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Palladium–Polypyrrole Nanocomposites (Pd@PPy) Efficiently Promoting Pyrroles and Imidazoles Direct C–H Functionalization with Bromoarenes

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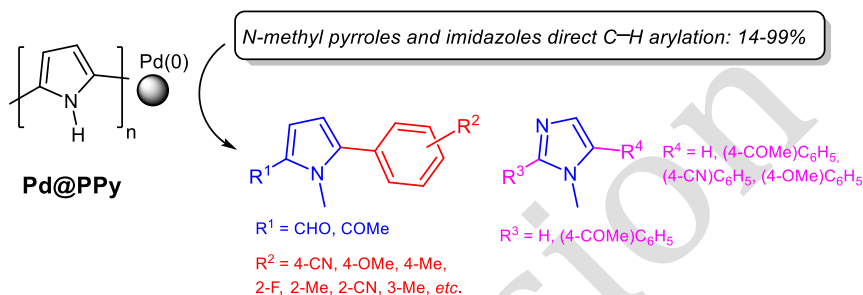
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Dedicated to the memory of Dr. Guy Lavigne

Abstract Palladium–polypyrrole nanocomposites (Pd@PPy) with unique combination of high palladium dispersion (NPs 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 classical Pd/C catalyst.

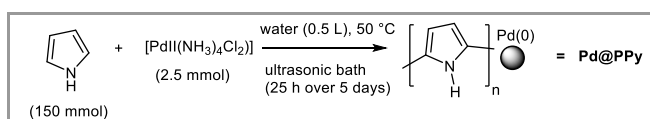
Key words palladium, polypyrrole, nanocomposite, C–H arylation, azoles

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 (NPs) 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 “NPs@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 Pd²⁺ cations by oxidized pyrrole monomer in acetonitrile solvent. The synthetic protocol led to Pd 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(NH₃)₄Cl₂] (Scheme 1).⁵ The nanocomposites formed were composed of highly dispersed zerovalent palladium nanoparticles embedded in spherical polypyrrole globules. A unique combination of high palladium dispersion (NPs 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 halides cyanation.^{6c}

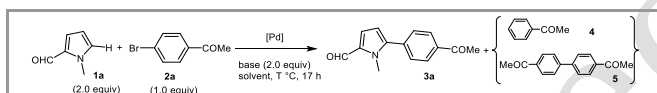


Scheme 1 In-water mild redox polymerization reaction of pyrrole with [Pd(NH₃)₄Cl₂] to Pd@PPy nanocomposite

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 NPs supported on organic material with a record high metal density.

We now report on the efficiency of these Pd@PPy for the selective arylation of more demanding azole substrates that are 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 in addition a much higher acidity for N–H in pyrrole (pKa = 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 2 equiv of pyrrole substrate was a practical way to diminish or obliterate these side reactions.



Scheme 2 Palladium Arylation of *N*-Methyl-Pyrrole-2-Carboxaldehyde (**1a**) with 4-Bromoacetophenone (**2a**)

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, runs 1-3 using toluene, CPME = cyclopentylmethylether, and dimethylformamide, DMF). We were glad to see that dimethylacetamide (DMAc) was very efficient for a full conversion of **1a** selectively in **3a** (run 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 K₂CO₃ was deleterious for conversion and promoted homocoupling of **2a** to **5** (run 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** (run 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% (runs 8, 9). Lower loading Pd(OAc)₂ at 0.02% (run 10), or higher loading Pd(OAc)₂ at 2% (run 7), were found detrimental to full conversion of **1a** and also favored homocoupling.

Table 1 Screening conditions to arylated pyrrole **3a** with Pd@PPy and comparison with other pertinent palladium-based catalysts^a

Run	Catalyst (%)	Solvent	T °C	Base	Conv%	3(%)	4(%)	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 ₂ CO 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.

With optimized conditions in hands using the recoverable catalytic material Pd@PPy (Table 1, run 4) we examined the scope of pyrroles C–H functionalization. We investigated in parallel the activity achieved under the best homogeneous conditions using Pd(OAc)₂ (Table 1, run 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*-methyl-pyrrole-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 homogenous system.

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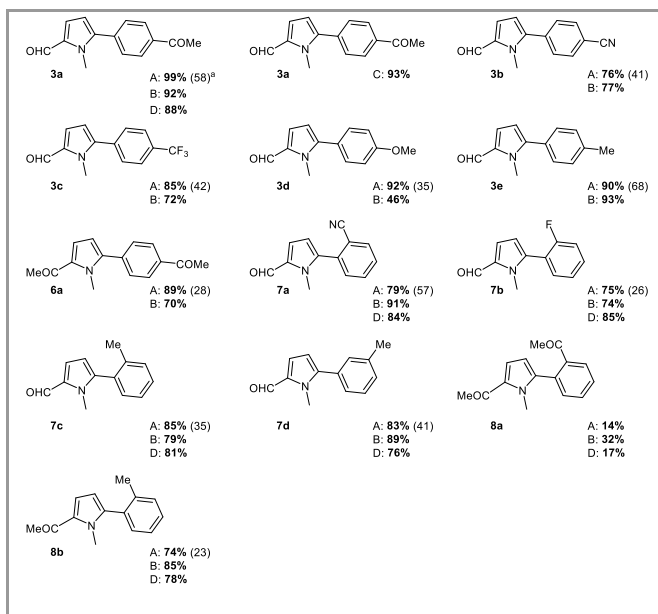
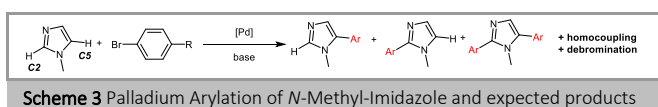


Figure 1 C5-Arylated pyrroles **3a-e**, **6a**, **7a-d**, **8a-b** synthesized from bromoarenes. Conditions: pyrrole (2 equiv), bromoarene (1 equiv), DMAc 2.5 mL, KOAc (2 equiv), 150 °C, 17 h; **A**: Pd@PPy 2.0 mol %; **B**: Pd(OAc)₂ 0.2 mol%; **C**: Recycling of conditions **A**; **D**: Pd(OAc)₂ 0.5 mol%. ^a NMR and GC consistent yields; isolated are in bracket, values are technically minored due to reactions achieved at 1.0 mmol very low scale.

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 non-supported 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 *N*-methyl-imidazole 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



Scheme 3 Palladium Arylation of *N*-Methyl-Imidazole and expected products

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*-methyl-imidazole **9** with aryl bromides (Figure 2). By using 2 equiv 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 2 equiv of Cs₂CO₃ as a base, with 1.0 equiv of CuI, arylation in C2 of *N*-methyl-imidazole 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 homogenous 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 **3a** synthesis (Scheme 2). A residual amount of palladium of 260 ppm which corresponds to 2.7% Pd leaching was detected. In comparison to fully insoluble heterogeneous systems (<10 ppm),¹³ this amount is consistent with our first hypothesis.

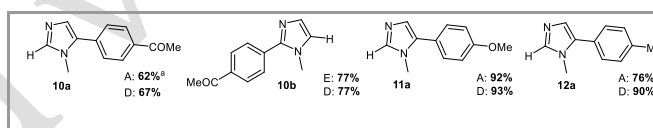


Figure 2 C5- and C2-Arylated Imidazoles **10a-b**, **11a** and **12a** from Bromoarenes coupled with **9**. Conditions: imidazole (2.0 equiv), bromoarene (1.0 equiv), DMAc 2.5 mL, 150 °C, 17 h; **A**: Pd@PPy 2.0 mol %, KOAc (2 equiv); **D**: Pd(OAc)₂ 0.5 mol%, KOAc (2.0 equiv); **E**: Pd@PPy 2.0 mol %, CuI (1.0 equiv), Cs₂CO₃ (2.0 equiv). ^a NMR and GC yields.

In summary, Pd nanoparticles of tiny 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.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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- (8) Reported pKa for thiophenes and furans are C5(or C2)-H = 33-36, and pKa 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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- (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. ¹H spectra were recorded with a Bruker 300 MHz spectrometer in CDCl₃ solutions. Chemical shifts are reported in ppm relative to CDCl₃ (7.25 for ¹H 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 to 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 gas chromatography and NMR to determine the conversion of aryl bromide. The solvent was then removed by heating the reaction vessel under vacuum, and the residue from was charged directly onto a silica gel column. The products were eluted, using an appropriate ratio of ethyl acetate 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 potassium acetate and sufficient Pd@PPy collected from several experiments.
- (15) 1-(4-(5-acetyl-1-methyl-1H-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. ¹H NMR (200 MHz, CDCl₃): δ = 8.02 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 4.0 Hz, 1H), 6.29 (d, J = 4.0 Hz, 1H), 3.91 (s, 3H), 2.64 (s, 3H), 2.48 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): 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. Elemental analysis: Calcd (%) for C₁₅H₁₅NO₂: C 74.67, H 6.27, 5.81. Found: C 73.92, H 6.33, N 5.40. HRMS + p ESI (m/z) [M+H⁺], Calcd for C₁₅H₁₅NO₂: 242.118. Found: m/z = 242.172.
- (16) 1-methyl-5-(m-tolyl)-1H-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. ¹H NMR (300 MHz, CDCl₃): 9.57 (s, 1H), 7.37-7.32 (m, 1H), 7.26-7.20 (m, 3H), 6.96 (dd, J = 4.1 Hz, 1H), 6.29 (d, J = 4.1 Hz, 1H), 3.93 (s, 3H), 2.41 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): 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. Elemental analysis: Calcd (%) for C₁₃H₁₃NO: C 78.36, H 6.58, N 7.03. Found: C 77.93, H 6.53, N 6.70. HRMS + p ESI (m/z) [M+H⁺], Calcd for C₁₃H₁₃NO: 200.107. Found: m/z = 200.190.