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Electrochemical flow-reactor for expedient synthesis of copper–N-heterocyclic carbene complexes†

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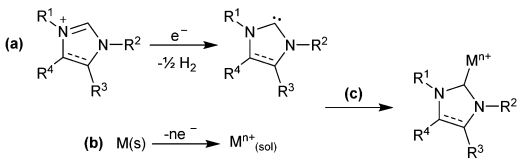
An electrochemical flow-cell for highly efficient and selective generation of Cu^{I}–N-heterocyclic carbene complexes under neutral and ambient conditions is reported. The feasibility of the flow-cell is demonstrated through the electrochemical synthesis of [Cu(IMes)Cl] and subsequent *in situ* flow directly into hydrosilylation reactions, with equal efficiency to the purified catalyst.

Since their isolation in 1991,[1] N-heterocyclic carbenes (NHCs) have become ubiquitous in organometallic chemistry and catalysis, including hydrogenation, hydrosilylation, cross-coupling reactions and olefin metathesis.[2–5] In recent years, metal–NHCs have also shown significant promise in biomedicine, particularly within the fields of antimicrobials and cancer chemotherapy.[6–8] The most common synthetic methods to prepare metal–NHCs use imidazolium salt precursors and often require the use of strong bases and strict inert conditions, or the use of basic metal precursors (*e.g.* Ag_2O).[9–12] The major disadvantages of these routes include the generation of unstable intermediates, formation of undesirable side-products and incompatibility with base-sensitive substituents. Chen and co-workers reported a simple and practical procedure for the production of metal–NHCs using *N*-pyridine or *N*-pyrimidine substituted imidazolium salts and metal plates.[13] We reported a valuable extension to this model by using ligands that do not comprise a pendant donor arm, to produce selectively both neutral and cationic complexes.[14] As basic conditions are not necessary, the route was found to be compatible with base-sensitive substituents, thus significantly widening the range of NHCs that may be developed. During the electrochemical reaction, an imidazolium ion (electrolyte) is reduced at the cathode, releasing H_2 to form a free NHC. Concomitantly, oxidation of the sacrificial copper anode occurs, liberating Cu^{+} ions into solution. These two species combine to deliver the desired Cu–NHC complex (Scheme 1).



Scheme 1 Electrochemical synthesis of metal–NHC complexes: (a) reduction of imidazolium to a free NHC; (b) oxidation of metal; (c) combination of NHC and metal.

Practical issues associated with the electrochemical batch process exist: (i) a large overpotential is required due to inefficient mass-transfer between the electrode surfaces; (ii) Faradaic efficiency tends to be low (Q generally >2). These problems can be overcome by moving into continuous mode, making the technology more accessible for academic, industrial and clinical use. An electrochemical microreactor for the synthesis of organic compounds in flow has previously been reported.[15] Herein, we report the design, construction and optimisation of an electrochemical flow-reactor for the synthesis of both neutral heteroleptic and cationic homoleptic Cu^{I}–NHC complexes. To the best of our knowledge, this is the first example of the electrochemical synthesis of metal complexes in continuous flow.

Our first prototype consists of a PTFE linear flow-channel (190 × 4 × 3.5 mm), which supports two parallel copper electrodes (190 × 4 × 0.5 mm) at a separation distance of 2.5 mm (see ESI†). The effective volume of the flow-channel is 1.9 cm^3. Preliminary experiments in MeCN under a N_2 atmosphere indicated that a significant amount of undesired $[Cu(NHC)_2][CuCl_2]$ (**3**) was formed, likely due to the large distance between electrodes and consequently poor mixing between the carbene and $[Cu(NCMe)_4]^{+}$ (Scheme 2). Glass beads (dia. 2.0 mm) were packed into the flow channel in staggered formation to reduce the effective volume of the reactor to 1.05 cm^3 and increase flow velocity. Residence time inside the cell was reduced and the formation of **3** was completely suppressed. All subsequent data recorded in the first flow-cell was therefore with the use of glass beads.

Flow-rate and applied potential were optimised for efficiency and selectivity using a solution of [IMesH]Cl (6.6 mM) in MeCN

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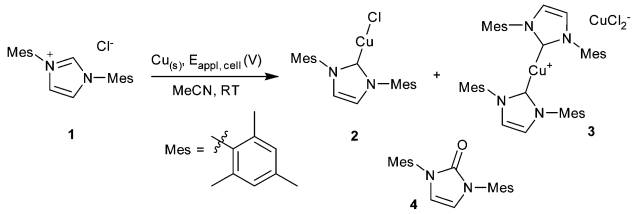


Scheme 2 Concomitant electrochemical reduction/complexation of [IMesH]Cl **1** in flow.

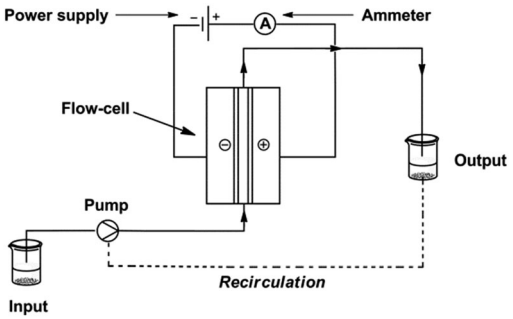


Fig. 1 Schematic diagram for the electrochemical synthesis of **2** in continuous mode.

(Fig. 1). The reduction potential of [IMesH]Cl in MeCN was determined to be −2.32 V (*versus* Fc/Fc^{+}) by cyclic voltammetry (see ESI†). Maximum conversion in single-pass mode was achieved with an applied potential of 2.5 V and flow-rate of 0.5 mL min^{-1} (residence time = 126 seconds), giving Cu(IMes)Cl (**2**) in 36% yield. An insoluble copper species was formed when a voltage ≥3 V was applied, with the current density at 2.5 V being calculated as 0.36 mA cm^{-2} (Table 1). When the concentration of [IMesH]Cl was increased five-fold, a decrease in conversion (25% yield) was observed, indicating that the surface area of the electrode is the limiting factor. Recirculation of the 6.6 mM solution (20 mL, 0.132 mmol) allowed full conversion of **1** to give complex **2** in 92% yield after 80 minutes, a significant improvement on the yield in batch (59%).[14] A small amount of imidazolinone **4** (8%) was observed, presumably as a consequence of air being introduced into the reactor during recirculation. Oxo-adducts of related NHCs have previously been observed, and can be induced from the imidazolium salt using CsOH.[16] The overall Faradaic efficiency of the cell was 98%.

Table 1 Comparison of the electrochemical synthesis of Cu(IMes)Cl (**2**) in first- and second-generation flow-reactors

	1st flow-cell	2nd flow-cell
Single electrode surface area (cm^2)	7.6	40
Distance between electrodes (mm)	2.5	1.0
Applied potential (V)	2.50	1.94
Observed current[a] (mA)	2.7	10.0
Current density (mA cm^{-2})	0.36	0.25
Residence time (s)	126	360
Time to convert 0.132 mmol of **1** to **2** (min)	80.0 (92%)[b]	29.9 (97%)[c]

[a] Registered at steady-state. [b] In recirculation mode. [c] In single-pass mode.

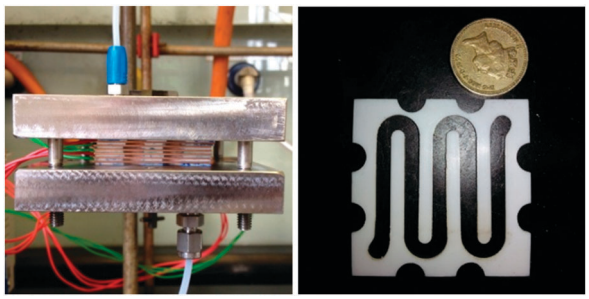


Fig. 2 Photograph of the second-generation electrochemical flow-reactor (left) and the shape of the reactor channel through a 1 mm thick Teflon spacer (right).

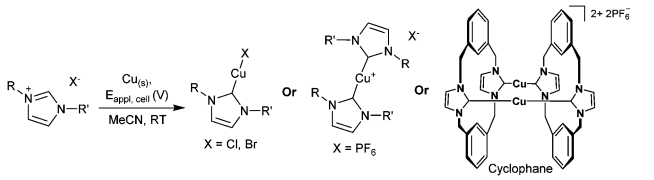
To further increase the electrode surface area, a second modular reactor design was developed. Six square copper plates (50 × 50 × 1 mm), separated by five PTFE spacers (1 mm thickness cut with a 4 mm wide and 200 mm long flow channel) were assembled as shown in Fig. 2. The copper plates alternate between cathode and anode to provide five consecutive parallel-plate electrochemical flow-reactors. This design allows reactor metrics (channel length, width, electrode separation, interfacial area and reactor volume) to be optimised as required. The short distance between electrodes and the tailored channel shape minimise the diffusive ion path-length and cell resistivity, whilst optimising current density. The second flow-cell had a total volume of 4.0 mL, and the surface areas of the anode and cathode electrodes were 40 cm^2 each.

Experimental evaluation of the revised flow-cell provided significant improvements in both the electrochemical output and selectivity. At 1.94 V and 0.67 mL min^{-1} (residence time = 360 seconds), a yield of 94% of complex **2** was achieved in single-pass mode. Imidazolinone **4** was reduced to 3%, presumably due to reduced distance between the electrodes increasing the rate of formation of Cu(IMes)Cl **2**. The lower potential required highlights the improved efficiency of the second flow-cell, and its capacity to selectively form desired complexes in the presence of redox sensitive functional groups. The overall reaction time to convert 0.132 mmol of [IMesH]Cl to complex **2** was reduced to 29.9 minutes (20 mL, 0.67 mL min^{-1}, single-pass). A comparison between the performance of the two electrochemical flow-cells is summarised in Table 1.

The versatility of the second-generation flow-cell was examined using a variety of imidazolium precursors (Table 2). These included *N*-substituents with decreased steric bulk (entries 3–6), in addition to base-sensitive allyl and ester *N*-substituents (entries 3–4) and a macrocyclic imidazolium salt (entry 6). Furthermore, imidazolium hexafluorophosphate salts were assessed (entries 2, 5 and 6), which form exclusively cationic homoleptic complexes. A variety of Cu^{I}–NHC complexes were prepared selectively and in high yields, validating that the optimised cell is suitable for the efficient synthesis of a broad range of Cu^{I}–NHCs.

To demonstrate the synthetic utility of our electrochemical flow-cell, the output stream containing complex **2** (*i.e.* formed in entry 1) in MeCN was introduced directly from the flow-cell into catalytic hydrosilylation reactions of functionalised ketones

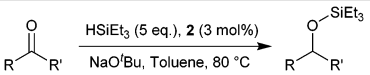
Table 2 Scope of Cu^{I}–NHC complexes prepared under continuous electrochemical conditions in the second-generation flow-cell



	R	R′	X^-	E_{appl} (V)	I^c (mA)	τ_R (min)	Yield[d] (%)
1	Mesityl[a]	Mesityl	Cl	1.94	10.0	29.9	94
2	Mesityl[a]	Mesityl	PF_6	2.54	20.1	20.0	93
3	Picolyl[a]	Allyl	Br	2.20	19.3	6.7	91
4	Methyl[a]	$CH_2CO_2{}^tBu$	Cl	2.40	31.0	13.3	95
5	Benzyl[a]	Benzyl	PF_6	2.95	28.7	20.0	94
6	Cyclophane[b]		PF_6	4.90	74.4	300	95

[a] In single-pass mode. [b] In recirculation mode. [c] Registered at steady-state. [d] Analysed by ^{1}H NMR spectroscopy.

Table 3 Hydrosilylation reactions using catalyst **2** directly from the electrochemical flow-cell



R	R′	Time[a] (h)	Yield[a,b] (%)	Time[c] (h)	Yield[b,c] (%)
Cyclohexyl	Cyclohexyl	2	97	2	98
2-Furyl	Methyl	6	95	6	94
2-Thiophenyl	Methyl	6	97	6	97
2-Pyridyl	Methyl	6	94	6.5	90
2-Chlorophenyl	Methyl	5	97	6	98

[a] Using catalyst from electrochemical flow-cell in MeCN. [b] Isolated yield. [c] Using isolated and purified catalyst **2**.

(Table 3). Near quantitative isolated yields, which were comparable to those reported by Nolan using CuCl/[IMesH]Cl as pre-catalyst, were achieved.[17] Identical reaction conditions using our 'dispensed' catalyst were reproduced using isolated and purified **2** as a catalyst, to provide very similar yields. The shorter reaction times observed by Nolan and co-workers when using *in situ* generated catalysts are likely to be a consequence of the formation of Cu^{I}-bis-NHC complexes. Such complexes were reported to be much more reactive, highlighting the importance of selective complex formation.[17] Our results demonstrate the potential of the electrochemical flow-reactor as an 'on-demand dispenser' of high purity catalyst directly into a reaction without the need for isolation and work-up.

In conclusion, two simple and effective electrochemical flow-reactors have been reported which perform highly selective and efficient syntheses of Cu^{I}–NHC complexes in excellent yields under neutral and ambient conditions. This was achieved through rational design and construction of a flow-cell to maximise interfacial area and mixing of species generated from the two electrodes, which resulted in much more controlled electrochemical conditions. The synthetic utility of the cell has been demonstrated through the preparation of a range of Cu^{I}-mono- and bis-NHCs comprising varying *N*-substituents. In addition, the flow-cell can be used to 'dispense' Cu(IMes)Cl **2** as catalyst directly into catalytic hydrosilylation reactions with virtually no difference in catalytic activity when compared to isolated catalyst.

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