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Palladium–Polypyrrole Nanocomposites Pd@PPy for Direct C–H Functionalization of Pyrroles and Imidazoles with Bromoarenes

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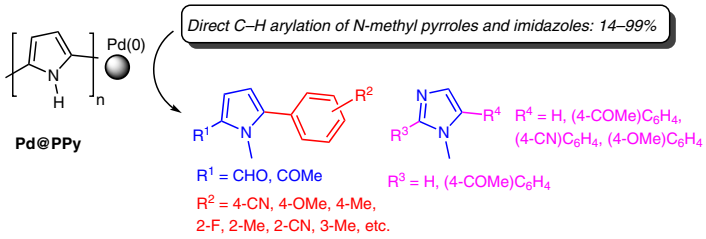
Dedicated to the memory of Dr. Guy Lavigne



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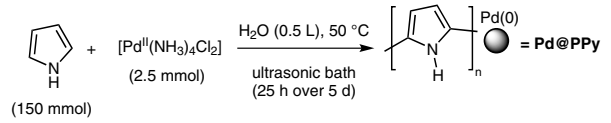
Abstract Palladium–polypyrrole nanocomposites (Pd@PPy) with unique combination of high palladium dispersion (nanoparticle size 2.4 nm) and high palladium content (35 wt%) are efficient catalysts for the selective arylation of substituted pyrroles and imidazoles with either activated or deactivated aryl bromides. The performances of the recoverable supported palladium catalyst matches the best performances of homogeneous systems based on $Pd(OAc)_2$ at 0.5–0.2 mol%, and largely overwhelm the classical Pd/C catalyst.

Key words palladium, polypyrrole, nanocomposite, C–H arylation, azoles

Palladium-catalyzed sp^2C–sp^2C bond formations are powerful modern synthetic methodologies, which include reactions between organometallic reagents and organic electrophiles. While very efficient, these reactions, which are based on organometallic reagents (for instance organoboron, organotin, organomagnesium, organozinc, or organosilane reagents), generate stoichiometric metallic waste and require prefunctionalization of aromatic substrates. Therefore, the research focus has shifted in the last decade to direct C–H functionalization of aromatic and heteroaromatic substrates.[1] Homogeneous conditions for these direct arylation reactions are well-established,[2] and the use of heterogeneous catalysts and stable nanoparticles (NP) is now a very appealing step forward for industrial application. The inertness of the C–H bond has rendered such auspicious advances rather difficult, and to date only few efficient heterogeneous catalytic systems have been reported, which are mainly based on [Pd/C] and $[Pd(OH)_2/C]$.[3] Matching the catalytic performances which are obtained under homogeneous conditions with supported catalysts is difficult to achieve from metal deposition on elusive carbon materials. Our group is thus looking for easily recoverable and potentially recyclable palladium composites 'NP@support', with the need of an accurate and reproducible control of the heterogeneous catalytic materials formation.

Vasilyeva and Vorotyntsev have reported on the production and characterization of an innovative composite material under the form of palladium supported on polypyrrole (Pd@PPy) obtained from a mixture of $Pd(OAc)_2$ and pyrrole.[4] The composite formation occurred *via* reduction of Pd^{2+} cations by oxidized pyrrole monomer in acetonitrile solvent. The synthetic protocol led to palladium nanoclusters of 2.0–2.5 nm diameters dispersed within spherical PPy of a few hundred nanometers. Improvements by Zinovyeva and Vorotyntsev have led to the formation of Pd@PPy hybrid catalytic materials in water *via* redox polymerization reaction of pyrrole with $[Pd(NH_3)_4Cl_2]$ (Scheme 1).[5] The nanocomposites formed were composed of highly dispersed zero-valent palladium nanoparticles embedded in spherical polypyrrole globules. A unique combination of high palladium dispersion (NP size: 2.4 nm) and high palladium content (35 wt%) has been obtained. These versatile synthesis can give access to supported palladium with sizes ranging between 1.0–2.0 nm that have been tested for Suzuki–Miyaura coupling,[6a] phenylacetylene Sonogashira arylation,[6b] and aryl halide cyanation.[6c]



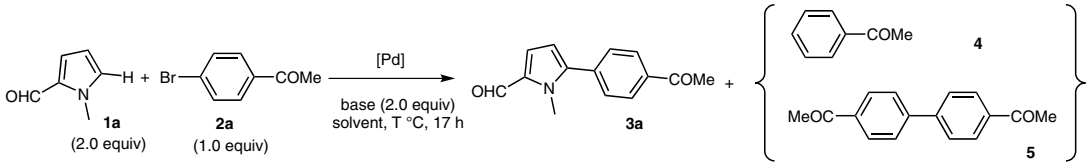
Scheme 1 In-water mild redox polymerization reaction of pyrrole with $[Pd(NH_3)_4Cl_2]$ to **Pd@PPy** nanocomposite

Our group has developed application of these novel hybrid nanomaterials in the palladium-catalyzed direct arylation of heteroaromatics.[5] High efficiency and perfect selectivity in C–C bond formation has been obtained for furans and thiophenes *C5*-arylation by using bromoarenes. Pd@PPy nanocomposites can efficiently couple *n*-butyl furan and *n*-butyl thiophene with bromobenzene and bromoquinoline, as well as with activated or deactivated electron-poor and electron-rich functionalized bromoarenes. As underlined by Felpin and Fairlamb,[3,7] this Pd@PPy nanocomposite is a rare example of palladium NP supported on organic material with a record high metal density.

We now report on the efficiency of these Pd@PPy nanocomposites for the selective arylation of more demanding azole substrates: pyrroles and imidazoles. We anticipated two main difficulties for an effective C–H arylation: the general lower acidity of *C5*–H (or *C2*–H) adjacent to nitrogen in pyrroles and other azoles,[8] and also the fact that heteroaromatic substrates and the polymeric organic support were of a similar nature, with a much higher acidity for *N*–H in pyrrole (pK_a = 23.0).

Screening of appropriate conditions for coupling *N*-methylpyrrole-2-carboxaldehyde (**1a**) to 4-bromoacetophenone (**2a**, Scheme 2) is reported in Table 1. We identified two main side reactions which are deleterious for the selectivity of C–H arylation: the dehalogenation of **2a** to **4**, and its homocoupling to form **5**. Using two equivalents of pyrrole substrate was a practical way to diminish or obliterate these side reactions.

The important role of solvent and temperature was first evidenced since activation temperatures around 150 °C in a polar solvent were necessary for achieving any conversion of **1a** [Table 1, entries 1–3 using toluene, cyclopentyl methyl ether (CPME), and dimethylformamide (DMF)]. We were glad to see that dimethylacetamide (DMAc) was very efficient for a full conversion of **1a** selectively into **3a** (Table 1, entry 4) despite the foreseen troubles above mentioned. These conditions (DMAc, 150 °C, 17 h, KOAc) were then selected to pursue our screening since we noted that changing KOAc base for K_2CO_3 was deleterious for conversion and promoted homocoupling of **2a** to **5** (Table 1, entry 5). For comparison we also investigated the efficiency of related catalytic systems. The use of palladium on activated charcoal (Pd/C 10 wt%, Aldrich, CAS: 7440-05-03) led to dehalogenation of **2a** (Table 1, entry 6), and evidenced in contrast the excellent conversion and high selectivity of Pd@PPy. The use of soluble $Pd(OAc)_2$ was found fairly efficient for loading ranging between 0.5 and 0.2% (Table 1, entries 8 and 9). Lower loading $Pd(OAc)_2$ at 0.02% (Table 1, entry 10),



Scheme 2 Palladium arylation of *N*-methyl-pyrrole-2-carboxaldehyde **1a** with 4-bromoacetophenone **2a**

Table 1 Screening Conditions to Arylated Pyrrole **3a** with Pd@PPy and Comparison with Other Pertinent Palladium-Based Catalysts[a]

Entry	Catalyst (%)	Solvent	Temp (°C)	Base	Conv. (%)	Yield of **3** (%)	Yield of **4** (%)	Yield of **5** (%)
1	Pd@PPy (2)	toluene	110	KOAc	0	–	–	–
2	Pd@PPy (2)	CPME	125	KOAc	0	–	–	–
3	Pd@PPy (2)	DMF	150	KOAc	99	92	0	2
4	Pd@PPy (2)	DMAc	150	KOAc	99	99	0	0
5	Pd@PPy (2)	DMAc	150	K_2CO_3	99[b]	0	0	60
6	Pd/C (2)	DMAc	150	KOAc	99	79	16	5
7	$Pd(OAc)_2$ (2)	DMAc	150	KOAc	99	80	0	20
8	$Pd(OAc)_2$ (0.5)	DMAc	150	KOAc	99	88	0	12
9	$Pd(OAc)_2$ (0.2)	DMAc	150	KOAc	99	92	5	2
10	$Pd(OAc)_2$ (0.02)	DMAc	150	KOAc	87	81	1	4

[a] ^1H NMR yields (consistent with GC) from at least 2 runs.
[b] Unidentified products are formed.

or higher loading $Pd(OAc)_2$ at 2% (Table 1, entry 7), were found detrimental to full conversion of **1a** and also favored homocoupling.

With optimized conditions in hands using the recoverable catalytic material Pd@PPy (Table 1, entry 4) we examined the scope of C–H functionalization of pyrroles. We investigated in parallel the activity achieved under the best homogeneous conditions using $Pd(OAc)_2$ (Table 1, entries 8 and 9). Roger and Doucet first reported on the efficiency for pyrroles C–H arylation of the $Pd(OAc)_2$ precatalyst used at low loading.[9] In our case, the coupling of *para*-substituted bromoarenes with *N*-methylpyrrole-2-carboxaldehyde **1a** using Pd@PPy was efficiently achieved under the optimized conditions (Figure 1, conditions A). Compound **3a** was isolated in 58% yield from full conversion of ArBr **2a**;[10] then recycling of Pd@PPy was achieved with the synthesis of **3a** in 93%. The arylation is tolerant to various electron-withdrawing or electron-donating functional groups on aryl bromide, including cyano (**3b**, 76%), trifluoromethyl (**3c**, 75%), methoxy (**3d**, 92%), and methyl (**3e**, 90%). The performances of Pd@PPy for **1a** arylation mostly compared well, and even sometimes outclassed (for instance with electron-rich **3d**) our results under optimized homogeneous conditions using $Pd(OAc)_2$ at 0.2 mol%. This tendency was confirmed with the coupling of *N*-methyl-2-acetylpyrrole **1b** to form **6a** in 89% with Pd@PPy and only 70% with the homogeneous system.

The scope was extended to *ortho*-substituted bromides, and good conversions were obtained for coupling pyrroles **1a** and **1b** to aryl bromides having *ortho* substituents with electron-attracting (CN: **7a**, 79%; F: **7b**, 75%) and electron-donating properties (Me: **7c**, 85%; **8b**, 74%). The formation of **8a** which bears a more bulky *o*-acetyl group was limited to 15–30% for supported and homogeneous catalytic systems. This remarkable steric effect has not been reported before and is supported by the fact that contrary to the case of *para*-substituted bromoarenes the nonsupported catalytic system appears significantly more efficient. Thus, yield improvement (up to 15%) might be attributed to more accessible catalytic centers in the homogeneous system. The coupling of a *meta*-substituted bromide was also achieved with good yield and led to **7d** in 83%. We investigated the coupling of electron-poor 4-chlorobenzonitrile to **1a**. Using 2.0 mol% of Pd@PPy less than 10% yield of **3a** was obtained. This result was improved up to about 30% by addition of excess of *tert*-butyl ammonium salt TBAB.

Encouraged by the good performances associated to bromoarenes coupling, we then investigated the coupling of

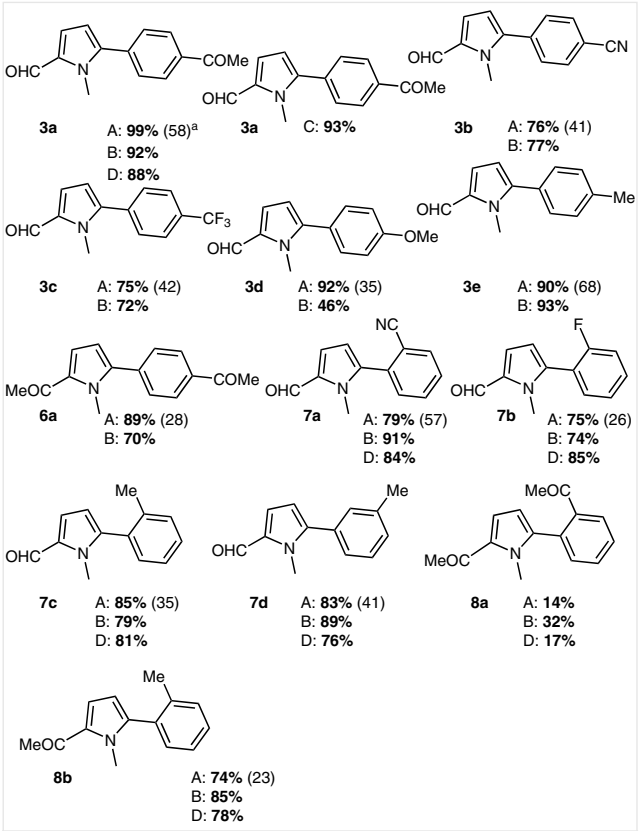
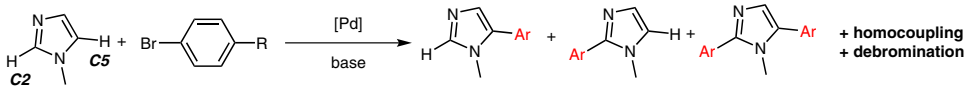


Figure 1 *C5*-Arylated pyrroles **3a–e**, **6a**, **7a–d**, and **8a**,**b** synthesized from bromoarenes. *Reagents and conditions*: pyrrole (2 equiv), bromoarene (1 equiv), DMAc (2.5 ml), KOAc (2 equiv), 150 °C, 17 h; conditions **A**: Pd@PPy (2.0 mol%); conditions **B**: $Pd(OAc)_2$ 0.2 mol%; conditions **C**: recycling of conditions **A**; conditions **D**: $Pd(OAc)_2$ (0.5 mol%). [a] NMR and GC yields (consistent); isolated yields are in brackets, values are diminished due to reactions being carried out on very low scale (1.0 mmol).

N-methylimidazole to bromoarenes (Scheme 3). In this type of coupling the competition between *C5*–H and *C2*–H functionalization may occur, leading to mono- and diarylated compounds.[11]

Conditions for selective coupling have been reported in which the control of selectivity is exerted by the base settings.[9,12] We examined the performances of the nanocomposite Pd@PPy for the arylation of *N*-methylimidazole **9** with aryl bromides (Figure 2). By using two equivalents of KOAc (previously optimized conditions A), selective *C5*-arylation led to **10a** (62%), **11a** (92%), and **12a** (76%) in good to high yields. These products are *para*-substituted either with electron-poor or electron-rich functions. By using two



Scheme 3 Palladium arylation of *N*-methylimidazole and expected products

equivalents of Cs_2CO_3 as a base, with 1.0 equivalents of CuI, arylation at *C2* of *N*-methylimidazole was favored, and the use of bromoarene **2a** selectively led to **10b** in 77% yield. Again, for imidazoles the supported system compared well with the best homogeneous palladium catalyst. We previously reported postcatalysis studies for this Pd@PPy system, which suggested releasing of molecular or colloidal soluble active species, delivered by the nanocomposite and susceptible to back redeposition and recycling.[5] To further scrutinize this hypothesis we achieved here inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the filtrate after synthesis of **3a** (Scheme 2). A residual amount of palladium of 260 ppm which corresponds to 2.7% palladium leaching was detected. In comparison to fully insoluble heterogeneous systems (<10 ppm),[13] this amount is consistent with our first hypothesis.

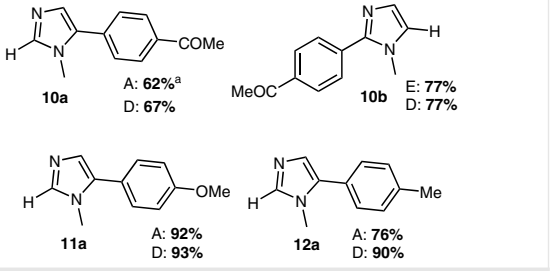


Figure 2 *C5*- and *C2*-arylated imidazoles **10a**,**b**, **11a**, and **12a** from bromoarenes coupled with **9**. *Reagents and conditions*: imidazole (2.0 equiv), bromoarene (1.0 equiv), DMAc (2.5 ml), 150 °C, 17 h; conditions **A**: Pd@PPy (2.0 mol%), KOAc (2 equiv); conditions **D**: $Pd(OAc)_2$ (0.5 mol%), KOAc (2.0 equiv); conditions **E**: Pd@PPy (2.0 mol%), CuI (1.0 equiv), Cs_2CO_3 (2.0 equiv). [a] NMR and GC yields.

In summary, palladium nanoparticles of 2 nm size, highly dispersed on polypyrrole support (35 Pd wt%), provided an efficient system for the selective direct arylation of substituted pyrroles and imidazoles by using unactivated aryl bromides functionalized in *para*, *meta*, and *ortho* positions.[14–16] These performances matches the best homogeneous systems known to date. Further works are focused at improving the recyclability of this recoverable system *via* anchoring of Pd@PPy nanocomposite.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561113.

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(8) Reported pK_a for thiophenes and furans are *C5* (or *C2*)–H = 33–36, and pK_a of *C5* (or *C2*)–H for pyrroles and indoles are in the range 38–40, see http://www.scripps.edu/baran/heterocycles/Essentials1-2009.pdf.

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(10) Improved isolated yields can be accessed for synthetic scales higher than 1.0 mmol. Recycling experiments were limited due to fractional material loss by paper filtration.

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(14) **Typical Procedure**

All reactions were run under argon in Schlenk tubes using vacuum lines. DMAc analytical grade was not distilled before use. KOAc (99%) was used. Commercial aryl bromides, pyrroles, and imidazoles were used without purification. The reactions were followed by GC and NMR spectroscopy. ^{1}H NMR spectra were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to $CDCl_3$ (7.25 for ^{1}H NMR). Flash chromatography was performed on silica gel (230–400 mesh).

In a typical procedure, the aryl bromide (1 mmol), pyrrole (2 mmol), and KOAc (2 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. The catalyst [either Pd@PPy,[5] or $Pd(OAc)_2$ at 0.02–2.0 mol%] and DMAc (2.5 ml) were added, and the Schlenk tube was purged several times using vacuum/argon flow. The Schlenk tube was placed in a pre-heated oil bath at 150 °C, and reactants were allowed to stir for 17 h. The reaction mixture was analyzed by GC and NMR to determine the conversion of aryl bromide. The solvent was then removed by heating the reaction vessel under vacuum, and the residue formed was charged directly onto a silica gel column. The products were eluted, using an appropriate ratio of EtOAc and heptane. Recycling procedure were based on simple Pd@PPy powder paper filtration, rinsing with a small portion of organic solvent, and drying under vacuum at 60 °C for 4 h. Subsequent catalytic tests were conducted using DMAc at 150 °C in the presence of KOAc and sufficient Pd@PPy collected from several experiments.

(15) **1-[4-(5-Acetyl-1-methyl-1*H*-pyrrol-2-yl)phenyl]ethanone (6a)**

The reaction of 4-bromoacetophenone (0.100 g, 1 mmol), 1-methyl-2-acetylpyrrole (0.120 mL, 2 mmol), and KOAc (0.098 g, 2 mmol) with Pd@PPy (0.003 g, 2% mol) affords the corresponding product **6a** in 28% isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 4.0 Hz, 1 H), 6.29 (d, *J* = 4.0 Hz, 1 H), 3.91 (s, 3 H), 2.64 (s, 3 H), 2.48 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 188.7, 141.4, 136.4, 136.3, 132.7, 129.3, 128.6, 119.7, 110.1, 35.4, 27.5, 26.7. Anal. Calcd (%) for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; 5.81. Found: C, 73.92; H, 6.33; N, 5.40. HRMS (ESI+): *m/z* [M + H$^+$] calcd for $C_{15}H_{15}NO_2$: 242.118; Found: 242.172.

(16) **1-Methyl-5-(*m*-tolyl)-1*H*-pyrrole-2-carbaldehyde (7d)**

The reaction of 3-bromotoluene (0.060 mL, 1 mmol), 1-methyl-2-formylpyrrole (0.100 ml, 2 mmol), and KOAc (0.098 g, 2 mmol) with Pd@PPy (0.003 g, 2 mol%) affords the corresponding product **7d** in 41% isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 7.37–7.32 (m, 1 H), 7.26–7.20 (m, 3 H), 6.96 (dd, *J* = 4.1 Hz, 1 H), 6.29 (d, *J* = 4.1 Hz, 1 H), 3.93 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 144.6, 138.4, 133.0, 131.1, 129.9, 129.4, 128.5, 126.3, 124.5, 110.7, 34.4, 21.5. Anal. Calcd (%) for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.93; H, 6.53; N, 6.70. HRMS (ESI+): *m/z* [M + H$^+$] calcd for $C_{13}H_{13}NO$: 200.107; found: 200.190.