ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 4887–4889

www.rsc.org/chemcomm

COMMUNICATION

Simple and versatile selective synthesis of neutral and cationic copper(I) N-heterocyclic carbene complexes using an electrochemical procedure†

Benjamin R. M. Lake,[a] Emma K. Bullough,[a] Thomas J. Williams,[b] Adrian C. Whitwood,[b] Marc A. Little[a] and Charlotte E. Willans*[a]

Received 7th February 2012, Accepted 6th March 2012
DOI: 10.1039/c2cc30862b

An electrochemical approach for the preparation of copper(I) N-heterocyclic carbene complexes has been developed to include a diverse range of ligand precursors. Importantly, the method is effective for a ligand precursor that contains several acidic protons and for which traditional methods of carbene formation are not suitable.

Over the past two decades, metal complexes of N-heterocyclic carbenes (NHCs) have become extremely important in catalytic processes such as cross-coupling, metathesis, C–H bond activation and polymerisation.[1–7] To a much lesser extent they have been investigated in biomedical applications, showing promise as antimicrobial and as antitumour agents.[8–10] The most common methods for the preparation of metal-NHCs are (i) deprotonation of an imidazolium salt followed by coordination of the free NHC to a metal centre, (ii) deprotonation of an imidazolium salt and coordination *in situ* using a basic metal precursor and (iii) transfer of an NHC ligand from silver.[11–14] The major disadvantages of these routes are the requirement of strong bases and the generation of unstable intermediates which require strict inert conditions, in addition to the generation of undesirable side-products such as silver salts. Furthermore, these routes are not compatible with many ligand precursors, particularly those that possess nitrogen substituents which are base-sensitive. A recently developed route to NHC complexes which does not require base or silver salts involves template synthesis, though this is limited to palladium, platinum and gold.[15]

NHC complexes of copper(I) have significant roles in several important catalytic processes such as cross-coupling reactions, hydrosilylation, amination and reduction of carbonyl compounds.[16–19] Copper(I)-NHCs have also shown significant cytotoxic profiles against various cancer cell lines.[20] The development of these materials for catalysis and biomedicine is of great interest due to the relatively low cost of copper. In addition, it has been shown that copper(I)-NHCs can act as ligand transfer reagents in a manner comparable to silver(I)-NHCs.[21–23] To make them viable, however, routes to their synthesis should be developed to eliminate the strict use of inert conditions, in addition to producing minimum side-products and complexes of high purity. Synthetic routes should also be compatible with a wide array of ligand precursors. A procedure involving the reaction of copper(I) oxide with imidazolium salts has been developed for the preparation of various copper(I)-NHCs (Fig. 1).[24–27] The route avoids the requirement of inert conditions, with the only side-product being water. Imidazolium chloride/bromide salts are used to prepare neutral complexes, though there are many ligand precursors for which this route is not suited, particularly those containing less bulky nitrogen substituents. More recently, an electrochemical method for the preparation of copper(I)-NHC complexes has been reported which uses an imidazolium hexafluorophosphate salt as both the electrolyte and the reactant, and a copper plate as the sacrificial anode.[28] To the best of our knowledge, this methodology is limited to ligands bearing N-pyridine or N-pyrimidine substituents, with cationic complexes of copper being formed. Herein, we report an improved, cheaper and versatile electrochemical method that allows controlled access to copper(I)-NHC complexes where the NHC ligands do not possess a pendant donor arm (Fig. 2). We have prepared both neutral and cationic copper(I)-NHCs using a range of ligand precursors.

The imidazolium chloride salts **1–3** were prepared through glyoxal condensation with N-substituted amines followed by cyclisation with paraformaldehyde (Fig. 2).[29] Imidazolium chloride **4** is commercially available, and imidazolium bromide **5** was prepared through reaction of benzimidazole with benzyl bromide in the presence of a base.[30] Ligand precursor **6** was prepared by addition of 1-methylimidazole to benzyl bromide.[31] Imidazolium bromide **7** was prepared through reaction of α,α′-dibromo-*meta*-xylene with α,α′- diimidazole-*meta*-xylene,[32] and ligand precursor **8** was prepared by reaction

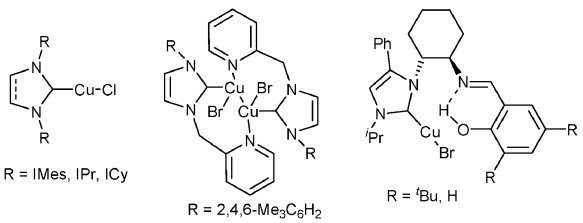


Fig. 1 Copper(I)-NHCs prepared using imidazolium salts with Cu_2O.[24–27]

[a] *School of Chemistry, University of Leeds, Woodhouse Lane, Leeds, LS2 9JT, UK. E-mail: c.e.willans@leeds.ac.uk*
[b] *Department of Chemistry, University of York, Heslington, York, YO10 5DD*

† Electronic supplementary information (ESI) available: Experimental procedures and crystallographic data. CCDC 865136–865140. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc30862b

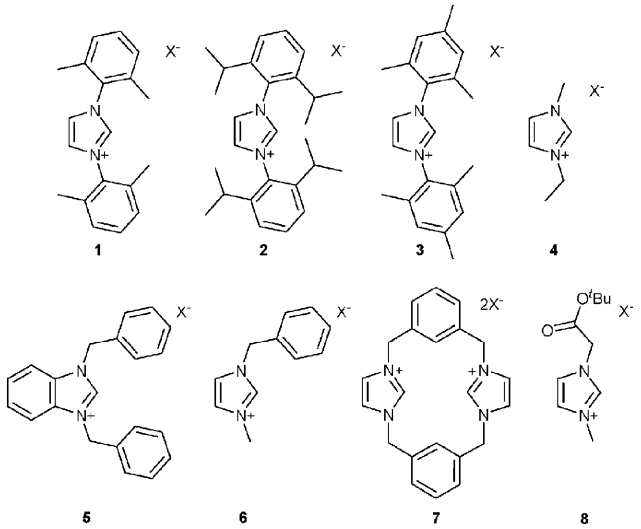


Fig. 2 Imidazolium salts used in the electrochemical study (**a** X = Cl/Br, **b** X = PF_6).

of 1-methylimidazole and *tert*-butyl 2-chloroacetate. The ligand precursors were fully characterised using NMR spectroscopy and mass spectrometry. A characteristic resonance at ~9 ppm in the ^{1}H NMR spectra (DMSO-d_6) is indicative of the (benz)imidazolium C2-proton. The anion was exchanged for hexafluorophosphate using NH_4PF_6 in either water or methanol. The hexafluorophosphate salts precipitated and the isolated solids were fully characterised.

The ligands shown in Fig. 2 were used in the electrochemical synthesis of copper(I)-NHC complexes. The chloride/bromide or hexafluorophosphate imidazolium salts in acetonitrile (1 mmol) were used as the electrolyte. Copper plates (1 × 3 cm) were used as both the sacrificial anode and cathode. At the anode the copper was oxidised to copper(I) and at the cathode the imidazoliums were reduced to free carbenes. The moieties combined in solution to form either Cu(NHC)X, $Cu(NHC)_2X$, or $[Cu(NHC)_2]^+X^-$, with the only side-product being hydrogen. The reactions were monitored by ^{1}H NMR spectroscopy and stopped when >95% conversion was attained. The mixtures were filtered to remove small amounts of copper oxide and metallic copper, and the products were isolated as white or off-white solids. All the complexes shown in Table 1 were characterised by NMR spectroscopy, mass spectrometry and elemental analysis. Solid state structures for several of the novel complexes have been obtained using X-ray crystallography† (Fig. 3). Reaction times are reported in minutes, and in approximate number of Q (total charge) based upon the reported current being maintained throughout the reaction period. This shows that the reactions to prepare cationic complexes take longer than those to prepare neutral complexes.

Using the electrochemical method, we have established that the use of imidazolium salts with a coordinating anion (chloride or bromide) results in the formation of a neutral Cu(NHC)X complex, whereas a non-coordinating anion (hexafluorophosphate) gives a cationic $[Cu(NHC)_2]^+$ complex. Although complexes **1c–3c** and **2d–3d** are known, we have used these ligands to demonstrate that the electrochemical route is compatible with imidazolium salts bearing bulky nitrogen substituents, and with both coordinating and non-coordinating anions. Complex **1d** is novel and exhibits the

Table 1 Electrochemical synthesis of Cu(I)-NHC complexes

Ligand	Complex	Time (mins)	Time (Q)	Current (mA)	Yield (%)
1a X = Cl	**1c** Cu(NHC)Cl	120	4	50	44
2a X = Cl	**2c** Cu(NHC)Cl	80	3	60	62
3a X = Cl	**3c** Cu(NHC)Cl	19	1	50	59
4a X = Cl	**4c** $Cu(NHC)_2Cl$	60	2	60	[a]
5a X = Br	**5c** Cu(NHC)Br	45	1.5	50	68
6a X = Br	**6c** Cu(NHC)Br	60	2	50	67
8a X = Cl	**8c** Cu(NHC)Cl	60	2	50	48
1b X = PF_6	**1d** $[Cu(NHC)_2]^+[PF_6]^-$	200	5	40	36
2b X = PF_6	**2d** $[Cu(NHC)_2]^+[PF_6]^-$	300	10	50	42
3b X = PF_6	**3d** $[Cu(NHC)_2]^+[PF_6]^-$	220	14	100	74
5b X = PF_6	**5d** $[Cu(NHC)_2]^+[PF_6]^-$	330	11	50	64
6b X = PF_6	**6d** $[Cu(NHC)_2]^+[PF_6]^-$	150	5	50	58
7b X = PF_6	**7d** $[Cu(NHC)]_2^{2+}2[PF_6]^-$	880	5.5	10	72

[a] Due to the air sensitive and oily/sticky nature of **4c**, an accurate yield could not be obtained.

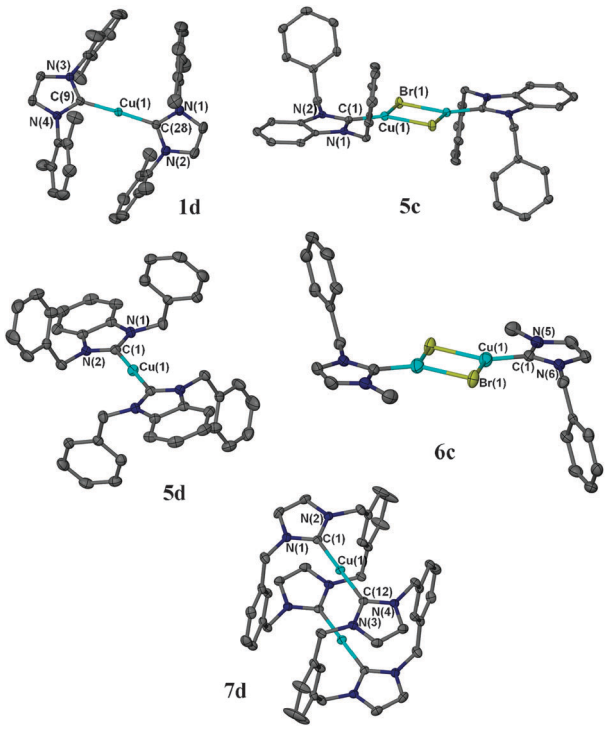
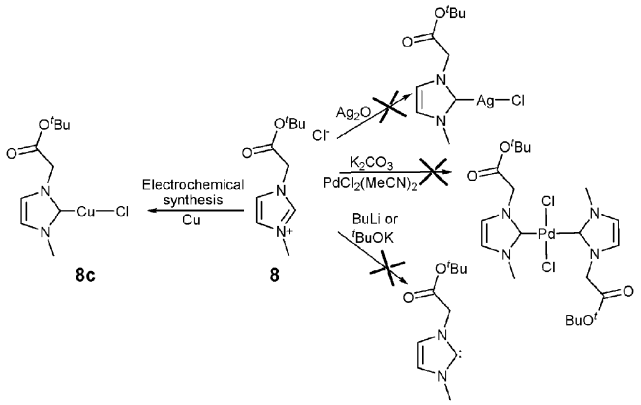


Fig. 3 Solid-state structures with selected bond distances (Å) and angles (°) of **1d** $[Cu(NHC)_2]^+$ (C(9)–Cu(1) 1.8918(17), C(9)–Cu(1)–C(28) 177.55(7)), **5c** $[Cu(NHC)Br]_2$ (C(1)–Cu(1) 1.914(3), C(1)–Cu(1)–Br(1) 125.58(8)), **5d** $[Cu(NHC)_2]^+$ (C(1)–Cu(1) 1.9066(15), C(1)–Cu(1)–C(1) 180.00(7)), **6c** $[Cu(NHC)Br]_2$ (C(1)–Cu(1) 1.932(6), C(1)–Cu(1)–Br(1) 127.94(18)) and **7d** $[Cu(NHC)]_2^{2+}$ (C(1)–Cu(1) 1.8966(17), C(1)–Cu(1)–C(12) 178.45(7)) (ellipsoids are shown at 50% probability, hydrogen atoms and PF_6^- anions are omitted for clarity).

expected near-linear geometry around the copper centre, with a C–Cu–C bond angle of 177.55° (Fig. 3). Complex formation using non-bulky nitrogen substituents is generally more problematic due to the instability of the 'unprotected' carbene centre. Using ligand precursors **4–8**, we have shown that copper(I)-NHCs with non-bulky nitrogen substituents can be easily prepared using this methodology. Ligand **4** possesses the particularly small methyl and ethyl substituents. The mass spectrometry data for **4c** indicates that two NHC ligands coordinate to the metal centre.



Scheme 1 Routes attempted to prepare an NHC of ligand **8**.

The complex is stable under an inert atmosphere and, upon exposure to air, turns green. The structures of **5c** and **6c** illustrate that these complexes exist as bromide-bridged dimers in the solid state, with the geometry around the copper centres being distorted trigonal planar (Fig. 3). The benzyl substituents are able to bend away from the metal centre, exposing it to dimerisation, and rendering these substituents 'non-bulky'. The structure of **5d** exhibits the expected bis-NHC cation with a linear copper centre. The benzyl units point up on one side of the copper and down on the opposite side, with π–π interactions between neighbouring benzyl rings.

Using the imidazolium salt **7b**, the novel macrocycle $[Cu(NHC)]_2^{2+}2[PF_6]^-$ (**7d**) has been prepared *via* the electrochemical route. The solid-state structure of **7d** is similar to that of the analogous gold and silver complexes, with the benzyl unit pointing towards the copper centre on one side, and away from the copper centre on the opposite side.[33,34] The copper centres are near-linear with normal copper-carbene bond lengths.

Imidazolium salts bearing ester substituents are of interest to our group for the preparation of NHC complexes for biomedical applications. Traditional routes to complex formation (deprotonation using various bases, reaction with different basic metal precursors *etc.*) using ligand **8** have, however, been unsuccessful to date (Scheme 1). Under basic conditions, the imidazolium C2-proton remains protonated, and it appears that the base reacts with the protons of the methylene bridge. This is indicative of the methylene protons being more acidic than the imidazolium C2-proton. Using the electrochemical method, we have prepared a neutral copper(I) complex of the ester-substituted ligand **8**. Deprotonation occurs only at the C2-site to prepare complex **8c** in high-purity. This finding will significantly extend the range of NHC ligands that can be explored in the field to include nitrogen substituents that are base-sensitive.

In summary, we have reported the versatility of an electrochemical method for the preparation of both neutral and cationic copper(I)-NHC complexes. We have used a range of monodentate and bidentate imidazolium and benzimidazolium salts with different nitrogen substituents (bulky and non-bulky) to prepare both known and novel complexes. Crucially and for the first time, we have shown that the method is compatible with an imidazolium salt that contains a range of acidic protons. Traditional methods of metal-NHC formation are not possible with these types of ligand due to the necessary requirement for basic conditions. The procedure is simple, clean and generally high-yielding and will be attractive as a general method for the preparation of copper(I)-NHCs, including with the use of base-sensitive ligand precursors. The methodology is being extended to other metals in our laboratory through the use of different metal electrodes.

The authors gratefully acknowledge the Royal Society, the School of Chemistry in Leeds and BP for financial support.

Notes and references

1 W. A. Hermann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290.
2 V. Dragutan, I. Dragutan, L. Delaude and A. Demonceau, *Coord. Chem. Rev.*, 2007, **251**, 765.
3 E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768.
4 J. A. Mata, M. Poyatos and E. Peris, *Coord. Chem. Rev.*, 2007, **251**, 841.
5 N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440.
6 R. Corberan, E. Mas-Marza and E. Peris, *Eur. J. Inorg. Chem.*, 2009, 1700.
7 A. John and P. Ghosh, *Dalton Trans.*, 2010, **39**, 7183.
8 A. Kascatan-Nebioglu, M. J. Panzner, C. A. Tessier, C. L. Cannon and W. J. Youngs, *Coord. Chem. Rev.*, 2007, **251**, 884.
9 M.-L. Teyssot, A.-S. Jarrousse, M. Manin, A. Chevry, S. Roche, F. Norre, C. Beaudoin, L. Morel, D. Boyer, R. Mahiou and A. Gautier, *Dalton Trans.*, 2009, 6894.
10 L. Meres and M. Albrecht, *Chem. Soc. Rev.*, 2010, **39**, 1903.
11 W. A. Herrmann and C. Köcher, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2162.
12 D. Bourissou, O. Guerret, F. P. Gabbaï and G. Bertrand, *Chem. Rev.*, 2000, **100**, 39.
13 I. J. B. Lin and C. S. Vasam, *Coord. Chem. Rev.*, 2007, **251**, 642.
14 C. E. Willans, K. M. Anderson, M. J. Paterson, P. C. Junk, L. J. Barbour and J. W. Steed, *Eur. J. Inorg. Chem.*, 2009, 2835.
15 A. S. K. Hashmi, C. Lothschütz, C. Böhling, T. Hengst, C. Hubbert and F. Rominger, *Adv. Synth. Catal.*, 2010, **352**, 3001.
16 S. Díez-González and S. P. Nolan, *Synlett*, 2007, 2158.
17 S. Díez-González and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 349.
18 C. Munro-Leighton, S. A. Delp, E. D. Blue and T. B. Gunnoe, *Organometallics*, 2007, **26**, 1483.
19 C. Munro-Leighton, S. A. Delp, N. M. Alsop, E. D. Blue and T. B. Gunnoe, *Chem. Commun.*, 2008, 111.
20 M. L. Teyssot, A. S. Jarrousse, M. Manin, A. Chevry, S. Roche, F. Norre, C. Beaudoin, L. Morel, D. Boyer, R. Mahiou and A. Gautier, *Dalton Trans.*, 2009, 6894.
21 G. Venkatachalam, M. Heckenroth, A. Neels and M. Albrecht, *Helv. Chim. Acta*, 2009, **92**, 1034.
22 M. R. L. Furst and C. S. J. Cazin, *Chem. Commun.*, 2010, **46**, 6924.
23 X. Liu, R. Pattacini, P. Deglmann and P. Braunstein, *Organometallics*, 2011, **30**, 3302.
24 C. A. Citadelle, E. L. Nouy, F. Bisaro, A. M. Z. Slawin and C. S. J. Cazin, *Dalton Trans.*, 2010, **39**, 4489.
25 J. Chun, H. S. Lee, I. G. Jung, S. W. Lee, H. J. Kim and S. U. Son, *Organometallics*, 2010, **29**, 1518.
26 A. A. D. Tulloch, A. A. Danopoulos, S. Kleinhenz, M. E. Light, M. B. Hursthouse and G. Eastham, *Organometallics*, 2001, **20**, 2027.
27 S. Simonovic, A. C. Whitwood, W. Clegg, R. W. Harrington, M. B. Hursthouse, L. Male and R. E. Douthwaite, *Eur. J. Inorg. Chem.*, 2009, 1786.
28 B. Liu, Y. Zhang, D. Xu and W. Chen, *Chem. Commun.*, 2011, **47**, 2883.
29 L. Jafarpour, E. D. Stevens and S. P. Nolan, *J. Organomet. Chem.*, 2000, **606**, 49; X. Bantreil and S. P. Nolan, *Nat. Protoc.*, 2010, **6**, 69.
30 H. V. Huynh, L. R. Wong and P. S. Ng, *Organometallics*, 2008, **27**, 2231.
31 J. Haider, K. Kunz and U. Scholz, *Adv. Synth. Catal.*, 2004, **346**, 717.
32 M. V. Baker, M. J. Bosnich, D. H. Brown, L. T. Byrne, V. J. Hesler, B. W. Skelton, A. H. White and C. C. Williams, *J. Org. Chem.*, 2004, **69**, 7640.
33 P. J. Barnard, M. V. Baker, S. J. Berners-Price, B. W. Skelton and A. H. White, *Dalton Trans.*, 2004, 1038.
34 M. V. Baker, D. H. Brown, R. A. Haques, B. W. Skelton and A. H. White, *Dalton Trans.*, 2004, 3756.