

High Surface Area CeO₂ Promoted Suzuki–Miyaura Cross-Coupling of Arylboronic Acids and Aryl Iodides

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Abstract: High surface area cerium oxide (240 m²/g) efficiently promoted the Suzuki–Miyaura cross-coupling of aryl iodides with arylboronic acids, in the absence of palladium or any other transition-metal catalyst. Excellent selectivity towards the cross-coupling product was observed. Cerium oxide could be recovered and reused at least three times without any loss of activity.

Key words: biaryls, cross-coupling, cerium oxide, Suzuki–Miyaura reaction, palladium-free

Asymmetric biaryl compounds are fundamental building blocks in synthetic organic chemistry. Due to the high occurrence of these organic substructures in a variety of natural products, pharmaceuticals, agrochemicals, as well as in material science, different methodologies have been developed for the transition-metal-catalyzed cross-coupling of aromatic electrophiles and aryl organometallic reagents.¹ Among them, the most popular and versatile protocol is the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of aryl boronic acids and aryl halides.^{1a,2} This powerful synthetic tool has received continuous attention for decades, mainly because of the low toxicity and stability of organoboranes, the mild experimental conditions and the compatibility with a wide range of functional groups.³ Although it is assumed that this palladium-catalyzed reaction is a homogeneous process, the use of soluble palladium complexes as catalysts is controversial for practical, environmental and economical considerations, due to the necessity of using expensive and/or toxic ligands and the difficult recovery/removal of the catalyst. In this sense, much effort has been devoted for the immobilization of palladium species on different supports,⁴ with Pd/C being the most explored catalytic system.⁵ More recently, palladium supported on different metal oxides has demonstrated to efficiently catalyze the Suzuki cross-coupling reaction.⁶ The use of these heterogeneous palladium catalysts is an attractive alternative because of their potential industrial application, for example in the biaryl syntheses demanded by the fine chemical and pharmaceutical industries; however, palladium leaching represents a serious drawback, since most of the fine

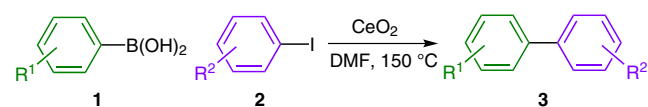
chemicals and pharmaceutical products must be completely free of residual metal.

On the other hand, the influence of MO₂-type supports (M = Ce, Ti, Zr, Si) on the selectivity (cross-coupling versus arylboronic acid homocoupling) of the Pd- and Au-catalyzed Suzuki reaction, has been addressed by different authors,⁷ showing that the characteristics of the metal oxide used as support (crystallite size, degree of hydroxylation, etc.) might have a relevant role in the activity/selectivity of these catalytic systems. These interesting results would suggest a non-innocent participation of the support, which could also be acting as a promoter of the desired reaction.

Taking into account these precedents, and prompted by our continuing interest in nanosized transition-metal-catalyzed organic transformations,⁸ we decided to study a catalytic system composed of palladium(0) nanoparticles supported on high surface area CeO₂ (240 m²/g) for its application in the Suzuki–Miyaura cross-coupling reaction. During the optimization of the reaction conditions, we surprisingly found that CeO₂, in the absence of palladium nanoparticles, can efficiently promote the desired coupling reaction.

It is known that CeO₂ is an effective heterogeneous catalyst for CO₂ fixation in processes involving the multicomponent construction of C–N or C–O bonds, such as the synthesis of carbonates, carbamates and ureas.⁹ The use of CeO₂ as a promoter of other synthetic transformations has been scarcely reported; in two recent papers, Nagarkar and co-workers published their findings on the nanosized CeO₂-catalyzed Ullmann-type cross-coupling reaction and the three-component synthesis of α -aminophosphonates.¹⁰

We want to present herein our results on the transition-metal-free Suzuki–Miyaura cross-coupling of aryl iodides with arylboronic acids, promoted by high surface area CeO₂, in the presence of K₂CO₃ as a base and *N,N*-dimethylformamide (DMF) as the solvent (Scheme 1). To our knowledge, this is the first report describing the Suzuki–



Scheme 1 CeO₂-promoted Suzuki–Miyaura cross-coupling

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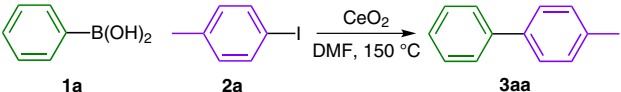
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Miyaura coupling promoted by cerium oxide, in the absence of palladium or any other transition-metal catalyst.

Phenylboronic acid (**1a**) and *para*-iodotoluene (**2a**) were chosen as model compounds for the optimization of the reaction conditions (Table 1). The reaction of **1a** (1.0 mmol) and **2a** (0.7 mmol) using K₂CO₃ as the base (2.0 mmol) in DMF under reflux (5 mL) and in the presence of CeO₂ (250 mg), gave the corresponding biaryl **3aa** in three hours of reaction time and in an excellent yield (Table 1, entry 1).¹¹

Table 1 Optimization of Reaction Conditions^a



Entry	Solvent	Base	T (°C)	Time (h)	Yield (%) ^b
1	DMF	K ₂ CO ₃	150	3	94
2	H ₂ O	K ₂ CO ₃	100	6	11
3	H ₂ O–EtOH ^c	K ₂ CO ₃	89	6	–
4	DMF	K ₂ CO ₃	100	6	5
5	DMSO	K ₂ CO ₃	150	12	2
6	DMF	Cs ₂ CO ₃	150	12	–
7	DMF	K ₃ PO ₄	150	12	–
8	DMSO	NaOH	150	12	3
9 ^d	DMF	K ₂ CO ₃	150	24	29

^a Reaction conditions: **1a** (1.0 mmol), **2a** (0.7 mmol), base (2.0 mmol), CeO₂ (250 mg), under a N₂ atmosphere. CeO₂ was calcined under vacuum prior to use as described in ref. 11.

^b GLC yield based on starting **2a**.

^c A 1:1 mixture was used as solvent.

^d Reaction was performed using 125 mg of CeO₂.

Working under the same conditions as in entry 1, but using bi-distilled water or a 1:1 mixture of ethanol–water as the solvent, under reflux, gave poorer results than those obtained in DMF (compare entries 2 and 3 with entry 1 in Table 1). Besides, the reaction performed in DMF at a lower temperature (100 °C) or in DMSO at 150 °C gave practically no conversion of the starting materials (Table 1, entries 4 and 5). These results would be indicating that, not only the reaction temperature but also the nature of the solvent, are crucial to obtain high conversions into the desired cross-coupling product. With regard to the base used for the coupling reaction, only K₂CO₃ proved to be effective; other bases tested, such as Cs₂CO₃, K₃PO₄ or NaOH, the latter being used in combination with DMSO as the solvent, gave practically no conversion of the starting aryl iodide (Table 1, entries 6–8). On the other hand, reducing by half the amount of CeO₂ (125 mg) resulted in a very low conversion into biaryl **3aa** after 24 hours of reaction time (Table 1, entry 9).

Following the optimized conditions, we then studied the scope of the method by coupling a series of aryl halides with different arylboronic acids. As shown in Table 2, activated aryl iodides substituted with electron-withdrawing groups (**2b**, **2c**), were cross-coupled with phenylboronic acid (**1a**) in excellent yields (Table 2, entries 2 and 3).

The reactivity of deactivated aryl iodides showed to be strongly dependent on the electron-releasing group attached to the aromatic ring. *para*-Iodotoluene (**2a**) gave the corresponding cross-coupling product **3aa** in only three hours (Table 2, entry 1), whereas the more deactivated *para*-iodoanisole (**2d**) needed longer reaction times to give a similar conversion into **3ad** (Table 2, entry 4) and *para*-iodoaniline remained unreacted after 24 hours of reaction time. On the other hand, aryl bromides and aryl chlorides proved to be inert under the reaction conditions; however, this drawback of the method allowed the selective cross-coupling of dihaloaryls, such as 1-chloro- and 1-fluoro-4-iodobenzene, with phenylboronic acid to obtain the corresponding halo-substituted biphenyls **3ae** and **3af** in excellent yield (Table 2, entries 5 and 6). Then, we tested other arylboronic acids than **1a**. By considering the low reactivity of deactivated aryl iodides, we focused on arylboronic acids bearing strong electron-releasing groups. Thus, the reaction of *para*-methoxyphenyl boronic acid (**1b**) and *para*-*N,N*-dimethylaminophenyl boronic acid (**1c**) with *para*-iodotoluene (**2a**) gave the cross-coupling products **3ba** and **3ca**, respectively, in good to excellent yields (Table 2, entries 7 and 8).

It is noteworthy that in all the reactions studied, the selectivity towards the cross-coupling product was excellent. Minor amounts (<5%) of the corresponding homocoupled products, resulting from the dimerization of the starting arylboronic acids, were observed in some cases.

Finally, and taking into account that the reaction seemed to be stoichiometric rather than catalytic, we studied the recovery and reutilization of the CeO₂. For this, **1a** and **2a** were reacted under the optimized conditions; once the reaction was complete, the mixture was filtered through a Büchner funnel and the solid was sequentially washed with bi-distilled water and diethyl ether. The CeO₂ thus recovered was dried in an oven for its reuse. As shown in Figure 1, by applying this procedure, CeO₂ could be reutilized for at least three reaction cycles without any loss of activity.

Although the specific role of cerium oxide in promoting the Suzuki cross-coupling reaction is difficult to ascertain at this stage, we have carried out some experiments in order to get additional information about the potential active species that could be participating as promoters of this transformation. *Experiment A*: The reaction of **1a** and **2a** performed under the optimized conditions, but using conventional cerium oxide of about 50 m²/g surface area, resulted in a very low conversion into biaryl **3aa** (12%) after 24 hours of reaction time. *Experiment B*: The reaction of **1a** and **2a** using uncalcined high surface area CeO₂ (240 m²/g), gave **3aa** in only 18% yield after six hours of reac-

Table 2 CeO₂-Promoted Suzuki–Miyaura Cross-Coupling of Aryl Halides with Arylboronic Acids^a

Entry	Boronic acid	Aryl halide	Time (h)	Product	Yield (%) ^b
1			3		94
2			3		93
3			3		99
4			24		75
5			3		87
6			6		95
7			3		91
8			5		88

^a Reaction conditions: **1a** (1.0 mmol), **2a** (0.7 mmol), base (2.0 mmol), CeO₂ (250 mg), in DMF (5 mL) at 150 °C, under N₂ atmosphere.

^b GLC yield based on the starting aryl halide.

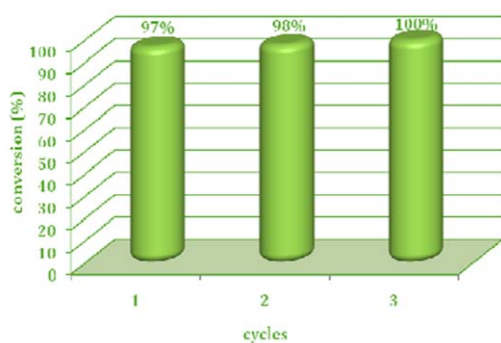


Figure 1 Activity of CeO₂ in the cross-coupling of **1a** and **2a**, after three consecutive reaction cycles

tion time. *Experiment C*: The reaction of **1a** and **2a** under the optimized conditions, in the presence of SiO₂ instead of CeO₂ gave **3aa** in only 15% yield after 24 hours of reaction time. *Experiment D*: The reaction of **1a** and **2a** under the optimized conditions but carried out under air, gave **3aa** in 58% yield after 24 hours of reaction time.

Experiment E: When recovered CeO₂ was not washed with water (only washed with organic solvent) for its reutilization in a second cycle, no conversion of starting **1a** and **2a** was observed. *Experiment F*: The reaction of **1a** and **2a** under the optimized conditions, but in the absence of high surface cerium oxide, led to the recovery of the starting materials together with minor amounts (10%) of a mixture composed of the cross-coupling product **3aa** and the biaryl derived from the homocoupling of the starting **2a**.

From the results above, it is clear that only high surface area CeO₂, previously submitted to calcination under vacuum,¹¹ is able to promote the title reaction. The calcination treatment could be removing adsorbed water on CeO₂, giving rise to a high concentration of surface sites active for the coupling reaction. When water is employed as the solvent, its interaction with the oxide surface would render CeO₂ quite inactive. Besides, the low activity developed by CeO₂ of 50 m²/g surface area should be related to its low surface area and concomitantly to the meager concentration of active surface sites. It is likely that such

sites are acidic ones, probably associated with surface hydroxyl groups. However, to give a more precise explanation about the way in which the substrate molecules are activated by the surface hydroxyl groups, further studies are needed. On the other hand, and taking into account that traces of palladium or other transition metals could catalyze Suzuki-type coupling reactions,¹² we analyzed samples of both high surface cerium oxide and post-reaction mixtures by atomic absorption spectrometry (AAS), without finding any trace of palladium, nickel, copper or iron. Although the presence of some metal species below the detection limit of the AAS can not be disregarded, some of the additional experiments carried out (Experiments A, B, D, E and F) indicate that potential sub-ppm amounts of palladium or other transition metals present in the reaction medium do not catalyze the Suzuki coupling under the optimized conditions.

In conclusion, we have described herein a simple and economical methodology for the Suzuki–Miyaura cross-coupling reaction, based on the use of high surface area CeO₂, in the absence of palladium or any other transition metal or ligands. Furthermore, the easy reuse of CeO₂ without loss of activity makes this new protocol a very attractive alternative not only for synthetic organic chemists but also for the fine chemical industry. Further studies are currently undertaken in our laboratories with the aim to disclose some relevant mechanistic aspects of these preliminary findings.

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- (11) **Typical Experimental Procedure:** High surface area CeO₂ (250 mg, 240 m²/g, Rhône-Poulenc) was calcined inside the reaction flask prior to use. The calcination treatment consisted in heating by means of a heat gun (160 °C) under vacuum (0.1 Torr) for 5 min. Once the reaction flask reached r.t., the corresponding boronic acid (1 mmol) and K₂CO₃ (2 mmol, 276 mg) were added together with DMF (2 mL). The reaction vessel was immersed in a pre-heated silicon oil bath at 150 °C. After stirring the mixture at this temperature for 5 min, a solution of the aryl halide (0.7 mmol) in DMF (1 mL) was added. The reaction progress was monitored by GC–MS. The resulting suspension was diluted with Et₂O (10 mL) and filtered by Büchner funnel. The filtrate was evaporated (15 Torr) and the resulting residue was purified by flash column chromatography (silica gel, hexane–EtOAc) to afford the corresponding biaryl product. The following known compounds included in Table 2 were characterized by comparison of their chromatographic and spectroscopic data (¹H NMR, ¹³C NMR, and MS) with those described in the literature: (1,1'-biphenyl)-4-carbonitrile (**3ab**; ref 13), 4-(trifluoromethyl)-1,1'-biphenyl (**3ac**; ref 14), 4-methyl-1,1'-biphenyl (**3aa**; ref 15), 4-methoxy-1,1'-biphenyl (**3ad**; ref 15), 4-chloro-1,1'-biphenyl (**3ae**; ref 15), 4-fluoro-1,1'-biphenyl (**3af**; ref 14), 4-methoxy-4'-methyl-1,1'-biphenyl (**3ba**; ref 16), N,N'-4'-trimethyl-(1,1'-biphenyl)-4-amine (**3ca**; ref 15).

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