A General Mechanochemical Synthetic Protocol to Late Transition Metal-NHC (N-Heterocyclic Carbene) Complexes

Gianmarco Pisanò^{\dagger} and Catherine S. J. Cazin^{\dagger *}

[†]Department of Chemistry and Centre for Sustainable Chemistry, Ghent University, Krijgslaan 281-S3, 9000 Ghent, Belgium.

*Corresponding author email: <u>catherine.cazin@ugent.be</u>

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ABSTRACT: A user-friendly and highly efficient mechanochemical strategy for the synthesis of a number of well defined, catalytically relevant N-heterocyclic carbene-metal complexes under aerobic conditions is reported. This protocol proceeds in good to excellent yields and limits solvent usage to the purification step, which can be carried out, after judicious selection, using minimal amounts of environmentally benign solvents.

INTRODUCTION

Under the pressing need for safer, cleaner and more sustainable synthetic transformations, the last two decades have witnessed a rapid expansion of methodologies that implement the use of mechanical energy (prevalently in the form of grinding and milling) as means to initiate and carry out chemical transformations.^{1,2} The reason behind this large interest prompted by such approaches is that they provide a solvent-free (or solvent-minimized) environment in order to perform synthesis.³ Indeed, from a sustainability perspective, the ability to operate under the partial or complete absence of solvent is highly desirable⁴ as, in many cases, solvent use is what contributes most in defining the environmental performance of any chemical and/or pharmaceutical process.⁵ With consumption levels having reached the alarming pace of approximately 20 million tons annually, our current solvent usage is indeed becoming increasingly unsustainable in both economic and environmental terms.^{6,7} On the basis of these considerations, many researchers have begun implementing the use of ball mills, shaker mill and similar automated devices in different areas of chemical sciences in an attempt to deliver a more sustainable approach to synthesis.⁸⁻¹⁴ In many instances though, mechanochemical methods have shown to be more than just a mere tool to improve the environmental footprint of any synthetic process: decreased reaction times, higher yields¹⁵ and the opportunity to explore uncharted chemical space by unlocking reactivities otherwise inaccessible in solution,¹⁶ are some of the advantages that the synthetic chemists have uncovered. Nevertheless, mechanochemical methods for the synthesis of important discrete organometallic complexes remain largely unexplored.¹⁷⁻²⁶ Considering the importance of such compounds as pre-catalysts and that their preparation seldomly relies on sustainable routes, synthetic approaches that would allow their access in a few steps, minimal generation of waste and in an operationally simple manner are highly desirable. This is not only important from an

environmental and economic perspective, but also has real practical impact. Among the arsenal of well-defined organometallic complexes that are used in both academia and industry, transition metal complexes bearing N-heterocyclic carbene (NHC) ligands play indisputably a prominent role.²⁷ From the isolation of the first "bottleable" carbene by Arduengo and co-workers in 1991,²⁸ N-heterocyclic carbene ligands have progressively evolved from being an academic curiosity to their current role as an ubiquitous ligand family in the design of novel catalysts.²⁹ Indeed, with their extraordinary ability to stabilize highly reactive metal centers and with their highly tunable steric and electronic properties, the use of NHC ligands has enabled numerous and previously unimagined synthetic methodologies.²⁷ With the exception of a few reports,³⁰⁻⁴² synthetic procedures that allow the introduction of NHC ligands to a metal center all revolve around traditional solution chemistry and can be roughly summarized to occur *via*: the free carbene route, the built-in base route, the transmetallation route, and the weak base route (**Scheme 1**).



Scheme 1. Synthetic access to transition metal-N-heterocyclic carbene (NHC) complexes.

The free carbene approach is the synthetic route most frequently encountered, and it involves the treatment of azolium salts with a strong base, such as NaH, NaO'Bu, KHMDS, LiHMDS or *n*-BuLi, in the presence of/or followed by the addition of a metal precursor (**Scheme 1a**). The major drawbacks of such strategy are the high moisture and thermal sensitivity of the free carbene species, which require the use of anhydrous and degassed solvents and operational handling under an inert atmosphere. Although, part of the environmental and operational burden that such approach carries can be alleviated under solvent-free conditions, as shown by Grela and co-workers for the assembly of various Ru-olefin metathesis catalysts,³⁰ even the ball-milling variant

of this route requires the use of a dry setup and the use of an inert atmosphere. An alternative that does not require the use of an expensive strong base, is the so-called built-in approach (Scheme 1b). Treatment of an azolium salt, generally under aerobic conditions and using green solvents, with a suitable metal precursor which already contains a base embedded, such as Pd(acac)2,43 Cu₂O,⁴⁴ or Ag₂O⁴⁵ as examples, leads to the corresponding carbene-metal complex and protonated moiety as sole by-product. In the solid state, Lamaty and co-workers were first to successfully translate this solution-base methodology into a reliable mechanochemical approach for the assembly of various N,N-dialkyl,³¹ and N,N-diaryl,^{32,33} NHC-Ag(I) chloride complexes, as well as a series of homoleptic N,N-diaryl NHC-Ag(I) cationic complexes.³⁴ Following the same synthetic approach, the mechanochemical assembly of a small number of N,N-diaryl NHC-Cu(I) chloride complexes,³⁵ as well as on the use of Pd(OAc)₂ for the synthesis of a benzimidazolin-2-ylidene Pd(II) complex, were reported.³⁶ Another very popular synthetic methodology used to affix NHC ligand onto a metal center is the transmetallation route (Scheme 1c). This methodology consists in transferring a carbene fragment starting usually from NHC-Ag(I) complexes,⁴⁵ or as we have recently reported using less expensive and more stable NHC-Cu(I) systems,⁴⁶⁻⁴⁹ to a metal center of interest. This strategy was shown to be applicable also under solvent-free conditions: Lamaty and co-workers provided the first example of such mechanochemical transmetallation in a 2017 report,³² using complexes of the type [Ag(Cl)(NHC)], they were able to successfully transfer the NHC ligand from Ag onto Au(I), Cu(I) and Pd(II) centers, as well as to deploy this route for the synthesis of various NHC-Ru(II) complexes.³⁷ A more recent advance in the synthetic access to transition metal-NHC complexes is the weak base approach (Scheme 1d).⁵⁰ Over the course of recent years, several groups, including ours,⁵¹⁻⁵³ have reported the use of a weak base, such as K_2CO_3 , NEt₃ or NaOAc, in solution for reactions involving the azolium salt and metallic precursor.

This approach has been shown to be effective for various NHC ligand salts and numerous Late Transition metals.⁵⁰ We have recently established the first mechanochemical synthetic route that makes use of a weak base, e.g. K₂CO₃, for the synthesis of complexes of the type [Cu(Cl)(NHC)].³⁸ Concomitantly, the same approach was used by Udvardy, Czégéni and co-workers in the mechanochemical assembly of poly-NHC Rh(I)-complexes of the type $[{Rh(Cl)(1,5-cod)}_2(\mu-di-$ NHC)].³⁹ In light of these exciting results, we pondered about the extent with which the weak base method could be deployed for the assembly of well-defined NHC-transition metal complexes under mechanochemical conditions (Scheme 1e). Herein, we describe a general, operationally simple and easily scalable mechanochemical approach for the synthesis of well-defined NHCtransition metal complexes. The versatility of the synthetic method was exemplified with a series of commonly encountered NHCs, namely: N,N'-bis-[2,6-(di-iso-propyl)phenyl]imidazol-2ylidene or IPr (1), N,N'-bis-[2,6-(di-iso-propyl)phenyl]imidazolidin-2-ylidene or SIPr (2), N,N'bis-[2,4,6-(trimethyl)phenyl]imidazol-2-ylidene or IMes (3), N,N'-bis-[2,4,6-(trimethyl)phenyl]imidazolidin-2-ylidene or SIMes (4), N,N'-bis-[2,6-bis(diphenylmethyl)-4methylphenyl]imidazol-2-ylidene or IPr* (5), N,N'-bis-(cyclohexyl) imidazol-2-ylidene or ICv (6), N,N'-bis(methyl)imidazol-2-ylidene or IMe₂ (7), N,N'-bis-(benzyl)benzimidazol-2-ylidene or Bn₂-BIm (8) (Figure 1).



Figure 1. N-heterocyclic carbene ligands used in this study.

Under the conditions that we hereby report, we were able to access the following classes of complexes (**Figure 2**): [Ag(Cl)(NHC)], [Au(Cl)(NHC)], [Pd(η^3 -R-allyl)(Cl)(NHC)], and[Rh(1,5-cod)(Cl)(NHC)] (1,5-cod = 1,5-cyclooctadiene). Linear dicoordinated silver(I) complexes, such as [Ag(Cl)(NHC)], represent an extensively studied class of compounds that own part of their popularity to their ability to act as carbene transfer reagents.⁵⁴ In addition, many research reports have provided evidence that NHC-Ag(I) complexes could be effectively used as broad-spectrum antimicrobials and antitumoral agents.^{55,56} Gold(I) complexes of the type [Au(Cl)(NHC)] are established reliable pre-catalysts for many organic transformations, including alkyne hydration,⁵⁷ enyne cycloisomerization,⁵⁸ rearrangement of allylic acetates,⁵⁹ just to name a few.⁶⁰ NHC-Au(I) complexes have also found applications as luminescent materials,⁶¹ and in medicinal chemistry, with reports highlighting their antimicrobial and anticancer properties.^{56,62} NHC-Pd(II) complexes

of the type $[Pd(\eta^3-R-allyl)(Cl)(NHC)]$ are another popular class of air-stable complexes that have found applications as a reliable pre-catalysts for many synthetic transformations:^{63,64} E.g. α arylations,⁶⁵ Suzuki-Miyaura and Buchwald-Hartwig cross-coupling reactions.⁶⁶ The family of NHC-Rh(I) complexes, such as [Rh(1,5-cod)(Cl)(NHC)], have found applications mainly in homogenous catalysis, demonstrating their utility in hydrosilylation,⁶⁷ and hydroformylation reactions.⁶⁸



Figure 2. N-heterocyclic carbene-metal complexes accessed in this study.

RESULTS AND DISCUSSION

All reactions were conducted on 100 mg scale, using a planetary ball mill and 12 mL zirconia milling jars loaded with 18 balls ($\emptyset = 5$ mm) of the same material (corresponding to a degree of filling for the milling bodies of $\Phi_{MB} = 0.1$). Having demonstrated the feasibility of the weak base route using mechanochemical methods for the synthesis of NHC-Cu(I) complexes,³⁸ we initially investigated the suitability of this method for the remaining elements of Group 11: Ag(I) and Au(I). Synthetic access to complexes of the type [Ag(Cl)(NHC)] is generally accomplished by treatment

of azolium salts with Ag₂O, although in 2013, Gimeno and co-workers developed an alternative solution-phase strategy, which involves the treatment of the azolium salt in the presence of a cheaper metal salt precursor (e.g. AgNO₃) and K₂CO₃ at room temperature, in technical grade dichloromethane.⁶⁹ We decided, therefore, to test the mechanochemical assembly of such [Ag(Cl)(NHC)] complexes in a planetary ball mill using the azolium chloride salt of IPr (1), an inexpensive metal precursor (AgCl), in the presence of an excess of K₂CO₃ (Scheme 2). Using the maximum operational speed available (400 rpm), the reaction yielded [Ag(Cl)(IPr)] (1a) in 77% after only 30 min of milling. Treating the azolium chloride salts of 2-7 under the same conditions lead to the formation of complexes 2a-7a in good to excellent yields with no particular restriction with respect to the steric bulk of the NHC ligand salt used. Unfortunately, no formation of the desired [Ag(Cl)(NHC)] complex was observed when the chloride salt of Bn₂-BIm (8) was subjected to the same reaction conditions or when the base was doubled up to 6 equivalents. As for the case of $Cu(I)^{51}$ and Au(I),⁷⁰ given the inability of the operational base to deprotonate the azolium salt, we suspect the involvement of an argentate intermediate in the formation of the final product (Scheme 2).



Scheme 2. Mechanosynthesis of [Ag(Cl)(NHC)] complexes. Reaction conditions: NHC·HCl (100 mg), AgCl (1 equiv.), K₂CO₃ (3 equiv.), 400 rpm, 30 min.

Similar result under identical conditions were obtained by using [Au(Cl)(DMS)] as metal precursor, leading to the formation of the [Au(Cl)(NHC)] complexes **1b-8b** (**Scheme 3**). The mechanochemical approach leads to the formation of **1b-8b** in good to excellent yields with substantially shorter reaction times (30 min) than that reported by solution chemistry.⁷⁰ By analogy

with the observations reported for the solution reactions, we suppose that the reaction involves the formation of an aurate species as intermediate, which is converted to the final complex in presence of K₂CO₃. We must mention here that, for the synthesis of [Au(Cl)(SIMes)] (4b), 6 equiv. of K₂CO₃ were necessary, and the use of only 3 equiv. leads to the isolation of the corresponding aurate intermediate [AuCl₂][IMes·H] as major product. Concerning the workup, although throughout the first synthetic campaign was conducted with non-environmentally friendly solvents (e.g. CH₂Cl₂, *n*-pentane), this methodology offers a good entryway to further improve the process sustainability by making an appropriate solvent selection for the workup phase. Indeed, we found that similar results can be obtained for the synthesis of the [M(Cl)(NHC)] complexes (with M = Ag, Au) here reported, when CH_2Cl_2 is replaced by greener solvent such as acetone, and *n*-heptane is used in placed of *n*-pentane (an "acceptable" replacement according to many solvent selection guides).⁷¹ In any case, for many of the syntheses here reported, even when non-green solvents are used for the workup phase (CH₂Cl₂, *n*-pentane, Et₂O, etc.), a rapid assessment of the E-factor shows that the mechanochemical variant significantly reduces the overall environmental footprint of the synthetic process with respect to the solution variant chemistry (see experimental details and E-factor calculations in ESI).



Scheme 3. Mechanosynthesis of [Au(Cl)(NHC)] complexes. Reaction conditions: NHC·HCl (100 mg), [Au(Cl)(DMS)] (1 equiv.), K₂CO₃ (3 equiv.), 400 rpm, 30 min. ^aK₂CO₃ (6 equiv.).

The conditions employed for Ag(I) and Au(I) proved to be suitable also for the assembly of Pd(II)-NHC complexes of the type $[Pd(\eta^3-R-allyl)(Cl)(NHC)]$ (Scheme 4). Again to underline the operational simplicity of the mechanochemical approach, the use of the metal precursor $[Pd(\eta^3-allyl)(\mu-Cl)]_2$ leads to the formation of **1c-5c** and **7c-8c** in high yields, in short reaction time, and this regardless of the steric properties of the ligand precursor. This is in contrast to the solution-phase chemistry, where long reaction times are necessary for the more sterically hindered ligands.⁵² The reaction presumably proceeds through the formation of a palladate intermediate, which can be isolated by carrying out the reaction in absence of K₂CO₃.



 $[Pd(\eta^3-allyl)(Cl)(IMes)]$ 3c (80%) $[Pd(\eta^3-allyl)(Cl)(SIMes)]$ 4c (78%)





 $[Pd(\eta^{3}-allyl)(Cl)(IPr^{*})]$ 5c (86%) $[Pd(\eta^3-allyl)(Cl)(IMe)]$ 7c (41%)



[Pd(η³-allyl)(Cl)(Bn₂-BIm)] 8c (67%)

Scheme 4. Mechanosynthesis of $[Pd(\eta^3-allyl)(Cl)(NHC)]$ complexes. Reaction conditions: NHC·HCl (100 mg), [Pd((η³-allyl)(µ-Cl)]₂ (0.5 equiv.), K₂CO₃ (3 equiv.), 400 rpm, 30 min.

To further highlight the versatility of the methodology, the nature of the allyl moiety was varied (**Scheme 5**). Treatment of the azolium chloride salt of SIPr (**2**) with $[Pd(\eta^3-cin)(\mu-Cl)]_2$ (cin = cinnamyl) leads to the formation of $[Pd(\eta^3-cin)(Cl)(SIPr)]$ (**2d**) in 89% yield.



Scheme 5. Mechanosynthesis of $[Pd(\eta^3-cin)(Cl)(SIPr)]$ complex. Reaction conditions: SIPr·HCl (100 mg), $[Pd((\eta^3-cin)(\mu-Cl)]_2$ (0.5 equiv.), K₂CO₃ (3 equiv.), 400 rpm, 30 min.

The methodology was shown to be scalable (Scheme 6): using a 500 mL zirconia reactor loaded 320.9 g of milling bodies of the same material ($n \approx 764$, $\emptyset = 5$ mm, with the same degree of filling as for the small scale: $\Phi_{MB} = 0.1$) 5.0 g of the azolium chloride of IPr (1) were successfully converted into [Pd(η^3 -allyl)(Cl)(IPr)] (1c) in a 77% yield.



Scheme 6. Large-scale mechanosynthesis of $[Pd(\eta^3-allyl)(Cl)(IPr)]$ complex. Reaction conditions: IPr·HCl (5.0 g, 11.8 mmol), $[Pd((\eta^3-allyl)(\mu-Cl)]_2$ (0.5 equiv., 2.15 g, 5.90 mmol), K₂CO₃ (3 equiv., 4.9 g, 35.3 mmol), 400 rpm, 30 min.

We next turned our attention to the mechanosynthesis of complexes of a Group 9 metal, namely the [Rh(1,5-cod)(Cl)(NHC)] complexes. Using the weak base approach, this type of complexes can be accessed, in solutions, by treatment of the NHC chloride salts with [Rh(1,5-cod)(μ -Cl)]₂ dimer and an excess of K₂CO₃ in refluxed acetone for 16-20 h, as showed by Plenio and coworkers.⁷² The use of K₂CO₃ as operational base was proven to be also effective for the cleavage of the [Rh(1,5-cod)(μ -Cl)]₂ dimer using our mechanosynthetic approach (**Scheme 7**), enabling the isolation of complexes **1f-5f** and **7f-8f** in excellent yields and after only 30 min of milling.



Scheme 7. Mechanosynthesis of [Rh(1,5-cod)(Cl)(NHC)] complexes. Reaction conditions: NHC·HCl (100 mg), [Rh(1,5-cod)(μ-Cl)]₂ (0.5 equiv.), K₂CO₃ (3 equiv.), 400 rpm, 30 min.

CONCLUSIONS

We have developed a general, operationally simple, and scalable mechanochemical synthetic approach that allows the synthesis of valuable well-defined transition metal-NHC complexes. This

procedure involves the use of an environmentally benign and inexpensive base (K₂CO₃) and it proved to be an efficient and reliable method for the synthesis of both saturated and unsaturated NHC complexes, as well as for sterically encumbered ligands, with good to excellent yields in very short reaction times for congeners of Group 9, 10, and 11 metals. This versatile method should encourage the use of solvent-less strategies and mechanochemical synthetic routes to easily access valuable organometallic complexes and catalysts.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and analytical data.

AUTHOR INFORMATION

Corresponding Author

Catherine S. J. Cazin – Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281-S3, 9000 Ghent, Belgium

Authors

Gianmarco Pisanò – Department of chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281-S3, 9000 Ghent, Belgium

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Notes

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TOC entry



SYNOPSIS: An efficient and operationally simple mechanochemical protocol for the sustainable synthesis of well-defined, catalytically relevant late transition metal-N-heterocyclic carbene complexes is reported.