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Electrochemical Generation of *N*-Heterocyclic Carbenes for Use in Synthesis and Catalysis

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Abstract: The electrochemical generation of *N*-heterocyclic carbenes (NHCs) offers a mild and selective alternative to traditional synthetic methods that usually rely on strong bases and air-sensitive materials. The use of electrons as reagents results in an efficient and clean synthesis that enables the direct use of NHCs in various applications. Herein, the use of electrogenerated NHCs in organocatalysis, synthesis and organometallic chemistry is explored.

Keywords: NHCs; Electrochemistry; Synthesis; Catalysis

1. Introduction

Electrochemistry has recently attracted increased attention as a tool in synthetic chemistry, despite it being discovered over a hundred years ago.[1] Electrochemical methods offer a very mild and atom efficient route to achieving selective oxidations and reductions, avoiding the use of harsh and often toxic chemical reducing and oxidizing agents. This often allows complementary pathways to traditional synthetic routes. As electrons are used as reagents, the oxidation or reduction potential can be dialed in, allowing for a highly selective process. A range of user-friendly reactors, both continuous and batch, have been developed and commercial reactors are also available,

making electrochemistry available as a versatile tool in synthetic chemistry.[2]

Since the pioneering work on the isolation and characterization of *N*-heterocyclic carbenes (NHCs) by Arduengo,[3] Bertrand,[4] and Enders[5] 30 years ago, NHCs have attracted considerable interest, particularly in the area of catalysis as both organocatalysts[6] and as ligands in metal catalysts.[7] Among other methods, NHCs are typically synthesized from the corresponding azolium salt, such as imidazolium, thiazolium and triazolium salts, via deprotonation with base (Scheme 1A).[6b] As structurally diverse azolium salts can easily be prepared, this enables access to a vast library of NHC analogues.[6g,8]

Electrochemistry has been used for the synthesis of NHCs as a selective and mild alternative to chemical

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methods (Scheme 1B).[9] Electrochemistry enables the in situ generation of a desired NHC concentration that is controlled by the current and total charge transferred into the reaction mixture. As NHCs are most often produced chemically via base deprotonation of the corresponding azolium salt, base sensitive groups

Scheme 1. Synthesis of NHCs, **A**: traditional chemical methods; **B**: electrochemical synthesis.[6b]

the NHC precursor in electrochemical synthesis results in a very clean reaction mixture as no further reactant or electrolyte is needed, simplifying downstream processes and purification.

Depending on the application, the electrochemical NHC synthesis might be followed by the addition of reagents for a subsequent synthesis. This allows the use of substrates that are not stable under the electrochemical conditions, i.e. when the reduction potentials overlap. In addition, the separation of the NHC production and a synthesis step allows for easy distribution of the NHC into several parallel reactor vessels.

A typical reaction setup constitutes two electrodes submerged into the reaction solution connected to a power supply unit. Modification to include a reference electrode or to separate anodic and cathodic reactions with a membrane are possible.[1o,2a,2h] Continuous electrochemical reactors have also been developed.[1s–u,2i,m,20,2p]

2. Electrochemical Synthesis of NHCs

The reduction potential of NHCs is highly dependent on the nature of the azolium salt, in addition to other factors such as the solvent. Typical ranges are from -1.5 V to -2.3 V, with the potential correlating to the acidity of the azolium salt (Figure 1).[13] Thiazolium salts (around -1.5 V) are typically more easily reduced than imidazolium salts (lower reduction potential around -2.2 V), as are benzannulated and saturated azolium salts. The substituents play a minor role, with electron rich substituents resulting in slightly higher reduction potentials. Bis-azolium salts are easier to reduce than their corresponding azolium salt indicating a cooperative reduction due to the proximity of the second azolium moiety during reduction of the first.[10] Bis-azolium salts show only one reduction peak and typically produce less stable bis-NHCs. The nature of the spacer between the azolium moieties plays a pivotal role on the stability, with a xylyl spacer resulting in a significantly less stable carbene due to benzylic elimination compared to aliphatic spacers. The oxidation potential of NHCs (potential of the reverse reaction) correlates to their nucleophilicity.[13b] This can be observed using cyclic voltammetry and

within the ligand architecture are typically not tolerated using these synthetic methods. The electrochemical synthesis of NHCs also proceeds from the corresponding azolium salt, but in this case the azolium is reduced to the carbene at the cathode with hydrogen as the only by-product.[10] An electrochemically synthesized NHC is thereby referred to as electrogenerated. The carbene can subsequently react with a substrate or with a metal to form a reaction product or metal complex respectively. At the anode the product depends on the reaction system, but can be decomposition of the solvent, oxidation of the counterion, or oxidation of a sacrificial anode to release metal ions. For example, Xiao and Johnson demonstrated that the tetrafluoroborate counterion is degraded to BF_3 and F_2 gas.[11] The direct electrochemical synthesis of metal complexes from sacrificial anodes has also been reported.[12] Using the corresponding azolium salt as
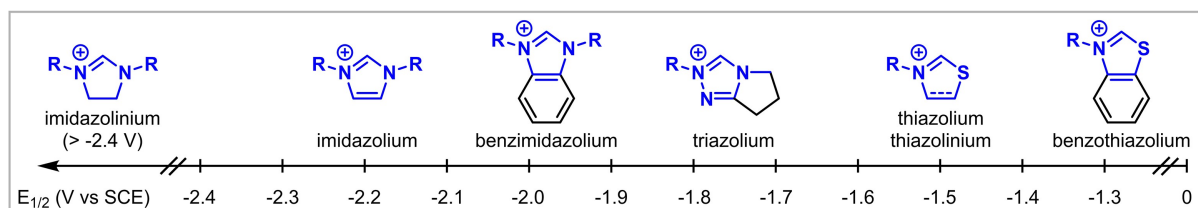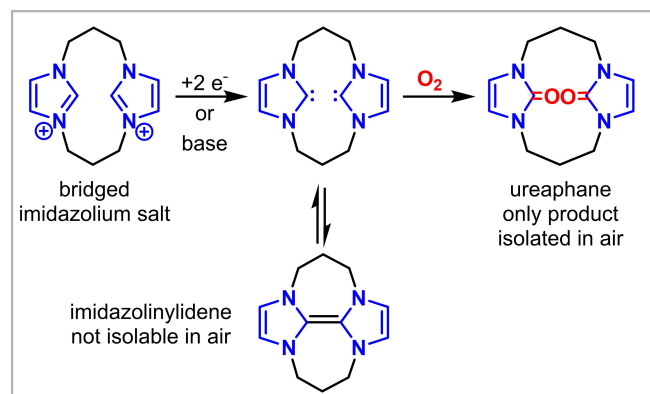

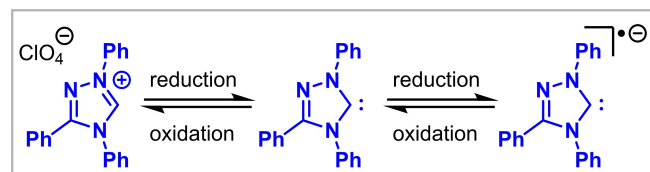**Figure 1.** Typical reduction potentials for azolium salts, in V vs SCE, data from Ogawa and Boydston.[13a]

also gives an indication of the stability of an NHC.[13b,30d]

The electrochemical reduction of an azolium salt was first demonstrated by Hünig and co-workers in 1973.[14] The authors synthesized a range of cyclic bridged azolium salts, with subsequent electrochemical ylidene formation to investigate the redox couples using absorption spectra. This was further investigated by Shi and Thummel using cyclic bridged imidazolium salts. Deprotonation using a base afforded ureaphanes (bridged imidazolones, through the NHC reacting with oxygen) instead of the desired imidazolinylidenes.[15] The authors propose the imidazolinylidene intermediate to be in equilibrium with the bis-NHC and performed the electrochemical synthesis as an alternative access to NHCs under inert conditions. This yielded the desired imidazolinylidenes, which slowly degraded to the ureaphane in air (Scheme 2).

In 1994, Fuller and Carlin investigated 1,3-bis-(4-methylphenyl) imidazolium chloride.[16] The authors performed cyclic voltammetry on the imidazolium salt in anhydrous THF and observed a reduction peak at -2.32 V vs Ag/Ag$^+$ and two oxidation peaks at -0.89 and -0.54 V, which the authors attributed to the reduction of the imidazolium salt and oxidation of one or two resulting products. These resulting products were unstable, as seen in the reduced intensity of the peaks, and the authors speculated that one of the peaks might have been a degradation product. However,

Enders later showed that some NHCs can be further reduced to the anion, so the two observed oxidation peaks may have been NHC and anion oxidation (Scheme 3).[17]

2.1. Electrogenerated NHCs in Organocatalysis

NHCs have emerged as a powerful and versatile tool in organocatalysis.[6] Due to the nucleophilic lone pair on the carbene center, the reactivity of NHCs can be compared to that of Lewis bases.

Most NHC-catalyzed reactions require the addition of the NHC to either an aldehyde or an α,β-unsaturated aldehyde, forming the Breslow intermediate and resulting in an umpolung of the electrophile (Scheme 4).[6c,e,18] The reverse reactivity can then be exploited for further modifications, such as a direct electrophilic attack before releasing the NHC.[6] Typical examples for the direct nucleophilic attack on the Breslow intermediate are benzoin condensation and the Stetter reaction.[6c–e,g,19]

The use of electrogenerated NHCs in synthesis and organocatalysis has largely been dominated by the groups of Feroci, Chiarotto and Inesi.[9,20] Many azolium salts, depending on the *N*-substituents, are liquid at room temperature and can be classified as ionic liquids (IL). ILs have become a popular choice of electrochemical solvent due to the high thermal stability, non-volatility, high polarity, high intrinsic conductivity, wide electrochemical windows and recyclability.[9a,b,d,e,21] In addition, intermediate radicals

Scheme 2. Reduction of bridged imidazolium salt to imidazolinylidenes and further oxidation to ureaphane, reported by Shi and Thummel.[15]

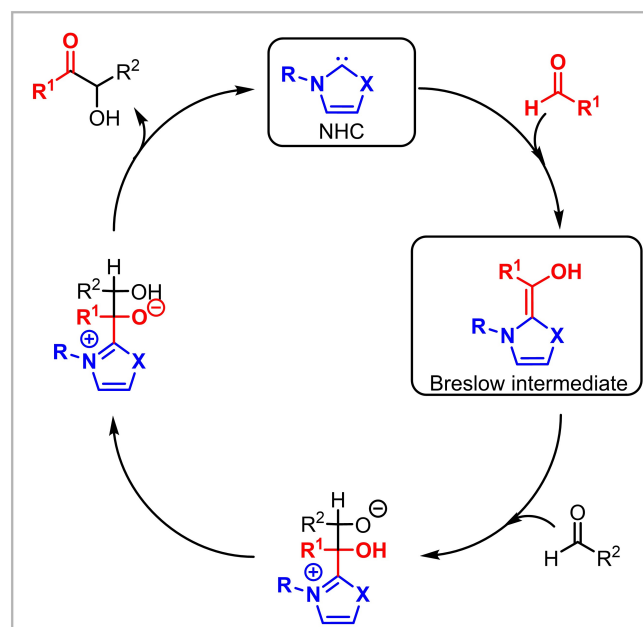**Scheme 3.** Reduction of Enders carbene to radical anion.[17]

Scheme 4. NHC organocatalysis via Breslow intermediate, Benzoin condensation as an example for electrophile addition to the Breslow intermediate.

are often stabilized by the azolium.[9d] Feroci and co-workers therefore perform most of their reactions in the neat azolium salt.[20] Feroci and Inesi first demonstrated the use of electrogenerated NHCs in organocatalysis in 2008 with the synthesis of β-lactams, after already highlighting the benefits of imidazolium-based ILs as reaction solvents in 2007.[9b,e,22] The authors first generated the NHC electrochemically from the IL before adding a bromoamide to the cathodic reaction chamber. In this case the electrogenerated NHC acts as a base to deprotonate the bromoamide, which can then cyclize to the desired 2-azetidinone (Scheme 5).

Feroci and Inesi further demonstrated the use of electrogenerated NHCs as bases in other applications, for example in the Henry reaction and Staudinger reaction.[22b,c,23] The first reported catalytic reaction with electrogenerated NHCs was the Benzoin condensation (Scheme 6A).[24] Orsini *et al.* achieved 85% yield of the desired product in 2 h by first producing 20 mol% of NHC electrochemically through electrolyzing the neat IL for the desired time and then adding benzaldehyde as the substrate. The reaction proceeded with a range of imidazolium salts. The authors compared typical organic solvents used in the electrochemical step (MeCN, DMSO and DMF) to the neat IL and found that the use of organic solvents drastically decreased yields.[29] Since the first reports, Feroci and Inesi have applied their methodology to a range of catalytic reactions, such as the Stetter reaction (via the Breslow intermediate, Scheme 6B),[25] Staudinger reaction (organocatalytic ketene activation, Scheme 6C),[23c,d] (trans-) esterifications including synthesis of lactones (via Breslow intermediate, Scheme 6D and E),[26–27,30] amidation (NHC mediated, via Breslow intermediate, Scheme 6F)[28] in addition to various other applications.[9b,c] In all cases, the NHC is first generated electrochemically by electrolyzing the IL for the time needed to produce the desired amount of NHC before the next substrate is added.

2.2. Electrogenerated NHCs in Synthesis

NHCs are viable building blocks in synthesis, with the use of electrogenerated NHCs having been demonstrated in this area (Scheme 7). Electrogenerated NHCs
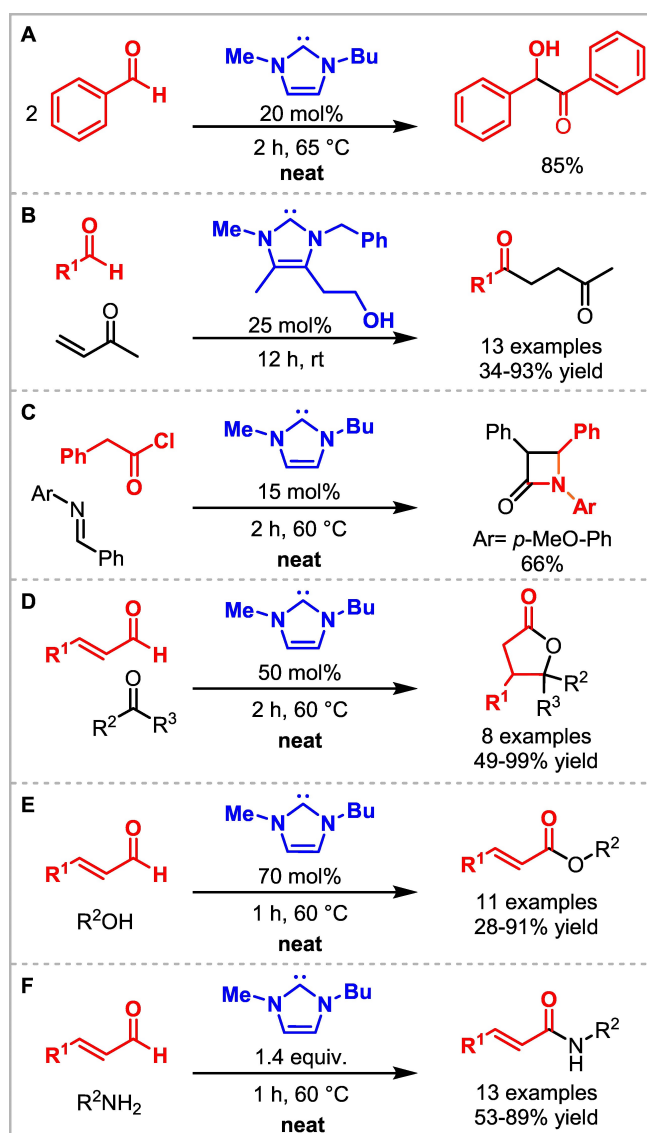
Scheme 6. Catalytic and mediated applications of electrogenerated NHCs by Feroci and Inesi, **A**: Benzoin condensation as the first example of electrocatalytic NHC use;[24] **B**: Stetter reaction;[25] **C**: Staudinger reaction;[23c] **D**: synthesis of lactones via conjugated addition to α,β-unsaturated aldehydes;[26] **E**: esterification of α,β-unsaturated aldehydes with alcohols;[27] **F**: amidation;[28] the moiety in red on the left of each scheme reacts with the NHC.
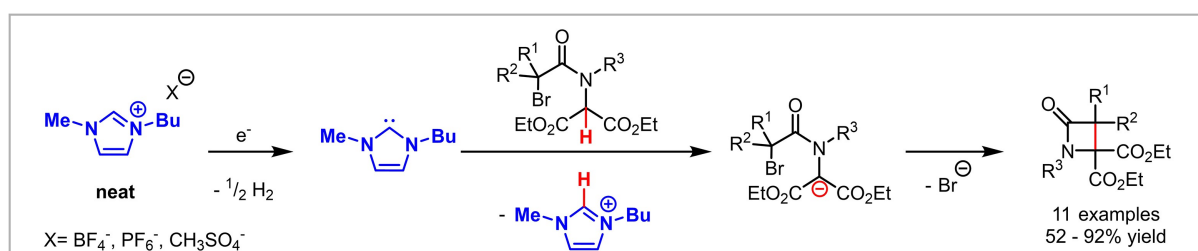
Scheme 5. Cyclization of bromoamides to 2-azetidinone catalyzed by electrogenerated NHCs.[22b,c]
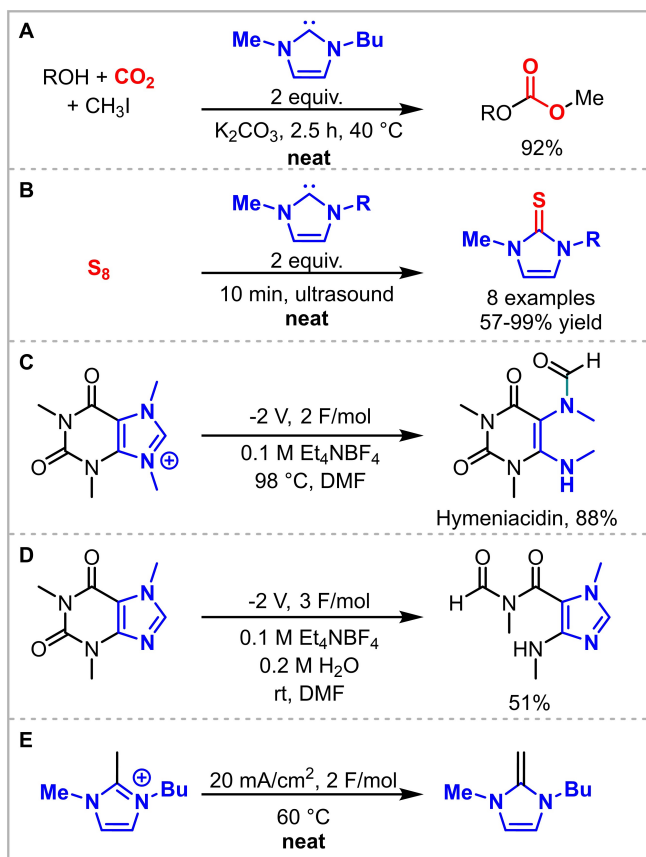
Scheme 7. Applications of electrogenerated NHCs, **A**: CO_2 activation for the synthesis of carbonates;[31a] **B**: Synthesis of imidazole-2-thiones through ultrasound irradiation;[32a] **C**: Electrolysis of 9-methylcaffeinium iodide;[33] **D**: Electrolysis of caffeine;[34] **E**: Electrogeneration of NHOs.[35]

have been used to capture CO_2, with subsequent release upon heating or ultrasound irradiation.[31] Up to ten cycles of catch and release have been demonstrated, resulting in 4 mmol of CO_2 consumed per Faraday.[31c] In addition, the NHC-CO_2 adduct is considerably more stable than the free NHC and can be kept in solution for days without any loss in catalytic activity.[31b,d] Therefore, it can be seen as a viable precursor to the free NHC (Scheme 1A).

The NHC-activated CO_2 has also been used as a building block for the synthesis of carbonates and carbamates (Scheme 7A).[31a,e]

Imidazole-2-thiones have been synthesized from electrogenerated NHCs and elemental sulfur (Scheme 7B).[32] Imidazole-2-thiones can be reduced back to the NHC, making them a common precursor (Scheme 1). The xanthinium salt derived through methylation of caffeine, 9-methylcaffeinium iodide, which has a different electronic structure to imidazolium salts due to the amide backbone, has been investigated.[33] Upon electrochemical reduction, the newly formed NHC is hydrolyzed and ring-opens to

produce the natural product hymeniacidin (Scheme 7C). Caffeine has also been reduced electrochemically, which results in the uracil ring-opening (Scheme 7D).[34] N-Heterocyclic olefins (NHOs), which are very similar to NHCs, have also been generated with base or electrochemically (Scheme 7E).[35] The authors showed through CV experiments, that the electrochemical reduction occurs similarly to the reduction to an NHC, via the C2 radical and concurrent further one electron reduction and loss of H^+. The reactivity of NHOs as a nucleophile and base is comparable to those of NHCs, as demonstrated in a transesterification reaction, however NHOs are typically more stable and exhibit a higher nucleophilicity resulting in a higher reactivity.

2.3. Electrogenerated Metal-NHC Complexes

The generation of metal-NHCs requires a metal precursor and the NHC (Scheme 9).[36] The NHC can be produced in situ (Scheme 8A) or isolated and the metal precursor added to the free NHC (Scheme 8B). The NHC is typically produced from the azolium precursor via deprotonation with a base. Other precursors are also feasible as shown in Scheme 1A. In addition, transmetalation of the NHC from other metals such as copper and silver is possible (Scheme 8C). These methods typically produce stoichiometric by-products from the metal precursor and the base, which can cause problems in downstream processing, and decomposition of the metal complex.[37] Depending on the reaction conditions, in particular the nature of the counterion, a neutral mono-NHC or cationic bis-NHC complex can be formed (only mono-NHC shown in Scheme 8).
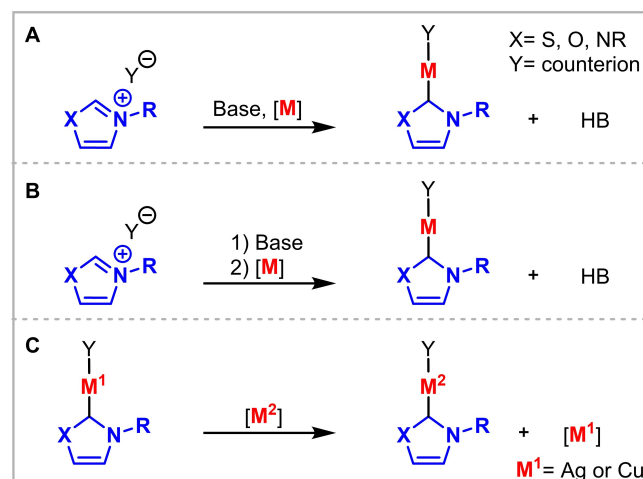
Scheme 8. Synthesis of NHC-metal complexes, **A**: in-situ via base deprotonation; **B**: metal precursor added to free NHC after deprotonation; **C**: transmetalation from silver or copper NHC-complex.
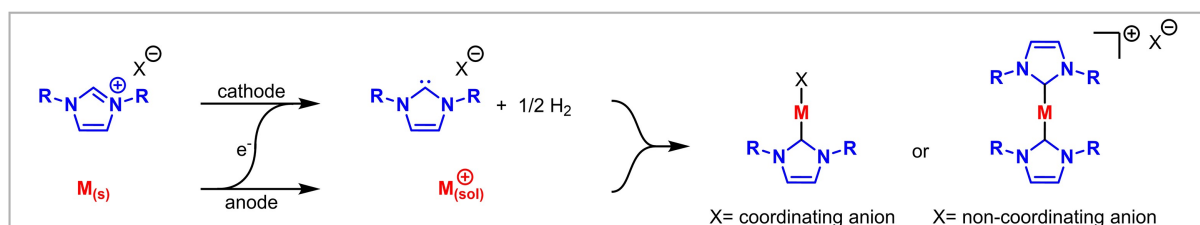
The direct electrochemical synthesis of metal complexes from sacrificial anodes in a solution containing the ligand precursor is simple and avoids the use of other metal precursors and oxidizing agents, which sometimes require another synthetic step.[12] Both the metal cation and the NHC are produced in situ. The cation is produced from the sacrificial anode via oxidation, and the NHC is produced from the corresponding azolium salt via reduction at the cathode, with hydrogen as the only by-product (Scheme 9). The NHC and metal cation then combine to form the metal complex.

There have only been a few reports on the electrochemical generation of metal-NHC complexes, which was pioneered by Chen and co-workers in 2011 (Figure 2A).[38] The authors used sacrificial anodes as the metal source and imidazolium salts bearing N-pyridine or N-pyrimidine substituents as NHC precursors. In this manner, the authors produced 14 metal-

NHC complexes with Cu(I), Cu(II), Ni(II) and Fe(II) and non-coordinating counterions leading to the bis-NHC complexes. This also included bis-imidazolium precursors leading to complexes with several metal centers.

Our group has added a valuable extension to this methodology using ligands that are void of pendant donor arms and that form both cationic bis-NHC complexes and neutral mono-NHC complexes of Cu(I), Au(I) and Fe(II), including ligands bearing base sensitive *N*-substituents (Figure 2B), and Cu(II), Zn(II), Fe(II), Fe(III), Mn(II) and Mn(IV) salen-complexes.[2d,39]

Abbehausen and co-workers synthesized gold(I)-NHC and phosphine complexes electrochemically from the corresponding imidazolium salt or a protonated trialkylphosphine and sacrificial gold electrode (Figure 2C).[40] The authors highlight the direct and

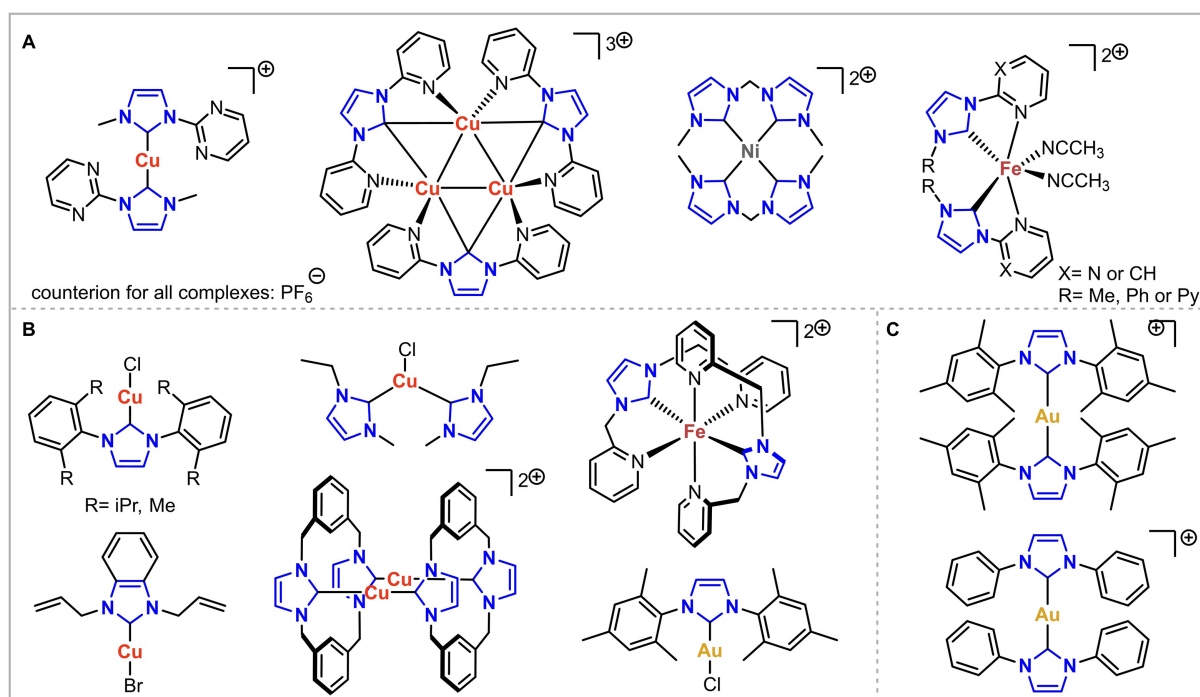**Scheme 9.** Electrochemical synthesis of metal-NHC complexes.

Figure 2. Selected examples of metal-NHC complexes synthesized electrochemically by **A**: Chen and co-workers;[38] **B**: Willans and co-workers;[2d,39] **C**: Abbehausen and co-workers.[40]

clean methodology, avoiding the use of other metal precursors, which might contaminate the final product.

## 2.4. Electrochemical Reactors for Metal-NHC Complexes

In addition to advancing electrochemical methods to metal-NHCs, we have developed a series of electrochemical flow reactors, giving access to mild reaction conditions and high effectivity of the process (Scheme 10A, B, C).[2j,41–42] The first-generation electrochemical flow reactor exhibits a linear channel created by the electrodes. Glass beads were inserted into this channel to ensure sufficient mixing and a Faradaic efficiency of 70% was achieved (0.132 mmol in 80 min). The second-generation electrochemical flow reactor exhibits a larger surface area to volume ratio, by cutting the flow channel into a PTFE spacer that is sandwiched between two electrodes. This eliminates the need for glass beads and increases both the Faradaic efficiency to 92% and the reaction throughput (0.132 mmol in 30 min). The volume of the reactor can easily be modified by stacking more or fewer electrodes and spacers, making the reactor versatile for different applications, reaction times and scales. The third-generation reactor is a scaled down version of the second-generation reactor, to enable electrochemical screening reactions, where smaller scales are desired. Due to the very mild and clean reaction conditions, the reaction solution only contains the imidazolium salt and resulting metal-NHC complex, hence the reaction

mixture could be flowed directly into a catalytic hydrosilylation reaction with no differences in yield compared to when the isolated and purified metal-NHC complex was used (Scheme 10D).[2j]

2.5. Miscellaneous

Other electrochemical syntheses that involve NHCs, but where the NHC is not necessarily produced electrochemically, have been reported. The Breslow intermediate can undergo an oxidation, which can be performed electrochemically, followed by a nucleophilic attack. This method has been applied by Diederich and co-workers who developed an NHC-mediated oxidative electrosynthesis of esters (Scheme 11).[43] The NHC catalyst is initially base generated rather than electrochemically, with the electrochemical step purely being the oxidation of the Breslow intermediate. The authors use a co-enzyme as an electrochemical mediator. Boydston and co-workers further developed this method by directly oxidizing the Breslow intermediate on the anode and expanded the substrate scope to thiols to form thioesters.[44] Brown and co-workers developed a continuous method for the NHC-mediated electrosynthesis of esters and expanded the substrate scope to amines to form amides.[45] The use of a continuous method allowed for mild conditions and a high productivity due to low residence times.

Devillers and co-workers performed a direct C–N coupling to form azolium salts from the corresponding
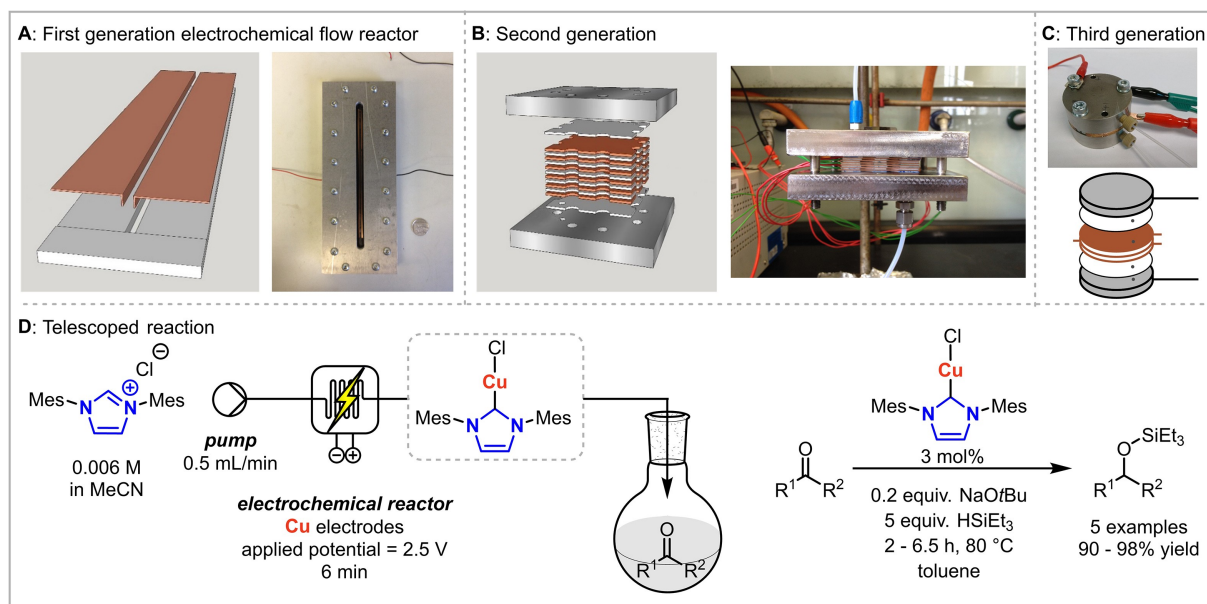
Scheme 10. Electrochemical flow reactors, **A**: single channel first-generation electrochemical reactor;[2j] **B**: parallel plate second-generation electrochemical reactor;[2j] miniaturized third-generation electrochemical reactor;[41] **D**: telescoped electrochemical and catalytic hydrosilylation.[2j]
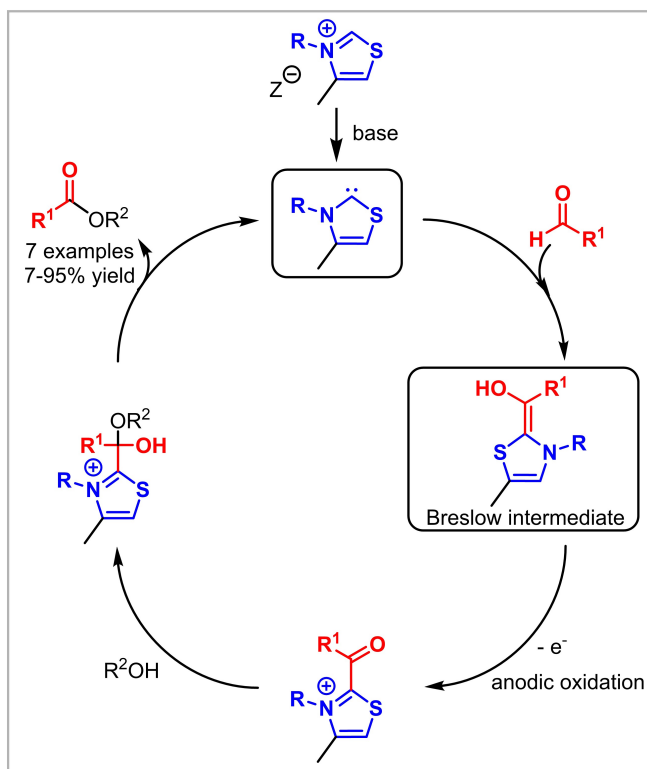
Scheme 11. NHC-mediated electrochemical formation of esters via anodic oxidation of the Breslow intermediate.[43]

Scheme 13. A: Electrochemical synthesis of polymeric imidazolate metal complexes;[48] **B**: Palladium catalyzed electrocarbonylation;[49] **C**: Electrochemical deposition of NHCs on metal surfaces;[51]
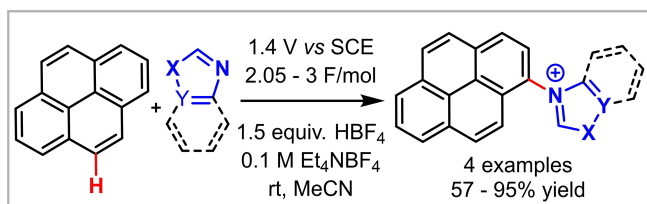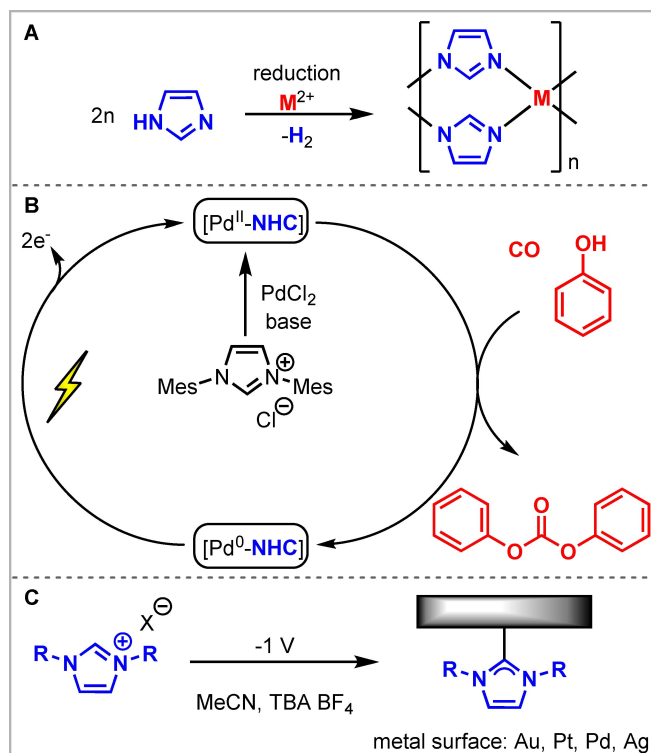
azole and pyrene via anodic C–H activation of the latter (Scheme 12).[46] Importantly, the authors use a divided cell to prevent reduction of the azolium to the NHC. This work was later continued by Yoshida and co-workers who protected imidazoles prior to electrolysis to selectively form mono-substituted imidazoles after deprotection.[47]

Vecchio-Sadus reported the electrochemical reduction of mono-substituted imidazoles and unsubstituted pyrazoles forming metal-imidazolate and -pyrazolate complexes in 1995 (Scheme 13A).[48] In this case, the azolate coordinates through the unsubstituted nitrogen atom giving access to polymeric chelate structures. Even though an NHC is not isolated, this was an important step towards electrogenerated metal-complexes from azoles.

Scheme 12. Electrochemical generation of azolium salts.[46]

Yamanaka and co-workers studied the palladium-catalyzed electrocarbonylation of phenol on gold anodes (Scheme 13B).[49] The NHC acts as a ligand on the palladium catalyst and is formed in situ from the corresponding imidazolium salt via deprotonation.

The palladium-NHC catalyst is then turned over by electricity during the electrocarbonylation. The authors acknowledge that the NHC could also be produced electrochemically but do not investigate this further.

In recent work, Birss and co-workers have demonstrated the use of an NHC decorated Au electrode for the electrochemical detection of the measles virus.[50] The NHC is covalently bonded to the measles antibody, creating a monolayer. The system is then used as an electrochemical biosensor. The authors prepared the Au-NHC via deprotonation of the corresponding imidazolium salt.

The electrochemical deposition of NHCs on a metal surface was first reported by Toste, Gross and co-workers (Scheme 13C).[51] The NHC is generated in situ from the corresponding imidazolium salt via deprotonation with electrogenerated hydroxide from water reduction.

3. Conclusion and Outlook

This review summarizes the use of electrogenerated NHCs in organocatalysis, synthesis and organometallic chemistry. Electrochemistry enables a very mild and selective synthesis of NHCs. As such, it must be considered as an important alternative to traditional synthetic methods. Whilst being complementary to traditional synthetic methods, we do not envisage that electrochemical routes will fully replace chemical methods for the synthesis of NHCs.

The use of synthetic electrochemistry on an industrial scale has already been well established, for example, for the production of adiponitrile.[1e,52] However, the adaption of electrochemistry on small-scale synthetic chemistry remains challenging due to unfamiliarity with the concepts and materials and the need of specialized equipment. Current developments in the field of synthetic electrochemistry will allow more chemists access to electrochemical methods. As such, tutorials[1o,1p] and the advancement of new, user-friendly equipment[2d,53] will catalyze the adoption of electrochemistry as an everyday method in the synthetic laboratory.

The electrogeneration of NHCs will therefore also become more important, as it is a versatile, mild and inexpensive method for a wide range of applications.

Acknowledgements

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