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Cu(0), O₂ and mechanical forces: a saving combination for efficient production of Cu–NHC complexes†

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Mechanical forces induced by ball-milling agitation enabled the highly efficient and widely applicable synthesis of Cu–carbene complexes from *N,N*-diaryl-imidazolium salts and metallic copper. The required amount of gaseous dioxygen and insoluble copper could be reduced down to stoichiometric quantities, while reaction rates clearly outperformed those obtained in solution. Utilisation of Cu(0) as the copper source enabled the application of this approach to a wide array of *N,N*-diaryl-imidazolium salts (Cl[−], BF₄[−] and PF₆[−]) that transferred their counter anion directly to the organometallic complexes. Cu–NHC complexes could be produced in excellent yields, including utilisation of highly challenging substrates. In addition, five unprecedented organometallic complexes are reported.

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Introduction

The application of mechanical forces to solvent-free or solvent-less reaction mixtures through the use of ball-mills offers many advantages over traditional solvent-based strategies,^{1–5} especially when using poorly soluble, undissolved or insoluble reactants such as metals.^{6–16} Yet, these examples are limited to reactions between solid chemicals with liquid or soft solid reagents. In addition, the use of ball-mills to promote reactions involving solid reactants with gaseous reagents has been described previously.^{17,18} Yet, the ball-milling efficiency in reacting chemicals with a high physical state heterogeneity (soft material, gas, liquid and solid) has been explored only scarcely. In 2015, the reduction of organic molecules (soft material) in the presence of H₂ (gas), generated by mechano-mediated reduction of water (liquid) with zero-valent chromium (solid), was reported.¹⁹ In the same year, a study described the mechanochemical Rh(III)-catalyzed C–H bond functionalization of acetanilides (soft material) in the presence of alkyl acrylates (liquid) and a large excess of molecular oxygen (gas) as the terminal oxidant.²⁰

Continuing our efforts to provide the community of chemists with more efficient ways to produce high value molecules,^{7,21–26} we describe herein the mechanosynthesis of Cu–NHC complexes (NHC = *N*-heterocyclic carbene). This study includes details

on the outstanding efficacy of using ball-mills to react materials with high physical state heterogeneity. Used as catalysts in a wide range of reactions,^{27–31} Cu–NHC complexes are generally synthesised by deprotonation of imidazolium precursors with a strong base followed by reaction with Cu(I). Although interesting, a less frequent alternative is the use of metallic Cu(0) as the copper source. This route enables the transfer of the imidazolium counter anion directly to the Cu–NHC complexes,^{32–36} thereby providing easier access to a wider range of copper complexes. Unfortunately, these solvent-based reaction conditions require a large excess of insoluble Cu(0) and long reaction times.

Results and discussion

When IMes·HCl was treated with 5 equivalents of Cu(0) under magnetic stirring in refluxing water (Fig. 1), only 19% conversion was obtained after 8 h of reaction. On the other hand, 80% of IMes·HCl was converted into [CuCl(IMes)] when mixed with 5 equivalents of Cu(0) in a planetary ball-mill (pbm) agitated at 450 rpm for 8 h, without external heating. When adding small amounts of water as a grinding assistant (0.3 μL per mg of reactants), complete conversion could be reached after only 3 h.³⁷ These ball-milling conditions were so efficient that only 1.0 equivalent of insoluble Cu(0) was enough to obtain >95% conversion after 8 h (Fig. 1). This impressive increase in the reaction rate could be explained by the highly concentrated reaction media, along with the highly efficient mixing that prevented mass transfer limitations. Indeed, no conversion could be observed when this reaction was performed with small amounts of water (0.3 μL per mg of reactants) and placed under reflux with magnetic stirring (Fig. 1). Though reactions

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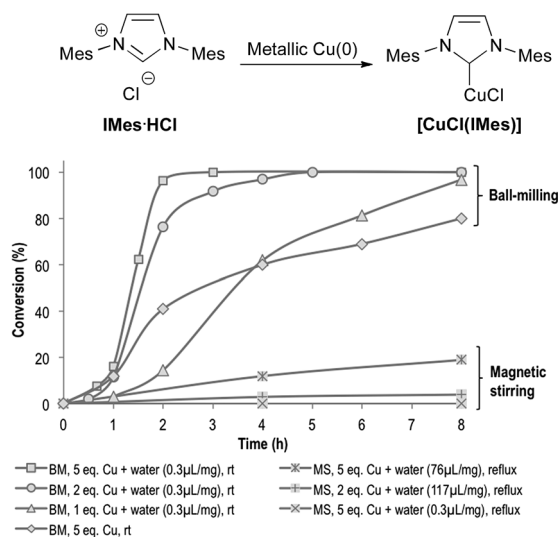


Fig. 1 Comparison of reaction conditions for the formation of [CuCl(IMes)]. Mes = mesityl; BM = ball-milling; MS = magnetic stirring.

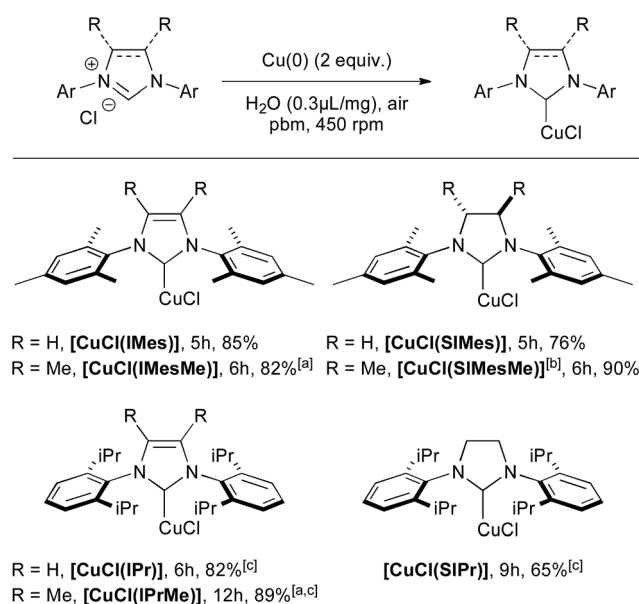
performed in refluxing water were limited to 100 °C, it is known that under peculiar conditions, the temperature inside a ball-mill can reach much higher levels.³⁸ In our case, the temperature of the reaction mixture after 6 h milling did not exceed 35 °C, in complete accordance with what was previously observed by us and by other research groups using similar milling conditions.³⁸

Conditions involving 2 equivalents of Cu(0) and water as the grinding assistant were selected for further transformations, since the full conversion of IMes·HCl could be reached in only 5 h (Scheme 1). Several [CuCl(NHC)] complexes, featuring unsaturated IMes, IPr and saturated SIMes and SIPr, could be

isolated efficiently within a few hours. The 4,5-dimethyl-substituted imidazolium derivatives IMes^{Me}·HCl and IPr^{Me}·HCl, which are known to be less reactive, could also be converted to the corresponding copper complexes in excellent yields with the ball-milling approach. Besides, the previously unreported [CuCl(SIMes^{Me})] complex was also isolated in excellent yield by applying these reaction conditions.

The role of dioxygen in the course of the reaction was next investigated (Fig. 2). When IMes·HCl was treated with 5 equivalents of Cu(0) under inert atmosphere (N₂) in a hermetically closed reactor, no conversion into [CuCl(IMes)] could be detected, thus confirming the participation of atmospheric O₂ to the overall process. According to eqn (1) (Fig. 2), 1 mmole of O₂ could react with 4 mmoles of imidazolium. The reaction was thus repeated under ambient atmosphere with 0.62 mmoles of IMes·HCl and 3.08 mmoles of Cu(0) in a 12 mL reactor for which the free volume contained 79.6 μmoles (0.52 equivalent) of O₂ under these conditions.^{39,40} Conversion of IMes·HCl into [CuCl(IMes)] reached a maximum at 29%, thereby confirming that with these conditions, the reaction was limited by the amount of O₂ present in the reactor.³⁹ When the same reaction was performed with the amount of O₂ ranging from 0.20 to 1.27 equivalents,³⁹ the conversion and yield were highly proportional to the amount of O₂ (Fig. 2). Gratifyingly, quasi-stoichiometric amounts of O₂ (1.27 equiv.) were sufficient to convert 100% of IMes·HCl, furnishing [CuCl(IMes)] in 83% yield (Table 1, entry 1). These results showed the impressive capacity of ball-milling to convert high proportions of a gaseous reactant spread among chemicals of high physical state heterogeneity (gas, solid and soft material). To the best of our knowledge, such efficacy in lowering the required quantity of a gaseous reactant in a reaction performed in a ball-mill has never been reported before.

In 2012, Mack reported the critical importance of the bromoalkane physical state when it was used as an alkylating agent of cyclohexanone in a ball-mill.⁴¹ Indeed, it was observed in this situation that gaseous bromoalkanes were less reactive than the liquid ones. In most reports, a different situation is observed, the



Scheme 1 Mechanosynthesis of various [CuCl(NHC)] complexes from Cu(0). [a] Benzonitrile was used in place of H₂O. [b] Previously unreported complex. [c] 5 equiv. of Cu(0) were used.

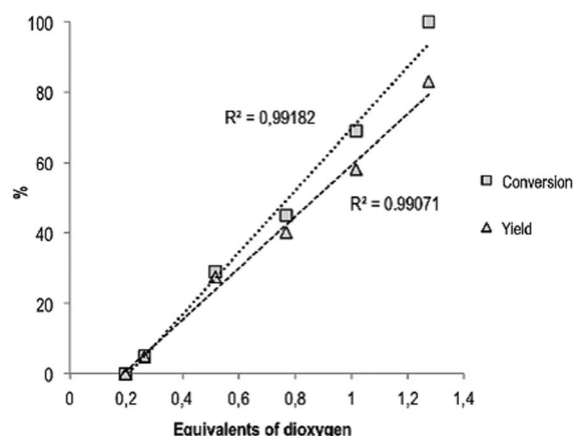
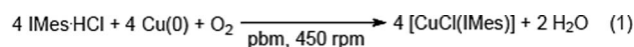
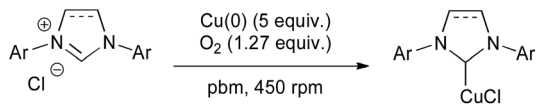


Fig. 2 Conversion and yield as a function of O₂ equivalents for the reaction of Cu(0), O₂ and IMes·HCl performed in a ball-mill.



Table 1 Mechanochemical synthesis of [CuCl(NHC)] complexes with 1.27 equivalents of dioxygen


Entry	Product	Time (h)	Yield (%)
1	[CuCl(IMes)]	6	83
2	[CuCl(SIMes)]	8	91
3	[CuCl(IPr)]	8	76
4	[CuCl(SIPr)]	8	69

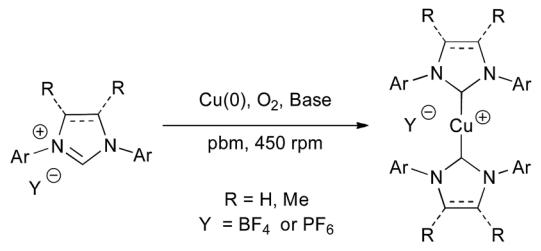
gaseous nature of a reagent is not an obstacle for its reactivity.^{17–20} In our case, gaseous O₂ is even close to being completely consumed. Although composed of reactants of high physical state heterogeneity, the reaction mixture was homogeneous at the macroscopic scale, as indicated by identical conversions of three samples withdrawn in three different locations inside the reactor. To confirm that such conditions with a low amount of dioxygen were general, [CuCl(SIMes)], [CuCl(IPr)] and [CuCl(SIPr)] were synthesised in good to excellent yields by using only 1.27 equivalents of O₂ (Table 1). Notably, the yields obtained under these conditions were very similar to those where the amount of dioxygen was not precisely controlled.

We next turned our attention to the less studied, poorly reactive and thus more challenging tetrafluoroborate and hexafluorophosphate imidazolium salts to produce their corresponding cationic [Cu(NHC)₂] homoleptic complexes that have previously shown superior catalytic activities than their neutral

derivatives in hydrosilylation and 1,3-dipolar cycloaddition reactions.^{42–44} Unfortunately, these complexes could not be obtained when IMes·HBF₄ and IMes·HPF₆ were ball-milled with Cu(0), with or without water (Table 2, entries 1 and 2). Yet, ball-milling of these substrates in the presence of 1.1 equivalents of NaOH furnished [Cu(IMes)₂]BF₄ and [Cu(IMes)₂]PF₆ in 79% and 87% yield, respectively (Table 2, entry 3). The necessity of using a stronger base could be explained by the weaker hydrogen bonds between the proton at C2 and the BF₄[–] and PF₆[–] counter anions than in Cl[–] salts, leading to a lower acidity of this proton.^{30,45} To our delight, the previously unreported [Cu(IMes^{Me})₂]BF₄ and [Cu(IMes^{Me})₂]PF₆ could be produced in excellent yields, showing the particularly high efficiency and wide applicability of this approach (Table 2, entry 4). Besides, the highly encumbered 1,3-bis-(2,6-diisopropylphenyl)-imidazolium derivatives reacted efficiently under these conditions, yet a stronger base, KHMDS, had to be employed in most cases to obtain acceptable conversion in a reasonable amount of time. By using KHMDS, two additional unprecedented complexes, [Cu(IPr^{Me})₂]BF₄ and [Cu(IPr^{Me})₂]PF₆, could be produced in satisfying yields (Table 2, entry 6).

Conclusions

In conclusion, these results have demonstrated the particularly high efficiency of ball-milling for the production of Cu–carbene complexes from *N,N*-diaryl imidazolium salts, dioxygen and metallic copper. It was shown for the first time that ball-milling enabled drastic reduction in the amount of gaseous reactant required down to the stoichiometric scale, without hampering conversion and yield. In addition, the rates of reaction clearly outperformed those obtained in traditional solvent-based

Table 2 Mechanochemical synthesis of [Cu(NHC)₂]BF₄ and [Cu(NHC)₂]PF₆ complexes


Entry	Substrate	Cu(0) (equiv.)	Additive (1.1 equiv.)	Y = BF ₄		Y = PF ₆	
				<i>t</i> (h)	Yield (%)	<i>t</i> (h)	Yield (%)
1	IMes·HY	3	None	6	0	6	0
2		2	H ₂ O ^a	6	0	6	0
3		3	NaOH	3	79	6	87
4	IMes ^{Me} ·HY	3	NaOH	6	91 ^b	6	97 ^b
5	IPr·HY	5	NaOH	6	85	—	—
		5	KHMDS	—	—	6	89
6	IPr ^{Me} ·HY	5	KHMDS ^c	8	72 ^b	6	78 ^{b,d}

^a 0.3 μL of water per mg of reactants. ^b Previously unreported complexes. ^c 5 equiv. were used. ^d Obtained as a mixture of two structures, one of which is identified as being [Cu(IPr^{Me})₂]PF₆.



conditions. Besides, five previously unreported Cu-NHC complexes could be isolated by using this approach. In an era of increasing demand for the discovery of innovative organometallic catalysts, as well as for efficiency and reduction of environmental impact, these results are a clear indication that mechanochemistry is a good choice to achieve these goals.

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