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Selectivity Studies Towards the Synthesis of Novel Biaryl Ureas by (Hetero)Nanocatalysis: Size Control and Support Effects

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A series of novel biaryl ureas containing different structural patterns have been prepared in good yields in the presence of palladium nanoparticles (PdNPs) with narrow particle size distribution. In particular, α, β-, and γ-hydroxypropylated cyclodextrins were used as reductants/stabilizers under different Pd-to-cyclodextrin ratios to tune the particle size and exploit the surface/cavity effects in the Suzuki–Miyaura reaction. Catalyst recovery in this process was pursued as well. Owing to its excellent performance, ceria was explored as a support for these PdNPs. The heterogeneous catalyst was characterized and investigated in the reaction of *N*-(4-iodo-aryl),*N'*-alkyl urea and phenylboronic acid. Our preliminary results revealed a high activity of the catalyst at 0.5 mol% Pd^0 during three consecutive cycles. It is suggested that the specific interface between Pd^0 and the high-surface-area ceria has a role in the catalytic performance.

Introduction

The ureido scaffold has a ubiquitous presence in several fundamental biological processes.[1] For instance, the urea-type backbone is related to HIV-1 protease inhibition,[2] antitumor,[3] antitrypanossomal,[4] and antituberculosis activities.[5] This structural unit and some related systems (e.g., thioureas, glycoluril-based ones) feature different properties, such as polarity, rigidity, and hydrogen-bonding capacity, which play a central role in molecular recognition, making these systems well suited to folding and self-assembly.[6] At the interface between biology, organic synthesis, and materials chemistry, urea units have also inspired the design of protein-like structures[7] (e.g., foldamers), as well as the fabrication of nanostructures with potential applications in bionanotechnology.[8] In addition, nature has incorporated ureas into a multitude of biologically active natural products,[9] thus further solidifying the widespread importance of this functional group.

From a medicinal chemistry perspective, representative structure–activity relationships (SAR) studies have pointed to the fact that hydrophobic substitution on the C–N bonds of ureas can improve the robustness of interactions as a result of the stabilization of some conformations, giving rise to collectively stronger non-covalent forces.[10] *N*-Aryl ureas are by far the most investigated as they provide a means to π-stacking interactions along with hydrophobic ones depending on their backbones. For example, a number of aryl ureas display significant potential to inhibit vascular endothelial growth factor receptor-2, which is related to angiogenesis suppression.[11] Moreover, some recent SAR studies suggested that the introduction of the biphenyl moiety could improve the antitumor[12] as well as anti-obesity[13] potencies of urea derivatives. Other *N*-biaryl urea systems are of high interest in the context of host–guest chemistry, especially in the dimeric form.[6b]

N-Biaryl ureas are most commonly prepared by palladium-catalyzed carbon–carbon bond-forming cross-coupling reactions[12,14] or by metal-catalyzed *N*-arylations,[14b–c] which generally provide high reaction yields. To minimize the relatively high scavenging ability of palladium,[15a,b] most of these procedures rely on prior *N*-protection along with the use of homogeneous catalysts based on bulky electron-rich commercial ligands (especially phosphine) to allow in situ generation of the active species. Despite the high activity given by this approach, these palladium-based catalysts suffer from high costs and difficulties of recovery, which also limit the possibilities for multistep reactions. The use of cleaner and inherently safer alternatives is promising owing to the attractive emphasis on sustainable chemistry. In this respect, ligand-free approaches, especially by using metal nanoparticles, are more cost-effective and may enable recycling of the catalyst system more effectively compared with the traditional methodologies.[16] In reac-

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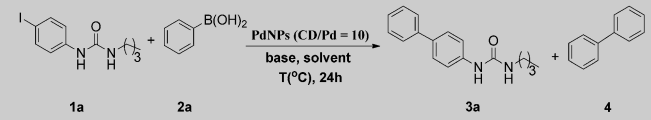
tions of sensitive compounds, these metal catalysts can also be tailored for optimal performance in view of the effects of catalyst nanoparticle shape and size on activity. Owing to environmental concerns, different approaches have been used for the synthesis of metal nanoparticles, including their phytosynthesis as well as the use of naturally derived reducing/capping agents.[17] Cyclodextrins (CDs), glyconanocavities obtained by biotechnological routes, often play a key role in these processes,[18] especially in the scope of aqueous-phase nanocatalysis.[18c–g]

Recently, we reported an efficient and green reaction protocol involving the synthesis of *N*-benzyl thioureas from papaya seeds.[19a] Extending the work, we engaged in the preparation of a novel set of *N*-benzyl and *N*-aryl ureas by the treatment of the respective thioureas with synthetically useful potassium dichloroiodate.[19b,c] In this case, by tuning the reaction conditions, sequential oxidation–iodination enabled access to 4-iodo aryl ureas in moderate to high yields. Based on the potential of *N*-biaryl ureas as promising lead compounds for medicinal chemistry and supramolecular chemistry, we herein report the introduction of CD-protected palladium nanoparticles (PdNPs) as catalysts in Suzuki–Miyaura reactions with unprotected *N*-iodoaryl ureas. To exploit the influence of different particle sizes in the performance/reaction selectivity, different nanocatalysts were investigated to prepare novel the *N*-biaryl-*N*′-alkyl ureas. Bearing in mind the advantages for catalyst reusability, the PdNPs were heterogenized[20a] by using a rare-earth metal oxide support (CeO_2), and were evaluated for reusability in three consecutive catalytic cycles.

Table 1. Survey of the reaction conditions.[a]



1a 2a 3a 4

Entry	Catalyst/CD type (Pd loading [mol%])	Conditions	Yield [%][e]
1	PdNPs[b]/α-HPCD (0.5)	H_2O, K_2CO_3, RT	30
2	PdNPs[c]/β-HPCD (0.5)	H_2O, K_2CO_3, RT	35
3	PdNPs[d]/γ-HPCD (0.5)	H_2O, K_2CO_3, RT	<10
4	PdNPs[b]/α-HPCD (0.5)	H_2O, K_2CO_3, 95–100 °C	48
5	PdNPs[c]/β-HPCD (0.5)	H_2O, K_2CO_3, 95–100 °C	52
6	PdNPs[c]/β-HPCD (2)	H_2O, K_2CO_3, 95–100 °C	55[f]
7	PdNPs[c]/β-HPCD (2)	H_2O, Cs_2CO_3, 95–100 °C	41[f]
8	PdNPs[c]/β-HPCD (2)	H_2O, K_3PO_4, 95–100 °C	45[f]
9	PdNPs[c]/β-HPCD (2)	H_2O/EtOH (2:1), K_2CO_3, 95–100 °C	60
10	PdNPs[c]/β-HPCD (2)	H_2O/EtOH (1:1), K_2CO_3, 95–100 °C	73
11	PdNPs[c]/β-HPCD (2)	H_2O/CH_3CN (1:1), K_2CO_3, 95–100 °C	36
12	PdNPs[c]/β-HPCD (2)	H_2O/THF (1:1), K_2CO_3, 95–100 °C	44
13	Na_2PdCl_4 (2)	H_2O/EtOH (2:1), K_2CO_3, 95–100 °C	25
14	Na_2PdCl_4 (2)	H_2O/EtOH (1:1), K_2CO_3, 95–100 °C	33

[a] Reaction conditions: *N*-4-iodophenyl-*N*′-butyl urea (0.5 mmol), phenylboronic acid (0.6 mmol), base (1.0 mmol), solvent (5 mL), 24 h. [b] Size dispersion range = 13–30 nm. [c] Size dispersion range = 20–46 nm. [d] Size dispersion range = 31–60 nm. [e] Isolated yield (**3a**). [f] 8–13% biphenyl (**4**).

Results and Discussion

Our initial experiments were guided by previous investigations concerning the effect of the CD/Pd ratio on the size of palladium nanoparticles stabilized by hydroxypropylated cyclodextrins.[20b] We demonstrated that the CD concentration influences the formation of regular assemblies, which may direct PdNPs growth towards uniform particles. Therefore, we were committed to identifying the correct ratio to achieve the utmost efficiency and economy in the implementation of this method. In addition, it was not clear whether we would encounter different catalytic activity for the α-, β-, and γ-forms of hydroxypropylated CDs given the fact that their internal cavity sizes are different and the number of α-D-glucopyranoside units has been demonstrated to exhibit distinct NPs size control.[18] Thus, we judiciously screened all platforms, assuming that their internal environments could influence the reaction outcome.

Firstly, our studies were focused on the coupling of phenylboronic acid with *N*-butyl-*N*′-(4-iodo)phenyl (**1a**) in water as the reductant/stabilizing agent is hydrophilic. Three separate initial sets of conditions were used based on the CD type. From Table 1 it can be seen that the use of 0.5 mol% PdNPs prepared with a lower excess (10-fold) of α- or β-2-hydroxypropyl-CD relative to the Pd precursor (Table 1, entries 1,2) generated the desired *N*-biaryl urea (**3a**) in low yields (30–35%) at 25 °C. With these conditions, it was noticed that the conversion of the substrate into the corresponding biaryl was similar regardless of whether the α- or β-form was used. Interestingly, the γ-form failed to provide significant starting material conversion in pure water (Table 1, entry 3). Application of refluxing water with PdNPs containing the α- or β-forms resulted in moderate yields of **3a** (Table 1, entries 4 and 5). The coupling reaction with 2 mol% PdNPs provided only a slight improvement in the performance, whereas the use of different bases was not rewarding and facilitated the formation of undesired byproducts (Table 1, entries 6–8). The effect of water on the cross-coupling was also studied and the results showed that substitution by a water/ethanol mixture improved the yield of **3a** (Table 1, entries 9 and 10). However, the use of less polar aprotic solvents did not provide good yields (Table 1, entries 11 and 12), suggesting a solvent effect.[22] Notably, control experiments showed that Na_2PdCl_4 alone afforded the expected product in low yields, even in a water/ethanol mixture (Table 1, entries 13 and 14). Nevertheless, to prove the importance of the NPs stabilization, the assay with 4-fold Pd loading (entry 14) was performed and shown to be still less active than the one with PdNPs, even with the NPs in water (entry 2). The particle size distribution with the 10-fold excess of CD is relatively broad;[20b] this result suggests that the poor activation/selectivity of PdNPs towards the unprotected aryl urea may be a result of strong interactions from the functional domains with the metal surface.

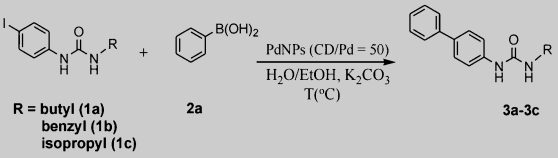
Recent elegant studies[18c,22] provide evidence that the solvent and base are decisive for the in situ formation of some Pd-based active species. In our case, however, we focused on

using a higher CD/Pd molar ratio as this condition allowed us previously to improve the size control of the PdNPs.[20b]

As the ability to catalyze the formation of biaryl ureas in moderate yields was similar with Pd^0 dispersions made from either α/β-CD, both of them were examined to explore the impact of catalyst nanoparticle size on the reactivity of the urea substrate.

The strategy was therefore adjusted by using PdNPs with narrow size distributions synthesized under a 50-fold excess of CD.[20b] Gratifyingly, the catalyst system composed of 2-hydroxypropyl-β-cyclodextrin (β-HCPD)-stabilized PdNPs improved the yield of **3a** to 98% under the same conditions as described (Table 2, entry 1). More satisfyingly, similar yields were obtained within 6 h (Table 2, entry 2). Notably, reaction with the α form proceeded with comparable yields (Table 2, entries 3 and 4).

Table 2. Studies with PdNPs with narrow size distributions.[a]



Entry	Catalyst/CD type	R	Conditions	Yield [%][d]	Product
1	PdNPs[b]/β-HPCD	$-(CH_2)_3CH_3$	95–100 °C, 24 h	98	**3a**
2	PdNPs[b]/β-HPCD	$-(CH_2)_3CH_3$	95–100 °C, 6 h	95	**3a**
3	PdNPs[c]/α-HPCD	$-(CH_2)_3CH_3$	95–100 °C, 24 h	90	**3a**
4	PdNPs[c]/α-HPCD	$-(CH_2)_3CH_3$	95–100 °C, 6 h	81	**3a**
5	PdNPs[b]/β-HPCD	$-CH_2Ph$	95–100 °C, 6 h	87	**3b**
6	PdNPs[b]/β-HPCD	$-CH(CH_3)_2$	95–100 °C, 6 h	–[c]	**3c**
7	PdNPs[b]/β-HPCD	$-CH(CH_3)_2$	50 °C, 24 h	75	**3c**

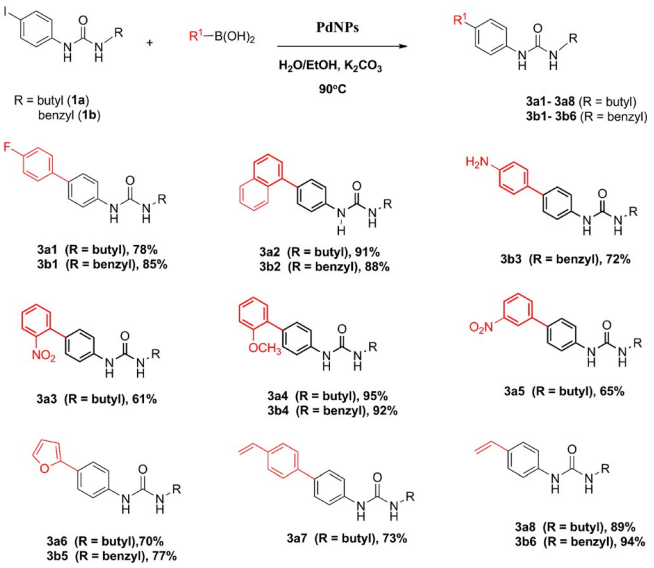
[a] Reaction conditions: *N*-4-iodophenyl-*N*′-butyl urea (0.5 mmol), phenylboronic acid (0.6 mmol), K_2CO_3 (1.0 mmol), H_2O/EtOH (1:1, 5 mL), PdNPs (2 mol%). [b] Size dispersion range = 10–15 nm. [c] Size dispersion range = 2–5 nm. [d] Isolated yield.

Substitution of the butyl by a benzyl group also allowed us the access to the biaryl urea in high yield within 6 h (Table 2, entry 5, 87%). In contrast, the presence of an isopropyl group (Table 2, entry 6) led to sub-products from the cleavage of the lateral chain at high temperatures (~100 °C). However, exploration of milder reaction conditions enabled the synthesis of the corresponding *N*-biphenyl-*N*′-isopropyl urea (Table 2, entry 7, 75%).

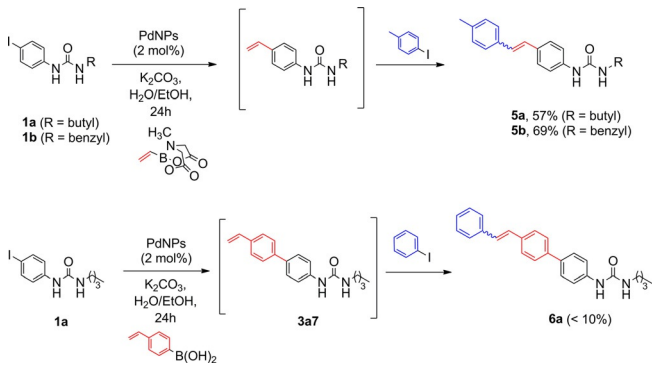
We propose that the reactivity differences between the CD forms are due to the inherent formation of inclusion complexes, which can affect the kinetics of the oxidative addition/transmetalation processes, according to the NP model.[20b] In this case, the cavity with the strongest complexation capacity—the β form—seems to dictate the relative reactivity instead of surface effects related to particle size distributions. When considering a short chain such as isopropyl, it is conceivable that the weaker association with the cavity can promote its fast cleavage.

Thus, to expand the repertoire of aryl ureas suitable for biological studies, we set out to test the generality of this catalytic condition by employing a variety of boronic acids and esters (Scheme 1). As expected, 4-substituted aryl substrates with electron-donating groups demonstrated good reactivity toward **1a**, resulting in satisfactory yields. Increasing the steric bulk on the boronic acid counterpart did not have any influence on the outcome of the cross-coupling reaction (products **3a2**–**3a4**, **3b2**, **3b4**). The use of electron-poor aryl boronic acids completely failed to provide any observable product under these conditions. Notably, the addition of an excess of base (4 equiv.) restored the catalytic cycle, thus providing the corresponding products in moderate to good yields (products **3a3** and **3a5**). This result supports the critical involvement of base in the second step (transmetalation) and is evidence in favor of the organoboron compound activation. Switching from 4-substituted aryl boronic acid to a heteroaromatic core, the catalytic reactivity led to similar yields (products **3a6**–**3b5**).

With these reaction conditions in hand and recognizing the utility of ureas **3a7**, **3a8**, and **3b6** for domino Suzuki/Heck reactions, we envisioned a consecutive C–C bond-forming transformation (Scheme 1). Treatment of urea **1a** with the vinyl boronate counterpart followed by the addition of 4-iodotoluene led to the corresponding *N*-styrylbenzyl ureas **5a** and **5b** in moderate to good yields with the β-HPCD-stabilized PdNPs as the catalyst (Scheme 2). However, when we attempted to employ the styrylboronic acid, the expected product **6a** was only observed in a low yield (<10%). In fact, the ^{1}H NMR spectra indicated recovery of the precursor, **3a7**. With regard to the stereoselectivity, a coupling constant of 13 Hz was observed for **5a** and **5b**, suggesting the formation of the more favorable *E* isomer (Scheme 1).

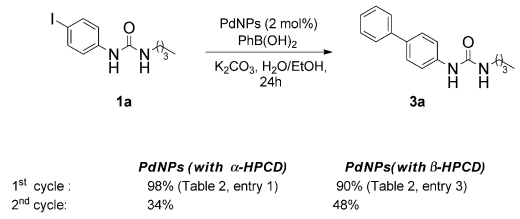


Scheme 1. Substrate scope. [a] *N*-4-iodophenyl-*N*′-butyl urea or *N*-4-iodophenyl-*N*′-benzyl urea (0.5 mmol), arylboronic acid (0.6 mmol), K_2CO_3 (1.0 mmol), H_2O/EtOH (1:1, 5 mL), PdNPs (β-HPCD, CD/Pd = 50, 2 mol% Pd), 24 h.



Scheme 2. Preliminary studies for PdNP-catalyzed one-pot cross-couplings.

In an effort to fulfill the demand for an ecologically and economically advantageous approach for the preparation of novel ureas by nanocatalysis, we initially evaluate the reusability of the PdNP-containing aqueous phase by exploring the reaction between urea **1a** and phenylboronic acid. Thus, after work-up from the first cycle, the aqueous phase revealed partial activity (Scheme 3), indicating that the PdNPs retain some activity de-



	PdNPs (with α-HPCD)	*PdNPs(with β-HPCD)*
1st cycle :	98% (Table 2, entry 1)	90% (Table 2, entry 3)
2nd cycle:	34%	48%

Scheme 3. Catalytic tests with recycled aqueous phases.

spite the slight agglomeration that was apparent on visual inspection. Under the same catalytic conditions, the NP dispersions containing α-HPCDs showed superior potential for recycling (Scheme 3). In fact, the PdNPs mean size distribution measured from AFM images indicates that the α-HPCD dispersion is more stable after work-up. However, it is often unclear if the PdNPs are just a reservoir of monometallic active species or are the real catalysts. By considering the first hypothesis, leaching to the organic phase could be a possible mechanism. Therefore, a tentative experiment involving adding iodinated aryl urea **1a** to the reaction medium containing the PdNPs was performed, as aryl halides (iodides/bromides) can induce the leaching process under appropriate conditions.[21] Analysis of X-ray fluorescence spectroscopy results indicated no significant Pd content was leached from the aqueous phase. On the other hand, the notable decrease in the activity of the aqueous phase with the simultaneous increase in particle agglomeration can be directly explained through Ostwald ripening. This fact is also in accordance with the findings recently reported by our group concerning the partial uncapping of CDs from metal surfaces induced by cavity complexation.[22]

On the basis of the potential biological profile of these biaryl ureas—by virtue of their structural resemblance to some antitumor compounds[23,24]—it was interesting to improve their synthetic conditions in terms of catalysis (mostly, turnover number and reusability). Considering the requirements envisaged for scale-up approaches, some issues might be solved by using heterogenized catalysts. From this point of view, small-sized palladium supported on carbonaceous[25] or inorganic oxides[26] has attracted considerable attention as some of these catalysts are able to promote selective transformations through collaborative effects.[26a] Previous reports indicate that the dispersion of colloidal metal species onto some supports, in the presence of cyclodextrins as protective agents, can improve the metallic dispersion and induce new selectivities.[25] At the same time, pure crystalline cerium oxide (ceria) contains sites that are able to perform several useful transformations.[26]

Surprisingly, only a handful of studies have focused on the use of pure ceria as a catalyst[27a–b] or as a support for C–C bond-forming reactions.[27c–d] An alternative approach is the preparation of CeO_2 with an alkaline-earth dopant (e.g,. Ca-doped ceria) as this reduces costs through use of much lower amounts of the expensive rare-earth metal. Based on the catalytic perspectives along with our interest in ceria-based materials,[28] we investigated Ca-doped ceria as a support for PdNPs. As α-HPCDs demonstrated similar catalytic behavior and were more able to stabilize the PdNPs after work-up compared with β-HPCDs, we decided to use them for the design of heterogenized PdNPs on CeO_2.

The synthesis of the supported catalyst was carried out in two stages: a) the preparation of doped ceria by means of a co-precipitation method and b) wet impregnation with the aqueous Pd/α-HPCD dispersion. The preparation route is described in the Supporting Information. Through this method, we performed the co-precipitation at pH 14 by using NaOH 1.0 M with CAN (cerium(IV) ammonium nitrate) and calcium nitrate as the precursors (in a proper stoichiometry) in an attempt to get material with a nominal composition of $Ce_{0.90}Ca_{0.10}O_{1.90}$ (see the Supporting Information). X-ray fluorescence indicated that the doped ceria has the composition $Ce_{0.88}Ca_{0.12}O_{1.88}$. Elemental analysis (CHN) detected 1.84% carbon in the doped ceria. We believe that this could be due to the presence of carbonate on the ceria particles surface.

To gain structural information, X-ray diffraction analysis was also used. The diffraction pattern is shown in Figure S1 (in the Supporting Information). No reliable data refinement from the indexing of the diffraction pattern was possible owing to the high signal-to-noise ratio; hence, no cell parameter was calculated. However, by using the Scherrer formula (see details in Supporting Information) we obtained an estimated value of 2.4 nm for the crystal size, indicating that it was nanoceria.

Additional confirmation of the doped nanoceria structure was acquired by using Raman spectroscopy (Figure S2, Supporting Information). For comparison, we also analyzed a non-doped ceria produced by using the same method. The F_{2g} band at ~450 cm^{-1}, assigned as the "breathing" vibration mode of oxygen atoms around cerium in the CeO_8 units, presents an asymmetric characteristic, which is indicative of nanomaterials.[29] Additionally, the second-order Raman mode at ~600 cm^{-1}, indicative of oxygen vacancies (V_o), is also ob-

served[30,31] for both samples. For the non-doped ceria, this leads to the conclusion that Ce^{3+} is present. For the doped ceria, it is apparent from the lower signal-to-noise ratio that the intensity of the Raman scattering is decreased. These findings definitively confirm the existence of non-stoichiometric nanoceria[29,32] and Ca-doping.[33]

The synthesis of the supported PdNPs involved the initial preparation of aqueous Pd^0 dispersions followed by stirring in the presence of doped ceria for 24 h at room temperature. After centrifugation, the impregnated material was washed with ethanol and finally dried at 70 °C for further characterizations.

We considered that all palladium content was adsorbed as, after centrifugation, the aqueous dispersion became clear and colorless, indicating the presence of less than 1% Pd (w/w). The presence of the organic moieties in the material was demonstrated by means of FTIR spectroscopy (Figure S3, Supporting Information). In this case, the interval 1250–1000 cm^{-1} indicated the presence of physically adsorbed cyclodextrin, the bands of which can be assigned as ν_{C-O-C} (1154 cm^{-1}), $\nu_{C-C/C-O}$ (1076 cm^{-1}), and ν_{C-O} (1033 cm^{-1}). Additional characterization by SEM energy-dispersive X-ray spectroscopy (EDS) showed that calcium and palladium are homogeneously distributed over the ceria surface (Figure 1). Finally, the atomic force microscopy (AFM) phase image demonstrates the presence of well-oriented CD domains forming the solid network (Figure 2, dark contrast). However, the noble-metal NP phase is not clear along the CeO_2 surface. This could be, in part, because of the possible contaminant layer (e.g., water), which can interfere with oscillation.

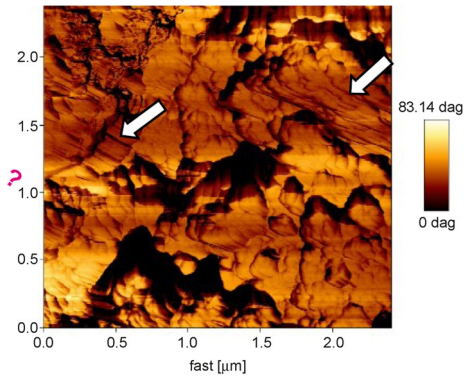


Figure 2. AFM image of $PdNPs/CeO_2$ (non-contact image, phase).

With the heterogeneous system in hand, we proceeded to test the catalytic efficiency starting with 0.5 mol% Pd^0 (w/w) by using urea **1a** as the substrate (Table 3, entry 2). We were delighted to find that this catalytic system provided compound **3a** in a markedly high yield (97%). In this case, the calculated turnover number (TON) was 194. Working with an even lower Pd loading resulted in a moderate conversion to the desired cross-coupling product (Table 3, entry 1).

Encouraged by these results, we next investigated whether this catalyst had recycling potential. If so, it could shed a light on whether the supported PdNPs act as a reservoir or as the

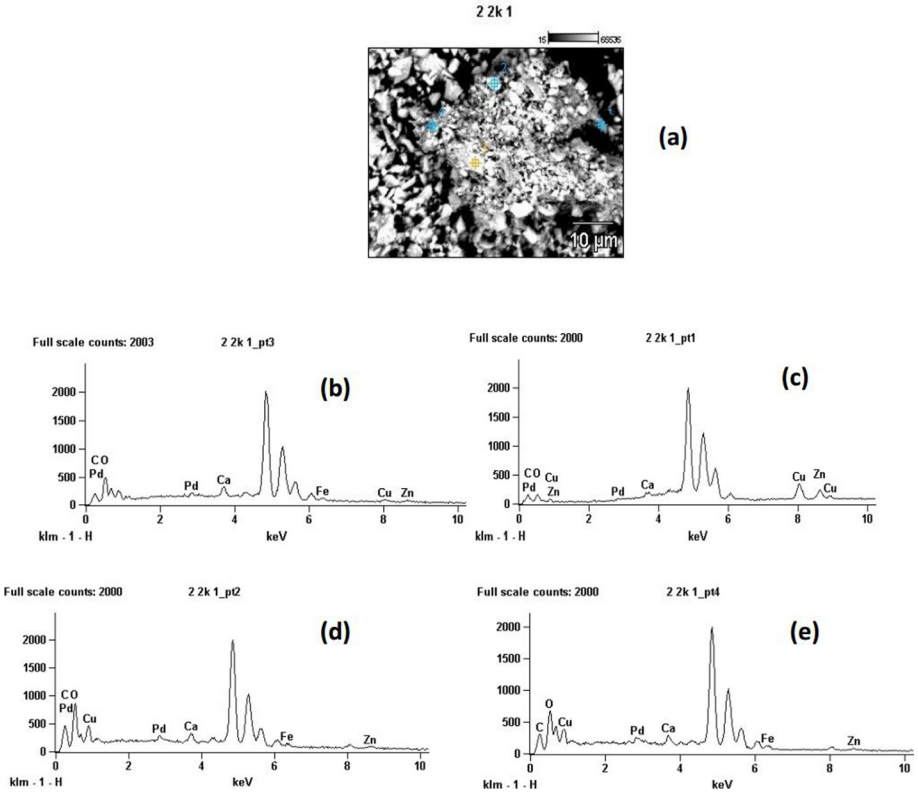
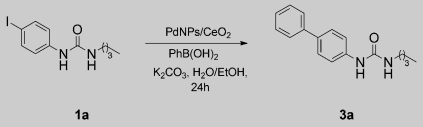


Figure 1. (a) SEM micrography of the supported catalyst. (b–e) EDS spectra showing Ce (most prominent), Ca, and Pd sites.

Table 3. PdNPs/CeO_2-promoted Suzuki–Miyaura cross-coupling between urea **1a** and phenylboronic acid.[a]



1a **3a**

Entry	Pd loading [%]	Yield **3a** [%]
1	0.1	62[b]
2	0.5	97[b]
3	–	<1[c]

[a] *N*-4-iodophenyl-*N*′-butyl urea (0.5 mmol), phenylboronic acid (0.6 mmol), K_2CO_3 (1.0 mmol), H_2O/EtOH (1:1, 5 mL), PdNPs/CeO_2, 90 °C, 24 h. [b] Isolated yield. [c] Estimated by ^{1}H NMR.

actual catalytically active species. Catalyst reusability was studied by recycling the material after each run. The yields of the recycled dispersion in the reaction between *N*-(4-iodo)phenyl-*N*′-butyl urea (**1a**) and phenylboronic acid in water, after 24 h, are presented in Figure 3. Gratifyingly, the heterogenized catalyst could be recycled without significant loss in activity over three consecutive runs.

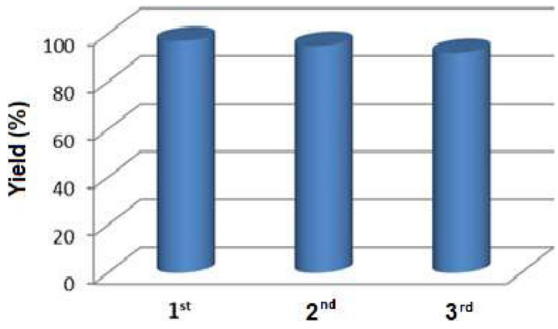


Figure 3. Catalytic activity of PdNPs/CeO_2 in three consecutive runs.

A control experiment with purely Ca-doped ceria was also performed to investigate the influence of the Ce^{x+} ($2 \leq x \leq 4$) sites on the catalysis. Interestingly, in the absence of palladium, the support proved to be inert under the reaction conditions. However, the possibility of synergic effects between both metals towards the cross-coupling process is strong, even though the specific role of cerium oxide remains unclear at this stage. A mechanistic hypothesis that electron-rich Pd domains may help to reduce the cationic Ce^{3+}/Ce^{4+} species in the support (facilitating greater surface interaction with the C_{sp^2} I sites) might be tentatively put forward.

Conclusions

We have demonstrated that unprotected 4-iodo aryl ureas can be reactive in Suzuki–Miyaura cross-couplings when using PdNPs stabilized by CDs with controlled size. In addition, consecutive Suzuki–Miyaura/Heck reactions were also explored to test the NPs ability for domino reactions. These procedures enabled the preparation of a series of *N*-biaryl-*N*′-alkyl ureas, novel candidate compounds with potential uses in medicinal chemistry. Considering the advantages of catalytic reusability along with our interest in future scalable reactions, preliminary catalytic tests involving supported PdNPs on CeO_2 as a heterogeneous catalyst provided a reliable synthesis of *N*-biaryl-*N*′-butyl urea over three consecutive catalytic cycles. The biological potential of these novel biaryl scaffolds as well as the role of ceria and its possible surface effects in the cross-coupling reaction are currently under investigation in our group.

Experimental Section

General remarks

All reactions were performed under air using conventional reflux glassware. All chemicals were purchased at the highest commercial grade and used as received. Analytical thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm thickness). Flash column chromatography was carried out by using E. Merck silica gel BW-300 (200–400 mesh).

^{1}H and ^{13}C NMR spectra were recorded on a Varian VNMRSYS-500 or a Bruker DPX-200 spectrometer at 25 °C. Chemical shift values are reported in δ (ppm) relative to tetramethylsilane with reference to internal residual solvent [^{1}H NMR: $(CH_3)_2SO$ (2.5); ^{13}C NMR: $(CD_3)_2SO$ (40.7–38.2)]. Coupling constants (*J*) are reported in hertz (Hz). Multiplicities of signals are designated as follows: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad. High-resolution mass spectra (HRMS) were obtained on a Bruker microTOF II mass spectrometer using ESI as source type.

X-ray fluorescence (XRF) analysis was performed with a Rigaku spectrometer model RIX3100, using a Rh tube with a power of 4 kW.

Elemental analysis (CHN) was carried out with a PerkinElmer 2400 CHN apparatus, using a PerkinElmer AD-4 Autobalance.

FTIR spectra were acquired with a Nicolet Magna-IR 760 apparatus. Samples were analyzed in KBr pellets in the 4000–400 cm^{-1} interval. The number of scans was 16, with resolution of 4 cm^{-1}.

X-ray diffraction patterns were obtained with a Rigaku diffractometer, model Ultima IV, with a Cu X-ray tube (λ-2θ goniometer, a Ni kβ filter, 40 kV voltage, and 20 mA current). Samples were analyzed in the $5° < 2\theta < 80°$ interval, with 0.05° steps and 1 second per step.

Scanning electron microscopy images were acquired with a JEOL JSM 6460-LV apparatus, operating in the 10–20 kV range coupled to an X-ray energy-dispersive spectrometer.

Raman spectra were collected on a Horiba Raman Microscope HR800 with an Olympus microscope and a CCD detector, the exciting radiation being a HeNe 20 mW laser at 632.8 nm

The atomic force microscope used was the Nanowizard model (JPK Instruments, USA). The equipment operation was performed using NCR-10 (AIBS) or CSC11 (AIBS) tips manufactured by Nanoworld. The height and phase contrast measurement distributions for the nanoparticles were determined by tapping-mode atomic force microscopy (AFM) under ambient conditions in air. To obtain AFM images of the dispersed PdNPs, the aqueous dispersions were diluted 20-fold in acetone before deposition of three drops (10 mL)

onto glass microscope slides and allowed to dry freely in air. The analysis of PdNPs/CeO_2 was done by deposition of a solid thin layer on a plate mounting tape contained in a glass slide. Before analyses, the glass microscope slides were cleaned with nitric acid/hydrochloric acid (1:3) for 30 min.

Representative experimental procedure for the synthesis of 3a by PdNPs

Pd nanoparticles were prepared by using a slightly modified[1] version of the published procedure.[20b] β-HPCD (0.345 g, 0.25 mmol), Na_2PdCl_4 aqueous solution (1.0 mL of 5 mmol L^{-1}, 5 μmol Pd), and distilled water (1.5 mL) were added in a round-bottom flask equipped with a reflux condenser. The mixture was stirred and heated at 90 °C (bath temperature) for 5 min. Then, urea **1a** (79.5 mg, 0.25 mmol), phenylboronic acid (30.4 mg, 0.25 mmol), potassium carbonate (69.1 mg, 0.5 mmol), and ethanol (2.5 mL) were added to the resultant dispersion. After stirring/heating for 6 h, the mixture was cooled and the solution was filtered through a pad of Celite and then extracted with EtOAc/CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 5–15% ethyl acetate/hexane) gave *N*-biaryl-*N'*-butyl urea **3a** (63.5 mg, 95%) as a light-yellow solid.

Representative one-pot experimental procedure for the synthesis of 5b by PdNPs

β-HPCD (0.345 g, 0.25 mmol), Na_2PdCl_4 aqueous solution (1.0 mL of 5 mmol L^{-1}, 5 μmol Pd), and distilled water (1.5 mL) were added in a round-bottom flask equipped with a reflux condenser. The mixture was stirred and heated at 90 °C for 5 min. Then, urea **1a** (79.5 mg, 0.25 mmol), vinylboronic *N*-methyliminodiacetic acid (MIDA) ester (45.7 mg, 0.25 mmol), potassium carbonate (69.1 mg, 0.5 mmol), and ethanol (2.5 mL) were added to the resulting dispersion. After stirring/heating for 24 h, 4-iodotoluene (54.5 mg, 0.25 mmol) was added to the mixture and the reaction was maintained at the same conditions for an additional 24 h. The solution was cooled, filtered through a pad of Celite, and extracted with EtOAc/CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 10–15% ethyl acetate/hexane) gave *N*-[(4-methyl)-styl-benyl]-*N'*-benzyl urea **5b** (59 mg, 69%) as a light-yellow solid.

Experimental procedure for the synthesis of PdNPs/CeO_2

CeO_2 synthesis: $Ca(NO_3)_2$ (0.00736 g, 0.3114 mmol) was added in a 50 mL aqueous solution of $(NH_4)_2Ce(NO_3)_6$ (1.5369 g, 2.80 mmol), in order to have the specific ion dopant (Ca^{2+}) with a nominal composition of 10 mol%. After this step, an aqueous solution of NaOH (1.0 mol L^{-1}) was added slowly until pH 14 was reached, resulting in a pale yellow gel. The mixture was filtered and the solid was washed with distilled water until pH 8. Finally, the solid was dried at room temperature and, subsequently, homogenized in an agate mortar.

[1] *Experiments involving the reduction under stirring/heating (90 °C) for 5 min indicated small variations concerning the NPs size distribution (within the error zone), according to the AFM images (unpublished results).*

PdNPs/CeO_2 synthesis: α-HPCD (1.18 g, 1.0 mmol), Na_2PdCl_4 aqueous solution (4.0 mL of 5 mmol L^{-1}, 20 μmol Pd), distilled water (6 mL) and ceria (250 mg) were added in a round-bottom flask. The mixture was stirred at room temperature for 96 h. After this time, the mixture was centrifuged twice and the solid phase was dried at room temperature. Homogenization was carried out in an agate mortar.

Representative experimental procedure for the synthesis of 3a by PdNPs/CeO_2

Urea **1a** (79.5 mg, 0.25 mmol), phenylboronic acid (30.4 mg, 0.25 mmol), potassium carbonate (69.1 mg, 0.5 mmol), and the heterogeneous catalyst PdNPs/CeO_2 (6.6 mg, 1.25 μmolPd) were added to a solution of H_2O/EtOH (1:1, 5.0 mL). The mixture was stirred and heated at 90 °C for 24 h. After this time, the reaction mixture was filtered and the catalyst was washed with water and dried. The filtrate was subjected to the work-up described above. Purification of the crude product by flash column chromatography (silica gel, 5–15% ethyl acetate/hexane) gave *N*-biaryl-*N'*-butyl urea **3a** (64.8 mg, 97%) as a light-yellow solid.

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