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1,2-Functionalized Imidazoles as Palladium Ligands: An Efficient and Robust Catalytic System for the Fluorine-Free Hiyama Reaction

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Dedicated to Professor Fernando Albericio on the occasion of his 60th birthday

Keywords: Synthetic methods / Nitrogen heterocycles / Palladium / Ligand design / Cross-coupling

A variety of hydroxy- and amino-functionalized imidazoles were prepared from 1-methyl- and 1-(diethoxymethyl)imidazole by means of isoprene-mediated lithiation followed by reaction with an electrophile. These compounds in combination with palladium acetate were screened as catalyst systems for the Hiyama reaction under fluorine-free conditions using microwave irradiation. The systematic study of the catalytic system showed 1-methyl-2-aminoalkylimidazole derivative **L1** to be the best ligand, which was employed under solvent-free conditions with a 1:2 Pd/ligand ratio and TBAB (20 mol-%) as additive. The study has revealed an interaction between the Pd/ligand ratio and the amount of TBAB. The established catalytic system presented a certain degree of robustness, and it has been successfully employed in the coupling of a range of aryl bromides and chlorides with different aryl siloxanes. Furthermore, both reagents were employed in an equimolecular amount, without an excess of organosilane.

Introduction

The palladium-catalyzed carbon–carbon bond formation between organosilicon reagents and organic halides, the Hiyama cross-coupling reaction,[1–3] was first described in 1988.[4] This type of transformation is particularly appealing due to the low toxicity, high stability, and ease of handling of silicon reagents. However, the strong carbon–silicon bond requires activation to enable transmetalation. Thus, activation of the organosilicon compounds was successfully achieved by Hiyama's group by employing fluoride ions, which produce the pentacoordinate silicon species (the so-called hypervalent silanes) necessary for the transmetalation step.[5] Indeed, the electron density at silicon decreases with reduced s-character of the orbital combination, whereas the electron density at the silicon ligands is increased.[6] This enhanced reactivity of pentacoordinate silicon is supported by calculations that show that the positive charge on the central silicon atom is maintained, or even increased, by coordination of the fifth ligand.[7,8] Regarding the synthesis of unsymmetrical biaryls[9] by means of Hiyama reaction, tetrabutylammonium triphenyldifluorosilicate was productively coupled with aryl iodides and aryl triflates in the presence of [Pd(dba)$_2$] catalyst in 1999.[10] The scope of the reaction was subsequently improved by the use of aryl siloxane derivatives as arylation reagents in the presence of fluoride ions as activating agent, and employing phosphine derivatives as ligands for the palladium.[11,12] The next remarkable advance was the development of alternative methods to active the siloxane reagent, removing the need for corrosive fluoride anions, and replacing them by hydroxy anions.[13,14] Later, with the aim of increasing both reactivity and catalyst stability, a number of ligands were developed and subsequently employed in the preparation of biaryl derivatives.[15] For example, N-heterocyclic carbenes (NHC) were employed as palladium ligands either in the presence of fluoride or hydroxy anions[16–20] and pincer-type palladium catalysts were also used in neat water under both fluoride- and base-induction conditions.[21] Hiyama reactions with oxime-derived palladacycles were carried out in aqueous sodium hydroxide[22,23] and palladium nanoparticles were reacted under aqueous fluoride-free conditions or fluoride-induction conditions.[24,25] The search for new, effective and robust catalytic systems for the coupling of organosiloxanes with aryl halides is still a challenging objective. In this sense, 2-functionalized imidazoles have been described in the preparation of transition-metal complexes and their catalytic activity has been investigated.[26–31] We have been working on the preparation of 2-hydroxyalkyl- and 2-aminoalkylimidazole derivatives, such as **L1**–**L12** (Figure 1), starting from a range of 1-substituted imidazoles.[32,33] Herein, we report in detail on the results ob-

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tained by employing this collection of ligands in the palladium-catalyzed Hiyama reaction under microwave irradiation.[34]

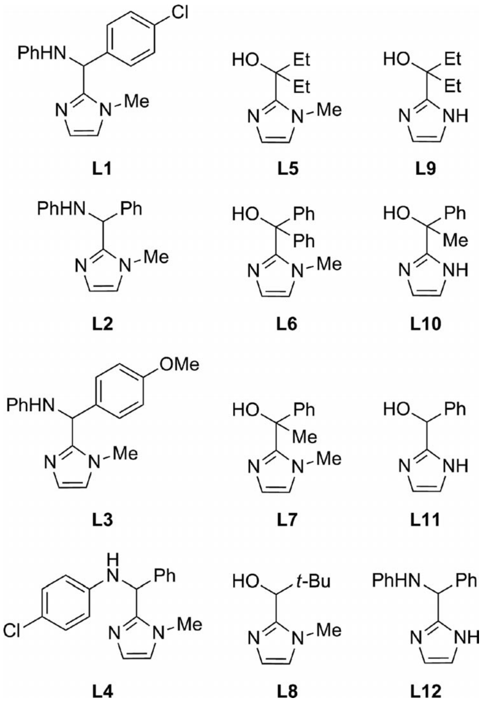
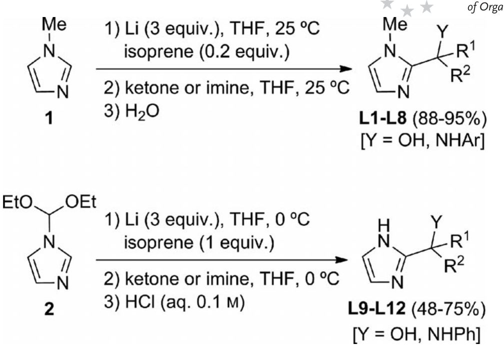


Figure 1. Imidazole derivatives **L1**–**L12**.

Results and Discussion

Preparation of Functionalized Imidazoles

The 2-functionalized imidazole derivatives were easily prepared by using an isoprene-mediated lithiation methodology that has been widely studied by our research group. On the basis of density functional calculations, the isoprene seems to act as a base, after being reduced by lithium metal, deprotonating the C-2 in the imidazole derivative and giving the corresponding 1,1-dimethylallyl radical. This allyl radical can be further reduced by the excess of lithium to produce an allyl anion that can proceed once more as a base.[35] Thus, commercially available 1-methylimidazole (**1**) was treated with lithium powder and isoprene (0.2 equiv.) in tetrahydrofuran (THF), producing the corresponding 2-lithioimidazole intermediate, which, after subsequent reaction with an electrophile and hydrolysis, gave the expected amino- and hydroxy-functionalized imidazoles **L1**–**L8** (Scheme 1 and Figure 1).[32] In addition, 2-functionalized imidazoles **L9**–**L12** were prepared starting from 1-(diethoxymethyl)imidazole (**2**), which was treated with an excess of lithium and isoprene (1 equiv.) followed by reaction with a range of electrophiles. The corresponding ligands **L9**–**L12** were obtained after acidic treatment of the reaction mixture (Scheme 1).[33] This simple synthetic strategy allowed a variety of 12 imidazole derivatives bearing different potential coordinating functional groups for the palladium metal center to be obtained.



Scheme 1. Preparation of ligands **L1**–**L12** by an isoprene-mediated lithiation methodology.

Ligand Screening

The set of 12 ligands was evaluated in the coupling of 4-bromoanisole with trimethoxy(phenyl)silane to give 4-methoxybiphenyl (**3**) under solvent-free conditions and microwave irradiation.[19] The reactions were carried out by using $Pd(OAc)_2$ (0.1 mol-%) with NaOH (solution, 50% w/w) as a source of hydroxide anion, and the reaction mixture was heated to 100 °C by microwave irradiation (80 W initial power) for 30 min. The reactions were quenched and the yield was then analyzed by GLC, employing tridecane as internal standard. The results are summarized in Figure 2, which shows the yield of **3** as a function of the ligand employed.

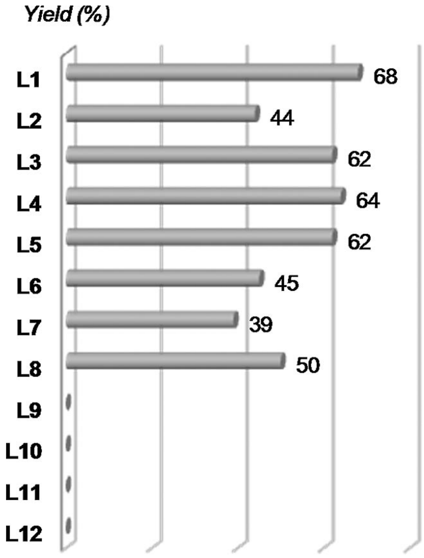


Figure 2. Yield of 4-methoxybiphenyl (**3**) using ligands **L1**–**L12**.

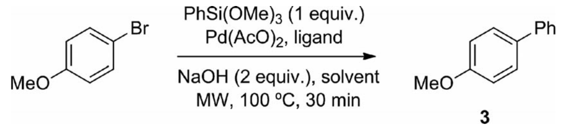
From the plot shown in Figure 2 it is evident that the substituent on the nitrogen of the imidazole moiety is crucial for the activity of the palladium catalyst formed in situ. In general, comparing both 1-methylimidazole series, amino-functionalized derivatives showed slightly higher activity than the corresponding hydroxy-functionalized derivatives, although the use of **L5** gave similar levels of activity (producing 4-methoxybiphenyl **3** in 62% yield) to those with **L1**, **L3** and **L4** (62–68%). Consequently, for further studies, we continued with ligands **L1** and **L5** to assess both amino and hydroxy functionalities in the ligand structure. Additionally, it is worth mentioning that the use of both ligands is helpful for the catalytic reaction, since the reaction employing only $Pd(OAc)_2$ as catalyst gave the product **3** with 42% yield.

Optimization of the Parameters

Our next aim was to optimize the process, employing a design of experiments (DOE)[36] to plan a minimum set of assays to check a variety of parameters, and to obtain the maximum information about which would be the critical factors and the best combination of variables. The coupling between 4-bromoanisole and trimethoxy(phenyl)silane, in 1:1 molar ratio, at 100 °C using microwave irradiation[37] for 30 min, was chosen as the model reaction to be optimized. The DOE was performed for five parameters with two or three levels: (a) solvent (water, ethanol, solvent-free conditions), (b) amount of palladium (0.1 and 0.5 mol-%), (c) ligand (**L1** and **L5**), (d) Pd/ligand ratio (1:1, 1:2, and 1:5), and (e) the use or not of an additive such as tetrabutylammonium bromide (TBAB). The first set of experiments was selected according to a Taguchi L18 array (Table 1, entries 1–18). On the basis of this series of experiments, we prepared a new collection of experiments (Table 1, entries 19–28) to gain more information on this catalytic system.

The reaction gave better yield when performed under solvent-free conditions (see the Supporting Information), and by using the amino-functionalized imidazole **L1** as ligand (see the Supporting Information). The level of palladium did not turn out to be a crucial factor, so we chose the lowest level of 0.1 mol-% palladium. The presence of TBAB (20 mol-%) in the reaction mixture seemed to increase the stability of the catalytic system, increasing the yield of the reaction (see the Supporting Information). However, the additive apparently affected the Pd/ligand ratio parameter, so this possible interaction was explored in more in detail. Accordingly, both parameters were considered in three levels (0, 20, and 50 mol-% TBAB, and 1:1, 1:2, and 1:5 for Pd/**L1** ratio) in a new set of experiments, following a 3^2 factorial design. The results are summarized in Figure 3 and, as anticipated, an interaction was found.[38] Thus, a suitable combination of both parameters was required for the best outcome of the reaction. Interestingly, a higher amount of **L1** was better when the 50 mol-% additive was used, but a lower the amount of **L1** was better when TBAB was omitted. Furthermore, when 20 mol-% TBAB was used, the behavior was not linear, with a maximum for the Pd/Ligand ratio of 1:2 being observed. Actually, comparing the levels of 0 and 20 mol-% TBAB, there was no interaction when using high amounts of ligand (ratio from 1:2 to 1:5), but there was for low amounts of ligand. In contrast, the interaction between the parameters appeared at high amounts of ligand when levels 20 and 50 mol-% TBAB were employed.

Table 1. Optimization of Hiyama coupling reaction under microwave irradiation.[a]



Entry	Solvent	$Pd(OAc)_2$ [mol-%]	Ratio Pd/ ligand	TBAB [mol-%]	Ligand	Yield [%][b]
1	neat	0.1	1:2	0	**L5**	62
2	neat	0.1	1:1	0	**L5**	54
3	neat	0.1	1:2	0	**L1**	68
4	neat	0.1	1:5	0	**L5**	23
5	neat	0.5	1:2	0	**L5**	52
6	H_2O	0.1	1:2	0	**L5**	15
7	H_2O	0.1	1:2	0	**L1**	14
8	H_2O	0.1	1:5	0	**L5**	11
9	EtOH	0.1	1:2	0	**L5**	48
10	EtOH	0.1	1:2	0	**L1**	11
11	neat	0.1	1:2	20	**L5**	70
12	neat	0.1	1:1	20	**L5**	59
13	H_2O	0.1	1:2	20	**L5**	21
14	EtOH	0.1	1:2	20	**L5**	22
15	EtOH	0.5	1:1	0	**L5**	30
16	neat	0.1	1:1	20	**L1**	78
17	neat	0.5	1:1	20	**L5**	50
18	neat	0.1	1:5	0	**L1**	78
19	neat	0.1	1:1	0	**L1**	60
20	neat	0.5	1:2	0	**L1**	60
21	neat	0.5	1:1	0	**L5**	62
22	neat	0.5	1:5	0	**L5**	16
23	EtOH	0.1	1:1	0	**L5**	24
24	EtOH	0.1	1:5	0	**L5**	27
25	neat	0.5	1:2	0	**L1**	73
26	neat	0.1	1:2	20	**L1**	89
27	neat	0.5	1:2	20	**L1**	79
28	neat	0.1	1:5	20	**L1**	74

[a] Reaction conditions: 4-bromoanisole (0.5 mmol), trimethoxy(phenyl)silane (0.5 mmol), NaOH (1 mmol), $Pd(OAc)_2$ (0.1 or 0.5 mol-%), ligand (0.1–2.5 mol-%), TBAB (0 or 20 mol-%), solvent (1 mL), 100 °C (initial power 80 W), 30 min. [b] The yield was calculated by GLC analysis employing tridecane as internal standard.

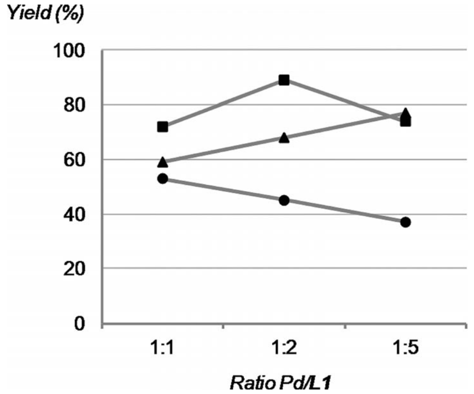


Figure 3. Interaction graph between ratio Pd/**L1** and the amount of TBAB: (●) 0 mol-% TBAB, (■) 20 mol-% TBAB, (▲) 50 mol-% TBAB.

The study was completed by employing levels of 10 and 100 mol-% TBAB together with Pd/ligand ratios of 1:1, 1:2 and 1:5, which revealed some interesting behavior. A contour map summarizing all the results is depicted in Figure 4. It can be seen that best conditions were identified at around 20 mol-% TBAB and 1:2 Pd/ligand ratio. Under these conditions, the product could be obtained in yields of over 85% by keeping the reaction conditions within small variations around this point, which represents a robust catalytic system. Moreover, we realized that for higher amounts of TBAB (i.e., more than 50 mol-%), the Pd/ligand ratio parameter was not the determinant in the outcome of the reaction, and the yield was in the range of 70–75% irrespective of the Pd/Ligand ratio used (Figure 4). In consequence, the proper choice of both factors considered in this study (i.e., 20 mol-% TBAB and 1:2 Pd/ligand ratio) has been demonstrated to be important. Additionally, there was certain robustness around the optimal reaction conditions that makes this catalytic system remarkable.

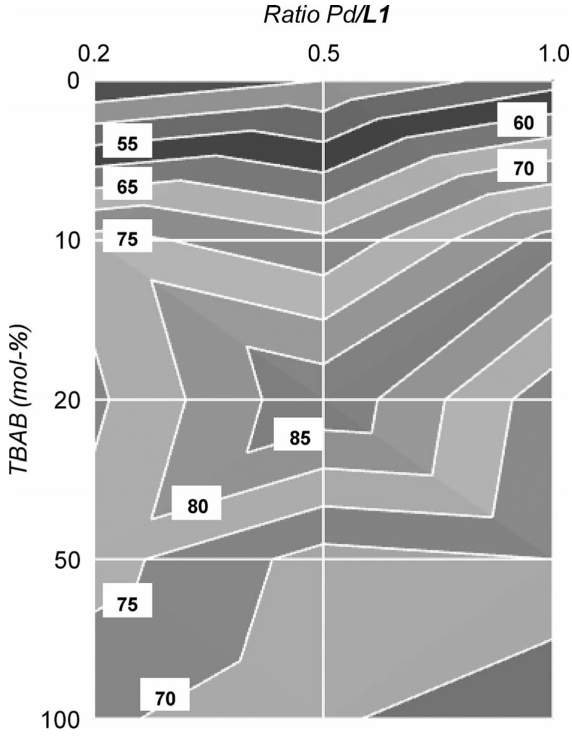


Figure 4. Contour map (% yield of **3**) as a function of the amount of TBAB (mol-%) and Pd/**L1** ratio.

Modeling the Interaction TBAB vs. Pd/Ligand Ratio

Design of experiment protocols allow further mathematical analyses. To gain a better understanding of the nature of the designed space and to map the curvature of the process, a study employing a response surface model was performed to complement the information obtained in the DOE. Figure 5 (a) shows the calculated model (2FI = Two Factor Interaction Model) for the yield in a 3D surface graph (range of 0 to 20 mol-% TBAB). The points for 0 mol-% TBAB gave yields of between 37 and 53%, which were below the value predicted by the linear 2FI model, thus indicating significant curvature.

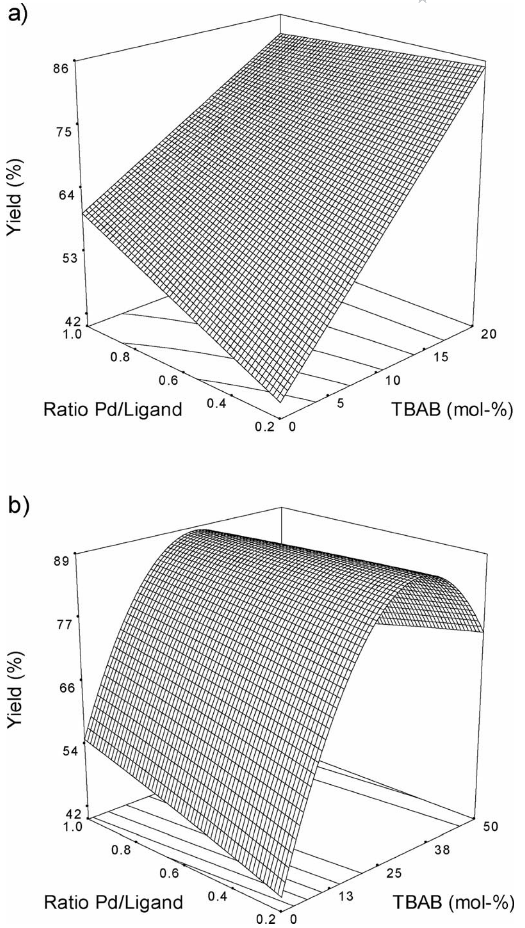


Figure 5. (a) Three-dimensional view of the 2FI model for the different Pd/ligand ratios in the range 0 to 20 mol-% TBAB; (b) Three-dimensional view of the Quadratic model for the different Pd/ligand ratios in the range 0 to 50 mol-% TBAB.

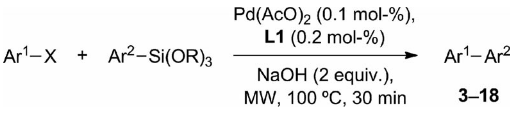
Taking into consideration the range from 0 to 50 mol-% TBAB, a quadratic model was generated, and the yields predicted under each reaction condition can be visualized in the three dimension surface graph depicted in Figure 5 (b). This model demonstrates that the interaction of the two considered factors is important for the outcome of the reaction, with the curvature being significant. This is a clear indication that a linear model within 2FI is not descriptive of the real response surface when the study is extended to higher amounts of additive (TBAB). However, any model derived from this can only give a rough indication for point predictions within the chosen boundaries. Within the boundaries of the quadratic model for the yield as a 3D surface graphic (Figure 5, b), the amount of TBAB can be determined as the more important factor in the outcome of the reaction, followed by suitable selection of Pd/ligand ratio. The model gives indications regarding the best conditions, but it is clear that the optimum area in which to operate this reaction is wider than predicted around the 1:2 ratio, and for higher and lower ratios the predicted values by the quadratic model were above the experimental values.

Scope of the Cross-Coupling Hiyama Reaction

With the results from the ligand optimization described above, we continued with an examination of substrate scope for the synthesis of a range of biaryl derivatives. Ligand **L1** (0.2 mol-%) was used in combination with $Pd(OAc)_2$ (0.1 mol-%) and TBAB (20 mol-%).[39] The reactions were performed for 30 min at 100 °C by using microwave irradiation,[40] and the aryl halides and siloxane reagents were employed in equimolecular amount. At this point it is worth mentioning that performing the reaction with higher amounts of siloxane (1.5 equiv.) gave the same results.

As seen in Table 2, coupling of aryl bromides, bearing a range of electron-donating and electron-withdrawing groups, with trimethoxy(phenyl)silane produced the expected biaryls **3**–**7** with isolated yields ranging from 78 to 89% (Table 2, entries 1–5), which demonstrates the robustness of the catalytic system with respect to substrates. In the case of more congested 2-bromotoluene, a similar yield (85%) of the coupling product **8** was obtained (Table 2, entry 6), whereas 2-bromophenol coupled with a more moderate yield (Table 2, entry 7). A plausible explanation for the poor reactivity obtained with the latter substrate can be found in deactivation of the catalyst by substrate coordination. The reaction with heteroaryl halides is usually less efficient, but the reaction with 3-bromopyridine under these reaction conditions resulted in the formation of 3-phenylpyridine **10** with 80% yield (Table 2, entry 8). On the other hand, 3-bromothiophene showed lower activity (Table 2, entry 9). Interestingly, the use of trimethoxy(4-methylphenyl)silane as coupling partner for aryl bromides resulted in the formation of the corresponding biaryl compounds **12**–**15** with yields ranging from 71 to 82% (Table 2, entries 10–13), whereas use of an aryl siloxane bearing an electron-donating group [i.e., triethoxy(4-methoxyphenyl)silane] was less reactive under the same reaction conditions (Table 2, entries 14 and 15).

Table 2. Biaryl synthesis by Hiyama reaction with the catalytic system $Pd(OAc)_2$/**L1**.[a]



$$Ar^1{-}X + Ar^2{-}Si(OR)_3 \xrightarrow[\text{NaOH (2 equiv.), MW, 100 °C, 30 min}]{Pd(AcO)_2\text{ (0.1 mol-\%)}, \mathbf{L1}\text{ (0.2 mol-\%)}} Ar^1{-}Ar^2 \quad \mathbf{3{-}18}$$

Entry	Aryl halide	Aryl(trialkoxy)silane	Product	Yield [%][b]
1	4-$MeOC_6H_4Br$	$PhSi(OMe)_3$	**3**	89
2	4-HOC_6H_4Br	$PhSi(OMe)_3$	**4**	78
3	4-$(NO_2)C_6H_4Br$	$PhSi(OMe)_3$	**5**	86
4	4-$(MeCO)C_6H_4Br$	$PhSi(OMe)_3$	**6**	89
5	4-*t*BuC_6H_4Br	$PhSi(OMe)_3$	**7**	82
6	2-MeC_6H_4Br	$PhSi(OMe)_3$	**8**	85
7	2-HOC_6H_4Br	$PhSi(OMe)_3$	**9**	40
8	3-bromopyridine	$PhSi(OMe)_3$	**10**	80
9	3-bromothiophene	$PhSi(OMe)_3$	**11**	44
10	4-$MeOC_6H_4Br$	4-$MeC_6H_4Si(OMe)_3$	**12**	78
11	4-*t*BuC_6H_4Br	4-$MeC_6H_4Si(OMe)_3$	**13**	80
12	2-MeC_6H_4Br	4-$MeC_6H_4Si(OMe)_3$	**14**	82
13	3-bromopyridine	4-$MeC_6H_4Si(OMe)_3$	**15**	71
14	4-*t*BuC_6H_4Br	4-$MeOC_6H_4Si(OEt)_3$	**16**	60
15	3-bromopyridine	4-$MeOC_6H_4Si(OEt)_3$	**17**	67
16	4-MeC_6H_4Cl	$PhSi(OMe)_3$	**18**	69
17	4-$(MeCO)C_6H_4Cl$	$PhSi(OMe)_3$	**6**	79
18	3-chloropyridine	$PhSi(OMe)_3$	**10**	30

[a] Reaction conditions: aryl halide (2 mmol), aryl(trialkoxy)silane (2 mmol), NaOH (2 equiv., 50% aqueous solution), $Pd(OAc)_2$ (0.1 mol-%), **L1** (0.2 mol-%), TBAB (20 mol-%), 100 °C (initial power of 80 W), 30 min. [b] Isolated yield of pure product after purification by flash chromatography (silica gel; hexane/ethyl acetate), or recrystallization.

Finally, use of the catalyst in the cross-coupling reaction of aryl siloxane with less reactive aryl chlorides resulted in the formation of the expected biaryls with slightly lower yields compared with the previous substrates (Table 2, entries 16–18). 4-Chlorotoluene reacted with trimethoxy(phenyl)silane to give 4-methyl-1,1′-biphenyl **18** in 69% yield, and more activated 4-chloroacetophenone gave biaryl **6** in 79% yield. However, the catalytic system was not effective when 3-chloropyridine was used, and compound **10** was obtained with only 30% yield.

Conclusions

We have demonstrated that amino- and hydroxy-functionalized 1-methylimidazoles function as efficient ligands for the palladium-catalyzed Hiyama reaction. The ligands were easily prepared by isoprene-mediated lithiation methodology followed by reaction with a carbonyl compound or an imine. When combined with palladium acetate, the catalytic system formed in situ promotes the fluorine-free Hiyama reaction under solvent-free conditions by using microwave irradiation. The utilization of Design of Experiments protocols has allowed for the examination of multiple variables simultaneously and facilitated formulation reaction conditions for aryl bromides. The information derived from the systematic study revealed an interaction between the amount of additive and the Pd/Ligand ratio. The use of palladium/ligand **L1** in a ratio of 1:2 together with 20 mol-% TBAB as additive were determined to be the optimal catalytic system. The resulting process represents a robust procedure capable of operating with a variety of aryl siloxanes and aryl bromides and chlorides in the preparation of biaryl derivatives.

Experimental Section

General Remarks: All commercially available reagents (Acros, Aldrich, Fluka) were used without further purification. Melting points were determined with a Reichert Thermovar hot-plate apparatus and are uncorrected. NMR spectra were recorded with a Bruker-Avance 300 or a Bruker-Avance 400 (300 and 400 MHz for ^1H NMR and 75 and 100 MHz for ^{13}C NMR); $CDCl_3$ was used as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constants (J) in Hertz. Mass spectra (EI) were obtained at 70 eV with an Agilent 5973 spectrometer, fragment ions in *m*/*z* with relative intensities (%) in parenthesis. Infrared spectra were recorded with a Perkin–Elmer Spectrum 100 spectrometer as neat solids. Analytical TLC was performed on Merck aluminum sheets with silica gel 60 F254. Silica gel 60 (0.004–

0.06 mm) was employed for flash chromatography. Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in glass vessels (10 mL) sealed with a septum under magnetic stirring.

General Procedure for the Cross-Coupling of Aryl Halides with Siloxanes: A 10 mL MW vessel was charged with Pd(OAc)$_2$ (0.002 mmol, 0.4 mg), ligand **L1** (0.004 mmol, 0.8 mg), aryl halide (2 mmol), organosilicon (2 mmol), and TBAB (0.2 mmol, 128 mg), then an aqueous solution of NaOH (50% w/w, 0.2 mL) was added dropwise. The vessel was sealed with a septum and the mixture was heated in air at 100 °C by microwave irradiation (initial power of 80 W) for 30 min. After allowing the reaction to cool to room temperature, the mixture was extracted with ethyl acetate (5 × 5 mL) and the combined organic layers were filtered through a pad of Celite and anhydrous Mg$_2$SO$_4$, and then evaporated. The obtained crude product was purified either by recrystallization (MeOH/H$_2$O) or by flash chromatography on silica gel (ethyl acetate/hexane), yields are given in Table 2. Physical, spectroscopic, and analytical data, as well as literature references of known compounds are given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Physical, spectroscopic, and analytical data, as well as literature references of known compounds.

Acknowledgments

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[38] In Figure 4: If the lines run, in: parallel, there is no interaction between the two parameters, but if they divert, then there is an interaction.
[39] The reaction between 4-bromoanisole and trimethoxy(phenyl)silane under the best reaction conditions but in the absence of **L1** gave the coupling product in 56% yield, calculated by GLC analysis employing tridecane as internal standard.
[40] The temperature was monitored in one experiment by an external probe and was found to be in the range 92–97 °C.

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