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# Bulky Monodentate Biphenylarsine Ligands: Synthesis and Evaluation of Their Structure Effects in the Palladium-Catalyzed Heck Reaction

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**Keywords:** Homogeneous catalysis / Cross coupling / Palladium / Ligand design / As ligands / Microwave chemistry

Biphenyl-based arsine ligands were prepared in two-step fashion by Pd-catalyzed arsination and microwave-assisted Suzuki–Miyaura coupling, providing sterically demanding arsine ligands in overall isolated yields up to 82 % as air-stable solids. Short reaction times were achieved with the assistance of microwave irradiation in the direct and simple described protocol for the synthesis of biarylarsine ligands. The activities of the biphenyl arsine ligands were explored in Pd-catalyzed Heck coupling. As a general trend, the ligands with "blocked" *ortho*-positions on the non-arsine-containing ring of the biphenyl backbone performed more efficiently in the coupling reaction. This catalytic system allowed several interesting stilbenes to be obtained in very good yields.

## Introduction

For the design of more selective and stable catalysts with high turnovers, the development of appropriate ligands is one of the first, and most important, factors to consider. In the field of rational ligand design, the biaryl unit is firmly established as a key structure in a variety of important monodentate[1] and bidentate[2] phosphine ligands, many of which are widely used for transition-metal-catalyzed C–C and C–heteroatom bond formation. The electron-rich biaryl monophosphines, first introduced by Buchwald,[3] have been shown to be excellent ligands for numerous Pd-catalyzed processes.[4] Catalyst performances for coupling reactions with Buchwald-type biphenyl-based phosphines have been further improved by introducing substituents on the *ortho*-positions on the non-phosphine-containing arene units, as well as by increasing the substituents' steric bulk.[5]

Because the biaryl motif appears to be successful as a basis for many ligands, it has been used as a main building block to develop alternative ligand systems.[6] We have also incorporated this basic design concept and recently described the first synthesis of new biphenyl-based arsine ligands by an approach including Pd-catalyzed arsination[7,8] and subsequent Suzuki–Miyaura coupling as the key synthetic tool for biaryl construction.[9] The newly prepared biphenyl-based ligand, with methoxy groups in the *ortho*-positions on the non-arsine-containing ring of the biphenyl backbone, showed outstanding activity in Pd-catalyzed arsination with perfluoroalkyl iodides ($R_fI$).[9]

It is important to note that, in contrast to the many phosphine-based ligands that have been synthesized, relatively few arsine ligands have been prepared and applied in catalysis, probably mainly due to the lack of readily available As-containing precursor compounds. Arsines have been shown to be excellent supporting ligands, and there are several examples in which they have provided more active or selective catalysts than phosphines in transition-metal-catalyzed reactions,[9] due to their reactivity and selectivity in addition to their high stability towards air, with respect to the structurally related phosphines.[10]

The Pd-catalyzed Heck reaction has become one of the most powerful tools as a general methodology for $sp^2$–$sp^2$ C–C bond formation,[11,12] finding wide application in the synthesis of valuable molecules and complex natural products. It is probably one of the most frequently applied Pd-catalyzed coupling reactions in the fine-chemical and pharmaceutical industries.[13] A comprehensive overview of the Heck reaction has recently been published.[14] The traditional Heck reaction is typically performed with a homogeneous catalyst and use of a phosphorus ligand in the presence of a suitable base.[15] However, numerous other catalysts based on electronically and structurally diverse ligands, such as different palladacycles,[16] and non-phosphine Pd catalysts, such as N-heterocyclic carbenes (NHCs)[17] and carbocyclic carbenes,[18] have been employed.

A number of studies have shown that sterically demanding phosphine ligands can function as active catalysts in Pd-catalyzed Heck olefination,[15d,15f,15j] with biphenyl-based phosphines included among them.[19] Furthermore, bulky phosphoramidite-based palladium catalysts have

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shown high activity with aryl iodides.[20] Studies on ligand effects and kinetics measures revealed that a suitable balance between the steric and the electronic properties of the ligands was responsible for the catalyst performance.

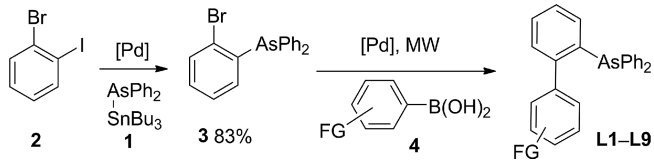
On the other hand, arsine ligands have also been used in the Pd-catalyzed Heck reaction.[21] Intramolecular asymmetric Heck reactions based on binaphthyl BINAs[22a] and BINAPAs[22b] ligands have been reported. Only a few examples in which $AsPh_3$ was determined to be a particularly useful ligand in the Pd-catalyzed Heck reaction are available in the literature.[23] Moreover, Heck-related reactions, such as Heck-type hydroarylation reactions of bi-, tri-, and tetracyclic alkenes in the presence of $AsPh_3$ as a highly efficient ligand have also been reported.[24] Recently, triphenylarsinyl-functionalized N-heterocyclic carbene ligands have been synthesized and applied in Heck, hydro-Heck, and π,σ domino-Heck reactions.[10] With these arsine ligands less Pd and ligand were needed than in the case of the phosphine analogue N-heterocyclic carbenes in order to obtain similar yields. Arsines are known to have coordination modes similar to those of phosphines; however, they are recognized to be poorer σ-donors than phosphines, and this leads to contrasting steric and electronic effects on coordination spheres different from those of phosphines. Pringle and co-workers investigated the catalytic activity of Pd complexes of a series of bulky arsine ligands, exploring their stereoelectronic effects.[25] They established that Pd-arsine complexes were generally more active in the Heck reaction than analogous complexes resulting from phosphine.

As part of our ongoing work on the synthesis and catalytic activity of arsine ligands, here we report an improvement in the synthetic methodology for production of biphenyl-based arsine ligands through the use of microwave (MW) irradiation assistance of Suzuki–Miyaura coupling for biaryl construction. Therefore, a fast and efficient methodology to obtain a family of sterically demanding arsine ligands in high yields is available. Additionally, as a first approach to exploring the application of these ligands in transition-metal-catalyzed reactions, we studied the scope of the biphenylarsine ligands in Pd-catalyzed Heck olefination with aryl bromides and iodides by evaluating their catalytic performance.

## Results and Discussion

### Synthesis of Biphenyl-Based Arsine Ligands by Microwave-Assisted Suzuki–Miyaura Coupling

The synthesis of the biarylarsine ligands was carried out by a strategy including initial Pd-catalyzed arsination, followed by MW-assisted Suzuki–Miyaura coupling as the key synthetic tool for biaryl construction (Scheme 1). (2-Bromophenyl)diphenylarsine (**3**) was employed as a synthetic intermediate for the synthesis of biarylarsine ligands. Arsination of the stannane $nBu_3SnAsPh_2$ (**1**) with 1-bromo-2-iodobenzene (**2**), catalyzed by $(PPh_3)_2PdCl_2$ in toluene, afforded the arsine **3** in 83% isolated yield (Scheme 1).[7b,9]



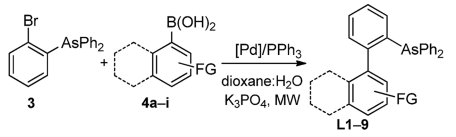

Scheme 1. Synthetic strategy for biphenylarsine ligands.

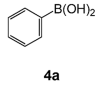
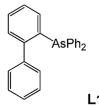
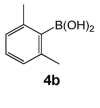
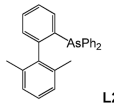
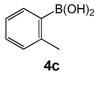
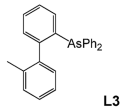
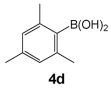
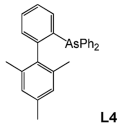
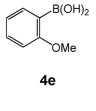
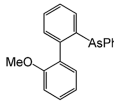
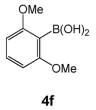
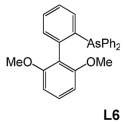
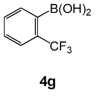
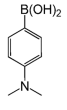
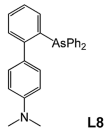
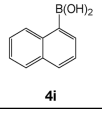
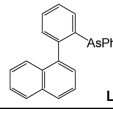
The Pd-catalyzed Suzuki–Miyaura reaction has emerged as an extremely efficient method for the construction of C–C bonds.[13a,26] It is an important tool in total synthesis and in medicinal chemistry, as well as in the synthesis of pharmaceuticals and fine chemicals.[27,28] Microwave-assisted heating under controlled conditions has been proven as an invaluable technology for organic synthesis[29] and its application has in several cases led to acceleration of reaction rates and to improvements in yields and selectivity.[30] MW irradiation has been used in Pd-catalyzed coupling reactions,[31] in particular in Suzuki–Miyaura reactions,[32] and can today be considered an efficient synthetic methodology.

Suzuki–Miyaura coupling to build the biaryl structure of biarylarsine ligands was carried out with the aid of MW irradiation (Scheme 1). In the first instance, Suzuki–Miyaura reactions between arsine **3** and phenylboronic acid (**4a**) and between **3** and 2,6-dimethylphenylboronic acid (**4b**, as a model sterically hindered boronic acid substrate) under MW irradiation conditions were examined (see the Supporting Information). We started with optimized reaction conditions based on our previous results[9] and explored different methods and systems for the MW irradiation coupling, such as dynamic heating at fixed temperature or fixed power in sealed vessels (use of sealed vessels being preferred in order to accomplish significant rate enhancements[30]). The best results were achieved with the MW dynamic method at a fixed 150 °C. Under the optimized conditions, the coupling reaction between arsine **3** and boronic acid **4a** in the presence of $K_3PO_4$ and catalyzed by $Pd(OAc)_2$ in dioxane/$H_2O$ under nitrogen afforded **L1** (BAs) in 93% yield in only 10 min (Entry 1, Table 1). This is a significant improvement on the 24 h required for the conventional process (time and yields for thermal reaction performed under the same reaction conditions are provided in square brackets in Table 1).[9] A screening was performed to determine the optimum Pd source and loading, ligand, and base for the sterically hindered boronic acid **4b** (see the Supporting Information).[33,34] The optimized conditions were with $Pd(dba)_2$/$PPh_3$ and $K_3PO_4$ as a base with an extra addition of boronic acid **4b** during the reaction and extension of the reaction time to 80 min (Entry 2, Table 1). Once we had thoroughly optimized the MW-assisted reaction conditions, Suzuki–Miyaura couplings with arylboronic acids **4a**–**i**, bearing different substituents, and bromoarsine **3** were carried out (Table 1). These reactions gave biaryl arsine ligands **L3**–**9** in excellent yields (70–99%). Thus, biphenyl-based arsine ligands **L1**–**9** could be readily prepared in two-step fashion in overall isolated yields of up to 82% as air-stable solids. Short reaction times were achieved by using MW-

Table 1. Suzuki–Miyaura coupling with (2-bromophenyl)diphenylarsine (**3**) and substituted arylboronic acids **4a**–**i**.[a],.[b]




| Entry | Boronic acid | Catalyst (loading) | Time [min][b] | Product | Yield (%)[c] |
|---|---|---|---|---|---|
| 1 |  **4a** | $Pd(OAc)_2$ (1 mol-%) | 10 [1440] |  **L1** | 93 (85) [98] |
| 2[d] |  **4b** | $Pd(dba)_2$ (3 mol-%) | 80 [2880] |  **L2** | 70 (65) [61] |
| 3 |  **4c** | $Pd(OAc)_2$ (1 mol-%) | 20 [1440] |  **L3** | 96 (88) [98] |
| 4[d] |  **4d** | $Pd(dba)_2$ (3 mol-%) | 100 [2880] |  **L4** | 71 (62) [89] |
| 5 |  **4e** | $Pd(OAc)_2$ (1 mol-%) | 20 [1440] |  **L5** | 90 (83) [96] |
| 6 |  **4f** | $Pd(OAc)_2$ (1 mol-%) | 40 [1440] |  **L6** | 91 (83) [83] |
| 7 |  **4g** | $Pd(OAc)_2$ (1 mol-%) | 50 |  **L7** | 86 (75) |
| 8 |  **4h** | $Pd(OAc)_2$ (1 mol-%) | 50 |  **L8** | 99 (92) |
| 9 |  **4i** | $Pd(OAc)_2$ (1 mol-%) | 10 [1440] |  **L9** | 80 (70) [80] |

[a] Reaction conditions: the coupling reactions were carried out with bromoarsine **3** (1 equiv.), a boronic acid **4** (1.5 equiv.), a [Pd] species, a phosphine ligand (Pd/L, 1:4), a base (2 equiv.), and dioxane/$H_2O$ (4:1, 5 mL) at a fixed 150 °C by the MW dynamic method in sealed vessels under nitrogen. [b] To simplify comparison between Suzuki–Miyaura reactions conducted with conventional and MW-assisted heating, the time and yields for normal thermal reactions carried out under the same conditions are provided in square brackets; for more detail see ref.[9] [c] GC yields. Isolated yields are given in parentheses (averages of two or more experiments). In square brackets the yields for the normal thermal conditions are given. [d] These coupling reactions were carried out with the appropriate boronic acid **4** (1.5 equiv.) and an extra 1.5 equiv. of **4** added after either 40 min (**4b**) or 50 min (**4d**). The reaction times were increased to 80 min for **L2** and 100 min for **L4**.

assisted Suzuki–Miyaura coupling according to the described protocol for the synthesis of biarylarsine ligands.

## Catalytic Activity of Biphenyl Arsine Ligands in Pd-Catalyzed Heck Reaction

With the set of biphenyl-based arsine ligands to hand, and in view of the high performances of bulky triarylarsine ligands in the Heck reaction,[10,25] this coupling reaction was selected as a model system for evaluation of the catalytic activity of biphenylarsine ligands. To determine the performance of these ligands, the challenging Heck reaction between *p*-bromotoluene (**5a**) and styrene (**6a**) was chosen as the model reaction (Figure 1). In this reaction neither the aryl halide nor the alkene is activated, so because of the low reactivities of the coupling partners a more demanding catalytic activity in terms of the Pd/L complexes is required. To initiate this study the ligand **L6** (diOMeBAs) was selected for evaluation of the reactions conditions, because in a previous work **L6** had shown outstanding activity in a Pd-catalyzed coupling reaction.[9] A broad range of reaction conditions – namely, the solvent, base, Pd source, Pd/ligand ratio, temperature, and reaction time – were systematically evaluated. Identification of the most suitable solvent for this reaction showed that the reaction rates were significantly enhanced by using polar nonprotic solvents, with DMF being the solvent of choice. It seems that the coordination abilities of the solvents play an important role in the catalyst activity, probably in connection with catalyst stability. Moreover, this is consistent with previous reports by Beller[35] and Herrmann,[36] in which polar nonprotic solvents tended to give the best results for Heck coupling.

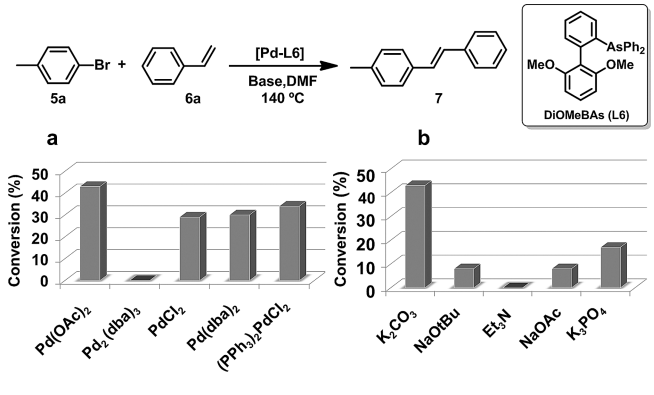



Figure 1. Optimization of the reaction conditions with *p*-bromotoluene (**5a**) and styrene (**6a**): (a) Pd source, and (b) base.

The most relevant results achieved in the optimization of Pd sources and bases are shown in Figure 1. The nature of the Pd precursor proved important, with the best results being obtained with $Pd(OAc)_2$ (Figure 1, a). Once the palladium source was established, the base effect was studied. Significant increases in the degree of conversion and selectivity were observed when the inorganic base $K_2CO_3$ was employed (Figure 1, b).

The use of 1 mol-% $Pd(OAc)_2$ and a Pd/L ratio of 1:2 were the best conditions to achieve the Heck product. Ad-

dition of fewer or more equivalents of ligand (Pd/L ratios of 1:1 and 1:3) decreased the catalyst activity. Thus, with employment of the ligand **L6**, $K_2CO_3$, $Pd(OAc)_2$, and DMF at 140 °C, the degree of conversion of **5a** into the stilbene **7** was 43% with a high selectivity in favor of the *trans* product (*trans*/*gem*/*cis* 38:4:1). It was previously reported that the reaction between **5a** and styrene in the presence of the ligand 2-diphenylphosphino-2-methylbiphenyl under similar reaction conditions took one hour to convert 90% of the reagent, but the stereoselectivity was remarkably poor, with a mixture of stilbenes being produced.[19a]

The activity of the synthesized biphenyl-based arsine ligands in Heck coupling was explored. In addition, $AsPh_3$ and the dimethoxybiphenyl-2-diphenylphosphine ligand (**L10/Phos**),[37] a phosphorus ligand homologue of **L6**, were screened to compare their activity in the Heck reaction (Figure 2). As can be seen from Figure 2, the ligand structure had a significant effect on the degree of conversion of substrate **5a**. The ligandless Heck arylation with **6a** proceeded only with difficulty. It is important to note that all reactions led to product **7** with high selectivity for the *trans* product. Moreover, the efficiency of catalysts derived from biphenyl ligands could be attributed to their steric bulk favoring the formation of the active monophosphine complex $LPd^0$.[38]

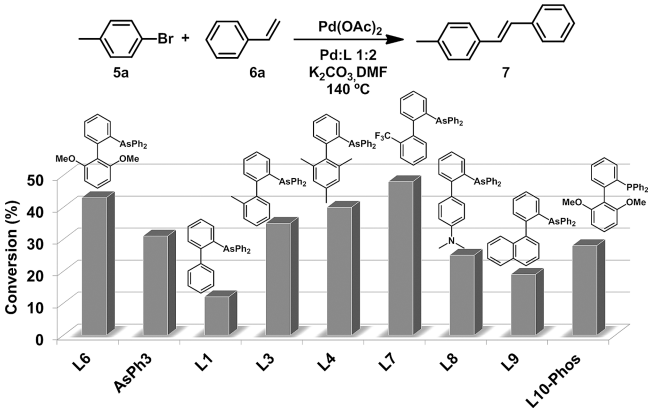



Figure 2. Evaluation of arsine and phosphine ligands in the coupling reaction between *p*-bromotoluene (**5a**) and styrene (**6a**).

A notable inhibition of the reaction was observed when the arsine ligand **L1** (BAs) was used; it provided a decelerating effect on the Heck reaction, possibly due to the formation of stable palladacycles.[39] The results clearly showed that the substituents on the non-arsine-containing ring of the biphenyl backbone of the ligand indeed have a significant impact on the efficacy of the reaction [**L1** vs. **L3** (MeBAs), **L4** (triMeBAs), **L6** (diOMeBAs), and **L7** ($CF_3$BAs)]. Ligands **L6** and **L7** provided higher yields of the alkene product, being the most active ligands, although exhibiting very different electronic characteristics.

Substitution of hydrogen atoms with alkoxide groups proved to be beneficial to catalyst stability and created more reactive catalyst for coupling processes.[5,40] In view of our results, Pd-O interactions with ligand **L6** could contribute to the stability, and thus to the efficiency, of the catalysts relative to other biarylarsine ligands. On the other hand, with **L7**, a more electron-withdrawing arsine, the observed high activity could be attributable to the formation of a less electron-rich Pd complex, which could easily promote the alkene coordination or insertion.[20]

In order to compare electron-donating character, as well as catalytic activity, the phosphine ligand **L10-Phos** was also employed in the Heck coupling of bromotoluene (**5a**) and styrene (**6a**). When **L10-Phos** was allowed to react under the optimized conditions a level of conversion lower than that seen in the reaction in the presence of **L6** was found (Figure 2). In consequence, although arsines are poorer σ-donors/better π-acceptors than the analogous phosphines, the catalysts derived from Pd/biphenyl-arsine complexes were particularly efficient in the Heck reaction, in agreement with the results obtained by Pringle and coworkers.[25] This is not a new finding: previous studies had suggested that the greater π-acceptor ability of sterically bulky phosphite ligands increased Heck reaction rates.[15j] Furthermore, phosphoramidite ligands [$P(OR)_2NR$] with a suitable balance between steric and basicity properties provided faster overall Heck reactions with aryl iodides.[20]

In an attempt to determinate the effect of the ligand structure over the catalytic cycle, the Pd-arsine catalysts were also evaluated with 4-bromoacetophenone (**5e**), an activated aryl halide, as electrophile (Figure 3). With this substrate, ligands **L6**, **L7**, and **L4** gave the corresponding coupling product in excellent yields, whereas the ligand **L1** showed a lower activity. On comparing this with the results obtained with the non-activated 4-bromotoluene (**5a**) (Figure 2), it might be inferred that the oxidative addition could be the partially determinate step in this Heck coupling reaction.

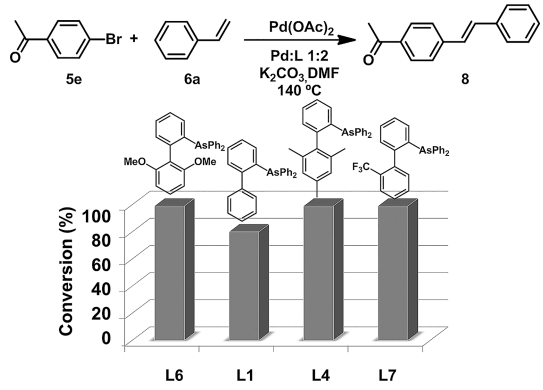


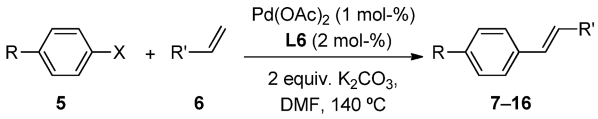

Figure 3. Ligand evaluation in the coupling reaction between *p*-bromoacetophenone (**5e**) and styrene (**6a**).

It should be considered that an overall catalytic transformation consists of several elementary steps with different requirements that will be influenced in different ways by ligands. As expected, with a less electron-rich arsine ligand the oxidative addition to aryl bromides could become a slower step. However, a less electron-rich Pd complex derived from arsine ligands could be beneficial for the catalyst performance during the alkene coordination or insertion.[20]

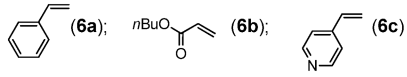
With the aim of exploring the scope of the catalytic system Pd·**L6**, several aryl halides and alkenes were examined in the Heck coupling reaction under the optimized conditions ($K_2CO_3$, 1 mol-% $Pd(OAc)_2$, 2 mol-% **L6**, 2 equiv. $K_2CO_3$, DMF, 140 °C). The results are summarized in Table 2.

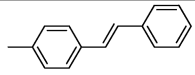
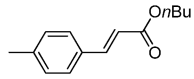
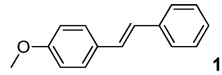
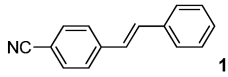
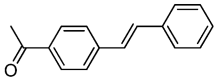
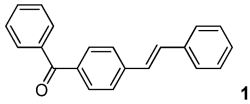
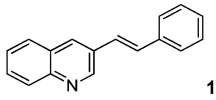
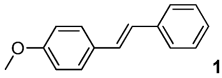
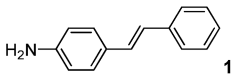
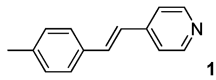
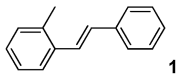
Table 2. Heck coupling between aryl halides and alkenes catalyzed by Pd·**L6**.[a]




**5** **6** **7–16**

**5**: X = Br, R = $CH_3$ (**5a**); X = I, R = $CH_3$ (**5b**); X = I, R = $OCH_3$ (**5c**); X = Br, R = CN (**5d**), X = Br, R = $COCH_3$ (**5e**); X = Br, R = COPh (**5f**); 3-bromoquinoline (**5g**); X = Br, R = $OCH_3$ (**5h**); X = I, R = $NH_2$ (**5i**); X = I, R = 2-$CH_3$ (**5j**);

**6**:  (**6a**); (**6b**); (**6c**)

| Entry | 5 | 6 | Time [h] | Product | Yield (%)[b] | Conv. (%) |
|---|---|---|---|---|---|---|
| 1 | **5b** | **6a** | 2.5 |  **7** | 78 | 100 |
| 2 | **5b** | **6b** | 2.5 |  **9** | 96 | 100 |
| 3 | **5c** | **6a** | 24 |  **10** | 84 | 93 |
| 4 | **5d** | **6a** | 2 |  **11** | 90 | 100 |
| 5 | **5e** | **6a** | 2.5 |  **8** | 95 | 100 |
| 6 | **5f** | **6a** | 2.5 |  **12** | 83 | 100 |
| 7 | **5g** | **6a** | 2.5 |  **13** | 76 | 100 |
| 8[c] | **5h** | **6a** | 24 |  **10** | 64 | 71 |
| 9 | **5i** | **6a** | 5 |  **14** | 70 | 95 |
| 10 | **5a** | **6c** | 24 |  **15** | 32 | 37 |
| 11[d] | **5j** | **6a** | 24 |  **16** | 88 | 95 |

[a] Reaction conditions: 1 mmol of ArX **5**, 1.5 mmol of an alkene **6**, 1 mol-% $Pd(OAc)_2$, 2 mol-% **L6**, 2 mmol $K_2CO_3$, 4 mL of DMF, 140 °C, under nitrogen. [b] NMR yields for the *trans* products. The yields reported represent the averages of at least two reactions. [c] $Pd(OAc)_2$, 3 mol-%. [d] GC yields.

All reactions led to the corresponding alkenes with high selectivity for the *trans* products. Total conversion and high yields of the alkene products were obtained with activated and deactivated aryl iodides and styrene (**6a**) or butyl acrylate (**6b**) as coupling partners (Entries 1–3 and 9, Table 2). Likewise, an *ortho*-substituted arene provided the desired product in very good yield (Entry 11, Table 2). Note that *trans*-stilbene **14** has been found to exhibit versatile biological activities.[41]

When aryl bromides activated with electron-withdrawing groups or based on a nitrogen heterocycle were employed, complete conversion and very good yields of the coupling products in short reaction times were observed (Entries 4–7, Table 2). The synthesis of substituted heteroaryl derivatives is of great importance; however, only a few examples of heteroaryl halides in Heck reactions have been reported.[42] Results comparable to ours were obtained with the same bromoquinoline **5g** and employment of higher catalyst loadings or longer reaction times.[41]

In addition, the heterocyclic alkene 4-vinylpyridine (**6c**) was employed as coupling partner, and afforded a low yield of the stilbene **15**[43] (Entry 10, Table 2). Likewise, when *p*-bromoacetophenone (**5e**) was allowed to react with the disubstituted olefin 1,1-diphenylethylene under the optimized conditions, the desired coupling product 1-[4-(2,2-diphenylvinyl)phenyl]ethanone (**17**) was afforded in only 5% yield.

Thus, the synthesized biphenyl-based arsine ligands can form catalytically active complexes with Pd that allow Heck coupling to be performed with a wide range of electrophiles. With activated electrophiles, the complex Pd·**L6** gave the coupling products in excellent yields, with high selectivity, in relative short reaction times, and with low catalyst loadings. With more demanding electrophiles, good yield of alkene products can be obtained.

## Conclusions

In summary, the synthesis of biphenylarsines was achieved by a two-step, high-yielding, Pd-catalyzed process from commercially available starting materials. MW-assisted Suzuki–Miyaura coupling was employed to build the biaryl structure of arsine ligands in short reaction times. Sterically demanding arsine ligands were obtained in overall isolated yields of up to 82% as air-stable solids. By this methodology, the properties of these ligands can be varied according to the steric and electronic effects associated with the substituents in the biaryl backbone.

The activity of the synthesized biphenyl-based arsine ligands in the Pd-catalyzed Heck reaction was explored. It was found that ligands with "blocked" *ortho*-positions on the non-arsine-containing ring of the biphenyl backbone were more efficient in catalyzing the coupling reaction. This effect could be a combination of factors, such as their steric bulk and the absence of *ortho* hydrogens, which prevents the formation of palladacycles. In addition, the Pd-O interactions with ligand **L6** could contribute to the stability, and

thus to the higher catalytic efficiency, of the Pd·**L6** complex. Although arsines are less bulky and poorer σ-donors than phosphines, the presence of the arsine group has an important effect on the catalytic activity; the biphenylphosphine homologue of ligand **L6** showed lower activity in the Heck reaction.

Finally, Pd·**L6** proved to be an effective catalyst for performing coupling between aryl iodides or bromides and several alkenes. In addition, with demanding substrates such as heterocycles or *ortho*-substituted and non-activated aryl halides, good results were achieved.

On the basis of the obtained results, the potential of biphenyl-based arsine ligands in coupling reactions was established. Further studies to explore the scope of these ligands in transition-metal-catalyzed reactions are currently in progress.

## Experimental Section

**General Methods:** All reactions were performed under nitrogen with magnetic stirring. All solvents were analytical grade and distilled before use. Air- and moisture-sensitive liquids and solutions were transferred by cannula and syringe to introduce them into Schlenk tubes. Toluene and dioxane were distilled under nitrogen from sodium benzophenone. DMF was stored under molecular sieves and then distilled under reduced pressure with bubbling of nitrogen. (2-Bromophenyl)diphenylarsine (**3**) was prepared as previously reported, from the corresponding 2-bromoiodobenzene.[7b] 2-Diphenylphosphino-2′,6′-dimethoxybiphenyl (**L10-Phos**) was prepared by literature methods.[37]

GC analyses were performed on a gas chromatograph with a flame ionization detector and a HP-1 25 m × 0.20 mm × 0.25 μm column. $^1$H, $^{13}$C, $^{31}$P, and $^{19}$F NMR spectra were recorded in $CDCl_3$ at 400 MHz, 101 MHz, 121 MHz, and 377 MHz, respectively, with a Bruker Advance II 400 spectrometer. Coupling constants (*J*) are given in Hz. GC–MS analyses were performed with a GC/MS QP 5050 spectrometer equipped with a VF-5ms column (25 m × 0.20 mm × 0.33 μm). Ionization was achieved by electronic impact (70 eV) and positive-mode detection setup. HRMS were recorded with Bruker, Micro TOF Q II equipment, operated with an ESI source in (positive/negative) mode, with use of nitrogen as nebulizing and drying gas and sodium formate (10 mM) for internal calibration. Melting points were dertermined with Büchi 510 equipment and are uncorrected. Microwave-induced reactions were performed with a single-mode instrument (CEM Focused Microwave TM Synthesis System, Model Discover) equipped with a noncontact infrared sensor to measure the temperature, a direct pressure control system to measure the pressure of the reaction vessel content, and cooling with compressed air.

**Typical Procedure for Pd-Catalyzed Suzuki–Miyaura Reaction under MW Irradiation Conditions:** The following reaction procedure is representative of all Suzuki–Miyaura cross-coupling reactions. $Pd(OAc)_2$ (1 mol-%, 0.01 mmol), $PPh_3$ (Pd/L, 1:4, 0.04 mmol), (2-bromophenyl)diphenylarsine (**3**, 1 mmol), the appropriate arylboronic acid (**4a**–**i**, 1.5 mmol), and $K_3PO_4$ (2 mmol) were placed in a 10 mL MW vessel containing a magnetic stirrer and equipped with an adapter with a nitrogen inlet, followed by dioxane (4 mL) and water (1 mL). The vessel was sealed with a pressure lock, and the mixture was heated by a dynamic method at 150 °C (fix temperature method) for the time reported on Table 2, in a CEM Discover MW reactor. After having been allowed to cool to room temperature, the mixture was quenched by addition of water and extracted three times with $CH_2Cl_2$ (30 mL each). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered, and concentrated under reduce pressure. The residue was purified by silica gel column chromatography to furnish the desired biarylarsine product.

The products were characterized by $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR, and $^{19}$F NMR, 2D NMR, GC–MS, and HRMS. All the spectroscopic data agreed with those previously reported for compound **L1**[7b] and for compounds **L2**–**L6** and **L9**.[9]

**Representative Procedure for Pd-Catalyzed Heck Reaction:** The following reaction procedure is representative for all Heck reactions. A mixture of $Pd(OAc)_2$ (1 mol-%, 0.01 mmol), the appropriate ligand (Pd/L, 1:2, 0.02 mmol), the appropriate aryl halide (1 mmol), the appropriate alkene (1.5 mmol), and $K_2CO_3$ (2 mmol) in DMF (4 mL) was stirred in a Schlenk tube under nitrogen at 140 °C for the desired time. After having been allowed to cool to room temperature, the mixture was quenched by addition of water and then extracted three times with ethyl acetate (30 mL each). The combined organic layers were dried with anhydrous $Na_2SO_4$, filtered, and concentrated under reduce pressure. The coupling product was purified by silica-gel column chromatography. All the spectroscopic data for the coupling products **7**, **8**, and **11**,[44] **9**,[45] **10**,[46] **12**,[47] **13**,[42] **14**,[41] **15**,[48] and **16**[49] agreed with those previously reported.

**2-Diphenylarsino-2′-(trifluoromethyl)biphenyl (L7):** Compound **L7** was obtained by the General Procedure for Pd-catalyzed Suzuki–Miyaura reactions under MW irradiation conditions and isolated from the reaction mixture by silica gel column chromatography (petroleum ether/dichloromethane 80:20) as a white solid (m.p. 127.2–128.4 °C), in 75% yield. After crystallization from $CH_3CN$, cubic-type crystals were obtained. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.75 (d, *J* = 7.6 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 1 H), 7.37–7.23 (m, 12 H), 7.19–7.16 (m, 3 H), 6.92 (d, *J* = 7.6 Hz, 1 H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 144.97, 140.91 (d, *J* = 1.7 Hz, 1 C), 140.14, 139.93, 139.68, 134.08, 134.02, 133.67, 132.66, 130.73, 129.74, 129.12 (q, *J* = 29.0 Hz, 1 C), 128.74, 128.66, 128.55, 128.33, 128.25, 127.92, 127.86, 126.04 (q, *J* = 5.2 Hz, 1 C), 124.21 (q, *J* = 272.6 Hz, 1 C) ppm. $^{19}$F NMR (377 MHz, $CDCl_3$): $\delta$ = –57.88 ppm. MS: *m*/*z* (%) = 451 (11), 450 (25), 382 (7), 381 (17), 227 (17), 202 (12), 201 (9), 184 (16), 183 (100), 181 (5), 171 (9), 154 (16), 152 (15), 151 (12). HRMS (EI): calcd. for $C_{25}H_{18}AsF_3$ 451.0655 $[M + H]^+$; found 451.0649.

**2-Diphenylarsino-4′-*N*′,*N*′-dimethylbiphenyl (L8):** Compound **L8** was obtained by the General Procedure for Pd-catalyzed Suzuki–Miyaura coupling under MW irradiation conditions. Product **L8** was isolated from the reaction mixture by silica gel column chromatography (petroleum ether/ethyl acetate 95:5) as a white solid (m.p. 156.1–157.0 °C), in 92% yield. After crystallization from $CH_3CN$, needle-type crystals were obtained. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.35 (d, *J* = 3.8 Hz, 2 H), 7.31–7.27 (m, 10 H), 7.21–7.17 (m, 1 H), 7.13–7.09 (m, 3 H), 6.67–6.63 (m, 2 H), 2.95 (s, 6 H) ppm. $^{13}$C NMR (101 MHz, $CDCl_3$): $\delta$ = 149.82, 148.53, 140.86, 138.78, 134.56, 134.02, 130.55, 130.46, 130.06, 128.66, 128.62, 128.25, 126.89, 111.75, 40.63 ppm. MS: *m*/*z* (%) = 425 (18), 281 (21), 270 (21), 209 (13), 208 (18), 207 (100), 133 (13), 96 (18), 73 (22), 44 (50), 43 (11), 40 (28). HRMS (EI): calcd. for $C_{26}H_{24}AsN$ 426.1203 $[M + H]^+$; found 426.1197.

**2-Diphenylphosphino-2′,6′-dimethoxybiphenyl (L10-Phos):**[37] Compound **L10-Phos** was prepared by the methodology previously describe in the literature.[32] Product **L10-Phos** was isolated as a white solid, after crystallization with ethanol. $^1$H NMR (400 MHz,

$CDCl_3$): $\delta$ = 7.41, (td, $J$ = 7.4, 1.2 Hz, 1 H), 7.29–7.17 (m, 13 H), 7.14 (ddd, $J$ = 7.7, 3.8, 0.8 Hz, 1 H), 6.52 (d, $J$ = 8.4 Hz, 2 H), 3.44 (s, 6 H) ppm. $^{13}C$ NMR (101 MHz, $CDCl_3$): $\delta$ = 158.19 (s), 141.79 (d, $J$ = 13.02 Hz), 138.58 (d, $J$ = 13.02 Hz), 138.15 (d, $J$ = 9.8 Hz), 134.44 (d, $J$ = 1.72 Hz), 134.28 (d, $J$ = 19.8 Hz), 131.25 (d, $J$ = 6.06 Hz), 129.47 (s), 129.13 (s), 128.35 (d, $J$ = 6.46 Hz), 128.28 (d, $J$ = 6.97 Hz), 127.59 (s), 119.52 (d, $J$ = 6.63 Hz), 103.92 (s), 55.70 (s) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = –12.55 ppm.

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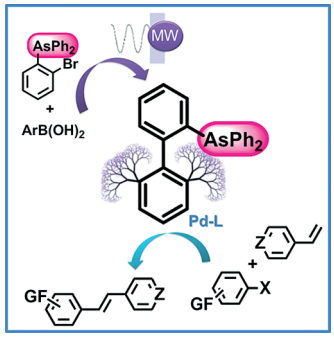
**Arsine Ligand Design**

Sterically demanding biphenyl-based arsine ligands were prepared in high overall yields by microwave-assisted Suzuki–Miyaura coupling. The ligands were evaluated in the Pd-catalyzed Heck coupling reaction; the most active were those with "blocked" *ortho*-positions on the non-arsine-containing ring of the biphenyl backbone.






**Keywords:** Homogeneous catalysis / Cross coupling / Palladium / Ligand design / As ligands / Microwave chemistry