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A versatile electrochemical batch reactor for synthetic organic and inorganic transformations and analytical electrochemistry

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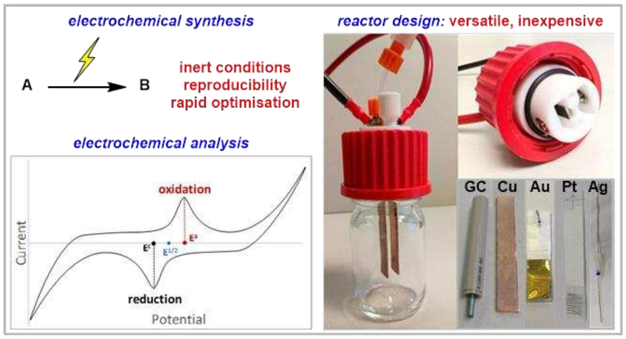


For Table of Contents Only

ABSTRACT

A standardized and versatile electrochemical batch reactor that has wide applicability in both organic and inorganic synthesis and analytical electrochemistry has been developed. A variety of synthetic electrochemical transformations have been performed to showcase the versatility and demonstrate the reactor, including the synthesis of five Cu(I)–NHC, two Au(I)–NHC and one Fe(II)–NHC complex, as well as an Fe(III)–salen complex. The reactor is based on a commercially available vial with an adapted lid, making it inexpensive and highly flexible. It features a fixed interelectrode distance which is crucial for reproducibility, along with the ability to accommodate a variety of interchangeable electrode materials. The reactor has also been used in conjunction with a parallel plate allowing rapid screening and optimization of an organic electrochemical transformation. Cyclic voltammetry has been performed within the reactor on a range of imidazolium salt analytes with the use of an external potentiostat. The ability to use this reactor for both analytical and synthetic organic and inorganic chemistry is enabled by a flexible and characterizable design.

KEYWORDS: Electrochemistry, electrosynthesis, reactor design, cyclic voltammetry.

INTRODUCTION

During the last decade synthetic electrochemistry has been receiving renewed interest as an enabling technology that typically provides a mild, atom efficient and sustainable method for performing chemical transformations.[1-8] This novel, and well-understood redox mode of activation,[1] coupled with broad applicability has resulted in the development of a raft of new methodology including the synthesis of inorganic and organometallic complexes and many other organic transformations.[9-13] While many of the benefits of electrosynthesis have been realized in these new methodologies, there remains a bottleneck to widespread adoption.[14] One reason for this impediment derives from a lack of simple, characterizable and reproducible experimental set-ups.[15-19]

Previously, our group and others have used three-neck flasks to perform electrochemical transformations.[9-13] Electrode leads were passed through the side-arms of the flask which allows electrodes to be lowered into solution. While this approach has led to the development of efficient methodology, there remain problems with reproducibility across experiments and particularly for the transfer of experimental procedures to other laboratories.[20] One reason for the lack of reproducibility is due to an inability to maintain a constant interelectrode gap, electrode angles and depth of electrode in solution resulting in variable resistance and current density across experiments both of which have a large effect on reaction outcome.[21]

More recently, several commercial reactors have been developed which provide a constant interelectrode distance, electrode angle and depth, with many being used in laboratories throughout the world.[22] A common issue with these reactors is the inability to perform transformations under inert atmospheres which is necessary for the synthesis of many organometallic and inorganic complexes as well as several organic transformations or analytical techniques.[23]

Currently, the electrosynthesis community has limited access to standardized, flexible and affordable electrochemical batch reactors. Herein, we report the design, development and characterisation of a simple yet versatile electrochemical batch reactor (bottle reactor) that has been used for the synthesis of sensitive organometallic and inorganic complexes as well as an organic electrochemical transformation. Cyclic voltammetry has also been performed in the reactor, showcasing the versatility of the set up.

RESULTS AND DISCUSSION

Reactor design

An electrochemical batch reactor based upon commercially available vials with an adapted lid was designed (Fig. 1); 30 mL vials were used in this study, however the lid is compatible with any vial that has a GL-32 thread. The lid is comprised of a cap with a hole cut into it and a PTFE insert which fits into this hole. The PTFE insert has an extrusion which overlaps with the lip of the vial such that when the cap is screwed into place a tight seal is created between the vial and the PTFE. The insert is machinable and exhibits four holes for a variety of purposes. Two of these form ports that have a standardized ¼-28 thread, which allows various standard fittings to be screwed into the lid. This enables the reactor to be attached to a Schlenk line through one of the ports *via* a short piece of tubing with a Luer fitting on the other end, whilst a blank fitting in the other port may be removed to enable the addition of reagents and solvents or the removal of aliquots for analytical purposes, or for insertion of an analytical probe for *in operando* studies. In addition, this may also be fitted with a septum and solutions can also be transferred to and from the reactor using a cannula. Alternatively, one of the ports can be used to insert a silver wire to act as a pseudo reference electrode and also allows the possibility for *in situ* analysis if a probe is inserted through one of the ports.

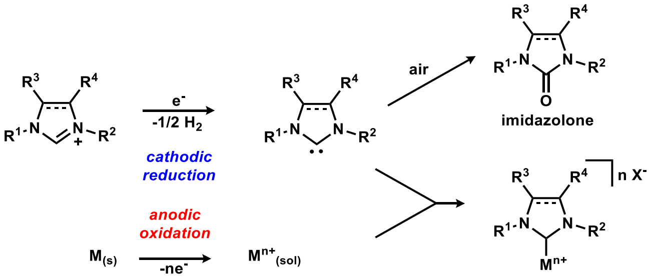
Figure 1. Images of the bottle reactor. Left: Fully assembled bottle reactor. Top right: PTFE head piece with O-ring seal as it sits within the bottle cap. Bottom right: PTFE head piece showing stainless steel electrode contacts.

Stainless steel electrode contacts were fashioned in a conical shape which is complementary to the shape of the remaining two holes in the PTFE insert. When screwed into place, the electrode contacts are pulled up and into the PTFE, creating a good seal. The top of the steel contacts are joined to cables which were connected to a power supply unit. Grooves were made in the bottom of the PTFE insert to allow the electrodes to contact the stainless-steel contacts (Fig. 1). A small grub screw in the wall of each groove can be tightened to hold the electrodes in place, thereby allowing any electrode with a thickness of up to 4 mm to be used, whilst maintaining a constant 5 mm interelectrode distance.

The ability to maintain a reproducible and constant interelectrode gap, whilst ensuring high flexibility of electrode materials were of great importance during the design process. The distance between the electrodes remains constant to increase reproducibility of reactions, whilst allowing a broad range of electrode materials, with an assortment of shapes, thicknesses and lengths to be accommodated. Furthermore, the electrodes are able to connect to a range of commercially available power supply units using simple, readily available connectors to permit use of the reactor with a simple power supply unit or potentiostat.

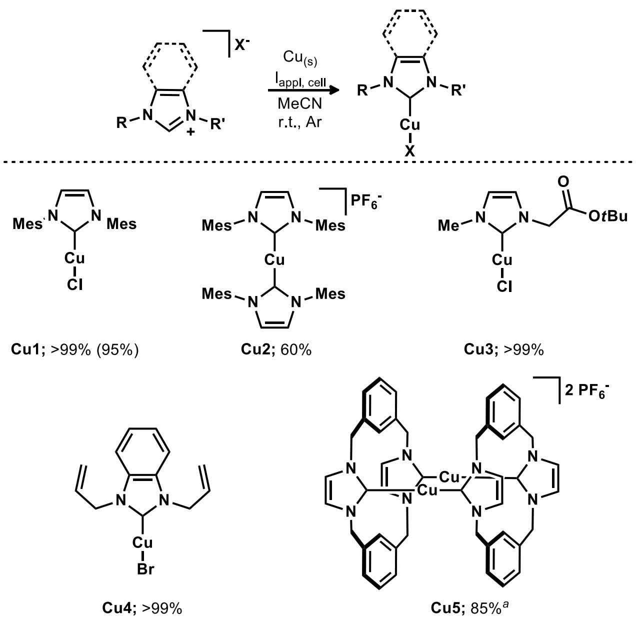
Synthetic applications

The electrochemical synthesis of metal–*N*-heterocyclic carbene (NHC) complexes has previously been reported by our group and others.[9,12] This procedure involves oxidation of a sacrificial anode which releases metal ions into solution and the cathodic reduction of imidazolium salts to produce metal–NHC complexes *via* highly reactive carbene intermediates (Scheme 1). These intermediates are sensitive to the presence of both oxygen and moisture which results in the formation of imidazolone side products.[11] Consequently, initial testing of the bottle reactor was performed by the preparation of a range of metal–NHC complexes whose syntheses rely upon the use of inert atmospheres and anhydrous solvents.



Scheme 1. Electrochemical synthesis of metal–NHC complexes.

Our investigations began with the preparation of various copper(I)–NHC complexes (Scheme 2) on a 1 mmol scale. These reactions were performed under galvanostatic conditions as this enabled control over the amount of electron equivalents (F mol^{-1}) delivered into solution, allowing a comparison with previously published results.[12] Imidazolium salts play a dual role in the reaction as both reactant and electrolyte. This dispenses with the need to add an additional supporting electrolyte in most cases. Under these conditions, five different copper(I)–NHC complexes were prepared (Scheme 2).



Scheme 2. Electrochemical synthesis of Cu(I)–NHC complexes. Yields determined by ^{1}H NMR spectroscopy, isolated yields in parentheses, reaction conditions: 1 mmol of ligand precursor, 50 mA, 1.2 F mol^{-1}, 39 min. ^{a} 0.5 mmol of ligand precursor, 30 mA, 1.2 F mol^{-1}, 65 min, 0.5 equiv Bu_4NBF_4 was added to the reaction mixture.

Initially, imidazolium salt, IMes·HCl (**L1**) was chosen as a model substrate as the electrochemical synthesis of the corresponding mono-NHC Cu(I) complex has been well documented.[11,12] Galvanostatic conditions utilising 50 mA were applied for 1.2 electron equivalents which resulted in complete conversion to the expected neutral mono-NHC complex. This complex could also be isolated in 95% yield after recrystallisation **(Cu1).** Using the same imidazolium cation but changing the counter anion to the non-coordinating hexafluorophosphate gave **L2** which under identical conditions resulted in 60% conversion to the expected cationic bis-NHC Cu(I) complex (**Cu2**). The non-coordinating nature of the anion results in a second NHC ligand coordinating to the Cu(I) centre. The lower conversion with hexafluorophosphate compared to a halide anion is consistent with previously reported results. The electrochemical synthesis of cationic, bis-NHC Cu(I) complexes typically require higher electron equivalents to reach full conversion.[11,12] When the precursor was replaced with imidazolium salt **L3** which contains a base-sensitive ester functionality, complete conversion was observed after 1.2 electron equivalents (**Cu3**). The synthesis of this complex highlights the complementary reactivity of the electrochemical approach to traditional chemical methods using strong bases as the base-sensitive ester functionality remains intact. This is not the case if strong bases are employed. The electrochemical approach provides a different mode of activation which allows access to new complexes. When benzimidazolium salt **L4** was used, full conversion was observed after 1.2 electron equivalents (**Cu4**). The reduction of benzimidazolium salt **L4** is significantly more facile than related imidazolium salts, potentially due to the electronic effect exerted by the annulated benzene ring (*vide infra)* and this may explain the good reactivity observed here. When cyclophane derived bis-imidazolium salt **L5** was subjected to a current of 30 mA for 1.2 electron equivalents an 85% conversion to the dicationic, dinuclear complex $[Cu_2(NHC)_2](PF_6)_2$ was observed as expected from previous literature (**Cu5**).[11,12] The addition of supporting electrolyte was necessary to complete the reaction in a reasonable time frame due to poor solubility of the ligand precursor **L5** and low conductivity of the solution.[12]

Time course experiments were performed to investigate the different rates of formation of the mono- and bis-NHC complexes when either ligand precursors **L1** or **L2** were used. Acetonitrile solutions containing the ligand precursors were subjected to a current of 50 mA for different amounts of electron equivalents. This required sampling the reactions at different time points while maintaining an inert atmosphere which required use of both the ports on the PTFE insert. The rate of formation of Cu(IMes)Cl (**Cu1**) is fast with quantitative conversion being achieved after 1 electron equivalent (Fig. 2). The rate of formation of [Cu(IMes)$_2$]PF$_6$ (**Cu2**) is slower with 85% conversion after 1.6 electron equivalents and only slightly more (92%) after 3.5 electron equivalents. The slower formation of **Cu2** is potentially attributed to either mass transfer limitations or lower conductivity of the imidazolium salt **L2** resulting in a higher resistance in solution which may promote side reactions.[12] The ability to take samples from the reaction mixture through one of the ports machined into the PTFE head piece while the other is connected to a Schlenk line highlights the ease of manipulation when using the bottle reactor.

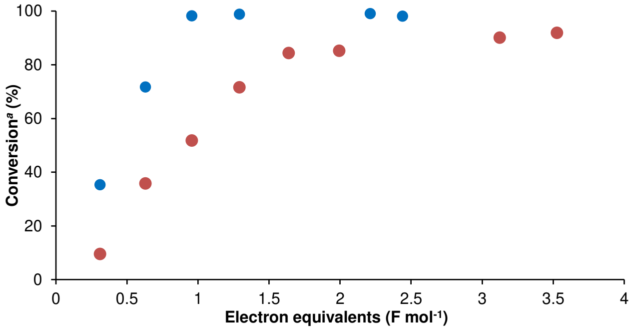
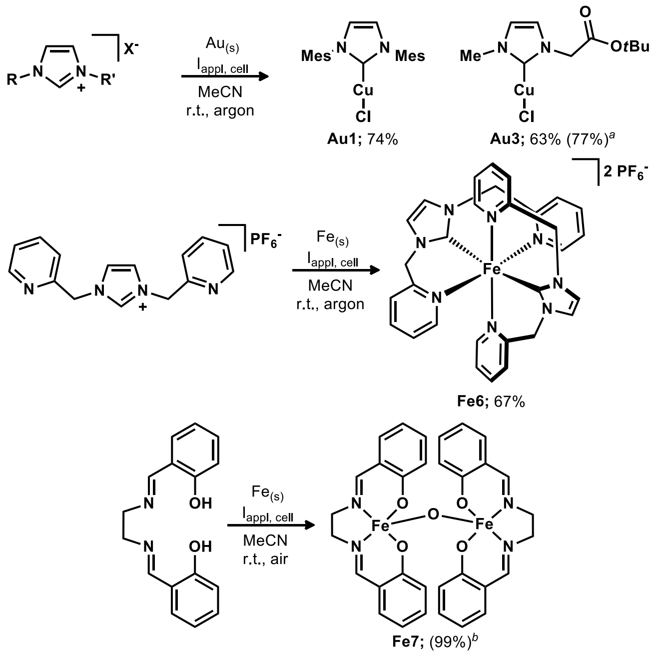


Figure 2. Time course monitoring of the formation of Cu(IMes)Cl (**Cu1**) (blue) and [Cu(IMes)$_2$]PF$_6$ (**Cu2**) (orange). ^{a} Determined by ^{1}H NMR analysis.

The synthetic methodology can be simply translated to other metals as the reactor provides the flexibility to change the electrodes to the material of choice. To this end, imidazolium salts **L1**,

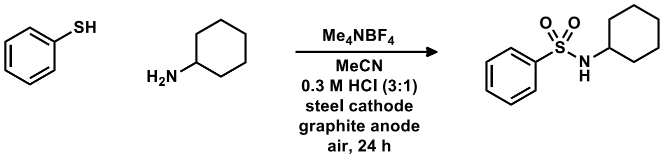
L3, **L6** and salen ligand **L7** were tested using either gold or iron electrodes (Scheme 3). When IMes·HCl (**L1)** was subjected to a current of 50 mA for 1.2 electron equivalents using PTFE-supported Au electrodes a conversion of 74% to the mono-NHC product was observed (**Au1**). Interestingly, a significant amount (10%) of bis-NHC complex was produced in this reaction in contrast to the analogous reaction with copper electrodes. Au(I)–NHC complexes are often isostructural with Cu(I)–NHC complexes however, in this case, the larger size of the Au cation may provide reduced steric hindrance resulting in the formation of bis-NHC Au(I) complex.[24,25] When imidazolium salt **L3** was subjected to identical reaction conditions using Au electrodes a conversion of 63% to the mono-NHC Au(I) complex was observed and no bis-NHC Au(I) complex was observed. This complex was also isolated in 77% yield when 2.0 electron equivalents were used (**Au3**). Iron foil was a suitable electrode material for the electrosynthesis of Fe complexes of different oxidation states. When imidazolium salt **L6** was subjected to the standard reaction conditions a 67% conversion to an Fe(II) complex was observed (**Fe6**). However, when salen ligand **L7** was used in place of the imidazolium salt and the reaction was carried out in air, full conversion to an Fe(III) complex was obtained with an isolated yield of 99% (**Fe7**). This reaction was performed using 2.4 electron equivalents as the ligand precursor must be reduced twice.[10,26] This highlights the versatility of the electrochemical procedure to allow access different metal oxidation states.



Scheme 3. Electrochemical synthesis of Au–NHC, Fe–NHC and Fe–salen complexes. Yields determined by ^{1}H NMR spectroscopy, isolated yields in parentheses, reaction conditions: 1 mmol of ligand precursor, 50 mA, 1.2 F mol^{-1}, 39 min. ^{a} 1 mmol of ligand precursor, 50 mA, 2.0 F mol^{-1}, 65 min. ^{b} 1 mmol of ligand precursor, 50 mA, 2.4 F mol^{-1}, 78 min.

To expand the applicability of the bottle reactor, its utility in synthetic organic electrochemistry was examined. Specifically, a sulfonamide synthesis recently reported by Noël and co-workers (Table 1) was investigated.[26] This reaction involves the oxidative coupling of amines and thiols through an electrochemical mechanism with H_2 gas being the only by-product. To begin the investigation the reported batch conditions were repeated. Unsurprisingly, the results obtained were different to those obtained by Noël and co-workers due to the different experimental set-up, with the most significant difference being the interelectrode gap and lower electrolyte concentration. Utilising reaction conditions described by Noël and co-workers involving a potentiostatic mode with the potential set at 3.7 V resulted in no observed product our set-up (Table 1, entry 1). Fortunately, the reaction was quickly optimized by employing a parallel plate and performing a set of three reaction conditions in duplicate, thus performing six reactions simultaneously (Fig. 3). Both galvanostatic and potentiostatic modes with a range of currents and potentials were screened (Table 3). The yield dramatically increased to 39% when the potential was lowered to 3.4 V (Table 1, entry 2). The increase in yield is potentially derived from the smaller interelectrode gap in this set-up (5 mm) compared to that used by Noël and co-workers (7 mm).[26] Decreasing the potential further to 3.2 V resulted in an increased 51% yield (Table 1, entry 3). The galvanostatic mode was found to be more efficient with a yield of 58% when applying a constant current of 20 mA (Table 1, entry 4). This yield is comparable to that reported by Noël and co-workers. Finally, given the success of the galvanostatic mode, a further experiment was performed. A constant current of 10 mA was applied for double the time (48 h) to deliver the same number of electron equivalents at a lower potential, though this delivered a decreased yield of 40% (Table 1, entry 5). The successful and fast optimization of this synthetic organic electrochemical reaction by performing six reactions in parallel showcases the bottle reactor's versatility and highlights the requirement for well-characterized experimental set-ups to enable inter-laboratory reproducibility.

Table 1. Rapid screening and optimization of an oxidative coupling of thiols and amines using a parallel plate.



	mode	$E/I_{appl, cell}$	yield 1 (%)	yield 2 (%)	average (%)
1	potentiostatic	3.7 V	<2	-	-
2	potentiostatic	3.4 V	41[a]	37[a]	39[a]
3	potentiostatic	3.2 V	48[a]	54[a] (48)[b]	51[a]
4	galvanostatic	20 mA	56[a]	60[a] (58)[b]	58[a]
5	galvanostatic	10 mA	40[a,c]	-	-

[a] Determined by ^{1}H NMR spectroscopy with the aid of an internal standard. [b] Isolated yield. [c] 48 h reaction time.

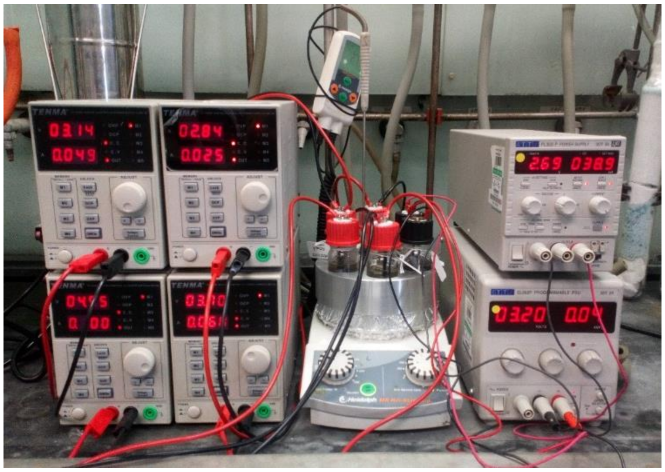


Figure 3. Parallel screening reactions performed to optimize an oxidative coupling of amines and thiols.

Cyclic voltammetry

In addition to a synthetic set-up, the bottle reactor can be used to perform cyclic voltammetry and other analytical experiments. When connected to an external potentiostat and with the use of a reference electrode, high quality voltammograms were obtained. This is achieved by connecting a glassy carbon disk working electrode and platinum wire counter electrode as they would be for synthetic electrochemistry in the bottle reactor. A silver wire, acting as a pseudo-reference electrode, was connected using a standard ¼-28 fitting through one of the ports.[23] Cyclic voltammograms of ligand precursors **L1-5** using ferrocene as an internal standard were obtained in this manner (Fig 4). All the voltammograms showed an irreversible reduction between -1.9 V and -2.5 V vs SCE, corresponding to reduction of the imidazolium salt (Figure 4). In addition **L1**, **L3** and **L4** displayed peaks corresponding to the oxidation of Cl^- and Br^-,[27] with additional peaks being observed for **L4** which are potentially due to oxidation of the allyl groups.[28]

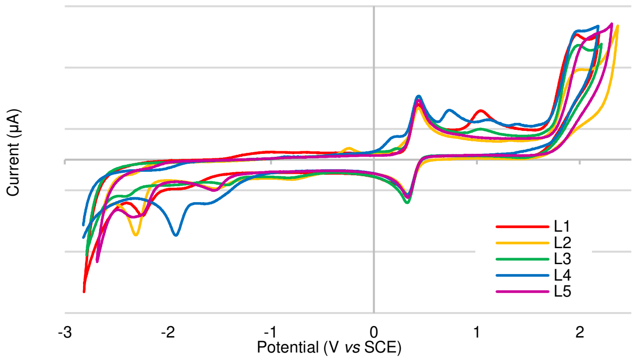


Figure 4. Cyclic voltammograms of imidazolium salts **L1-5** (1 mM). Experiments were performed in MeCN with $TBAPF_6$ as supporting electrolyte (0.1 M). Ferrocene (1 mM) was added as an internal standard. **L1**: red, **L2**: yellow, **L3**: green, **L4**: blue, **L5**: purple.

CONCLUSIONS

A new flexible and standardized electrochemical batch reactor enabling both organic and inorganic transformations and analytical electrochemistry has been designed, developed and tested. This has enabled the synthesis of Cu(I)–, Au(I)– and Fe(II)–NHC complexes as well as an Fe(III)–salen complex. Furthermore, the batch reactor has been used to perform a synthetic organic reaction in conjunction with a parallel plate which allowed six reactions to be screened simultaneously. This allows rapid screening and optimization of reaction conditions. Cyclic voltammetry can be performed in the reactor with the use of an external potentiostat. This allows low concentrations of analyte and high sensitivity to be achieved. The design of this batch reactor is freely available, inexpensive and versatile, enabling a range of synthetic and analytical electrochemistry.

EXPERIMENTAL

Synthesis of metal complexes: General Procedure

A bottle reactor vial was charged with the ligand precursor (1 mmol), then the reactor was assembled with the appropriate electrodes (Cu, Au or Fe) and placed under an atmosphere of argon. MeCN (anhydrous, 15 mL) was added and a constant current of 50 mA for 39 minutes (1.2 F mol^{-1}) was applied from a bench top power supply (Tenma 72-10480 from Farnell). A sample of 0.5 mL was taken at the end of the reaction and filtered through Celite (under an inert atmosphere when the complexes were not air stable; **Cu3**, **Cu4** and **Au3**), after which the solvent was removed under reduced pressure. The resultant solid was redissolved in a suitable deuterated solvent and analyzed using ^1H NMR spectroscopy. Integrals for the complex and ligand were used to calculate the conversion.

Oxidative coupling of thiols and amines: General Procedure

A bottle reactor vial was charged with tetramethylammonium tetrafluoroborate (32 mg, 0.2 mmol), MeCN (15 mL) and aqueous HCl (0.3 M, 5 mL). Then cyclohexylamine (0.345 mL, 3 mmol) and thiophenol (0.205 mL, 2 mmol) were added. The bottle reactor lid was fitted with an IKA graphite anode and an IKA stainless steel cathode and a potential difference was applied for the specific time (potentiostatic or galvanostatic). After completion the reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure to deliver the crude product as a light brown oil. To that 2,4,6-trimethoxybenzene (internal standard, 112 mg, 0.66 mmol) and $CDCl_3$ (3 mL) were added to form a homogeneous solution which was analyzed by ^1H NMR spectroscopy. The sample was further purified *via* flash column chromatography (silica gel, 0-20% EtOAc in hexane) to deliver the product as an off-white solid.

Cyclic voltammetry

Cyclic voltammetry of **L1-5** was performed at room temperature in the bottle reactor using a Metrohm, DropSens, μSTAT 400 potentiostat and data acquired with DropView 8400 software. Experiments were performed in anhydrous, degassed MeCN (1 mM), Bu_4NPF_6 (0.1 M) supporting electrolyte (scan rate of 300 mV s^{-1}), with a Metrohm glassy carbon disk (1 mm) working electrode, platinum wire counter electrode, and silver wire pseudo-reference electrode. Ferrocene (Fc) was added as an internal standard (1 mM, Fc^+/Fc at +0.380 V vs SCE) to reference experiments.

ASSOCIATED CONTENT

The following files are available free of charge:

Supporting information. Bottle reactor design, experimental methods and characterisation (PDF)

Crystallographic information (CSD #1987952).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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