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Development of a room temperature Hirao reaction

Mark C. Kohler, Joseph G. Sokol, Robert A. Stockland Jr. *

Department of Chemistry, Bucknell University, Lewisburg, PA 17837, United States

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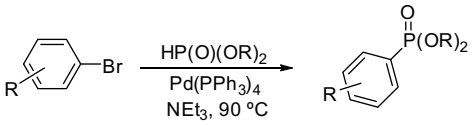
ABSTRACT

Arylphosphonates were prepared at 25 °C through the palladium-catalyzed coupling of aryl iodides with a silver phosphonate. A wide range of aryl iodides were successfully employed including phenolic substrates as well as those containing an ortho substituent.

Arylphosphonates and their derivatives are important classes of compounds with applications in medicinal,[1–8] organic,[9–11] and polymer chemistries.[12–14] Due to the poor reactivity of arylhalides in classic Arbusov-type chemistry, methodology for the synthesis of these compounds was limited until Hirao developed a palladium-catalyzed coupling of aryl halides with hydrogen phosphonates (Eq. 1).[15,16] While this and other metal-catalyzed processes generate the desired arylphosphonates, the reactions typically require elevated temperatures (above 90 °C).[10,17–23] Recent work by Montchamp has demonstrated that judicial choice of palladium precursor as well as supporting ligand has a dramatic effect on the yield of the arylphosphonate.[24] The use of dppf/$Pd(OAc)_2$ as the catalyst system faciliated the preparation of a range of Ar-$P(O)(OR)_2$ species in refluxing acetonitrile. As part of our continuing efforts to discover facile routes to P(O)–C bond forming reactions,[25–27] we have investigated several catalyst systems for the generation of arylphosphonates at 25 °C.



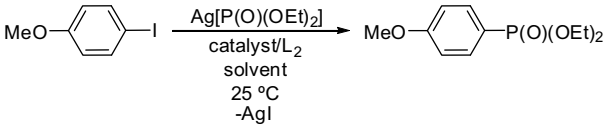
(1)

Initial attempts at developing a room temperature process centered on using $Pd(OAc)_2$ as the palladium source and a large bite-angle diphosphine (dpephos) as the supporting ligand.[28] The large bite-angle diphosphine was selected due to its ability to accelerate reductive elimination reactions.[29] 4-iodoanisole was used as the aryl halide, and diethylphosphite was chosen as the hydrogen phosphonate. After extensive screening of bases, solvents, catalyst loadings, and Pd/L ratios, only traces of the desired arylphosphonates were observed in the reaction mixtures at 25 °C.

In the course of developing new procedures for the generation of metal phosphonates, we recently found that silver phosphonates are outstanding sources of the phosphonate fragment.[30–32] Using these reagents, palladium halides are readily transformed into metal phosphonates under mild conditions and can be isolated by simple filtration and removal of the volatiles. It seemed appropriate to investigate the efficacy of these reagents in the Hirao reaction. Replacing the hydrogen phosphonate/base combination with 1.0 equiv of the silver phosphonate in the cross-coupling reaction resulted in a near quantitative conversion into the desired arylphosphonate at 25 °C (Table 1).

To probe the scope and effectiveness of using silver phosphonates in the cross-coupling reaction, a series of reactions were

Table 1
Cross coupling using a silver phosphonate at 25 °C[a]



	L_2	Catalyst	Conv.[b] (THF)	Conv.[b] (CH_3CN)	Conv.[b] (CH_2Cl_2)
1	bu_2bipy	Pd_2dba_3	0	0	0
2	bu_2bipy	$Pd(OAc)_2$	0	0	0
3	bu_2bipy	—	0	0	0
4	dppe	Pd_2dba_3	2	2	3
5	dppe	$Pd(OAc)_2$	3	2	3
6	dppe	—	0	0	0
7	dppf	Pd_2dba_3	80	39	28
8	dppf	$Pd(OAc)_2$	81	43	41
9	dppf	—	0	0	0
10	dpephos	Pd_2dba_3	77	50	42
11	dpephos	$Pd(OAc)_2$	95	76	53
12	dpephos	—	0	0	0
13	—	Pd_2dba_3	0	0	0
14	—	$Pd(OAc)_2$	0	0	0
15	—	—	0	0	0

[a] Coupling reactions were carried out on a 0.20 mmol scale in 3.0 mL of solvent with 5 mol % Pd loading and 10 mol % L_2 for 16 h at 25 °C.

[b] Yields of the screening reactions were determined using ^1H or $^{31}P\{^1H\}$ NMR spectroscopy with hexamethylbenzene or triphenylphosphine oxide as internal standards.

* Corresponding author. Tel.: +1 570 577 1665; fax: +1 570 577 1739.
E-mail address: rstockla@bucknell.edu (R. A. Stockland Jr.).

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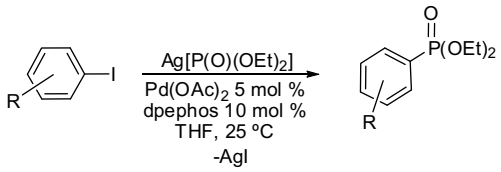
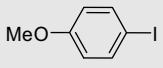
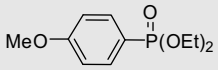
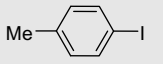
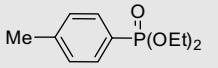
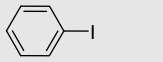
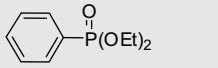
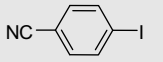
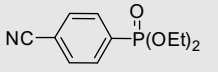
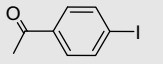
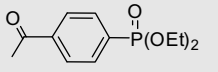
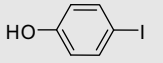
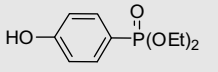
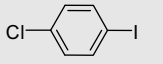
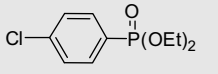
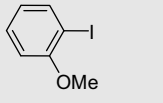
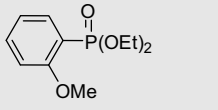
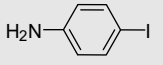
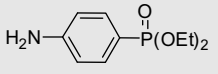
Table 2
Scope of the cross-coupling reaction[a]

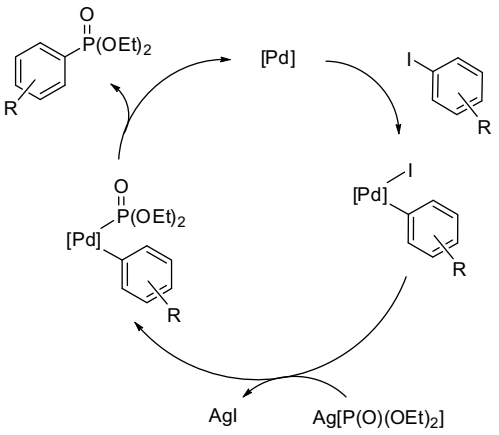


	Aryl halide	Product	Conv.[b]
1			92
2			87
3			86
4			77
5			89
6			69
7			44
8			82
9			77

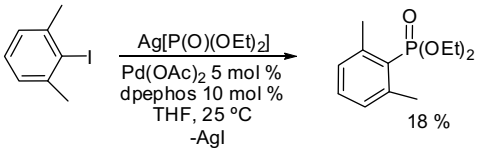
[a] Coupling reactions were carried out on a 0.41 mmol scale in 3.0 mL of THF with 5 mol % $Pd(OAc)_2$ and 10 mol % dpephos.
[b] Yields are based upon isolated material.

carried out with different metal sources, solvents, and ancillary ligands (Table 1). These studies revealed that a large bite-angle diphosphine was a critical component of the successful catalytic system given that small bite-angle diphosphines, such as dppe, were ineffective in the coupling reaction. Additionally, solvents such as dichloromethane and acetonitrile were not as effective as tetrahydrofuran. Palladium acetate was found to be superior to Pd_2dba_3 in the screening reactions. It is also noteworthy to mention that the silver phosphonate did not catalyze the reaction in the absence of the palladium salt (entry 15).

Once an effective system was found, the chemistry was extended to a range of aryl iodides (Table 2).[33,34] Moderate to high yields of the arylphosphonates were obtained with both electron-donating and electron-withdrawing groups in the para-position of the aryl halide. The methodology was also tolerant of sensitive functional groups such as carbonyls and phenols (Table 2: entries 5 and 6). While the incorporation of a single ortho substituent did not significantly affect the chemistry (Table 2: entry 8), analogous reactions involving 2,6-dimethyliodobenzene were sluggish, and only 18% conversion into the desired arylphosphonate was observed after stirring the reaction for 48 h (Eq. 2).



Scheme 1. Mechanism for the formation of arylphosphonates.



(2)

The proposed mechanism for the coupling reaction is shown in Scheme 1. Initial oxidative addition of the aryl halide to the low-valent palladium center generates the arylpalladium iodide. Reaction of this intermediate with $Ag[P(O)(OEt)_2]$ generates the arylpalladium phosphonate species through a transmetallation reaction. Reductive elimination affords the desired arylphosphonates and regenerates the Pd(0) species.

In summary, a room temperature synthesis of arylphosphonates has been developed. This palladium-catalyzed reaction utilizes dpephos as the supporting ligand and silver phosphonates as transmetallating agents and affords moderate to excellent yields of the arylphosphonates. Work is currently underway to extend this methodology to aryl bromides and chlorides.

Acknowledgments

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Supplementary data

Supplementary data including detailed experimental procedures as well as ^{1}H, $^{13}C\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra for the aryl phosphonates. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.040.

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28. *dppe = bis(diphenylphosphino)ethane*, *dppf = bis(diphenylphosphino)ferrocenee*, *dpephos = (Oxydi-2,1-phenylene)bis(diphenylphosphine)*, *bu_2bipy = 4,4′-ditertbutyl, 2-2′-bipyridine*.
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33. A reaction vial (10 mL) was charged with the aryl halide (0.41 mmol), $Pd(OAc)_2$ (0.0046 g, 20.4 μmol), dpephos (0.022 g, 40.8 μmol), $Ag[P(O)(OEt)_2]$ (0.10 g, 0.41 mmol) and a magnetic stirring bar. After evacuation and refilling with N_2, THF (3.0 mL) was added. If the aryl halide was a liquid, it was added after the solvent. The reaction was stirred in the dark for 16 h and centrifuged. The solution was decanted and the volatiles were removed under vacuum at 25 °C. The arylphosphonates were isolated using column chromatography (silca gel, pentane/ethyl acetate).
34. The silver salt prepared in this study was stored under nitrogen and in the absence of light (25 °C). Under these conditions, the salt was quite stable for several weeks. Slight decomposition was noted after several months.