

Article

Stabilized Palladium Nanoparticles from Bis-(*N*-benzoylthiourea) Derived-Pd^{II} Complexes as Efficient Catalysts for Sustainable Cross-Coupling Reactions in Water

Samet Poyraz ¹ , H. Ali Döndaş ^{1,2,*} , Samet Belveren ¹ , Senanur Taş ², Raquel Hidalgo-León ³, José Trujillo-Sierra ³ , Lesly V. Rodríguez-Flórez ³, M^a de Gracia Retamosa ³ , Ana Sirvent ³ , Mohammad Gholinejad ^{4,5} , Sara Sobhani ^{6,7} and José M. Sansano ^{3,*} 

- ¹ Department of Basic Pharmaceutical Sciences, Faculty of Pharmacy, Çukurova University, Balcalı, Adana 01330, Türkiye; s.poyraz88@gmail.com (S.P.); bvrnsamet@mersin.edu.tr (S.B.)
- ² Department of Biotechnology, Institute of Natural and Applied Sciences, Çukurova University, Balcalı, Adana 01330, Türkiye; senanurtas99@gmail.com
- ³ Departamento de Química Orgánica, Instituto de Síntesis Orgánica (ISO), Centro de Innovación en Química Avanzada (ORFEO-CINQA), University of Alicante, P.O. Box 99, 03690 Alicante, Spain; raquel.hidalgo@ua.es (R.H.-L.); josetrujillosierra98@gmail.com (J.T.-S.); lesly.rodriguez11@ua.es (L.V.R.-F.); graciretamosa@hotmail.com (M.d.G.R.)
- ⁴ Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), P.O. Box 45195-1159, Zanjan 45137-66731, Iran; gholinejad@iasbs.ac.ir
- ⁵ Research Center for Basic Sciences & Modern Technologies (RBST), Institute for Advanced Studies in Basic Sciences (IASBS), Zanjan 45137-66731, Iran
- ⁶ Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran; ssobhani@birjand.ac.ir
- ⁷ Department of Chemistry, College of Sciences, University of Birjand, Birjand 9717434765, Iran
- * Correspondence: adondas@cu.edu.tr (H.A.D.); jmsansano@ua.es (J.M.S.)



Citation: Poyraz, S.; Döndaş, H.A.; Belveren, S.; Taş, S.; Hidalgo-León, R.; Trujillo-Sierra, J.; Rodríguez-Flórez, L.V.; Retamosa, M.d.G.; Sirvent, A.; Gholinejad, M.; et al. Stabilized Palladium Nanoparticles from Bis-(*N*-benzoylthiourea) Derived-Pd^{II} Complexes as Efficient Catalysts for Sustainable Cross-Coupling Reactions in Water. *Molecules* **2024**, *29*, 1138. <https://doi.org/10.3390/molecules29051138>

Abstract: Stable palladium (II) complexes, incorporating a double (*N*-benzoylthiourea) arrangement bonded to a complex heterocyclic scaffold, are used as precursors of catalytic species able to promote Suzuki–Miyaura, Mizoroki–Heck, Hiyama, Buchwald–Hartwig, Hirao and Sonogashira–Hagihara cross-coupling transformations in water. These sustainable processes are chemoselective and very versatile. The nanoparticles responsible for these catalytic reactions were analyzed and studied. Their usefulness is demonstrated after several tests and analyses. The heterogeneous character of this species in water was also confirmed.

Keywords: nanoparticles; palladium; Suzuki; Heck; Hiyama; Buchwald–Hartwig; Hirao; Sonogashira; water; heterogeneous catalysis

Academic Editors: Yinghuai Zhu and Lin Huang

Received: 30 January 2024
Revised: 22 February 2024
Accepted: 27 February 2024
Published: 4 March 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The element Palladium constitutes a crucial component in many scientific areas and industrial processes [1]. Due to its low presence in the ore deposits around the world, the synthesis of palladium nanoparticles (PNPs) represents an extraordinary advance. It is very well known that there is a larger surface area exhibited by PNPs rather than palladium bulk metal. Concerning this, automobile sector, electronics, catalysis, dentistry, jewelry and biomedical therapies for cancer take advantage of this property to expand the applications [1]. In the field of the catalysis, the carbon–carbon bond-forming reactions represent a very exploited and useful tool in general organic synthesis [2,3]. Implementing the concept of PNPs in these transformations, the term green process can be associated with them [4]. Thus, for example, Kumada–Tamao–Corriu [5], Mizoroki–Heck [6], Negishi [7], Stille [8], Sonogashira–Hagihara [9], Suzuki–Miyaura [10,11], Hiyama [12], Hirao [13] couplings, Buchwald–Hartwig reaction [13], etc., have been published using PNPs in a green manner. Another important detail in this field is the procedure employed to prepare PNPs

(physical or chemical). From the industrial point of view, the physical methods require large energy costs due to the high temperatures and/or pressures involved. The chemical methods usually require harmful solvents and hazardous reducing or stabilizing agents, generating toxic by-products [1]. Thus, electrochemical, sonochemical, sol-gel, supercritical fluid, plant/bacteria-mediated methodologies, etc., have been implemented [1].

In this work, we will survey the ability to generate stabilized PNPs in the reaction media from already-known palladium(II) complexes, testing their efficiency in sustainable cross-coupling reactions such as Suzuki–Miyaura, Mizoroki–Heck, Sonogashira–Hagihara, Hirao, Hiyama couplings and Buchwald–Hartwig reactions in water [14]. The characterization of the PNPs prepared in situ, as well as their recyclability, will also be analyzed.

2. Results and Discussion

2.1. Suzuki–Miyaura Cross-Coupling

Using the known methodology developed by our group, the amphiphilic palladium complexes **1** and **2** were obtained (Figure 1). For this purpose, the starting *endo*-prolinates **3**, isolated after 1,3-dipolar cycloaddition [15–17], were allowed to react with phenyl isothiocyanate in refluxing acetonitrile to obtain compounds **4** in good yields. Finally, chelation was achieved using palladium(II) acetate in methanol at rt for 48 h. *Cis*-complexes **1** and **2** were isolated in yields depicted in Figure 1. The relative configuration of complex **1** was unambiguously determined according to an X-ray diffraction pattern observed in a preceding work [18]. It is characterized and evaluated as a potential anti(myc)obacterial and antifungal agent [18,19]. The structure of complex **2** was deduced according to NMR experiments. These two aggregates are very stable and can be stored for a long time under argon atmosphere [20,21]. They were evaluated to a classical Suzuki–Miyaura cross-coupling, keeping in mind the aim to complete a sustainable process. In this reaction, and that described in the manuscript, the stoichiometry of the reagents was briefly optimized but was always based in our previous contributions.

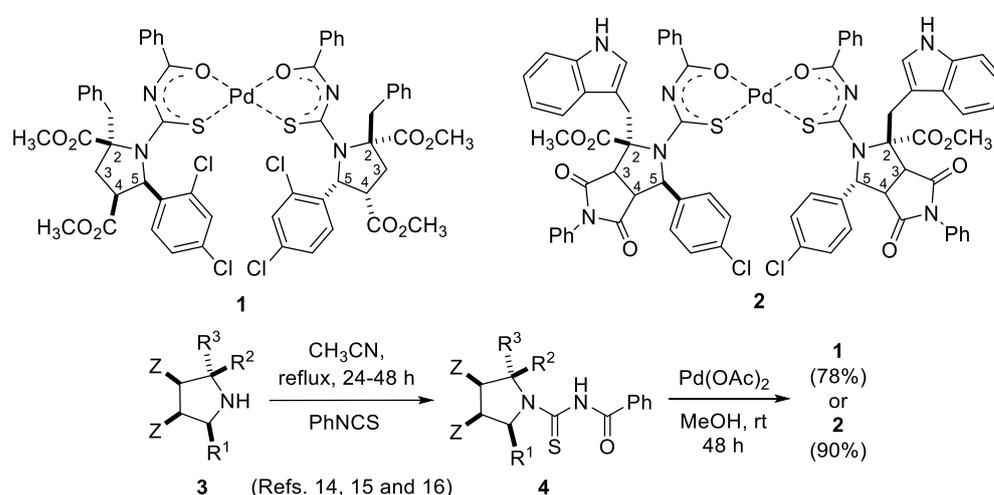
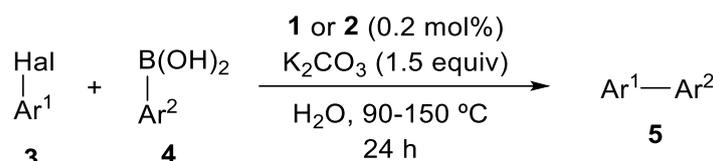


Figure 1. Structure of the palladium(II) complexes (**1** and **2**) precursors of PNPs and their preparation.

The first idea was using water as a solvent under standard conditions, set up by our group in a previous contribution [22]. The optimized reaction between 4-iodoanisole and phenylboronic acid operated at 90 °C using potassium carbonate as a base and 0.2 mol% of the catalyst for 24 h (Scheme 1). The best precursor of the palladium catalytic species was complex **1** rather than complex **2** (compare entries 10p and 20p of Table 1). The influence of the solvent was analyzed; thus, when the reaction was performed in toluene, 1,4-dioxane and DMF, the chemical yields did not improve compared with the yield obtained using water (entries 10p and 30p-50p of Table 1). The addition of 0.1 mol% palladium complex did not offer high yields (Table 1, entry 60p), and the lowering of the temperature was unfruitful

(Table 1, entry 7op). The reaction did not occur at all in the absence of the pre-catalyst. Electron-donating and electron-withdrawing groups, bonded to iodoarene **3**, allowed for the reaction in very good yields (Table 1, entries 1op and 8–11). The carbon–chlorine bond remained intact after the reaction shown in entry 11 of Table 1. The Suzuki–Miyaura coupling (Scheme 1) between iodobenzene and different arylboronic acids afforded biaryls **5** in high yields (Table 1, entries 12 and 13). The reaction of aryl bromides needed 120 °C to obtain the same range of yields than the corresponding iodoarenes (Table 1, entries 14–16). However, chloroarenes **3** reacted slowly and required higher temperatures (150 °C) to obtain moderate to good chemical yields of **5** (Table 1, entries 17–19).



Scheme 1. Suzuki–Miyaura cross coupling promoted by complexes **1** or **2**.

Table 1. Optimization and scope of the Suzuki–Miyaura coupling using complexes **1** or **2**¹.

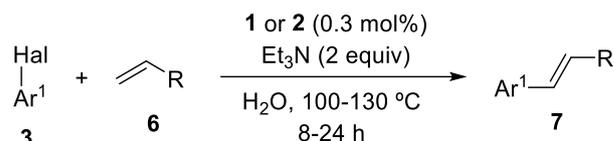
Entry	Pd Source	Ar ¹ -Hal 3	Ar ² 4	Solvent	T (°C)	5	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	5a	89
2op	2	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	5a	65
3op	1	4-MeO-C ₆ H ₄ I	Ph	PhMe	90	5a	37
4op	1	4-MeO-C ₆ H ₄ I	Ph	1,4-dioxane	90	5a	88
5op	1	4-MeO-C ₆ H ₄ I	Ph	DMF	90	5a	43
6op ³	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	5a	66
7op	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	70	5a	78
8	1	4-MeC ₆ H ₄ I	Ph	H ₂ O	90	5b	89
9	1	3-(CN)C ₆ H ₄ I	Ph	H ₂ O	90	5c	88
10	1	3-(CHO)C ₆ H ₄ I	Ph	H ₂ O	90	5d	90
11	1	4-ClC ₆ H ₄ I	Ph	H ₂ O	90	5e	90
12	1	PhI	4-MeO-C ₆ H ₄	H ₂ O	90	5a	87
13	1	PhI	4-Me-C ₆ H ₄	H ₂ O	90	5b	87
14	1	4-MeO-C ₆ H ₄ Br	Ph	H ₂ O	110	5a	79
15	1	3-(CHO)C ₆ H ₄ Br	Ph	H ₂ O	110	5d	81
16	1	4-(Ac)C ₆ H ₄ Br	Ph	H ₂ O	110	5f	80
17	1	4-MeO-C ₆ H ₄ Cl	Ph	H ₂ O	150	5a	54
18	1	4-Me-C ₆ H ₄ Cl	Ph	H ₂ O	150	5b	68
19	1	4-(CN)-C ₆ H ₄ Cl	Ph	H ₂ O	150	5g	70

op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), phenylboronic acid (0.75 mmol), K₂CO₃ (0.75 mmol), **1** (0.2 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 24 h. ² Chemical yields isolated after flash chromatography. ³ A measure of 0.1 mol% of palladium complex **1** was employed.

2.2. Mizoroki–Heck Reaction

Having the results of the previous coupling reaction, the Mizoroki–Heck reaction in water (Scheme 2) was next surveyed employing a set of conditions implemented in our group [23]. In this manner, the optimized reaction between 4-iodoanisole (**3a**) and *n*-butyl acrylate (**6a**) operated at 100 °C using triethylamine as a base, and 0.3 mol% of the catalyst for 8 h was performed. The best precursor of the palladium catalytic species was again complex **1** (Table 2, entries 1op and 2op). Toluene, 1,4-dioxane and DMF afforded similar chemical yields to the reaction run with water, but the ¹H NMR spectra of these three crude products were not very clean (Table 2, entries 3op, 4op and 5op). Potassium carbonate afforded similar results (Table 1, entry 6op), whilst sodium hydroxide was not a suitable base for this process (Table 1, entry 7op). Lowering of the catalyst loading (0.2 mol%) and the temperature of the reaction (90 °C) furnished lower yields of the expected alkene

7 (Table 1, entries 8op and 9op). The combination of assorted iodoarenes **3** and *n*-butyl acrylate (**6a**) or styrene (**6b**) produced compounds **7** in high isolated yields (Table 1, entries 1op and 10–14). Again, the chlorine atom remained intact in the reaction shown in entries 13 and 14 of Table 2. Bromobenzene and *p*-bromoanisole reacted with *n*-butyl acrylate (**6a**) or styrene (**6b**) at 120 °C in 8 h (Table 2, entries 15–18). This higher temperature was required to obtain almost complete conversions. However, the reaction of chlorobenzene was very difficult to achieve. In this case, moderate chemical yields of **7c** and **7d** were isolated (50 and 54%, respectively) using 130 °C and 24 h of reaction (Table 2, entries 19 and 20).



Scheme 2. Mizoroki–Heck reaction promoted by complexes **1** or **2**.

Table 2. Optimization and scope of the Mizoroki–Heck reaction using complexes **1** or **2**¹.

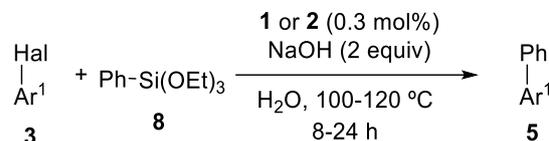
Entry	Pd Source	Ar ¹ -Hal 3	R 6	Solvent	T (°C)	7	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7a	83
2op	2	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7a	64
3op	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	PhMe	100	7a	80
4op	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	1,4-dioxane	100	7a	77
5op	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	DMF	100	7a	80
6op ³	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7a	81
7op ⁴	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7a	58
8op ⁵	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7a	43
9op ⁶	1	4-MeO-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	90	7a	66
10	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	100	7b	80
11	1	PhI	CO ₂ Bu ⁿ	H ₂ O	100	7c	81
12	1	PhI	Ph	H ₂ O	100	7d	80
13	1	4-Cl-C ₆ H ₄ I	CO ₂ Bu ⁿ	H ₂ O	100	7e	81
14	1	4-Cl-C ₆ H ₄ I	Ph	H ₂ O	100	7f	77
15	1	PhBr	CO ₂ Bu ⁿ	H ₂ O	120	7c	76
16	1	PhBr	Ph	H ₂ O	120	7d	75
17	1	4-MeO-C ₆ H ₄ Br	CO ₂ Bu ⁿ	H ₂ O	120	7a	79
18	1	4-MeO-C ₆ H ₄ Br	Ph	H ₂ O	120	7b	80
19	1	PhCl	CO ₂ Bu ⁿ	H ₂ O	130 ⁶	7c	50
20	1	PhCl	Ph	H ₂ O	130 ⁶	7d	54

op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), olefin (0.55 mmol), triethylamine (1 mmol), H₂O (1.5 mL) and **1** (0.3 mol%), were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature. ² Chemical yields isolated after flash chromatography. ³ K₂CO₃ was used as base. ⁴ NaOH was used as base. ⁵ A measure of 0.2 mol% of palladium complex **1** was employed. ⁶ Represents 24 h of reaction.

2.3. Hiyama Cross-Coupling

To probe the catalytic activity of the palladium active species toward the Hiyama cross-coupling reactions (Scheme 3), the reaction of iodoanisole (**3a**) and triethoxyphenylsilane (**8**) in aqueous media was chosen as a model reaction [23]. Various reaction parameters were rapidly screened, obtaining the following results summarized in Table 3: (a) the efficiency of the catalyst precursor **1** was higher than the analogous one obtained for the catalytic species precursor **2** (Table 3, compare entries 1op and 2op); (b) toluene, 1,4-dioxane and DMF afforded similar chemical yields to the reaction run with water, but the ¹H NMR spectra of these three crude products were not very clean (Table 3, entries 3op, 4op and 5op); (c) the most appropriate base was NaOH rather than potassium carbonate or triethylamine (Table 3, entries 6op and 7op); (d) the optimal operation temperature was 100 °C (Table 3, entry 8op); (e) and the suitable catalyst loading was generated in the presence of 0.3 mol%

of **1** (Table 3, entry 9op). In general, iodoarenes reacted at 100 °C (Table 3, entries 1op and 10–12) and bromoarenes at 110 °C (Table 3, entries 13–15), achieving chemical yields in the same range (80–75%). Despite using 130 °C and reaction times of 24 h, the yields of product **5** were moderate when aryl chlorides were used as starters (Table 3, entries 16–18).



Scheme 3. Hiyama cross-coupling promoted by complexes **1** or **2**.

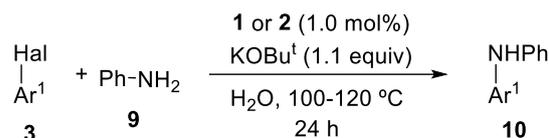
Table 3. Optimization and scope of the Hiyama cross-coupling using complexes **1** or **2**¹.

Entry	Pd Source	Ar ¹ -Hal 3	Solvent	T (°C)	5	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	5a	81
2op	2	4-MeO-C ₆ H ₄ I	H ₂ O	100	5a	55
3op	1	4-MeO-C ₆ H ₄ I	PhMe	100	5a	80
4op	1	4-MeO-C ₆ H ₄ I	1,4-dioxane	100	5a	80
5op	1	4-MeO-C ₆ H ₄ I	DMF	100	5a	81
6op ³	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	5a	81
7op ⁴	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	5a	58
8op	1	4-MeO-C ₆ H ₄ I	H ₂ O	90	5a	53
9op ⁵	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	5a	66
10	1	4-Me-C ₆ H ₄ I	H ₂ O	100	5b	80
11	1	3-(CN)-C ₆ H ₄ I	H ₂ O	100	5c	78
12	1	4-Cl-C ₆ H ₄ I	H ₂ O	100	5e	80
13	1	4-MeO-C ₆ H ₄ Br	H ₂ O	110	5a	75
14	1	3-(CHO)-C ₆ H ₄ Br	H ₂ O	110	5d	76
15	1	4-(Ac)-C ₆ H ₄ Br	H ₂ O	110	5f	75
16	1	4-MeO-C ₆ H ₄ Cl	H ₂ O	120 ⁶	5a	49
17	1	4-Me-C ₆ H ₄ Cl	H ₂ O	120 ⁶	5b	50
18	1	4-(CN)-C ₆ H ₄ Cl	H ₂ O	120 ⁶	5g	56

op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), catalyst **1** (0.3 mol%), triethoxyphenylsilane (0.6 mmol), NaOH (0.5 mmol) water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature. ² Chemical yields isolated after flash chromatography. ³ K₂CO₃ was used as base. ⁴ Et₃N was used as base. ⁵ A measure of 0.2 mol% of palladium complex **1** was employed. ⁶ Represents 24 h of reaction.

2.4. Buchwald-Hartwig Cross-Coupling

The catalytic activity of the species studied before was assessed in the Buchwald-Hartwig reaction (Scheme 4) following the established conditions in water detailed in the literature [24,25]. The conditions displayed in entry 1op of Table 4 were achieved using the catalyst precursor **1**, 4-iodoanisole and aniline [26]. The 41% yield could be improved neither by the presence of the pre-catalyst **2** nor by increasing the temperature (compare entries 1op–3op of the Table 4). The employment of potassium phosphate as a base, lower temperatures than 100 °C, and a catalyst loading of 2 mol% were not appropriate (Table 4, entries 4op–6op). Toluene, 1,4-dioxane and DMF did not improve the yield obtained in the reaction run with water. The reaction offered modest yields with iodoarenes (41–58%, Table 4, entries 1op, 7 and 8), but the scope was not so wide as it was described in the previous coupling transformations. In fact, 4-bromoanisole afforded a very low yield after reaction with aniline at 120 °C for 24 h (Table 4, entry 9).



Scheme 4. Buchwald–Hartwig cross-coupling promoted by complexes **1** or **2**.

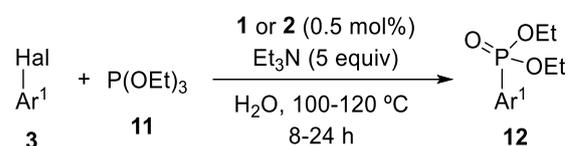
Table 4. Optimization and scope of Buchwald-Hartwig reaction using complexes **1** or **2**¹.

Entry	Pd Source	Ar ¹ -Hal 3	T (°C)	10	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	100	10a	41
2op	2	4-MeO-C ₆ H ₄ I	100	10a	<10
3op	1	4-MeO-C ₆ H ₄ I	120	10a	40
4op ³	1	4-MeO-C ₆ H ₄ I	100	10a	38
5op	1	4-MeO-C ₆ H ₄ I	90	10a	nr
6op ⁴	1	4-MeO-C ₆ H ₄ I	100	10a	38
7	1	4-Me-C ₆ H ₄ I	100	10b	45
8	1	4-Cl-C ₆ H ₄ I	100	10c	58
9	1	4-MeO-C ₆ H ₄ Br	120	10a	35

op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), aniline (0.5 mmol), KOBu^t (2.00 mmol), **1** (1.0 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 24 h. ² Chemical yields isolated after flash chromatography. ³ K₃PO₄ was used as base. ⁴ A measure of 2.0 mol% of palladium complex **1** was employed.

2.5. Hirao Cross-Coupling

A Hirao cross-coupling reaction (Scheme 5) means the formation of a C(sp²)-P bonds catalyzed by transition metals [27], and it allows us to obtain arylphosphonates **12**, which are valuable intermediates and molecules in organic synthesis [23]. The reaction between triethylphosphite (**11**) and 4-iodoanisole (**3a**) was chosen as a model reaction to find the best suitable reaction conditions. Initially, the reaction was performed with the catalyst and triethylamine in water. The efficiency of the precatalyst **1** was higher once more, yielding **12a** in 88% (compare entries 1op and 2op of the Table 5). Other solvents tested were not as effective as water (Table 5, entries op3-op5). Triethylamine was the most appropriate base (compare entries 1op and 6op and 7op of the Table 5), and the reaction did not operate completely at 90 °C after 8 h (Table 5, entry 8op). A lower amount of the catalyst loading was not beneficial for the full transformation (Table 5, entry 9op). Iodoarenes reacted satisfactorily under the optimal conditions defined in entry 1op of the Table 5 (entries 1op, 10 and 11 of the same Table) as did bromoarenes, but afforded slightly lower chemical yields (Table 5, entries 12–14). Aryl chlorides also gave very interesting results of products **12**, although using higher temperatures (120 °C) for 24 h (Table 5, entries 15–17).



Scheme 5. Hirao cross-coupling promoted by complexes **1** or **2**.

Table 5. Optimization and scope of Hirao reaction using complexes **1** or **2**¹.

Entry	Pd Source	Ar ¹ -Hal 3	Solvent	T (°C)	12	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	12a	88
2op	2	4-MeO-C ₆ H ₄ I	H ₂ O	100	12a	51
3op	1	4-MeO-C ₆ H ₄ I	PhMe	100	12a	75
4op	1	4-MeO-C ₆ H ₄ I	1,4-dioxane	100	12a	76
5op	1	4-MeO-C ₆ H ₄ I	DMF	100	12a	74
6op ³	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	12a	42
7op ⁴	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	12a	58
8op	1	4-MeO-C ₆ H ₄ I	H ₂ O	90	12a	76
9op ⁵	1	4-MeO-C ₆ H ₄ I	H ₂ O	100	12a	38
10	1	PhI	H ₂ O	100	12b	91
11	1	4-Cl-C ₆ H ₄ I	H ₂ O	100	12c	85
12	1	PhBr	H ₂ O	100	12b	75

Table 5. Cont.

Entry	Pd Source	Ar ¹ -Hal 3	Solvent	T (°C)	12	Yield (%) ²
13	1	4-Me-C ₆ H ₄ Br	H ₂ O	100	12d	72
14	1	4-MeO-C ₆ H ₄ Br	H ₂ O	100	12a	72
15	1	PhCl	H ₂ O	120 ⁶	12b	68
16	1	4-Me-C ₆ H ₄ Cl	H ₂ O	120 ⁶	12d	66
17	1	4-MeO-C ₆ H ₄ Cl	H ₂ O	120 ⁶	12a	59

op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), triethylphosphite (1.0 mmol), Et₃N (2.5 mmol), **1** (0.5 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 8 h. ² Chemical yields isolated after flash chromatography. ³ NaOH was used as base. ⁴ K₂CO₃ was used as base. ⁵ A measure of 0.3 mol% of palladium complex **1** was employed. ⁶ Represents 24 h of reaction.

2.6. Sonogashira–Hagihara Cross-Coupling

The Sonogashira–Hagihara cross-coupling reaction (Scheme 6) was next assessed using these two palladium catalyst precursors. Using the parameters displayed by our group [28], the optimization was performed with phenylacetylene (**13a**) and 4-iodoanisole (**3a**). The employment of 90 °C, DABCO as a base in water for 10 h afforded compound **14a** in 91% yield in the presence of the catalyst generated by **1** (Table 6, entry 1op). However, an 81% yield was achieved when complex **2** was used as a pre-catalyst (Table 6, entry 2op). Using toluene, 1,4-dioxane, or DMF, similar yields were obtained (Table 6, entries op3–op5), but water was selected for operational simplicity and further recycling of the catalytic suspension. DABCO as a base gave the best results rather than other bases such as triethylamine or potassium carbonate (compare entries 1op, 6op and 7op of the Table 6). Lower temperature and catalyst loadings were also not productive for the reaction completion at the same reaction time (Table 6, entries 8op and 9op). Iodoarenes reacted with phenylacetylene (**13a**) or propargyl alcohol (**13b**), furnishing the corresponding alkynes **14** in very good yields (Table 6, entries op1 and 10–14). Also, good yields were obtained employing bromoarenes at the same conditions with these two different terminal alkynes **14a** and **14b** (Table 6, entries 15–18). Aryl chlorides were demonstrated to be good starting materials, obtaining results similar to the obtained ones for the reactions performed with bromides but while heating the reaction to 120 °C for 24 h (Table 6, entries 19–22).

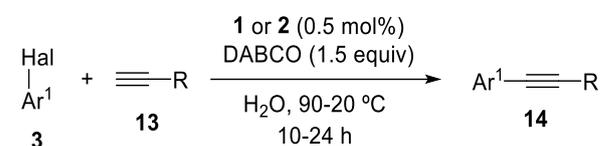
**Scheme 6.** Sonogashira–Hagihara cross-coupling promoted by complexes **1** or **2**.

Table 6. Optimization and scope of Sonogashira–Hagihara cross-coupling using complexes **1** or **2**¹.

Entry	Pd Source	Ar ¹ -Hal 3	R 13	Solvent	T (°C)	14	Yield (%) ²
1op	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	14a	91
2op	2	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	14a	81
3op	1	4-MeO-C ₆ H ₄ I	Ph	PhMe	90	14a	85
4op	1	4-MeO-C ₆ H ₄ I	Ph	1,4-dioxane	90	14a	90
5op	1	4-MeO-C ₆ H ₄ I	Ph	DMF	90	14a	90
6op ³	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	14a	72
7op ⁴	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	14a	50
8op	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	70	14a	46
9op ⁵	1	4-MeO-C ₆ H ₄ I	Ph	H ₂ O	90	14a	29
10	1	PhI	Ph	H ₂ O	90	14b	87
11	1	4-Cl-C ₆ H ₄ I	Ph	H ₂ O	90	14c	85
12	1	4-(CN)-C ₆ H ₄ I	Ph	H ₂ O	90	14d	83

Table 6. Cont.

Entry	Pd Source	Ar ¹ -Hal 3	R 13	Solvent	T (°C)	14	Yield (%) ²
13	1	PhI	CH ₂ OH	H ₂ O	90	14e	80
14	1	4-MeO-C ₆ H ₄ I	CH ₂ OH	H ₂ O	90	14f	80
15	1	PhBr	Ph	H ₂ O	90	14b	75
16	1	4-MeO-C ₆ H ₄ Br	Ph	H ₂ O	90	14a	72
17	1	PhBr	CH ₂ OH	H ₂ O	90	14e	70
18	1	4-MeO-C ₆ H ₄ Br	CH ₂ OH	H ₂ O	90	14f	69
19	1	PhCl	Ph	H ₂ O	120 ⁶	14b	68
20	1	4-MeO-C ₆ H ₄ Cl	Ph	H ₂ O	120 ⁶	14a	61
21	1	PhCl	CH ₂ OH	H ₂ O	120 ⁶	14e	69
22	1	4-MeO-C ₆ H ₄ Cl	CH ₂ OH	H ₂ O	120 ⁶	14f	70

Op = optimization test. ¹ Typical procedure: 4-iodoanisole (0.5 mmol), phenylacetylene (0.55 mmol), DABCO (0.75 mmol), **1** (0.5 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 10 h. ² Chemical yields isolated after flash chromatography. ³ Et₃N was used as base. ⁴ K₂CO₃ was used as base. ⁵ A measure of 0.3 mol% of palladium complex **1** was employed. ⁶ Represents 24 h of reaction.

2.7. Characterization of the Catalyst and Study of Their Separation and Recycling

Complexes **1** or **2** were presumably reduced during all the experiments with palladium(0) by the cooperative effect of all reagents and additives present in the aqueous reaction media under light exposure. Thus, for example, Suzuki–Miyaura and Mizoroki–Heck cross coupling reactions were successfully promoted by freshly generated nanoparticles under these particular conditions in the absence of phosphines [29]. A brief analysis of the morphology of the catalytic species was performed. Focusing on the Suzuki–Miyaura and Hirao reactions catalyzed by adding complex **1**, once the transformations were finished, the aqueous suspensions (Figure 2a) were washed twice with ethyl acetate, and the water was slowly evaporated under reduced pressure and then completely dried under vacuum at 60 °C. The XRD patterns of finely dispersed powder showed that the main bands of the generation of Pd⁰ species at (111), (200), (220) and (311) crystallographic planes were detected at 40.2°, 46.7° and 68.2° (Figure 2b) [30]. The XRD patterns for the Pd nanoparticles showed a wide peak centered at around 40.35°. The TEM image (Figure 3) and the internal measurements revealed a particle size ranging between 5.0 and 3.5 nm, which is in accordance with the estimated value using the Scherer model (The average size of the Pd nanoparticles (4.8 nm) was calculated from the overall width at half maximum of the strongest diffraction peak {111} using the Scherer equation. Please, see Ref. [22]) [28].

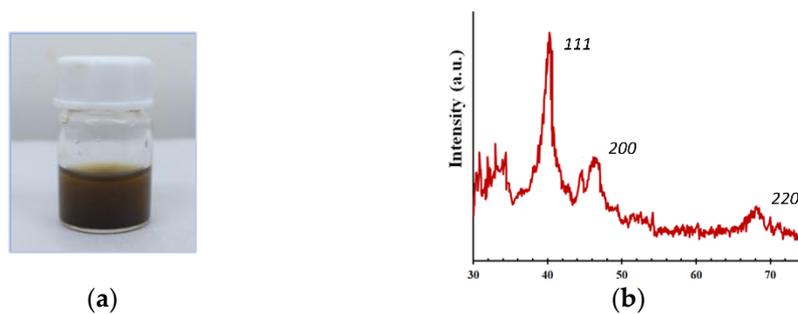


Figure 2. (a) Nanoparticle suspension in water studied in this section. (b) XRD pattern of the intensity of the signal of nanoparticles versus 2θ angle ($^\circ$).

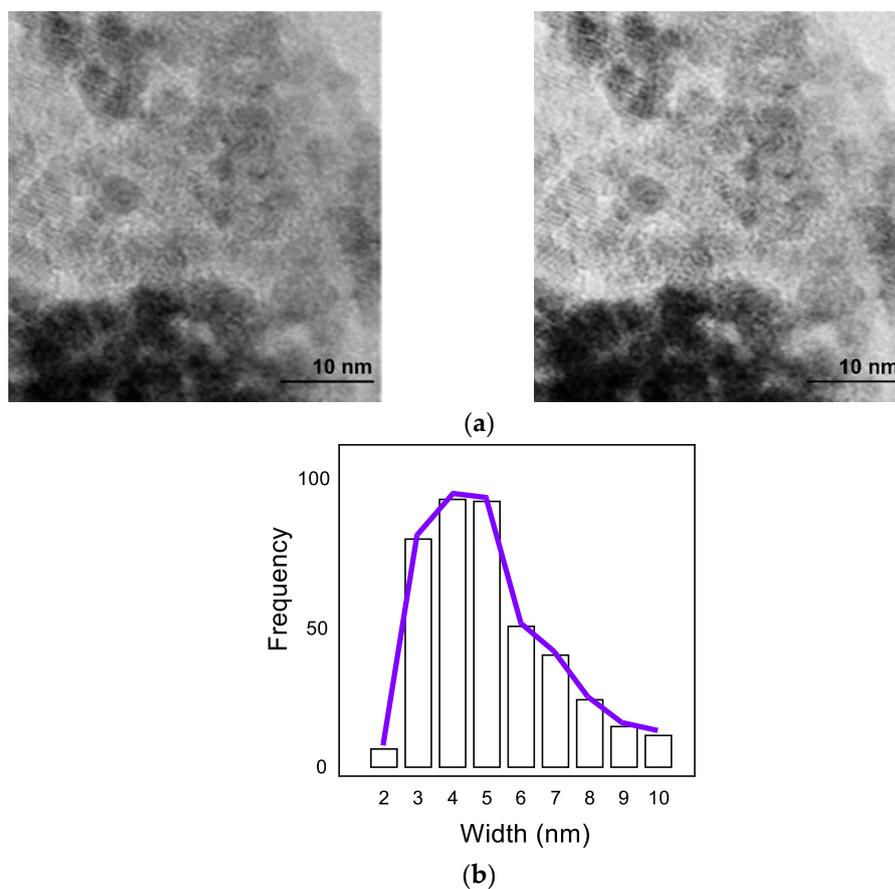


Figure 3. (a) TEM image of the nanoparticles isolated after the first cycle of the Suzuki–Miyaura/Hirao cross coupling transformation. (b) Estimated size distribution of the nanoparticles according to TEM histogram.

The presence of the palladium(0) in these nanoparticles was also confirmed by XPS analysis (Figure 4), showing intensities corresponding to Pd^0 $3d_{3/2}$ and $3d_{5/2}$ peaks centered at 335.4 and 340.7 eV [30].

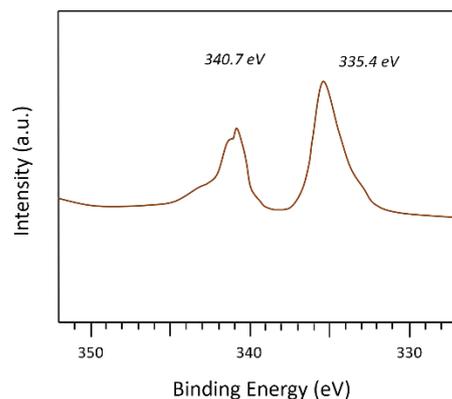


Figure 4. XPS analysis of the nanoparticles obtained after the first Suzuki–Miyaura/Hirao cross coupling transformations.

The composition of the catalytic species was determined using XPS, ICP and elemental analysis (EA) of three different samples for each transformation (both Suzuki–Miyaura and Hirao reactions, Table 7). According to all of the limitations of each instrumental techniques and the complementary character of them, it is possible to conclude that values of the surface shown by XPS are very closed to the EA and ICP ones. The range of palladium composition is 98.9–98.5%, which is contaminated with small amounts of carbon, hydrogen, nitrogen and sulfur, but no traces of chlorine were detected (see Table 7).

Table 7. Average of the elemental composition of the three samples of nanoparticles after a Suzuki–Miyaura reaction and other three samples after Hirao cross-coupling.

Analysis	C (%)	H (%)	N (%)	O (%)	S (%)	Pd (%)
XPS	0.6–0.8	nd	0.2–0.3	0.0–0.1	0.2–0.3	98.9–98.3
ICP	0.7–0.8	nd	nd	nd	0.2–0.3	98.9–98.5
EA	0.7–0.8	0.2–0.2	0.2–0.3	nd	0.2–0.2	nd

nd = not determined.

With the aim to extract an accurate and reliable result given by the mercury test, we followed the recommendations and suggestions published in the literature [31]. Thus, keeping in mind the colloidal aspect of the nanoparticles in water obtained at the end of the reaction (Figure 2a), the addition of mercury (500 equivalent relative to the palladium loading) onto a freshly set Suzuki–Miyaura cross coupling a 300 rpm, under the optimized conditions detailed in entry 10p of the Table 1, after 24 h at 90 °C, a 39% yield of **5a** was isolated.

Another experiment performed with the colloidal nanoparticles in water described before (Figure 2a), was the filtration of this suspension at 90 °C (hatman Paper for Quantitative Analysis 1450-110 was employed with a nominal particle retention of 2.7 µm) and immediately tested in the Suzuki–Miyaura coupling. In this experiment (entry 10p of the Table 1), the result of the isolated **5a** was 44% yield. So, a heterogeneous system in water can be confirmed employing the metal complex **1** under these specific conditions.

Continuing with this suspension of nanoparticles in Figure 2a, the recycling of them in the two selected transformations (Suzuki–Miyaura and Hirao) was assessed (Figure 5). The chemical yields of both transformations maintained the general range along the six cyclic batches analyzed in the two plots of the Figure 5. Two recycling experiments were consecutively run in the Mizoroki–Heck, Hiyama, Buchwald–Hartwig, and Sonogashira–Hagihara cross-couplings, obtaining 83 and 84%, 81 and 80%, 41 and 41%, 91 and 92% yields, respectively.

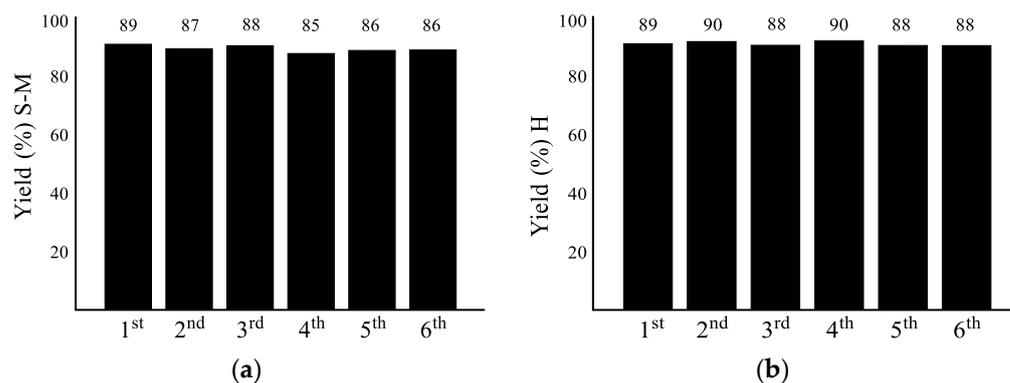


Figure 5. Recycling study of the catalyst in (a) the Suzuki–Miyaura cross-coupling and (b) Hirao cross coupling.

TEM images of the catalyst system were also analyzed after the sixth reaction cycle/batch (Figure 6). On them, an increment of the particle size was detected but maintained very small diameters in some nanoparticles, as can be seen in parts of the images; that means the distribution range was wider as a consequence of a small sinterization process along the series of repetitive cycles (Figure 6a,b).

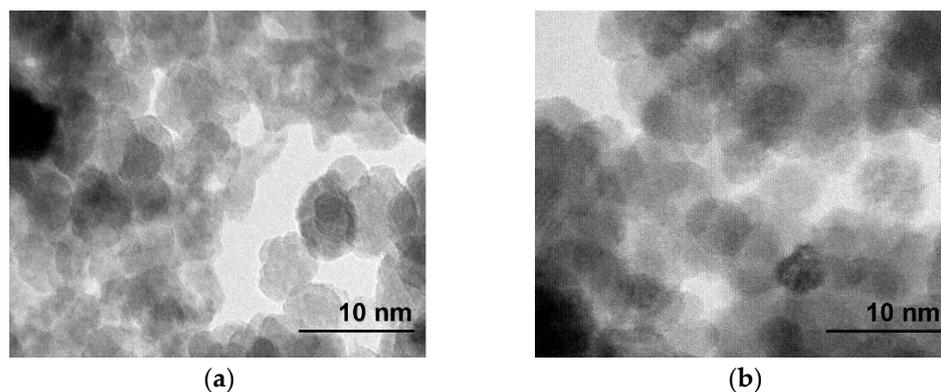


Figure 6. TEM image of the nanoparticles isolated after the fifth cycle in (a) Suzuki–Miyaura and (b) Hirao cross coupling transformations.

3. Materials and Methods

3.1. General

All reagents and solvents were commercially employed and used without further purification. The aldehydes were distilled under reduced pressure prior to use. Analytical TLC was conducted on Schleicher and Schuell F1400/LS 254 silica gel plates, and the different compounds distributed along the plate were visualized with UV light ($\lambda = 254$ nm). Flash chromatography was performed on hand-packed columns of Merck silica gel 60 (0.040–0.063 mm). ICP-MS analysis was carried in an Agilent-7700x (ICP-MS) apparatus. XRD studies were conducted in a Bruker D8-Advance with an X-ray tube cathode Cu K α , and a 3D Pixel detector. NMR spectra were obtained using a Bruker AC-300 or AC-400 and were recorded at 300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR, using CDCl_3 as the solvent and TMS as internal standard (0.00 ppm) unless otherwise stated. The following abbreviations are used to describe the signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and br s = broad signal. Coupling constants (J) are given in Hz, and chemical shifts in ppm. ^{13}C NMR spectra were referenced to CDCl_3 at 77.0 ppm. The ultrasound bath employed was Argo Lab AU-32, and the centrifuge was Hettich Zentrifugen (universal 320). The TEM images were recorded on a microscope JEOL model JEM-2010. XPS analyses were performed using a

VG-Microtech Multilab 3000 spectrometer, equipped with an Al anode and on a K-Alpha Thermo-Scientific spectrometer.

3.2. General Procedure for the Preparation of the Pd(II) Complexes

The palladium complexes **1** and **2** were prepared by modifying the procedure found in the literature [18,19]. Thus, palladium acetate (113 mg, 0.5 mmol) dissolved in methanol (15 mL) was added dropwise to the *N*-benzoyl thiourea **4** as a ligand (1 mmol) dissolved in methanol (20 mL) and stirred for 36 h at room temperature. The precipitation was filtered and purified by crystallization from methanol, finally obtaining complexes **1** and **2**.

Palladium(II) complex 1 [18]: Brownish yellow solid, 99 mg, 78% yield; mp 187–189 °C (MeOH, decom.). ¹H NMR (400 MHz) δ: 8.18–8.15 (m, 6H, minor and major), 8.01–7.94 (m, 4H, minor and major), 7.54–7.14 (m, 16H, minor and major), 5.56 (d, *J* = 9.9 Hz, 1H-5, major), 5.48 (d, *J* = 10.1 Hz, 1H-5, minor), 4.28 (d, *J* = 14.0 Hz, 1H-6, major), 4.23 (d, *J* = 14.1 Hz, 1H-6, minor), 3.80 (s, 3H, minor), 3.75 (s, 3H, major), 3.36–3.43 (m, 2H, major and minor), 3.22 (s, 3H, minor), 3.21 (s, 3H, major), 2.99–2.91 (m, 2H, major and minor), 2.35–2.28 (m, 2H, major and minor), 2.26–2.16 (m, 2H, major and minor). ¹³C NMR (100 MHz) δ: 173.1 (C=S minor), 173.0 (CS major), 172.2 (CO minor), 172.1 (CO major), 172.0 (CO minor), 172.05 (CO major), 169.7 (CO minor), 169.6 (CO major), 136.5 minor, 136.4 major, 136.3 minor and major, 135.3 major, 135.2 minor, 134.1 major, 134.0 minor, 133.9 minor and major, 132.2 (C major), 130.2 (3C minor), 130.1 minor and major, 130.0 (4C minor), 129.6 minor, 129.5 major, 129.2 (3C major), 129.0 minor, 128.8 major, 128.2 (4C major), 127.9 minor, 127.8 major, 127.6 (2C minor), 73.5 minor, 73.4 major, 64.1 minor, 63.9 major, 53.1 minor, 53.0 major, 51.6 major and minor, 45.9 major, 45.5 minor, 40.1 minor, 40.0 major, 36.8 minor, 36.6 major IR (cm⁻¹) ν_{max}: 3027, 2948, 1737, 1497, 1396, 1361, 1246, 1101, 701 cm⁻¹. MS (ESI) *m/z* (%): 1283 (29), 1282 (46), 1281 (60), 1280 (96), 1279 (M⁺, 62%), 1278 (100), 1277 (81), 1276 (78), 1275 (66). Elemental Analysis required for C₅₈H₅₄Cl₄N₄O₁₀PdS₂: C, 54.5; H, 4.3; N, 4.4; S, 5.0%; found: C, 54.9; H, 4.0; N, 4.6; S, 4.7%.

Palladium complex 2: Brownish-yellow solid, 123 mg, 90% yield; mp 253–255 °C (MeOH, decom.); IR (cm⁻¹) ν_{max}: 3417, 3060, 2952, 1790, 1716, 1495, 1391, 1258, 1201, 1168, 1093, 743. δ_H (400 MHz, CDCl₃): 8.39 (s, 2H, *N*-H), 8.20 (d, 4H, *J* = 7.3 Hz, ArH), 7.73 (d, 2H, *J* = 7.8 Hz, ArH), 7.55 (d, 2H, *J* = 7.3 Hz, ArH), 7.51–7.36 (m, 9H, ArH), 7.32–7.26 (m, 9H, ArH), 7.19 (d, 4H, *J* = 7.7 Hz, ArH), 7.10 (d, 2H, *J* = 1.9 Hz, ArH), 6.52–6.45 (m, 4H, ArH), 5.40 (d, 2H, *J* = 11.0 Hz, 5-*H*), 4.52 (d, 2H, *J* = 15.10 Hz, 6-*H*), 3.95 (s, 6H, OCH₃), 3.89 (d, 2H, *J* = 15.00 Hz, 6'-*H*), 3.84 (d, 2H, *J* = 9.5 Hz, 3-*H*), 2.60 (dd, 2H, *J* = 10.8 Hz, 9.1 Hz, 4-*H*). δ_C (100 MHz, CDCl₃): 172.6 (2x C=S), 172.6 (2x C=O), 172.2 (2x C=O), 172.0 (2x C=O), 169.6 (2x C=O), 136.0 (2C), 135.9 (2C), 135.8 (2C), 133.8 (2C), 132.5 (2C), 130.7 (2C), 130.1 (6C), 129.0 (6C), 128.7 (2C), 128.3 (6C), 127.7 (2C), 125.7 (6C), 124.3 (2C), 122.9 (2C), 120.8 (2C), 117.8 (2C), 111.9 (2C), 108.7 (2C), 68.9 (2C), 54.1 (2C), 53.1 (2C), 48.5 (2C), 31.7 (2C), 30.9 (2C). HRMS: calculated for C₇₄H₆₀Cl₂N₈O₁₀PdS₂: 1462.7717, found: 1462.7711. EA calculated for C₇₄H₆₀Cl₂N₈O₁₀PdS₂: C 60.8, H 4.1, N 7.7, S 4.4%; found: C 60.5, H 4.4, N 7.7, S 4.5%.

3.3. General Procedure for Suzuki–Miyaura Cross Coupling Reaction

Aryl halide (0.5 mmol), arylboronic acid (0.75 mmol), K₂CO₃ (103 mg, 0.75 mmol), complex **1** (1.3 mg, 0.001 mmol, 0.2 mol%) and water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 24 h. Progress of the reactions was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was dried and evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (six different catalytic cycles, see Figure 5a) or employed for the characterization of the nanoparticles. The final compounds **5a–f** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. The pure compounds offered matching spectroscopic data with the analogous ones obtained by our group [22].

4-Methoxy-1,1'-biphenyl (5a) [32]: Isolated 82 mg (89%, Table 1, entry 10p), 80 mg (87%, Table 1, entry 12), 73 mg (79%, Table 1, entry 14), 50 mg (54%, Table 1, entry 17) as colorless solid. M.p. 88–89 °C (*n*-hexane/AcOEt), Lit. 86–87 °C (hexanes) [32]. $R_f = 0.2$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.60 (t, $J = 8.4$ Hz, 4H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.36 (t, $J = 7.3$ Hz, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz) δ (ppm): 159.2, 140.8, 133.8, 128.8, 128.2, 126.8, 126.7, 114.3, 55.4.

4-Methyl-1,1'-biphenyl (5b) [33]: Isolated 75 mg (89%, Table 1, entry 8), 73 mg (87%, Table 1, entry 13), 68 mg (81%, Table 1, entry 15), 57 mg (68%, Table 1, entry 18) as colorless solid. M.p. 49–50 °C (*n*-hexane/AcOEt), Lit. 50–51 °C (hexanes) [34]. $R_f = 0.6$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.65 (dd, $J = 33.6, 7.6$ Hz, 4H), 7.55–7.41 (m, 3H), 7.35 (d, $J = 7.8$ Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (100 MHz) δ (ppm): 141.38, 138.5, 137.1, 129.6, 128.8, 127.1, 127.1, 21.2.

[1,1'-Biphenyl]-3-carbonitrile (5c) [35]: Isolated 79 mg (88%, Table 1, entry 9) as colorless solid. M.p. 39–40 °C (*n*-hexane/AcOEt), Lit. 38–39 °C (hexanes/EtOAc) [36]. $R_f = 0.2$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.92 (s, 1H), 7.87 (d, $J = 7.9$ Hz, 1H), 7.69 (d, $J = 7.7$ Hz, 1H), 7.63–7.59 (m, 3H), 7.56–7.46 (m, 3H). ^{13}C NMR (101 MHz) δ (ppm): 142.4, 138.9, 131.5, 130.7, 129.7, 129.1, 128.6, 127.1, 118.9, 112.9.

[1,1'-Biphenyl]-3-carbaldehyde (5d) [37]: Isolated 82 mg (90%, Table 1, entry 10) as colorless solid. M.p. 54–55 °C (*n*-hexane/AcOEt), Lit. 53–54 °C (hexanes/EtOAc) [38]. $R_f = 0.4$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 10.15 (s, 1H), 8.17 (s, 1H), 7.95–7.41 (m, 8H). ^{13}C NMR (101 MHz) δ (ppm): 192.4, 142.2, 139.7, 136.9, 133.1, 129.5, 129.0, 128.7, 128.2, 128.0, 127.2.

4-Chloro-1,1'-biphenyl (5e) [39]: Isolated 85 mg (90%, Table 1, entry 11) as colorless solid. M.p. 78–79 °C (*n*-hexane/AcOEt), Lit. 77–78 °C (*n*-hexane/EtOAc) [40]. $R_f = 0.4$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.62 (dd, $J = 15.3, 7.9$ Hz, 4H), 7.49 (ddt, $J = 20.3, 14.6, 7.3$ Hz, 5H). ^{13}C NMR (101 MHz) δ (ppm): 140.0, 139.7, 133.4, 128.9, 128.9, 128.4, 127.6, 127.0.

Biphenyl-4-carbaldehyde (5f) [41]: Isolated 78 mg (80%, Table 1, entry 16) as colorless solid. M.p. 59–60 °C (*n*-hexane/AcOEt), Lit. 59–60 °C (*n*-hexane/EtOAc) [36]. $R_f = 0.3$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 10.15 (s, 1H), 8.17 (s, 1H), 7.92 (m, 2H), 7.68 (m, 3H), 7.50 (dt, $J = 31.1, 7.3$ Hz, 3H). ^{13}C NMR (101 MHz) δ (ppm): 192.0, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4.

[1,1'-Biphenyl]-4-carbonitrile (5g) [42]: Isolated 63 mg (70%, Table 1, entry 19) as colorless solid. M.p. 85–86 °C (*n*-hexane/AcOEt), Lit. 85–86 °C (*n*-hexane/EtOAc) [43]. $R_f = 0.4$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.77 (q, $J = 8.2$ Hz, 4H), 7.69–7.44 (m, 5H). ^{13}C NMR (101 MHz) δ (ppm): 145.7, 139.2, 132.6, 129.1, 128.7, 127.7, 127.2, 119.0, 110.9.

3.4. General Experimental Procedure for Mizoroki-Heck Reaction

Aryl halide (0.5 mmol), olefin (0.55 mmol), triethylamine (0.14 mL, 1 mmol), H_2O (1.5 mL) and **1** (1.9 mg, 0.0015 mmol, 0.3 mol%) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature. Progress of the reactions was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3x5 mL). The organic layer was dried and evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (first cycle 83%; second cycle 84%). The final compounds **7a–f** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. They offered matching spectroscopic data with the analogous ones obtained by our group [23].

(E)-*n*-Butyl 3-(4-methoxyphenyl)acrylate (7a) [23]: Isolated 97 mg (83%, Table 2, entry 10p), 92 mg (79%, Table 2, entry 17) as colorless powder. M.p. 84–85 °C (*n*-hexane/EtOAc), Lit. 84–85 °C (pentanes/EtOAc) [44]. $R_f = 0.3$ (*n*-hexane). ^1H NMR (400 MHz) δ (ppm): 7.58 (d, $J = 16.0$ Hz, 1H), 7.39 (d, $J = 4.2$ Hz, 3H), 6.24 (d, $J = 16.0$ Hz, 1H), 4.13 (m, $J = 7.0$ Hz, 2H), 3.72 (s, 3H), 1.60–1.62 (m, 2H), 1.35–1.40 (m, 2H), 0.91 (t, $J = 7.0$ Hz, 3H). ^{13}C NMR (100 MHz) δ (ppm) = 167.1, 161.2, 144.0, 129.5, 127.0, 115.5, 114.1, 64.0, 55.0, 30.7, 19.1, 13.6.

(*E*)-4-Methoxystylbene (**7b**) [23]: Isolated 84 mg (80%, Table 2, entry 10), 84 mg (80%, Table 2, entry 18) as colorless powder. M.p. 138–139 °C (*n*-hexane/EtOAc), Lit. 138 °C (water) [45]. $R_f = 0.2$ (*n*-hexane/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.46–7.52 (m, 3H), 7.36 (t, $J = 7.6$ Hz, 2H), 7.09 (d, $J = 16.0$ Hz, 2H), 6.99 (d, $J = 16.4$ Hz, 2H), 6.92 (d, $J = 8.4$ Hz, 2H), 3.89 (s, 3H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 159.3, 137.7, 130.1, 128.7, 128.2, 127.8, 127.2, 126.6, 126.3, 114.1, 55.3.

(*E*)-*n*-Butyl cinnamate (**7c**) [23]: Isolated 83 mg (81%, Table 2, entry 11), 78 mg (76%, Table 2, entry 15), 51 mg (50%, Table 2, entry 19), as colorless oil. $R_f = 0.4$ (*n*-hexane). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.60 (d, $J = 16.4$ Hz, 1H), 7.43–7.45 (m, 2H), 7.29–7.30 (m, 3H), 6.36 (d, $J = 16.0$ Hz, 1H), 4.13 (t, $J = 6.8$ Hz, 2H), 1.59–1.62 (m, 2H), 1.34–1.36 (m, 2H), 0.88 (t, $J = 7.6$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 166.8, 144.4, 134.4, 130.1, 128.8, 128.0, 118.2, 64.3, 30.8, 19.2, 13.7.

(*E*)-Stylbene (**7d**) [23]: Isolated 72 mg (80%, Table 2, entry 12), 68 mg (75%, Table 2, entry 16), 49 mg (54%, Table 2, entry 20), as colorless solid. M.p. 124–125 °C (*n*-hexane/EtOAc), Lit. 123–125 °C (Merck, commercially available). $R_f = 0.9$ (*n*-hexane). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.58 (d, $J = 7.2$ Hz, 4H), 7.42 (t, $J = 7.0$ Hz, 4H), 7.33 (t, $J = 6.8$ Hz, 2H), 7.18 (s, 2H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 137.4, 128.8, 127.8, 126.7.

(*E*)-*n*-Butyl 3-(4-chlorophenyl) acrylate (**7e**) [23]: Isolated 96 mg (81%, Table 2, entry 13) as colorless solid. M.p. 35–36 °C (*n*-hexane/EtOAc), Lit. 35–36 °C [46]. $R_f = 0.4$ (*n*-hexane). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.65 (d, $J = 16.0$ Hz, 1H), 7.47 (d, $J = 8.5$ Hz, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 6.43 (d, $J = 16.0$ Hz, 1H), 4.24 (t, $J = 6.6$ Hz, 2H), 1.40–1.52 (m, 2H), 1.67–1.76 (m, 2H), 0.99 (t, $J = 7.3$ Hz, 3H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 166.7, 143.0, 136.0, 132.9, 129.4, 129.1, 118.8, 64.4, 30.7, 19.2, 13.7.

(*E*)-1-Chloro-4-styrylbenzene (**7f**) [23]: Isolated 82 mg (77%, Table 2, entry 14) as colorless solid. M.p. 127–128 °C (*n*-hexane/EtOAc), Lit. 126–128 °C [47]. $R_f = 0.8$ (*n*-hexane). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.50–7.52 (m, 2H), 7.43–7.46 (m, 2H), 7.28–7.39 (m, 5H), 7.07 (s, 2H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 137.0, 135.8, 133.2, 129.3, 128.8, 128.7, 127.9, 127.7, 127.4, 126.6 ppm.

3.5. General Experimental Procedure for Hiyama Cross-Coupling

Aryl halide (0.5 mmol), catalyst **1** (1.9 mg, 0.0015 mmol, 0.3 mol%), triethoxyphenylsilane (0.119 mL, 0.6 mmol), NaOH (40 mg, 1 equiv) water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature. Progress of the reactions was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was dried and evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (first cycle 81%; second cycle 80%). The final compounds **5a–g** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. They offered matching spectroscopic data with the analogous ones obtained by our group [23].

(**5a**): Isolated 75 mg (81%, Table 3, entry 10p), 69 mg (75%, Table 3, entry 13), 45 mg (49%, Table 3, entry 16).

(**5b**): Isolated 67 mg (80%, Table 3, entry 10), 42 mg (50%, Table 3, entry 17).

(**5c**): Isolated 70 mg (78%, Table 3, entry 11).

(**5d**): Isolated 69 mg (76%, Table 3, entry 14).

(**5e**): Isolated 75 mg (80%, Table 3, entry 12).

(**5f**): Isolated 74 mg (75%, Table 3, entry 15).

(**5g**): Isolated 50 mg (56%, Table 3, entry 18).

3.6. General Experimental Procedure for Buchwald-Hartwig Cross-Coupling

Aryl halide (0.5 mmol), aniline (0.047 mL, 0.5 mmol), KOBu^t (224 mg, 2.00 mmol), **1** (6.5 mg, 0.005 mmol, 1.0 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 24 h. Progress of the reactions

was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was dried and evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (first cycle 41%; second cycle 41%). The final compounds **10a–c** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. They offered matching spectroscopic data with the analogous ones obtained in the literature [24–26].

4-Methoxy-N-phenylaniline (10a) [48]: Isolated 41 mg (41%, Table 4, entry 10p), 35 mg (35%, Table 4, entry 9) as colorless solid. M.p. 105–106 °C (*n*-hexane/EtOAc), Lit. 105 °C (*n*-hexane/EtOAc) [48]. $R_f = 0.3$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.40 (d, $J = 8.4$ Hz, 2H), 7.25–7.10 (m, 5H), 6.90 (d, $J = 8.4$ Hz, 2H), 5.50 (s, 1H), 3.81 (s, 3H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 153.4, 145.7, 135.5, 129.1, 123.4, 120.1, 115.1, 55.3.

4-Methyl-N-phenylaniline (10b) [49]: Isolated 41 mg (45%, Table 4, entry 7) as colorless solid. M.p. 90–91 °C (*n*-hexane/EtOAc), Lit. 90 °C (*n*-hexane/EtOAc) [49]. $R_f = 0.5$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.26 (t, $J = 7.2$ Hz, 2H), 7.20–6.90 (m, 6H), 6.85 (m, 1H), 5.61 (s, 1H), 2.32 (s, 3H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 143.9, 140.2, 130.9, 129.8, 129.1, 120.3, 118.8, 116.9, 20.6.

4-Chloro-N-phenylaniline (10c) [49]: Isolated 59 mg (58%, Table 4, entry 8) as colorless solid. M.p. 68–69 °C (*n*-hexane/EtOAc), Lit. 69 °C (*n*-hexane/EtOAc) [49]. $R_f = 0.3$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.35–7.20 (m, 2H), 7.20 (dt, $J = 9.0, 3.3$ Hz, 2H), 7.70–6.90 (m, 5H), 5.60 (s, 1H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 142.5, 141.9, 129.3, 129.2, 125.5, 121.0, 118.5, 118.2.

3.7. General Experimental Procedure for Hirao Cross-Coupling

Aryl halide (0.5 mmol), triethylphosphite (0.166 mL, 1.0 mmol), Et_3N (0.342 mL, 2.5 mmol), **1** (3.3 mg, 0.0025 mmol, 0.5 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 8 h. Progress of the reactions was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was dried, evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (six different catalytic cycles, see Figure 5b) or using for the characterization of the nanoparticles. The final compounds **12a–d** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. They offered matching spectroscopic data with the analogous ones obtained in the literature [23].

Diethyl 4-methoxyphenylphosphonate (12a) [23]: Isolated 107 mg (88%, Table 5, entry 10p), 88 mg (72%, Table 5, entry 14), 72 mg (59%, Table 5, entry 17) as colorless oil. $R_f = 0.4$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 8.30 (dd, $J = 8.7$ and 3.3 Hz, 1H), 8.00 (dd, $J = 12.7$ and 8.7 Hz, 1H), 4.27–4.06 (m, 4H), 1.34 (t, $J = 6.9$ Hz, 6H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 150.2 (d, $J = 3.7$ Hz), 135.8 (d, $J = 185.2$ Hz), 133.0 (d, $J = 10.5$ Hz), 123.3 (d, $J = 15.0$ Hz), 62.7 (d, $J = 5.2$ Hz), 16.3 (d, $J = 6.0$ Hz), 16.1 (d, $J = 6.7$ Hz).

Diethyl phenylphosphonate (12b) [23]: Isolated 97 mg (91%, Table 5, entry 10), 80 mg (75%, Table 5, entry 12), 73 mg (68%, Table 5, entry 15) as colorless oil. $R_f = 0.5$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.80 (dd, $J = 13.2$ and 8.4 Hz, 2H), 7.50–7.48 (m, 1H), 7.48–7.40 (m, 2H), 4.15–4.05 (m, 4H), 1.30 (t, $J = 6.8$ Hz, 6H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 132.3 (d, $J = 3.0$ Hz), 131.7 (d, $J = 10.0$ Hz), 128.4 (d, $J = 15.0$ Hz), 128.3 (d, $J = 186.0$ Hz), 62.0 (d, $J = 5.0$ Hz), 16.3 (d, $J = 7.0$ Hz).

Diethyl 4-chlorophenylphosphonate (12c) [23]: Isolated 105 mg (85%, Table 5, entry 11) as colorless oil. $R_f = 0.3$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.76 (dd, $J = 12.8$ and 8.4 Hz, 2H), 7.46 (dd, $J = 8.2$ and 3.6 Hz, 2H), 4.20–4.05 (m, 4H), 1.34 (t, $J = 7.2$ Hz, 6H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 139.9 (d, $J = 4.0$ Hz), 133.2 (d, $J = 10.0$ Hz), 128.8 (d, $J = 16.0$ Hz), 126.9 (d, $J = 190.0$ Hz), 62.2 (d, $J = 5.0$ Hz), 16.3 (d, $J = 7.0$ Hz).

Diethyl 4-methylphenylphosphonate (12d) [23]: Isolated 82 mg (72%, Table 5, entry 13), 75 mg (66%, Table 5, entry 16) as colorless oil. $R_f = 0.6$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.72 (dd, $J = 13.2$ and 8.1 Hz, 2H), 7.29 (dd, $J = 8.1$ and 3.3 Hz, 2H), 4.21–4.01 (m, 4H), 2.42 (s, 3H), 1.33 (t, $J = 6.9$ Hz, 6H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 142.9 (d, $J = 3.0$ Hz), 131.8 (d, $J = 9.7$ Hz), 129.2 (d, $J = 15.0$ Hz), 124.9 (d, $J = 188.2$ Hz), 61.9 (d, $J = 5.2$ Hz), 21.6 (d, $J = 6.7$ Hz), 16.1 (d, $J = 6.7$ Hz).

3.8. General Experimental Procedure for Sonogashira-Hagihara Cross-Coupling

Aryl halide (0.5 mmol), terminal alkyne (0.55 mmol), DABCO (84 mg, 0.75 mmol), **1** (3.3 mg, 0.0025 mmol, 0.5 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 10 h. Progress of the reactions was monitored by GC or TLC. Afterwards, the crude product was extracted using ethyl acetate (3×5 mL). The organic layer was dried, evaporated and further purified by column chromatography. The colloidal aqueous suspension was reused in other identical reactions (first cycle 91%; second cycle 92%). Final compounds **14a–f** were isolated and purified by flash chromatography (silica gel) using mixtures of *n*-hexane/EtOAc as eluent. They offered matching spectroscopic data with the analogous ones obtained in the literature [28].

1-Methoxy-4-(phenylethynyl)-benzene (14a) [50]: Isolated 95 mg (91%, Table 6, entry 10p), 75 mg (72%, Table 6, entry 16), 63 mg (61%, Table 6, entry 20) as colorless crystals. M.p. 68–69 °C (*n*-hexane/EtOAc), Lit. 65 °C (*n*-hexane/EtOAc) [50]. $R_f = 0.8$ (*n*-hexane:EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.56–7.48 (m, 4H), 7.36–7.33 (m, 3H), 6.80 (dd, $J = 4.2$ and 2.0 Hz, 1H), 3.83 (s, 3H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm) 159.2, 133.0, 131.4, 128.3, 127.9, 123.5, 115.2, 113.9, 89.3, 88.0, 55.2.

1,2-Diphenylethyne (14b) [50]: Isolated 77 mg (87%, Table 6, entry 10), 67 mg (75%, Table 6, entry 15), 61 mg (68%, Table 6, entry 19) as colorless crystals. M.p. 59–60 °C (*n*-hexane/EtOAc), Lit. 59–60 °C (*n*-hexane) [50]. $R_f = 0.5$ (*n*-hexane). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.54–7.51 (m, 4H), 7.36–7.31 (m, 6H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm) 131.6, 128.3, 128.2, 123.2, 89.3.

1-Chloro-4-(phenylethynyl)benzene (14c) [50]: Isolated 90 mg (85%, Table 6, entry 11) as colorless crystals. M.p. 85–87 °C (*n*-hexane/EtOAc), Lit. 84 °C (*n*-hexane) [50]. $R_f = 0.9$ (*n*-hexane/EtOAc, 3:1). $^1\text{H NMR}$ (300 MHz) δ (ppm): 7.55–7.48 (m, 2H), 7.41–7.47 (m, 2H), 7.37–7.27 (m, 5H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm) 134.2, 132.8, 131.6, 128.7, 128.45, 128.36, 122.9, 121.8, 90.3, 88.2.

4-(Phenylethynyl)benzotrile (14d) [28,50]: Isolated 84 mg (83%, Table 6, entry 12) as colorless crystals. M.p. 105–107 °C (*n*-hexane/EtOAc), Lit. 106–108 °C (*n*-hexane/EtOAc) [51]. $R_f = 0.8$ (*n*-hexane/EtOAc, 3:1). $^1\text{H NMR}$ (400 MHz) δ (ppm): 7.68–7.61 (m, 4H), 7.58–7.54 (m, 2H), 7.42–7.39 (m, 3H). $^{13}\text{C NMR}$ (100 MHz) δ (ppm): 132.0, 132.0, 131.8, 129.1, 128.5, 128.2, 122.2, 118.5, 111.4, 93.7, 87.7).

3-Phenyl-2-propyn-1-ol (14e) [52]: Isolated 53 mg (80%, Table 6, entry 13), 46 mg (70%, Table 6, entry 17), 46 mg (69%, Table 6, entry 21) as colorless solid. M.p. 120–121 °C (*n*-hexane/EtOAc), Lit. 119–121 °C [52]. $R_f = 0.2$ (*n*-hexane/EtOAc, 3:1). $^1\text{H NMR}$ (300MHz) δ (ppm): 7.40–7.45 (m, 2H), 7.30–7.35 (m, 3H), 4.5 (s, 2H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 131.7, 128.5, 128.3, 122.3, 87.1, 85.6, 51.6.

3-(4-Methoxyphenyl)-2-propyn-1-ol (14f) [53]: Isolated 65 mg (80%, Table 6, entry 14), 56 mg (69%, Table 6, entry 18), 57 mg (70%, Table 6, entry 22) as colorless solid. M.p. 65–66 °C (*n*-hexane/EtOAc), Lit. 65–68 °C [53]. $R_f = 0.3$ (*n*-hexane/EtOAc, 3:1). $^1\text{H NMR}$ (300MHz) δ (ppm): 7.35 (d, $J = 8.9$ Hz, 2H), 6.83 (d, $J = 8.9$ Hz, 2H), 4.46 (s, 2H), 3.80 (s, 3H). $^{13}\text{C NMR}$ (75 MHz) δ (ppm): 159.6, 133.4, 114.4, 114.0, 85.9, 85.4, 55.6, 51.8.

3.9. General Experimental Procedure for the Recycling Tests in (a) Suzuki-Miyaura and (b) Hirao Cross-Couplings

(a) Measures of 4-Iodoanisole (117 mg, 0.5 mmol), phenylboronic acid (92 mg, 0.75 mmol), K_2CO_3 (103 mg, 0.75 mmol), complex **1** (1.3 mg, 0.001 mmol, 0.2 mol%) and water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corre-

sponding temperature for 24 h. Afterwards, crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was separated, and the aqueous suspension of nanoparticles was mixed with 4-iodoanisole (117 mg, 0.5 mmol), phenylboronic acid (92 mg, 0.75 mmol), and K₂CO₃ (103 mg, 0.75 mmol), and the process was repeated as described before.

- (b) Measures of 4-Iodoanisole (117 mg, 0.5 mmol), triethylphosphite (0.166 mL, 1.0 mmol), Et₃N (0.342 mL, 2.5 mmol), **1** (3.3 mg, 0.0025 mmol, 0.5 mol%), water (1.5 mL) were introduced in a pressure tube and warmed in an oil bath at the corresponding temperature for 8 h. Afterwards, crude product was extracted using ethyl acetate (3 × 5 mL). The organic layer was separated, and the aqueous suspension of nanoparticles was mixed with 4-iodoanisole (117 mg, 0.5 mmol), triethylphosphite (0.166 mL, 1.0 mmol), and Et₃N (0.342 mL, 2.5 mmol), and the process repeated as described before.

4. Conclusions

In this work, a suspension of nanoparticles in water (generated from complex **1**) was introduced as an effective and versatile catalyst in six classical cross-coupling reactions. The tolerance to multiple functional groups was also demonstrated in the Suzuki–Miyaura, Mizoroki–Heck, Hiyama, Buchwald–Hartwig, Hirao and Sonogashira–Hagihara reactions. The less productive transformation was Buchwald–Hartwig coupling, affording modest chemical yields. The reaction with iodides and bromides was satisfactory, whilst aryl chlorides required harsh conditions. Temperature is also a key parameter for performing chemoselective transformations; thus, at lower temperatures, the carbon–iodine bond was activated in the presence of a carbon–chlorine bond. The nanoparticles were characterized, and their presence was confirmed in the coupling reactions. The catalyst loading was very small, and the suspension in water was easily separated and reused for up to six catalytic batches, maintaining the chemical yield. The degree of sinterization was very low after this sixth stage. The processes can be classified as heterogeneous, sustainable and able to take care of the environment using the lower amount of waste chemicals and solvents. Water ensures a fast and homogeneous dispersion of nanoparticles and favors the approach of the organic reagents, avoiding the solvation of them, as is what occurred in the reactions performed with other organic solvents (see Tables 1–6). It was also demonstrated that there was already-known lower reactivity of aryl chlorides due to their higher dissociation energies. Concerning the efficiency of this process *versus* catalysis conducted in the absence of nanoparticles, it is remarkable that there was a higher catalytic surface of nanoparticles, and also that there was higher stability. This last fact was demonstrated by the recyclability study performed in Suzuki–Miyaura and Hirao cross-coupling reactions.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules29051138/s1>, NMR spectra.

Author Contributions: S.P., S.B., H.A.D., S.T., R.H.-L., J.T.-S., L.V.R.-F., M.d.G.R., M.G., S.S. and J.M.S. Conceptualization, H.A.D., M.G., S.S. and J.M.S.; methodology, H.A.D., M.G., S.S., M.d.G.R. and J.M.S.; validation, S.T., L.V.R.-F. and M.d.G.R.; formal analysis, S.P., S.B., R.H.-L., J.T.-S. and M.d.G.R.; investigation, A.S., S.P., S.B., R.H.-L., J.T.-S. and L.V.R.-F.; resources, H.A.D., M.d.G.R. and J.M.S.; writing—original draft preparation, J.M.S.; writing—review and editing, A.S., S.P., S.B., H.A.D., R.H.-L., J.T.-S., M.G., S.S., M.d.G.R. and J.M.S.; supervision, H.A.D., M.d.G.R. and J.M.S.; project administration, H.A.D., M.d.G.R. and J.M.S.; funding acquisition, H.A.D., M.d.G.R. and J.M.S. All authors have read and agreed to the published version of the manuscript.

Funding: We gratefully acknowledge financial support from Çukurova University (Project nos. TSA-2023-16116, TSA-2022-15050 and TSA-2023-15939) and Mersin University (Project nos. 2020-1-AP4-3982). A part of this work is a part of Samet POYRAZ's Ph.D. thesis. We are also thankful for financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (RED2022-134287-T ORFEO CINQA and RED2022-134331-T CASI) the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2017-82935-P and PID2019-107268GB-I00), the Generalitat Valenciana (IDIFEDER/2021/013, GVA-COVID19/2021/079 and CIDEGENT/2020/058), Medalchemy S. L.

(Medalchemistry-22T) and the University of Alicante (VIGROB-068, UAUSTI21-05). LVR-F thanks Generalitat Valenciana for Grisolia's fellowship (GRISOLIAP/2020/111). JT thanks Generalitat Valenciana for APOTI contract (CIAPOT/2021/23).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article and Supplementary Materials.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Joudeh, N.; Saragliadis, A.; Koster, G.; Mikheenko, P.; Linke, D. Synthesis methods and applications of palladium nanoparticles: A review. *Front. Nanotechnol.* **2022**, *4*, 1062608. [[CrossRef](#)]
2. Horbaczewskyj, C.S.; Fairlamb, I.J.S. Pd-Catalyzed Cross-Couplings: On the Importance of the Catalyst Quantity Descriptors, mol % and ppm. *Org. Process Res. Dev.* **2022**, *26*, 2240–2269. [[CrossRef](#)]
3. Vasu, G.R.P.; Venkata, K.R.M.; Kakarla, R.R.; Ranganath, K.V.S.; Aminabhavi, T.J. Recent advances in sustainable N-heterocyclic carbene-Pd(II)-pyridine (PEPPSI) catalysts: A review. *Environm. Res.* **2023**, *225*, 115515. [[CrossRef](#)]
4. Chaturvedia, S.; Pragnesh, N.D. Chapter 13 Nanocatalyst: As Green Catalyst. In *Handbook of Greener Synthesis of Nanomaterials and Compounds*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 445–458. [[CrossRef](#)]
5. Zielinska, A.A.; Trzaska, P.; Budny, M.; Bosiak, M.J. Kumada–Tamao–Corriu Type Reaction of Aromatic Bromo- and Iodoamines with Grignard Reagents. *J. Org. Chem.* **2023**, *88*, 16167–16175. [[CrossRef](#)] [[PubMed](#)]
6. Baran, N.Y.; Baran, T.; Nasrollahzadeh, M. Synthesis of palladium nanoparticles stabilized on Schiff base-modified ZnO particles as a nanoscale catalyst for the phosphine-free Heck coupling reaction and 4-nitrophenol reduction. *Sci. Rep.* **2023**, *13*, 12008. [[CrossRef](#)]
7. Hu, Y.; Li, X.; Jin, G.; Lipshutz, B.H. Simplified Preparation of ppm Pd-Containing Nanoparticles as Catalysts for Chemistry in Water. *ACS Catal.* **2023**, *13*, 3179–3186. [[CrossRef](#)] [[PubMed](#)]
8. Simon, A.; Mathai, S. Recent advances in heterogeneous magnetic Pd-NHC catalysts in organic transformations. *J. Organomet. Chem.* **2023**, *996*, 122768. [[CrossRef](#)]
9. Mohammadi, P.; Heravi, M.M.; Mohammadi, L.; Saljooqi, A. Preparation of magnetic biochar functionalized by polyvinyl imidazole and palladium nanoparticles for the catalysis of nitroarenes hydrogenation and Sonogashira reaction. *Sci. Rep.* **2023**, *13*, 17375. [[CrossRef](#)]
10. Daneshafroz, H.; Mohammadi, P.; Barani, H.; Sheibani, H. Magnetic bentonite decorated with Pd nanoparticles and cross-linked polyvinyl pyridine as an efficient nanocatalyst for Suzuki coupling and 4-Nitrophenol reduction reactions. *Sci. Rep.* **2023**, *13*, 2001. [[CrossRef](#)]
11. Saadh, M.J.; Khasawneh, H.E.N.; Ortiz, G.G.R.; Ahsan, M.; Sain, D.K.; Yusuf, K.; Sillanaa, M.; Iqbal, A.; Akhavan-Sigari, R. Synthesis and characterization of ZrFe₂O₄@SiO₂@Ade-Pd as a novel, recyclable, green, and versatile catalyst for Buchwald–Hartwig and Suzuki–Miyaura cross-coupling reactions. *Sci. Rep.* **2023**, *13*, 14728. [[CrossRef](#)]
12. Brick, K.J.; Lim, M.Q.; Keske, E.C. [(NHC)Pd(allyl)Cl] Precatalysts in The Hiyama Reaction of Aryl Chlorides with Aryl Trimethoxysilanes: A Study in Side Reactions. *Organometallics* **2023**, *42*, 3192–3198. [[CrossRef](#)]
13. Hong, L.-H.; Feng, W.-J.; Chen, W.-C.; Chang, Y.-C. Highly efficient and well-defined phosphinous acid-ligated Pd(II) precatalysts for Hirao cross-coupling reaction. *Dalton Trans.* **2023**, *52*, 5101–5109. [[CrossRef](#)] [[PubMed](#)]
14. Hikawa, H.; Nakayama, T.; Takahashi, M.; Kikkawa, S.; Azumaya, I. Direct Use of Benzylic Alcohols for Multicomponent Synthesis of 2-Aryl Quinazolinones Utilizing the π -Benzylpalladium(II) System in Water. *Adv. Synth. Catal.* **2021**, *363*, 4075–4084. [[CrossRef](#)]
15. Belveren, S.; Poyraz, S.; Pask, C.M.; Ulger, M.; Sansano, J.M.; Dondas, H.A. Synthesis and biological evaluation of platinum complexes of highly functionalized aroylaminocarbo-*N*-thioyl prolinatate containing tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione moieties. *Inorg. Chim. Acta* **2019**, *498*, 119154. [[CrossRef](#)]
16. Dondas, H.A.; Altinbas, O. Novel Highly Functionalized Benzoylaminocarbothioyl Pyrrolidine from Benzoylisothiocyanate and Substituted Pyrrolidine Derived From α -Amino acid Ester via Imine-Azomethine Ylide-1,3-Dipolar Cycloaddition Cascade. *Heterocycl. Commun.* **2004**, *10*, 167–173. [[CrossRef](#)]
17. Belveren, S.; Larrañaga, O.; Poyraz, S.; Dondas, H.A.; Ülger, M.; Şahin, E.; Ferrándiz-Saperas, M.; Sansano, J.M.; Retamosa, M.G.; de Cózar, A. From Bioactive Pyrrolidino[3,4-c]pyrrolidines to more Bioactive Pyrrolidino[3,4-b]pyrrolidines via Ring-Opening/Ring-Closing Promoted by Sodium Methoxide. *Synthesis* **2019**, *51*, 1565–1577. [[CrossRef](#)]
18. Poyraz, S.; Belveren, S.; Aydınoğlu, S.; Ulger, M.; de Cózar, A.; Retamosa, M.G.; Sansano, J.M.; Döndaş, H.A. Biological properties and conformational studies of amphiphilic Pd(II) and Ni(II) complexes bearing functionalized aroylaminocarbo-*N*-thioylpyrrolinate units. *Beilstein J. Org. Chem.* **2021**, *17*, 2812–2821. [[CrossRef](#)]
19. Nural, Y.; Kilincarslan, R.; Dondas, H.A.; Cetinkaya, B.; Serin, M.S.; Grigg, R.; Ince, T.; Kilner, C. Synthesis of Ni(II), Pd(II) and Cu(II) metal complexes of novel highly functionalized aroylaminocarbo-*N*-thioyl pyrrolidines and their activity against fungi and yeast. *Polyhedron* **2009**, *28*, 2847–2854. [[CrossRef](#)]

20. Garoufis, A.; Hadjikakou, S.K.; Hadjiliadis, N. Palladium coordination compounds as anti-viral, anti-fungal, anti-microbial and anti-tumor agents. *Coord. Chem. Rev.* **2009**, *253*, 1384–1397. [[CrossRef](#)]
21. Salishcheva, O.V.; Prosekov, A.Y. Antimicrobial activity of mono- and polynuclear platinum and palladium complexes. *Foods Raw Mater.* **2020**, *8*, 298–311. [[CrossRef](#)]
22. Khosravi, F.; Gholinejad, M.G.; Lledó, D.; Grindlay, G.; Nájera, C.; Sansano, J.M. 1-Butyl-3-methyl-2-(diphenylphosphino)imidazolium hexafluorophosphate as an efficient ligand for recoverable palladium-catalyzed Suzuki–Miyaura reaction in neat water. *J. Organomet. Chem.* **2019**, *901*, 120941. [[CrossRef](#)]
23. Sobhani, S.; Moghadam, H.H.; Skibsted, J.; Sansano, J.M. A hydrophilic heterogeneous cobalt catalyst for fluoride-free Hiyama, Suzuki, Heck and Hirao cross-coupling reactions in water. *Green Chem.* **2020**, *22*, 1353–1365. [[CrossRef](#)]
24. Fors, B.P.; Buchwald, S.L. A Multiligand Based Pd Catalyst for C–N Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 15914–15917. [[CrossRef](#)] [[PubMed](#)]
25. Sheng, Q.; Hartwig, J.F. [(CyPF-tBu)PdCl₂]: An Air-Stable, One-Component, Highly Efficient Catalyst for Amination of Heteroaryl and Aryl Halides. *Org. Lett.* **2008**, *10*, 4109–4112. [[CrossRef](#)] [[PubMed](#)]
26. Sobhani, S.; Zarei, H.; Sansano, J.M. A new nanomagnetic Pd-Co bimetallic alloy as catalyst in the Mizoroki–Heck and Buchwald–Hartwig amination reactions in aqueous media. *Sci. Rep.* **2021**, *11*, 17025. [[CrossRef](#)] [[PubMed](#)]
27. Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. A Novel Synthesis of Dialkyl Arenephosphonates. *Synthesis* **1981**, *1981*, 56–57. [[CrossRef](#)]
28. Gholinejad, M.; Esmailoghli, H.; Khosravi, F.; Sansano, J.M. Ionic liquid modified carbon nanotube supported palladium nanoparticles for efficient Sonogashira–Hagihara reaction. *J. Organomet. Chem.* **2022**, *963*, 122295. [[CrossRef](#)]
29. Sigeev, A.S.; Peregodov, A.S.; Cheprakov, A.V.; Beletskaya, I.P. The Palladium Slow-Release Pre-Catalysts and Nanoparticles in the “Phosphine-Free” Mizoroki–Heck and Suzuki–Miyaura Reactions. *Adv. Synth. Catal.* **2015**, *357*, 417–429. [[CrossRef](#)]
30. Gholinejad, M.; Afrasi, M.; Nikfarjam, N.; Nájera, C. Magnetic crosslinked copoly(ionic liquid) nanohydrogel supported palladium nanoparticles as efficient catalysts for the selective aerobic oxidation of alcohols. *Appl. Catal. A-Gen.* **2018**, *563*, 185–195. [[CrossRef](#)]
31. Chernyshev, V.M.; Astakhov, A.V.; Chikunov, I.E.; Tyurin, R.V.; Eremin, D.B.; Ranny, G.S.; Khrustalev, V.N.; Ananikov, V.P. Pd and Pt Catalyst Poisoning in the Study of Reaction Mechanisms: What Does the Mercury Test Mean for Catalysis? *ACS Catal.* **2019**, *9*, 2984–2995. [[CrossRef](#)]
32. Justik, M.W.; Protasiewicz, J.D.; Updegraff, J.B. Preparation and X-ray structures of 2-[(aryl)iodonio]benzenesulfonates: Novel diaryliodonium betaines. *Tetrahedron Lett.* **2009**, *50*, 6072–6075. [[CrossRef](#)]
33. Liu, H.; Yin, B.; Gao, Z.; Li, Y.; Jiang, H. Transition-metal-free highly chemo- and regioselective arylation of unactivated arenes with aryl halides over recyclable heterogeneous catalysts. *Chem. Commun.* **2012**, *48*, 2033–2035. [[CrossRef](#)]
34. Xie, L.-G.; Wang, Z.-X. Nickel-Catalyzed Cross-Coupling of Non-Activated or Functionalized Aryl Halides with Aryl Grignard Reagents. *Chem. Eur. J.* **2010**, *16*, 10332–10336. [[CrossRef](#)] [[PubMed](#)]
35. Zong, Y.; Hu, J.; Sun, P.; Jiang, X. Synthesis of Biaryl Derivatives via a Magnetic Pd-NPs-Catalyzed One-Pot Diazotization-Cross-Coupling Reaction. *Synlett* **2012**, *23*, 2393–2396. [[CrossRef](#)]
36. Tao, B.; Boykin, D.W. Simple Amine/Pd(OAc)₂-Catalyzed Suzuki Coupling Reactions of Aryl Bromides under Mild Aerobic Conditions. *J. Org. Chem.* **2004**, *69*, 4330–4335. [[CrossRef](#)]
37. Mao, J.; Hua, Q.; Xie, G.; Guo, J.; Yao, Z.; Shi, D.; Ji, S. Iodine-Catalyzed Suzuki–Miyaura Coupling Performed in Air. *Adv. Synth. Catal.* **2009**, *351*, 635–641. [[CrossRef](#)]
38. Demir, A.S.; Findik, H.; Saygili, N.; Tuna-Subasi, N. Manganese (III) acetate-mediated synthesis of biaryls under microwave irradiation. *Tetrahedron* **2010**, *66*, 1308–1312. [[CrossRef](#)]
39. Monguchi, Y.; Hattori, T.; Miyamoto, Y.; Yanase, T.; Sawama, Y.; Sajiki, H. Palladium on Carbon-Catalyzed Cross-Coupling using Triarylbiimides. *Adv. Synth. Catal.* **2012**, *354*, 2561. [[CrossRef](#)]
40. Ghorbani-Choghamarani, A. Palladium supported on modified magnetic nanoparticles: A phosphine-free and heterogeneous catalyst for Suzuki and Stille reactions. *App. Organomet. Chem.* **2016**, *30*, 140–147. [[CrossRef](#)]
41. Li, P.; Wang, L.; Zhang, L.; Wang, G.W. Magnetic Nanoparticles-Supported Palladium: A Highly Efficient and Reusable Catalyst for the Suzuki, Sonogashira, and Heck Reactions. *Adv. Synth. Catal.* **2012**, *354*, 1307. [[CrossRef](#)]
42. Liu, N.; Liu, C.; Jin, Z. Poly(ethylene glycol)-functionalized imidazolium salts–palladium-catalyzed Suzuki reaction in water. *Green Chem.* **2012**, *14*, 592–597. [[CrossRef](#)]
43. Chen, X.; Wang, L.; Liu, J. Cross-Coupling of Aryl Grignard Reagents with Aryl Halides Catalyzed by an Immobilized Nickel Catalyst. *Synthesis* **2009**, 2408–2412. [[CrossRef](#)]
44. Yang, L.; Zhang, X.; Mao, P.; Xiao, Y.; Bian, H.; Yuan, J.; Maia, W.; Qua, L. NCN pincer palladium complexes based on 1,3-dipicolyl-3,4,5,6-tetrahydropyrimidin-2-ylidenes: Synthesis, characterization and catalytic activities. *RSC Adv.* **2015**, *5*, 25723–25729. [[CrossRef](#)]
45. Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanari, D.; Marrocchi, M.; Drees, M.; Facchetti, A.; Vaccaro, L. A biomass-derived safe medium to replace toxic dipolar solvents and access cleaner Heck coupling reactions. *Green Chem.* **2015**, *17*, 365–372. [[CrossRef](#)]
46. Mi, X.; Huang, M.; Guo, H.; Wu, Y. An efficient palladium(II) catalyst for oxidative Heck-type reaction under base-free conditions. *Tetrahedron* **2013**, *69*, 5123–5128. [[CrossRef](#)]
47. Kang, L.; Zhang, F.; Ding, L.T.; Yang, L. Rhodium-catalyzed oxidative decarbonylative Heck-type coupling of aromatic aldehydes with terminal alkenes. *RSC Adv.* **2015**, *5*, 100452–100456. [[CrossRef](#)]

48. Rout, L.; Jammi, S.; Punniyamurthy, T. Novel CuO Nanoparticle Catalyzed C–N Cross Coupling of Amines with Iodobenzene. *Org. Lett.* **2007**, *9*, 3397–3399. [[CrossRef](#)]
49. Ackermann, L.; Sandmann, R.; Song, W. Palladium- and Nickel-Catalyzed Aminations of Aryl Imidazolylsulfonates and Sulfamates. *Org. Lett.* **2011**, *13*, 1784–1786. [[CrossRef](#)]
50. Cívicos, J.F.; Alonso, D.A.; Nájera, C. Microwave-Promoted Copper-Free Sonogashira–Hagihara Couplings of Aryl Imidazolylsulfonates in Water. *Adv. Synth. Catal.* **2013**, *355*, 203–208. [[CrossRef](#)]
51. Susanto, W.; Chu, C.-Y.; Ang, W.J.; Chou, T.-C.; Lo, L.-C.; Lam, Y. Fluorous Oxime Palladacycle: A Precatalyst for Carbon–Carbon Coupling Reactions in Aqueous and Organic Medium. *J. Org. Chem.* **2012**, *77*, 2729–2742. [[CrossRef](#)]
52. Yu, S.; Wu, J.; He, X.; Shang, Y. Ferrocenyl bisoxazoline as an efficient non-phosphorus ligand for palladium-catalyzed copper-free Sonogashira reaction in aqueous solution. *Appl. Organomet. Chem.* **2018**, *32*, e4156. [[CrossRef](#)]
53. Lima, H.M.; Sivappa, R.; Yousufuddin, M.; Lovely, C.J. Total Synthesis of 7'-Desmethylkealiiquinone. *Org. Lett.* **2012**, *14*, 2274–2277. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.