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A Gentler Touch: Synthesis of Modern Ruthenium Olefin Metathesis Catalysts Sustained by Mechanical Force

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Mechanochemical synthesis of nine contemporary ruthenium catalysts used for olefin metathesis is described, being the first reported example of formation of Ru carbene organometallic complexes in solid state. Three key organometallic transformations commonly used in the synthesis of the second and third generations of Ru catalysts in solution—phosphine ligand (PCy_3) exchange with *in situ* formed N-heterocyclic carbene (NHC) ligand, PCy_3 to pyridine ligand replacement, and benzylidene ligands interchange—were proved to work under mechanochemical conditions, affording the targets in high purity. Mechanochemical approach not only requires less amounts of organic solvent (null for synthesis, only for purification) and is scalable, but also allows for transformations that were reported impossible in the solution phase.

Introduction

Catalytic olefin metathesis evolved into a powerful and versatile methodology for the assembly of carbon-carbon bonds.[1–2] So-called second and third generation ruthenium metathesis catalysts bearing the privileged N-heterocyclic carbene (NHC) ligands, are currently finding their first applications in pharmaceutical production.[3] Industrially, the biggest application (by volume) utilizing olefin metathesis is located in polymers and composites area.[4] For this purpose a highly specialized class of so-called latent metathesis catalysts has been developed.[5–7] Recent advances expanding the potential of the free carbenes (particularly cyclic (alkyl)(amino) carbenes (CAAC))[8–9] as ligands for Ru, made another large-scale application of metathesis finally possible—a biomass transformation via ethenolysis.[10–11] At the same time, the most popular benzylidene, indenylidene and Hoveyda-Grubbs complexes continue to dominate current academic research.[1–3] The second and third generation catalysts are typically accessed *via* ligand exchange reactions utilizing easily obtainable Ru complexes as starting materials. The most frequently used routes can be classified as follows:

(a) Route 1: Exchange reaction in which a PCy_3 ligand is replaced with a carbene ligand (NHC or CAAC; Figure 1)
(b) Route 2: Alkylidene ligand metathesis-exchange, where a Ru complex (usually benzylidene or indenylidene one) reacts in a stoichiometric metathesis reaction with a corresponding styrene derivative (Figure 1).
(c) Route 3: Exchange reaction in which a PCy_3 ligand is replaced with a pyridine ligand to obtain third generation Ru catalysts (Figure 1).

All these transformations (with a partial exception of Route 3, where the excess of a liquid pyridine serves as the solvent)[12] have been made always in solutions, utilizing organic solvents, such as toluene, dichloromethane (DCM) or hexane to dissolve the reagents.[1–2] In addition to obvious practical inconvenience (handling of anhydrous solvents under inert atmosphere), in some cases these routes (Figure 1) suffer also from loses of product due to its partial solubility, decomposition during isolation and contamination with various impurities, which is discussed in detail below.

At the same time, mechanochemistry and, more specifically, ball-milling is becoming an increasingly valuable technique for solvent-free (or at least partially solvent free) and environmentally friendly synthesis of organic compounds (catalysed and uncatalysed).[13–15] The metal-catalysed organic syntheses under mechanochemical conditions include also one report on olefin metathesis reactions in a ball-mill.[16] On contrary, examples of organometallic complexes assembled by mechanochemistry are less populated, however, recently a number of elegant contributions have been published on synthesis of simple NHC complexes of Pd, Cu and Au[17–22] as well as on the synthesis of NHC ligand precursors.[23]

However, according to our knowledge, a mechanochemical approach to synthesis of sophisticated multi-ligand carbene-alkylidene complexes of ruthenium has never been reported. The reason for this can be associated to the relative fragility of these complexes and their sensitivity to heat resulted during grinding. During the key study on mechanochemical olefin metathesis it was reported that Ru catalysts were unstable when steel jar and balls were used.[16] On the other hand, problems related to synthesis of these complexes in solution are also known. For example, oxygen, moisture, Brønsted bases and some other reagents or solvents used during the solution phase synthesis pose threats to quality of the obtained complex (see below for a more detailed discussion). Fogg has proven

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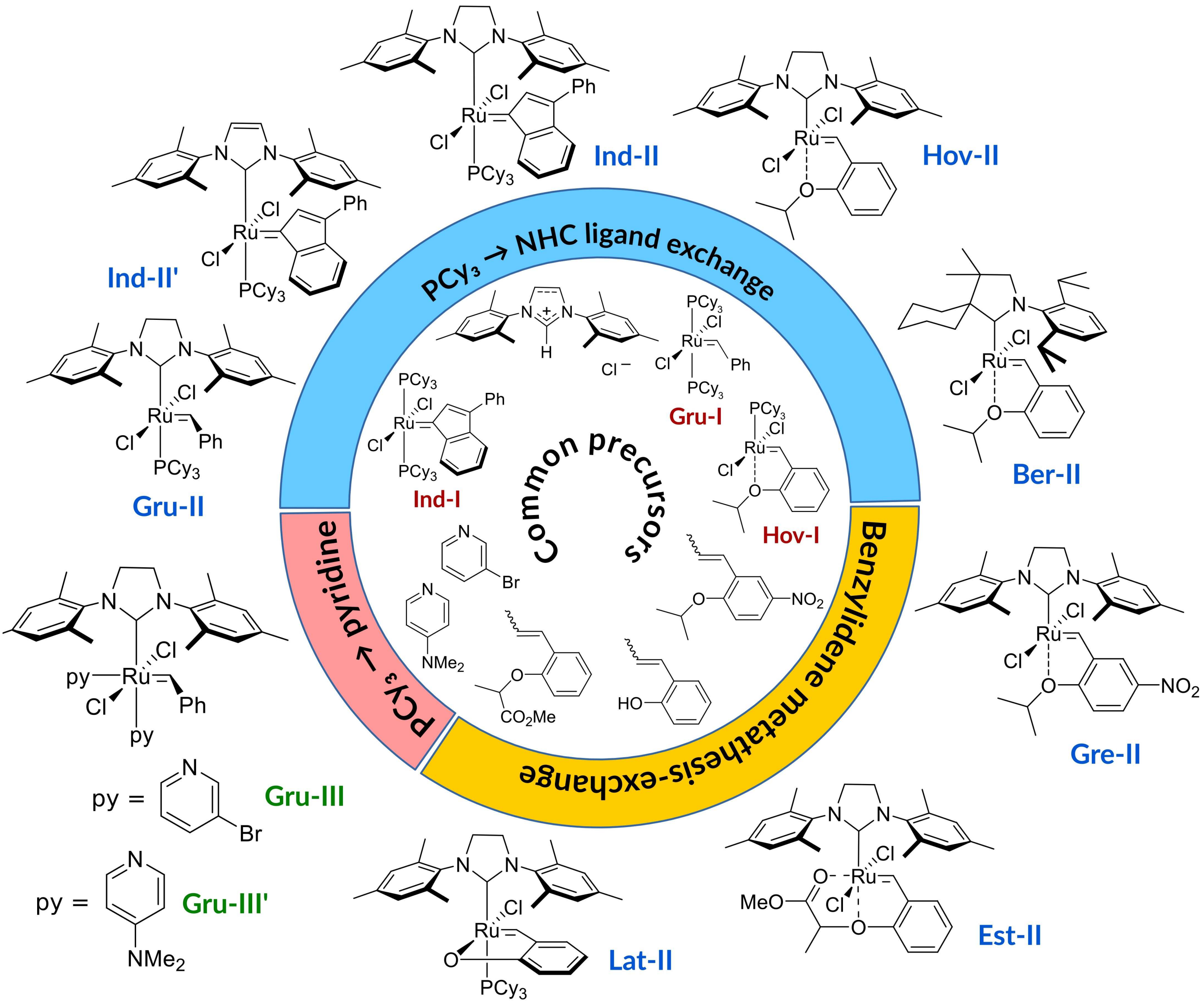


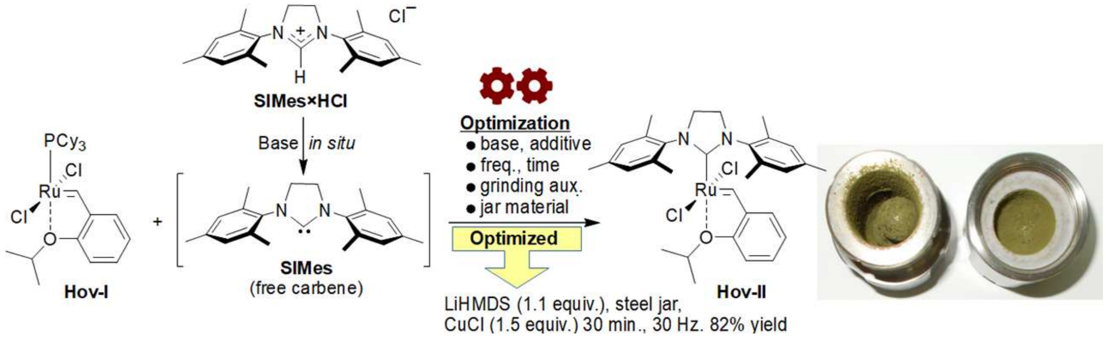
Figure 1. Modern Ru metathesis catalysts and key transformations in their preparation. Outside the circle are selected second (marked blue) and third generation catalysts (**Gru-III** and **Gru-III'**, marked green), inside the circle are common precursors, incl. first generation catalysts **Hov-I**, **Gru-I**, **Ind-I** (marked red). Circle represents three key transformations in second and third generation catalysts synthesis.

that various batches of commercial catalysts can contain Ru nanoparticles that can cause unwanted side reactions.[24]

Therefore, we decided to check the utility of the mechanochemical methods in preparation of advanced second and third generation Ru metathesis catalysts. Here we report the success of this approach, illustrated with synthesis of nine contemporary catalysts, some of them being already the classics (**Hov-II**, **Ind-II**, **Ind-II'**), two being activated analogues of robust Hoveyda-Grubbs system (**Gre-II**, **Est-II**), and third generation complex **Gru-III** and **Gru-III'**. In addition, two specialized complexes designed for industrially important transformations —ring opening metathesis polymerization (**Lat-II**) and ethenolysis (**Ber-II**)—were targeted, due to their increasing commercial potential.

Results and Discussion

Mechanochemical synthesis of Hoveyda-Grubbs catalysts Hov-II ($PCy_3 \rightarrow$NHC exchange reaction). Proof-of-concept and optimization. Second generation catalysts can be economically accessed from the corresponding inexpensive first-generation complexes *via* Route 1, in which a PCy_3 is replaced with an NHC ligand. Classically, this route relies on *in situ* generation of free carbenes, *via* treatment of various imidazolinium salts with a strong base such as *t*-BuOK, LiHMDS, potassium *t*-amylate (*t*-AmOK), etc. This method is deceptively simple experimentally, and utilizes inexpensive imidazolinium salts, however a long list of warnings and failures related to it was reported in literature, forcing chemists to look for alternatives.[25–31] The catalytic activity of the resulted second generation Ru complex can be



Scheme 1. Mechanochemical synthesis of Hoveyda-Grubbs catalyst **Hov-II**. General concept and optimization variables. LiHMDS = lithium 1,1,1,3,3,3-hexamethyldisilazane.

Table 1. Optimization of **Hov-II** catalyst preparation by PCy_3 to NHC exchange.[a]

Entry	Grinding Auxiliary	Jar	Additive (1.5 equiv.)	Frequency [Hz]	Time [min]	Isolated Yield [%]
1	NaCl	agate	none	28	120	15
2	none	agate	none	28	120	43
3	none	agate	CuCl[b]	28	180	53
4	none	steel	CuCl	28	90	47
5	none	steel	CuCl	28	45	61
6	none	steel	CuCl	30	30	82
7	NaCl	steel	CuCl	30	30	69
8	celite	steel	CuCl	30	30	40
9	none	steel	tartaric acid	30	30	56
10	none	steel	citric acid	30	30	59
11	none	steel	benzoic acid	30	30	18
12	none	steel	NH_4Cl	30	30	56
13	none	steel	$CHCl_3$	30	30	42
14	toluene	steel	CuCl	30	30	43
15	CH_2Cl_2	steel	CuCl	30	30	67

[a] Reaction conditions: jar charged under argon with **SIMes×HCl** (1.2 equiv.), **Hov-I** (1 equiv.), LiHMDS (1.1 equiv.), grinding auxiliary (100 wt.% for solids; 25 µL for liquids), additive (1.5 equiv.). The temperature of the vessel at the end of milling was not exceeding 37 °C, [b] 1.2 equiv.

reduced or even spoiled completely by traces of unreacted imidazolinium salts or alkali metal base, and various other contaminants, including dangerous Ru-hydrides, formed during the process, or during the work-up upon action of methanol or water added to quench the excess of base.[31] The *in situ* generated free NHC is sensitive to water and CO_2, so unintended exposure to air must be avoided during the reaction course. On the other hand, high crystalline nature of the popular imidazolinium salts and possibility of drying them and storing over long periods of time is a valuable aid to the reproducibility. Therefore, despite all difficulties discussed so diligently by Fogg,[31] we decided to choose the imidazolinium salt **SIMes×HCl** as the model NHC precursor due to its low cost and easy synthesis.

To check if the concept of free carbene generation and ligand exchange in solid state is doable, a set of initial reactions (Scheme 1) was conducted in a Retsch MM400 mill, using 0.15 mmol reaction scale in a 10 mL steel milling jar charged under argon, milled at 28 Hz using one stainless steel ball (12 mm diameter) and NaCl as grinding auxiliary. Different bases (*t*-AmOK, *t*-BuOK, Cs_2CO_3, K_2CO_3, KHMDS, LiHMDS) were screened to convert **SIMes×HCl** into free **SIMes** that can react with solid **Hov-I** present in the same jar. The best result (around 15 % of yield) was obtained in the case of LiHMDS. In order to improve the yield, different jar materials (steel, agate, Teflon), grinding auxiliaries (none, Al_2O_3, NaCl, and liquids), number of balls and milling frequencies (25–30 Hz) were tested. In an agate jar at 28 Hz the yield was improved to 43 %, the value that allowed us to demonstrate the validity of our proof-of-concept, but not high enough to be competitive with classical "in solution" synthesis. It is well known that formation of **Hov-II** can be inhibited by the interaction of PCy_3 ligand, and therefore the synthesis of this complex is commonly driven by addition of various phosphine scavengers, such as solid CuCl,[32] various exchange resins,[30,31,33] or even $CHCl_3$.[34]

In our screening we tested, therefore, various additives starting from previously optimized conditions (Table 1, entries 1–2) and applying modifications in due course. Surprisingly, conventional steel jars gave best results,[35] and we found that shorter milling time and higher frequency give better results. The best PCy_3-scavenger was undoubtedly CuCl (entry 5), however, interesting results were found with citric and tartaric acid, never tested before in the context of second generation catalyst preparation (entries 9–10). Promising was ammonium chloride (NH_4Cl, entry 12), unfortunately observed corrosion of the stainless steel jar surface discouraged us from further trials. (Similar effect was exhibited by $KHSO_4$, see SI).

Benzoic, *p*-toluenesulfonic and camphorsulfonic acids as well as liquid auxiliaries (as in the liquid assisted grinding technique)[36] gave lower yields of **Hov-II** (Table 1).

Under the optimized conditions we used CuCl (added after 15 minutes of milling to avoid formation of NHC–Cu complex), a steel jar with two balls and 30 minutes of total milling time at 30 Hz, to afford cleanly **Hov-II** as a green powder in 82% isolated yield (Scheme 1, Table 1 entry 6), after the usual SiO_2 filtration and crystallization (the same conditions were tested also in a larger scale without silica gel use, *vide infra*). In comparison, the original route gave **Hov-II** in 85% yield after work-up and purification.[37] This complex was virtually pure by analytical techniques (see SI). To finally check if the activity profile of such obtained **Hov-II** can match the activity of the commercial catalyst (from Sigma-Aldrich) two model ring-closing metathesis (RCM) tests were conducted utilising the catalysts at loading of 0.1 mol% (see ESI) and 500 ppm (Figure 2). The first target (**1**) is a standard benchmark RCM substrate, recommended by Grubbs,[38] while the second diene (**3**), being more susceptible to a Ru–H promoted isomerization of the double bond, was chosen to check if the catalyst produced by us is free from traces of hazardous ruthenium by-products. We were, therefore, pleased to see that in both reactions the catalytic profiles exhibited by the mechanochemically obtained catalyst matched or even slightly outperformed in activity the commercial sample. Importantly, despite the RCM of diene **3** was conducted at relatively high temperature, no other products than **4** were observed. The lack of C–C double bond isomerization observed for both 0.1 mol% and 500 ppm loadings suggests that no traces of ruthenium hydrides nor other impurities that can deviate the reaction course were present in the sample of **Hov-II** prepared by grinding.

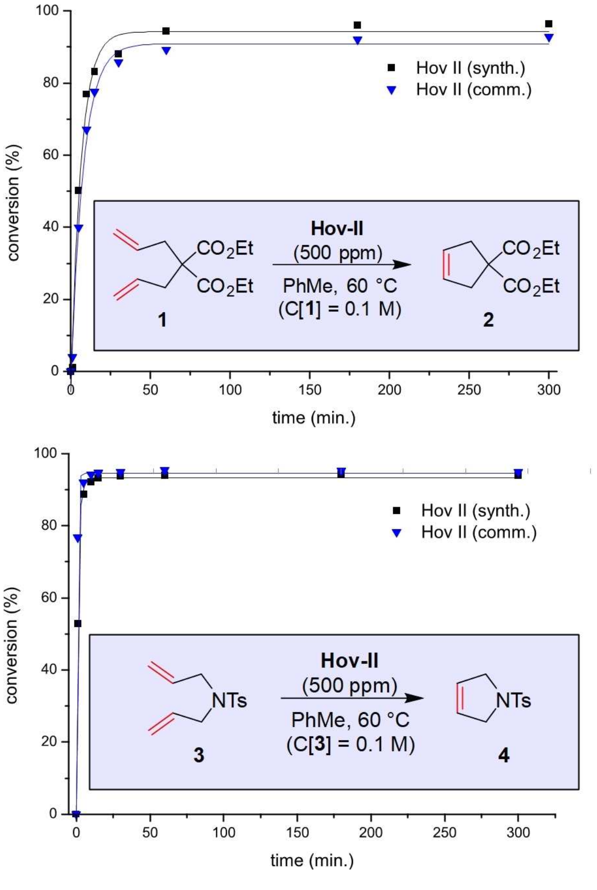
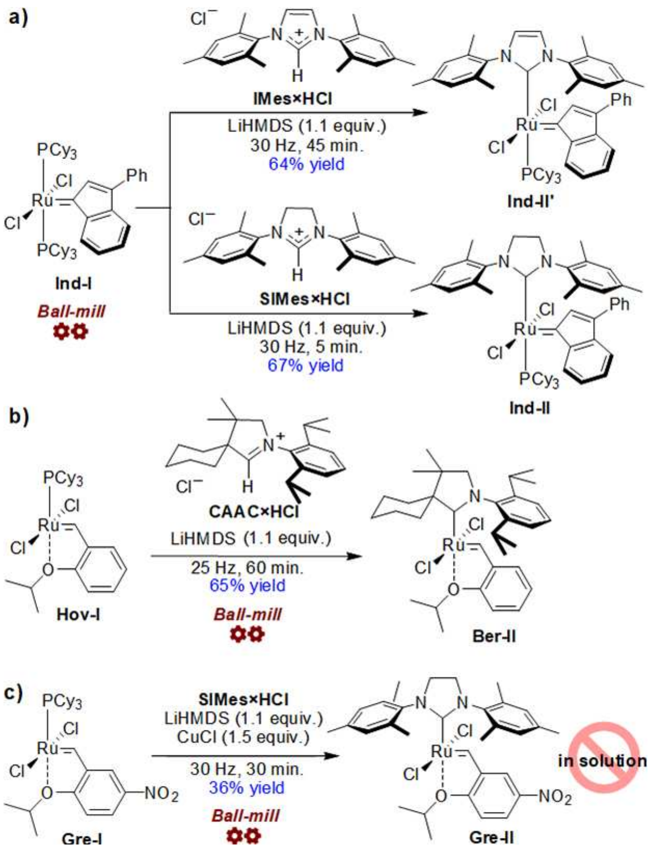


Figure 2. Testing the catalytic activity of mechanochemically prepared Hoveyda-Grubbs complex. Top: Model RCM reaction of **1** (500 ppm catalyst loading). Bottom: Model RCM reaction of **2** (500 ppm catalyst loading). Conversion by GC against an internal standard. Comm. = Commercial catalyst; Synth. = catalyst synthesized mechanochemically. Lines are visual aid only.

Mechanochemical synthesis of other modern catalysts *via* $PCy_3 \rightarrow$NHC and CAAC exchange reaction. Having proven the possibility of NHC generation and exchange under mechanochemical conditions, we attempted to check the scope and limitations of this method by preparing other advanced second generation catalysts. First, we studied phosphine to SIMes and IMes ligands exchange in popular **Ind-I** complex (Scheme 2a).

We were pleased to find that the milling sequence we have developed previously, works also in this case, and afforded, after filtration through SiO_2 and evaporation of the solvent, the ex-Evonik Catmetium® RF catalyst (**Ind-II′**) in 64% yield and excellent purity (Scheme 2a). While the originally reported



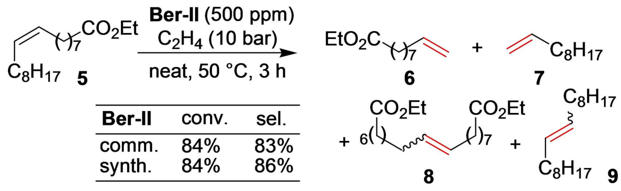
Scheme 2. Mechanochemical synthesis of other Ru catalysts *via* PCy_3 with NHC (or CAAC) exchange. a) Synthesis of Umicore Grubbs M2 (**Ind-II**) and Evonik Catmetium® RF catalyst (**Ind-II′**); b) Synthesis of Bertrand-Grubbs CAAC complex **Ber-II**; c) Preparation of nitro-catalyst **Gre-II.**

method in an anhydrous hexane solution was giving **Ind-II**′ in 79%, so in 15% higher yield,[39] we think that simplicity of the milling method that does not require drying the solvent, is in part balancing this. Repeating the same procedure with **SIMes × HCl** gave the saturated analogue **Ind-II** in similar isolated yield (Scheme 2a).

Bertrand-Grubbs complex (**Ber-II**) is an important catalyst in the context of ethenolysis of bio-sourced unsaturated fatty acids.[8–10] Therefore, we were pleased to see that under previously established conditions **CAAC × HCl** can be deprotonated to form the free cyclic (alkyl)(amino) carbene that reacts in the same milling chamber with solid **Hov-I** to yield the ethenolysis catalyst **Ber-II** in 65% yield (Scheme 2b).

In order to compare the activity of catalysts obtained in a ball mill with the classically made **Ber-II**, a model ethenolysis reaction of ethyl oleate **5** was made (Scheme 3). Importantly, this experiment exhibited the same activity and selectivityof the mechanochemically made complex (for details see SI).

The above described PCy_3 to NHC and CAAC ligand exchange reactions were successful, but one can point out that the yields obtained by us were only comparable (Scheme 1) or even slightly lower (Scheme 2a–b) than those obtained in classical reactions in solution. To check if the milling method can really bring a new opportunity into some "problematic" Ru catalysts syntheses, we decided to try a direct ligand exchange between **Gre-I** and the SIMes ligand. Direct synthesis of the nitro-activated catalyst **Gre-II** from its first generation precursor was tried by us in the solution many times, but without success,[40] probably because of low stability of **Gre-I** under strongly basic conditions required for *in situ* generation of the free NHC ligand. Therefore, we were pleased to see that in the solid state 36% of **Gre-II** can be obtained by a direct metalation of SIMes (Scheme 2c).



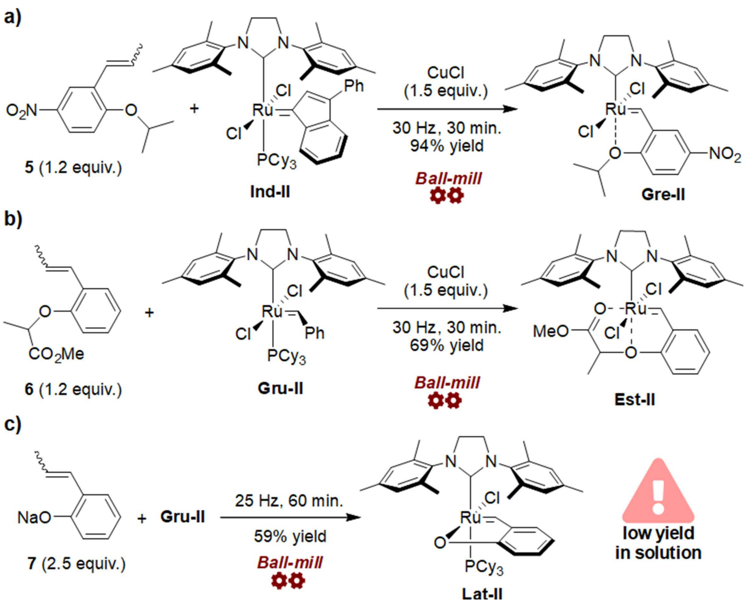
Ber-II	conv.	sel.
comm.	84%	83%
synth.	84%	86%

Scheme 3. Ethenolysis of ethyl oleate **5** utilising commercial (comm.) and mechanochemically (synth.) prepared **Ber-II**. Conv. = 100−[(final moles of **5**) × 100/(initial moles of **5**); Sel. = 100 × (moles of **6** + **7**)/([moles of **6** + **7**) + (2 × moles of **8** + **9**)].

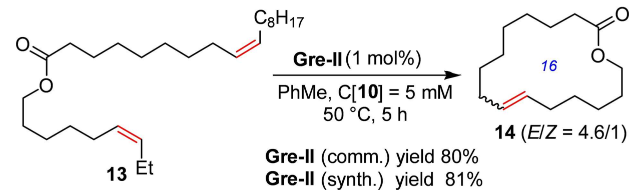
Mechanochemical synthesis of Ru catalysts *via* alkylidene metathesis-exchange. The second most popular method for synthesis of advanced ruthenium benzylidene metathesis catalysts is based on alkylidene ligands metathesis-exchange process.[41] In this method a 2nd generation complex (e.g. **Gru-II** or **Ind-II**) reacts with a corresponding styrene derivative, undergoing a cross metathesis-alkylidene ligands exchange reaction. Such reactions are very well optimized in a solution, leading to many useful catalysts in a laboratory and semi-preparative scale. Analogously, we decided to check if the same reaction can be made under mechanochemical conditions (Scheme 4).

As we found, the EWG-activated complex **Gre-II** can be straightforwardly obtained without a solvent in almost quantitative yield (94%, Scheme 4a). It shall be noted that the same reaction in solution gives slightly lower yield (76%). To check the activity of the mechanochemically made EWG-activated catalyst **Gre-II** we used it in a challenging RCM macrocyclisation of **13** leading to a macrocyclic musk **14**,[42] and were pleased to find that it shows the same activity as the commercial Apeiron-Synthesis catalyst (Scheme 5).

Similarly, the chelating-ether modified complex **Est-II**, utilized in BILN 2061 hepatitis C antiviral agent production,[43]



Scheme 4. Mechanochemical synthesis of Ru catalysts via alkylidene metathesis-exchange. a) Synthesis of Apeiron Nitro Catalyst (**Gre-II**) b) Synthesis of an 18-electron bis-chelated catalyst (**Est-II**); c) Preparation of Apeiron LatMet polymerization catalyst (**Lat-II**).



Scheme 5. RCM of diene **13** utilising commercial (comm.) and mechanochemically (synth.) prepared **Gre-II**.

was obtained using ball milling in the yield comparable to the one reported previously in a solution (71 %).[44]

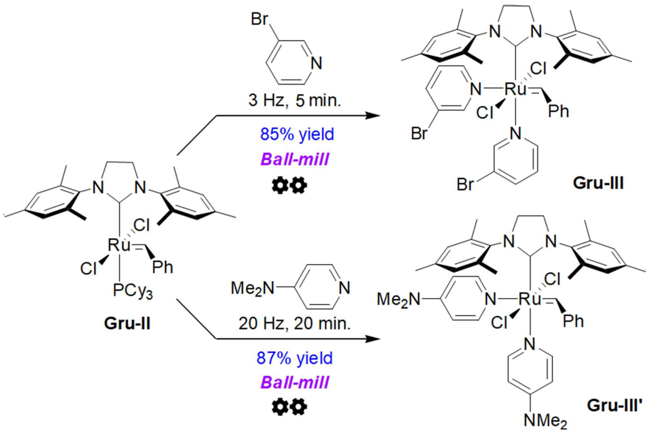
Next, we decided to check if the mechanochemistry can bring some additional value to synthesis of a latent catalyst for olefin metathesis polymerization reactions. A ruthenium phenolate complex **Lat-II**, a commercially available catalysts for ROMP,[5] is typically synthesized from **Gru-II** precursor and 2-propenylphenol in a presence of PCy_3 used to bind HCl formed in the reaction.[45,46] As the use of the costly and air-sensitive cycloalkyl phosphine is not advantageous practically, we were looking for a more economical and simpler method, utilizing the easily available and inexpensive sodium salt **12** (Scheme 4c). Interestingly, while the same reaction in a solution was giving only 18 % isolated yield (see SI) and suffered from low reproducibility, under mechanochemical conditions complex **Lat-II** was formed in a satisfactory yield of 59 %.

Mechanochemical synthesis of a third generation catalysts via PCy_3→pyridine exchange. To test yet another type of exchange in the coordination sphere of Ru, we attempted to obtain a so-called third generation catalyst **Gru-III**, bearing pyridine ligands instead of phosphines. Interestingly, this valuable polymerization catalyst is prepared in solvent free conditions, because the excess of a liquid pyridine used in the exchange reaction can act as the solvent.[12] Using mild mechanochemical conditions (one Telfon ball and low frequency), we were able to obtain the popular **Gru-III** under conditions that can be related to the liquid assisted grinding[47] (Scheme 6 top). In contrast, synthesis of other III-generation catalysts from solid pyridine derivatives, such as 4-dimethylaminopyridine (DMAP) must be done in an organic solvent.[47] To illustrate the applicability of mechanochemical methods in synthesis of this type of complexes, we obtained catalyst **Gru-III**′, disclosed in the patent literature.[47] As we checked, milling of a mixture of solid **Gru-II** and DMAP (two steel balls) led to formation of **Gru-III**′ in 87 % yield (Scheme 6 bottom).

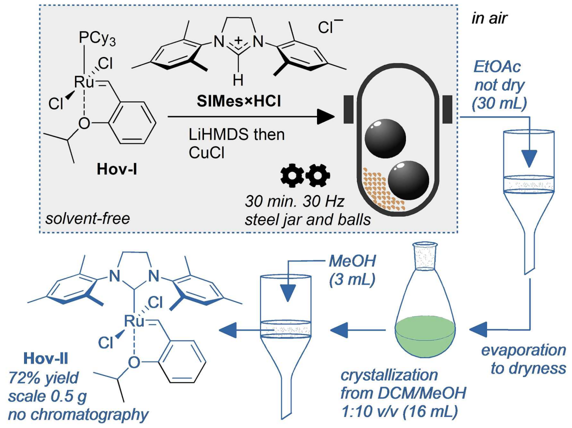
Outlook, larger scale experiment and green chemistry context. Experiments described herewith show that despite some initial fears, diverse types of advanced Ru alkylidene complexes can be obtained mechanochemically, in steel. Three prototypical methods of assembling the 2nd generation Ru metathesis catalysts were tested (NHC metalation; benzylidene ligands metathesis; neutral ligands exchange) and all of them seem to be operational at milling conditions. The yields obtained were in some cases lower, in some cases higher as compared with classical methods, however, importantly, at least in two cases (**Gre-II**, **Lat-II**) we have shown that the reactions that are problematic in a solution proceed better under mechanochemical conditions. We can only speculate that this is because of different stability of reactive species, such as NHC free carbenes or **Gre-I**, in the solid form. This observation is also of practical importance and can have some consequences in synthesis of specialized Ru-complexes.

In addition, the scalability of mechanochemical methods was preliminary tested by us by repeating the synthesis of **Hov-II** in 0.5 g scale without the use of column chromatography (Scheme 7). We were pleased to see that the reaction proceeded in this scale without problems, and despite the product was purified only by crystallization, without use of silica gel purification, it was obtained in good yield and in high purity (see SI).

Excluding—even in part[48]—of solvents during the synthesis of sophisticated organometallic complexes, such as the modern Ru catalysts, is advantageous from the practical point of view, as the solvents must be rigorously dried and degassed before use, which is costly, and if not done correctly leads to non-



Scheme 6. Mechanochemical synthesis of Ru third generation catalyst **Gru-III** and **Gru-III**′ *via* PCy_3→pyridine exchange.



Scheme 7. Mechanochemical synthesis of **Hov-II** without using column chromatography. Grey box shows the solvent-free part of the preparation; operations marked in blue were made in air with standard not-dried solvents. Scale of synthesis: 0.5 g. For details see SI.

reproducible results.[31] Minimizing the use of solvents is also important from the green chemistry point of view. Using the preparation of **Gre-II** from **Ind-II** (Scheme 4a) as the practical example, we conducted calculations of green chemistry metrics.[49] We found that *Reaction Mass Efficiency* (RME) and especially the Environmental (E) factor were better in the case of mechanochemical synthesis of **Gre-II** (see SI for details).

The benefit of metathesis catalysts production by milling of solid reagents, as compared to classical conditions in a solution is, however, the most visible when so-called *Ecoscale* score[50] is considered. *Ecoscale* gives a score from 0 to 100 taking into account variables such as cost, safety, technical set-up, energy and purification. According to the definition, the *Ecoscale* is calculated by assigning a value of 100 to an ideal reaction and then subtracting penalty points for non-ideal conditions. As we calculated, the *Ecoscale* score for the preparation of **Gre-II** by mechanochemical methods is 54, while the same reaction conducted in a solution gives only 32 points, which shall be considered as less favourable in a modern chemical synthesis.[49] As the key NHC-precursors used by us can also be obtained under mechanochemical conditions,[23] this renders the additional advantage of the presented methodology.

Conclusions

To sum up, the mechanochemical methodology can be seen as a valuable addition to the existing solution-based preparation methods of selected 2nd generation Ru metathesis catalysts,[51] affording the expected targets in high purity and activity fully comparable to the same catalysts obtained in solution. Not only does it reduce the amount of solvent used for synthesis, but it can also expedite catalyst production relative to traditional methods.[52] We believe that this technique will gain more importance for synthesis of advanced organometallic complexes, especially in the context of its very recent recognition by IUPAC as one of top ten chemistry innovations that will change the world.[53,54]

Experimental Section

Mechanochemical preparation of Hov-II: A dry 10 mL stainless steel ball mill jar was equipped with two stainless steel balls (12 mm) and placed under inert atmosphere. The jar was charged with **SIMes×HCl** (1.2 equiv., 350 mg), Ru 1st generation complex (**Hov-I**) (1 equiv., 511 mg) and lithium bis(trimethylsilyl)amide (1.1 equiv., 161 mg) and subjected for milling at 30 Hz frequency for 15 minutes. Then solid CuCl (1.5 equiv., 128 mg) was added in one portion to the same reaction jar and further subjected to ball milling for 30 min at 30 Hz. After this point forth, all manipulations were carried out in air. The dark brown-green solid mass was extracted with ethyl acetate (25–30 mL). The solution was filtrated through a Büchner funnel with glass frit filled with neutral Celite. Then the filtrate was evaporated to dryness under reduced pressure. The dark brown residue was then dissolved in 1:10 v/v mixture of CH_2Cl_2 and methanol (16 mL) at ambient temperature. After concentration of one fourth of the initial volume using a rotary evaporator (without immersion in a water bath, the flask should be covered by frost) green crystals were precipitated. The green crystals were filtered off on a Büchner funnel with glass frit and, washed twice with small portions of methanol (2–3 mL). The resulted crystals were dried under vacuum to afford Hoveyda-Grubbs 2nd generation catalyst **Hov-II** (382 mg, isolated yield 72 %). ^1H NMR (400 MHz, CD_2Cl_2) δ 16.51 (s, 1H), 7.57-7.53 (m, 1H), 7.08 (s, 4H), 6.98-6.89 (m, 2H), 6.84 (d, $J=8$ Hz, 1H), 4.89 (sept, $J=8$ Hz, 1H), 4.15 (s, 4H), 2.44 (s, 12H), 2.41 (s, 6H), 1.22 ppm (d, $J=4$ Hz, 6H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 296.1 (d, $J=16.2$ Hz), 211.3, 152.5, 145.7, 139.4, 129.9, 129.8, 122.8, 122.7, 113.5, 75.7, 52.1, 21.4, 21.3, 19.7 ppm. The spectra correspond to those described in the literature.[37]

Mechanochemical synthesis of Gre-II from Ind-II. A dry 10 mL stainless steel ball mill jar was equipped with two stainless steel balls (12 mm) and placed under inert atmosphere. The jar was charged with 1-isopropoxy-4-nitro-2-propenylbenzene (1.2 equiv., 21.2 mg), complex **Ind-II** (1 equiv., 75.9 mg) and CuCl (1.5 equiv., 12 mg) and subjected for milling at 30 Hz frequency for 30 minutes. After this point forth, all manipulations were carried out in air. The green solid mass was extracted with ethyl acetate (12-15 mL), concentrated in vacuo, and the resulting material was purified by filtering through a column of silica. Elution with n-hexane/EtOAc (8:2 v/v) removed the desired compound as a green band. Removal of the solvent, the green residue was then dissolved in a 1:3 v/v mixture of CH_2Cl_2 and methanol at ambient temperature. After concentration of this solution to ca. one-fourth of the initial volume at room temperature using a rotary evaporator green crystals were precipitated. The rest of the methanol was decanted, and the product was washed with n-hexane (2×1.5 mL) and dried in a rotary evaporator and then on the vacuum pump (50.5 mg, 94 %).

Note: Authors contributions: NM made majority of ball-mill experiments, except **Gru-III** synthesis; AM participated in early experiments; AS made comparative metathesis experiments and obtained **Gru-III**; GS initiated this research, AK and KG supervised it and wrote manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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FULL PAPERS

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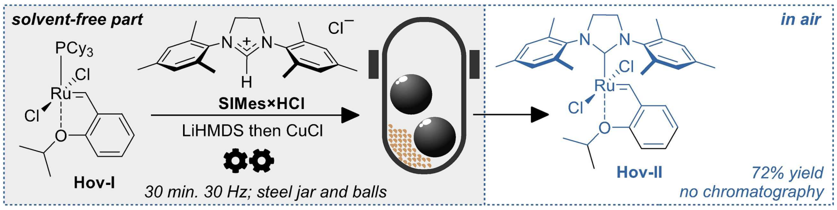
1 – 9

A Gentler Touch: Synthesis of Modern Ruthenium Olefin Metathesis Catalysts Sustained by Mechanical Force



The first solid state synthesis of ruthenium carbene organometallic complexes used asolefin metathesis catalysts is described. It was shown that three key organometallic transformations commonly used in the synthesis of the second and third generations of Ru catalysts in solution—phosphine ligand (PCy_3) exchange with *in situ* formed N-heterocyclic carbene (NHC) ligand, PCy_3 to pyridine ligand replacement, and benzylidene ligands interchange—work efficiently under mechanochemical conditions.