an O-nucleophile was used to initiate the arylation of 4-phenylbenzaldehyde (**1a**) with tetraphenylphosphonium iodide (**2a**) (Table 1, entries 1–4). Neither Na₂CO₃ nor K₂CO₃ could initiate the transformation (entries 1 and 2). Interestingly, Cs₂CO₃ was found to be a good initiator (entry 3), which is likely because of the better solubility of the caesium salt. Because the caesium salt was effective, another O-initiator with caesium as the cation (CsOAc; entry 4) was examined. To our surprise, no desired product was detected,

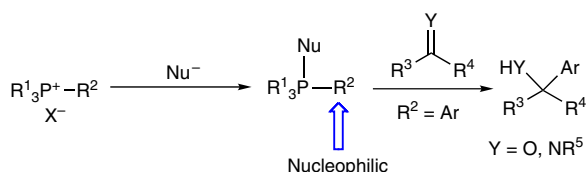


Figure 1 | Design of arylation reaction with phosphonium salt. An aryl substituent on phosphorus can act as a nucleophile to realize the nucleophilic arylation of carbonyls and imines.

which might be caused by the lower nucleophilicity of the acetate anion. Further screening of non-O-initiators (entries 5 and 6) showed that Cs₂CO₃ was the best initiator (entry 3), indicating that the high P–O affinity may have an important role in this reaction. The yield was increased to 65% with the elongation of reaction time (entry 7 versus entry 3). The effects of other solvents were also investigated (entries 8–10). The reaction in 1,4-dioxane gave the product in comparable yield (entry 8 versus entry 7), while acetonitrile was not as effective, probably because its acidic α -proton can quench the leaving phenyl group from salt **2a** (entry 10). Increasing the loading of salt **2a** and caesium carbonate (entries 11 and 12) increased the yield significantly (entry 12), while lowering the temperature led to significantly lower yield (entry 13). The reaction was not particularly sensitive to water, as evidenced by the moderate yield obtained with the addition of water into the reaction system (entry 14). Both of the chloride (Ph₄P⁺ Cl[−]) and bromide (Ph₄P⁺ Br[−]) instead of the iodide **2a** gave lower yields, which should be due to the lower solubility of the chloride and bromide (entries 15–16).

Substrate scope for phenylation of aldehydes. With the optimized reaction conditions in hand (Table 1, entry 12), we then explored the substrate scope for the phenylation of aldehydes with phosphonium salt **2a** (Table 2). The transformation can be applied to a variety of aldehydes and gave the desired products in moderate to excellent yields. Increasing the scale of the reaction by 20-fold still afforded the desired product **3aa** in good yields, which is highly important in the synthetic application, albeit the longer reaction time or higher loading of Cs₂CO₃ was required. Investigation of the electronic effects showed that the electron-donating or -withdrawing groups

Table 1 | Screening reaction conditions*.

Entry	Initiator	Ratio [†]	Solvent	Temperature (°C)	Time (h)	Yield (%) [‡]
1	Na ₂ CO ₃	1:1.5:2.0	THF	65	6	0
2	K ₂ CO ₃	1:1.5:2.0	THF	65	6	0
3	Cs ₂ CO ₃	1:1.5:2.0	THF	65	6	56
4	CsOAc	1:1.5:2.0	THF	65	6	0
5	CsF	1:1.5:2.0	THF	65	6	13 [§]
6	Et ₃ N	1:1.5:2.0	THF	65	6	0
7	Cs ₂ CO ₃	1:1.5:2.0	THF	65	12	65
8	Cs ₂ CO ₃	1:1.5:2.0	1,4-dioxane	65	12	64
9	Cs ₂ CO ₃	1:1.5:2.0	DMF	65	12	52
10	Cs ₂ CO ₃	1:1.5:2.0	CH ₃ CN	65	12	0
11	Cs ₂ CO ₃	1:2.0:2.5	THF	65	12	80
12	Cs ₂ CO ₃	1:2.5:3.0	THF	65	12	90
13	Cs ₂ CO ₃	1:2.5:3.0	THF	40	12	68
14	Cs ₂ CO ₃	1:2.5:3.0	THF	65	12	49
15 [¶]	Cs ₂ CO ₃	1:2.5:3.0	THF	65	12	29
16 [#]	Cs ₂ CO ₃	1:2.5:3.0	THF	65	12	44

*Conditions: **1a** (0.5 mmol), **2a** and Cs₂CO₃ in solvent (4 ml).
[†]Molar ratio of **1a**:**2a**:initiator.
[‡]Isolated yield.
[§]Yield determined by ¹H NMR.
^{||}2 equivalents of H₂O added.
[¶]Chloride salt (Ph₄P⁺ Cl[−]) was used instead of **2a**.
[#]Bromide salt (Ph₄P⁺ Br[−]) was used instead of **2a**.

Table 2 | Substrate scope of phenylation of aldehydes*.

$1 + \text{Ph}_4\text{P}^+ \text{I}^- \xrightarrow[2) \text{HCl}]{1) \text{THF, Cs}_2\text{CO}_3, 65^\circ\text{C, 12 h}}$ 3

3aa R = <i>p</i> -Ph, 90 % (84 % [†] , 75 % [‡]) 3ba R = <i>p</i> -NMe ₂ , 69 % 3ca R = <i>p</i> -OMe, 89 % 3da R = <i>o</i> -OMe, 80 % 3ea R = 2,4,6-Me ₃ , 86 % 3fa R = <i>p</i> -F, 94 % 3ga R = <i>p</i> -Br, 69 %	3ha R = <i>m</i> -Br, 62 % 3ia R = <i>p</i> -CF ₃ , 86 % 3ja R = <i>m</i> -CF ₃ , 84 % 3ka R = <i>o</i> -CF ₃ , 88 % 3la R = <i>m</i> -CN, 73 % 3ma R = <i>p</i> -CN, 68 % 3na R = <i>p</i> -CO ₂ CH ₃ , 75 % 3oa R = <i>o</i> -Ph, 90 %
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3aa–3oa (substituted benzene ring), **3pa**, 88% (naphthalene), **3qa**, 91% (pyridine), **3ra**, 93% (thiophene), **3sa**, 95% (furan), **3ta**, 85% (cyclohexane), **3ua**, 60% (benzyl).

*Conditions: **1** (0.5 mmol), **2a** (2.5 equivalents) and Cs₂CO₃ (3.0 equivalents) in THF (4 ml). Yields are isolated yields;
[†]increasing the scale of the reaction by 20-fold (**1a**, 10 mmol, 1.8 g), 5 days of reaction time was needed to obtain **3aa** in 84% isolated yield with the use of 3 equivalents of Cs₂CO₃;
[‡]increasing the scale of the reaction by 20-fold (**1a**, 10 mmol, 1.8 g), 12 h of reaction time can give **3aa** in 75% isolated yield with the use of 5 equivalents of Cs₂CO₃.

on the aryl ring did not significantly influence the reaction (**3aa–3ra**). A broad functionality tolerance was demonstrated for aryl aldehydes bearing different substituents, including cyano (**3la–3ma**) and ester groups (**3na**). The conversion was not quite sensitive to steric effects, given that high yields were obtained for products **3ea**, **3ka** and **3oa**. It is noteworthy that the enolizable aldehydes were also converted into the expected products in good yields (**3ta** and **3ua**) without self-aldol condensation.

Substrate scope for phenylation of ketones. Although ketone is less reactive than aldehyde, the phenylation of ketones with salt **2a** still proceeded smoothly to give the desired products (Table 3). However, increased loading of salt **2a** and caesium carbonate to 4 and 4.5 equivalents, respectively, was necessary to achieve good yields. Both aromatic (**5a–5l**) and aliphatic ketones (**5m** and **5n**) were reactive under the optimal conditions. The successful conversion of hindered ketones indicates that the reaction is moderately tolerant to steric effects (**5f–5h**, **5j**). In addition, no reaction at the carbonyl-activated ester group of **5k** suggests that the transformation shows high chemoselectivity.

Compared with the traditional arylation of carbonyl groups with arylmetallic reagents, which are strong nucleophiles and can lead to the arylation of cyano³⁸ and ester¹² groups, this mild reaction clearly exhibits a higher level of functional group tolerance. More importantly, the reaction is applicable to enolizable aldehydes and ketones, indicating that the *in situ*-generated phenyl-anion equivalent exhibits high nucleophilicity and low basicity.

Substrate scope for phenylation of imines. The successful conversion of aldehydes and ketones prompted us to examine the phenylation of imines with salt **2a** (Table 4). Imines containing electron-donating groups on the phenyl ring were effectively converted into the desired products, but for imines with a strong electron-withdrawing substituent such as cyano, the reaction failed to give the desired product. It is likely that under these reaction conditions, the imine is prone to hydrolysis to give the aldehyde, which would then react with salt **2a** to afford the alcohol. In contrast to tosyl-protected imines (*N*-Ts),

Table 3 | Substrate scope of phenylation of ketones*.

$4 + \text{Ph}_4\text{P}^+ \text{I}^- \xrightarrow[2) \text{HCl}]{1) \text{THF, Cs}_2\text{CO}_3, 65^\circ\text{C, 24 h}}$ 5

5a R ³ = <i>p</i> -Ph, R ² = Me, 75% 5b R ³ = <i>p</i> -F, R ² = Me, 74% 5c R ³ = <i>p</i> -CN, R ² = Me, 65% 5d R ³ = <i>p</i> -CF ₃ , R ² = Me, 86% 5e R ³ = <i>p</i> -CF ₃ , R ² = Et, 87% 5f R ³ = H, R ² = ^t Pr, 65%	5g R ³ = H, R ² = cyclohexyl, 60% 5h R ³ = H, R ² = ^t Bu, 50% 5i R ³ = H, R ² = CH ₂ Ph, 60% 5j R ³ = H, R ² = (<i>p</i> -CF ₃)C ₆ H ₄ , 89% 5k R ³ = H, R ² = COOEt, 63%
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5a–5k (substituted benzene ring), **5l**, 66% (naphthalene), **5m**, 60% (cyclohexane), **5n**, 56% (benzyl).

*Conditions: **4** (0.4 mmol), **2a** (4.0 equivalents) and Cs₂CO₃ (4.5 equivalents) in THF (4 ml). Yields are isolated yields.

p-methoxyphenyl-protected imine (*N*-PMP) is inert under the reaction conditions.

The investigation of the reactivity of phosphonium salts. The reactivities of different tetraarylphosphonium salts were also investigated. Compared with tetraphenylphosphonium iodide (**3aa**, Table 2), tetra-*p*-methoxyphenylphosphonium iodide (Table 5, entry 1) and tetra-*p*-methylphenylphosphonium iodide (entry 2) showed lower reactivity towards arylation and gave the corresponding arylation products in lower yields. This is probably because the *in situ*-generated aryl-anion equivalent containing an electron-donating group is less stable and would readily abstract a proton from the trace amount of water present.

To this point of our study, the four aryl groups on the phosphorus were identical. It will be interested to know the different leaving ability when one aryl group was different from the others. To address this issue, a variety of aryl triphenylphosphonium salts were prepared and tested for the arylation of aldehyde **1a** (Table 5, entries 3–9). If the aryl moiety contained a weak electron-withdrawing group, the corresponding arylation product was obtained in low yield (entry 3), with simultaneous formation of more phenylation product **3aa** (43% yield). This might be because the leaving ability between the phenyl and aryl group is similar owing to their comparable electron-withdrawing effect, and three phenyl groups compete with one aryl group, thus leading to more phenylation product **3aa**. However, if the aryl moiety was substituted with a strong electron-withdrawing group, the phenylation product **3aa** would be greatly suppressed and the arylation became the main reaction, indicating that electron-withdrawing ability has an important role in the selectivity (entries 4–7). In the case of **3ai**, the low yield was not because of the phenylation reaction to produce **3aa**, but because of a side reaction to give 4'-phenylacetophenone (27% yield based on aldehyde; entry 8). Pyridyl triphenylphosphonium iodide was also suitable for the desired pyridylation (entry 9).

In the case of the salts containing strong electron-withdrawing groups (**2e'–2i'**), it would be better to change the salt anion from iodide to bis(trifluoromethanesulfonyl)imide anion (TF₂N⁻) and the procedure for arylation should be modified accordingly. For example, the *in situ*-generated aryl-anion equivalent would readily attack the phosphonium salt to give the diaryl by-product (33% based on aldehyde) because of the increased electrophilicity of the salt. To avoid this problem, the phosphonium salts were added slowly to the reaction to keep the substrate aldehyde in constant excess. And this required the salts to be soluble in tetrahydrofuran (THF) so as to realize the addition of the salts via

Table 4 | Substrate scope of phenylation of imines*.

Entry	R	7, Yield (%) [†]
1	Ph	7a , 72
2	4-PhC ₆ H ₄	7b , 75
3	4-MeC ₆ H ₄	7c , 74
4	2,4,6-Me ₃ C ₆ H ₂	7d , 86
5	4-MeOC ₆ H ₄	7e , 71
6	2-MeOC ₆ H ₄	7f , 74
7	4-CF ₃ OC ₆ H ₄	7g , 43
8	4-BnOC ₆ H ₄	7h , 85
9	4-FC ₆ H ₄	7i , 70
10	2-naphthyl	7j , 75

*Conditions: **6** (0.4 mmol), **2a** (2.5 equivalents), and Cs₂CO₃ (3 equivalents) in THF (4 ml).
[†]Isolated yields.

syringe. The phosphonium salts containing Tf₂N⁻ were soluble in THF and the corresponding arylation proceeded smoothly by the addition of the phosphonium salt solution into the reaction (Table 5, entries 4–8).

Mechanistic investigation. As for the reaction mechanism, the analysis of trace transition metal in phosphonium salts and caesium carbonate by ICP spectrometry (Supplementary Table 1) revealed that this arylation is a transition-metal-free reaction. Although salt **2a** is quite stable, an equilibrium might be established between this salt and Ph₃P/PhI under the phenylation conditions. But the use of Ph₃P/PhI system instead of salt **2a** for the phenylation of aldehyde **1a** failed to give the desired product at all (equation 1 Fig. 2), meaning that the equilibrium cannot account for the arylation. Neither radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] nor single-electron-transfer inhibitor *p*-dinitrobenzene can dramatically suppress the phenylation of aldehyde **1a** with salt **2a**, indicating that the arylation may not proceed via a single-electron-transfer mechanism (equation 2, Fig. 2). Nothing happened while refluxing aldehyde **1a**/salt **2a** system or aldehyde **1a**/Cs₂CO₃ system in THF. But the full conversion of salt **2a** into Ph₃PO was observed by refluxing salt **2a** and Cs₂CO₃ in THF, suggesting that the interaction between salt **2a** and Cs₂CO₃ initiates this arylation reaction.

The alkaline hydrolysis of phosphonium salts has been well-studied for the past decades^{30,39–47}. As a third-order reaction (first order with respect to phosphonium salt, second order to hydroxide)^{40,41}, the alkaline hydrolysis of tetraphenylphosphonium salt would lead to the formation of triphenylphosphine oxide (Ph₃PO) (refs 46,48). Since Ph₃PO was detected by gas chromatography mass spectrometry (GC–MS) in every phenylation reaction system using **2a** (Ph₄P⁺ I⁻) and Ph₃PO was isolated in high yield for the phenylation of substrate **1a** (equation 1, Fig. 3), it is reasonable to conceive that the arylation might proceed via this hydrolysis process. Although the solvent THF purchased from commercial source was extra dry ('Extra Dry over Molecular Sieve', <0.005% water content) and the arylation was performed under N₂ atmosphere, trace amount of water may still be unavoidable in the reaction system, thus leading to the hydrolysis of caesium carbonate (equation 2). The resulting hydroxide anion would decompose the phosphonium salt to generate Ph₃PO, suggesting that the oxygen in Ph₃PO

Table 5 | Substrate scope of arylation of 4-phenylbenzaldehyde*.

Entry	2, X	Ar	3, Yield (%) [†]
1 [‡]	2b , I	4-MeOC ₆ H ₄	3ab , 55
2 [§]	2c , I	4-MeC ₆ H ₄	3ac , 49
3	2d , I	4-PhC ₆ H ₄	3ad , 35
4	2e' , Tf ₂ N	4-CNC ₆ H ₄	3ae , 73
5	2f' , Tf ₂ N	3-CNC ₆ H ₄	3af , 75
6	2g' , Tf ₂ N	4-CF ₃ C ₆ H ₄	3ag , 78
7	2h' , Tf ₂ N	4-EtO ₂ CC ₆ H ₄	3ah , 66
8	2i' , Tf ₂ N	4-AcC ₆ H ₄	3ai , 35
9	2j , I	2-Pyridyl	3aj , 73

*Conditions: **1a** (0.5 mmol), **2** (2.5 equivalents), and Cs₂CO₃ (3 equivalents) in THF (4 ml).
[†]Isolated yields.
[‡][(4-MeOC₆H₄)₄P]⁺ I⁻ (**2b**) was used.
[§][(4-MeC₆H₄)₄P]⁺ I⁻ (**2c**) was used.
^{||}The reaction also gave **3aa** in 43% isolated yield.

could partially come from water. Indeed, the reaction of phosphonium salt with caesium carbonate in the presence of H₂¹⁸O gave both Ph₃PO and Ph₃P¹⁸O (equation 3). The molar ratio of Ph₃PO: Ph₃P¹⁸O determined by ³¹P NMR was 1:1.26. This ratio was consistent with elemental analysis of the mixture (see Supplementary Methods for the formation of Ph₃P¹⁸O). It seems that this hydrolysis process might be involved in the arylation, which was further supported by the observation that the direct use of caesium hydroxide instead of caesium carbonate also gave the expected product in 63% yield (equation 4). Compared with the 90% yield while using Cs₂CO₃, lower yield might result from the presence of hydrated water in CsOH (note: anhydrous CsOH is not commercially available). Although water can promote the hydrolysis of Cs₂CO₃ to produce CsOH, excessive water would suppress the subsequent arylation through the capture of the *in situ*-generated phenyl nucleophile. In addition, this possible hydrolysis process of Cs₂CO₃ could also explain why moderate yield (49%) of phenylation product could be obtained with the deliberate addition of water (entry 14 of Table 1).

Nevertheless, all reagents including highly dry Cs₂CO₃ (99.994% purity, metals basis) and the solvent THF (<0.005% water content) were stored in a glove box, and the arylation were conducted under N₂ atmosphere, suggesting that the water content in the reaction system should be extremely low. This trace amount of water cannot cause the complete hydrolysis of Cs₂CO₃, indicating that another reaction process should exist. As shown in Table 2, for the large-scale phenylation to give **3aa**, significantly less reaction time (12 h versus 120 h) was needed to achieve comparable yield (75% versus 84%) with the use of more Cs₂CO₃ (5 equivalents versus 3 equivalents). The water contents (trace) in both reaction systems should be the same since these reactions were conducted under the same reaction conditions. The faster arylation with the use of more Cs₂CO₃ means that Cs₂CO₃ may be able to promote the arylation without the involvement of water. If this is the case, more Cs₂CO₃ would result in a faster conversion of Ph₄P⁺ I⁻ into Ph₃PO. Indeed, for the reaction of Ph₄P⁺ I⁻ with Cs₂CO₃ in THF for 4 h, the more Cs₂CO₃ was used, the more Ph₃PO was produced (note: Ph₄P⁺ I⁻ was not completely consumed in every reaction; Fig. 4). These results indicate that Cs₂CO₃, for the most part, directly promoted this arylation.

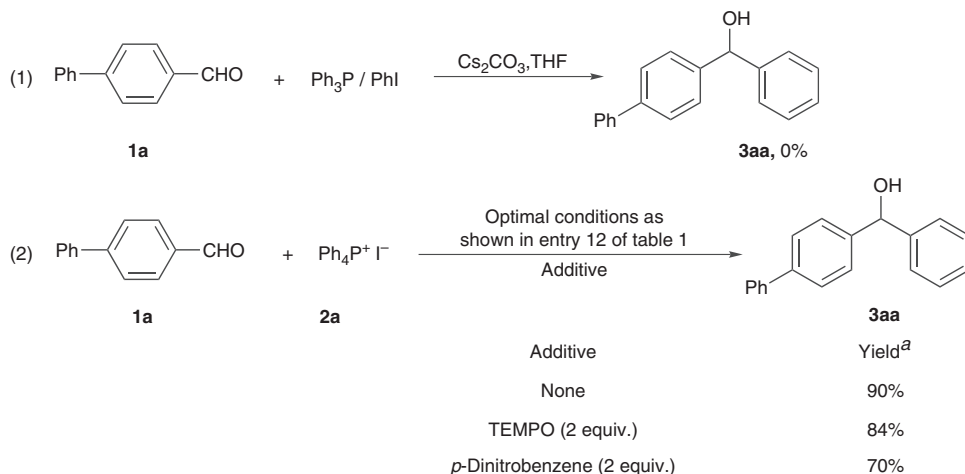


Figure 2 | Mechanistic experiments. (1) The use of Ph₃P/PhI system instead of salt **2a** failed to convert aldehyde **1a** into product **3aa**. (2) Neither radical scavenger TEMPO nor single-electron-transfer inhibitor *p*-dinitrobenzene can obviously suppress the phenylation reaction. ^aIsolated yields.

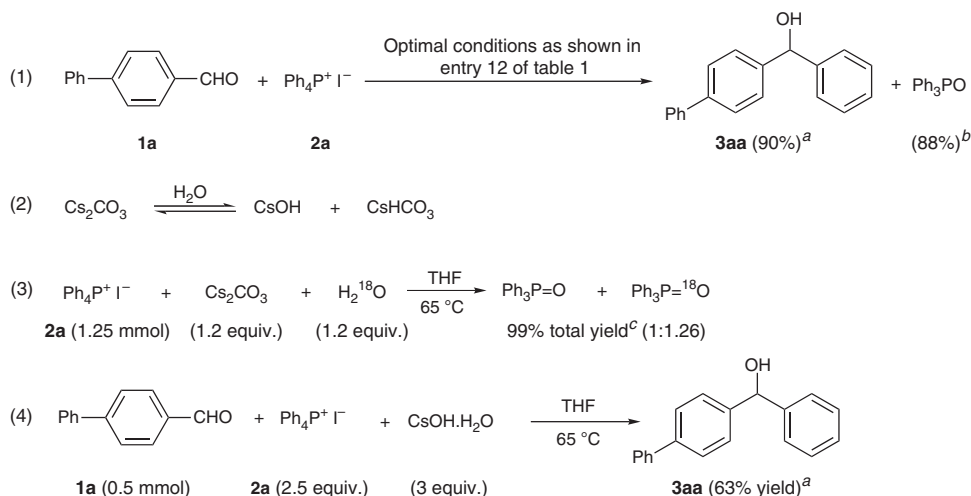


Figure 3 | Evidence to support the path via alkaline hydrolysis. (1) Ph₃PO was isolated as a by-product for phenylation reaction. ^aIsolated yield based on **1a**; ^bIsolated yield based on **2a**; (2) An equilibrium between Cs₂CO₃ and CsOH may be established under the reaction conditions. (3) The presence of H₂¹⁸O led to the formation of Ph₃P¹⁸O. ^cIsolated yield. (4) CsOH can also initiate the phenylation reaction.

Apparently, nucleophilic phenyl species was formed in the process of the arylation. Salt **2a**, also as an electrophilic species, might be able to trap this nucleophilic phenyl group to give Ph₅P (ref. 49). To ascertain whether Ph₅P is generated or not, more evidences were collected. ³¹P NMR measurement of the reaction of **1a** with salt **2a** only detected the formation of Ph₃PO. Furthermore, instead of the phosphonium salt **2a**, Ph₅P was directly used in its reaction with aldehyde (See Supplementary Methods for the procedure for arylation of **1a** with Ph₅P)^{50,51}. However, no desired product **3aa** was detected without the presence of Cs₂CO₃. And even in the presence of Cs₂CO₃, the yield of **3aa** was very low (11%), indicating that Ph₅P may not be involved in the above arylation.

On the basis of the above results, we proposed a plausible mechanism shown in Fig. 5. The direct attack of Cs₂CO₃ at the phosphonium cation is the predominant path (Path I). Nucleophilic addition to the positive phosphorus would always be along the axial co-ordinate and pseudorotation would occur afterwards to place the electronegative substituent in the other

axial position^{30,39,47,52}, generating trigonal bipyramidal tetraaryloxyphosphorane **A**. The simultaneous decarboxylation and nucleophilic attack of Ar in intermediates **A** to carbonyl or imino groups afford Ph₃PO and the adduct **B**, which is then protonated by acid to furnish the final product. However, owing to the unavoidable presence of trace amount of water, an equilibrium between Cs₂CO₃ and CsHCO₃/CsOH may be established (path II). CsHCO₃ might gradually decompose into Cs₂CO₃, water and carbon dioxide at the reaction temperature. The generated CsOH would promote the subsequent arylation via an alkaline-hydrolysis path^{30,39–47}. Nucleophilic addition of hydroxide to phosphorus and the subsequent pseudorotation generate intermediate **C**, deprotonation of which by CsOH gives an oxyanionic phosphorane **D**. The expulsion of the aryl anion from intermediate **D** and the nucleophilic addition of this Ar group to substrate also afford the adduct **B** and Ph₃PO. Therefore, the two paths might coexist. It should be noted that none of the intermediate **A**, **C** or **D** was detected by ³¹P NMR, although *P*-hydroxytetraorganophosphorane has recently been

observed and characterized by low-temperature NMR⁵³. Considering that cyano and ester groups are stable under the optimized reaction conditions and the enolizable carbonyl compounds were successfully converted, the naked aryl anion is not believed to be formed in the arylation process. Carbon dioxide cannot be detected by GC-MS in the gas phase of the reaction system because the gas phase was full of the solvent THF. Fortunately, when DMF was used instead of THF in the reaction of aldehyde **1a** with salt **2a**, GC-MS analysis of the gas phase of the reaction mixture successfully detected the generation of CO₂ (see ‘determination of CO₂ by GC-MS spectroscopy’ in Supplementary Methods) albeit that the desired product was isolated in only 60% yield, further supporting the proposed reaction mechanism.

Discussion

Although phosphonium salts are electrophilic species, we found that a substituent on the positive phosphorus can act as a nucleophile for the construction of C-C bond while initiated by another appropriate nucleophile. The successful application of tetraarylphosphonium salts to the nucleophilic transition-metal-free arylation of carbonyl and imino compounds in the presence of caesium carbonate is described herein. The high P-O affinity has an important role in this arylation strategy. This practical protocol is attractive because the reaction is not particularly sensitive to water, shows wide substrate scope under mild conditions, and is compatible with a variety of functional groups. It provides a highly valuable method for C-arylation and

easy access to α -aryl-alcohols and α -aryl-amines. In addition, the success of the strategy means that phosphonium salts may find applications in other areas of chemistry.

Methods

General procedure for phenylation of aldehydes. Under N₂ atmosphere, the mixture of aldehyde (0.50 mmol), tetraphenylphosphonium iodide (583.0 mg, 1.25 mmol) and Cs₂CO₃ (488.7 mg, 1.50 mmol) in THF (4 ml) and stirred at 65 °C for 12 h. The reaction was quenched by 3 N HCl (0.5 ml). The resulting mixture was extracted with dichloromethane (DCM; 3 × 30 ml). The combined organic phase was dried over Na₂SO₄. After filtration, the solvent was removed by concentration, and the residue was subjected to column chromatography to afford the pure product.

General procedure for phenylation of ketones. Under N₂ atmosphere, the mixture of ketone (0.40 mmol), tetraphenylphosphonium iodide (745.8 mg, 1.60 mmol) and Cs₂CO₃ (586.4 mg, 1.80 mmol) in THF (4 ml) was stirred at 65 °C for 24 h. The reaction was quenched by 4.5 N HCl (1.5 ml). The resulting mixture was extracted with DCM (3 × 30 ml). The combined organic phase was dried over Na₂SO₄. After filtration, the solvent was removed by concentration, and the residue was subjected to column chromatography to afford the pure product.

General procedure for phenylation of imines. Under N₂ atmosphere, the mixture of imine (0.50 mmol), tetraphenylphosphonium iodide (583.0 mg, 1.25 mmol) and Cs₂CO₃ (488.7 mg, 1.50 mmol) in THF (4 ml) was stirred at 65 °C for 12 h. The reaction was quenched by 3 N HCl (0.5 ml). The resulting mixture was extracted with DCM (3 × 30 ml). The combined organic phase was dried over Na₂SO₄. After filtration, the solvent was removed by concentration. The residue was subjected to column chromatography to afford the pure product.

Ph ₄ P ⁺ I ⁻	Cs ₂ CO ₃	THF (1.5 ml)	Ph ₃ PO
1 mmol	X equiv.	65 °C, 4 h	
	X (equiv.)		Yield ^a
	1.0		34%
	1.5		44%
	2.0		50%
	3.0		66%

Figure 4 | Evidence to support the Cs₂CO₃ promoted arylation without water. The more Cs₂CO₃ was used for the reaction of Ph₄P⁺ I⁻ with Cs₂CO₃ for the same period of time, the more Ph₃PO was produced, ^a yields were determined by ³¹P NMR.

Arylation of **1a with various tetraarylphosphonium salts.** *Method A.* Under N₂ atmosphere, the mixture of [1,1'-biphenyl]-4-carbaldehyde (**1a**; 91.2 mg, 0.50 mmol), tetraarylphosphonium iodide (1.25 mmol) and Cs₂CO₃ (488.7 mg, 1.50 mmol) in THF (4 ml) was stirred at 65 °C until phosphonium salt was completely consumed as monitored by ³¹P NMR. The reaction was quenched by 3 N HCl (0.5 ml). The resulting mixture was extracted with DCM (3 × 30 ml). The combined organic phase was dried over Na₂SO₄, and the residue was subjected to column chromatography to afford the pure product.

Method B. Under N₂ atmosphere, into the mixture of [1,1'-biphenyl]-4-carbaldehyde (**1a**; 91.2 mg, 0.50 mmol) and Cs₂CO₃ (488.7 mg, 1.50 mmol) in THF (2 ml) at 65 °C was added the solution of phosphonium bis(trifluoromethanesulfonyl)amide (1.25 mmol) in THF (2 ml) slowly for 6 h. On completion of addition, the reaction was stirred for another 10 min. The mixture was quenched by 3 N HCl (0.5 ml) and extracted with DCM (3 × 30 ml). The combined organic phase was dried over Na₂SO₄. After filtration, the solvent was removed by concentration, and the residue was subjected to column chromatography to afford the pure product.

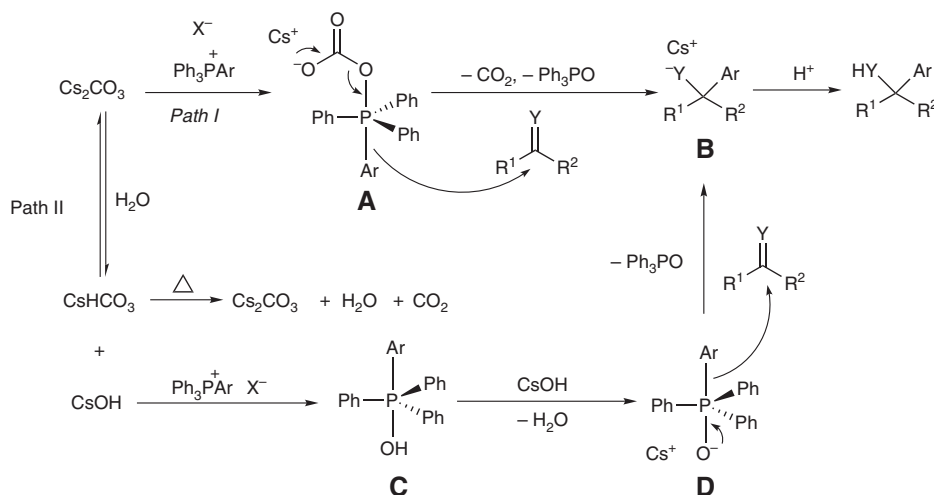


Figure 5 | Proposed nucleophilic arylation mechanism. The reaction should be predominantly initiated by Cs₂CO₃ (path I), and may also be promoted by CsOH due to the trace amount of water present in the reaction system (path II).

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Author contributions

D.Z. performed the experiments. L.J.-H. analysed the data and wrote the manuscript. X.J.-C. designed the experiments and wrote the manuscript.

Additional information

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