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Efficient, Facile, and Green Synthesis of Ruthenium Carboxylate Complexes by Manual Grinding

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Abstract: Recently, scientists have been developing sustainable processes, and in this context, mechanochemistry is commonly associated with green chemistry for its ability to reduce waste generation from chemical reactions. The well-known acetate complex, diacetate bis(triphenylphosphine) ruthenium(II) [Ru(OAc)$_2$(PPh$_3$)$_2$], is a versatile precursor for preparing active complexes for several catalytic reactions. This report presents an efficient and straightforward manual grinding protocol for the sustainable synthesis of ruthenium carboxylate complexes starting from the commercially available [RuCl$_2$(PPh$_3$)$_3$] and metal carboxylates. This work represents a novel and preliminary investigation into carboxylate precursors' alternative solventless synthesis route based on manual grinding. To our knowledge, this is the first time [Ru(OAc)$_2$(PPh$_3$)$_2$] has been prepared via a mechanochemical procedure. The synthesis method has also been investigated for other alkali metal carboxylates and yields ranging from 30 to 80% were obtained. A comparison of sustainability and environmental impact between conventional solution synthesis and the grinding route has been carried out using the E-factor and Mass Productivity. While for the acetate complex E-factor and MP were only slightly better compared with the solvent method (3 vs. 4 for E-factor and ~6 vs. 5 for MP), for benzoate higher results were found (1 vs. ~4 for E-factor and 10 vs. 5 for MP).

Keywords: ruthenium(II) complexes; acetate; carboxylate; manual grinding; sustainable processes

1. Introduction

In recent decades, the development of sustainable processes has received much attention. A key aspect of the assimilation and implementation of these processes is that this new concept came along with a series of guidelines according to the Twelve Principles of Green Chemistry, which provided the parameters to extend the idea of sustainability to a higher level, resulting in the design of new reactions and products and to the development of new processes and concepts [1]. In this context, mechanochemistry has stimulated the scientific community's interest, providing physicochemical transformations promoted by mechanical energy originating from compression, shear, impact, extension, etc. [2–6]. Mechanochemistry is commonly associated with green chemistry for its ability to reduce waste production in chemical synthesis and reactions. In addition to their efficiency and practicality, mechanochemical reactions are also recognized for their sustainability, due to the solvent-free nature of most mechanochemical protocols. Several works demonstrate the potential of mechanochemistry as an alternative route that could reduce the costs and environmental footprint of fine chemical production [7–11].

Phosphine ligands have proven very attractive due to their crucial role as ancillary ligands in organometallic complexes which have been widely investigated and applied in homogeneous catalytic reactions [12–15]. Grubbs [16–18] for the olefin metathesis and

Noyori [19–23] for the asymmetric hydrogenation of the C=X (X = C, N, O) bonds have obtained ground-breaking results (Figure 1).
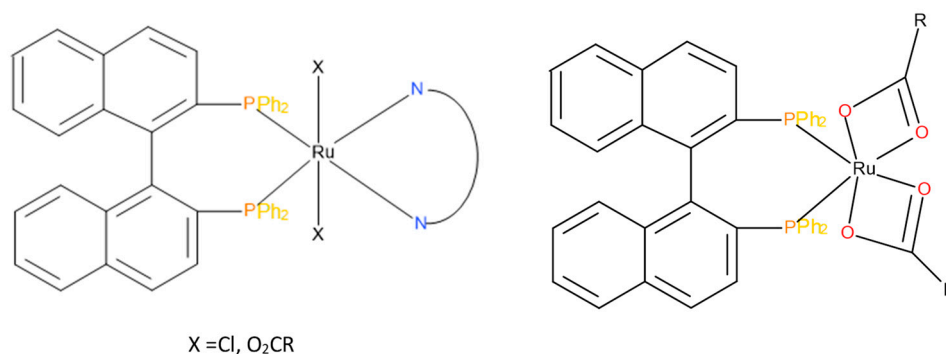
Figure 1. Noyori's catalysts [16,20,21].

On the other hand, carboxylate complexes display attractive catalytic properties, and a large number of ruthenium complexes have been synthesized [12,13,24–26]. Specifically, ruthenium diphosphine complexes with carboxylate ligands have been investigated for their valuable activity in catalytic hydrogenation reactions [12,27–33].

The well-known bis(triphenylphosphine) diacetate ruthenium(II) ([Ru(OAc)$_2$(PPh$_3$)$_2$]), is a versatile precursor for the preparation of active complexes for several catalytic reactions [27,34,35]. Carboxylate ruthenium complexes are prepared from the commercially available precursor RuCl$_2$(PPh$_3$)$_3$ by exchange of the chloride with the correspondence carboxylate and, eventually, modification of the phosphine ligand. In Scheme 1 is displayed the preparation of [Ru(OAc)$_2$(PPh$_3$)$_2$] which is a key intermediate of this chemistry, via the classical route in solution with t-BuOH at reflux and via the new mechanochemical process at RT.
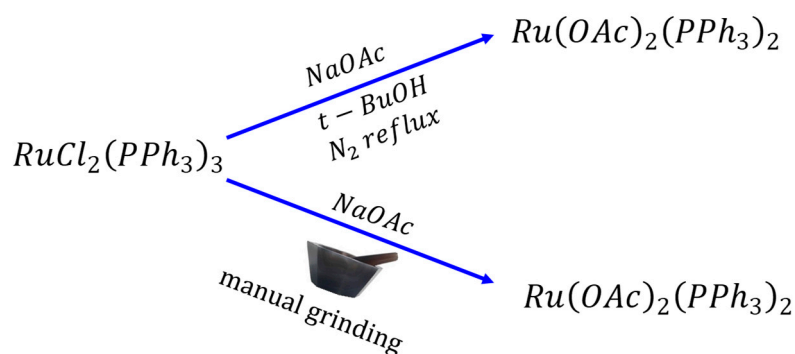
Scheme 1. Traditional procedure (**top**) and manual grinding route (**bottom**) to obtain [Ru(OAc)$_2$(PPh$_3$)$_2$] from [RuCl$_2$(PPh$_3$)$_3$].

Carboxylate complexes have been widely used for several applications. The Noyori's catalysts BINAP-Ru(O$_2$CR)$_2$ [36–39] have shown to be highly active in the enantioselective hydrogenation of a wide range of prochiral functionalized olefins such as terpenes, amino acids, and isoquinoline alkaloids [40], some α,β-unsaturated carboxylic acids [41], and ketoesters [19], while ampy, cyclometalated, and pincer complexes have been found to be active in the hydrogenation and transfer hydrogenation of carbonyl compounds [24,26–28,42].

Thus, on account of the wide applications of carboxylate ruthenium complexes, we investigated the synthesis of the carboxylate PPh$_3$ ruthenium precursors via an alternative solventless synthesis route based on the manual grinding of the reagents.

Milling reactions provide several advantages over solution chemistry, such as working at room temperature and shorter reaction times [4,43]. It also offers a platform for reagents with poor or no solubility and hence low performance in organic solvents [44], overcoming

the need to use biphasic solvent systems to achieve high reactivity. This preliminary work investigates the applicability of new sustainable procedures for the preparation of homogenous catalysts. The conventional method is relatively simple, but the possibility of a solvent-free synthesis route is increasingly attractive due to the need to convert conventional solution-based transformations into more environmentally friendly processes, improve sustainability, and provide feasible solutions to realize the concepts of Green Chemistry and the United Nations Sustainable Development Goals (UN SDGs). Thus, this work aims to investigate a new facile route for synthesizing ruthenium(II) carboxylate complexes via manual grinding.

To the best of our knowledge, this is the first preparation of $[Ru(OAc)_2(PPh_3)_2]$ via a mechanochemical route from $[RuCl_2(PPh_3)_3]$ and sodium acetate. The process has also been investigated for other alkali metal carboxylates.

The E-factor has been used to compare the sustainability and environmental impact of conventional solution synthesis and the grinding route.

The E-factor is a green metric developed by Roger Sheldon in 1992 [45,46], focused on the quantity of waste produced for a given mass of product. The assessment of the E-factor evidenced the resource efficiency and the environmental footprint of the process. In addition, mass productivity (MP) was also calculated. In this case, all the materials used in the process are considered (reagents, solvents, catalysts, etc.) [47,48].

2. Materials and Methods

Ru carboxylate complexes have been prepared by grinding a defined amount of alkali metal carboxylate and dichlorotris(triphenylphosphine)ruthenium(II) ($[RuCl_2(PPh_3)_3]$) in an agate mortar for a specific time (Scheme 1). After grinding, the obtained powder was collected with a spatula. The carboxylates are listed in Scheme 2.

Lithium acetate	CH_3COOLi	
Sodium acetate	CH_3COONa	
Potassium acetate	CH_3COOK	
Sodium benzoate	C_6H_5COONa	
Sodium pyruvate	$CH_3C_2O_3Na$	
Sodium phenylglyoxylate	$C_6H_5C_2O_3Na$	

Scheme 2. Alkali metal carboxylates used in this study.

Although $[RuCl_2(PPh_3)_3]$ can be easily synthesized [49], in this study we used a commercial product loaned from Johnson Matthey Inc. (Royston, UK) Metal carboxylates (reagent-grade chemicals) were used as purchased. Lithium acetate (>99%), sodium benzoate (99%), and sodium phenylglyoxylate (95%) were purchased from Sigma Aldrich (Saint Louis, MO, USA), potassium acetate (98%) and sodium acetate anhydrous (99%) were purchased from Riedel-de Haen (Charlotte, NC, USA), sodium pyruvate (>99%) from

Calbiochem (San Diego CA, USA). Dichloromethane d2 and methanol d4, for NMR analysis, were purchased from Sigma Aldrich (Saint Louis, MO, USA).

Three different molar ratios of $[RuCl_2(PPh_3)_3]$ and sodium acetate (1:10, 1:5, and 1:3) have been used for the preparation of the acetate complex, while 1:5 has been adopted for all other carboxylate complexes; we chose a 1:5 ratio because it is a good compromise between saving reagents in line with an environmentally friendly process and a good yield. The manual grinding has been carried out for 10, 20, and 30 min.

The progress of the reaction and the purity of the final product were checked by ^{1}H and ^{31}P NMR using a Avance III HD 400 MHz spectrometer (Bruker, MA, USA) at 298 K. The deuterated solvent, CD_2Cl_2, was used without any further purification. Notably, 10 mg of the reaction mixture was dissolved in 500 μL of CD_2Cl_2 or CD_3OD. ^{31}P NMR spectra have been integrated by the ERETIC (Electronic REference To access In vivo Concentrations) method [50] with the software TopSpin 4.1.4. The ERETIC method provides a reference signal synthesized by an electronic device that can be calibrated against absolute concentrations. Once the ERETIC peak has been calibrated, the concentration of the compound can be easily obtained. The reported conversions are an average of three runs.

Work-up of $[Ru(OAc)_2(PPh_3)_2]$: after the grinding of $[RuCl_2(PPh_3)_3]$ and NaOAc in a ratio of 1:10 for 30 min, the resulting mixture was collected and kept under reduced pressure overnight; then it was transferred to a filter. The washing procedure was performed under an argon atmosphere. The solid was washed with 15 mL of H_2O (3 × 5 mL), 15 mL of CH_3OH (3 × 5 mL), and 15 mL of Et_2O (3 × 5 mL). The powder was then dried under reduced pressure.

The sustainability of the proposed reaction has been assessed using the E-factor and MP. The green metric factors were calculated after the work-up procedure to also consider the solvent used for product isolation. The E-factor has been calculated for grinding procedures and conventional solution synthesis of diacetate bis(triphenyl phosphine) ruthenium(II) and dibenzoate bis(triphenyl phosphine) ruthenium(II) using Equation (1):

$$\text{E-factor} = \frac{\text{mass waste}}{\text{mass of desired product}} \qquad (1)$$

MP is the percentage ratio between the mass of the desired product and the total mass of the materials used (Equation (2)):

$$\text{MP } (\%) = \frac{\text{mass of desired product } \times \ 100}{\text{total mass of used materials}} \qquad (2)$$
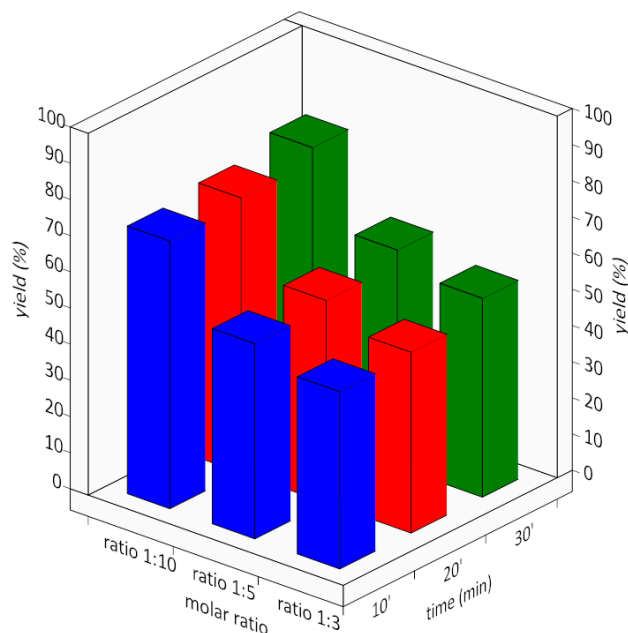
3. Results

All reactions were carried out by grinding 50 mg of $RuCl_2(PPh_3)_3$ and the corresponding amount of alkali metal carboxylate (Scheme 2) in an agate mortar with an internal diameter of 70 mm.

3.1. Alkali Metal Acetates

Manual grinding of $[RuCl_2(PPh_3)_3]$ with sodium acetate (NaOAc), in a molar ratio of 1:10, for 30 min leads to the formation of the corresponding complex $[Ru(OAc)_2(PPh_3)_2]$ in 80% yield (yield from ^{31}P NMR analysis). A color change from black to brown-red was observed during milling (Figure S1). The 1:10 molar ratio was chosen for the comparison with the conventional solution synthesis [51]. The molar ratio between $[RuCl_2(PPh_3)_3]$ and NaOAc, was progressively reduced to 1:5 and 1:3 to investigate the possibility of carrying out the synthesis with a smaller amount of reagents in light of a more sustainable procedure (Figure 2).

As the excess acetate decreases, the yield of the final product decreases. However, the 1:5 ratio can be considered a good compromise between saving reagents and maintaining acceptable yield; thus, this ratio was chosen for subsequent studies. The time dependence

of the reaction was then investigated by grinding the reagent for 10 and 20 min (Figure 2); the yield of the reaction progressively increased as the grinding time increased.

Figure 2. Dependence of the reaction between [RuCl$_2$(PPh$_3$)$_3$] and NaOAc on reagents molar ratio and grinding time (10′, blue; 20′ red; 30′ green).

These results show that the mechanochemical synthesis of [Ru(OAc)$_2$(PPh$_3$)$_2$] is a facile alternative synthesis route to conventional solution procedure. Indeed, similar yields are obtained, but the reaction is faster and solvent-free. In addition, the alkali metal cation has been varied, and lithium and potassium acetate have been exploited (Figure 3).
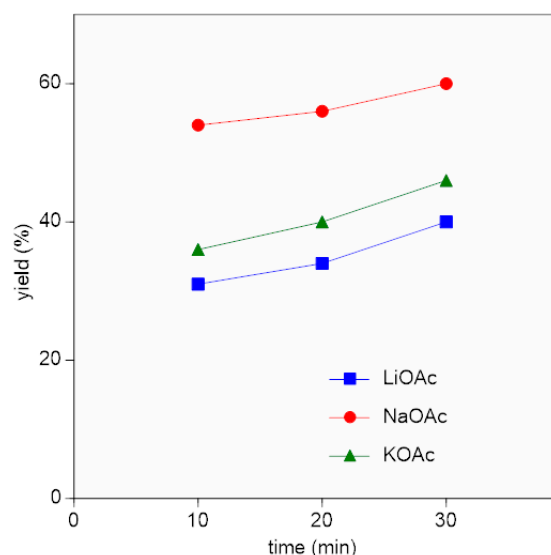
Figure 3. Yield of the reaction between [RuCl$_2$(PPh$_3$)$_3$] and MOAc as a function of the nature of the alkali metal ion (M$^+$ = Li$^+$, Na$^+$ and K$^+$) and grinding time (1:5 molar ratio).

Again, the final products were obtained with good yields in a short grinding time. When lithium or potassium acetate has been used, the dependence of the reaction yield on grinding time is more evident. Considering the reaction after 30 min, a better result is obtained with sodium acetate than with the other alkali metal precursors; with sodium acetate, 60% of the product was obtained against 40% (LiOAc) and 46% (KOAc).

The reaction between $RuCl_2(PPh_3)_3$ and metal acetate formed $Ru(OAc)_2(PPh_3)_2$ and MCl. Calculating the difference in the standard molar enthalpy of formation, ΔH_f^0 (Table 1) between the product (MCl) and the reactant (MOAc), it is observed that the reaction with potassium is thermodynamically favored, but the yield is higher for sodium acetate. From thermodynamic data, the conversion does not follow the $\Delta H^0_{reaction}$, but it is correlated to the $\Delta_f H^0$ of the acetate, suggesting, to a first approximation, that the grinding reaction of metal acetates in the presence of $RuCl_2(PPh_3)_3$ may be governed by a kinetic factor.

Table 1. $\Delta_f H^0$ (from [52]) and product yields for alkali metal acetates.

| Alkali Metal Acetate	$\Delta_f H^0$ MOAc (kJ/mol)	$\Delta_f H^0$ MCl (kJ/mol)	Product Yield (%)
LiOAc	−741	−409	40
NaOAc	−709	−411	60
KOAc	−723	−436	46

Indeed, the yield of conversion is in the order NaOAc > KOAc > LiOAc and follows the $\Delta_f H^0$ of the respective acetates, and can be related to the fact that the Na-OAc bond is easier to break, compared to the other M-OAc (M = Li, K) bonds (Table 1).

After a work-up starting from 150 mg of $RuCl_2(PPh_3)_3$, the acetate product $[Ru(OAc)_2(PPh_3)_2]$ was isolated in a 69% yield which is mostly the same as that obtained through the classical synthesis in solution [51], confirming that mechanosynthesis is an efficient route for the preparation of ruthenium carboxylate complexes.

3.2. Sodium Carboxylates

To further highlight the versatility of the method, other ruthenium complexes were prepared by mechanosynthesis, starting from sodium benzoate, sodium pyruvate, and sodium phenylglyoxylate (Scheme 2). Manual grinding for 30 min of $[RuCl_2(PPh_3)_3]$ with sodium carboxylate (RCO_2Na) in a molar ratio of 1:5 leads to the formation of the corresponding complexes $[Ru(O_2CR)_2(PPh_3)_2]$ in good to excellent yields (Figure 4). Reactions have also been carried out with shorter grinding times (10 and 20 min).
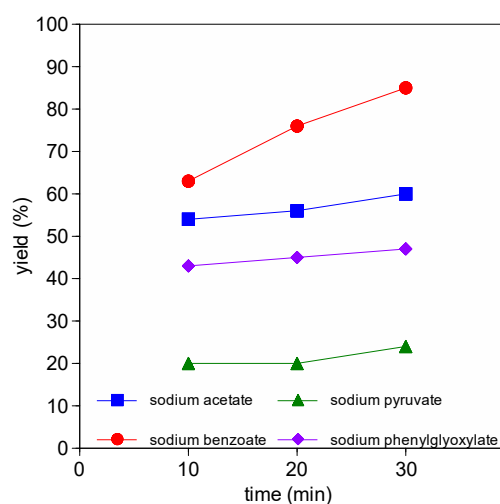
Figure 4. Dependence of the reaction between $[RuCl_2(PPh_3)_3]$ and sodium carboxylate on grinding time (1:5 molar ratio).

By reacting $[RuCl_2(PPh_3)_3]$ with sodium benzoate, the formation of the product is strongly influenced by grinding time. After 10 min, 63% of the benzoate derivative is obtained; then, the yield progressively increases to 76 and 85% after 20 and 30 min, respectively. Thus, the synthesis of the benzoate complex obtained by grinding is very fast, with

a yield comparable to that obtained by the conventional solution procedure, using a lower excess of sodium carboxylate without solvent [53].

When [RuCl$_2$(PPh$_3$)$_3$] was ground with sodium phenylglyoxylate, only 47% of the corresponding carboxylate complex was obtained. The grinding time only slightly affects product formation, as 45% yield was already achieved after 10 min. The additional time does not significantly improve the yield. By contrast, poor conversion is achieved for sodium pyruvate, with a 24% yield after 30 min.

It is worth noting that under these conditions a dicarboxylate species [Ru(OCOR)$_2$ (PPh$_3$)$_2$] is formed, as inferred from ^{31}P NMR measurements showing a singlet in the range of 55–63 ppm (Figures S2–S6). Conversely, the monocarboxylate derivative [Ru(OCOR) Cl(PPh$_3$)$_3$] displaying three non-equivalent P signals has not been detected.

It is interesting to evaluate the difference between the carboxylate salts (sodium acetate and benzoate, blue bars) and the corresponding sodium salt of alpha-keto acids (sodium pyruvate and phenyl glyoxylate, green bars); indeed, when sodium carboxylates are used, higher yields are obtained compared to salts of alpha-keto acids, respectively, 60 and 85% vs. 24 and 47% (Figure 5). This effect could be related to the different acidity of the carboxylic acids and alpha-keto acids. In contrast, pyruvic and phenylglyoxylic acids are moderately acidic with a pKa in the range of 2.39–2.15; acetic and benzoic acids have a higher pKa (4.75–4.21). The higher the acidity, the lower the donor ability of the carboxylate anions to coordinate with ruthenium metal and form the metal complex [54]. This observation is consistent with the trend found in a previous study between the stability constant of some metal carboxylate complexes and the basicity of the anions [55].
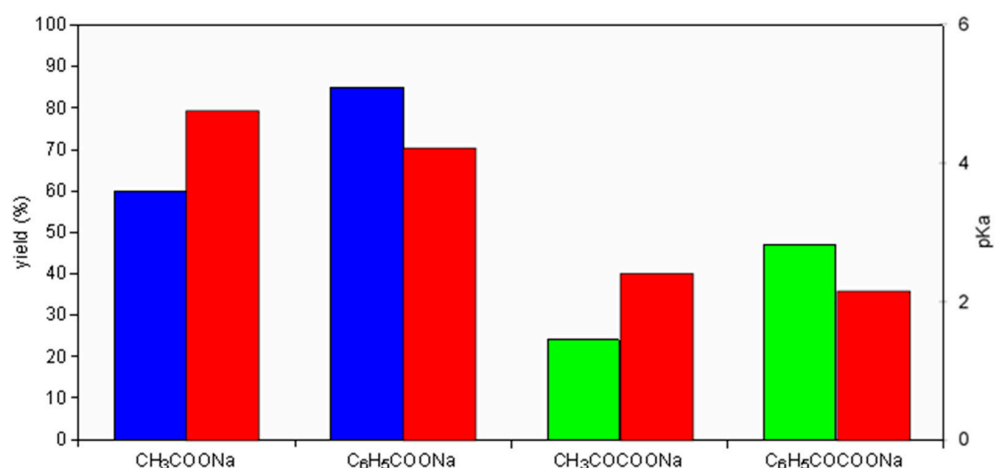
Figure 5. Product yield for carboxylates (blue bars) and alpha-keto acids (green bars), sodium salts (reaction conditions: 1:5 molar ratio and 30 min of grinding), and pKa of the correspondent carboxylic acids (red bars).

For carboxylates and the salts of alpha-keto acids, the variation of the substituent, CH$_3$- or C$_6$H$_5$-, induces a significant effect on the product yield. CH$_3$- is inductively electron-donating. In this case, the inductive effect pushes electron density onto the carboxylate anion, producing a destabilizing effect, while C$_6$H$_5$- is electron-withdrawing and draws electron density away from the carboxylate anion, dispersing the charge and creating a stabilizing effect that enhances the formation of the ruthenium carboxylate complex.

In summary, the ability of the carboxylate anion to react with the metal complex is primarily related to the basicity of the anion. Still, when the basicity is similar, the conjugate effect of the substituent can influence the electron cloud density of the carboxylate salt modifying its ability to react with the ruthenium metal center [54].

3.3. Comparison of Green Chemistry Metrics

An evaluation of green chemistry factors for two selected ruthenium carboxylate complexes, [Ru(OAc)$_2$(PPh$_3$)$_2$] and [Ru(O$_2$CPh)$_2$(PPh$_3$)$_2$], has been carried out to assess the

green efficiency of the grinding procedure. The green metrics have been calculated for the ruthenium complexes obtained after the work-up procedures. For a better understanding of the sustainability of the process, two green chemistry metrics, the E-factor and the MP (mass productivity), have been calculated for both the ruthenium complexes isolated by grinding and by the classical solution procedure (Figure 6). When the grinding route is used, moderately better results in green chemistry metrics are achieved, with a lower E-factor and higher MP, thus demonstrating the sustainability and the low environmental impact of the mechanosynthesis of these ruthenium complexes. While the E-factor and MP for the OAc complex were slightly better compared with the established solvent method (3 vs. 4 for E-factor and ~6 vs. 5 for MP), higher results were found for O_2CPh (1 vs. ~4 for E-factor and 10 vs. 5 for MP).
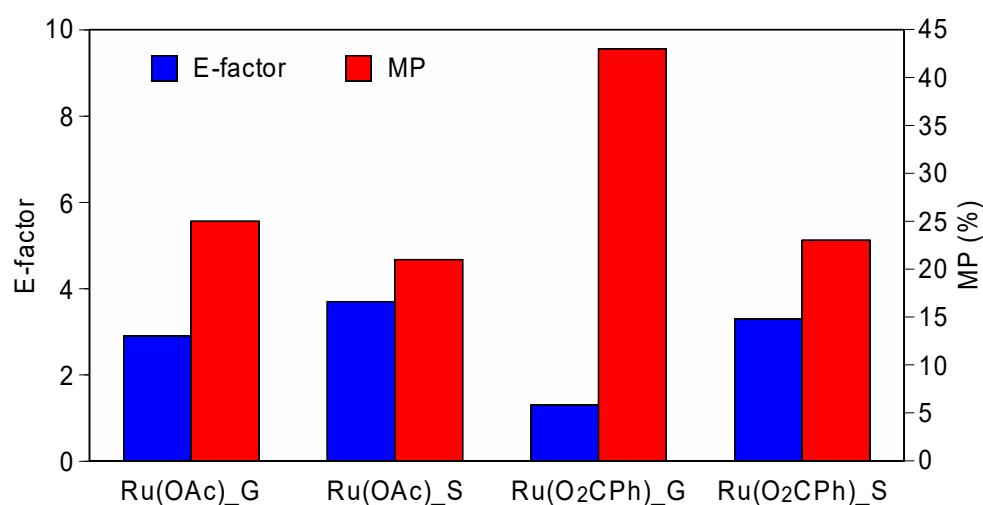
Figure 6. Comparison of E-factor and mass productivity (MP) for ruthenium acetate ([Ru(OAc)$_2$ (PPh$_3$)$_2$]: Ru(OAc)) and ruthenium benzoate ([Ru(O$_2$CPh)$_2$(PPh$_3$)$_2$]: Ru(O$_2$CPh)) complexes prepared by grinding (G) route (ratio 1:10, 30 min) and by classical solution (S) procedures.

This confirms that mechanochemistry can be useful for the sustainable synthesis of ruthenium complexes.

4. Conclusions

Here, a general and straightforward mechanochemical synthetic approach for synthesizing valuable ruthenium carboxylate complexes by manual grinding (mortar and pestle) has been developed. This procedure is an efficient method for synthesizing these complexes, with good yields in very short reaction times. This procedure was carried out in a mortar at room temperature and was compared to the traditional synthesis conducted in t-BuOH under N_2 reflux. This preliminary study should open a new perspective for solventless strategies by the mechanosynthesis route of ruthenium complexes. The yield of the final product is strongly influenced by the molar ratio of [RuCl$_2$(PPh$_3$)$_3$] to metal carboxylate, the grinding time, and the alkali metal cation.

In particular, more considerably, a larger excess of metal acetate and longer grinding times result in higher yields. Higher yields were obtained when sodium acetate was used as the precursor due to its better tendency to react to form ruthenium complexes than lithium and potassium salts. The different acidity of the carboxylate salts and the corresponding sodium salt of alpha-keto acids can affect the ability to react with the ruthenium metal center; the higher the acidity, the lower the yield of the product. Furthermore, an electron-withdrawing substituent can enhance the formation of Ru-carboxylate complexes. A comparison of green chemistry metrics between the conventional synthesis in solution and the grinding route indicates the low environmental impact of the mechanosynthe-

sis procedures, thus opening new perspectives for the development of new ruthenium complexes by milling.

Conflicts of Interest: The authors declare no conflicts of interest.

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