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Anchored Pd(0) Nanoparticles on Synthetic Talc for the Synthesis of Biaryls and a Precursor of Angiotensin II Inhibitors

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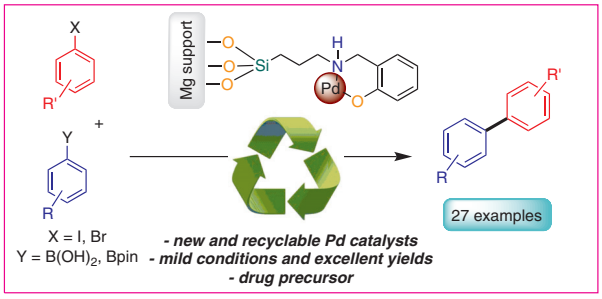

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Abstract The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction is one of the most important and efficient reactions to prepare a variety of organic compounds, including biaryls. Despite the overwhelming number of reports related to this topic, some methodological difficulties persist in terms of catalyst handling, recovery, and reuse, as well as the reaction media. This work reports the rational design of new, efficient, cost-effective, and reusable palladium catalysts supported on synthetic talc for the Suzuki–Miyaura reaction. From the results, key points were identified: both designed catalysts accelerated the reaction in EtOH and an open-flask setup, affording moderate to excellent yields within a short time (e.g., 30 min) even for deactivated aryl halides; the protocol can be applied to a great number of both cross-coupling partners, showing an excellent functional group tolerance; the catalysts can be recovered and reused without significant loss of activity. This protocol was used for the synthesis of a precursor of angiotensin II inhibitors such as valsartan, losartan, irbesartan, and telmisartan.

Key words cross-coupling, palladium, supported catalysts, Suzuki–Miyaura reaction, synthetic talc

Cross-coupling reactions, specifically the Suzuki–Miyaura reaction, are a powerful method for the formation of C–C bonds.[1] This reaction is performed by using a palladium catalyst, organoborons, and organic halide or triflate reagents, and produces a variety of compounds, including biaryls. The biaryl moiety is found in a range of compounds as it is an important building block for polymers[2] and ligands,[3] as well as in a wide variety of natural products (biphenomycin B) and biologically active target molecules (boscalid) and pharmaceuticals[1,4] (e.g., diflunisal and flurbiprofen) (Figure 1).[4] Unlike other types of C–C cross-coupling reactions involving organometallic reagents, the Suzuki–Miyaura reaction can be performed under mild conditions using boronic acids, which are simple to use, easily accessible, and show good functional group tolerance.[5] These characteristics of boronic acids result in excellent structural diversity in the corresponding products and render them safe,[5] thus making them the ideal starting materials. Furthermore, boronic acids are highly stable to heat, oxygen, and water, and are easily separated from byproducts.[6] Over the last few years, some important advances have been made in the Suzuki–Miyaura reaction, including the use of aryl chlorides, low catalyst loading, and room-temperature reactions.[7] However, the major drawback of the Suzuki–Miyaura coupling lies in the use of palladium salts and expensive ligands.[8] Despite its disadvantages of high cost and low abundance, palladium is still the most widely used metal for designing new catalysts and is often applied in reactions aiming at the formation of C–C bonds.[9]

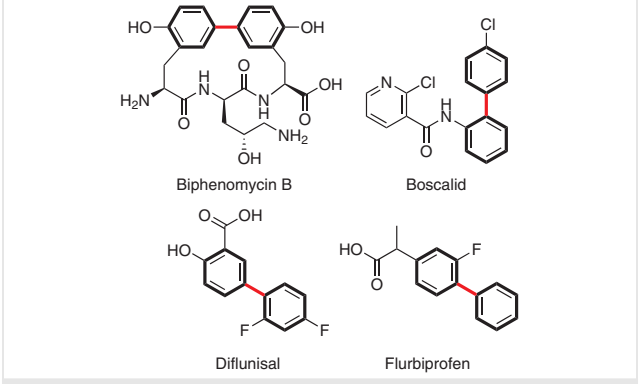


Figure 1 Bioactive molecules containing a biaryl nucleus

As a result, many researchers have developed heterogeneous and reusable palladium catalysts,[10] as homogeneous palladium catalysts are expensive and difficult to separate from the reaction, meaning they are not recoverable; further, the final product can be contaminated by the metal, which poses an issue for the pharmaceutical industry.[11] In

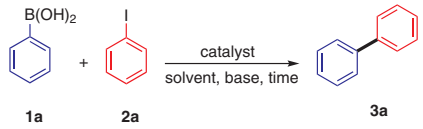
most cases, a heterogeneous catalyst consists of the metal encapsulated in a polymeric shell[12] or adsorbed on different organic[13] or inorganic[14] supports.

The development of improved heterogeneous palladium catalysts is crucial for their application on an industrial scale so that considerable cost savings can be achieved owing to their ease of removal and reuse.[12] However, the catalytic activity of immobilized palladium catalysts is sometimes low due to the presence of the support,[12] which necessitates higher catalyst loading. In this sense, synthetic talc (magnesium organosilicates) has become an important and efficient tool in catalytic organic synthesis due to its physicochemical properties.[15] Despite magnesium organosilicates having very attractive characteristics, such as low cost and adsorption capacity of organic substances,[15] there are limited studies on the applications of this material in organic reactions.

With this goal, our group has been investigating cross-coupling reactions, and we have previously described protocols for C–S cross-coupling by using a heterogeneous palladium catalyst.[16,17] As a continuation of this research, we herein introduce synthetic talc as an efficient, inexpensive, and eco-friendly heterogeneous support for immobilized palladium catalyst synthesis – LACOB-Pd1 and LACOB-Pd4. The difference between these two catalysts lies in the labels 1 and 4 which refer to the initial loading of the palladium salt added to synthetic talc (see the Supporting Information). Initially, we chose this support because it is insoluble and stable in many organic solvents as well as easy and inexpensive to synthesize.

We initially prepared the LACOB-Pd1 catalyst as described in the experimental section. Next, we evaluated the catalytic activity of the supported palladium catalyst. We selected phenylboronic acid (**1a**) and iodobenzene (**2a**) as starting materials in the standard reaction for optimizing the reaction conditions (Table 1). Then, the effect of palladium catalyst loading on the yield was assessed, as well as the effect of the stoichiometric amount of phenylboronic acid, solvent, and reaction time. First, the standard reaction was carried out with 5% w/w (in relation to the theoretical weight of the product) of catalyst in water due to our interest in establishing a 'greener' procedure[18] (entry 1), but this afforded the product in only a moderate yield (67%). When the same reaction was carried out in EtOH, the yield increased (entry 2, 88% yield). As EtOH is also a 'green' solvent, we chose this as the solvent for the subsequent reactions. Aiming to improve the yield, we changed the amount of phenylboronic acid; however, there was no improvement in the yield when using a decreased amount of phenylboronic acid (entries 3 and 4) in comparison to that in entry 1. Gratifyingly, when the stoichiometric amount was increased to 2.0 equivalents, the Suzuki–Miyaura cross-coupled product **3a** was obtained in 97% yield (entry 5). We also carried out a blank reaction (without catalyst) but did not obtain the product, implying that the catalyst is essential for the reaction (entry 6). We also performed studies regarding catalyst loading (entries 7 and 8). For this, we used the standard reaction but decreased the catalyst loading to 2.5% w/w (entry 7) and 1.5% w/w (entry 8), and the yields dropped to 94% and 76%, respectively. However, the data obtained for entry 7, with a similar yield as the standard reaction, led us to assess the influence of the reaction time on the yield. Thus, we performed a further standard reaction (entry 9); however, decreasing the reaction time to 2 hours drastically reduced the yield (67%), as expected. Finally, we carried out the reaction with 3% w/w catalyst for 3 hours (entry 10) but observed no increase in the yield. Thus, the optimized reaction conditions were determined as follows: boronic acid (2.0 mmol), iodoarene (1.0 mmol), catalyst (5% w/w), 3 h reaction time.

Table 1 Optimization of the Reaction Conditions



Entry	Phenylboronic acid (mmol)	LACOB-Pd1 (% w/w)	Time (h)	Solvent	Yield[a] (%)
1	1.5	5.0	3	water	67
2	1.5	5.0	3	EtOH	88
3	1.0	5.0	3	EtOH	67
4	1.3	5.0	3	EtOH	50
5	2.0	5.0	3	EtOH	97
6	2.0	–	3	EtOH	–
7	2.0	2.5	3	EtOH	94
8	2.0	1.5	3	EtOH	76
9	2.0	5.0	2	EtOH	67
10	2.0	3.0	3	EtOH	90

[a] Reaction conditions: iodobenzene (1.0 mmol), K_2CO_3 (1.0 mmol), solvent (3 mL), 80 °C.
[b] Isolated (column chromatography) yields.

The characteristics of the synthesized catalyst were determined by X-ray diffraction (XRD), scanning electron microscopy (SEM), and energy-dispersive spectroscopy (EDS) analyses. As shown in Figure 2, all the reflection planes for the modified materials (Figure 2a) changed compared with the magnesium chloride salt (Figure 2b). Besides, two new reflections appeared at 2θ = 40.32° and 46.44° for the palladium catalyst, corresponding to the reflection planes (111) and (200), which are characteristic of the face-centered cubic (fcc) structure of Pd nanoparticles.[19] These data indicate that the Pd element exists in the form of Pd^0 and not Pd^{2+}.[20] Based on the half-width of the (111) reflection, the average

crystallite size (1.3 nm) of the synthesized Pd nanoparticles was estimated through the Scherrer equation. The elemental composition of the palladium catalyst was also determined by EDS, which is shown in Figure 3a. The presence of palladium is clearly indicated in the figure, along with other elements including oxygen, nitrogen, and magnesium. Furthermore, the morphology of the palladium catalyst was investigated by using SEM analysis (Figure 3b).

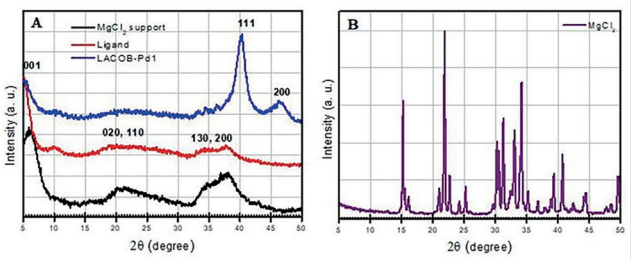


Figure 2 (a) XRD patterns of the main components of the LACOB-Pd1 catalyst; (b) XRD pattern of the magnesium chloride salt

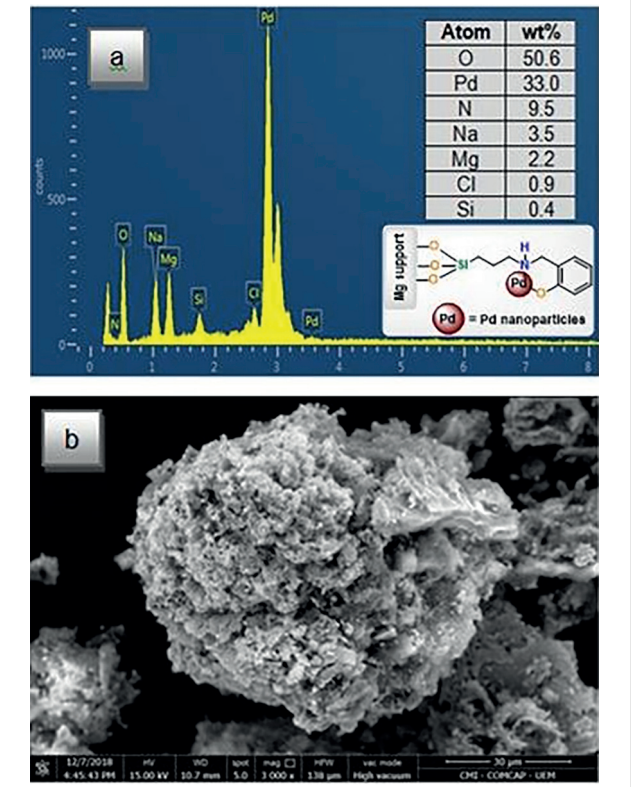
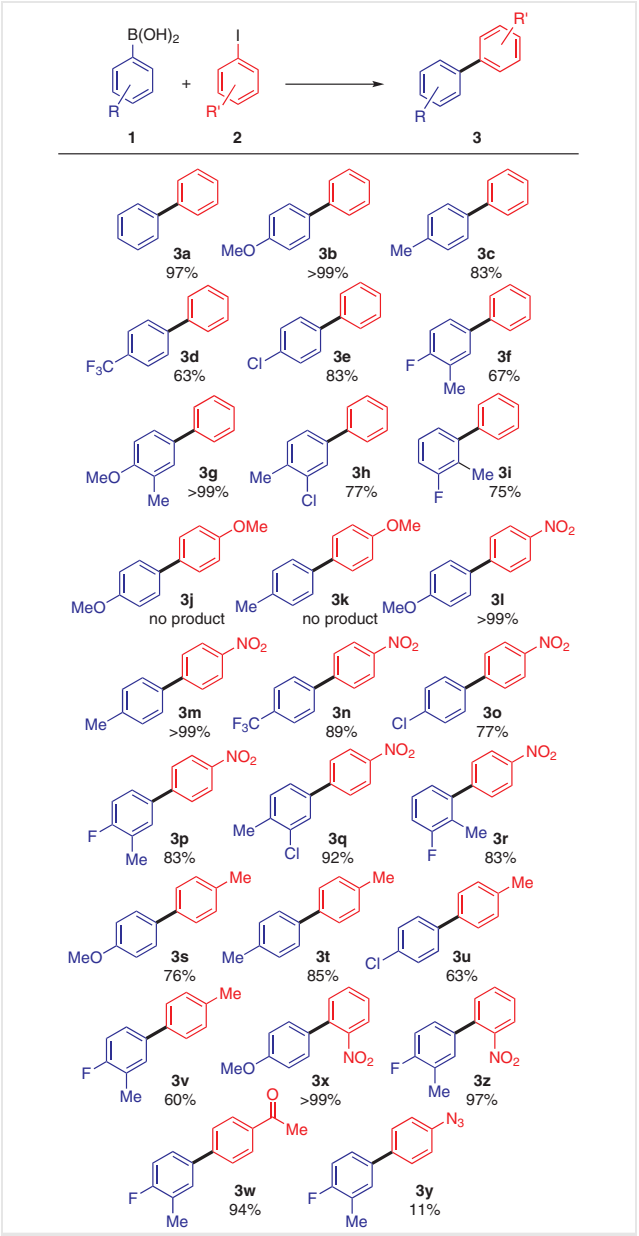


Figure 3 (a) EDS analysis of the LACOB-Pd1 catalyst; (b) SEM analysis of the LACOB-Pd1 catalyst

Having established the optimized reaction conditions, we performed the reaction with different boronic acids and iodoarenes (Scheme 1). Regarding the phenylboronic acids, the electronic nature of the functional groups, as expected, has a great effect on the reaction (**3a–3i**). The best results were obtained when electron-donating groups were present on the phenylboronic acid (**3b**, **3g**, **3l**, **3m**, and **3x**). An electronic effect for the iodoarene can also be observed (entries **3a–3y**), with iodoarenes bearing an electron-deficient group affording high yields. Even when we carried out the reaction by using an *ortho*-nitro, the electron-deficient property has a greater influence than the stereo effect from the nitro group in the *ortho* position (**3x** and **3z**). Products **3f**, **3g**, **3h**, and **3i**, derived from disubstituted phenylboronic acids, were obtained in moderate to excellent yields.



Scheme 1 Substrate scope for the Suzuki–Miyaura cross-coupling reaction using LACOB-Pd1. *Reagents and conditions*: arylboronic acid (2 mmol), iodoarene (1 mmol), LACOB-Pd1 (5% w/w), K_2CO_3 (1 mmol), EtOH (3 mL), 80 °C, 3 h; isolated yields.

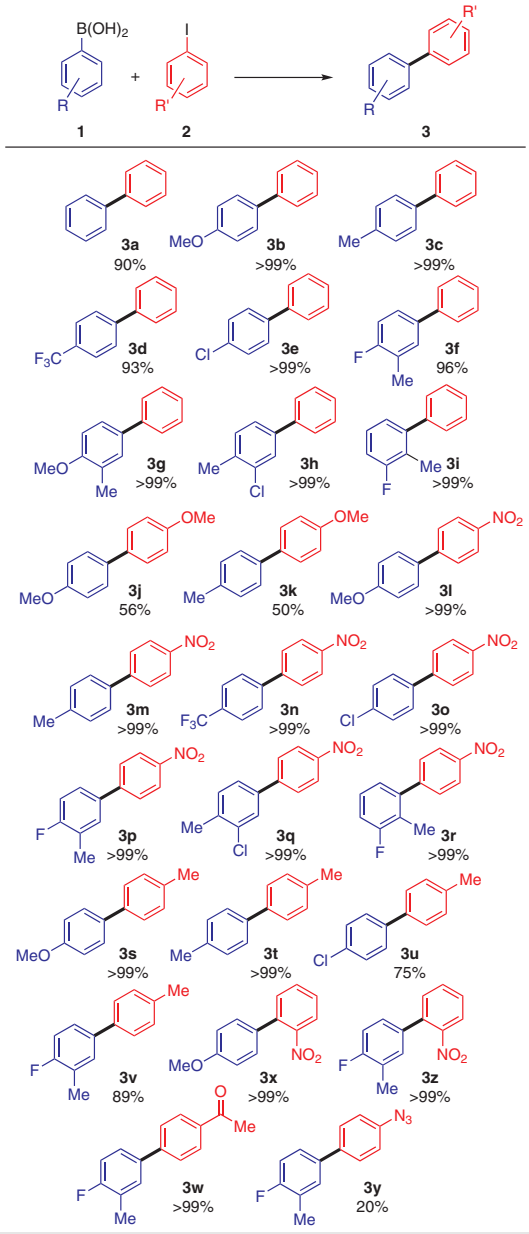
Unexpected results were obtained for **3r** and **3i** (83% and 75% yield, respectively) obtained from 2,3-disubstituted boronic acids. However, from the literature, we concluded that for these compounds there is an important stereoelectronic effect, mainly from the *ortho*-substituted group, in the transition state for the reductive elimination step, which affords the best geometry for the orbital overlap.[21] This is very clear when analyzing the similar compounds of **3r** and **3i**, in other words compounds **3p** and **3f**, respectively. Both similar compounds **3p** and **3f** present disubstituted groups like **3r** and **3i**, but now at positions 3 and 4. For compound **3f**, the yield decreased, which proves the role of the stereoelectronic effect on the transition state. Additionally, when we observe the yield for compound **3z** which is obtained from the 3,4-disubstituted boronic acid, but now using as a cross-coupling partner the *ortho*-substituted (nitro group) iodoarene, it is clear that *ortho*-substitution positively affects the yields for this reaction. It is worth mentioning that 4-iodoacetophenone was also a suitable substrate for this transformation, giving the desired product **3w** in 94% yield. Additionally, product **3y** was obtained in a small amount when an azide group was present on the iodobenzene.

These results from the use of LACOB-Pd1 were a great delight for us, but aiming to increase the yields, and having the goal to produce the cross-coupling compounds from deactivated iodoarenes (**3j** and **3k**), we tried to enhance the efficiency of the catalyst. In this sense, we assessed the catalyst synthesized by using 0.4 g of palladium acetate, from now on named as LACOB-Pd4. The results for the Suzuki–Miyaura cross-coupling reaction using LACOB-Pd4 are presented in Scheme 2. To our delight, we observed that for almost all the reactions, even for deactivated iodoarenes, there was a significant increase in the yields. Allied to this, there was a deeply decreased reaction time.

Thus, with LACOB-Pd4 (synthesized by using an initial fourfold increased palladium loading), the Suzuki–Miyaura cross-coupling reaction time decreased sixfold compared with the same reactions performed with LACOB-Pd1, which we concluded relates to the increased palladium loading on LACOB-Pd4. To verify this possibility, we performed EDS and SEM analyses for LACOB-Pd4, which confirmed that LACOB-Pd4 presents twice the palladium loading than LACOB-Pd1 and a very high degree of morphological homogeneity (Figure 4).

It is important to note that nitrobiphenyls can be reduced to aminobiphenyl compounds which are key molecules in organic chemistry. These amino compounds and derivatives have been widely used in the chemical industry and many examples have known antitumor activity (Scheme 3).[22]

To demonstrate a direct application of LACOB-Pd4 in the Suzuki–Miyaura cross-coupling reaction, we performed the synthesis of an intermediate of angiotensin II inhibitors under similar conditions (Scheme 4). Specifically for this precursor, the reaction was performed using 2-bromobenzonitrile, 4-formylphenylboronic acid pinacol ester, LACOB-Pd4, and NMP as the solvent. It is worth mentioning that here the reaction time was increased to 4 hours. The reason for that is twofold: (a) the significant hindrance increasing on the boronic group, now used as the pinacol instead of hydroxide group, and (b) the leaving group at arene was



Scheme 2 Substrate scope for the Suzuki–Miyaura cross-coupling reaction using LACOB-Pd4. *Reagents and conditions*: arylboronic acid (2 mmol), iodoarene (1 mmol), LACOB-Pd4 (5% w/w), K_2CO_3 (1 mmol), EtOH (3 mL), 80 °C, 30 min; isolated yields.

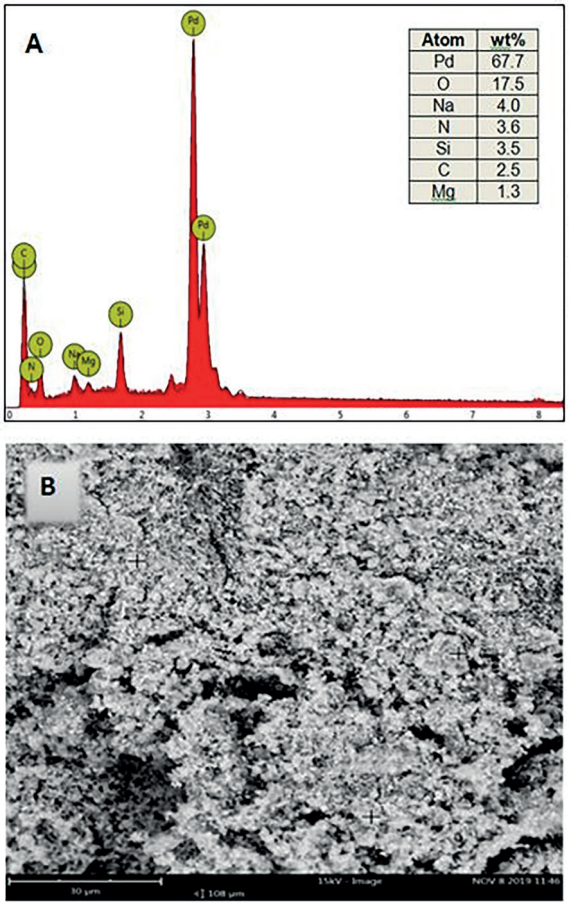
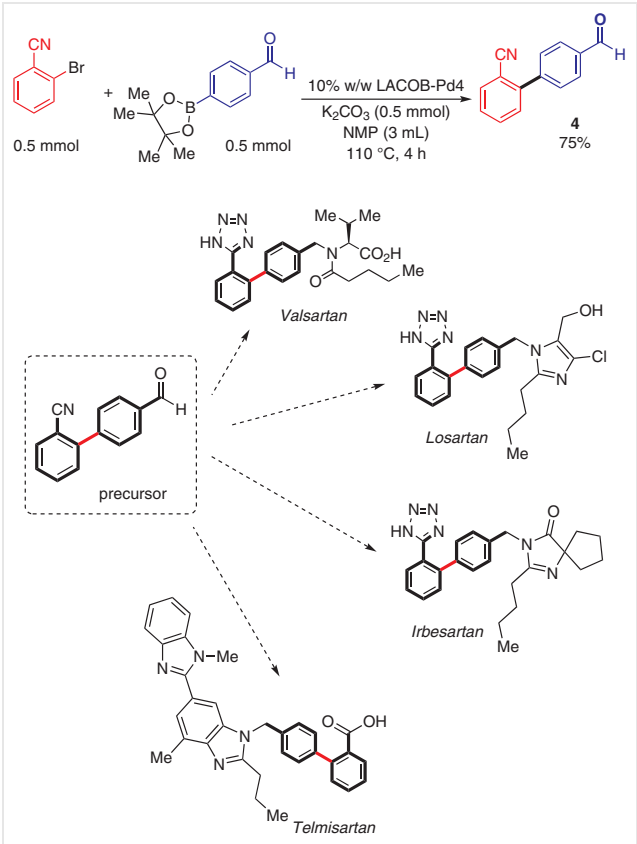


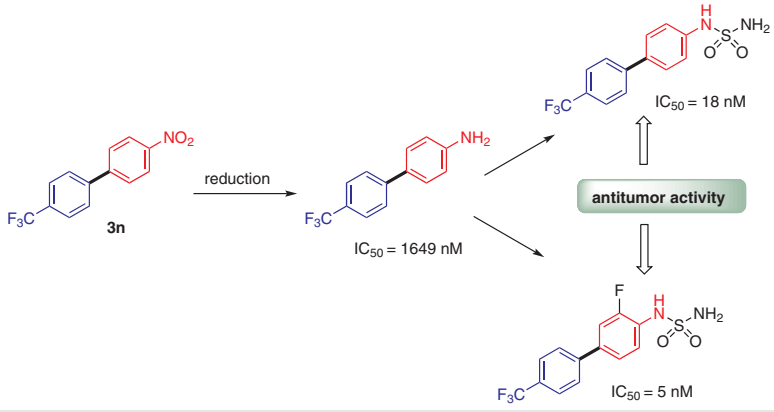
Figure 4 (a) EDS analysis of the LACOB-Pd4 catalyst; (b) SEM analysis of the LACOB-Pd4 catalyst

bromide, known to be a worse leaving group than iodine. However, even with these structural modifications, the drug precursor **4** was obtained in 75% yield.

Finally, we focused on the catalyst recycling process. Notably, we realized that the immobilized palladium catalysts are insoluble in EtOH and other organic solvents such as DMF, DCM, chloroform, and toluene. To recover and reuse the used catalysts, the standard reaction was first performed [**1a** (2.0 mmol), **2a** (1.0 mmol), catalyst (5% w/w), EtOH, 3 h or 30 min depending on the catalyst]. After the initial run was finished, the catalyst was separated from the reaction crude by centrifugation followed by washing with distilled water, and left to dry in air for 24 hours. The catalyst weight was then measured, which indicated that there was no loss of the catalysts. Further, the catalysts were



Scheme 4 Precursor and angiotensin II inhibitors



Scheme 3 Biologically active aminobiphenyl compounds

reused in the subsequent reaction. This methodology was performed five times. The results for catalyst recycling in the Suzuki–Miyaura reaction demonstrated the possibility of reusing the catalysts in up to five successive cycles, as shown in Figure 5. Moreover, the high catalytic activity of the recovered catalysts implies that the Pd nanoparticles were not leached into the solvent during the reaction cycles. To prove this statement, we performed a hot filtration test. Firstly, a standard reaction of **1a** with **2a** was carried out under the conditions described in Scheme 2. After 30 minutes, the LACOB-Pd4 catalyst was removed by filtration, and then the starting materials **1a** and **2a**, as well as base, were added again to the supernatant liquid. The reaction mixture was heated at 80 °C for another 30 minutes and the product was isolated by column chromatography. After all, compound **3a** was obtained in 96% yield indicating that the second step coupling product was obtained in only a 6% yield. These data testify that LACOB-Pd4 plays a crucial role in the efficiency of the Suzuki–Miyaura reaction.

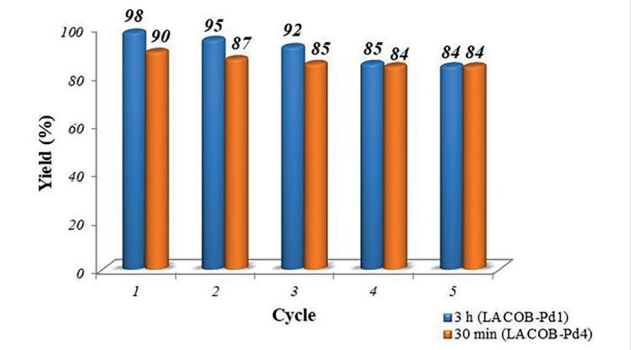


Figure 5 Reusability of the palladium catalysts in the Suzuki–Miyaura reaction between phenylboronic acid (**1a**) and iodobenzene (**2a**) with 5% w/w catalyst for 3 hours or 30 minutes

To compare the efficiency of our catalyst (LACOB-Pd4) with some reported heterogeneous palladium catalysts in the Suzuki–Miyaura reaction,[23] we have tabulated the results of these catalysts for the synthesis of compound **3a**. As shown in Table 2, our catalyst is superior to some of the previously reported catalysts in terms of reaction conditions and reaction time. This comparison revealed that the present protocol with LACOB-Pd4 presents better efficiency in terms of catalytic loading used (7 mg) and regarding the reaction time (30 min). Besides, the other advantage lies in the support; in other words, synthetic talc is inexpensive, stable, and easily prepared.

In summary, we have demonstrated new, efficient, and recyclable immobilized palladium catalysts for the Suzuki–Miyaura reaction based on a simple and inexpensive $MgCl_2$ support. We have designed LACOB-Pd1 and LACOB-Pd4, and both catalysts showed efficiency in the optimization protocol developed in that study. The methodology developed here also tolerates a variety of groups in both counterpartners for the Suzuki–Miyaura reaction. Thus, several biaryl compounds were successfully synthesized in good to excellent yields under mild reaction conditions and by using low catalyst loading in short reaction times, reaching 30 minutes for LACOB-Pd4. Further, this protocol presents an eco-friendly approach that uses EtOH as the solvent in an open-flask procedure. All those reaction parameters led us to apply this protocol in the synthesis of a precursor to drugs such as valsartan, losartan, irbesartan, and telmisartan, affording high yield (75%). Even products obtained from deactivated iodoarenes can be achieved by changing the catalyst used in the process, which makes this protocol highly applicable in organic synthesis. In terms of the reusability of the catalysts, they can be easily recovered and reused without any significant loss of catalytic activity for at least five cycles. Additionally, these data proved that the catalysts are not leached during the recycling runs.

Table 2 Results Comparison of Compound **3a** Synthesized Using LACOB-Pd4 with Reported Catalysts

Entry	Catalyst and conditions	Halide	Yield (%)
1 (this work)	LACOB-Pd4 (5% w/w, 0.007 g), K_2CO_3, EtOH, 30 min, 80 °C	I	90
2[23a]	Fe_3O_4@SiO_2@SePh@Pd(0) (0.01 mol%), K_2CO_3, water, 2 h, 80 °C	I	90
3[23b]	Pd NP/THH-CO_2H@$CoFe_2O_4$ (0.08 g), K_2CO_3, PEG, 45 min, 120 °C	I	90
4[23c]	Pd(0)–pDAB (0.14 mol%), K_2CO_3, toluene, 8 h, 90 °C	I	90
5[23d]	PANI-Pd (0.06 g), K_2CO_3, dioxane/water, 4 h, 95 °C	I	91

All reactions were carried out using chemical reagents and solvents without any specific treatment. The respective reactions were monitored by TLC (MACHEREY-NAGEL, SIL G/UV_{254}) and were visualized by fluorescence quenching with UV light at 254 nm. Purification of compounds was performed by column chromatography using hexane. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 300 MHz or 500 MHz spectrometers. ^1H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant(s) (*J*, Hz), integration. IR spectra were recorded on a Jasco FT/IR 4100 type A spectrophotometer.

$MgCl_2$ Support

The $MgCl_2$ support synthesis was performed by following the report by Jasra and co-workers.[24] $MgCl_2$ (8.36 g) was dissolved in a beaker containing MeOH (200 mL) and the solution was stirred at 25 °C for 10 min. In another beaker, APTES (9.8 g, 10.35 mL) was dissolved in MeOH (50 mL). This solution was added dropwise to the $MgCl_2$ solution, with the resulting mixture forming a white suspension. Then, 0.5 M NaOH solution was slowly added until the pH reached 10.5 under stirring at 25 °C. The suspension obtained was aged for 1 week at 25 °C and the gel formed was centrifuged, washed with distilled water, and dried at 65 °C.

LACOB-Pd1 and LACOB-Pd4 Immobilized Catalysts

In a flask, the $MgCl_2$ support (0.1 g) and KOH (0.1 g, dissolved in distilled water) were added to EtOH (5 mL) and stirred for 10 min at 25 °C. Next, salicylaldehyde (0.1 g, 94 μL) was added and the mixture was stirred at 25 °C for 2 h. Then, $NaBH_4$ was added until the solution became white and turbid. The reaction mixture was stirred overnight. After this period, the white solid was centrifuged and washed with distilled water. For the synthesis of the immobilized catalysts, the ligand was stirred with NaOH (0.1 g) in EtOH for 15 min. Then, $Pd(OAc)_2$ (0.1 g for LACOB-Pd1 or 0.4 g for LACOB-Pd4) was added, and the mixture was stirred at 25 °C for 2 h. The black solid formed was centrifuged and washed with chloroform.

Suzuki–Miyaura Cross-Coupling Reaction; General Procedure

In a 5 mL round-bottom flask, the palladium catalyst (5% w/w, in relation to the theoretical weight of product), arylboronic acid (2 mmol), iodoarene (1 mmol), and K_2CO_3 (1 mmol) were stirred in EtOH (3 mL) at 80 °C (using an oil bath) for 3 h or 30 min. The progress of the reaction was monitored by TLC (EtOAc/hexane, 10:90). After this time, the solution was cooled to room temperature, diluted with EtOAc (20 mL), and washed with water (3 × 20 mL). The organic phase was separated, dried with Na_2SO_4, and concentrated under vacuum. The obtained product was purified by column chromatography (hexane).

1,1′-Biphenyl (3a)[23a]

White solid; yield: 149 mg (97%) for LACOB-Pd1, 139 mg (90%) for LACOB-Pd4; mp 69 °C.

IR (KBr): 3031, 1478, 1427, 729, 695 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.63 (m, 4 H), 7.50–7.47 (m, 4 H), 7.41–7.37 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.21, 128.72, 127.22, 127.14.

4-Methoxy-1,1′-biphenyl (3b)[23a]

White solid; yield: 182 mg (>99%) for LACOB-Pd1, 182 mg (>99%) for LACOB-Pd4; mp 92 °C.

IR (KBr): 2961, 1606, 1522, 1488, 835, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.54 (ddt, *J* = 11.9, 5.2, 2.1 Hz, 4 H), 7.46–7.42 (m, 2 H), 7.34–7.31 (m, 1 H), 7.02–6.99 (m, 2 H), 3.87 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.18, 140.86, 133.81, 128.75, 128.18, 126.77, 126.69, 114.23, 55.36.

4-Methyl-1,1′-biphenyl (3c)[23a]

White solid; yield: 139 mg (83%) for LACOB-Pd1, 167 mg (>99%) for LACOB-Pd4; mp 43 °C.

IR (KBr): 2915, 2855, 1485, 823, 754, 689 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.65–7.64 (dd, *J* = 5.0, 3.3 Hz, 2 H), 7.57–7.55 (m, 2 H), 7.50–7.47 (m, 2 H), 7.40–7.37 (dd, *J* = 8.2, 6.6 Hz, 1 H), 7.32–7.30 (d, *J* = 8.5 Hz, 2 H), 2.46 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.23, 138.43, 137.07, 129.55, 128.78, 127.06, 127.04, 21.16.

4-(Trifluoromethyl)-1,1′-biphenyl (3d)[25]

White solid; yield: 139 mg (63%) for LACOB-Pd1, 207 mg (93%) for LACOB-Pd4; mp 70 °C.

IR (KBr): 2925, 1613, 842, 769 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.70 (s, 4 H), 7.62–7.60 (dd, J_1 = 8.1 Hz, J_2 = 1.0 Hz, 2 H), 7.50–7.47 (m, 2 H), 7.43–7.40 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.73, 139.76, 128.97, 128.17, 127.41, 127.27, 125.70, 125.67.

4-Chloro-1,1′-biphenyl (3e)[25]

White solid; yield: 157 mg (83%) for LACOB-Pd1, 187 mg (>99%) for LACOB-Pd4; mp 78 °C.

IR (KBr): 1477, 1398, 1097, 832, 757 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 4 H), 7.46–7.35 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 140.01, 139.68, 133.39, 128.92, 128.90, 128.40, 127.60, 127.00.

4-Fluoro-3-methyl-1,1′-biphenyl (3f)[26]

Colorless oil; yield: 125 mg (67%) for LACOB-Pd1, 179 mg (96%) for LACOB-Pd4.

IR (KBr): 3031, 2924, 1511, 1484, 1232, 1119, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.78 (d, *J* = 7.3 Hz, 2 H), 7.70–7.56 (m, 5 H), 7.35–7.29 (t, *J* = 8.9 Hz, 1 H), 2.60 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.92, 159.68, 140.71, 137.34, 137.28, 130.51, 130.45, 129.00, 127.37, 127.25, 126.26, 126.15, 125.37, 125.14, 115.63, 115.33, 14.96, 14.91.

4-Methoxy-3-methyl-1,1′-biphenyl (3g)[27]

White solid; yield: 196 mg (>99%) for LACOB-Pd1, 196 mg (>99%) for LACOB-Pd4; mp 74 °C.

IR (KBr): 2971, 1604, 1511, 1240, 1133, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.66 (m, 2 H), 7.55–7.50 (m, 4 H), 7.44–7.38 (m, 1 H), 7.00–6.97 (m, 1 H), 3.95 (s, 3 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.70, 141.37, 133.64, 129.79, 129.00, 127.19, 127.07, 126.85, 125.71, 110.47, 55.66, 16.73.

3-Chloro-4-methyl-1,1′-biphenyl (3h)[28]

Colorless oil; yield: 156 mg (77%) for LACOB-Pd1, 201 mg (>99%) for LACOB-Pd4.

IR (KBr): 2923, 1553, 1480, 1052, 758, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.57 (ddd, *J* = 8.2, 5.3, 2.0 Hz, 3 H), 7.50–7.30 (m, 5 H), 2.46 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.68, 140.00, 135.11, 135.00, 131.48, 129.10, 127.83, 127.80, 127.16, 125.49, 19.96.

3-Fluoro-2-methyl-1,1′-biphenyl (3i)[29]

Colorless oil; yield: 140 mg (75%) for LACOB-Pd1, 184 mg (>99%) for LACOB-Pd4.

IR (KBr): 2927, 1575, 1464, 1238, 759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.30 (m, 5 H), 7.24–7.17 (m, 1 H), 7.06–7.01 (dd, *J* = 11.8, 4.7 Hz, 2 H), 2.20–2.19 (d, *J* = 2.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.38, 160.15, 129.40, 128.37, 127.38, 126.72, 126.60, 125.52, 125.47, 114.12, 113.82, 12.38, 12.31.

4,4′-Dimethoxy-1,1′-biphenyl (3j)[30]

White solid; yield: 120 mg (56%) for LACOB-Pd4, mp 178 °C.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 4 H), 7.00–6.95 (m, 4 H), 3.85 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.73, 133.52, 127.75, 114.19, 55.37.

4-Methoxy-4′-nitro-1,1′-biphenyl (3l)[27]

Yellow solid; yield: 227 mg (>99%) for LACOB-Pd1, 227 mg (>99%) for LACOB-Pd4; mp 124 °C.

IR (KBr): 2928, 2835, 1596, 1509, 1343, 756 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.29–8.24 (m, 2 H), 7.71–7.66 (m, 2 H), 7.61–7.56 (m, 2 H), 7.05–7.00 (m, 2 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.66, 147.40, 146.74, 131.25, 128.77, 127.26, 124.34, 114.82, 55.63.

4-Methyl-4′-nitro-1,1′-biphenyl (3m)[31]

Yellow solid; yield: 211 mg (>99%) for LACOB-Pd1, 211 mg (>99%) for LACOB-Pd4; mp 170 °C.

IR (KBr): 3079, 2924, 1593, 1511, 1341, 1105, 823 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.26 (m, 2 H), 7.74–7.70 (m, 2 H), 7.55–7.52 (m, 2 H), 7.33–7.30 (m, 2 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.78, 147.05, 139.31, 136.04, 130.10, 127.67, 127.43, 124.30, 21.42.

4-Nitro-4′-(trifluoromethyl)-1,1′-biphenyl (3n)[32]

Yellow solid; yield: 238 mg (89%) for LACOB-Pd1, 265 mg (>99%) for LACOB-Pd4; mp 140 °C.

IR (KBr): 3077, 1599, 1519, 1346, 1323, 1069, 829 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.32 (m, 2 H), 7.79–7.72 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.89, 146.23, 142.49, 128.34, 128.01, 126.40, 126.34, 126.29, 126.25, 124.47.

4-Chloro-4′-nitro-1,1′-biphenyl (3o)[33]

Yellow solid; yield: 180 mg (77%) for LACOB-Pd1, 231 mg (>99%) for LACOB-Pd4; mp 174 °C.

IR (KBr): 3072, 1595, 1511, 1343, 815, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.27 (m, 2 H), 7.73–7.68 (m, 2 H), 7.59–7.54 (m, 2 H), 7.49–7.45 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.46, 146.52, 137.39, 135.46, 129.58, 128.84, 127.88, 124.42.

4-Fluoro-3-methyl-4′-nitro-1,1′-biphenyl (3p)[34]

Yellow solid; yield: 192 mg (83%) for LACOB-Pd1, 229 mg (>99%) for LACOB-Pd4; mp 68 °C.

IR (KBr): 2925, 1597, 1509, 1340, 1232, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.30–8.25 (m, 2 H), 7.70–7.66 (m, 2 H), 7.46–7.38 (m, 2 H), 7.15–7.09 (m, 1 H), 2.36 (d, *J* = 1.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.81, 160.52, 147.16, 147.01, 134.83, 134.78, 130.82, 130.74, 127.79, 126.66, 126.56, 126.11, 125.87, 124.32, 116.13, 115.82, 14.93, 14.88.

3-Chloro-4-methyl-4′-nitro-1,1′-biphenyl (3q)

Yellow solid; yield: 228 mg (92%) for LACOB-Pd1, 245 mg (>99%) for LACOB-Pd4; mp 109 °C.

IR (KBr): 3079, 2922, 1599, 1509, 1340, 828, 753 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.31–8.26 (m, 2 H), 7.72–7.67 (m, 2 H), 7.61–7.60 (d, *J* = 1.9 Hz, 1 H), 7.44–7.33 (m, 2 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.41, 146.27, 138.06, 137.15, 135.43, 131.84, 128.01, 127.77, 125.66, 124.39, 20.07.

3-Fluoro-2-methyl-4′-nitro-1,1′-biphenyl (3r)

Yellow solid; yield: 192 mg (83%) for LACOB-Pd1, 229 mg (>99%) for LACOB-Pd4; mp 125 °C.

IR (KBr): 3107, 2932, 1597, 1514, 1348, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.32–8.27 (m, 2 H), 7.52–7.47 (m, 2 H), 7.29–7.22 (m, 1 H), 7.12–7.02 (m, 2 H), 2.18 (d, *J* = 2.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.40, 160.16, 147.56, 147.52, 147.32, 142.03, 141.97, 130.37, 127.29, 127.17, 125.21, 125.16, 123.71, 123.06, 122.83, 115.40, 115.09, 12.35, 12.28.

4-Methoxy-4′-methyl-1,1′-biphenyl (3s)[27]

White solid; yield: 151 mg (76%) for LACOB-Pd1, 196 mg (>99%) for LACOB-Pd4; mp 129 °C.

IR (KBr): 2913, 1607, 1498, 1250, 1038, 807 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.46 (m, 4 H), 7.27–7.24 (m, 2 H), 7.02–6.97 (m, 2 H), 3.87 (s, 3 H), 2.41 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.16, 138.19, 136.57, 133.97, 129.67, 128.18, 127.96, 126.81, 114.39, 55.56, 21.28.

4,4′-Dimethyl-1,1′-biphenyl (3t)[35]

White solid; yield: 155 mg (85%) for LACOB-Pd1, 180 mg (>99%) for LACOB-Pd4; mp 148 °C.

IR (KBr): 3022, 2915, 1502, 804 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.56 (m, 4 H), 7.34–7.31 (dd, *J* = 8.4, 0.6 Hz, 4 H), 2.48 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.58, 136.96, 129.73, 127.10, 21.37.

4-Chloro-4′-methyl-1,1′-biphenyl (3u)[25]

White solid; yield: 128 mg (63%) for LACOB-Pd1, 152 mg (75%) for LACOB-Pd4; mp 152 °C.

IR (KBr): 3026, 2922, 1479, 1089, 808 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.39 (m, 6 H), 7.29–7.26 (m, 2 H), 2.42 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.82, 137.66, 137.33, 133.25, 129.82, 129.07, 128.41, 127.04, 21.33.

4-Fluoro-3,4′-dimethyl-1,1′-biphenyl (3v)[36]

White solid; yield: 120 mg (60%) for LACOB-Pd1, 178 mg (89%) for LACOB-Pd4; mp 38 °C.

IR (KBr): 3029, 2921, 1593, 1495, 1238, 808, 757 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.34 (m, 4 H), 7.28–7.24 (m, 2 H), 7.10–7.04 (m, 1 H), 2.42 (s, 3 H), 2.37–2.36 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.73, 159.49, 137.82, 137.23, 137.19, 137.09, 130.27, 130.21, 129.70, 127.05, 126.02, 125.91, 125.26, 125.03, 115.54, 115.25, 21.29, 14.94, 14.90.

1-(4′-Fluoro-3′-methyl-[1,1′-biphenyl]-4-yl)ethanone (3w)[37]

White solid; yield: 215 mg (94%) for LACOB-Pd1, 226 mg (>99%) for LACOB-Pd4; mp 87 °C.

IR (KBr): 2924, 1681, 1600, 1491, 1267, 1235, 815 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.04–8.00 (m, 2 H), 7.65–7.61 (m, 2 H), 7.46–7.38 (dtdd, *J* = 4.8, 2.9, 2.4, 0.5 Hz, 2 H), 7.12–7.06 (m, 1 H), 2.64 (s, 3 H), 2.36–2.35 (d, *J* = 1.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.90, 163.43, 160.15, 145.17, 135.92, 130.64, 130.57, 129.13, 127.23, 126.45, 126.34, 125.73, 125.50, 115.87, 115.57, 26.85, 14.93, 14.88.

4′-Methoxy-2-nitro-1,1′-biphenyl (3x)[38]

Yellow solid; yield: 227 mg (>99%) for LACOB-Pd1, 227 mg (>99%) for LACOB-Pd4; mp 59 °C.

IR (KBr): 3019, 2927, 1610, 1516, 1357, 1177, 751 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.79 (m, 1 H), 7.62–7.56 (m, 1 H), 7.47–7.42 (tt, *J* = 7.1, 1.5 Hz, 2 H), 7.29–7.24 (m, 2 H), 6.99–6.94 (m, 2 H), 3.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.91, 149.62, 136.06, 132.37, 132.14, 129.70, 129.34, 127.95, 124.21, 114.44, 55.52.

4′-Azido-4-fluoro-3-methyl-1,1′-biphenyl (3y)

Brown solid; yield: 25 mg (11%) for LACOB-Pd1, 45 mg (20%) for LACOB-Pd4.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.50 (m, 2 H), 7.38–7.30 (ddd, *J* = 7.2, 6.7, 2.2 Hz, 2 H), 7.11–7.04 (m, 3 H), 2.35–2.34 (d, *J* = 1.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.90, 159.64, 139.22, 137.46, 136.23, 136.18, 130.20, 130.12, 128.49, 125.95, 125.85, 125.51, 125.28, 119.59, 115.71, 115.41, 14.93, 14.88.

4′-Fluoro-3′-methyl-2-nitro-1,1′-biphenyl (3z)

Yellow solid; yield: 224 mg (97%) for LACOB-Pd1, 229 mg (>99%) for LACOB-Pd4; mp 54 °C.

IR (KBr): 3070, 2926, 1604, 1572, 1519, 1357, 1227, 1122, 896, 851 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86–7.83 (dd, *J* = 8.1, 1.0 Hz, 1 H), 7.64–7.58 (td, *J* = 7.6, 1.3 Hz, 1 H), 7.51–7.40 (m, 2 H), 7.17–7.02 (m, 3 H), 2.32–2.31 (d, *J* = 1.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.19, 159.93, 149.49, 135.70, 133.34, 133.28, 132.50, 132.16, 131.28, 131.21, 128.42, 127.20, 127.09, 125.67, 125.43, 124.29, 115.69, 115.39, 14.82, 14.77.

4′-Formyl-[1,1′-biphenyl]-2-carbonitrile (4)[39]

Light yellow solid; yield: 78 mg (75%) for LACOB-Pd4; mp 181 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.10 (s, 1 H), 8.03–8.01 (m, 2 H), 7.83–7.80 (d, *J* = 8.2 Hz, 1 H), 7.78–7.68 (ddd, *J* = 8.5, 5.9, 1.4 Hz, 3 H), 7.57–7.50 (ddd, *J* = 13.0, 6.5, 2.7 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.94, 144.21, 144.15, 136.39, 134.15, 133.28, 130.27, 130.21, 129.76, 128.74, 118.43, 111.50.

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Supporting Information

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