

Mechanochemical solid state synthesis of a bifunctional copper(I)/N-heterocyclic carbene complex and its catalytic activity in hydrogenative transformations

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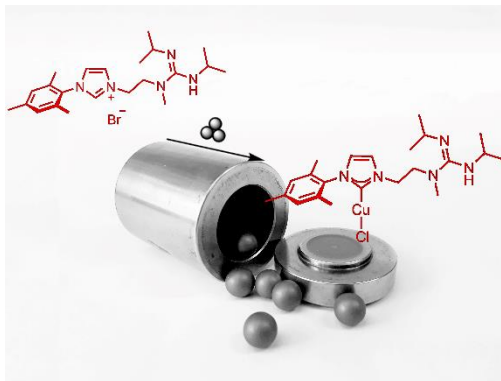
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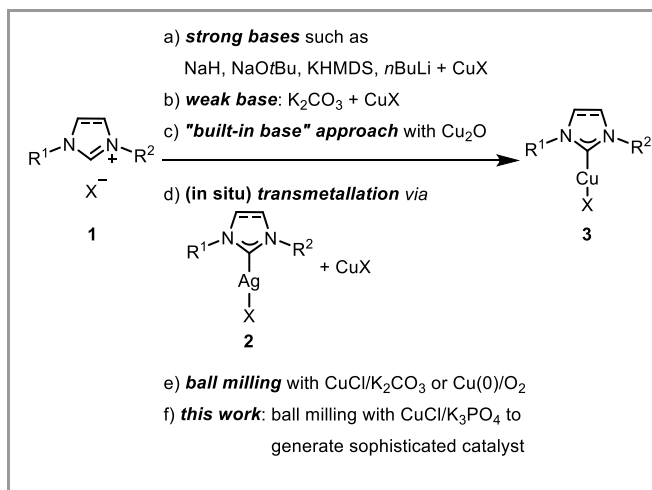
Abstract A sophisticated bifunctional catalyst bearing a copper(I)/N-heterocyclic carbene and a guanidine organocatalyst has been prepared by a mechanochemical synthesis in a ball mill. This approach circumvents commonly employed silver(I) complexes which are associated with significant and undesired waste formation. Due to the bifunctional nature of the desired complex, earlier mechanochemical conditions were not applicable and a new protocol based on cheap and readily available K₃PO₄ as base has been developed. The resulting complex has been shown to be active in a variety of reduction/hydrogenation transformations employing dihydrogen as terminal reducing agent.

Key words mechanochemical synthesis, planetary ball mill, copper, N-heterocyclic carbenes, bifunctional catalysis, hydrogen activation

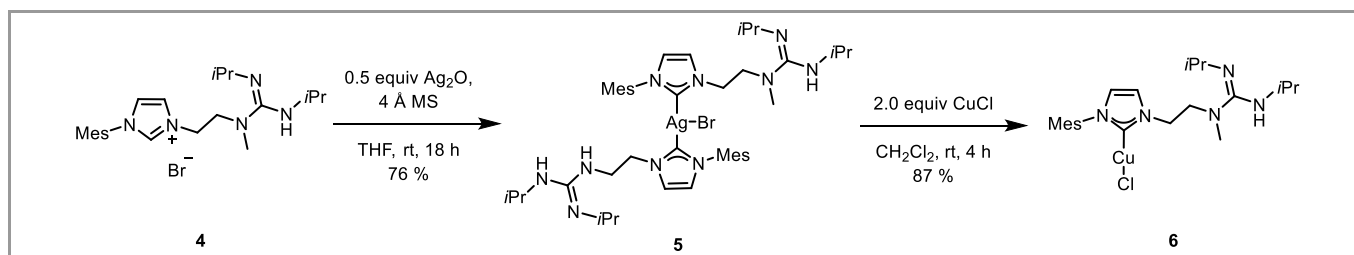
Some prominent goals of green chemistry heralded for synthetic chemistry are minimization or even complete prevention of chemical waste, the use of innocuous chemicals and replacement of hazardous reagents, atom efficient reactions and overall safer chemical processes.^{1,2} Therefore, one current challenge for synthesis is the development of green and environmentally friendly routes to access value-added products. One important way to more economical syntheses is the concept of catalysis to avoid stoichiometric amounts of reactants and to design reactions more atom efficient.^{1–3} As one case in point, copper(I)/N-heterocyclic carbene (NHC) complexes are broadly applicable for a wide variety of catalytic transformations.^{4–6}

While generally there are many different synthetic routes to transition metal/NHC complexes^{7,8–10} not all of them are applicable to the preparation of copper(I)/NHC compounds (Scheme 1).^{5,6,8,11–14} Generally, the so-called “direct route” via the appropriate imidazol(in)ium salt, a copper precursor and a suitably strong base (NaH, NaOtBu, KHMDS or *n*BuLi)¹⁵ is challenging for copper complexes such as **3** as it tends to give low yields (Scheme 1, a).^{5,6,8,11–14} An elegant protocol employing K₂CO₃ as weak base in combination with copper(I) salts for simple copper(I)/NHC complexes has been disclosed (Scheme 1, b).¹⁶ While this variant is the method of choice due its simplicity and practicability, other alternatives have to be sought in cases where this direct synthesis approaches fail: On the one hand, the so-called “built-in base” route relies on the use of Cu₂O which can be directly reacted with

a suitable precursor **1** (Scheme 1, c).¹⁷ On the other hand, the most common approach hinges upon the use of the preliminary preparation of a silver(I)/NHC complex (**2**) followed by facile transmetalation to copper(I) (Scheme 1, d). In some cases, this transmetalation step is carried out in situ.^{9,10,18} Notably, these generally successful synthetic routes produce a considerable amount of transition metal waste and are therefore in misalignment with the principles of green chemistry.



Scheme 1 General synthetic routes to copper(I)/NHC complexes (X = Cl, Br).



Scheme 2 Published liquid state synthesis of **6** via silver complex **5** (Mes = Mesityl).^{19,20}

Synthesis via mechanochemical methods offers elegant and atom-economic alternatives to liquid state synthesis approaches.^{21,22} Very recently, the possibility of synthesizing copper(I)/NHC complexes in the ball mill has been disclosed (Scheme 1, e).^{23–25} These approaches are promising due to the avoidance of unwanted transition metal waste and/or organic solvents. Two possible mechanochemical pathways have been presented for the synthesis of copper(I)/NHC complexes: First, the complexes can be synthesized by milling the ligand precursor **1** with metallic copper powder in air.²³ Another mechanochemical pathway was published using K_2CO_3 as a base and copper(I) chloride.^{24,25} This procedure is practical, avoids the use of solvents, and relies on an abundant and cheap base.

We have recently disclosed an unprecedented ester reduction with H_2 as terminal reducing agent utilizing bifunctional copper(I)/NHC complex **6** bearing a guanidine moiety as additional catalytic unit.²⁰ This catalyst acts by employing the copper(I)/NHC complex for H_2 activation on the one hand and by using the guanidine subunit for organocatalytic simultaneous activation of the ester on the other hand. Following a previously established synthetic pathway,¹⁹ we have found that transmetalation via silver(I)/NHC complex **5** was the only viable entry point to this sophisticated bifunctional catalyst (Scheme 2).²⁶ First, the silver(I)/NHC complex **5** had to be synthesized and isolated prior to transmetalation with copper(I) chloride.^{19,20} The required formation of silver(I) complex **5** diminishes the overall yield of copper complex **6**. As an additional disadvantage, the silver(I) byproducts have to be carefully removed in order to maintain reproducible results in the copper(I) catalysis.²⁰ We deemed this synthetic route unattractive with regards to sustainable synthesis due to the silver waste generated in the process and sought to replace the transmetalation route with a more atom economic approach to circumvent these problems.

We therefore examined different approaches to avoid the transmetalation step and to establish a protocol for direct synthesis of **6** in solution (Table 1, liquid state approaches). The use of strong bases such as NaOtBu or *n*BuLi or the weak base Et_3N in an attempted direct approach did not lead to the desired product (Table 1, a and c). Furthermore, utilizing CuCl and K_2CO_3 as a base or Cu_2O for a “built-in base” approach lead to the formation of a catalytically inactive CO_2 adduct of the desired complex **6** (Table 1, b and c).^{27,28} We hypothesize that in the CO_2 adduct, the guanidine moiety is unavailable to perform its assisting part in catalysis through hydrogen-bonding interaction.²⁰

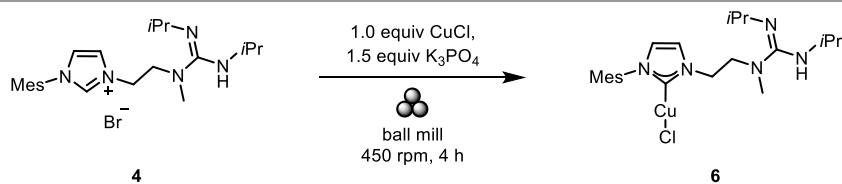
Since our attempts to establish direct synthetic routes to **6** in liquid state were not fruitful, we turned our attention to mechanochemical synthesis of bifunctional catalyst **6**, based on two recent reports of preparation of copper(I)/NHC complexes in a ball mill.^{23–25} However, with each of the two approaches, additional

challenges associated with the bifunctional nature of complex **6** arose. On the one hand, the use of copper powder and oxygen²³ as starting materials for the mechanochemical approach seemed not feasible for the synthesis of complex **6** due to its high propensity to oxidation. On the other hand, the second published mechanochemical synthesis protocol employing copper(I) chloride and K_2CO_3 ^{24,25} seemed not applicable due to the facile formation of CO_2 adducts as observed in the liquid state synthesis with K_2CO_3 . Nevertheless, using copper(I) chloride as the copper source seemed promising, therefore the mechanochemical synthesis of **6** was attempted using CuCl and various bases (Table 1, solid state approaches).

Table 1 Liquid and solid state approaches to synthesize complex **6**.

	Reagents	Results
Liquid state approaches		
a) Strong bases	CuCl and <i>n</i> BuLi or NaOtBu	No product formation observed
b) “Built-in base” approach	Cu_2O	Catalytically inactive CO_2 adduct
c) Weak bases	CuCl and NEt_3	No product formation observed
	CuCl and K_2CO_3	Catalytically inactive CO_2 adduct
Solid state approaches		
d) Strong bases	CuCl and NaOtBu or NaOH or KHMDS	No product formation observed
	CuCl and NaH	Unselective product formation observed, purification not feasible
e) “Built-in base” approach	Cu_2O	No product formation observed
f) Weak base	CuCl and K_3PO_4	Successful product formation

The mechanochemical synthesis was carried out in a planetary ball mill.²⁹ Copper(I) chloride, imidazolium salt **4** and the appropriate base were mixed in a molar ratio of 1 : 1 : 1.5 and grinded for 4 hours. Employing strong bases such as KHMDS, NaOtBu or NaOH did not lead to the desired product. All three approaches have in common that the conjugated acid is a liquid. In the literature, the improvement of mechanochemical



Equation 1 Mechanochemical synthesis of complex **6**.

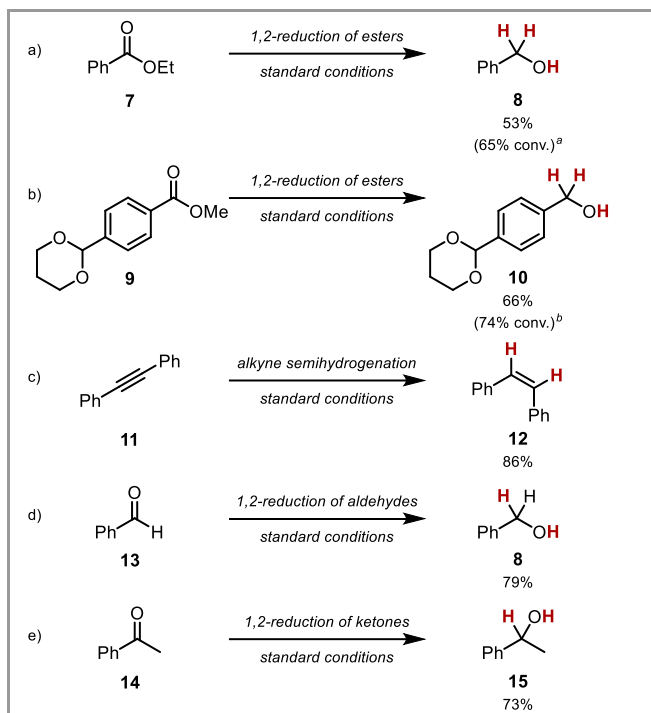
syntheses by addition of small amounts of a liquid have been reported (LAG, liquid-assisted grinding).²² However, in our case, the formation of small amounts of liquid during the milling process lead to agglutination of the remaining powder and therefore insufficient homogenization of the reaction mixture. This led to a mixture of compounds, in which the envisaged complex **6** could not be identified (Table 1, d).

A different approach was made using sodium hydride as a base. Instead of small amounts of liquid, here, deprotonation leads to the formation of dihydrogen. Hence, another mill was utilized for this approach.³⁰ Unfortunately, a successful synthesis of **6** directly from **4** was not possible under these conditions. NMR analysis of the resulting mixture indicated the presence of **6**, but also of unwanted side-products that could not be identified. Purification of **6** from this complex mixture turned out not to be feasible (Table 1, d). Further modifications of the milling conditions did not lead to the elimination of these side-products, therefore the experiments with NaH as a base were discontinued.

The direct transition of the “built-in base” approach conditions to mechanochemical synthesis (copper(I) oxide and imidazolium salt **4** as starting materials), lead to no product formation (Table 1, e).

Based on these results, we devised new mechanochemical conditions for the preparation of bifunctional copper(I)/NHC complex **6** relying on a weak base approach. Successful formation of copper(I) complex **6** was achieved by using readily available K_3PO_4 as a base in combination with CuCl (Equation 1; Table 1, f).³¹ The starting materials were mixed in a steel vessel and grinded at 450 rpm for a total of four hours. After ball milling, an off-white powder was obtained which gave complex **6** in very good yield of 91% after the usual workup and no further purification step. NMR analysis of **6** matched previously reported data^{19,20} and showed no side products. It has to be mentioned that complex **6** synthesized via the mechanochemical route is isolated as a CH_2Cl_2 adduct (**6**/ CH_2Cl_2 = 1:1) as confirmed by NMR spectroscopy and elemental analysis.³²

Comparing catalyst **6** from mechanochemical synthesis (**6bm**) with its counterpart from the liquid state transmetalation route (**6ls**), we found that **6bm** was catalytically active, however displaying slightly diminished activity (Scheme 3). This was shown in lower overall conversion of ethyl benzoate (**7**) to benzyl alcohol (**8**) and lower yield (65 % conv. and 53 % yield with **6bm**, in comparison to 100 % conv. and 80 % yield with **6ls**; Scheme 3, a). We hypothesize that the higher amount of CH_2Cl_2 , which is not a suitable solvent for catalytic ester reduction with H_2 ,²⁰ led to lower catalyst activity.³³ The copper(I)-catalyzed 1,2-reduction of functionalized ester **9** was also successfully achieved using the ball mill synthesized bifunctional catalyst **6bm**, again with slightly diminished yields and conversions (Scheme 3, b).



Scheme 3 Scope of ball mill-synthesized bifunctional catalyst **6bm**. Isolated yields under standard conditions: Substrate (0.40 mmol), 10 mol% [Cu] **6bm**, 1.1 equiv NaOtBu, 1.3 equiv 15-crown-5, 100 bar H_2 , 1,4-dioxane (3 mL), 70 °C, 24 h. ^aWith liquid state synthesis complex **6ls**: full conversion and 80 % yield. ^bWith liquid state synthesis complex **6ls**: full conversion and 74 % yield.

We were further interested in the demonstration of the applicability of the mechanochemically synthesized bifunctional complex **6**. Application of the ball mill-synthesized complex **6bm** in an alkyne semihydrogenation of tolane (**11**) gave (Z)-stilbene (**12**) with full stereoselectivity in good yield (86 %, Scheme 3, c). Therefore, **6bm** behaves similarly to other copper(I)/NHC complexes in this transformation.³⁴ The catalytic 1,2-reduction of carbonyl compounds is mainstay for copper(I)/NHC complexes,³⁵ which is why we also tested **6bm** in these transformations: The 1,2-reduction of benzaldehyde (**13**) and acetophenone (**14**) proceeded with good yields (Scheme 3, d and e). No aldol addition for the acetophenone substrate has been observed although working under strongly basic conditions.³⁶

In conclusion, we have disclosed a practical approach to a sophisticated bifunctional copper(I)/NHC complex based on a mechanochemical protocol. This operationally simple synthetic route circumvents the previously necessary use of surplus transition metal reagents and therefore diminishes unwanted waste formation. The new protocol presented here is based on K_3PO_4 and has successfully displayed the activity of the resulting catalyst in a variety of hydrogenative transformations. Our results do not only add to the wide area of applications of mechanochemical synthesis

but also showcase that transition metal complexes bearing additional functional groups can be prepared with a ball milling synthesis. We think that our protocol could be useful for the atom economic preparation of other complex catalysts, which are difficult or wasteful to be prepared by typical liquid state synthesis methods.

Funding Information

This research was funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) under Germany's Excellence Strategy EXC 2008-390540038-UniSysCat, and through an Emmy Noether Fellowship for J.F.T. (TE1101/2-1). M.G. is supported by a fellowship by the Einstein Center for Catalysis (EC²).

Acknowledgment

Prof. Dr. Martin Oestreich (TU Berlin) is kindly thanked for generous support.

Conflict of Interest

The authors declare no conflict of interest.

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- (29) Experiments were carried out with a Fritsch Pulverisette 7 *classic line* in a 12 mL steel beaker with six steel balls (1 cm in diameter). See the Supporting Information for more details.
- (30) To prevent damage due to the development of pressure inside the milling vessel, gastight 45 mL zirconia beakers equipped with six zirconia balls (1.5 cm in diameter) and the Fritsch Pulverisette 7 *premium line* were used.
- (31) Mechanochemical synthesis procedure for **6**: The product was synthesized using a Fritsch Pulverisette 7 *classic line*, a high-energy planetary ball mill. The starting materials 1-(2-(2,3-diisopropyl-1-methylguanidino)ethyl)-3-mesityl-1H-imidazol-3-ium bromide (**4**, 75 mg, 0.16 mmol, 1.0 equiv), CuCl (17 mg, 0.16 mmol, 1.0 equiv) and K₃PO₄ (53 mg, 0.25 mmol, 1.5 equiv) were filled into a 12 mL steel vessel equipped with six steel balls (1 cm diameter). The beaker was sealed in an Ar-filled glovebox. Milling was carried out with 450 rpm for a total of four hours. After each hour the milling was paused for 30 minutes to avoid overheating of the machine. The raw product was obtained as an off-white powder after milling. The ground product was mixed with CH₂Cl₂ (3 mL) and the resulting suspension was filtered over a PTFE syringe filter (0.45 µm). The filtrate was concentrated under reduced pressure. The product **6** was obtained as the CH₂Cl₂ adduct as a colourless solid (86 mg, 0.15 mmol, 91 %).

- (32) If complex **6** is formed via the liquid state synthesis, see ref. (19) and (20), also a CH₂Cl₂ adduct is isolated, however with a **6**/CH₂Cl₂ ratio of 2:1.
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