Practical Protocol for the Palladium-Catalyzed Synthesis of Arylphosphonates from Bromoarenes and Diethyl Phosphite

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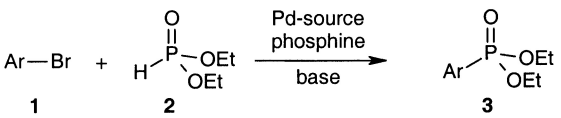
Abstract: A greatly improved, reliable protocol for the palladium-catalyzed cross-coupling of dialkyl phosphites with aryl bromides has been developed. The use of an alcoholic solvent was the key to high yields in the synthesis of a broad variety of arylphosphonates, with $Pd(OAc)_2/PPh_3$ as the catalyst and a sterically demanding tertiary amine as the base.

Key words: palladium, catalysis, arylphosphonates, cross-coupling, aryl halides

Aryl- and vinylphosphonic acid moieties are key functionalities in many biologically active compounds,[2] flame retardants,[3] or polymer additives.[4] Traditional synthetic entries into this important substrate class include Friedel–Crafts reactions of arenes with phosphoric acid derivatives,[5] Cu-catalyzed reactions of diazonium salts with PCl_3,[6] nucleophilic substitution reactions of activated aryl halides with sodium dialkylphosphites,[7] Ni- or Cu-mediated couplings between aryl halides and trialkyl phosphites,[8] and reaction of arylmetal derivatives and trialkyl phosphites.[9] However, due to the aggressive reagents or harsh conditions required, these transformations tend to be incompatible with sensitive functionalities, impeding applications in combinatorial chemistry and in the synthesis of complex, functionalized molecules.

A potentially more general access to dialkyl arylphosphonates based on the palladium-catalyzed reaction of aryl halides with dialkyl phosphite has been disclosed by Hirao et al. (Scheme 1).[10,11] In the initial protocol using $Pd(PPh_3)_4$ as the catalyst and triethylamine as the base, the best yields were obtained in the absence of a solvent. Beletskaya et al. reported that the reaction can also be performed under phase-transfer conditions using potassium carbonate as the base.[12]



Scheme 1 Pd-catalyzed synthesis of arylphosphonates

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Since, in our opinion, these protocols represented the most convenient synthetic entry, we attempted to apply them to the preparation of various functionalized aryl phosphonates as starting materials for an ongoing synthetic project. Unfortunately, we were confronted with strongly varying and often unsatisfactory yields. In order to elucidate the reason for this and potentially come to a more reliable reaction protocol, we chose the reaction of 4-bromoanisole (**1a**) with diethyl phosphite (**2**) as a model system to screen various catalysts and reaction conditions. Selected results are summarized in Table 1.

In our hands, this model reaction did not go to completion when applying literature conditions (entries 1 and 2).[10] Further studies revealed that among all reaction parameters studied, the choice of the solvent had the strongest influence on the reaction outcome: The addition of polar solvents proved to be beneficial, and alcoholic solvents such as ethanol led to excellent yields even at lower temperatures (entries 2–6). Further experiments revealed that even small amounts of ethanol, which may arise from partial hydrolysis of the starting material diethyl phosphite, strongly facilitate the reaction. This may explain why our yields strongly depended on the quality of the starting materials and the water content of the solvents when following the literature protocols.

We then examined several Pd-sources and found $Pd(OAc)_2$ to be the most effective precatalyst (entries 6–9). Using ethanol as the solvent, inorganic bases did not give satisfactory yields as they facilitated side reactions such as dehalogenation of the bromoanisole (entries 10–12). Tertiary amines with a low nucleophilicity led to much higher selectivities (entries 9, 13–16), and the best results were obtained using sterically crowded derivatives such as Hünig's base or dicyclohexylmethylamine.

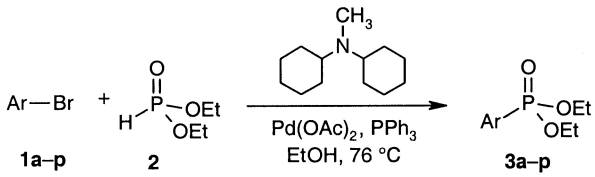
The choice of the phosphine was also important (entries 17–22). Interestingly, neither chelating nor electron-rich alkyl phosphines gave satisfactory results in this transformation, although these ligands had proved to be highly effective in other Pd-catalyzed couplings. Instead, the best results were obtained with simple triaryl phosphines such as P(*p*-MeO-Ph)$_3$ and P(*p*-Cl-Ph)$_3$. However, since the inexpensive triphenylphosphine was found to be almost as effective, we considered it to be the best choice.

After having identified convenient and reliable reaction conditions, we investigated the scope of the new reaction protocol using a variety of aryl bromides (Scheme 2). Selected results are summarized in Table 2.[13] Gratifyingly, it

Table 1 Cross-Coupling of 4-Bromoanisole with Diethyl Phosphite[a]

Entry	Pd-source	Phosphine	Base	Solvent	Yield (%)
1[b]	$Pd(PPh_3)_4$	–	Et_3N	–	11
2[b]	$Pd(PPh_3)_4$	–	Et_3N	Toluene	32
3	$Pd(PPh_3)_4$	–	Et_3N	Dioxane	34
4	$Pd(PPh_3)_4$	–	Et_3N	NMP	26
5	$Pd(PPh_3)_4$	–	Et_3N	DMSO	65
6	$Pd(PPh_3)_4$	–	Et_3N	EtOH	85
7	$Pd(dba)_2$	PPh_3	Et_3N	EtOH	64
8	$PdCl_2$	PPh_3	Et_3N	EtOH	30
9	$Pd(OAc)_2$	PPh_3	Et_3N	EtOH	94
10	$Pd(OAc)_2$	PPh_3	K_2CO_3	EtOH	12
11	$Pd(OAc)_2$	PPh_3	KF	EtOH	0
12	$Pd(OAc)_2$	PPh_3	K(O-*t*-Bu)	EtOH	0
13	$Pd(OAc)_2$	PPh_3	Pyridine	EtOH	0
14	$Pd(OAc)_2$	PPh_3	DBU	EtOH	5
15	$Pd(OAc)_2$	PPh_3	$N(i\text{-}Pr)_2Et$	EtOH	96
16	$Pd(OAc)_2$	PPh_3	$N(c\text{-}Hex)_2Me$	EtOH	97
17	$Pd(OAc)_2$	$P(p\text{-}MeO\text{-}Ph)_3$	$N(c\text{-}Hex)_2Me$	EtOH	98
18	$Pd(OAc)_2$	$P(p\text{-}Cl\text{-}Ph)_3$	$N(c\text{-}Hex)_2Me$	EtOH	98
19	$Pd(OAc)_2$	$P(o\text{-}Tol)_3$	$N(c\text{-}Hex)_2Me$	EtOH	50
20	$Pd(OAc)_2$	$P(c\text{-}Hex)_3$	$N(c\text{-}Hex)_2Me$	EtOH	66
21	$Pd(OAc)_2$	$P(t\text{-}Bu)_2biPh$	$N(c\text{-}Hex)_2Me$	EtOH	51
22	$Pd(OAc)_2$	BINAP	$N(c\text{-}Hex)_2Me$	EtOH	0

[a] Conditions: 1.0 mmol 4-bromoanisole, 1.2 mmol diethyl phosphite, 1.5 mmol base, 2 mol% Pd-source, 6 mol% phosphine (3 mol% when bidentate), 4 mL solvent, 80 °C, 16 h. Yields were determined by GC using *n*-tetradecane as the internal standard.
[b] At 90 °C.



Scheme 2 Pd-catalyzed synthesis of arylphosphonates

proved to be applicable to a great variety of substrates. Electron-poor and electron-rich compounds were found to be equally suitable, and even sterically hindered aryl bromides gave good results.

Remarkably clean reactions were observed even with functionalized molecules bearing keto, nitro, ester, thioether, nitrile and even hydroxyl groups. Solely the synthesis of the heterocyclic compounds **3h** and **3p** failed to give any conversion of the starting materials. A possible explanation for their lack of reactivity could be an interaction of their donor groups with the palladium, preventing catalytic turnover.

In summary, a highly efficient and broadly applicable protocol for the cross-coupling of aryl bromides with dialkyl phosphites was developed, providing a convenient entry to arylphosphonic esters. Key features of the new process are the use of the protic solvent ethanol, along with a sterically demanding tertiary amine as the base.

Acknowledgment

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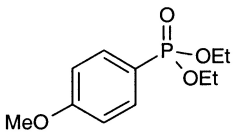
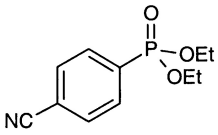
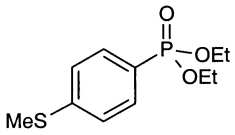
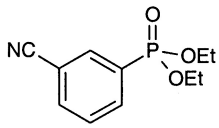
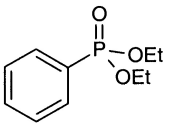
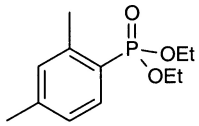
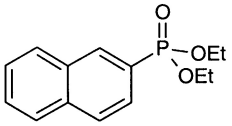
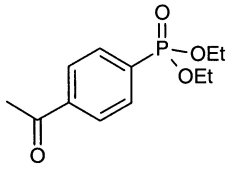
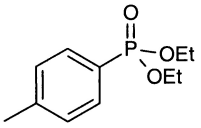
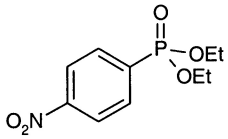
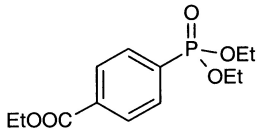
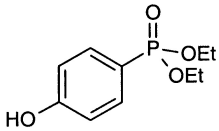
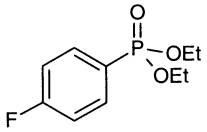
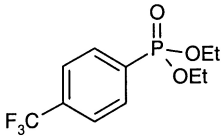
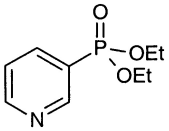
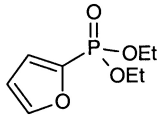
Table 2 Scope and Limitations of the Reaction Protocol

Compound	Structure	Yield (%)[a]	Compound	Structure	Yield (%)[a]
3a		86	**3i**		92
3b		88	**3j**		85
3c		88	**3k**		83
3d		91	**3l**		87
3e		87	**3m**		84
3f		89	**3n**		80
3g		90	**3o**		93
3h		0	**3p**		0

[a] Conditions: 1.0 mmol aryl bromide, 1.2 mmol diethyl phosphite, 1.5 mmol di(*c*-hex)$_2$NMe, 0.02 mmol Pd(OAc)$_2$, 0.06 mmol PPh$_3$, 4 mL EtOH, reflux, 16 h, isolated yields.

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(13) **Synthesis of Diethyl *p*-Toluenephosphonate (Representative Experimental Procedure).** A 200 mL round bottom flask equipped with a reflux condenser and a magnetic stirring bar was charged with $Pd(OAc)_2$ (45 mg, 0.2 mmol) and PPh_3 (157 mg, 0.6 mmol). The reaction vessel was evacuated and purged with argon. Subsequently, EtOH (40 mL), *p*-bromotoluene (1.71 g, 10 mmol), dicyclohexylmethylamine (2.93 g, 15 mmol) and diethyl phosphite (1.55 mL, 12 mmol) were added via syringe. The reaction mixture was stirred at reflux for 16 h, and the resulting yellow solution was diluted with EtOAc (300 mL) and washed with 1 N HCl, sat. aq $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, the volatiles were removed in vacuo and the residue was purified by column chromatography (SiO_2, hexanes–EtOAc, 1:3), yielding 2.06 g (90%) of **3e** as a colorless oil. The reactions in Table 2 were performed on 1 mmol scale, the products were purified by flash chromatography (SiO_2, hexanes–EtOAc) and characterized by means of ^1H NMR and ^{13}C NMR, GC-MS and HRMS.