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[Cp*RhCl₂]₂: mechanosynthesis and applications in C–H bond functionalisations under ball-milling conditions†

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A mechanochemical synthesis of [Cp*RhCl₂]₂ has been developed. Under LAG conditions the organometallic complex can be prepared in a shorter reaction time compared to the standard solution-based protocol. The obtained Rh(III) dimer is then applicable as catalyst in subsequent solvent-free mechanochemical C–H bond functionalisations of 2-phenylpyridine.

In the past decade, mechanochemical reactions¹ have experienced rising interest in both inorganic² and organic chemistry.³ In the latter, for example, initially studied stoichiometric transformations such as condensations⁴ have been evolved into more challenging metal-catalysed⁵ and asymmetric organocatalytic reactions,⁶ where mechanochemical approaches often reveal significant advantages over their solution-based counterparts. Hence in many cases, mechanochemical reactions lead to a reduction in the use of bulk solvents during the synthesis and isolation of the products,⁷ a lowering of energy consumption,⁸ a control on the stoichiometry of the products,⁹ and the discovery of new reactivity types.¹⁰

The success of mechanochemical synthesis in the aforementioned fields has affected many areas of research as evidenced by various groups exploring the effects of milling and grinding in preparative organo-metallic chemistry. Although still in its early stages, mechanochemical synthesis has already proven applicable in preparations of organo-metallic complexes containing iron,^{11a} nickel,^{11a,b} gold,¹² rhenium,¹³ manganese,^{13b} strontium,¹⁴ palladium,¹⁵ platinum,^{15b} and aluminium.¹⁶

The fact that organometallic reagents can be prepared or specifically converted by milling has implications far beyond the initial goal of establishing advantageous alternatives for existing syntheses. It also suggests that, at least in certain cases, organometallic compounds tolerate the high-energy conditions of the milling process. Consequently, catalytic applications of

such reagents in mechanosynthesis become possible. Along these lines, Friščić and co-workers recently developed an elegant mechanochemical methodology for conducting cross-metathesis and ring-closing olefin metathesis reactions using ruthenium-based Hoveyda–Grubbs catalysts in a ball mill.¹⁷ Our group introduced the first solvent-free mechanochemically induced C–H bond functionalisation of acetanilides catalysed by [Cp*RhCl₂]₂ (**4**).¹⁸ In the ball mill the oxidative olefination of acetanilides occurs without additional heating in the presence of catalytic amounts of Cu(OAc)₂ and molecular oxygen as the terminal oxidant. Considering the general effectiveness of **4** as catalyst in a wide range of C–H bond functionalisations and realizing its recurrent use as precursor for more active rhodium species,¹⁹ we wondered about establishing a protocol for a mechanochemical preparation of Rh(III) dimer **4**. The success of this approach is reported here.

Guided by the well-known synthesis of ferrocene (**1**) performed in a ball mill by reacting iron(II) chloride with potassium cyclopentadienide (Scheme 1, eqn (1)),^{11a} we hypothesised that a direct synthesis of [Cp*RhCl₂]₂ (**4**) could be achieved by mechanochemical reaction of rhodium(III) chloride hydrate (**2**) with pentamethylcyclopentadiene (Cp*H, **3**) (Scheme 1, eqn (2)). If successful, a reduction of the reaction time and a minimisation of the solvent amount was envisaged, as the classical protocols for preparing **4**²⁰ typically involved refluxing of Rh(III) salts with an excess of **3** in an alcoholic solution for several hours.²¹ Liquid assisted

- Previous work: mechanosynthesis of ferrocene (1999)

- This work: mechanosynthesis of [Cp*RhCl₂]₂

Scheme 1 Mechanochemical approaches towards organometallic complexes.

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grinding (LAG)²² was expected to be beneficial because it allowed retaining the polar protic environment during the targeted complex formation.

As first step, the LAG reaction (with MeOH) between **2** and **3** to give **4** was screened in a mixer mill (MM) and in a planetary mill (PM) using three types of milling media: stainless steel (SS), zirconium oxide (ZrO₂) and tungsten carbide (WC). As conceived, the Rh(III) dimer was formed, and after only 2 h of milling **4** was obtained in yields ranging from 29% to 62%. The highest yield was observed when a WC vessel with WC balls was used. In ZrO₂ milling media the yield of **4** was lower (Table 1, entries 1–3). The dependence of the yield on the density of the milling material (with WC being the most effective) was in accord with the need for a high energy input (elevated temperature) when **4** is prepared in solution.^{20,21} Subsequently, the milling time was varied from 1 h to 6 h. After 3 h of milling the yield of **4** had increase to 74%. Longer milling times did not lead to a significant change in the yield of **4** (Table 1, entries 3–7). This observation suggested that the complex was stable under the milling conditions, fulfilling an essential requirement for a potential use of the compound as catalyst in a ball mill. It is worth mentioning that the synthesis of the **4** was also successful when MeOH was substituted by EtOH in the LAG reaction or when a combination of RhCl₃ hydrate (**2**) and **3** was ground neat. In both cases, however, the yield of the Rh(III) dimer was lower than before (Table 1, entries 8 and 9). Finally, the effect of the amount of Cp*H (**3**) on the yield of **4** was studied, and to our delight, milling of the RhCl₃ hydrate (**2**) with 2 or 3 equivalents of diene **3** revealed a positive effect affording **4** in 81% and 87% yield, respectively (Table 1, entries 10 and 11).

Table 1 Optimisation of the milling conditions for the synthesis of the [Cp*RhCl₂]₂ (**4**)^a

Entry	Type of mill	Milling media	LAG	Frequency	Time (h)	Yield (%)
1	MM ^b	SS	MeOH	30 Hz	2	45
2	PM ^c	ZrO ₂	MeOH	800 rpm	2	29
3	PM ^d	WC	MeOH	800 rpm	2	62
4	PM	WC	MeOH	800 rpm	1	44
5	PM	WC	MeOH	800 rpm	3	74
6	PM	WC	MeOH	800 rpm	4	75
7	PM	WC	MeOH	600 rpm	6	76
8	PM	WC	EtOH	800 rpm	3	54
9	PM	WC	—	800 rpm	3	40
10 ^e	PM	WC	MeOH	800 rpm	3	81
11 ^f	PM	WC	MeOH	800 rpm	3	87

^a Reaction conditions: **2** (150.05 mg, 0.576 mmol), **3** (118.32 mg, 0.868 mmol, 1.5 equiv.), LAG, $\eta = 0.25$ (where η is the volume of solvent (in μ L) divided by the sample weight (in mg)).²² ^b Reaction conducted in a mixer-mill (MM), using a 10 mL stainless steel (SS) jar with one SS ball of 10 mm in diameter. ^c Reaction conducted in a planetary mill (PM), using a 12 mL ZrO₂ vessel with 20 ZrO₂ balls of 5 mm in diameter. ^d Reaction conducted in a planetary mill (PM), using a 12 mL tungsten carbide (WC) vessel with 20 WC balls of 5 mm in diameter. ^e Use of 2 equiv. of **3**. ^f Use of 3 equiv. of **3**.

¹H NMR analysis of the reaction mixture immediately after the grinding was stopped revealed the presence of the Rh complex **4**. A control reaction in which a mixture of RhCl₃ hydrate (**2**), Cp*H (**3**) and MeOH was stirred at room temperature in CDCl₃ for 6 h did not show the presence of the dimer **4**, confirming the formation of [Cp*RhCl₂]₂ upon milling rather than during the analysis or work-up in solution (Fig. S1 in ESI†).

After having developed a mechanochemical route towards rhodium complex **4** and realising that, in general, only little attention has been paid to the potential use of mechanochemically prepared complexes in catalytic mechanochemical reactions,²³ we wondered about a direct application of **4** in a subsequent C–H bond functionalisation. As test reaction, the catalysed halogenation of 2-phenylpyridine (**5**) in the ball mill was selected. The results are summarised in Table 2.

In the absence of the Rh complex no reactivity was observed when **5** was milled with 1.1 equiv. of *N*-bromosuccinimide (NBS) for 4 h (Table 2, entry 1). Conversely, in the presence of (mechanochemically prepared) [Cp*RhCl₂]₂ and AgSbF₆, **5** reacted with 1.1 equiv. of NBS to afford a mixture of the *ortho* mono- and dibrominated phenylpyridines (Table 2, entry 2).

The lack of selectivity exhibited here by the pyridine moiety as a directing group is a common difficulty known from the solution-based methods.²⁴ To circumvent this problem 2.2 equiv. of NBS were used, which led to the formation of dibrominated 2-phenylpyridine **6** as the major product in 60% yield (Table 2, entry 3). A higher reactivity was observed in the mechanochemical iododination of **5** with *N*-iodosuccinimide (NIS), yielding **7** in 78% (Table 2, entry 4). Finally, the long milling time required to prepare **6** and **7** in the planetary mill was reduced along with an increase in their yields after conducting the reactions in a mixer mill (Table 2, entries 5 and 6). This improvement appeared to be not just the

Table 2 Mechanochemical Rh(III)-catalysed halogenation of 2-phenylpyridine (**5**)^a

Entry	Rh cat. (mol%)	Type of mill	Milling media	NXS (equiv.)	Time (h)	Yield (%)
1	0	PM ^b	ZrO ₂	NBS (1.1)	4	0
2	5	PM ^b	ZrO ₂	NBS (1.1)	4	Di- and mono-products
3	5	PM ^b	ZrO ₂	NBS (2.2)	8 ^c	60
4	5	PM ^b	ZrO ₂	NIS (2.2)	8 ^c	78
5	5	MM ^d	SS	NBS (2.2)	3	74
6	5	MM ^d	SS	NIS (2.2)	3	84

^a Reaction conditions: **5** (54.3 mg; 0.349 mmol), NXS, AgSbF₆ (0.4 equiv.) and [Cp*RhCl₂]₂. ^b Reaction conducted in a planetary mill at 800 rpm, using a 12 mL ZrO₂ vessel with 20 ZrO₂ balls of 5 mm in diameter. ^c Cyclic milling (1 h $\times$ 8 times; 5 min of pause), with change in the direction of the rotation after each cycle to improve the mixing. ^d Reaction conducted in a mixer mill at 30 Hz, using a 10 mL stainless steel jar with one SS ball of 10 mm in diameter.

Scheme 2 Mechanochemical synthesis of rhodacycle **8** and its stoichiometric reaction with NBS to give **6**.

result of having used a denser milling media (SS vs. ZrO_2), but of the better mixing achieved in the MM compare with the PM where inadequate mixing was observed, even with WC milling media.

In order to gain insight into the mechanism of the Rh-catalyzed mechanochemical halogenations, some stoichiometric reactions were carried out. First, based on a solution protocol to synthesize rhodium complex **8**,²⁵ 2-phenylpyridine (**5**) was reacted with $[\text{Cp}^*\text{RhCl}_2]_2$ in the presence of sodium acetate in a planetary mill (Scheme 2, top). After 3 h of milling the solvent-free C–H bond activation^{15a} of **5** had generated rhodacycle **8** in 89% yield. Noteworthy, this yield was comparable to the one obtained in solution, but overall the reaction was faster than in DCM.^{25a} Complex **8** was then milled with NBS and AgSbF_6 to afford **6** as the major product in 71% yield (Scheme 2, bottom), evidencing that **8** could be an intermediate in the original catalytic reaction in the ball mill.

In summary, we have established the first mechanochemical protocol to prepare the valuable $[\text{Cp}^*\text{RhCl}_2]_2$ (**4**). The LAG reaction was faster than the solution-based one affording **4** in good yield at room temperature. Furthermore it was demonstrated that **4** catalyzed the solvent-free C–H bond halogenation of 2-phenylpyridine in a ball mill.²⁶ The reactions occurred without heating and in a short reaction time. Finally, the mechanochemical formation of rhodacycle **8**, which in solution is known to be a key intermediate in reactions involving 2-phenylpyridine as directing group,¹⁹ and its subsequent transformation to **6**, suggests that Rh(III)-catalysed solvent-free mechanochemical C–H bond functionalisations occur in a similar manner than in solution.²⁷

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