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Dial-a-base mechanochemical synthesis of N-heterocyclic carbene copper complexes†

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Liquid assisted ball milling of [NHC]HBr (NHC = N-heterocyclic carbene) salts with copper(ı) chloride, and a range of alkali metal complexes was shown to efficiently produce (NHC)CuX (NHC = normal or RE-NHC, X = halide, alkoxide, amide, alkyl, aryl; RE-NHC = ring-expanded NHC).

Mechanochemistry continues to revolutionise fields from organic synthesis[1] to polymer chemistry.[2] Its impact is also increasingly evident in the area of organometallic synthesis, with ball milling providing access to both unprecedented new motifs and widespread utility reagents.[3] Ball milling has numerous attractive properties from a green chemistry perspective; it results in significantly reduced solvent demand and can reduce energy costs in terms of heating and lower reaction times.[4] Another key approach to maximising sustainability is catalysis. N-heterocyclic carbene (NHC) copper alkoxides are widely implicated as precatalysts in a huge swathe of reactions.[5] Moreover, the ring-expanded NHC (RE-NHC) 6-Dipp has been found to be a privileged motif in isolating and structurally characterising a wide range of interesting copper complexes. Routes to these generally start from (6-Dipp)CuOtBu and have provided access to an isolable NHC-copper hydride dimer,[6] a range of highly stable NHC-copper boryls,[7–9] as well as a copper formimidoyl,[10] copper phosphide,[11] copper stannyl,[12] and copper germyl,[13] amongst others.

Synthetic access to NHC-copper complexes has been the subject of intensive study. Initial work employed strong bases such as NaH or NaOtBu to generate the corresponding free carbene from a carbene salt, followed by addition of CuCl. Subsequent work showed that Cu_2O could do double duty as both the copper source and a "built-in base".[14] Most recently,

generation of a metallate, [NHC-H][CuClX], *via* reaction of the NHC precursor salt with CuCl, and subsequent deprotonation by a weak base has been established as a widely applicable solution-based route to (NHC)CuCl systems.[15,16] This strategy is attractive as it is tolerant to air, and exploits inexpensive bases such as potassium carbonate. Alongside a single report of a microwave assisted weak base method,[17] access to RE-NHC systems relies on the strong base approach. For example, synthesis of (6-Dipp)CuCl generally occurs *via* the deprotonation of [6-Dipp]HCl with NaHMDS followed by addition of CuCl. Access to (6-Dipp)CuOtBu can then be achieved *via* the addition of the corresponding alkali metal alkoxide[6] or, alternatively, CuCl can be replaced by CuMes in the first step to provide (6-Dipp)CuMes which is then a competent base towards *tert*-butanol.[18]

Mechanochemical approaches have contributed to the synthesis of NHC-copper(ı) systems. An initial report by Lamaty validated formation of (NHC)CuCl systems from metallic copper and the corresponding [NHC]HCl salt by ball milling under air.[19] They also reported mechanochemical transmetallation of NHC-silver complexes to copper.[20] Cazin and co-worker reported that ball milling an appropriate carbene precursor salt plus copper(ı) chloride with subsequent addition of potassium carbonate provided access to (NHC)CuCl systems.[21] This extension of their well-established "weak base" method[22] tolerated a range of 5-membered saturated and unsaturated NHCs encompassing imidazolin-2-ylidene, imidazolidin-2-ylidene, and triazolylidene systems. They showed the reaction could be scaled to generate 5 g of (IPr)CuCl in good yields, and subsequently to a range of metals.[23] Expanding on this work, Teichert and co-workers showed that K_3PO_4 provided similar access to (NHC)CuCl systems.[24] They further noted that strong bases such as NaOtBu, NaHMDS and NaH provided no desired product in the first two cases and an intractable mixture containing the targetted (NHC)CuCl in the third instance under mechanochemical conditions.

Cognisant of the fact that, thus far, no group have described a mechanochemical synthesis of RE-NHC copper complexes, and that a direct route to systems where the copper is bound to a range of anionic ligands other than chloride

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would be useful, we sought to develop a "Dial-a-Base" method as a means of general access to (NHC)CuX (NHC = normal or RE-NHC, X = halide, alkoxide, amide, alkyl, aryl). Using the synthesis of (6-Dipp)CuOtBu as a model system, we initially investigated the addition of 3 equivalents of KOtBu to a pre-ground mixture of [6-Dipp]HCl and CuCl followed by ball-milling. This gave conversion to the desired product, albeit contaminated with significant amounts of free 6-Dipp. A switch to liquid assisted grinding (toluene, $\eta \approx 0.5$) provided complete conversion by NMR and a 77% yield of (6-Dipp) CuOtBu. As workup was performed by extraction into toluene, filtration, and removal of all volatiles we settled on a slurrying regime ($\eta \approx 5$) as our optimised conditions as doing so provided no deleterious effects on yield, but greatly facilitated work-up providing an 83% isolated yield. We extended these conditions to a range of 5-, 6- and 7-membered NHCs which provided moderate to good yields in all cases on a synthetically useful 2 mmol scale (Scheme 1, **1–3**).

Conscious of the dual role played by the KOtBu in this reaction, we then set out to extend the range of bases exploited in the reaction, once again focussing on the 6-Dipp ligand. Exploitation of NaOMe provided access to an additional alkoxide, (6-Dipp)CuOMe, **4**, in marginally reduced yields. The use of KOH failed to provide the 6-Dipp analogue of Nolan's cuprous synthon, (IPr)CuOH,[25] which we attribute to the effect of water on RE-NHCs. The reaction tolerated KHMDS to generate the corresponding amide, **5**, in good yield, albeit with a minor tweak to the conditions applied. Use of potassium carbonate provided a mixture of products when reacted with [6-Dipp]HBr and CuCl, but switching the carbene precursor to [6-Dipp]HCl gave good conversion overnight (58%) to (6-Dipp) CuCl, **6**. Finally, attempts to exploit KH in this reaction provided crude NMR data consistent with the formation of some

(6-Dipp)CuH however no appreciable quantity could be accessed upon workup.

Extension of this reactivity to MeLi, BuLi, tBuLi and PhLi gave access to the corresponding alkyl and aryl systems (Scheme 2, **7–10**), all four of which were structurally characterised (Fig. 1). For **7–9** organolithium reagents were added as commercially available solutions, affecting the η parameter ($\eta \approx 10$). MesLi, on the other hand, provided poor conversion and reaction mixtures containing a large range of products.

The synthesis of compounds **7–10** gives an opportunity to interrogate a homologous set of NHC-copper carbohydryls. Whilst NHC-copper n-alkyls are well known, and aryls are common, **9** constitutes the first structurally characterised example of a *tert*-butyl complex of an NHC-stabilised copper(I) fragment, and in fact the third copper(I) *tert*-butyl compound to ever be structurally characterised and reported. The geometry at the metal is close to linear. The carbene carbon–copper bond is marginally shorter than that of the alkyl carbon–copper bond (**9**: C_{NHC}–Cu, 1.9148(18) Å; C_{anion}–Cu, 1.949(2) Å; C–Cu–C, 177.18(8)°). The 5-membered analogue of **7**, (IPr) CuMe, described by Sadighi and co-workers[26] exhibits ideal linearity and marginally shortened copper–carbon bond distances (IPrCuMe: C_{anion}–Cu, 1.913(6) Å; C_{NHC}–Cu, 1.887(5) Å; C–Cu–C, 180.000(1)°). **7**: C_{NHC}–Cu, 1.9229(16) Å; C_{anion}–Cu, 1.926(2) Å; C–Cu–C, 175.45(9)°, an effect commonly observed when comparing 5- and 6-membered carbene copper complexes. The closest literature analogue of **8**, (IPr*Me)Cu-hexyl was reported by Tran, Bullock and co-workers[27] and it contains two distinct molecules in the asymmetric unit, with near-linear C–Cu–C angles (C–Cu–C, 177.7(2), 177.1(2)°) and copper–carbon bond distances which are, once again, shorter for the carbene carbon to copper bond (C_{NHC}–Cu, 1.890(4), 1.900(4) Å) than the hexyl carbon to copper bond (Cu–C, 1.931(5), 1.927(5) Å). This contrasts with **8** (C_{NHC}–Cu, 1.9264(17) Å; Cu–C_{anion}, 1.939(2) Å; C–Cu–C 171.80(9)°), wherein the ring-
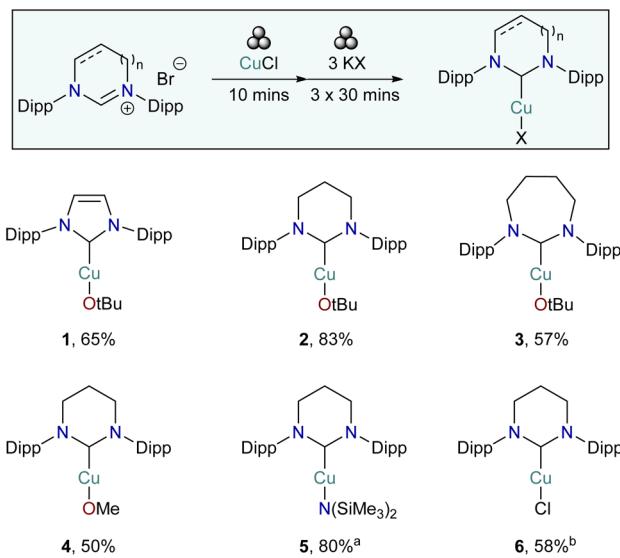
Scheme 1 Mechanochemical synthesis of a range of 5-, 6-, and 7-membered NHC–copper alkoxides, an amide and a halide. (a) 2 KHMDS, t = 16 h. (b) KX = K$_2$CO$_3$, t = 16 h.
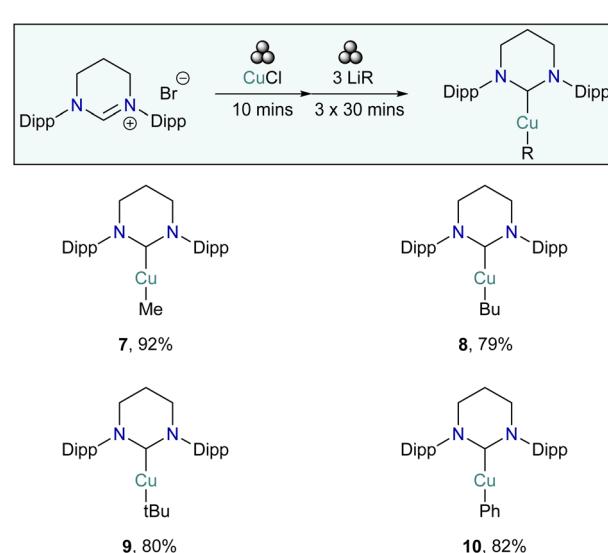
Scheme 2 Mechanochemical synthesis of a range of 6-Dipp-organo-copper reagents.
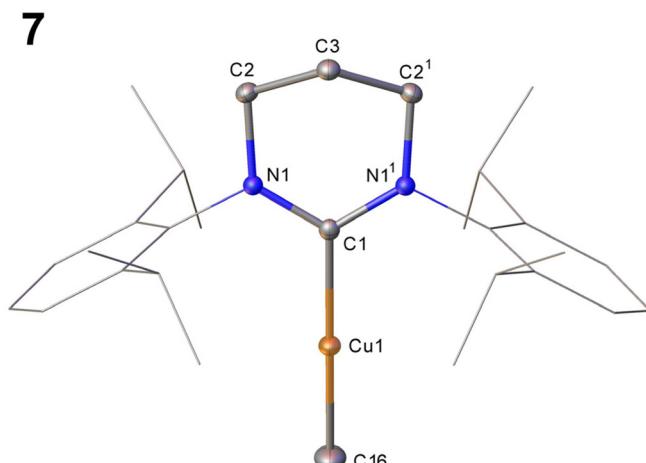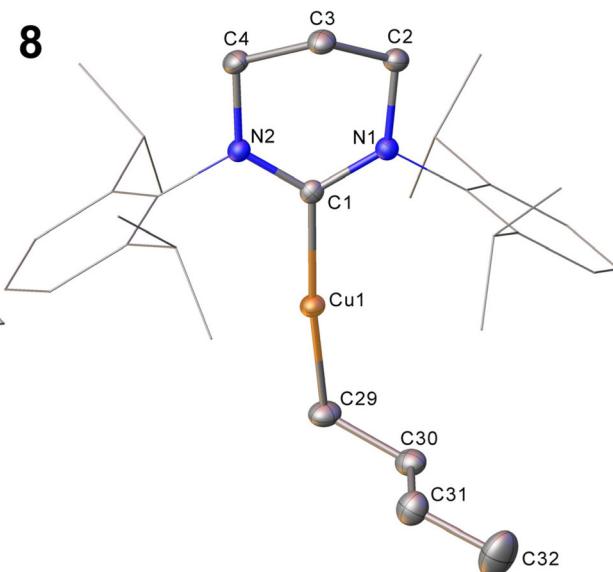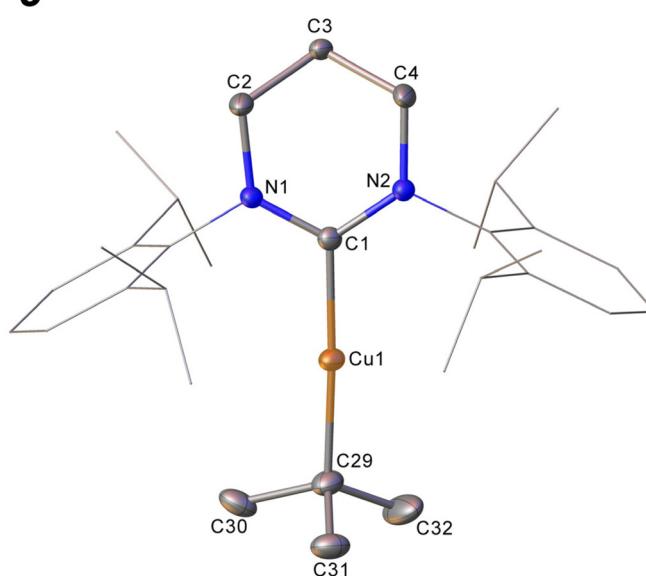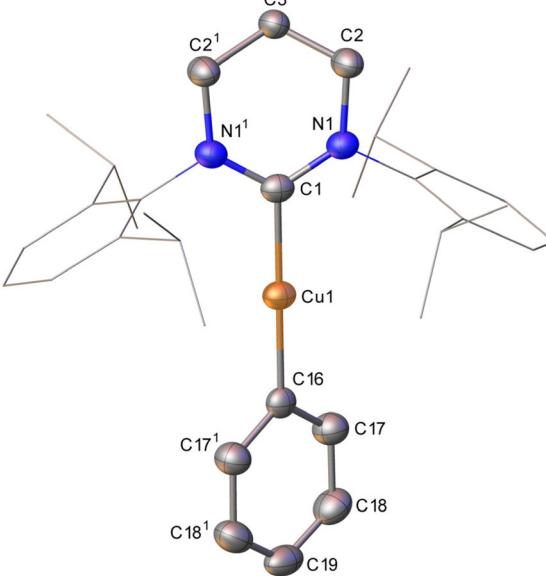
Fig. 1 Plots depicting the molecular structures of **7–10**. Ellipsoids are depicted at 30% probability. Hydrogen atoms and minor disordered components (**9** and **10**) and have been omitted and Dipp substituents are depicted as wireframes, for visual ease. **7**: symmetry operations: [1] x, $3/2 - y$, z. **10**: symmetry operations: [1] $1/3 - y + x$, $2/3 - y$, $7/6 - z$.†

expansion of the carbene elongates the carbon–copper bonds once more, but less so when comparing the alkyl–carbon copper bonds than the carbene–carbon copper bonds, possibly due to steric demand of the flanking groups in IPr*Me.

(IPr)CuPh was reported by Kleeberg and co-workers[28] and shows shorter copper–carbon bonds and a narrow C–Cu–C angle than **10** (C_{NHC}–Cu, 1.906(3) Å, 1.892(3) Å; C_{anion}–Cu: 1.898(3) Å, 1.907(3) Å; C–Cu–C: 174.1(1)°, 173.9(1)°; **10**: C_{NHC}–Cu 1.919(3) Å C_{anion}–Cu 1.926(3)° C–Cu–C 180.0°). Comparison of **7–10** shows no clear trend in C–Cu–C angles, or C_{NHC}–Cu distances, but a steady elongation of the alkyl copper–carbon distance from **7–9** is observed, corresponding to increased steric bulk at the anionic carbon. In contrast, the phenyl

carbon in **10** is similarly distant from the copper as the methyl carbon of **7**. This may be a consequence of the flat phenyl ring in **10** being more capable of orienting itself to evade steric clash with the flanking Dipp groups compared to the primary and tertiary alkyl groups in **8** and **9**.

Whilst these routes that rely on inexpensive commercial bases are attractive, the use of 3 equivalents of base/proligand would be prohibitively expensive in the case of more complex anionic ligands, and would also have negative sustainability impacts. We thus investigated the mechanochemical reaction of (6-Dipp)CuCl, **6**, with protic substrates in the presence of K_2CO_3 to provide an inexpensive route to complexes of the form (6-Dipp)CuX (X = acetylide, amide, alkoxide). This
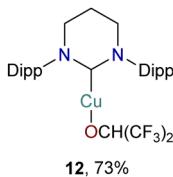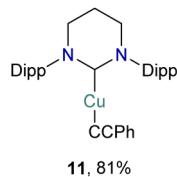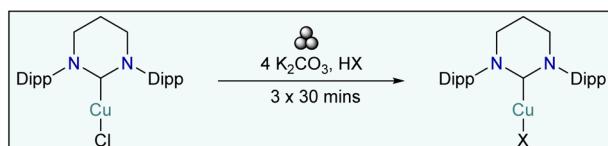
Scheme 3 Mechanochemical salt metathesis to access an acetylide and alkoxide.

approach tolerated an acetylene and hexafluoro-iso-propanol,[29] providing the respective acetylide (**11**) and alkoxide (**12**) in good yields (Scheme 3).

The formation of **11** is somewhat surprising given the respective pK_a values of phenyl acetylene, and the conjugate acid of K_2CO_3. We propose that the formation of potassium phenylacetylide under these conditions is unlikely although not impossible, and a reaction analogous to the formation of **6** from an NHC-salt is operant.

In conclusion, we have developed a simple "Dial-a-Base" route to NHC-copper complexes, providing access to a wide-range of systems of the form (NHC)CuX under mechanochemical conditions. The reaction tolerates both normal and ring-expanded NHCs, and in our hands provides convenient access to examples of copper alkyl, aryl, acetylide, amide, alkoxide, and chloride complexes, many of which are well-established (pre)catalysts, or have otherwise useful properties.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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