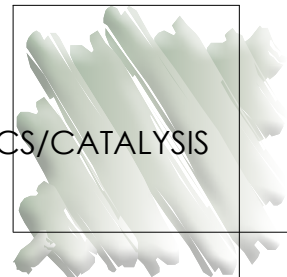




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Highly efficient palladium-catalyzed arsination On the way to arsine ligands

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ABSTRACT *Since arsines are drawing particular attention as ligands in metal-catalyzed reactions, the development of new methods to obtain organoarsines is increasingly recognized as central in the synthesis of new ligands. Transition metal-catalyzed reactions with organoheteroatom compounds are widely used to acquire different heteroatom-contained compounds. This article reviews a highly efficient one-pot, two-step Pd-catalyzed arsination with $n\text{-Bu}_3\text{SnAsPh}_2$ and diverse electrophiles. The cross-coupling reactions of these stannanes with ArI afforded the functionalized triarylsines, and with R_f as electrophiles new perfluoroalkylarsines were achieved. By following this methodology, a biphenyl arsine ligand was acquired. The use of the commercially available, air-stable, and inexpensive AsPh_3 as the initial reagent and the one-pot process make this methodology a useful approach to obtaining a wide range of organoarsines.*

INTRODUCTION

Transition-metal catalyzed C-heteroatom bond formation reactions are largely used for the synthesis of different heteroatom-contained compounds, and represent a powerful tool to accomplish highly complex molecules (1). Particularly, Pd-catalyzed cross-coupling reaction of organic electrophiles with organostannanes is an extensively used methodology not only for C-C (2), but also for C-heteroatom (3) bond formation under conditions compatible with a broad range of functional groups.

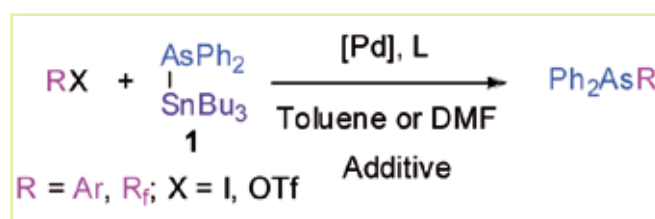
Although tertiary phosphines constitute the group of ligands most widely used in transition metal chemistry, arsines are gaining particular attention as ligands in metal-catalyzed reactions. The efficiency of such reactions largely depends on the fine electronic and structural properties of the ligands, and even with well-designed phosphine ligands, unsatisfactory results may still be observed; therefore, novel types of ligands are generally required.

It should be noted that arsines have been reported as ligands more suitable than phosphines in several transition-metal-catalyzed organic reactions. However, arsine ligands have not yet, to a large extent, been developed, probably due to the need of methodologies for the synthesis of functionalized tertiary arsines. Most of the available synthetic methods are complicated

or limited in scope. For instance, the classic arsination involves the reaction of organolithium or organomagnesium reagents with haloarsines (4). A further method implies the reaction of aryl halides with Ph_2AsM ($M = \text{Li, Na, K}$) prepared *in situ* (5). The first catalyzed arsination using Ni was described by Shibasaki and co-workers for the synthesis of BINAs and BINAPAs ligands, by reaction of BINOL ditriflate with Ph_2AsH (6). Furthermore, a solvent free Pd-catalyzed arsination of aryl triflates to achieve functionalized arsines was reported (7, 8). The catalytic reaction proceeded by a Pd-Ar/As-Ph exchange with triphenylarsine as the arsinating agent, affording no more than 51 percent yield of triarylsines after 4-5 days. Even though this approach provides a convenient route to obtain arsines with different functional groups ($\text{FG} = \text{COOMe, COMe, CHO, CN, NO}_2, \text{OMe}$), arsines were achieved in moderate yields after long reaction times. Additionally, an application of this Pd-catalyzed arsination to the synthesis of a chiral (As,N) ligands was also reported.

The development of new methods to obtain arsines is thus increasingly recognized as central in the synthesis of new ligands. Accordingly, we have developed a versatile methodology that allows for C-heteroatom bond formation through a cross-coupling Pd-catalyzed reaction of different electrophiles with organoheteroatom stannanes R_3SnZPh_n ($Z = \text{P, Se}$) in one-pot two-step reactions (3e, h, 9). To extend the applications of this procedure, we studied the Pd-catalyzed cross-coupling of organoheteroatom stannanes containing Sn-As and Sn-Sb bonds (10). While the scope of the Pd-catalyzed cross coupling reactions of group-15-derived organostannanes such as aminostannanes (3a-d) and (trialkylstannyl)phosphines (3e, h) has been examined, the use of organotin-arsines and organotin-stilbines to form C-As and C-Sb bonds has not yet been described, and our work was the first report on the synthesis of $n\text{-Bu}_3\text{SnZPh}_2$ ($Z = \text{As, Sb}$) and the exploration of its chemistry.

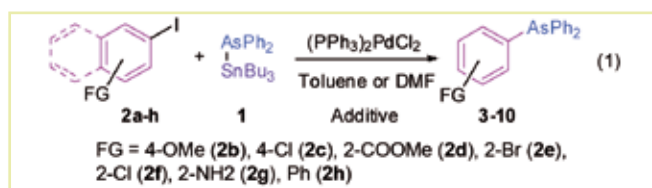
This article reviews a highly efficient one-pot, two-step Pd-catalyzed arsination with $n\text{-Bu}_3\text{SnAsPh}_2$ (1) and different electrophiles (Scheme 1). This methodology allowed the synthesis of functionalized arsines and arsine ligands.



Scheme 1.

Pd-CATALYZED ARSINATION WITH *n*-Bu₃SnAsPh₂ AND ARYL IODIDES

Recently, our group has developed a versatile methodology to accomplish C-As bond formation through a cross-coupling Pd-catalyzed reaction with the organoarsine stannane *n*-Bu₃SnAsPh₂ (**1**). We described for the first time the Pd-catalyzed arsination of aryl iodides, providing a few examples of the synthesis of triaryl-functionalized arsines (**5**). These preliminary studies were extended to more sterically hindered aryl iodides and to additional common functional groups present in the substrate (**11**). Stannane **1** was generated *in situ* by the reaction of Ph₂As⁻ anion with *n*-Bu₃SnCl. Afterwards, the Pd-catalyzed cross-coupling reaction of **1** with aryl iodides (**2a-h**) was carried out, all in a one-pot two-step procedure (eq. 1). The *in situ* generation of the stannanes eliminates the isolation and purification of tin reagents. The most relevant results of the Pd-catalyzed arsination are shown in Table 1 (5, 11).



Eq. 1

The system was shown to provide high-yields of triarylarisines and to be effective, since only 1.5 mol % of the Pd catalyst was used. Despite that, other sources of Pd were considered; for all Pd-catalyzed coupling reactions with organoheterostannanes studied, the best catalyst was (PPh₃)₂PdCl₂ (**5**).

	Substrate	Conditions	Product	Isolated Yield (%)
1		Toluene		85 ^b
2		Toluene		98 ^b
3		DMF		90 ^b
4		Toluene		75
5		Toluene		83
6		Toluene		88
7		Toluene		75
8		Toluene, PPh ₃ , CuI		71

^aReaction conditions: Ph₂As⁻ anion was prepared in liquid ammonia (300 mL) from AsPh₃ (1 mmol) and Na metal (2 mmol); *n*-Bu₃SnCl (1 mmol) was then added. The cross-coupling reaction was carried out with ArI (0.7 mmol) and (PPh₃)₂PdCl₂ (1.5 mol%), PPh₃ (Pd:L 1:4), CuI (Pd:Cu 1:2) for 24 hours at 80 °C when toluene was used, or at 120 °C with DMF.
^bGC yields.

 Table 1. Pd-catalyzed arsination of ArI (**2a-e**) with *n*-Bu₃SnAsPh₂ (**1**) in the presence of (PPh₃)₂PdCl₂.^a

*A highly efficient one-pot, two-step Pd-catalyzed arsination with *n*-Bu₃SnAsPh₂ to obtain functionalize arsines*

This method could be applied to a variety of aryl iodides, establishing that the arsination reaction can be carried out in the presence of different functional groups. Bromide and chloride halides did not react under these conditions; thus this selectivity for the arsination allowed further transformation of the remaining halides in the products. In addition, no significant electronic effect was observed since both electron-withdrawing and electron-donating groups showed similar rates and yields of reaction. A noticeable feature of this Pd-catalyzed arsination is that sterically hindered *ortho*-substituted aryl iodides reacted efficiently. Finally, it is particularly noteworthy that the products of the arsination reaction are Pd ligands; nevertheless, the reaction proceeded almost to completion.

Synthesis of a biphenyl arsine ligand

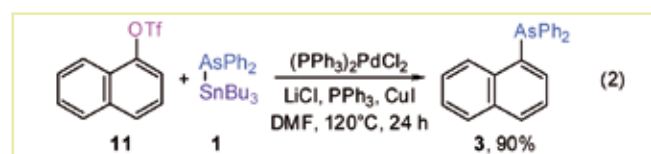
Over the past few years, there has been a growing interest in the synthesis and application of biphenyl-based monophosphine ligands, first introduced by Buchwald (12). A family of these ligands have been developed and shown to be excellent ligands for numerous Pd-catalyzed coupling processes. Thus, keeping the biphenyl backbone, and considering that the coordinating ability of ligands can also be tuned through the donor atom, by the Pd-catalyzed arsination a novel biphenyl arsine ligand was obtained.

The arsination with stannane **1** and 2-iodobiphenyl (**2h**) catalyzed by (PPh₃)₂PdCl₂ in toluene with PPh₃ and CuI afforded the arsine ligand biphenyl-2-yl-diphenylarsine (**10**, AsPh₂(bph), bph = biphenyl) with 71 percent isolated yield (entry 8, Table 1). In this case, the coupling reaction became more efficient by the use of Cu(I) as co-catalyst (13).

With this simple synthetic methodology, a new biphenyl arsine ligand could be achieved. Moreover, 2-(diphenylarsino)aniline (**9**) could also be regarded as a bidentate (As,N) ligand itself (14).

Pd-CATALYZED CROSS-COUPLING REACTION WITH 1-NAPHTHYL TRIFLATE

Although aryl halides are one of the most thoroughly studied groups, organic triflates are readily available and have become important coupling partners in synthesis. It should be noted that only a few examples of organoheteroatom stannanes application in cross-coupling reactions with organic triflates have been reported. A comprehensive study on the scope and limitations of the organoheteroatom stannanes R₃SnZPh_n (Z = P, As, Sb, Se) in coupling reactions was performed (9). To further extend the methodology above-described, the Pd-catalyzed arsination with stannane **1** and 1-naphthyl triflate (**11**) was also studied (9). The reaction can be successfully carried out, and naphthalenarsine **3** was obtained in excellent yields (eq. 2).



Eq. 2

Couplings of triflates show several experimental features that need to be considered. One of them is the effect of the addition of LiCl. A noticeable improvement in the yield of **3** was found when the cross-coupling reaction was carried out with both LiCl and PPh₃ as free ligand. The combination of PPh₃ and

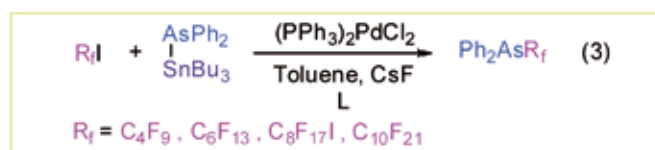
LiCl seems to be a key step in this system (9). Moreover, in the presence of CuI (13), the cross-coupling reaction became more efficient.

Pd-CATALYZED ARSINATION WITH PERFLUOROALKYL IODIDES

Organofluorine compounds have attracted particular interest in recent years for displaying unique reactivities and selectivities and for their promising applications in biological and material science (15). Among organofluorine compounds, those containing perfluoroalkyl groups (R_f) have become increasingly important; thus, it is required to develop new approaches to introducing these groups.

We found those containing As- R_f bonds especially interesting, considering that these compounds have potential applications as ligands. Although some tertiary arsine ligands with substituents such as alkyl or aryl groups were achieved, electron-poor or electroneutral arsine ligands were less developed (16), probably due the need of methods for introducing electron-withdrawing substituents.

We have recently provided a convenient route to obtain perfluoroalkylselenides via the Pd-catalyzed cross-coupling reaction of stannane $n\text{-Bu}_3\text{SnSePh}$ with $\text{C}_8\text{F}_{17}\text{I}$ and $\text{C}_{10}\text{F}_{21}\text{I}$ (3h). This approach was the first report of the Pd-catalyzed reaction for heteroatom- R_f bond formation. Following the same methodology, we have also performed the Pd-catalyzed cross-coupling reaction of $n\text{-Bu}_3\text{SnAsPh}_2$ (**1**) with $R_f\text{I}$ to achieve novel diphenylperfluoroalkylarsines (eq. 3) (17).



Eq. 3

Optimization studies of the cross-coupling arsination reaction were performed to evaluate the effect produced by different additives, ligands, solvents and catalysts, and to establish the optimal reaction conditions with these particularly electrophiles. These studies revealed that the most favourable conditions were those of $(\text{PPh}_3)_2\text{PdCl}_2/\text{PPh}_3/\text{CsF}$ in toluene. Table 2 shows the main results of this coupling reaction.

In all the reactions reported, no remaining substrate was found, and the other product achieved was the reduced perfluoroalkane ($R_f\text{H}$). The involvement of stannane in the reduction of $R_f\text{I}$ was demonstrated (17). Although a competitive reduction of the substrates took place, arsines were obtained in moderate to good yields (entries 1, 3, 5 y 7, Table 2). Novel perfluoroalkyldiphenylarsines with perfluoroalkyl chains between four and ten C atoms were obtained.

The low reactivity of $R_f\text{I}$ could be ascribed to its reluctance to participate in oxidative addition, where the structure of the ligand has a significant influence. Thus, to further improve the Pd-catalyzed arsination with $R_f\text{I}$, the activity of a variety of phosphine and arsine ligands was evaluated. In view of the success of various arsine ligands in Pd-catalyzed Stille reactions, we also evaluated the effectiveness of the $\text{AsPh}_2(\text{bph})$ (**10**) ligand. The yields obtained were highly dependent on the ligand, and $\text{AsPh}_2(\text{bph})$ was the most efficient one (entries 2, 4, 6 y 8, Table 2). The effectiveness of our sterically demanding ligand $\text{AsPh}_2(\text{bph})$ could arise from the formation of monoligated Pd species (18), and these species could be responsible for a rapid oxidative addition of the $R_f\text{I}$ to the Pd(0) centre.

By this methodology new types of potential perfluoroalkylarsine ligands were achieved. Particularly noteworthy is the fact the reaction worked for perfluoroalkyl chains longer than four.

Entry	Substrate	Ligand Pd:L (1:4)	Product	Yield % ^b
1	$\text{C}_4\text{F}_9\text{I}$ (12a)	PPh_3	$\text{Ph}_2\text{AsC}_4\text{F}_9$ (13)	47
2		$\text{AsPh}_2(\text{bph})$		45
3	$\text{C}_6\text{F}_{13}\text{I}$ (12b)	PPh_3	$\text{Ph}_2\text{AsC}_6\text{F}_{13}$ (14)	43
4		$\text{AsPh}_2(\text{bph})$		55
5	$\text{C}_8\text{F}_{17}\text{I}$ (12c)	PPh_3	$\text{Ph}_2\text{AsC}_8\text{F}_{17}$ (15)	65
6		$\text{AsPh}_2(\text{bph})$		87
7	$\text{C}_{10}\text{F}_{21}\text{I}$ (12d)	PPh_3	$\text{Ph}_2\text{AsC}_{10}\text{F}_{21}$ (16)	48
8		$\text{AsPh}_2(\text{bph})$		78

^aReaction conditions: Ph_2As^- anion was prepared in liquid ammonia (300 mL) from AsPh_3 (1 mmol) and Na metal (2 mmol); then $n\text{-Bu}_3\text{SnCl}$ (1 mmol) was added. The cross-coupling reaction was carried out with $R_f\text{I}$ (0.7 mmol), $(\text{PPh}_3)_2\text{PdCl}_2$ (10 mol%), ligand (Pd:L 1:4) and CsF (3 equiv) for 24 h in toluene at reflux. ^bCG yields. The yields reported represent at least the average of two reactions.

Table 2. Pd-catalyzed cross-coupling reaction with $n\text{-Bu}_3\text{SnAsPh}_2$ (**1**) and $R_f\text{I}$ (**12a-d**) as electrophile.^a

CONCLUSION AND PERSPECTIVE

A convenient route that allows for C-As bond formation, through an efficient one-pot two-step Pd-catalyzed arsination with $n\text{-Bu}_3\text{SnAsPh}_2$ (**1**) and different electrophiles, has been developed. This methodology includes some notable features: (i) starting with the commercially available, air-stable and inexpensive triphenylarsine; (ii) the feasibility of a one-pot reaction; (iii) a high-yield preparation method of functionalized triarylsarsines; (iv) a high functional group compatibility. Functionalized arsines can be obtained from aryl iodides or triflates. Notably, $R_f\text{I}$ were viable electrophiles in the Pd-

catalyzed cross-coupling and the synthesis of Ph_2AsR_f by this reaction proved a new versatile tool.


The interest in this direct and simple methodology is further increased

by the potential application of the final products as a new class of ligands.

Development of a new methodology to obtain functionalized arsines by Pd-catalyzed arsination

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