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Carbonylative Suzuki Coupling Catalyzed by Pd Complexes Based on [N,P]-Pyrrole Ligands: Direct Access to 2-Hydroxybenzophenones

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Abstract: The Suzuki-Miyaura cross-coupling is one of the most useful synthetic tools to build C–C bonds, but the use of hydroxyaryl halides to direct access hydroxy-biaryls still remains a challenge. For the carbonylative version of the reaction, the synthesis of hydroxybiaryl ketones is commonly solved by protecting group strategies. In this work, we report a protocol of carbonylative Suzuki-Miyaura coupling catalysed by a [N,P]-PdCl₂ complex using aryl halides, various aryl boronic acids and CO. We were able at first to obtain biphenyls, finding a singular reactivity towards 2-bromophenol, that later was extended to the carbonylation reaction, resulting in methodology that allows the obtention of 2-hydroxybiaryl ketones, with a functional group tolerance toward amines, alkoxy, ketones, esters, and halides.

Keywords: [N,P]-donor ligands; Carbonylative Suzuki Coupling; biaryl ketones; biphenyls; palladium

Introduction

Carbonylative Suzuki coupling (CSC) of aryl halides using carbon monoxide as C1 building block represents one of the most straightforward and convenient processes for the construction of symmetrical and unsymmetrical biaryl ketones.^[1] Numerous photosensitizers, natural products, advanced organic materials, and pharmaceutically apposite agents are comprised of biaryl ketone units (Figure 1).^[2]

Particularly, 2-hydroxybenzophenone scaffold is an important building block, widely present in functional materials, biologically active molecules, and natural products.^[3] Currently, a highly regioselective catalytic

approach to obtain 2-hydroxybenzophenones is an attractive challenge in organic synthesis. This kind of compounds could be obtained from classical methods such as the Friedel-Crafts acylation of phenols,^[4] and Fries rearrangement of aryl benzoates,^[5] but with the drawback of the lack of site-selectivity. Recently, some catalytic protocols like C–H activation, mainly C_{sp2}-H hydroxylation of benzophenone,^[6] C_{formyl}-H arylation of salicylaldehyde,^[7] and the carbonylative Suzuki coupling have been developed.^[8] Nonetheless, few examples exist due to the incompatibility of the hydroxyl group in these kinds of reactions.

Since the publication of the first carbonylative Suzuki coupling in 1993,^[9] several improvements and

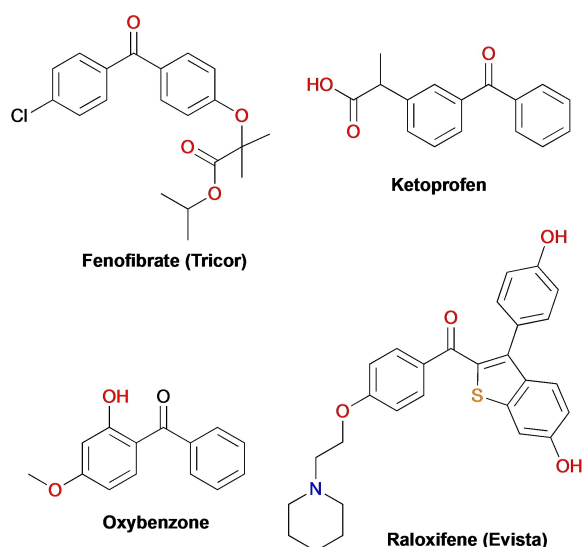


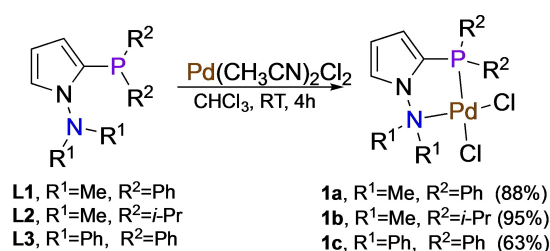
Figure 1. Some relevant molecules including the biaryl ketone fragment.

applications of the original synthetic protocol have been described,^[1] but some limitations remain like the formation of biaryls as side-products, the use of additives, or the restriction to special substrates. While the palladium-catalyzed Suzuki coupling has been accomplished using a myriad of ligands containing significantly different chemical functionalities,^[10] scarce information about hybrid ligands in the carbonylative Suzuki coupling exists. Despite that nitrogen donor ligands in synergic combination with the coordinative properties of the phosphorus atom could enhance catalytic behavior of palladium complexes,^[11] only scarcely reports are found on the use of [N,P]-ligands in carbonylative Suzuki coupling, showing low yields and modest selectivity towards CSC product.^[12]

In our continuous interest to promote catalytic applications for the privileged pyrrole based [N,P] ligand **L1**,^[13] we have developed a Pd-based catalytic system for the carbonylative Suzuki coupling giving high yields, good selectivity with wide tolerance of several functional groups, under mild conditions. Moreover, we have extended the reaction to produce 2-aryl phenols and 2-hydroxyphenyl ketones using unprotected phenols in short reaction times, under low CO pressure.

Results and Discussion

Initially, we synthesized the ligands **L1-3** and palladium complexes **1a-c** following our previous findings.^[13] Complexes **1a-c** were obtained in good yields after purification by recrystallization in dichloromethane (Scheme 1). As the NMR data revealed, a $\Delta\delta^{31\text{P}}$ chemical shift of ca. 40 ppm and $\Delta\delta^{13\text{C}}$ chemical shift of ca. 10 ppm (for C–N) towards lower



Scheme 1. Synthesis of the palladium complexes **1a-c**.

field confirmed that **L1-3** behave as [N,P]-bidentate ligands. To correlate the electronic properties of **L1-3**, we prepared the corresponding selenides (See, SI). The $^1J_{\text{PSe}}$ values can be correlated with the electronic character of phosphine group.^[14] The data obtained revealed that both ligands **L1** and **L3** display a similar π -acceptor behavior, while **L2** behaves as a σ -donor phosphine (Table 1).

To assure the success in the carbonylative Suzuki coupling, **1a-c** were first tested in the classical Suzuki-Miyaura coupling (SMC) (Table 2). Initially, 1-bromonaphthalene and phenylboronic acid were coupled using 2 equivalents of K_2CO_3 as base. Several bio-sourced solvents were tested. Using methanol, the best yield was up to 93% (Table 2, entry 1). Moreover, ethanol and ethanol/ H_2O mixture (8:2) gave similar yields in the reaction (85 and 89% respectively, Table 2, entries 2–3). Once selected methanol as solvent, we explored the nature of the base but none of the other bases improved the result previously obtained with potassium carbonate (Table 2, entries 6–9 versus 1). Additionally, all our attempts to modify the amount of base were unfruitful showing that 2 eq. of K_2CO_3 is the optimal amount (Table 2, entries 1, 10–13).

We also tested the palladium complexes **1a-c** to evaluate the electronic effects of the substituents on the donor atoms. Thus, the complex **1a** and **1b** led to the best yields (Table 2, entries 1, 14) while **1c** did not catalyze efficiently the C–C coupling, probably because this complex is not very stable in methanol (solution) for a long time (Table 2, entry 15).

Table 1. ^{31}P chemical shift (ppm) for the [N,P]-ligands and the complexes **1a-c**.

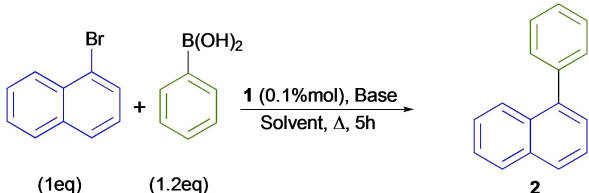
Ligand	$\delta^{31\text{P}}$ (a)	$\delta^{31\text{P}}$ (P=Se) ^[a]	$1J_{\text{PSe}}$ ^[b]	$\Delta\delta^{31\text{P}}$ ^[c]
L1	–29.9	47.3	734	46.6
L2	–16.5	56.3	703	67.4
L3	–31.9	16.2	745	42.9
PPh₃	4.0	45.7	708	20.5 ^[d]

^[a] ppm.

^[b] Hz.

^[c] ($\Delta\delta = \delta_{\text{complex}} - \delta_{\text{ligand}}$) ppm.

^[d] according to ref. [15].

Table 2. Optimization of conditions for the Suzuki-Miyaura coupling.^[a]


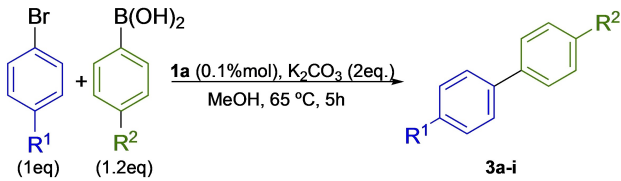
Entry	[Pd]	Solvent	Base (eq.)	Yield (%) ^[b]
1	1 a	Methanol	K ₂ CO ₃ (2)	93
2	1 a	Ethanol/H ₂ O ^c	K ₂ CO ₃ (2)	89
3	1 a	Ethanol	K ₂ CO ₃ (2)	85
4	1 a	Ethylene glycol	K ₂ CO ₃ (2)	43
5	1 a	Ethyl acetate	K ₂ CO ₃ (2)	76
6	1 a	Methanol	K ₃ PO ₄ (2)	76
7	1 a	Methanol	Na ₃ PO ₄ (2)	61
8	1 a	Methanol	NaOH (2)	86
9	1 a	Methanol	KOH (2)	49
10	1 a	Methanol	K ₂ CO ₃ (0.5)	7
11	1 a	Methanol	K ₂ CO ₃ (1)	11
12	1 a	Methanol	K ₂ CO ₃ (1.5)	63
13	1 a	Methanol	K ₂ CO ₃ (3)	80
14	1 b	Methanol	K ₂ CO ₃ (2)	84
15	1 c	Methanol	K ₂ CO ₃ (2)	45

^[a] Reaction conditions: 0.41 g (2 mmol) of 1-bromonaphthalene, 0.3 g (2.4 mmol) of phenyl boronic acid, 4 mmol of base (2 eq.), 1 mg (0.002 mmol) of **1 a**, 5 mL of solvent, T = 70 °C, t = 5 h.

^[b] Isolated yield after SiO₂ flash chromatography. c) Ethanol/H₂O (8:2).

Analysing the catalytic performance of complex **1 a** vs **1 c**, it is evident that the acceptor properties of phosphorus atom are important, but the steric hindrance of phenyl groups on the nitrogen atom must contribute to the de-coordination from the palladium center (Table 2, entries 1 and 15). On the other side, although complex **1 b** exhibited a good catalytic result, it seems that the donor properties of **L2** are less effective to provide a good catalytic tuning to palladium atom in comparison to **1 a**.

Once obtained the best conditions, we explored the scope of the reaction (Table 3). The system showed a remarkable tolerance and efficiency to both electron donor and electron withdrawing groups in *para*-position of the arylbromide (Table 3, entries 1–9), even with coordinating groups like cyano and dimethylamino and a restrictive substrate like 4-bromophenol. Moreover, the reaction was performed in open-vessel without a strictly dry environment. In all cases, the reaction was clean since just one product was isolated after hexane extraction. Nevertheless, with strong electron withdrawing (NO₂) or coordinating amine substituents in the boronic acid, the coupling did not occur (Table 3, entries 10 and 12).

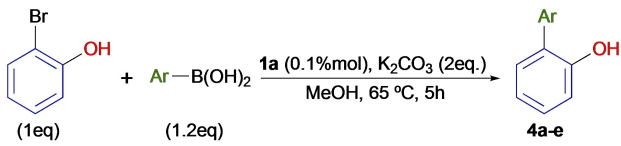
Table 3. Scope of the aromatic bromide in SMC.^[a]


Entry	R ¹	R ²	Compound	Yield ^[b]
1	CH ₃	H	3 a	78
3	OH	H	3 b	91
4	N(CH ₃) ₂	H	3 c	98
4	OCH ₃	H	3 d	90
5	H	H	3 e	99
6	COCH ₃	H	3 f	87
7	CN	H	3 g	99
8	CF ₃	H	3 h	86
9	NO ₂	H	3 i	90
10	H	N(CH ₃) ₂	3 c	0
11	H	COCH ₃	3 f	85
12	H	NO ₂	3 i	0

^[a] Reaction conditions: 2 mmol of aromatic bromide, 2.4 mmol of phenyl boronic acid, 4 mmol of base, 0.002 mmol of **1 a**, 5 mL of methanol.

^[b] Isolated yield after SiO₂ flash chromatography.

Encouraged by the result obtained with 4-bromophenol (Table 3, entry 2), we tested a more demanding substrate like 2- and 3-bromophenol (Table 4). The reaction failed with 3-bromophenol but, the coupling proceeded efficiently with 2-bromophenol and some arylboronic acids, giving easy access to 2-arylphenols in good (76%) to excellent (97–99%) yields (Table 4, entries 1, 5 and 2, 4), except for that including the dimethylamino group on the phenyl boronic acid (Table 4, entry 3).

Table 4. Reaction of 2-bromophenol with different boronic acids.^[a]


Entry	Ar	Product	Yield ^[b]
1	Ph	4 a	76
2	1-Naphtyl	4 b	97
3	4-N(CH ₃) ₂ -C ₆ H ₄ -	4 c	25
4	4-COCH ₃ -C ₆ H ₄ -	4 d	99
5	2-Thienyl	4 e	76

^[a] Reaction conditions: 0.34 g (2 mmol) of 2-bromophenol, 2.4 mmol of phenyl boronic acid, 0.55 g (4 mmol) of K₂CO₃, 5.4 mg (0.002 mmol) of **1 a**, 5 mL of methanol.

^[b] Isolated yield after SiO₂ flash chromatography.

As the **1a** complex proved to be efficient in the Suzuki reaction, we decided to involve it in the carbonylative Suzuki reaction. Initially, the reaction was carried out with 4-bromotoluene and phenylboronic acid in toluene at 100 °C, 5 bar of CO in presence of 1% mol of **1a**. Unfortunately, the corresponding biaryl ketone was not obtained. So, we selected the 4-iodotoluene as aryl halide, TBAF as additive to facilitate both the oxidative addition^[16] and transmetalation steps and toluene as solvent because CO is more soluble in non-polar solvents (Table 5, entry 1).^[17] But the result was disappointing with no product obtained.

Next, we tried anisole as non-toxic solvent with the same outcome (Table 5, entry 2). We switched again to K₂CO₃ (Table 5, entries 4 and 5) obtaining excellent conversions and selectivities up to 97%. This result was maintained even by reducing the catalytic load of **1a** to 0.5% mol, the CO pressure (5 to 2.5 bar) and the reaction time (from 6 to 3 h) (Table 5, entry 6).

Considering the results gained in the SMC reaction (Tables 3 and 4), we evaluated the temperature, conducting the carbonylation at 65 °C, obtaining a lower conversion with good selectivity (Table 5, entry 7). We decided to keep the reaction temperature at 100 °C. Then, we performed a poisoning test with Hg (Table 5, entry 8) giving a quasi-total conversion with comparable selectivity towards the ketone. This experiment gave insights about the homogeneous

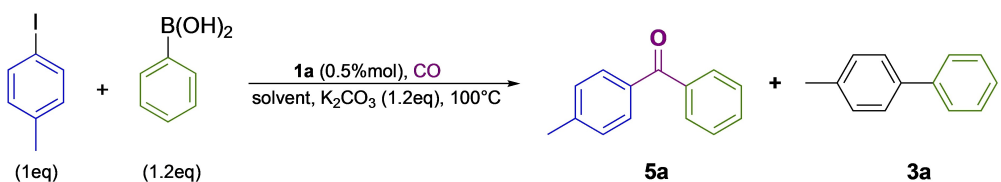
behavior of **1a** in the C–C coupling, excluding the participation of Pd nanoparticles in the reaction.

We also studied the influence of the reactants concentration in the reaction. Thus, increasing it from 0.2 M to 0.6 M (Table 5, entry 9), a good conversion was reached but surprisingly the selectivity was reversed giving mostly the biphenyl product **3a**. This behavior is presumably due to saturation of the solution with boronic acid that favors the conventional Suzuki coupling.

Finally, we tested PdCl₂ as palladium precursor, using 0.5% mol. The reaction was not complete after the time reaction. We then increased the palladium loading to 1% mol, observing total conversion. However, the selectivity decreases to 65:35 ratio (Table 5, entry 10) showing the crucial role of the pyrrole based [N,P]-ligand in the selectivity. At this stage, the carbonylative Suzuki reaction of a set of *para*-substituted phenyl iodides together with phenyl boronic acid was carried out using the complex **1a** (Table 6, entries 1–8).

The conversion obtained for all the substrates including electron donor or withdrawing groups was excellent (98–100%). However, the selectivity was affected by the acceptor groups on the aryl iodide. Indeed, with cyano and methyl ester substituents, the selectivity decreased around 70:30 (Table 6, entries 4 and 8) and in case of the nitro group it was the only example where the biaryl ketone was not the main

Table 5. Optimization of the reaction conditions for the Carbonylative Suzuki-Miyaura coupling.^[a]



Entry	Solvent	additive	Time (h)	CO Pressure (bar)	% [1 a]	Conversion (%) ^[b]	Selectivity (5 a:3 a)
1	Toluene	TBAF	6	5	1	–	–
2	Anisole	TBAF	6	5	1	–	–
3	Anisole	LiF	6	5	1	–	–
4	Anisole	K ₂ CO ₃	6	5	1	97	97:3
5	Toluene	K ₂ CO ₃	6	5	1	99	95:5
6	Toluene	K ₂ CO ₃	3	2.5	0.5	100	97:3
7 ^[c]	Toluene	K ₂ CO ₃	3	2.5	0.5	15	94:6
8 ^[d]	Toluene	K ₂ CO ₃	3	2.5	0.5	98	90:10
9 ^[e]	Toluene	K ₂ CO ₃	3	2.5	0.5	99	16:84
10 ^[f]	Toluene	K ₂ CO ₃	6	5	1	89	65:35

^[a] Reaction conditions: 1 mmol of 4-iodotoluene, 1.2 mmol of phenyl boronic acid, 1.2 mmol of base, 5 mL of solvent.

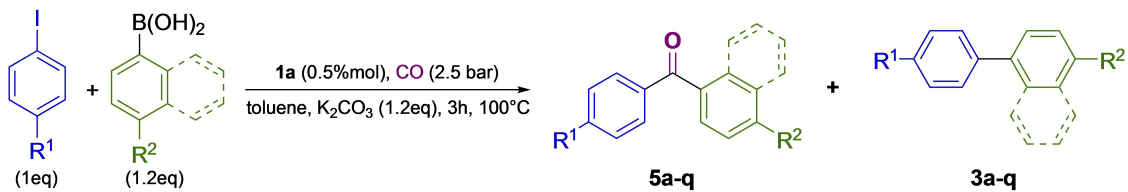
^[b] Conversion was determined by GC/MS and confirmed by ¹H NMR.

^[c] Reaction conducted at 65 °C.

^[d] Reaction conducted in the presence of a Hg(0) drop.

^[e] Reaction conditions: 3 mmol of 4-iodotoluene, 3.6 mmol of phenyl boronic acid, 3.6 mmol of base, 5 mL of solvent.

^[f] Reaction conducted using 1% mol of PdCl₂ as catalytic precursor.

Table 6. Scope of 4-aryliodides and the boronic acids in the carbonylative SMC.^[a]


Entry	R1	R2	Conversion (%) ^[b]	Selectivity (5:3)	Yield (%) ^[c] (5)
1	CH ₃	H	100	97:3	81 (5a)
2	OCH ₃	H	98	91:9	88 (5d)
3	COCH ₃	H	100	98:2	86 (5f)
4	CN	H	100	75:25	73 (5g)
5	CF ₃	H	100	99:1	99 (5h)
6	NO ₂	H	100	41:59	37 (5i)
7	NH ₂	H	100	100:0	80 (5j)
8	COOCH ₃	H	100	68:32	66 (5k)
9	CH ₃	OCH ₃	100	95:5	77 (5l)
10	CH ₃	CH ₃	100	96:4	75 (5m)
11	CH ₃	CF ₃	79	94:6	60 (5n)
12	CH ₃	NO ₂	0	–	– (5o)
13	CH ₃	Cl	99	96:4	92 (5p)
14	CH ₃	1-Naphtyl	91	100:0	71 (5q)

Reaction conditions:

^[a] 1 mmol of Aryl iodide, 1.2 mmol of the corresponding phenyl boronic acid, 0.05 mmol of **1a**, 1.2 mmol of K₂CO₃ and 5 mL of toluene under 2.5 bar of CO.

^[b] Conversion was determined by GC and confirmed by ¹H NMR.

^[c] Isolated yield after purification on preparative SiO₂ TLC.

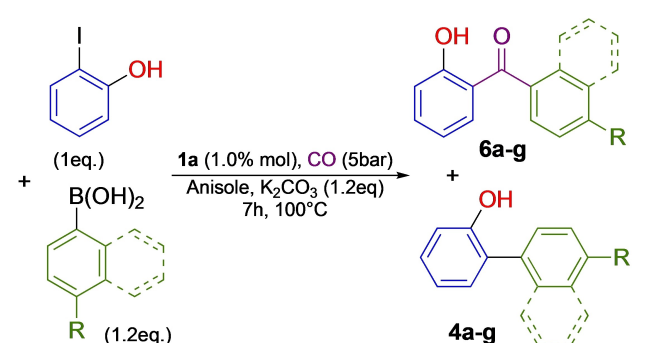
product, (**5:3** ratio of 41:59, Table 6, entry 6). Exceptionally the presence of the -CF₃ and -COCH₃ groups preserved a high selectivity towards the biaryl ketone, with 99:1 and 98:2 ratio, respectively. Likewise, we demonstrated that the system was also compatible with various aryl boronic acids (Table 6, entries 9–14). The conversion and selectivity were remarkable in these conditions, but the conversion dropped significantly with 4-nitrophenyl boronic acid (Table 6, entry 12). Looking at the selectivity, good results up to 90% were achieved in both cases with electron withdrawing and donating groups on the arylboronic acid, favoring the formation of the non-symmetric biaryl ketone **5a–q**.

Inspired by the results achieved in the SMC with 2-bromophenol, we explored the carbonylative coupling reaction using 2-iodophenol and different boronic acids. At first, we used the previous established conditions and only a conversion of 79% was obtained (Table 7, entry 1). We increased the time reaction to 5 h (Table 7, entry 2), but the conversion remained the same. So, we modified the catalytic parameters such as catalyst loading, the reaction time, the CO pressure and used anisole as solvent (Table 7, entry 3). Under these conditions, full conversion was obtained with a good selectivity of the 2-hydroxybenzophenone **6a** (**6:4** ratio of 80:20). We explored again the reactivity using different boronic acids. As we pointed out

earlier, the presence of the hydroxyl group in the substrate represents a challenge for accomplishing this coupling. Thus, under the new reaction conditions, the catalytic system was efficient in the coupling of 2-iodophenol with a variety of aryl boronic acids. As seen previously, the conversion was dramatically affected by the strong electron withdrawing groups as -NO₂ (0%, Table 7, entry 6) and -CF₃ (27%, Table 7, entry 9). Similar behavior was observed with strong electron donating groups such as -OCH₃ (47% Table 6, entry 8). Nevertheless, the selectivity of the reaction favored the formation of the biaryl ketone, depending on the substituent on the boronic acid (Table 7, entries 3, 5, 8–9). As far as we know, this is the first report of the synthesis of 2-hydroxybenzophenones through carbonylative SMC using an aryl iodide containing the hydroxyl group in *ortho*-position, improving the synthetic protocols for obtaining 2-hydroxyphenyl arylketones.

Comparing the catalytic performance of some palladium precursors containing [N,P]-ligands,^[12,18,19] included in Table 8, we can observe that the **1a** complex gives better catalytic performance in terms of conversion and selectivity in the carbonylative SMC reaction. Moreover, the catalytic applications of most of these complexes were not extended to phenols. On the other side, the presence of **L1** in **1a** offers a good

Table 7. Carbonylative SMC of 2-iodophenol, with different boronic acids.^[a]



Entry	R	Conv. (%) ^[b]	Selectivity (6:4)	Yield (%) ^[c]
1 ^[d]	H	79	78:22	58 (6a)
2 ^[e]	H	77	73:27	55 (6a)
3	H	100	80:20	72 (6a)
4	1-Naph-tyl	96	77:23	67 (6b)
5	CH ₃	98	86:14	78 (6f)
6	NO ₂	0	–	– (6g)
7	Cl	91	67:33	57 (6h)
8	OMe	47	100:0	45 (6i)
9	CF ₃	27	85:15	18 (6j)

^[a] Reaction conditions: 1 mmol of 2-iodophenol, 1.2 mmol of the respective phenyl boronic acid, 0.01 mol of **1a**, 1.2 mmol of K₂CO₃ and 5 mL of anisole under 5 bar of CO.

^[b] Conversion was determined by GC and confirmed by ¹H NMR.

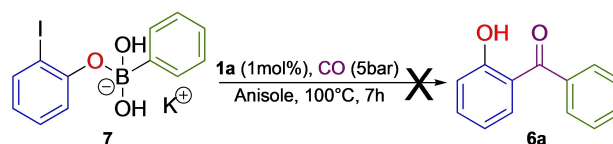
^[c] Isolated yield after purification on preparative SiO₂ TLC.

^[d] Reaction conditions: **1a** (0.5%mol), 2.5 bar CO, t=3 h.

^[e] Reaction conditions: **1a** (0.5%mol), 2.5 bar CO, t=5 h.

electronic balance to palladium center, allowing the synthesis of several biaryl ketones, as well as extending its catalytic application successfully to challenged substrates as 2-iodophenol (Table 8, entry 4). This catalytic system is robust, air-moisture stable and operates under low CO pressure conditions.

To gain insights about the role of hydroxyl group in the carbonylative coupling, we have performed some experiments. Initially, we tested the possible formation of adduct **7** between the phenylboronic acid and 2-iodophenol. Therefore, we synthesized **7** in methanol under reflux and potassium carbonate. After consumption of 2-Iodophenol, we recovered **7** by just filtration in 85% of yield. With **7** in our hands, we performed the carbonylative reaction (Scheme 2), the GC-MS analysis did not reveal the formation of any carbonylative product or the biphenyl product. This result suggests that the OH group does not assist a plausible intramolecular transmetalation step in the catalytic cycle, in concordance with the literature.^[20]

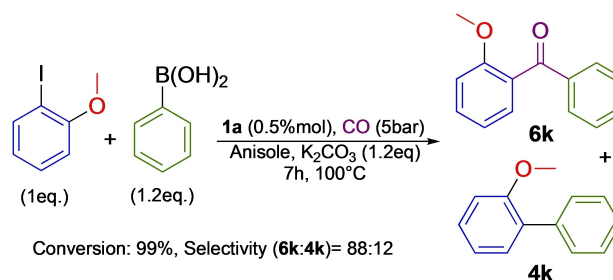


Scheme 2. Carbonylative SMC using the adduct **7**.

To rule out the presence of any possible H-bond interaction and/or a side-reaction between the hydroxyl group with the boronic acid,^[21] we explored the carbonylative SMC using 2-iodoanisole instead of 2-iodophenol (Scheme 3). In this case, we observed a complete reaction with a selectivity slightly better than that with 2-iodophenol (Table 7, Entry 3).

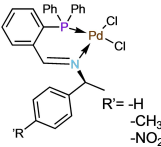
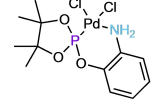
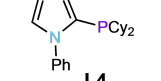
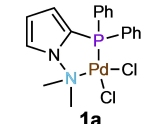
Based on the experimental evidence, we propose the following mechanism for this carbonylative SMC reaction (Scheme 4). After the activation of the palladium precursor **1a** in presence of the arylboronic acid,^[22] the species (**A**) suffers the oxidative addition of the aryl iodide leading (**B**). This species reacts with CO forming the transient species (**C**) which readily allows the migratory CO insertion giving (**D**). Even if the experiments carried out previously showed that the hydroxyl group included in the substrate has no direct influence on the reaction (Scheme 3), it is plausible that the OH and/or OMe group can coordinate the palladium atom giving the species (**D'**). This could explain why the **L1** ligand improves the catalytic performance of the palladium complex. Similar acyl hydroxo complexes have been reported in literature.^[7a] Both species can undergo transmetalation leading (**E**) and (**E'**), and finally to conduct to the corresponding 2-hydroxybenzophenone after reductive elimination.

The species (**B**) formed at the first stage of this catalytic cycle can also react with the arylboronic acid forming (**F**) that after a reductive elimination gives the 2-arylphenol compound. These pathways are in competition and the selectivity of the carbonylative-coupling product strongly depends on the electron withdrawing character of the groups included in the aryl boronic acid. Likewise, the π -acceptor properties of [N,P]-ligand **L1** also contribute to the best



Scheme 3. Carbonylative SMC of 2-iodoanisole.

Table 8. Catalytic performance of different palladium systems in the carbonylative SMC reaction.

Entry	Palladium catalyst	Conditions	CO pressure (bar)	Time (h)	Conversion (%)	Ratio A/B	Examples	Ref
1		0.02% mol [Pd], K ₂ CO ₃ , 1,4-Dioxane, 80 °C	1	2	35–85	1:0	4	12
2		1.5% mol [Pd], K ₂ CO ₃ , 1,4-Dioxane, 100 °C	1	2	80–99	1:0	9 ^[a]	18
3		1.5% mol L4/0.05% mol Pd(OAc) ₂ , TMEDA, Toluene, 100 °C	5	24	26	27	1	19
4		0.5% mol [Pd], K ₂ CO ₃ , anisole, 100 °C	2.5–5	3–7	91–100	6:4 to 1:0	24 ^[b]	This work

^[a] 4-Iodophenol fails as substrate in the carbonylative SMC reaction.

^[b] The carbonylative SMC was successfully extended to 2- and 4-iodophenol.

electronic balance in the metallic center, allowing the carbonylative SMC with strong coordinating substrates as 2-hydroxyarylhalides.

Conclusion

In summary, we have developed a catalytic system for obtaining biaryl- and non-symmetric biaryl ketones under mild conditions of Suzuki-Miyaura and carbonylative Suzuki-Miyaura coupling.

This Pd/pyrrole based [N,P] ligand catalytic system is stable toward air and moisture and reacts with challenging substrates such as 2-bromo and 2-iodophenols for synthesizing 2-hydroxybiphenyls and 2-hydroxybenzophenones. This catalytic system operates at 2.5 bar of CO pressure for the carbonylative SMC of aryl iodides, being necessary to increase the CO pressure to 5 bar, when 2-iodophenol was used as the substrate.

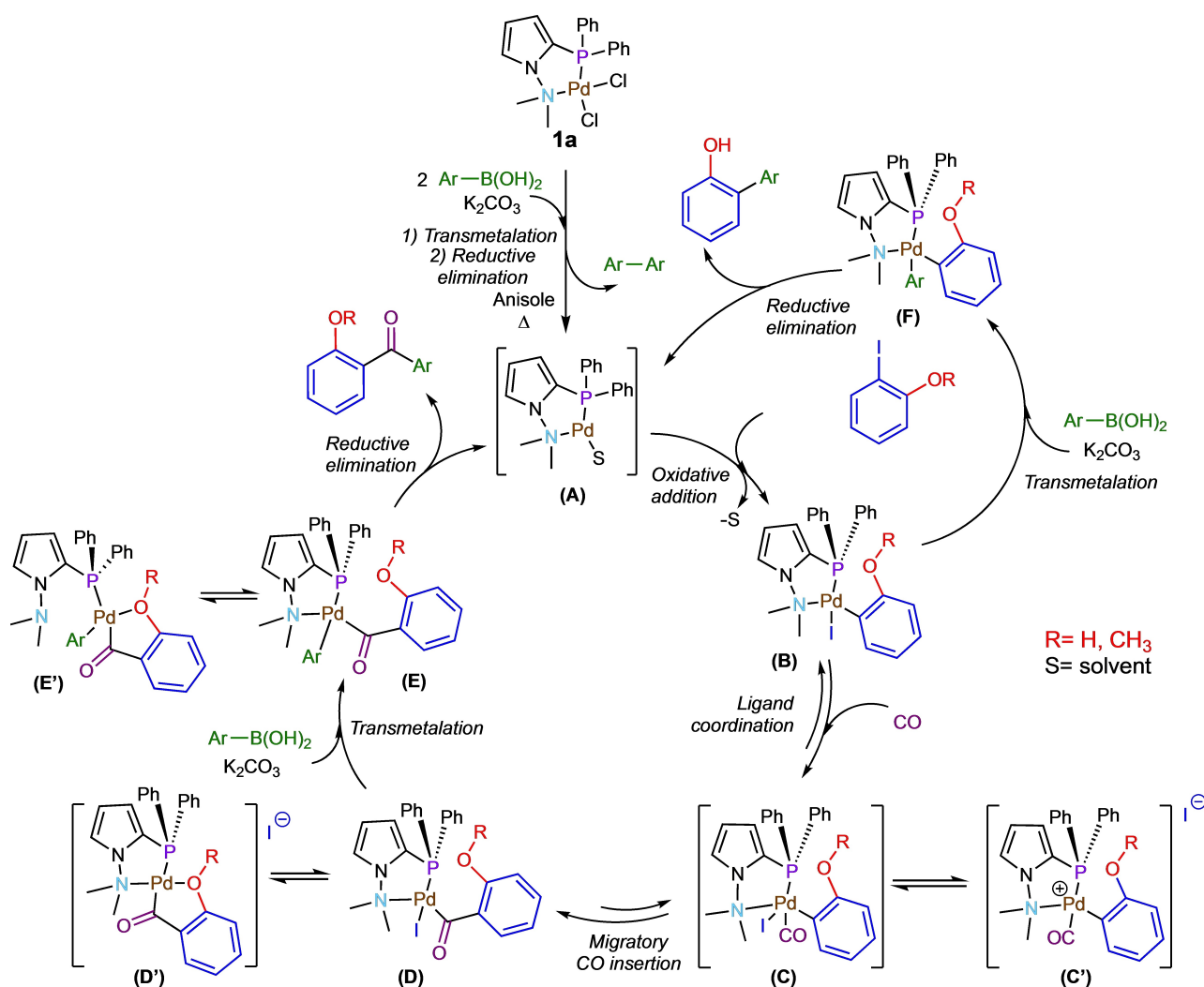
Thus, complex **1a** can be exploited in the synthesis of 2-hydroxybiphenyls and 2-hydroxybenzophenones, which are structural motifs included in a variety of natural products and pharmaceuticals.

Experimental Section

Details of experimental conditions, characterization data and copies of ¹H and ¹³C NMR, MS and IR spectra for all isolated compounds are included in the Supporting Information.

General procedure for the Suzuki-Miyaura Coupling. In a 20 mL flask with a magnetic bar was placed 2 mmol of the corresponding aryl bromide, 2.4 mmol of the aryl boronic acid, 4 mmol of potassium carbonate, 0.002 mmol of the catalyst and 5 mL of methanol. The reaction was heated at 65 °C, for 5 h in open atmosphere. Then, the mixture was allowed to reach room temperature and extracted with hexane (2 × 30 mL). The organic phase was dried with anhydrous Na₂SO₄. Finally, the solvent was evaporated under reduced pressure leading to the pure biaryls.

General Procedure for the Carbonylative Suzuki coupling. A 10 mL vial was filled with the corresponding aryl iodide (1 mmol), the boronic acid 1.2 mmol, according to the case 0.05 mmol or 0.01 mmol of the catalyst, 1.2 mmol of potassium carbonate and 5 mL of solvent (toluene or anisole), a magnetic bar was put in, and the vial was introduced into a stainless-steel reactor, which was charge with the respective pressure of CO and placed in an oil bath at the working temperature. Once the reaction was completed, the reaction was cooled to room temperature and decompressed carefully. The reaction mixture was diluted with ethyl acetate and washed with brine, the organic phase was separated and dried with anhydrous Na₂SO₄, after the evaporation of the ethyl acetate and toluene, in the



Scheme 4. Proposed mechanism for the carbonylative SMC.

case of anisole, was distilled in a Kugelrohr apparatus, the residue was analysed by GC-MS and confirmed by $^1\text{H-NMR}$.

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References

- [1] a) M. Beller, in *Catalytic Carbonylation Reactions*, Springer, Berlin, 2006; b) L. Kollar, in *Modern Carbonylation Methods*, Wiley-VCH, Weinheim, 2008; c) X.-F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; d) D. Bhattacharjee, M. Rahman, S. Ghosh, A. K. Bagdi, G. V. Zyryanov, O. N. Chupakhin, P. Das, A. Hajra, *Adv. Synth. Catal.* **2021**, *363*, 1597–1624.
- [2] K. M. Bjerglund, T. Skrydstrup, G. A. Molander, *Org. Lett.* **2014**, *16*, 1888–1891.
- [3] a) T. Ali, M. Inagaki, H.-B. Chai, T. Wieboldt, C. Rapplye, L. H. Rakotondraibe, *J. Nat. Prod.* **2017**, *80*, 1397–1403; b) J. M. Grandner, R. A. Cacho, Y. Tang, K. N. Houk, *ACS Catal.* **2016**, *6*, 4506–4511; c) Z. Klimová, J. Hojerová, M. Beránková, *Food Chem. Toxicol.* **2015**, *83*, 237–250.
- [4] P. H. Gore, *Chem. Rev.* **1995**, *55*, 229–281.
- [5] J. A. Miller, *J. Org. Chem.* **1987**, *52*, 322–323.

- [6] a) G. Shan, X. Yang, L. Ma, Y. Rao, *Angew. Chem. Int. Ed.* **2012**, *51*, 13070–13074; *Angew. Chem.* **2012**, *124*, 13247–13251; b) F. Mo, L. J. Trzepkowski, G. Dong, *Angew. Chem. Int. Ed.* **2012**, *51*, 13075–13079; *Angew. Chem.* **2012**, *124*, 13252–13256; c) P. Y. Choy, F. Y. Kwong, *Org. Lett.* **2013**, *15*, 270–273; d) L. Massignan, X. Tan, T. H. Meyer, R. Kuniyil, A. M. Messinis, L. Ackermann, *Angew. Chem. Int. Ed.* **2020**, *59*, 3184–3189; *Angew. Chem.* **2020**, *132*, 3210–3215.
- [7] a) T. Satoh, T. Itaya, M. Miura, M. Nomura, *Chem. Lett.* **1996**, *25*, 823–824; b) N. Nowrouzi, S. Motevalli, D. Tarokh, *J. Mol. Catal. A.* **2015**, *396*, 224–230; c) M. L. Rao, B. S. Ramakrishna, *Eur. J. Org. Chem.* **2017**, *2017*, 5080–5093.
- [8] a) M. Niakan, Z. Asadi, M. Emami, *Catal. Lett.* **2020**, *150*, 404–418; b) W. J. Ang, L. C. Lo, Y. Lam, *Tetrahedron* **2014**, *70*, 8545–8558.
- [9] T. Ishiyama, H. Kizaki, N. Miyaura, A. Suzuki, *Tetrahedron Lett.* **1993**, *34*, 7595–7598.
- [10] Some recent reviews about the Suzuki-Miyaura coupling, see: a) B. S. Kadu, *Catal. Sci. Technol.* **2021**, *11*, 1186–1221; b) S. Akkoç, *J. Chin. Chem. Soc.* **2021**, *68*, 942–951; c) S. E. Hooshmand, B. Heidari, R. Sedghi, R. S. Varma, *Green Chem.* **2019**, *21*, 381–405; d) A. T. K. Koshvandi, M. M. Heravi, T. Momeni, *Appl. Organomet. Chem.* **2018**, *32*, e4210; e) A. Chatterjee, T. R. Ward, *Catal. Lett.* **2016**, *146*, 820–840; f) I. Hussain, J. Capricho, M. A. Yawer, *Adv. Synth. Catal.* **2016**, *358*, 3320–3349.
- [11] Selected reviews on [N,P] ligands in Suzuki coupling, see: a) R. Connon, B. Roche, B. V. Rokade, P. J. Guiry, *Chem. Rev.* **2021**, *121*, 6373–6521; b) S. M. Wong, C. M. So, K. H. Chung, C. P. Lau, F. Y. Kwong, *Eur. J. Org. Chem.* **2012**, *2012*, 4172–4177; c) T. Mahamo, M. M. Mogorosi, J. R. Moss, S. F. Mapolie, J. C. Slootweg, K. Lammertsma, G. S. Smith, *J. Organomet. Chem.* **2012**, *703*, 34–42; d) W.-H. Zhang, S.-W. Chein, T. S. Hor, *Coord. Chem. Rev.* **2011**, *255*, 1991–2024; e) J. A. Weeden, R. Huang, K. D. Galloway, P. W. Gingrich, B. J. Frost, *Molecules* **2011**, *16*, 6215–6231; f) Z. Weng, S. Teo, T. S. A. Hor, *Acc. Chem. Res.* **2007**, *40*, 676–684.
- [12] M. K. Yilmaz, H. Keles, S. Ince, M. Keles, *Appl. Organomet. Chem.* **2017**, *32*, e4002.
- [13] a) E. P. Sánchez-Rodríguez, S. Cortés-Mendoza, J.-C. Daran, M. C. Ortega-Alfaro, J. G. López-Cortés, M. Gouygou, *Appl. Organomet. Chem.* **2020**, *34*, e5709; b) E. P. Sánchez-Rodríguez, A. J. Fragoso-Medina, E. Ramírez-Meneses, M. Gouygou, M. C. Ortega-Alfaro, J. G. López-Cortés, *Catal. Commun.* **2018**, *115*, 49–54; c) J. V. Suárez-Meneses, A. Oukhirb, M. Gouygou, M. Urrutigoity, J.-C. Daran, A. Cordero-Vargas, M. C. Ortega-Alfaro, J. G. López-Cortés, *Dalton Trans.* **2016**, *45*, 9621–9630; d) J. V. Suárez-Meneses, E. Bonilla-Reyes, E. A. Blé-González, M. C. Ortega-Alfaro, R. A. Toscano, A. Cordero-Vargas, J. G. López-Cortés, *Tetrahedron* **2014**, *70*, 1422–1430.
- [14] a) U. Beckmann, D. Süslüyan, P. C. Kunz, *Phosphorous, Sulfur, and Silicon* **2011**, *186*, 2061–2070; b) D. W. Allen, I. W. Nowell, *J. Chem. Soc. Dalton Trans.* **1985**, 2505–2508.
- [15] F. McLachlan, C. J. Mathews, P. J. Smith, T. Welton, *Organometallics* **2003**, *22*, 5350–5357.
- [16] a) T. Yamada, J. Jiang, N. Ito, K. Park, H. Masuda, C. Furugen, M. Ishida, S. Otori, H. Sajiki, *Catalysis* **2020**, *10*, 1209; b) T. Jeffery, *Tetrahedron* **1996**, *52*, 10113–10130; c) T. Jeffery, *Tetrahedron Lett.* **1985**, *26*, 2667–2670; d) T. Jeffery, *J. Chem. Soc. Chem. Commun.* **1984**, 1287–1289.
- [17] H. M. Colquhoun, D. J. Thompson, M. V. Twigg, in *Carbonylation*, Plenum Press, New York, 1991.
- [18] P. Wójcik, L. Sygellou, A. Gniewek, A. Skarżyńska, A. Trzeciak, *ChemCatChem* **2017**, *9*, 4397–4409.
- [19] H. Neumann, A. Brennfhrer, M. Beller, *Chem. Eur. J.* **2008**, *14*, 3645–3652.
- [20] a) A. A. Thomas, S. E. Denmark, *Science* **2016**, *352*, 329–332; b) A. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2011**, *17*, 2492–2503; c) B. P. Carrow, J. F. Hartwing, *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119; d) A. F. Schmidth, E. V. Kurokhtina, E. V. Larina, *Russ. J. Gen. Chem.* **2011**, *81*, 1573–1574.
- [21] J. Ruan, J. A. Iggo, N. G. Berry, J. Xiao, *J. Org. Chem.* **2010**, *132*, 16689–16699.
- [22] a) K. H. Shaughnessy, *Isr. J. Chem.* **2019**, *59*, 1–16; b) M. Moreno-Mañas, M. Pérez, R. Pleixats, *J. Org. Chem.* **1996**, *61*, 2346–2351.