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Cite this: *Chem. Sci.*, 2024, **15**, 3365

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Solid-state mechanochemistry for the rapid and efficient synthesis of tris-cyclometalated iridium(III) complexes†

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Received 31st October 2023
Accepted 18th January 2024

DOI: 10.1039/d3sc05796h

rsc.li/chemical-science

Tris-cyclometalated iridium(III) complexes have received widespread attention as attractive prospective materials for *e.g.*, organic light-emitting diodes (OLEDs), photoredox catalysts, and bioimaging probes. However, their preparation usually requires prolonged reaction times, significant amounts of high-boiling solvents, multistep synthesis, and inert-gas-line techniques. Unfortunately, these requirements represent major drawbacks from both a production-cost and an environmental perspective. Herein, we show that a two-step mechanochemical protocol using ball milling enables the rapid and efficient synthesis of various tris-cyclometalated iridium(III) complexes from relatively cheap iridium(III) chloride hydrate without the use of significant amounts of organic solvent in air. Notably, a direct one-pot procedure is also demonstrated. The present solid-state approach can be expected to inspire the development of cost-effective and timely production methods for these valuable iridium-based complexes, as well as the discovery of new phosphorescent materials, sensors, and catalysts.

Introduction

Tris-cyclometalated iridium(III) complexes such as *fac*-Ir(ppy)$_3$ have been widely employed as phosphorescent dopants in electroluminescent organic light-emitting diodes (OLEDs), bioimaging probes, sensors, and photoredox catalysts (Fig. 1a).[1–5] The development of efficient, low-cost, time-saving, and environmentally friendly synthetic pathways to these complexes has thus attracted considerable attention in a broad range of scientific research fields. To date, a variety of useful procedures for their preparation has already been reported.[1,6–8] Among these, a two-step procedure that involves the reaction of iridium(III) chloride hydrate (**1**) with the pyridine-based ligand (**2**) to give the chloride-bridged dimer (**3**), followed by silver-triflate-mediated ligand exchange to give the desired complex **4**, has been widely used as one of the most general and practical methods (Fig. 1b).[1,6–8] The advantages of this protocol include the facts that the overall yield of **4** is often higher than that in other methods and iridium(III) chloride hydrate is a relatively cheap starting material compared to other iridium-based precursors, such as iridium(III) acetylacetonate.[1,2,6–8] However, this established route requires significant amounts of high-boiling organic solvents, inert-gas-line techniques, and long reaction times (commonly 24 h for the first step and 48 h for the second step; Fig. 1b).[2,6] In particular, reactions of the poorly soluble chloride-bridged dimer **3** require substantial amounts of solvent, making the second step very slow.[1,2,6] These requirements represent major drawbacks from both a production-cost and an environmental perspective. Although microwave irradiation can accelerate the ligand-exchange reactions, a large excess of the ligands (>50 equiv.) is required.[9]

As a new tool for conducting solvent-less solid-state organic transformations, ball milling has attracted considerable interest.[10–13] The advantages of solid-state mechanochemical synthesis include the avoidance of harmful organic solvents, much faster reaction kinetics, and simpler operational handling. In addition to these benefits, poorly soluble materials that are barely reactive under solution-based conditions can often be used as substrates.[10,11] Inspired by these attractive features of ball-milling reactions, we envisioned that solid-state mechanochemistry could potentially provide an efficient, rapid, low-cost, and environmentally friendly synthetic route to various tris-cyclometalated iridium(III) complexes.[10k,14]

In this study, we succeeded in developing a two-step mechanochemical protocol that enables the rapid solid-state synthesis of various tris-cyclometalated iridium(III) complexes (**4**) from readily available and relatively cheap iridium(III) chloride hydrate (**1**). This protocol represents a practical synthetic solution to the aforementioned drawbacks of conventional solution-based approaches (Fig. 1b). Specifically, the first ligand exchange is complete within 30 min, while the second ligand exchange with silver triflate is complete within 90 min,

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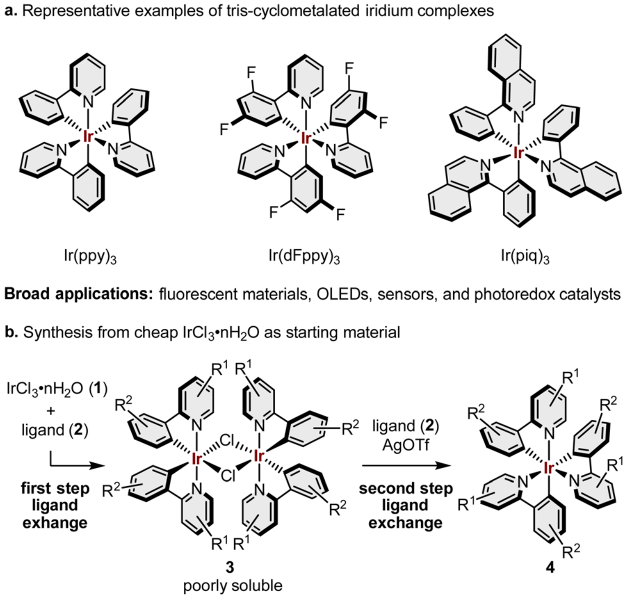
† Electronic supplementary information (ESI) available. See DOI: **https://doi.org/10.1039/d3sc05796h**



In solution		This work: solid-state	
first step	**second step**	**first step**	**second step**
$MeOC_2H_4OH/H_2O$ (3:1, 0.5 M) >120 °C, **~24 h**	$MeOC_2H_4OH$ (0.01 M) >100 °C, **~48 h**	$MeOC_2H_4OH$ (as additive) 135 °C, **~30 min**	$MeOC_2H_4OH$ (as additive) 135 °C, **~90 min**
direct one-pot protocol: **difficult**		direct one-pot protocol: **feasible**	

Fig. 1 Synthesis of tris-cyclometalated iridium(III) complexes bearing *N*-heteroaryl ligands.

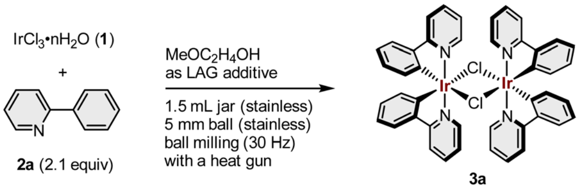
showcasing the effectiveness of solid-state mechanochemistry. We further demonstrate that a direct one-pot sequential protocol is feasible under these solid-state conditions. These results can be expected to inspire the development of cost-effective, faster, and environmentally friendly production methods for these valuable complexes, as well as the discovery of new phosphorescent materials, sensors, and catalysts.

Results and discussion

All mechanochemical reactions were conducted using a Retsch MM400 mill (1.5 mL stainless-steel milling jar; 30 Hz; 5 mm stainless-steel ball). First, we attempted the reaction between iridium(III) chloride hydrate (**1**) and 2-phenylpyridine (**2a**) at room temperature without any additives (entry 1) (Table 1). Unfortunately, the desired product (**3a**) was not produced. The addition of 2-methoxyethanol (0.20 μL mg^{-1}) as a liquid-assisted-grinding (LAG) additive did not improve the reactivity at room temperature (entry 2). In order to carry out the reaction at higher temperature, we used a commercially available temperature-controllable heat gun, which was placed directly above the ball-milling jar (for details, see the ESI†).[11d] The reaction was conducted with the heat gun preset to 200 °C, and the internal temperature of the reaction mixture (100 °C) was determined by thermography immediately after opening the milling jar (for details, see the ESI†). Pleasingly, we found that under these conditions, **3a** was obtained in 72% yield (entry 3). Further increasing the reaction temperature (135 °C) by increasing the heat gun preset to 300 °C did not improve the yield of **3a** (70%, entry 4). The reaction at 135 °C without the LAG additive decreased the yield of **3a** (62%; entry 5). Surprisingly, the reaction was complete within 10 min to afford **3a** in 80% yield (entry 6), and 5 min was also sufficient (74%; entry 7). The appearance of the solid-state reaction mixture changed from colorless to a yellow solid (Fig. 2). The amount of 2-methoxyethanol used did not significantly affect the reactivity (entries 8 and 9).

Next, we turned our attention to the reaction between **3a** and **2a** to form the target tris-cyclometalated iridium(III) complex **4a**

Table 1 Optimization of the first step: solid-state ligand exchange of **1** with 2-phenylpyridine (**2a**)[a]



Entry	Amount of $MeOC_2H_4OH$ (μL mg^{-1})	Time (min)	Internal temp.[b] (°C)	Yield (%) of **3a**[c]
1	0	30	30	<1
2	0.20	30	30	<1
3	0.20	30	100	72
4	0.20	30	135	70
5	0	30	135	62
6	0.20	10	135	80
7	0.20	5	135	74
8	0.10	10	135	82
9	0.30	10	135	80

[a] Conditions: **1** (0.20 mmol), **2a** (0.42 mmol), 2-methoxyethan-1-ol in a stainless-steel milling jar (1.5 mL) with a stainless-steel ball (5 mm). [b] The reaction temperature was controlled using a heat gun (for details, see the ESI). The internal temperature was confirmed by thermography immediately after opening the milling jar. [c] Isolated yields are shown.

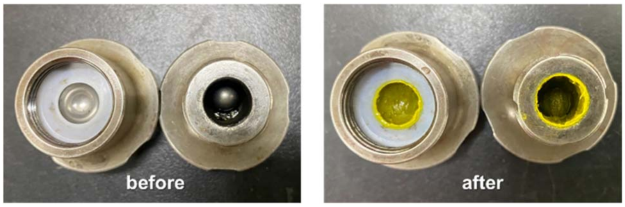


Fig. 2 Reaction mixture before and after ball milling (entry 6, Table 1).

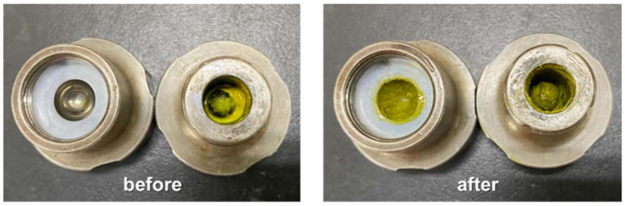
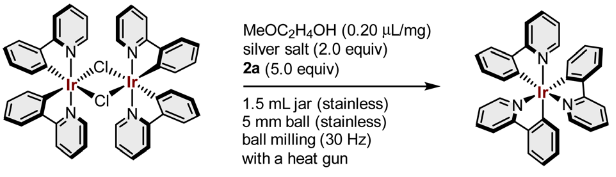


Fig. 3 Reaction mixture before and after ball milling (entry 1, Table 2).

under mechanochemical conditions (Table 2). We found that the reaction with AgOTf and a small amount of 2-methoxyethanol (0.20 μL mg^{-1}) reached completion within 60 min to form **4a** in 73% yield. The appearance of the solid-state reaction mixture did not change significantly after the reaction (Fig. 3). Given that the conventional solution-based conditions require a long reaction time (commonly 48 h), it is feasible to conclude that the solid-state mechanochemical strategy greatly accelerates the ligand-exchange process. The addition of AgOTf and high temperature are both essential for this reaction (entries 2 and 3). We found that 30 min of reaction is in general sufficient (70%; entry 4). The use of other silver salts such as Ag_2O or Ag_2CO_3 afforded **4a** in lower yield (10%; entry 5 and 14%; entry 6).

With the optimized reaction conditions in hand, we proceeded to synthesize various tris-cyclometalated iridium(III) complexes *via* the newly developed two-step solid-state protocol. Most of the iridium chloride dimers **3** are sparingly soluble in common organic solvents, which complicates their isolation and characterization. Therefore, the crude products obtained by washing with water and CH_2Cl_2 after the first ligand exchange were used directly in the second ligand exchange under mechanochemical conditions (for details, see the ESI†). We found that the developed two-step protocol allowed the preparation of

Table 2 Optimization of the second step: solid-state ligand exchange of **3a** with 2-phenylpyridine (**2a**) in the presence of silver salt[a]

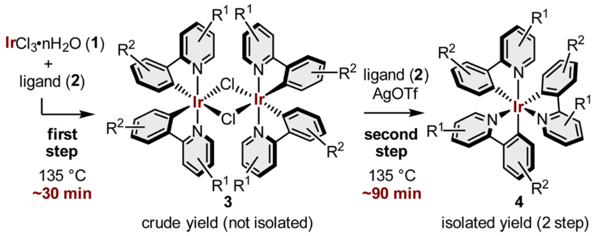


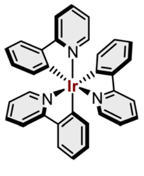
3a **4a**

Entry	Silver salt (2.0 equiv.)	Time (min)	Internal temp.[b] (°C)	Yield (%) of **4a**[c]
1	AgOTf	60	135	73
2	None	60	135	12
3	AgOTf	60	30	5
4	AgOTf	30	135	70
5	Ag_2O	60	135	10
6	Ag_2CO_3	60	135	14

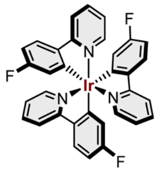
[a] Conditions: **3a** (0.05 mmol), silver salt (0.10 mmol), **2a** (0.25 mmol), 2-methoxyethan-1-ol (0.20 μL mg^{-1}) in a stainless-steel milling jar (1.5 mL) with a stainless-steel ball (5 mm). [b] The reaction temperature was controlled using a heat gun (for details, see the ESI). The internal temperature was confirmed by thermography immediately after opening the milling jar. [c] Isolated yields are shown.

Table 3 Solid-state synthesis of various tris-cyclometalated iridium(III) complexes[a],[b]

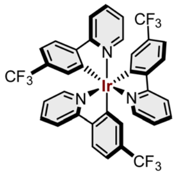




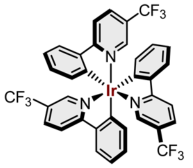
4a
stepwise (2 steps): 59%
[81% (first), 73% (second)]



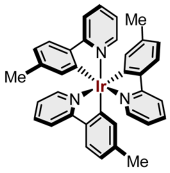
4b
stepwise (2 steps): 61%
[81% (first), 81% (second)]



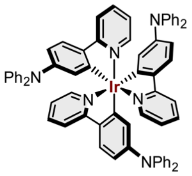
4c
stepwise (2 steps): 53%
[96% (first), 59% (second)]



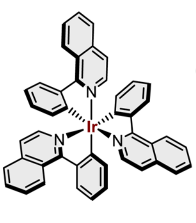
4d
stepwise (2 steps): 32%
[53% (first), 67% (second)]



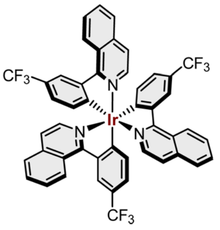
4e
stepwise (2 steps): 25%
[86% (first), 31% (second)]



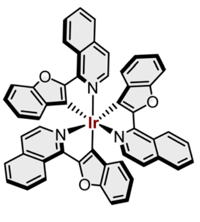
4f
stepwise (2 steps): 21%
[99% (first), 21% (second)[b]]



4g
stepwise (2 steps): 56%
[61% (first), 91% (second)[b]]



4h
stepwise (2 steps): 53%
[99% (first), 61% (second)]



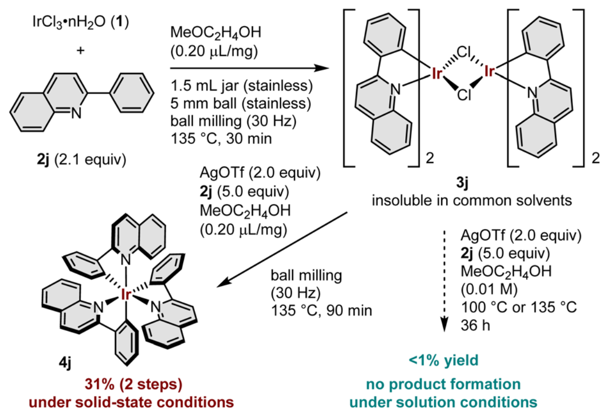
4i
stepwise (2 steps): 61%
[91% (first), 70% (second)]

[a] Conditions: for the first step: **1** (0.20 mmol), **2** (0.42 mmol), 2-methoxyethan-1-ol (0.20 μL mg^{-1}) in a stainless-steel milling jar (1.5 mL) with a stainless-steel ball (5 mm). Crude yields are shown. For the second step: **3** (0.05 mmol), AgOTf (0.10 mmol), **2** (0.25 mmol), 2-methoxyethan-1-ol (0.20 μL mg^{-1}) in a stainless-steel milling jar (1.5 mL) with a stainless-steel ball (5 mm). Isolated yields are shown. [b] DMF (0.50 μL mg^{-1}) was used in a 5 mL jar with a 10 mm ball.

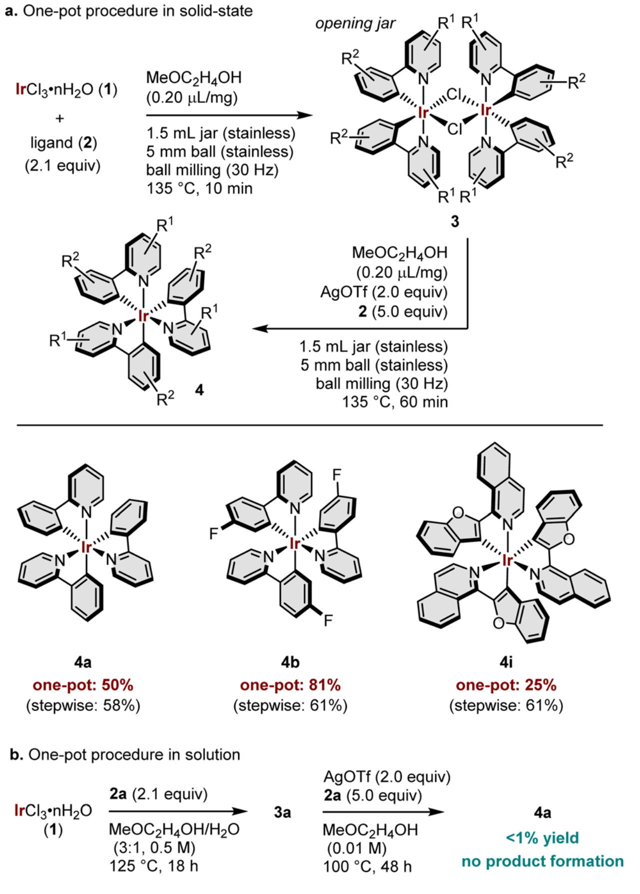
iridium complexes that bear fluoro- and trifluoromethyl groups (**4a–4d**) in good yield (32–61% over two steps) and a short reaction time (10 min for the first step and 60 min for the second step). The reactions with 2-(*p*-tolyl)pyridine (**2e**) also proceeded smoothly to give **4e** (25% over two steps). Unfortunately, the second ligand exchange did not produce the iridium complex with a diphenylamino group (**4f**) under the optimized conditions. However, we found that a modification of the conditions, in which *N*,*N*-dimethylformamide (DMF) was used as the LAG additive (0.40 μL mg^{-1}) in a 5 mL jar with a 10 mm ball at 20 Hz, allowed the synthesis of **4f** in 21% yield over two steps. These modified conditions were also effective for the reaction with 1-phenylisoquinoline (**2g**) to give **4g** in good yield (56% over two steps). Although further investigations are needed, we speculate at present that the higher mechanical impact from the larger ball (10 mm) may be important to achieve better mixing, especially for dimer complexes with particularly low solubility and thus facilitate the second ligand-exchange reaction. The reactions with 1-[3-(trifluoromethyl)phenyl]isoquinoline (**2h**) and 1-(benzofuran-2-yl)isoquinoline (**2i**) proceeded to give **4h** and **4i** 53% and 61% yield over two steps, respectively. It should be noted here that the generation of meridional tris-cyclometalated iridium(III) complexes was not observed in the crude reaction mixtures, and the facial complexes were obtained exclusively under the applied mechanochemical conditions (Table 3).[13]

In some cases, the conventional solution-based protocol is not efficient, not even under harsh reaction conditions due to the low solubility of the iridium chloride dimers **3**.[1,2,6] For example, the iridium dimer **3j** obtained from the reaction using 2-phenylquinoline (**2j**) is only very poorly soluble in common organic solvents, and the second ligand exchange did not proceed under solution-based conditions neither at 100 °C nor at 135 °C (Scheme 1). However, we found that our developed solid-state conditions allowed the synthesis of **4j** from **3j** in 31% yield over two steps. This result demonstrates the high practical utility of this solid-state approach.

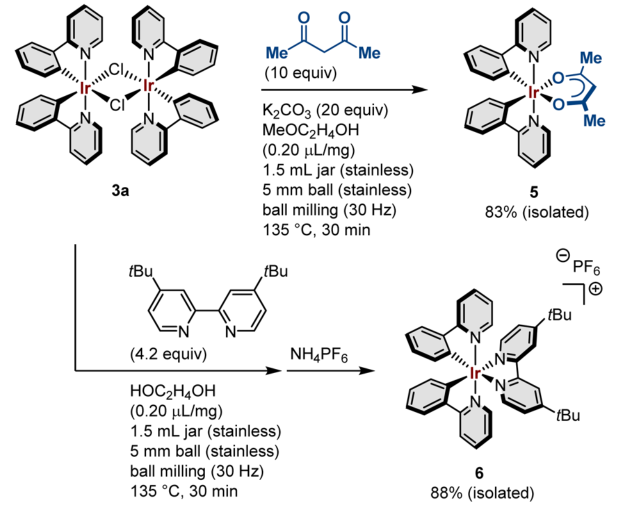
To further showcase the practical utility of this method, we investigated a direct one-pot sequential protocol using mechanochemistry (Scheme 2). For this purpose, the crude mixture including **3** was directly subjected to a one-pot solid-state ligand exchange with AgOTf. We found that the desired tris-cyclometalated iridium complexes (**4a**, **4b**, and **4i**) were obtained in good yield over two steps (Scheme 2a). In contrast,



Scheme 1 Mechanochemical synthesis of tris-cyclometalated iridium(III) complex 4j from 2-phenylquinoline 2j.

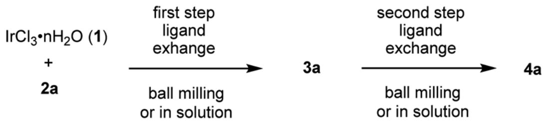


Scheme 2 One-pot sequential ligand-exchange reactions.



Scheme 3 Mechanochemical synthesis of Ir(ppy)$_2$(acac) complex (5) and [Ir(ppy)$_2$(dtbpy)]PF$_6$ (6).

Table 4 Calculation of the *E*-factors[a]



Conditions	*E*-factor for the first step	*E*-factor for the second step
Mechanochemical conditions (this work)	1.39	4.82
Solution-based conditions[2,6]	2.16	76.88

[a] For the details of the calculations, see the ESI.

our attempt at a one-pot protocol under conventional solution conditions was unsuccessful, and **4a** was not obtained (Scheme 2b). These results suggest that the one-pot mechanochemical strategy enables the rapid construction of various tris-cyclometalated iridium complexes under simple operational conditions and can reduce the amount of solvent waste.

Acetylacetonato cyclometalated iridium(III) complexes have also been widely used as luminescent materials.[1,2,7,8] We found that the reaction of **3a** with pentane-2,4-dione in the presence of 2-methoxyethanol (0.20 μL mg^{-1}) as a LAG additive under ball-milling conditions afforded the desired acetylacetonato complex **5** in excellent yield (83%) (Scheme 3). Furthermore, the reaction of **3a** with 4,4′-di-*tert*-butyl-2,2′-bipyridyl under mechanochemical conditions also proceeded smoothly to furnish the corresponding cationic tris-cyclometalated iridium complex in high yield (88%) (Scheme 3).[15] Notably, these reactions reach completion within 30 min, while conventional solution conditions usually require >24 h.[15] These results highlight the considerable potential of this solid-state mechanochemical synthetic approach for the rapid preparation of various luminescent iridium complexes in an economically and environmentally friendly manner.

In order to quantify the environmental benefits of this mechanochemical method, we evaluated the *E*-factor of the present solid-state conditions to those of the previously reported representative solution-based conditions in the literature.[2,6,14*h*,16] The *E*-factor is an index for the quantitative evaluation of the environmental impact of a chemical process.[16] For our solid-state method, the *E*-factors are 1.39 for the first step and 4.83 for the second step, whereas the *E*-factors of a representative solution-based method are 2.16 for the first step and 76.88 for the second step (Table 4). This difference is mainly due to the absence of bulk solvents under our solid-state conditions. According to these results, the present solid-state approach is substantially more eco-friendly than conventional solution-based approaches.

Conclusions

In conclusion, we have developed a solid-state protocol that allows the rapid synthesis of various tris-cyclometalated iridium(III) complexes from relatively cheap iridium(III) chloride hydrate without the use of significant amounts of high-boiling solvents. Notably, these mechanochemical reactions reach completion in much shorter reaction times than those required for solution-based protocols, and all experimental operations can be carried out in air. The present study can thus be feasibly expected to inspire the development of highly efficient, cost-effective, time-saving, and environmentally friendly routes to valuable iridium-based luminescent materials, sensors, and catalysts.

Data availability

All experimental data is available in the ESI.†

Author contributions

K. K. and H. I. conceived and designed the study. K. K. and H. I. co-wrote the paper. K. K. and T. E. performed the chemical experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Japan Society for the Promotion of Science (JSPS) *via* KAKENHI grants 22H00318, 21H01926, 22K18333, and 22H05328; by the JST *via* CREST grant JPMJCR19R1; by FOREST grant JPMJFR201I; and by the Institute for Chemical Reaction Design and Discovery (ICReDD), which was established by the World Premier International Research Initiative (WPI), MEXT, Japan. The authors also would like to thank Mitsubishi Chemical Corporation for their cooperation and helpful discussions. We thank Mr. Naoki Shizukuishi for his help in cross-checking the experiments.

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