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Mechanochemical synthesis of Cu(I)-N-heterocyclic carbene complexes†

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We report a general, operationally simple and scalable mechanochemical method for the synthesis of [Cu(Cl)(NHC)] complexes. This solid-state and solvent-less methodology was shown to be applicable to a wide range of NHC ligand precursors, allowing access to complexes of the type [Cu(Cl)(NHC)] under aerobic conditions and with minimised environmental impact.

The use of mechanochemical milling or grinding as a method to carry out reactions has witnessed a growing interest over recent years.[1] The primary motivation behind the current expansion of mechanochemical methodologies is the urgent need for synthetic strategies that ally sustainable management of resources with decreased environmental impact. One way to reduce the environmental impact of a synthetic process is through minimisation of waste production.[2] In this regard, solvents indubitably represent the major contributors to the magnitude of the E-factor of any fine-chemical/pharmaceutical synthetic process.[3] This generalised use of solvents, with an annual consumption of 20 million tons,[4] is becoming economically and environmentally problematic, not only with regard to their production, but also because their purification and recycling are generally energy-intensive steps.[5] Consequently, ball milling and other automated techniques are currently being explored in order to drastically minimise, if not completely eliminate, solvent usage.[6] Minimisation of solvent use and simplified workups are not the only advantages that these techniques have shown to offer to the synthetic chemist.[7] Decreased reaction times, higher reaction yields[7] and access to new reactivity patterns[8] have also shown to be common beneficial features from solvent-free techniques. In light of all these advantages, the implementation of mechanochemical techniques for the synthesis of organic,[9] main group,[10] supramolecular molecules,[11] as well as for transition metal[12] and enzymatic-mediated[13] reactions, have been reported. In spite of these developments, the assembly of well-defined organometallic complexes under milling conditions represents an underdeveloped area of research.[14,15] Even rarer are reports on mechanochemical synthesis of complexes bearing N-heterocyclic carbene (NHC) ligands.[16–24] With their outstanding ability to stabilise highly reactive transition-metal species, including those of copper, NHC ligands have led to a plethora of fascinating developments in homogenous catalysis. These ancillary ligands have become workhorses in many catalytic transformations.[25,26]

Over the past decade, in trying to develop greener approaches to chemistry, research efforts have been directed toward the development of catalytic systems based on inexpensive and Earth-abundant metals.[27] Copper species of the type [Cu(X)(NHC)] (X = halide) have shown their effectiveness in many catalytic applications,[28] including reduction of carbonyl compounds,[29] reductive aldol condensation,[30] amination reactions[31] and trifluoromethylation reactions,[32] to name a few. Additionally, Cu(I)-NHC complexes have also emerged as robust and inexpensive reagents for carbene transfers,[33–36] capable of replacing the more sensitive and expensive systems based on Ag(I), whose carbene-transfer capability under ball-milling has been assessed by Lamaty and co-workers.[16,19]

The main barrier to developing novel catalytic systems is often the synthetic access to the catalysts themselves. In the area of NHC-metal mediated transformations, the most commonly encountered synthetic route has been performed in solution and has involved the formation of a free-carbene species (Scheme 1a). The main drawbacks to this synthetic approach is the high sensitivity (oxygen, moisture, thermal) of the free carbene species, and the need for a strong and expensive base for the successful deprotonation of the carbene precursor.[24,25] In 2010, our group reported an improved protocol, which, by leveraging the incorporation of a base functionality on the metal salt used as precursor, allows for the synthesis of this class of complexes under aerobic and operationally simple conditions (Scheme 1b).[37]

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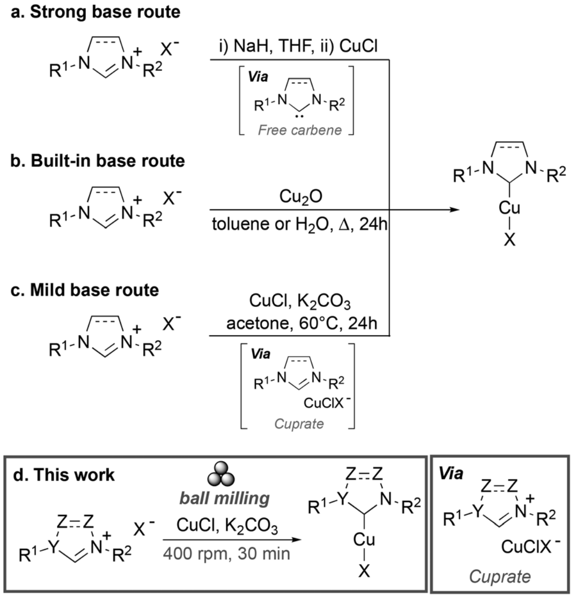


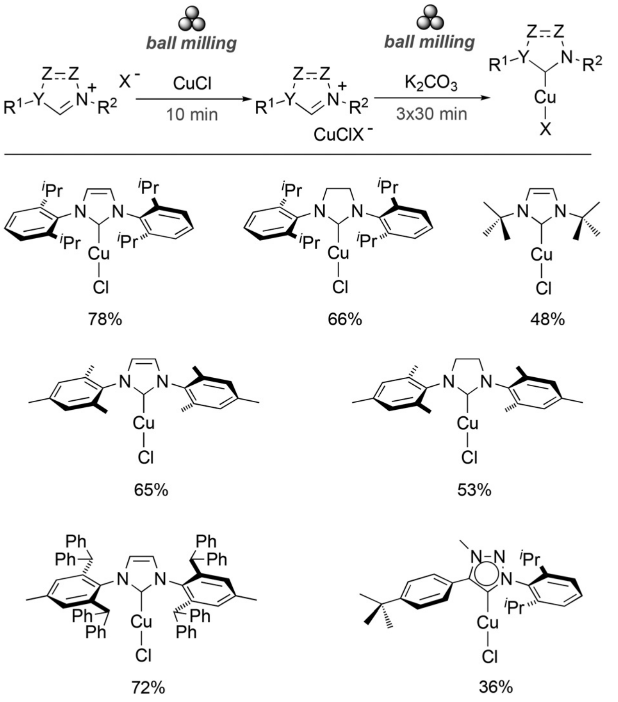
Scheme 1 Synthetic access to [Cu(X)(NHC)] complexes.

Since the publication of this report, other groups have adapted this methodology. All these efforts have aimed at improving the overall sustainability of the synthetic route.[38,39] Lamaty and co-workers were the first to translate this synthetic approach into a solid-state version, for the synthesis of Ag(I)-NHC complexes.[20,21]

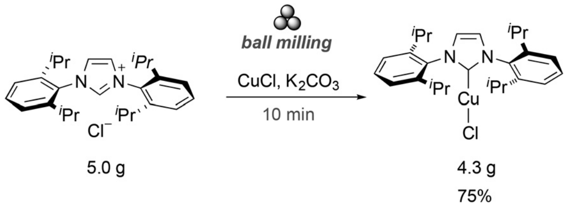
In 2013, we disclosed another approach for the more general synthesis of [Cu(X)(NHC)] complexes which capitalises on the ability of the metal to form metallate species with azolium salts (Scheme 1c).[40] In the presence of an inexpensive base, *i.e.* K_2CO_3, and under aerobic conditions, the metallate intermediate is easily converted to the desired final complex. Given the value of this class of copper-NHC complexes in catalysis, we considered the feasibility of carrying out such syntheses under solvent-free conditions. In this report we describe for the first time the synthesis of various Cu(I)-NHC complexes of the type [Cu(X)(NHC)] under ball-milling conditions using a mild base approach (Scheme 1d).‡

N,*N*′-Bis-[2,6-(di-iso-propyl)phenyl]imidazolium chloride (IPr·HCl) was chosen as benchmark substrate and a rapid optimisation of reaction conditions was carried out. It was found that efficient reactivity was obtained when the reaction was carried out using an excess of the base, a high rotation speed, with a relatively long reaction time. This is presumably a consequence of improved homogenisation of the reactants inside the milling reactor (optimal homogeneous conditions are not always achieved in these types of systems and in many cases, liquid assisted grinding (LAG) has been shown necessary).[41] However we must note that, under dry milling conditions, increase of the reaction times does not generally lead to improved yields as the continuous grinding of the solids inside the reactor leads to a point where solid particles are compacted rather than mixed. Regardless, we found that, on a small scale, while complete conversion to the cuprate intermediate was achieved in less than 10 minutes, to reach efficient synthesis of the corresponding N-heterocyclic carbene complex, three 30 minutes-periods of milling time were necessary; which is shorter than most reaction times required in solution involving conventional heating or cooling. These promising results with IPr·HCl prompted us to examine the applicability of this new synthetic method to other carbene precursors. As depicted in Scheme 2, the ball milling strategy is widely applicable, and the method was exemplified using a range of NHC ligand precursors. Imidazolylidene, imidazolinylidene, and triazolylidene copper complexes were thus successfully obtained, bearing *N*-aryl or *N*-alkyl substituents. Interestingly, no apparent trend with regard to steric bulk was observed. This is in contrast with solution phase syntheses which are largely sensitive to ligand bulk, with larger ligand precursors requiring substantially longer reaction times to produce higher yields.

The results depicted in Scheme 2 were carried out on a relatively small scale (200 mg of ligand precursor). It was thus of interest to show the scalability of our methodology. This was carried out with success, as shown in Scheme 3, as scaling up from 200 mg to 5 g led to essentially the same isolated yield of [Cu(Cl)(IPr)], but in a drastically reduced reaction time and simpler operating procedure. Indeed, the large scale reaction leading to the formation of 4.3 g of [Cu(Cl)(IPr)], was carried out in one-pot within 10 minutes (Scheme 3). This increased reactivity probably results from a temperature rise observed in



Scheme 2 Mechanochemical synthesis of Cu(I)-complexes. Reaction conditions: (i) NHC·HCl (200 mg), CuCl (1 equiv.), 10 min; (ii) K_2CO_3 (3 equiv.) 3 × 30 min 30 min.



Scheme 3 Large scale mechanochemical synthesis of [Cu(Cl)(IPr)]. Reaction conditions: IPr·HCl (5 g), CuCl (1 equiv.), K_2CO_3 (3 equiv.) 10 min.

the grinding vessel, which is presumably due to the increased number of milling bodies used, as both degree of filling of the reactor and rate of rotation were kept constant from small to large scale. In the latter case, the increased number of milling bodies led to a higher number of collisions leading to a greater overall energy input and to improved efficiency.

In conclusion, the mechanochemical synthesis of copper(I)-NHC complexes using the mild base route has been reported. We have demonstrated that this protocol is readily carried out in the absence of reaction solvents, and applicable to a wide range of NHC ligand precursors. The method greatly improves the overall sustainability of the process.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

‡ General synthetic procedure: A milling jar (12 mL, ZrO_2) equipped with 18 balls (5 mm Ø, ZrO_2) was charged with NHC·HCl and CuCl which were ground (400 rpm) for 10 min. K_2CO_3 was added and the reaction mixture was ground for 3 × 30 min (400 rpm). The crude product was extracted (CH_2Cl_2 or acetone) and filtered through SiO_2. After concentration, pentane was added, and the product/precipitate was collected by filtration. When the product was extracted from the reactor using acetone, filtration through SiO_2 and reducing of the solvent volume by vacuum permits the product to precipitate and alleviates the need for pentane co-solvent use.

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