

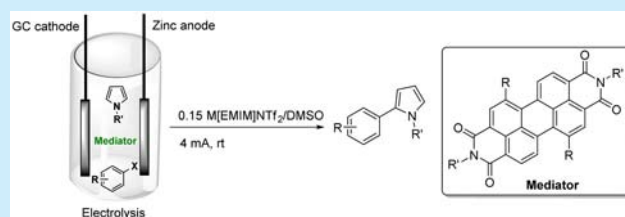
Direct Arylation of Pyrroles via Indirect Electroreductive C–H Functionalization Using Perylene Bisimide as an Electron-Transfer Mediator

Guoquan Sun, Shuya Ren, Xinhai Zhu,* Manna Huang, and Yiqian Wan

School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, P. R. of China

S Supporting Information

ABSTRACT: The indirect electroreductive coupling of aryl halides and pyrroles was successfully conducted using a catalytic amount of perylene bisimide as a mediator in 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide ([EMIM]NTf₂)/DMSO.



Electroorganic synthesis has been recognized as an environmentally friendly methodology for the oxidation and reduction of organic compounds because the dangerous and toxic redox reagents often used in classic reactions are replaced with an electric current.¹ The traditional electrochemical methods in electroorganic syntheses were reviewed a few years ago.² In recent years, novel strategies and applications of new methods for effecting organic electrooxidative reactions³ and electroreductive reactions⁴ have been developed. Compared with direct electrolysis, indirect electroorganic conversions that use redox mediators to achieve indirect processes are attaining increased significance and exhibiting numerous advantages.⁵ For example, indirect electroorganic synthesis exhibits higher reaction selectivity because the electrolysis is conducted at lower potentials than the redox potentials of the starting materials. Although the concept of indirect electrolysis was established many years ago,⁶ many new exciting and useful developments continue to be reported, especially with respect to indirect electrooxidation reactions.⁵ However, progress in indirect electroreductive chemistry remains slow and appears to be restricted to the use of nickel and cobalt complexes,⁷ diphenyl diselenide,⁸ other transition-metal complexes,⁹ fullerenes,¹⁰ and carboranes.^{4f} Notably, reports on the use of aromatic hydrocarbons as mediators for electroreductive reactions have only been found in selected numbers in older literature.¹¹ As far as we know, the indirect electrochemical method for the aryl C–C coupling reactions are rare, although a powerful and practical indirect electrooxidation method for the cross-coupling of phenols with arenes, reported by Waldvogel and co-workers, impressed us.¹²

Functionalized pyrroles are abundant in natural products and medicinal agents.¹³ The direct arylation of pyrroles through C–H bond activation has been demonstrated to be a very powerful method for the synthesis of various functionalized pyrroles. However, most of the reported methods involve the utilization of transition metals such as palladium, rhodium, copper, and cobalt as catalysts.¹⁴ In contrast, metal-free methodologies are rare and

challenging. For example, Gryko and co-workers pioneered the base-mediated direct arylation of pyrroles.¹⁵ However, harsh conditions such as the use of strong bases or high reaction temperatures were required as a prerequisite, making this method less practicable.

Perylene-3,4,9,10-tetracarboxylic acid diimide derivatives (abbreviated in this paper as **PDIs**) are an outstanding class of organic dye molecules and have more recently been used in the field of organic electronics and fluorescence materials.¹⁶ Recently, Ghosh and co-workers reported the use of **PDIs** as photocatalysts for the reduction of aryl halides to generate aryl radicals.¹⁷ Moreover, some catalysts that are frequently used as photoredox catalysts are useful mediators for electrochemical applications,⁵ such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).¹⁸ The electrochemical properties of **PDIs**¹⁹ suggest that they could be used as possible mediators for indirect electroorganic syntheses because of their lower reversible redox potentials.⁵ However, to the best of our knowledge, **PDIs** have never been used in indirect electroorganic syntheses. Hence, we report the direct C–H arylation of pyrroles using **PDIs** as electron transfer mediators.

Initially, two types of **PDIs** with good solubility were synthesized (Figure 1, left). The electrochemical properties of these compounds were investigated using cyclic voltammetry (CV). As illustrated in Figure 1 (right), the cyclic voltammograms of **PDI-1** and **PDI-2** both showed two reversible one-electron reduction waves, which indicates that the molecules could be controllably reduced to stable radical mono- and dianionic species with distinctive optical properties.

To explore the production of stable radical mono- and dianionic species in more detail, the absorption spectra of the radical mono- and dianionic species of **PDI-1** were measured by implementing a potentiostatic electrochemical experiment with

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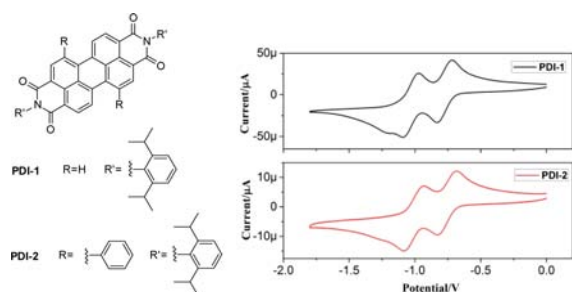


Figure 1. Left: Chemical structures of the synthesized PDIs. Right: Cyclic voltammograms of PDI-1 and PDI-2. Conditions: 5 mM PDI in 0.15 M [EMIM]NTf₂/DMSO (ν = 100 mV/s) using a glassy carbon working electrode; potentials vs Ag/AgNO₃ in CH₃CN.

an in situ spectroelectrochemistry measuring technique (Figure 2).²⁰

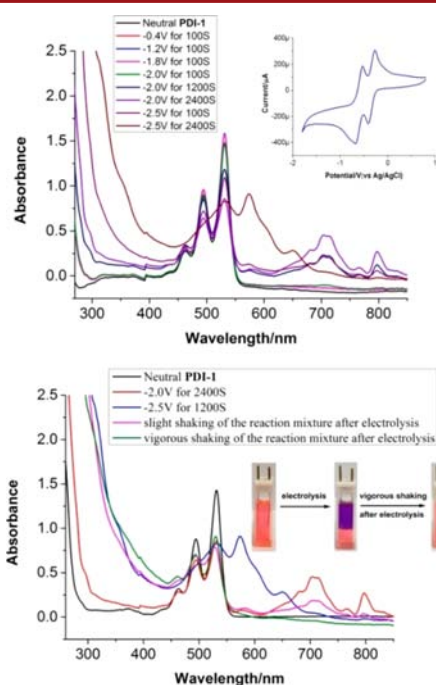


Figure 2. Spectroelectrochemistry of PDI-1. Conditions: PDI-1 (2×10^{-5} M) in 0.15 M [EMIM]NTf₂/DMSO using a platinum minigrid working electrode, a platinum wire counter electrode and a Ag/AgCl reference electrode, without the protection of N₂. Potentiostatic electrolysis at marked potentials vs Ag/AgCl.

According to the CV results (with Ag/AgCl as a reference electrode), reduction potentials of -0.4 , -1.2 , -1.8 , -2.0 , and -2.5 V were applied separately to compound PDI-1 for 100 s before the absorption spectra were collected. As shown in Figure 2 (above), the absorption spectrum of PDI-1 remained unchanged when the potential was increased from -0.4 to -1.8 V, which was probably because of the low current density. Interestingly, when the potential was increased to -2.0 V, new bands located at 704 and 798 nm emerged and increased in intensity with increasing duration of electrolysis time; these bands composed the diagnostic absorption spectrum of the electrochemically generated PDI-1 radical monoanions.¹⁷ When the potential was increased from -2.0 to -2.5 V, the intensities of the bands at 704 and 798 nm decreased, whereas those of the bands at 653 and 576 nm increased, which indicated the

formation of PDI dianions.¹⁷ Notably, the intensity and profile of the spectrum collected immediately after the power was turned off was unchanged after electrolysis for 20 min at -2.5 V. However, slight shaking of the reaction mixture resulted in the regeneration of the radical monoanion, whereas vigorous shaking induced the regeneration of the neutral PDI-1 (Figure 2, below). These results suggest that the neutral, monoanionic, and dianionic species of PDI-1 were interchangeable and were favorable for mediatory use in an electrocatalytic reaction.

To determine whether redox catalysis of the PDIs was possible, we also recorded the cyclic voltammograms of PDI-1 and PDI-2 in the presence of 4-bromoacetophenone (**1a**). As illustrated in Figure 3, the reductive current for PDI-1 increased and the

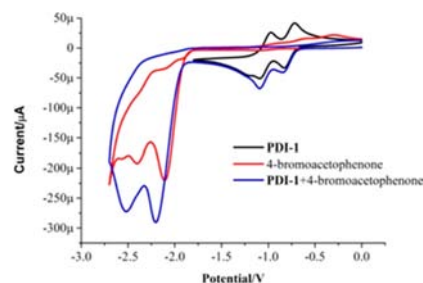
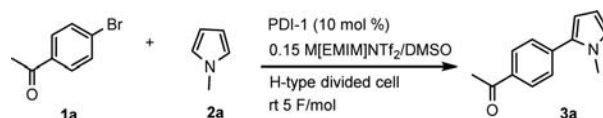


Figure 3. Electrocatalysis and reversibility. Experimental conditions: PDI-1 (5 mM), substrate **1a** (20 mM), mixture (5 mM PDI + 20 mM **1a**); measured in 0.15 M [EMIM]NTf₂/DMSO (ν = 100 mV/s) using a glassy carbon working electrode; potentials vs Ag/AgNO₃ in CH₃CN.

reoxidation peak disappeared, thereby indicating the presence of a typical catalytic current. These results indicate that the transfer of electrons from the electrode to PDI-1 occurred initially, with subsequent electron transfer from the mono- or dianionic species of PDI-1 to **1a**. This result confirms that PDI-1 could mediate electron transfer between the electrode and substrate. Compared with the cyclic voltammogram of PDI-1 in the presence of substrate **1a**, that of PDI-2 showed no obvious catalytic current (Figure S3), likely as a consequence of the lower peak current of PDI-2 at the same concentration. Hence, PDI-1 was demonstrated to be a better candidate than PDI-2 and was used for further research on indirect electroreductive C–H functionalization reactions.

In studies of indirect cathodic reduction, a divided cell is usually used for the mediator system to prevent anodic oxidation of the reductive species after they have been generated at the cathode. Initially, the model reactions of 1-methyl-1H-pyrrole (**2a**) and **1a** with or without a catalytic amount (10 mol %) of mediator PDI-1 in 0.15 M [EMIM]NTf₂/DMSO were carried out at room temperature in an H-type divided cell equipped with a glassy carbon (GC) cathode and a graphite rod anode (Scheme 1). After 5 F/mol of electricity were consumed, the product, **3a**, was not detected in the absence of PDI-1; only the byproduct, acetophenone generated from the dehalogenation reaction, was obtained in 10% yield, as determined by gas chromatography (GC) (Table S1, entry 1). In contrast, when PDI-1 was used as a

Scheme 1. Indirect Electrocatalyzed Arylation of 1-Methyl-1H-pyrrole **2a** with **1a**



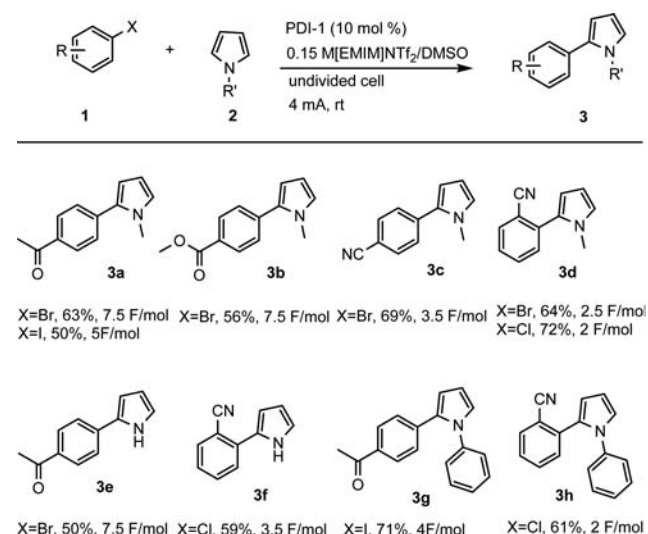
mediator, the coupling product of **3a** was obtained in 70% GC yield (Table S1, entry 2). These results revealed the efficiency of PDI-1.

The reaction parameters were further optimized under constant-current electrolysis conditions (Table S1). Among the solvents we had examined to this point, all except CH_2Cl_2 were effective in promoting the conversion of **1a**. However, the major product of the reaction was the unexpected byproduct that resulted from the dehalogenation of **1a** in DMF and DMAc (Table S1, entries 6, 7). Fortunately, target **3a** was generated in higher yield in DMSO (70%) than when the reaction was conducted in CH_3CN (59%) (Table S1, entries 2, 4). In addition, the type of electrolyte used in the reactions substantially affected the outcome of the model reaction (Table S1, entries 2, 8–12). We determined that only imidazolium-based ionic liquids were effective and that 1-ethyl-3-methylimidazolium bis((trifluoromethyl)sulfonyl)imide ([EMIM]NTf₂) was more suitable as the electrolyte in accelerating the reaction. Control experiments confirmed that light was not necessary for the electroreduction reaction (Table S1, entry 16); however, the extent of conversion decreased substantially when the same amount of electricity was used if the reaction was carried out with bubbling air (Table S1, entry 17). We also investigated the stability of the PDI-1 mediator under constant-current electrolysis conditions (4 mA). Up to 90% of the PDI-1 mediator was recovered even after 5 F/mol of electricity were consumed. However, the relatively low isolated yields of **3a** (38%) prompted us to examine our reaction conditions further.

When we analyzed the current (i.e., by collecting potential curves of the reaction under constant-current electrolysis conditions (4 mA)), we observed that the potential was very high (as high as -7 V) because of the high electric resistance of the H-type divided cell in the absence of electrodes with large specific surface areas. And the selectivity of the target compound **3a** was directly related to the electrode potential. However, when the electrode potential was reduced to below -2 V, the current was too low to promote the reaction to occur. Thus, the model reaction was conducted in an undivided cell. As expected, when a graphite rod was used as an anode, conversion of the substrate was only 30% even after 7.5 F/mol of electricity were consumed (Table S2, entry 1). This low yield presumably resulted from the reoxidation of PDI-1 radical anions to neutral PDI-1 moieties, which inhibited the redox reaction between PDI-1 radical anions and substrate **1a**, leading to a significant decrease of the faradaic efficiency of the reaction. To avoid such undesired anodic reactions, we investigated the use of sacrificial anodes such as zinc, iron, and brass (Table S2). Encouragingly, the conversion of **1a** and the yield of **3a** were satisfactory when the reaction was run with a zinc anode (Table S2, entry 2).

Then, electroreductive C–C bond-forming arylation reactions using the PDI-1 mediator were successively applied to aryl halides with substituted pyrroles (Scheme 2). Aryl bromides, aryl iodides, and even aryl chlorides bearing electron-withdrawing groups reacted with 1H-pyrrole, *N*-methylpyrrole, and *N*-phenylpyrrole, affording the corresponding arylated products in moderate-to-good isolated yields. Even the *ortho*-substituted aryl halides generated the desired products in good yields. Although there are many palladium-catalyzed methods that now can use cheap aryl chlorides for pyrrole arylation,^{14c–e} it should be noted that this method should be an alternative to the arylation of pyrroles to be suitable for the C-arylation of NH pyrroles with activated aryl chlorides as starting materials. However, the analogs to pyrrole, such as furan, thiophene, or indole, which were

Scheme 2. Indirect Electrocatalyzed C–H Arylation Reactions of Aryl Halides with Substituted Pyrroles^a

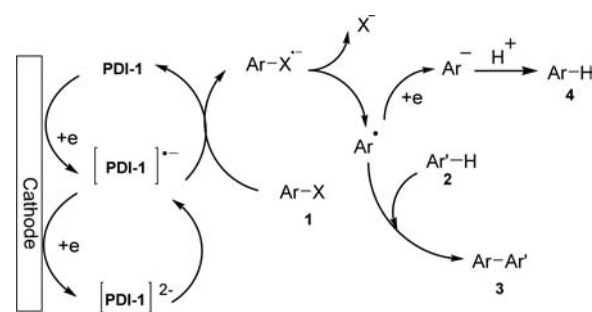


^aReactions were electrolyzed with 0.2 mmol of **1** and 25 or 50 equiv of **2** and PDI-1 (10 mol %) in 0.15 M [EMIM]NTf₂/DMSO (10 mL) at room temperature under N₂ protection; isolated yield.

regarded to be less reactive for the addition reaction of radicals,⁵ did not carry out the C-arylation under the experimental conditions. As a result, use of almost the same substrate scope as that for our indirect electroreductive arylation of pyrroles together with a shorter time and without Et₃N, in comparison to the previously reported PDI-mediated photocatalyzed protocol,¹⁷ encouraged us to explore the mechanism further.

A plausible mechanism for the electrocatalytic coupling reactions of arylhalides **1** with pyrroles **2** using the PDI-1 mediator is shown in Scheme 3. PDI-1 is reduced at the cathode

Scheme 3. Plausible Catalytic Cycle for the Indirect Electroreductive Arylation of Pyrroles Using PDI-1 as a Mediator



to generate PDI-1 radical anions by constant-current electrolysis. The electron transfer between PDI-1 radical anions and **1** occurs rapidly, yielding $\text{ArX}^{\bullet-}$ and regenerating neutral PDI-1. The $\text{ArX}^{\bullet-}$ is unstable and undergoes a cleavage reaction yielding the aryl radical, Ar^{\bullet} , which then reacts with pyrroles, yielding C–C coupling products **3**, or is further reduced to generate Ar^- and eventually the hydrocarbon, ArH (**4**). The neutral PDI-1 generated is then further reduced at the cathode to complete the catalytic cycle. However, possibly because of that the aryl radical, Ar^{\bullet} , is much easier to reduce than the ArX in the electrochemical conditions,²¹ the expected TEMPO (2,2,6,6-tetramethylpiperidinoxyl) adduct was unfortunately not detected

upon electroreduction. The reversible redox behavior of **PDI-1** suggested that it was reduced to stable radical mono- and dianionic species. To confirm the generation of these species, we collected absorption spectra of the reaction mixture via a constant-current electrochemical experiment involving an in situ spectroelectrochemistry measuring technique. As shown in Figure S4, both **PDI-1** radical anions and **PDI-1** dianion species were detected under these reaction conditions. However, the intensity of the absorption of **PDI-1** radical anions at a low potential was higher than that at a high potential. In addition, the formation of **PDI-1** dianions was more rapid at a high potential. Notably, electroreduction afforded the coupling products at either high or low potentials after consumption of the same amount of electricity. However, the higher potential condition resulted in higher reaction rates, and the lower potential condition resulted in better target product selectivity according to GC-MS analyses (Table S3). These results suggest that **PDI-1** radical anions were the effective mediator for the coupling reactions, which was also confirmed through the higher yield of the coupling product when the reaction was conducted in an undivided cell with a lower electric potential (less than -2.0 V).

In conclusion, novel methodology for indirect electroreductive direct coupling of aryl halides and pyrroles was developed using a catalytic amount of perylene bisimide as a mediator in [EMIM]NTf₂/DMSO. Using a sacrificial zinc anode, indirect electrocatalytic C–C bond formation was efficiently carried out in a simple undivided cell. Compared with previously reported methods, the reaction reported here proceeded at room temperature without the use of a metal catalyst or the addition of a base. To the best of our knowledge, this study is the first to report the use of perylene bisimides as indirect electroreductive mediators. Furthermore, the good electron transfer abilities and high stabilities of perylene bisimides, along with their flexibility for structural modification, make them promising candidates as indirect electroreductive mediators. The application of the **PDIs** as indirect electroreductive mediators for the arylation of other unsaturated compounds is currently being investigated in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03581.

Experimental procedures and ¹H and ¹³C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhuxinh@mail.sysu.edu.cn.

Notes

The authors declare no competing financial interest.

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