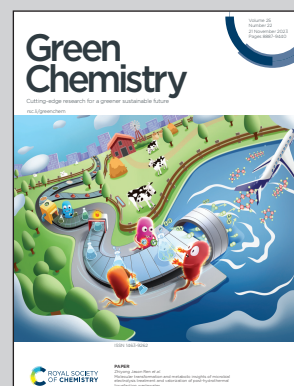


Showcasing work from the Pilarski lab from the Department of Chemistry - BMC at Uppsala University, Sweden.

Solvent-free and ball mill-free catalytic C-H methylation

A method for regioselective Rh-catalysed C-H methylation is presented. The method avoids the use of toxic solvents on which some previous approaches relied, and does not require automated ball milling, which makes the sustainability benefits of the solvent-free approach broadly accessible. Other advantages include high functional group compatibility and shorter reaction times compared to previous methods. Preliminary insights from scanning electron microscopy are also presented.

As featured in:



See Lukasz T. Pilarski *et al.*,  
*Green Chem.*, 2023, 25, 9138.



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## Solvent-free and ball mill-free catalytic C–H methylation†

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An expedient, mechanochemical, operationally simple protocol is reported for the Rh-catalysed C–H methylation of (hetero)arenes under solvent-free conditions without the use of a ball mill. Reagent mixing and activation are delivered using simple pestle-and-mortar grinding and subsequent heating, providing access to the same sustainability benefits as ball milling without the need for specialised equipment. Calculated *E*-factors are identical to those of ball milling and 5–25 times lower than for solution based conditions. The C–H methylation displays complete regioselectivity and good functional group tolerance. Reaction mixture analyses using scanning electron microscopy and differential scanning calorimetry are described.

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### Introduction

Growing concern with the environmental impact of chemical synthesis has revitalised interest in mechanochemistry – the promotion of reactivity through mechanical action, such as milling or grinding.<sup>1</sup> Mechanochemical synthesis can enhance sustainability in various ways,<sup>1a</sup> including – most prominently – decreasing reliance on hazardous, toxic or environmentally harmful solvents. In pharmaceutical production alone, bulk solvent constitutes an estimated eighty-five percent of generated waste by mass.<sup>2</sup> Other advantages of mechanochemistry include reduced reaction times and temperatures, the prospects of conducting ordinarily air-sensitive transformations under aerobic conditions,<sup>3</sup> and even routes to new products *via* otherwise inaccessible mechanistic pathways.<sup>4</sup> Significant advances have been made recently in the mechanistic understanding of mechanochemical reactions<sup>5</sup> and IUPAC recently recognized mechanochemistry as one of the top ten “chemical innovations that will change our world”.<sup>6</sup>

Meanwhile, developments in C–H functionalisation methodology continue apace, providing previously impossible transformations and streamlining access to valuable molecules

through the direct substitution of classically ‘inert’ C–H bonds.<sup>7</sup>

New approaches to catalytic C–H methylation rank amongst the most sought-after<sup>8</sup> because the introduction of a methyl group to bioactive molecules can improve their activity, lipophilicity, metabolic stability, pharmacokinetics and pharmacodynamics – benefits collectively termed the ‘magic methyl effect’.<sup>9</sup>

Combining the advantages of mechanochemistry and C–H functionalisation has garnered increasing interest.<sup>10</sup> As part of our ongoing work in these areas,<sup>8h,11</sup> we developed a mechanochemical Rh-catalysed C–H methylation carried out in an automated ball mill.<sup>8h</sup> Our approach avoided the toxic solvents (*e.g.* carcinogenic 1,2-DCE) previous C–H methylations were reported to require, and some of which have been effectively regulated into obsolescence.<sup>12</sup> Other advantages of our mechanochemical protocol included dramatically reduced reaction times (from a typical 18 h to 0.5–2 h), and the possibility of late-stage C–H methylation of biologically active molecules.<sup>13</sup>

Importantly, however, automated ball milling can present up-front costs and is not yet a mainstream practice in reaction development for most laboratories. Notably, reports describing the advantages of ball milling in organic methodology very rarely consider pestle-and-mortar grinding as an accessible, low-cost alternative to deliver solvent-free reaction mixing and activation.

Some solvent-free C–H functionalisations that do not use ball milling have been reported,<sup>14</sup> but many involve heating neat mixtures that include one or more liquid reagents used in large excess, some of which presumably act as *de facto* solvents.

Here, we describe an approach to catalytic C–H methylation where reagent mixing and activation energy are delivered without the use of a ball mill, but instead by very simple and

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brief pestle-and mortar grinding<sup>15</sup> and subsequent heating of neat mixtures under air. This approach offers several benefits: (1) it affords the green credentials of a solvent-free, mechanochemical approach (*i.e.* exclusion of toxic solvents, reduction in waste, low temperature and short reaction times) in an accessible, low-cost way; (2) it allows for a comparison between automated ball milling and the cheaper alternative, which is largely absent from the literature.

We describe the applicability of the 'grind-and-heat' approach to diversely substituted substrates and provide some initial insights into the role played by the grinding and heating stages of our procedure obtained from Scanning Electron Microscopy (SEM) and Differential Scanning Calorimetry (DSC).

## Results & discussion

### Optimisation

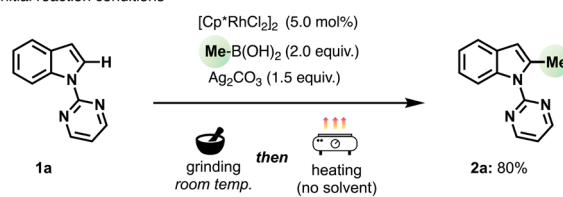
Initially, we tested the prospect of replacing a ball mill's reagent mixing and energy delivery using an agate pestle and mortar in which all reaction components were combined and ground manually for 1–5 min, and from which they were then transferred into a glass vial and heated conventionally under air, without solvent, liquid additives, stirring or exclusion of air ('grind-and-heat' conditions). We selected Rh-catalysed oxidative C–H methylation of 1-pyrimidylindole (**1a**) as a 'work-horse' reaction to test our approach.<sup>16</sup> In an initial reaction using **1a**, [Cp\*RhCl<sub>2</sub>]<sub>2</sub> as the catalyst precursor, MeB(OH)<sub>2</sub> as the methyl source and Ag<sub>2</sub>CO<sub>3</sub> as oxidant, all reaction components were ground manually for 5 min, then heated at 40 °C for 30 min, giving the corresponding C2-methylated compound **2a** in 80% yield (Fig. 1A). In a separate run of reactions (Fig. 1B), we compared the effect of the grinding time (1–5 min) on the yield. Longer grinding times correlated with greater yields (after heating); grinding for more than 3 min returned **2a** in yields >70%, with 5 min giving 79% and thus confirming the reproducibility of the reaction in Fig. 1A. Grinding times >5 min gave no further advantage.

Fig. 1C shows the effect of temperature variations for the heating portion of our protocol, for which all reagents were ground together (for 5 min) and heated for 120 min. No conversion of **1a** to **2a** took place at or below 25 °C. In the reaction run at 30 °C, **2a** formed in 78% yield, in 80% yield for the reaction performed at 40 °C and 85% yield for the reaction heated to 50 °C. Fig. 1D delineates the effect of heating duration. Extending the heating period to longer than 30 min gave only a small increase in yield (79% after 30 min, *vs.* 83% after 60 min). Magnetic stirring of the reaction mixture during the heating step had no effect on yields.

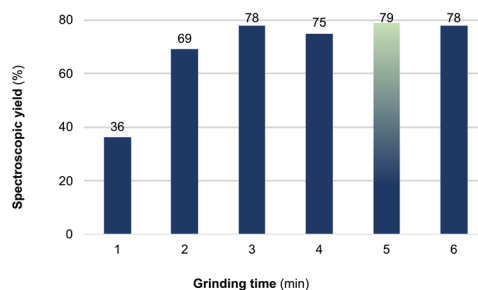
As under our ball milling conditions,<sup>8h</sup> amongst a variety of oxidants tested, Ag<sub>2</sub>CO<sub>3</sub> gave the highest yields and only Ag<sup>I</sup> salts (Ag<sub>2</sub>CO<sub>3</sub>, Ag<sub>2</sub>O, AgF and AgOAc) resulted in any conversion to methylated products; other common oxidants, including Cu(OAc)<sub>2</sub>, Cu(TFA)<sub>2</sub>, MnO<sub>2</sub> and Fe<sub>2</sub>O<sub>3</sub> proved ineffective (see SI for more details). We obtained **2a** in 81% spectroscopic

### Solvent-free & ball-mill free C–H methylation of the indole core

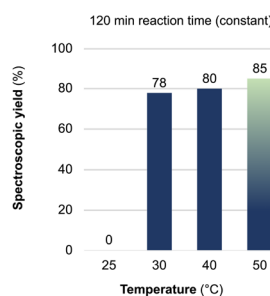
#### A. Initial reaction conditions



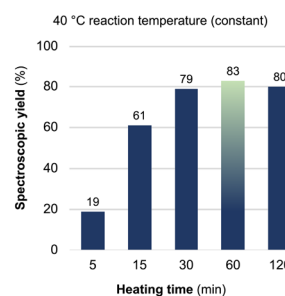
#### B. Variation of grinding time



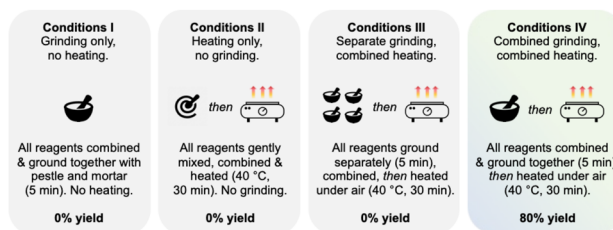
#### C. Variation of temperature



#### D. Variation of heating time



#### E. Reagent grinding and combination



**Fig. 1** Optimisation of conditions for the oxidative C2–H methylation of **1a**. Conditions: **1a** (0.3 mmol), [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (5.0 mol%), MeB(OH)<sub>2</sub> (2.0 equiv.), Ag<sub>2</sub>CO<sub>3</sub> (1.5 equiv.). Yield determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

yield upon lowering the Ag<sub>2</sub>CO<sub>3</sub> loading to 1.2 equiv. Other Rh salts, including RhCl<sub>3</sub>·H<sub>2</sub>O, [RhCl(cod)]<sub>2</sub> and [RhCl(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>]<sub>2</sub> gave no conversion to **2a** when used instead of [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (see Table S4† for more details), although cyclometalated complexes were catalytically active (see below).

Conditions I–IV (Fig. 1E) summarise variations in how the reagents were ground and heated. Grinding the starting materials, catalyst and oxidant only (*i.e.*, excluding the heating step) gave no conversion of **1a** to **2a** (Conditions I). Replacing the grinding step with gentle mixing of the starting materials, catalyst and oxidant (without grinding), and then heating the resulting mixture at 40 °C for 30 min resulted in no formation



of **2a** (Conditions II). Grinding the reagents, catalyst and oxidant *separately* for 5 min, then combining them and heating at 40 °C for 30 min also resulted in no conversion (Conditions III). Only combined grinding of the reagents, catalyst and oxidant for 5 min, and subsequent heating, gave **2a** in good yield (Conditions IV, 80%).

### Scope of C–H methylation

Under the optimised conditions described above, a variety of decorated 1-pyrimidyl indoles (**1a–h**) underwent efficient C2–H methylation to give derivatives **2a–h** with total reaction times of 35 min and optimal reaction temperatures in the 40–60 °C range (Scheme 1).

Generally, for these conditions, we observed the evolution of ethane gas arising from competitive oxidative homocoupling

of MeB(OH)<sub>2</sub> (see ESI† for more information). Increasing reaction temperatures above 70 °C gave lower yields due to an acceleration of the homocoupling. A methyl group at the indole C3 position did not provide enough steric hindrance to inhibit the methylation (product **2b**). Good tolerance towards electron-donating groups (e.g., –OMe, product **2c**) and electron-withdrawing groups (e.g., –NO<sub>2</sub>, product **2d**) on the indole's benzenoid ring was observed. The superior performance of electron-rich substrates is consistent with the outcome of reactions performed under ball milling conditions.<sup>8h</sup> Substrates with chloro- (product **2e**), bromo- (**2f–2g**) and iodo- (**2h**) groups, each of which can serve as useful synthetic handles for subsequent derivatisation, gave generally very good yields.

C2–H Methylation of thiophene (**2i**) and pyrrole (**2j**) rings also proved viable, whereas the imidazole (**2k**) core did not participate in the reaction. Substrates with oxygen-based directing groups (1-acetylindole and *N*-methyl-acetanilide) gave no conversion.

2-Phenoxy-pyridines (**4**, Scheme 2) occur in various biologically active molecules as well as luminescent materials,<sup>17</sup> and can also serve as masked phenols<sup>18</sup> or as pseudohalides in transition metal catalysis.<sup>19</sup> In Rh-catalysed *ortho*-directed C–H methylation (to form products **5**), 2-phenoxy-pyridines react *via* six-membered rhodacyclic intermediates (**6**).<sup>20</sup> As under ball milling conditions,<sup>8h</sup> optimised yields for **5** relied on a switch of methyl source from MeB(OH)<sub>2</sub> to MeBF<sub>3</sub>K,<sup>21</sup> an increase of its loading to 3–6 equivalents and the inclusion of sub-stoichiometric AgSbF<sub>6</sub>. We attribute the need for these changes to the greater difficulty of transmetalation<sup>22</sup> or reductive elimination from six-membered rhodacyclic intermediates.<sup>8h</sup> In all cases, increasing the reaction temperature to 60 °C and the duration to 120 min proved beneficial. Generally, methylated products were obtained in very good or excellent yields from unsubstituted (**5a**) as well *ortho*- (**5a–c**), *meta*- (**5d**), and *para*-substituted (**5g,h**) substrates (Scheme 2). Exceptions included the primary amine **5e** and carbazole derivative **5f**.

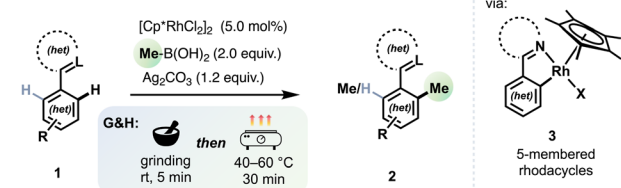
### E-Factors and sustainability

A foremost sustainability credential of mechanochemistry is its avoidance of bulk solvents as reaction media, which greatly reduces waste and helps side-step key environmental and human health hazards.<sup>1a</sup> Practically all advances in mechanochemical C–H functionalisation methodology rely on automated ball milling.<sup>10b</sup>

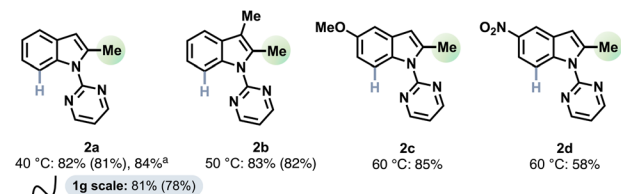
Schemes 1 and 2 include a comparison of *E*-factors (the mass ratio of waste/product)<sup>23</sup> for the syntheses of representative products **2a** and **5a**, respectively, each under three sets of conditions: 'grind-and-heat' (G&H), automated ball milling, and in solution.

For both **2a** and **5a**, our 'grind-and-heat' protocol and automated ball milling gave identical *E*-factors: 3.5 for **2a** and 10.3 for **5a**. We calculated the highest yielding solution-based system reported for generating **2a** *via* C–H methylation to have an *E*-factor of 17.9.<sup>16</sup> Thus, both solvent-free approaches reduce the *E*-factor more than fivefold for **2a**. For **5a**, the highest yielding solution-based system has an *E*-factor of

#### Solvent-free C–H methylation via 5-membered Rh-cycles & 'grind-and-heat' (G&H) conditions

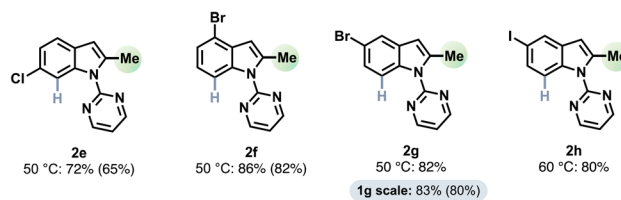


#### A. Methylation of indole-based substrates

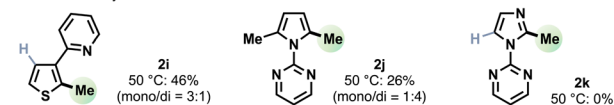


#### E-factor comparison

- G&H (as above): pestle-and-mortar, rt, 5 min then 40 °C, 120 min; **E-factor: 3.5**
- Ball milling:<sup>8h</sup> steel jar, steel ball ( $\phi = 10$  mm), mixer mill, 36 Hz, 120 min; **E-factor: 3.5**
- Solution-phase:<sup>16</sup> [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (5.0 mol%), MeBF<sub>3</sub>K (2.0 equiv.), AgF (2.0 equiv.), 1,2-dichloroethane, 120 °C, 20 h; **E-factor: 17.9**



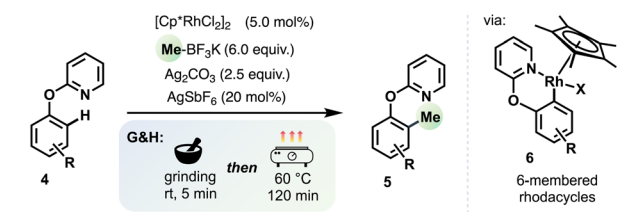
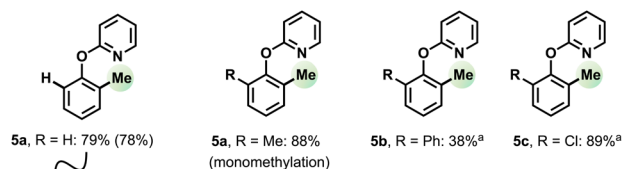
#### B. Other heterocyclic motifs



**Scheme 1** Scope with respect to (hetero)cyclic substrates able to form 5-membered rhodacycles: (a) indole substrates; (b) other heterocyclic motifs; (c) scope with respect to oxygen-based directing groups. Conditions: **1** (0.3 mmol), [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (5.0 mol%), MeB(OH)<sub>2</sub> (2.0 equiv.), Ag<sub>2</sub>CO<sub>3</sub> (1.2 equiv.), pestle-and-mortar grinding 5 min, heating at indicated temperature for 30 min. Yields determined by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Percentages in brackets refer to isolated yields. <sup>a</sup>Complex **3a** (derived from **1a**, X = Cl, 10 mol%) used instead of [Cp\*RhCl<sub>2</sub>]<sub>2</sub>.

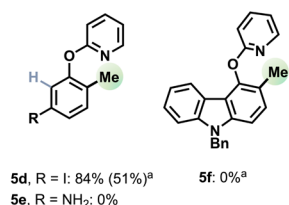
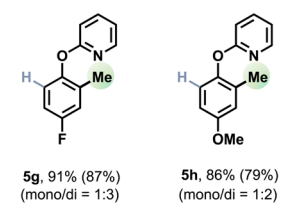


## Solvent-free C–H Methylation of 2-phenoxyppyridines under ‘grind-and-heat’ (G&amp;H) conditions

A. Unsubstituted/*ortho*-substituted 2-phenoxyppyridines

## E-factor comparison

- G&H (as above): pestle-and-mortar, rt, 5 min then 60 °C, 120 min; **E-factor: 10.3**
- Ball milling:<sup>8h</sup> Teflon™ jar, steel ball ( $\phi = 15$  mm), mixer mill, 36 Hz, 120 min; **E-factor: 10.3**
- Solution-phase:<sup>8h(SI)</sup> 1,2-dichloroethane, 100 °C, 120 min; **E-factor: 259.2**

B. *meta*-Substituted 2-phenoxyppyridinesC. *para*-Substituted 2-phenoxyppyridines

**Scheme 2** Scope with respect to 2-phenoxyppyridines, which can form 6-membered rhodacycles: Conditions: **4** (0.3 mmol),  $[\text{Cp}^*\text{RhCl}_2]_2$  (5.0 mol%),  $\text{AgSbF}_6$  (20 mol%),  $\text{MeBF}_3\text{K}$  (6.0 equiv.),  $\text{Ag}_2\text{CO}_3$  (2.5 equiv.), pestle-and-mortar grinding 5 min, heating at 60 °C, 120 min. Yields determined by  $^1\text{H}$  NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. Percentages in brackets refer to isolated yields. <sup>a</sup> $\text{MeBF}_3\text{K}$  (3.0 equiv.),  $\text{Ag}_2\text{CO}_3$  (1.5 equiv.).

259.2.<sup>8h</sup> Therefore, in this case, both solvent-free approaches offer a twenty-five-fold improvement. It is additionally noteworthy that for both **2a** and **5a** (and their analogues) the previous highest yielding reported solution-based systems used 1,2-DCE as solvent, a potent carcinogen that has been banned for all practical purposes in some jurisdictions.<sup>12a</sup>

By these metrics, both ‘grind-and-heat’ and automated ball milling significantly outperform their solution-based counterparts in sustainability terms. However, we stress that, in contrast to automated ball milling, ‘grind-and-heat’ conditions require *no specialised equipment*. Thus, the sustainability benefits of solvent-free, mechanochemical catalytic C–H functionalisation may be much more widely and cheaply accessible than might be commonly assumed. This is an important and overlooked aspect of solvent-free C–H functionalisation methodology and we anticipate its extension to many other reaction types.

## Late-stage functionalization (LSF)

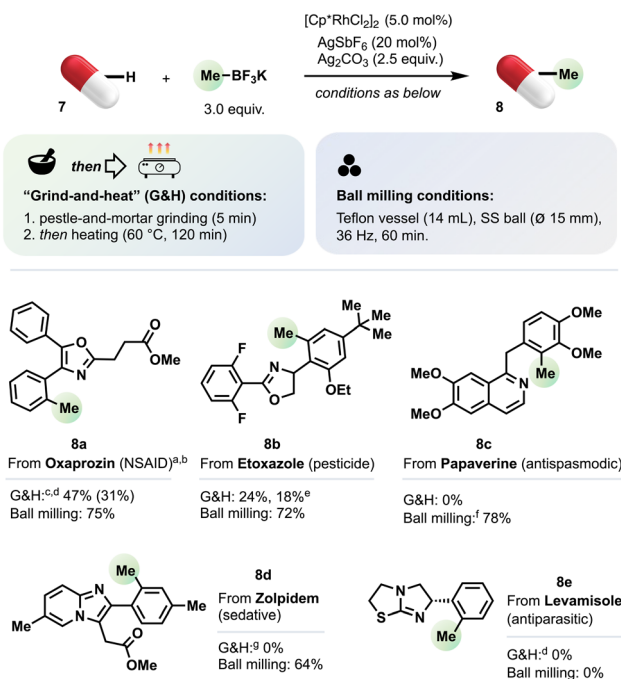
Research into strategies for late-stage functionalization (LSF) of bioactive compounds, natural products and advanced inter-

mediates is presently a ‘hot topic’.<sup>10c,13b–d,24</sup> LSF can streamline access to derivatives of valuable molecules by reducing significantly the need for their *de novo* synthesis. Thus, LSF can accelerate the exploration of chemical space and, for example, expedite drug development.<sup>13d,24,25</sup> We reported previously that several biologically active molecules (or their close relatives) underwent efficient late stage C–H methylation under conditions based on automated ball milling.<sup>8h</sup> We sought to compare this with the ‘grind-and-heat’ approach.

Under ‘grind-and-heat’ conditions, methylated Oxaprozin (**8a**) and Etozazole (**8b**) derivatives formed in 47% and 24% yield, respectively (Scheme 3), somewhat lower than for automated ball milling.<sup>8h</sup> Although the ‘grind-and-heat’ regime was not effective for Papaverine (**8c**), Zolpidem derivative **8d** or Levamisole (**8e**), the amounts of **8a** and **8b** we obtained would be generally considered useful for physicochemical and biological testing.

Interest in the mechanochemical synthesis and reactivity of coordination and organometallic complexes has also experienced recent growth.<sup>3a–c,10d,j,26</sup> We previously reported that rhodacyclic complexes of the types **3** or **6** can be generated efficiently under ball milling conditions and that they are competent precatalysts for oxidative C–H methylation.<sup>8h</sup> Under ‘grind-and-heat’ conditions, rhodacycle **3a** (X = Cl) formed in 28% yield from **1a** and  $[\text{Cp}^*\text{RhCl}_2]_2$  (see Table S1†). Complex

## Late-stage methylation: ‘Grind-and-heat’ (G&amp;H) versus automated ball milling:



**Scheme 3** Reactions conducted on a 0.3 mmol scale of **7**. Yields determined by  $^1\text{H}$  NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard, isolated yields shown in parentheses. <sup>a</sup> $[\text{Cp}^*\text{RhCl}_2]_2$  (10 mol%),  $\text{AgSbF}_6$  (40 mol%), <sup>b</sup> $\text{MeBF}_3\text{K}$  (2.5 equiv.), <sup>c</sup>70 °C, <sup>d</sup>30 min heating time. <sup>e</sup>**3a** (10 mol%) used in place of  $[\text{Cp}^*\text{RhCl}_2]_2$ , <sup>f</sup>120 min milling time, <sup>g</sup>50 °C.



**3a** catalysed the C–H methylation of indole derivative **1a** to give **2a** in 84% yield (Scheme 1) and the C–H methylation of **7b** to give **8b** in 18% yield (Scheme 3). Hernandez and co-workers recently described the formation and role of rhodacycles in mechanochemical C–H functionalisation.<sup>26b,c</sup>

### Scanning electron microscopy (SEM)

Scanning Electron Microscopy (SEM) allowed a comparison of morphological changes in the reaction mixtures corresponding to different steps of the ‘grind-and-heat’ C–H methylation of **1a** (Fig. 2).

For Sample 1, all the reagents were first mixed gently (Conditions A), then subjected to pestle-and-mortar grinding (Conditions B) and, finally, heated (Conditions C). An SEM image was recorded after each step (Fig. 2A–C). After gentle mixing only (Conditions A), SEM imaging revealed fine particles aggregated around larger crystalline fragments approximately 10  $\mu\text{m}$  in diameter (Fig. 2A). Elemental analysis using Energy Dispersive X-ray Spectroscopy (EDS) confirmed only the larger fragments contained Rh, and these were there therefore assigned as crystals of  $[\text{Cp}^*\text{RhCl}_2]_2$ . After 5 min of manual

pestle-and-mortar grinding (Conditions B), SEM revealed the sample to be significantly more homogenised and compacted (Fig. 2B) and X-ray elemental analysis revealed uniform distribution of Rh-, Cl- and Ag-containing particles throughout the sample. After heating (Conditions C), Sample 1 retained its homogeneity but acquired a porous appearance (Fig. 2C), which we ascribe to the background oxidative ethane formation discussed above.

For Sample 2, all reagents were gently mixed by spatula only and heated directly (Conditions D), by-passing the pestle-and-mortar grinding stage (this corresponds to Conditions II in Fig. 1E). In this case, the SEM image (Fig. 2D) showed smooth, coated particles for which X-Ray elemental analysis indicated very even nitrogen distribution across the surface. We assign this to a coating of **1a**, which we measured to have a melting temperature range starting at 35  $^\circ\text{C}$ , as determined by Differential Scanning Calorimetry (DSC). The smooth appearance is evidence that the background oxidative ethane formation did not occur. As the pestle-and-mortar grinding step proved necessary for successful C–H methylation without a ball mill (Fig. 1E), the present result indicates substrate melting alone does not ensure successful C–H methylation under ‘grind-and-heat’ conditions.

For Sample 3, all reagents were loaded into a 14 mL stainless steel milling vessel with a ball bearing ( $\phi = 15$  mm) and subjected to automated ball milling at 36 Hz for 30 min (Conditions E). This produced the most homogenized and compressed sample of the set (Fig. 2E). The absence of the porosity seen in Sample 3 is ascribed to the continuous mechanical action of the mill even after complete consumption of  $\text{MeB}(\text{OH})_2$ .

To give **2a** in 82% yield (Scheme 1) using a 5.0 mol% loading of  $[\text{Cp}^*\text{RhCl}_2]_2$ , each Rh centre must, on average, interact with 8.2 equivalents of substrate. The results above suggest that sufficient sample homogenisation by pestle-and-mortar grinding (Fig. 2B) combined with substrate mobility (*e.g.*, from melting, Fig. 2D) can enable this for some, even all-solid solvent-free reaction mixtures. For such reactions, therefore, the more thorough mixing offered by ball milling is not needed.

By contrast, ‘grind-and-heat’ conditions did not provide **8d** from Zolpidem analogue **7d**. For the corresponding Sample 4 (Fig. 3F), SEM analysis revealed homogenised but sharp-edged, brittle-looking particles lacking the evidence of ethane evolution or substrate melting observed for **1a** (*cf.* Fig. 2C and D). However, **8d** formed in 64% yield using ball milling (Scheme 3). The corresponding SEM image (Sample 5, Fig. 3G) and elemental X-Ray analysis showed a very homogeneous distribution of all elements in a mixture coated onto flakes of Teflon originating from the milling vessel. The melting point of **7d** (120  $^\circ\text{C}$ ) is significantly above the reaction temperature of both the ‘grind-and-heat’ conditions we used (40  $^\circ\text{C}$ ) and the temperatures the Teflon vessels (which rose to 50–90  $^\circ\text{C}$  during milling). These results suggest continuous reagent mixing is achieved through the mechanical action of ball bearings even for all-solid reaction mixtures under milling con-

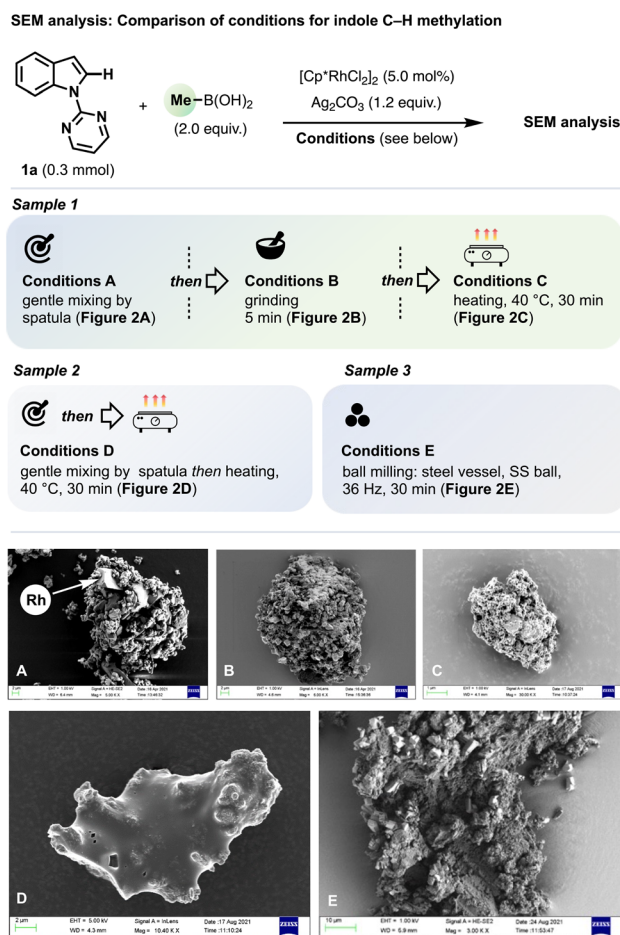
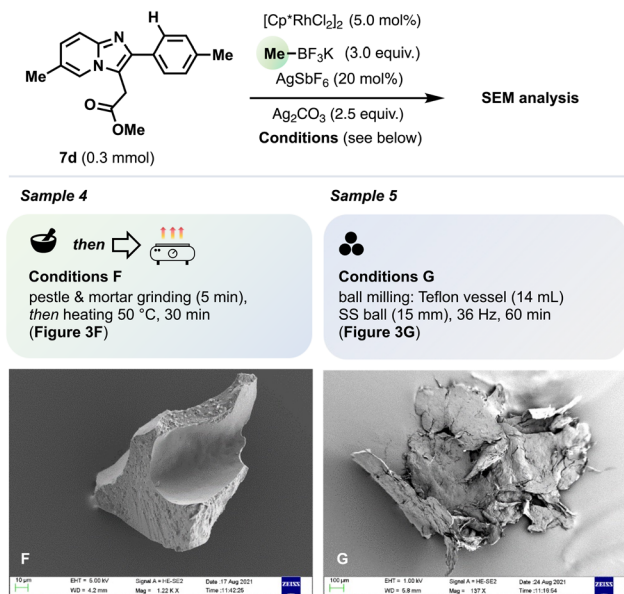


Fig. 2 Comparison of reaction mixtures for the Rh-catalyzed C–H methylation of **1a** using different conditions using scanning electron microscopy (SEM).



SEM analysis: Comparison of conditions for C–H methylation of Zolpidem analogue



**Fig. 3** Comparison by scanning electron microscopy (SEM) of 'grind-and-heat' versus ball milling conditions for the attempted C–H methylation of 7d.

ditions, whereas 'grind-and-heat' C–H methylation requires sufficient sample homogenisation first but also depends on additional reagent mobility, e.g., afforded through a substrate's melting window starting below the reaction temperature. We confirmed using DSC that successful C–H methylation under 'grind-and-heat' conditions requires either the substrate or reaction mixtures (after grinding) to have a melting temperature range beginning below the reaction temperature or, otherwise, a glass transition temperature,  $T_g$ , lower than the reaction temperature.<sup>27</sup> We note that these properties and associated reaction outcomes may also depend on co-crystal formation during the grinding step; Hernández and co-workers recently described the formation of  $[\text{Cp}^*\text{RhCl}_2]_2$ /substrate co-crystals prior to C–H rhodation under ball milling conditions.<sup>26b,c</sup>

## Conclusions

We have demonstrated that selective and efficient Rh-catalysed C–H methylation is viable under solvent-free and ball mill-free conditions – even for some all-solid reaction mixtures – using a simple 'grind-and-heat' protocol. This approach boasts broad functional group tolerance and can be applied to some more complex, biologically active molecules. Whilst it is not a full replacement for automated ball milling, we suspect a 'grind-and-heat' approach is likely to work for a large range of mechanochemical reactions for which only ball milling conditions have been reported previously. The 'grind-and-heat' approach offers essentially identical sustainability benefits to automated ball milling, but it is operationally simpler and cheaper, as it

requires no specialised equipment. Thus, it may become a route through which greener, solvent-free reactions become more often considered as increasing emphasis is placed on sustainable synthetic method development.<sup>28</sup>

## Conflicts of interest

There are no conflicts to declare.

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