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Nanostructures

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Microfluidic Synthesis of Palladium Nanocrystals Assisted by Supercritical CO_2: Tailored Surface Properties for Applications in Boron Chemistry**

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Main challenges associated with heterogeneous catalysis rely on designing flexible methods to modulate catalytic efficiencies.[1] In that context, semi-heterogeneous catalysis[2] with metal nanocrystals (NCs) provides a nice entry into designing such materials. Indeed transition-metal NCs[3] can be prepared with excellent control of the physical properties including the size, nature, composition, and morphology. NCs combine high surface area, thus conferring excellent reactivity capacity,[4] with tunable surface functionalization, possibly with various ligands.

In this regard, microfluidic processes turned out to be powerful tools to produce hierarchically organized multiple particles with good control over size and shape.[5] Combining specific characteristics of micronized processes with high pressure/high temperature[6]—including supercritical conditions[7]—leads to multiple additional advantages. Hydrodynamical parameters, heat and mass transfer, and process safety are greatly improved.[8] Inspired by previous studies of NCs synthesis using supercritical milli- and microfluidics achieved in our group,[7c,9] the approach takes advantage of process flexibility and ability to build a small cohort of nanocatalysts stabilized by specific ligands.

Herein, we report the contribution of a supercritical microfluidic process to access a library of new tunable functionalized NCs, namely a palladium core stabilized by various ligands. Those NCs were designed to catalyze reactions of broad applicability, namely Vaultier[10] and Miyaura[11] borylation and Suzuki–Miyaura cross-coupling.[12]

Palladium NCs were synthesized at 100 °C and 25 MPa in a co-flow capillary microsystem (Figure 1 A). Coaxial flows appeared to be suitable for generating NCs stabilized by various organic shells, as previously demonstrated.[7c] In classical homogeneous catalysis, ligands are coordinated to Pd^0 or Pd^{II} centers and modulate the reactivity of the complex towards a given transformation. As such, we envisioned that different catalytic activities would arise from functionalization with various ligands such as phosphanes, bisphosphanes, and N-heterocyclic carbenes. The operating conditions were controlled by an oil bath (T), a back pressure regulator (p) placed downstream in the microsystem, and three high-pressure pumps (flow rates), with the residence time being fixed at 17 seconds. The inner palladium precursor solution was flow-focused by the outer flow, which contained the ligands, therefore confining the formation of NCs to the center of the main stream with subsequent functionalization.

Palladium nanocatalysts were prepared from the hydrogen reduction of bis(hexafluoroacetylacetonate)palladium(II) ($[Pd(hfa)_2]$) in a toluene/CO_2 mixture, in the presence of organic stabilizers (Figure 1 A). Palladium(0) atoms were then prone to nucleation and growth processes, thus providing naked NCs. The poor solubility of hydrogen in toluene usually results in mass-transfer limitations for the palladium(II) precursor reduction.[13] This issue was overcome thanks to additional $scCO_2$ ($Tc = 31\,°C$, $Pc = 7.38\,MPa$), which greatly enhances H_2 solubility in the mixture.[14] In a second step, the surface of the palladium NCs was decorated with various ligands and collected as a colloidal solution—upon depressurization—for a direct application in catalysis reactions without further purification steps. We deliberately used ligands displaying different electronic and steric properties to evaluate their influences on the catalytic process. Those ligands are classically employed in homogeneous catalysis for tuning stereoelectronic properties of the metal center, namely: bis(mesityl)imidazoliumchloride leading in situ to the corresponding N-heterocyclic carbene (NHC; **NC1**),[15] cyclohexyl JohnPhos (**NC2**), di(phenylphosphino)propane (dppp; **NC3**), *tert*-butyl XPhos (**NC4**), tricyclohexyl phosphane (**NC5**), tri(3-furyl)phosphane (**NC6**), 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap; **NC7**), SPhos (**NC8**), 1,1′-bis(diphenylphosphino)ferrocene (dppf; **NC9**); see Figure 2.

Palladium NCs complexed by dppf (**NC9**) were used as a reference for full characterization of the NCs.[16] The formation of organic–inorganic hybrid nanocrystals was first evidenced by high-resolution transmission electron microscopy (HRTEM; Figure 1 B), thus revealing the presence of small spherical palladium NCs with a narrow size distribution (3.6 ± 0.6) nm (Figures 1 B and C). Complexation of the ligand to the palladium surface was proven by conducting ^1H, ^{13}C, ^{19}F, and ^{31}P NMR experiments (Figure 1 D and see the Supporting Information). ^1H NMR spectra of dppf-complexed NPs show signals for the cyclopentadienyl moiety at $\delta = 4.76$ and 4.30 ppm. Compared to the signals in the ^1H NMR spectra of free dppf at $\delta = 4.27$ and 4.01 ppm,

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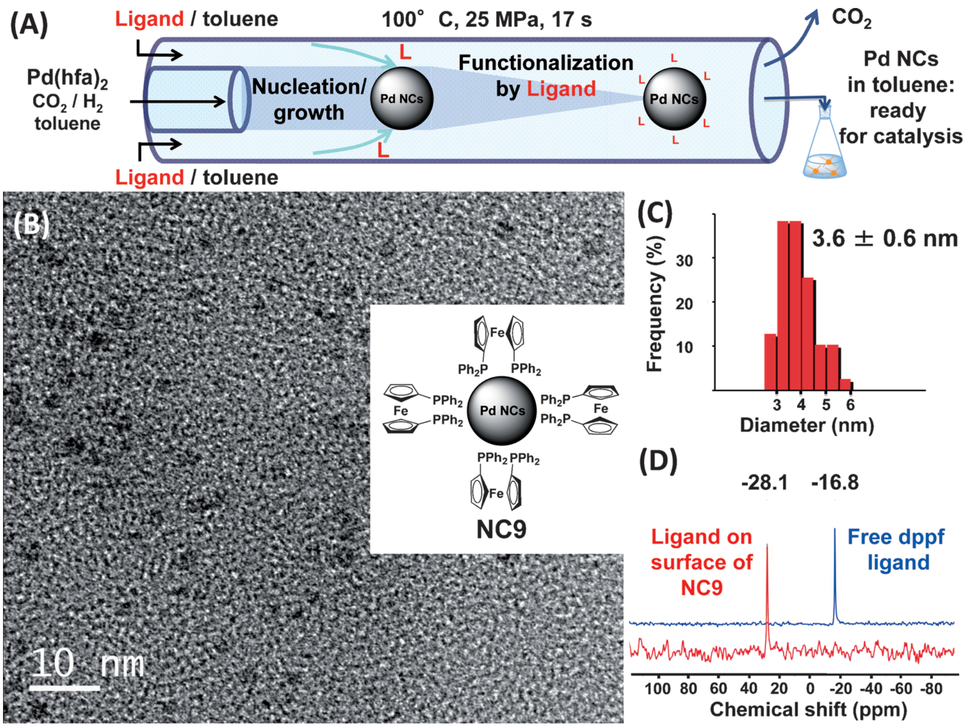


Figure 1. A) Microfluidic co-flow process for the synthesis of palladium NCs having tailored surface properties. B) HRTEM snapshot and C) size distribution of typical as-synthesized palladium NCs. D) ^{31}P NMR spectra of dppf-ligated **NC9** and free dppf ligand.

a clear upfield shift is observed, and is caused by a downfield shielding effect resulting from the complexation of the organic molecule to the metallic core.[17] A similar shielding effect is also detected in the ^{31}P NMR spectra of the free dppf ($\delta = -16.8$ ppm) compared to the NCs-ligated dppf ($\delta =$ 28.1 ppm; Figure 1 D). Moreover, the ^{13}C NMR spectra and complementary ^{19}F NMR spectra show the absence of residual hfa ligands or related degradation products. HRTEM and NMR studies evidence the composition and morphology of the palladium NCs complexed with dppf. We decided to extend this co-flow process to the synthesis of a library of NCs complexed by previously mentioned ligands (Figure 2). The colloidal catalyst solutions show excellent stability within the timescale of the study. Following our previous work on boron derivatives,[10,18] we investigated the palladium NCs catalytic properties in the borylation reaction. To the best of our knowledge, heterogeneous or semi-heterogeneous catalysis of borylation reactions are scarce and limited to the [B$_2$pin$_2$] Miyaura borylation.[19] This work would offer a new synthetic route to afford highly reactive borylated species. Two main reagents can be used for this reaction, di(isopropyl)aminoborane (BH$_2$N(*i*Pr)$_2$; **1**)[10] being a cheaper and easier-to-handle alternative to bis(pinacolato)diboron (**2**).[11]

Arylaminoboranes derived from **1** are not sufficiently stable towards air and moisture as far as isolation is concerned. They can be however easily transformed into boronic acids, boronates, or borates. First, catalytic nanomaterials were all evaluated using 4-bromoanisole (**3**) as a model substrate. The carbon–boron bond-forming reaction was performed in the presence of triethylamine and a catalytic amount of palladium at 100 °C for 1 hour with subsequent methanolysis and pinacol transesterification (Table 1). Catalytic systems bearing electron-rich phosphanes complexed to palladium, namely PCy$_3$ and dialkylbiarylphosphane ligands, led to full conversion into the expected product **4** (Table 1, entries 2, 4, 5, and 8) along with more than 10 % of the competitive reduction by-product **5**. So far, dppf-complexed NCs (Table 1, entry 9) led to exclusive formation of the pinacol boronate **4**, in a 92 % yield upon isolation after three steps. Contrasting to bulky alkylphosphanes, dppf-complexed NCs afforded only a minor amount of the reduction compound (3 %), as a result of faster

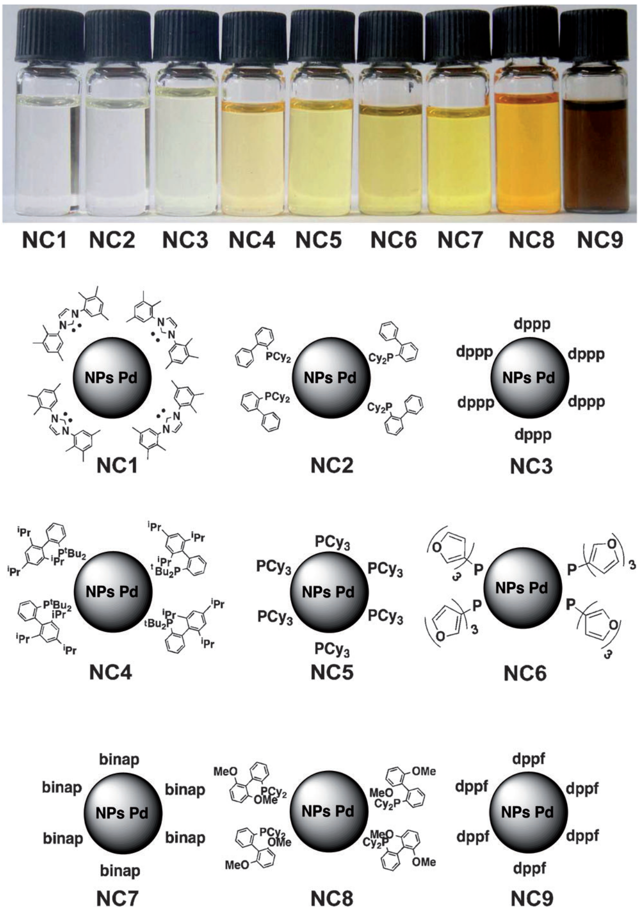
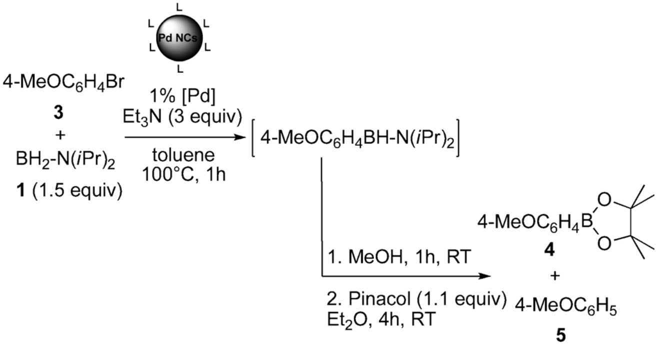


Figure 2. Generation of functionalized palladium NCs with controlled surface properties and their appearance in toluene solution.

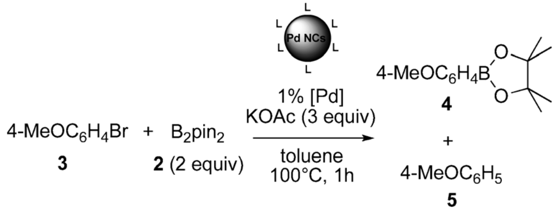
Table 1: Borylation reaction using di(isopropyl)aminoborane.



Entry	Pd NCs	Conv. [%]	Yield [%][a]		
			3	4	5
1	**NC1**	45	55	6	39
2	**NC2**	>99	–	87	12
3	**NC3**	83	17	70	13
4	**NC4**	>99	–	83	16
5	**NC5**	>99	–	78	21
6	**NC6**	4	96	1	3
7	**NC7**	44	56	11	33
8	**NC8**	>99	–	83	16
9	**NC9**	>99	–	96 (92)[b]	3
10[c]	**NC9**	95	5	89	6

[a] Determined by GC analysis using 1,3,5-mesitylene as an internal standard. [b] Yield of isolated product within parentheses. [c] 0.1% mol [Pd] after 16 h.

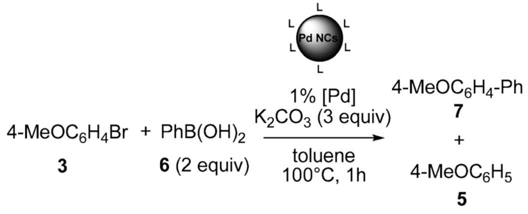
Table 2: Borylation reaction using bis(pinacolato)diboron (**2**).



Entry	Pd NCs	Conv. [%]	Yield [%][a]		
			3	4	5
1	**NC1**	59	40	42	17
2	**NC2**	>99	–	99	–
3	**NC3**	49	50	25	24
4	**NC4**	94	5	85	9
5	**NC5**	>99	–	97	2
6	**NC6**	60	39	41	19
7	**NC7**	79	21	69	10
8	**NC8**	>99	–	98	1
9	**NC9**	72	27	59	13

[a] Determined by GC analysis using 1,3,5-mesitylene as internal standard.

Table 3: Suzuki–Miyaura cross-coupling.



Entry	Pd NCs	Conv. [%]	Yield [%][a]		
			3	7	5
1[b]	**NC1**	>99	–	98 (95)[c]	1
2[b]	**NC2**	>99	–	98	1
3	**NC3**	92	8	81	11
4[b]	**NC4**	>99	–	98	1
5	**NC5**	>99	–	93	6
6[b]	**NC6**	65	35	55	10
7	**NC7**	>99	–	95	4
8	**NC8**	>99	–	95	4
9[b]	**NC9**	97	2	78	19

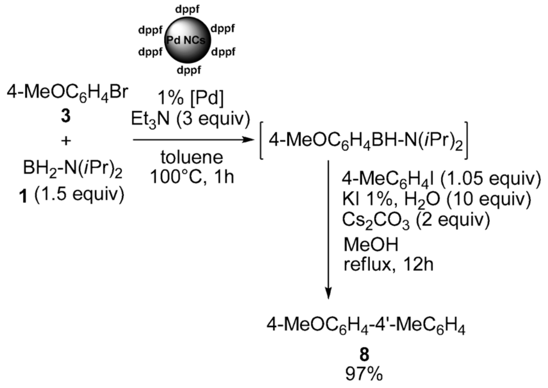
[a] Determined by GC analysis using 1,3,5-mesitylene as an internal standard. [b] 30 min. [c] Yield of isolated product within parentheses.

reductive elimination. Moreover, decreasing the palladium catalytic loading to 0.1% allows formation of **4** with 89% conversion after 16 hours (Table 1, entry 10). Previous studies identify dppp as the best ligand for homogeneous catalysis of borylation with aminoborane[20] whereas dppp-complexed palladium NCs led to incomplete conversion, thus confirming the strong reactivity differences between molecular and colloidal catalysts. This method allows fast identification of the best catalyst for a desired transformation.

Additionally, comparative borylation reaction using **2** was also conducted on 4-bromoanisole (Table 2), using potassium acetate as an appropriate weak base to avoid the competitive Suzuki–Miyaura coupling of the corresponding pinacol ester with the reactant.[11a] Confirming our previous results, electron-rich bulky ligands, namely PCy_3 and biarylphosphanes, are well suited and led to quantitative formation of the pinacol ester (Table 2, entries 2, 5, and 8). This is certainly induced by a smooth transmetalation and a more favorable reductive elimination step with **2**. In this case, contrasting with results obtained in homogeneous palladium-catalyzed borylation,[11a] dppf-complexed NCs are not the best candidates for borylation with **2** and nearly 30% of unreacted starting material was observed.

Confronted by the differences observed for catalytic activities, we extended this study to a Suzuki–Miyaura cross-coupling between **3** and phenylboronic acid **6** (Table 3) at 100°C. The highest yields for 4-methoxybiphenyl were obtained after 30 minutes with NCs complexed to an NHC (Table 3, entry 1), binap, and dialkylbiaryl ligands (Table 3, entries 2, 4, 7 and 8). Once again, different catalytic systems than those mentioned above, are suited to this transformation. Overall, **NC9** is the most efficient catalyst for Vaultier borylation, the B_2pin_2 borylation required **NC5** or biaryl-ligand-complexed **NC2** and **NC8**, and carbene-ligated **NC1** and bulky **NC2** and **NC4** are superior to others for the Suzuki–Miyaura coupling. Thus, it is possible to tune the activity of palladium NCs for a specific transformation by modulating their reactivity thanks to ligand stereoelectronic properties and binding strength of these capping agents to the metal center. Moreover, an adsorption/desorption mechanism, postulated and proven by De Vries, may also be relevant.[21]

We then, took advantage of the high catalytic activity of NCs to achieve a one-pot sequence including the borylation step of 4-bromoanisole and subsequent Suzuki–Miyaura coupling of the arylaminoborane with 4-iodotoluene under



Scheme 1. One-pot palladium-catalyzed borylation/Suzuki–Miyaura sequence.

optimized reaction conditions (Scheme 1).[10e] The corresponding unsymmetrical biaryl compound **8** was isolated in 97% yield without any purification except filtration over a silica pad to remove salts. Dppf-ligated NCs were shown to retain their catalytic properties even after completion of the borylation reaction and the catalyst shows consistent activity after several cycles.

In summary, catalytic activity of NCs is highly dependent on surface properties of the metal NC, which is tuned by the stabilizing ligand interaction. Among recent and promising technologies, supercritical microfluidics is perfectly suited to generate highly active NCs in continuous systems. The coaxial flow process allows precise construction of the catalyst architectures, as intended for a targeted reaction, thanks to a flexible functionalization. Continuous flow multistep and one-pot processes dedicated to heterogeneous catalysis are currently under investigation.

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