

A general synthesis of aryl phosphines by palladium catalyzed phosphination of aryl bromides using triarylphosphines

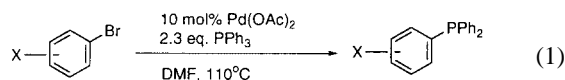
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Palladium catalyzed phosphination of substituted aryl bromides using triarylphosphines as the phosphinating agents has been developed; this method tolerates ketone, aldehyde, ester, nitrile, ether and chloride functional groups.

Triarylphosphines constitute one of the most important class of ligands in transition metal catalyzed reactions.¹ Although there is a necessity to incorporate functional groups in aromatic phosphines in order to tailor the phosphines for modifying catalysis, synthetic methods available are limited in scope. Traditional methods for preparation of these phosphines can be classified into two major categories. The first method involves the reactions of aryl Grignard or organolithium reagents with chlorophosphine, but it is limited to compounds that are not base sensitive.² The second method is transition metal catalyzed phosphination. Though it is useful, limitations do exist. Both nickel catalyzed phosphination of aryl triflates using diphenylphosphine³ or chlorodiphenylphosphine⁴ require use of air- and moisture-sensitive phosphinating reagents and the latter method is not tolerant to easily reducible functional groups since Zn metal is used.⁴ The Pd/Ph₂P(O)H route requires subsequent reduction by trichlorosilane.⁵ The Pd/(trimethylsilyl)diphenylphosphine system is limited to aryl iodides and cannot tolerate aldehyde functional groups.⁶ The Pd/phosphine–borane method requires an extra deprotection step and cannot tolerate amine containing functional groups.⁷ Generally, the above methods require the use of air-sensitive reagents and are limited in functional group tolerance. Herein, we report palladium catalyzed phosphination using readily available triarylphosphines as the phosphinating agent and functionalized aryl bromides as substrates to synthesize functionalized aromatic phosphines [eqn. (1)].



4-Bromoacetophenone was reacted with 2.3 equivalents of triphenylphosphine in the presence of 10 mol% palladium acetate catalyst in DMF at 110 °C to yield 4-(diphenylphosphino)acetophenone in 40% yield (Table 1, entry 1).[†] In addition, 4-bromobenzaldehyde can be phosphinated by triphenylphosphine to form 4-(diphenylphosphino)benzaldehyde in 32% yield (Table 1, entry 2). In contrast, the previous method for the preparation⁸ of this phosphine, which finds many applications for water soluble polymers⁹ and water soluble porphyrins,¹⁰ involved a multi-step synthesis which required protection of the aldehyde.⁸ Other functional groups, such as esters, nitriles, methyl ethers and halogens, are tolerant to this phosphination reaction (Table 1, entries 3–7). In contrast, previous syntheses of ester and nitrile containing phosphines required a long synthetic pathway.¹¹

Similar rates of reaction were observed for electronically different non-coordinating aryl bromides (Table 1, entries 1,5,7). The rate of the reaction of coordinating substrates which contain ester, aldehyde or nitrile groups (Table 1, entries 2–4), required a longer reaction time. Presumably strongly coordinat-

Table 1 Palladium catalyzed phosphination of different aryl bromides with triphenylphosphine

Entry	Substrate	Reaction time/h	Yield ^a (%)
1 ⁶		20	40
2 ¹⁰		64	32
3 ^{11c}		36	30
4 ¹⁵		48	36
5 ¹⁶		24	27
6 ¹⁷		18	38
7 ¹⁸		20	51 ^b
8		26	58 ^b
9 ¹⁹		19	59 ^b
10 ²⁰		18	51 ^b

^aIsolated yield. ^bGC yield is reported as an average of two runs.

ing substrates rendered the complex coordinatively saturated and hence reduced the catalytic efficiency. For 3- and 4-bromoanisole, the reaction times are similar but the yield of 3-(diphenylphosphino)anisole was higher (Table 1, entries 5 and 6).

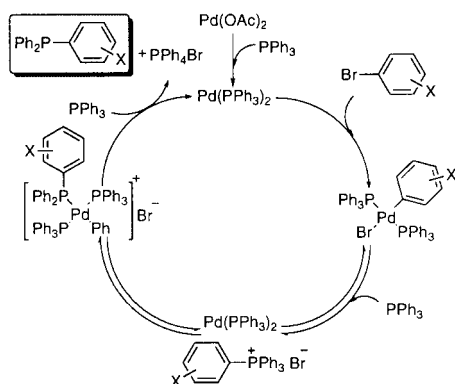
Either Pd(PPh₃)₄ or Pd(OAc)₂ can catalyze this reaction. Pd(OAc)₂ was employed as the catalyst since other triarylphosphines can be used as phosphinating reagents, such as trixylylphosphine, tri(*p*-methoxyphenyl)phosphine and tri(*p*-tolyl)phosphine (Table 2, entries 1–3). Therefore, a variety of different substituted phosphines can be readily prepared through this direct methodology.

A plausible mechanism (Scheme 1) for this phosphination starts with the *in situ* reduction of Pd(OAc)₂ by triphenylphosphine to Pd(0).¹² Subsequent oxidative addition with aryl bromide yields a aryl Pd(II) species. Reductive elimination with triphenylphosphine gives a phosphonium salt,¹³ which then undergoes oxidative addition with the palladium species to

Table 2 Palladium catalyzed phosphination of *p*-bromoacetophenone with different triarylphosphines

Entry	PAR ₃	Product	time/h	Yield ^a (%)
1			32	34
2			34	33
3			33	39

^aisolated yield



Scheme 1 A plausible mechanism for palladium catalyzed phosphinylation.

generate the coordinated phosphine product.¹⁴ Finally ligand substitution by the other triphenylphosphine regenerates the Pd(0) species and substituted phosphine product.

In conclusion, our phosphination method tolerates a number of functional groups including ketones, aldehydes, esters, nitriles, methyl ethers and chloride. This palladium catalyzed phosphination avoids the problems of traditional raw materials and utilizes the most cost effective triphenylphosphine as the phosphinating reagent. This process has a great potential to tailor a variety of substituted phosphines by using different triarylphosphines as the reagent. Studies are continued to extend the scope of this reaction.

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Notes and references

† *General experimental procedure:* 4-bromoacetophenone (100 mg, 0.5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol) and PPh₃ (301 mg, 1.15 mmol) were dissolved in dry DMF (2 mL) under nitrogen in a Teflon stopcock flask. The solution was heated to 110–115 °C and the reaction was monitored by GC–MS. The reaction mixture was then cooled down and DMF was removed by vacuum evaporation. After 20 h, the crude product was purified by column chromatography on silica gel using a solvent mixture of hexane–ethyl acetate (20: 1) as the eluent to give 4-(diphenylphosphino)acetophenone in 40% yield as a white solid.

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