

Mechanochemical Ruthenium-Catalyzed Olefin Metathesis

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S Supporting Information

ABSTRACT: We describe the development of a mechanochemical approach for Ru-catalyzed olefin metathesis, including cross-metathesis and ring-closing metathesis. The method uses commercially available catalysts to achieve high-yielding, rapid, room-temperature metathesis of solid or liquid olefins on a multigram scale using either no or only a catalytic amount of a liquid.

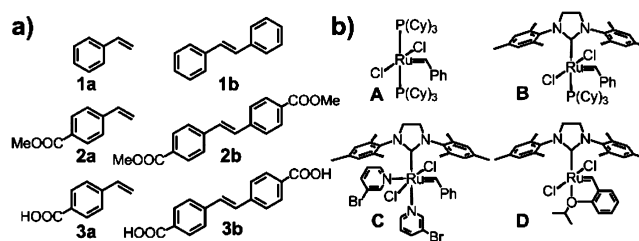
Olefin metathesis (OM) is one of the most versatile and powerful tools for the formation and interconversion of C–C double bonds.¹ Ru-based metathesis, brought to the forefront of organic and materials synthesis with the introduction of well-defined Ru catalysts,² is now a well-established approach with applications ranging from polymer synthesis and pharmaceuticals to medicinal chemistry and natural product synthesis.³ The exploration of new catalysts, reaction media, and concepts for improving the sustainability of OM remain dynamic and challenging research areas.⁴ In that context, the solid state has remained almost unexplored as a medium for OM.

Here we describe the development of the first mechanochemical (MC) methodology for cross-metathesis (CM) and ring-closing metathesis (RCM) of solid olefins. This methodology, developed on carefully selected substrates, opens a new, unexplored reaction environment for OM and permits high-yielding, scalable transformations using commercial Ru catalysts.⁵ MC reactions^{6,7} by solvent-free milling or milling with a catalytic liquid (liquid-assisted grinding, LAG^{8–10}) have emerged as excellent alternatives to synthesis in solution, providing not only rapid and clean reactivity but also the ability to use poorly soluble reactants, access reactions that are difficult to achieve under conventional conditions,¹¹ and achieve excellent stoichiometric control and stereoselectivity.¹² Organic mechanochemistry has reached an advanced stage¹³ that permits multistep and one-pot reaction sequences^{14–16} and the development of entirely solvent-free syntheses.¹⁷ To date, the exploration of MC metal-catalyzed processes has focused mostly on condensation¹⁸ and coupling reactions.^{19–23} Thus, the present study makes a new range of metal-catalyzed reactions available to mechanosynthesis. Whereas OM in neat liquids is known,²⁴ we were intrigued by a report of the Wagener group that mixing solid poly(1,4-butadiene) with a Ru catalyst leads to depolymerization.²⁵ However, a subsequent attempt at RCM of solid olefins was unsuccessful.²⁶

Reactions were conducted in a Retsch MM400 mill using 2 mmol (~300 mg) of olefin in a 14 mL Teflon milling jar²⁷ milled at 30 Hz using one stainless steel ball (10 mm diameter, 4.0 g). Conventional steel jars gave irreproducible results, most likely

due to enhanced catalyst reduction by impact of steel media against the steel vessel.^{28,29} The jar was sealed, but not hermetically, allowing loss of ethylene. We first compared the reactivity of a liquid, styrene (**1a**), with those of a low (37 °C)-melting solid, methyl 4-vinylbenzoate (**2a**), and a high (144 °C)-melting solid, 4-vinylbenzoic acid (**3a**) (Scheme 1a).

Scheme 1. MC CM Substrates/Products (a) and Catalysts (b)

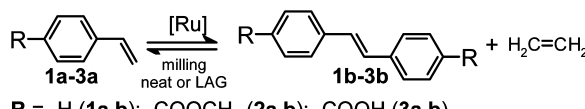


We also compared the performance of the first- (A) and second-generation (B) Grubbs catalysts, a fast-initiating catalyst (C), and the second-generation Hoveyda–Grubbs catalyst (D) (Scheme 1b).³⁰ Products were characterized by PXRD, FTIR-ATR, ¹H and ¹³C NMR, and MS analyses.^{31–33}

The reactivity screen (Table 1) reveals clear differences between liquid and solid olefins. On the basis of earlier work on metathesis of neat liquids,²⁴ we anticipated that CM of **1a** should proceed readily. Indeed, as long as Teflon jars were used, **1b** was obtained in high yields within 30 min (entries 2–4). In contrast, **2a** took 1.5 h of milling to provide **2b** in 30% yield (entries 5–11), while **3a** gave no product even after 5 h (entries 12–15). Overall, D was the most efficient of the explored catalysts,³⁰ while A was ineffective in all experiments and C required cooling during milling (e.g., entry 8 vs 9). Adding the catalysts in 2–4 equal portions gave higher yields, indicating that catalyst degradation slowly took place upon milling (e.g., entry 6 vs 7 or 10 vs 11). Next, we attempted LAG, which uses a substoichiometric liquid additive to improve the reactivity (entries 16–24). LAG reactions are characterized by ratios of added liquid volume to reactant weight (η) of 0.1–1 $\mu\text{L mg}^{-1}$.³⁴ Although LAG (50 μL of THF, $\eta \approx 0.16 \mu\text{L mg}^{-1}$) did improve the yield of **2b** and enabled the metathesis of **3a**, the yields remained mediocre and difficult to reproduce.³⁵ However, we noted that the reaction mixtures formed a thick shell around the ball (Figure 1a,b), suggesting that the low yields and irreproducibility might be due to poor mixing.

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Table 1. Exploration of CM by Neat Milling and LAG^a


entry	olefin	catalyst (mol %)	liquid (μL)	time (h)	yield (%)
1	1a	A (5)	—	1	—
2	1a	B (1)	—	0.5	92
3	1a	C (2)	—	0.5	80 ^b
4	1a	D (0.5)	—	0.5	90
5	2a	A (5)	—	1	—
6	2a	B (5) ^c	—	1.5	16 ^c
7	2a	B (5)	—	1.5	31
8	2a	C (2)	—	1.5	0
9	2a	C (2)	—	1.5	27 ^b
10	2a	D (1) ^c	—	1.5	19 ^c
11	2a	D (1)	—	1.5	30
12	3a	A (5)	—	5	—
13	3a	B (5)	—	5	—
14	3a	C (5)	—	5	— ^b
15	3a	D (2)	—	5	—
16	2a	A (5)	THF (50)	1	—
17	2a	B (5)	THF (50) ^d	1.5	45 ^e
18	2a	C (2)	THF (50) ^d	1.5	35 ^{b,e}
19	2a	D (1)	THF (50) ^d	1.5	40 ^e
20	3a	A (5)	THF (50)	5	—
21	3a	B (5)	THF (50) ^d	5	15 ^e
22	3a	B (5)	THF (100)	5	37 ^e
23	3a	C (5)	THF (50) ^d	5	45 ^{b,e}
24	3a	D (2)	THF (50) ^d	5	49 ^e

^aUnless otherwise noted, catalyst was added in 2–4 equal portions.
^bReaction was cooled using ice water. ^cCatalyst was added all at once.
^dThe reactivity was not strongly affected by the choice of liquid (see ref 35). ^eDifficult to reproduce; only the highest yield is given here.

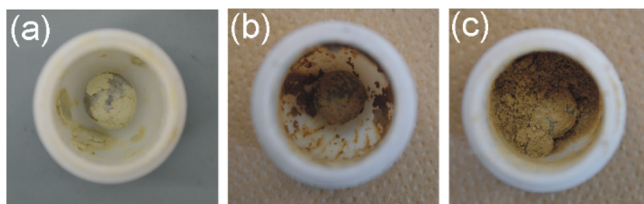


Figure 1. Reaction mixture (3a, 2 mol % D) after LAG with and without a solid auxiliary: aggregation on the milling ball (a) after 15 min, (b) after 5 h, and (c) after 2 h of milling with NaCl (34% yield).

Therefore, we attempted milling with an abrasive, inert auxiliary (Table 2).³⁶ As auxiliaries we used ubiquitously available salts (450 mg, ca. 150% of the reactant weight) that are easily removable with water.^{12b} This led to a striking increase in yield of the **2b** to >90% reproducibly and independent of the choice of auxiliary, and **3a** reproducibly gave **3b** in >70% yield upon LAG with a solid auxiliary.^{20d} The reaction mixtures appeared as fine powders (Figure 1c). All salt auxiliaries gave similar and reproducible results, indicating that the improved reactivity is not related to a specific cation or anion. Thus, LAG with a solid auxiliary enables reproducible, high-yielding CM of solid olefins.

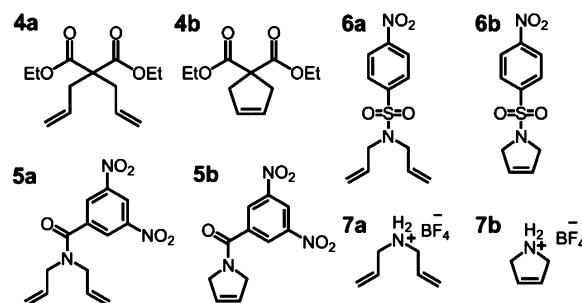
With conditions for CM of solid olefins established, we addressed RCM starting with the liquid **4a** (Scheme 2). Consistent with the CM of liquid **1a**, cyclopentene **4b** was obtained in 94% yield after 30 min using 0.25 mol % D.^{31–33} For

Table 2. Exploration of CM by Neat Milling or LAG with a Solid Auxiliary Using Catalyst D^{a,b}

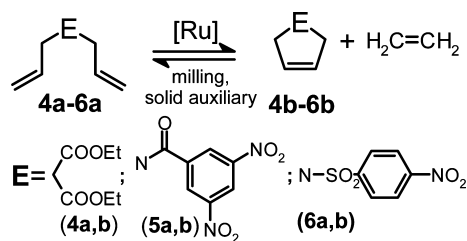
entry	olefin	catalyst (mol %)	liquid (μL)	solid auxiliary	time (h)	yield (%)
1	2a	D (1)	—	—	1.5	30
2	2a	D (1)	—	NaCl	1.5	93
3	2a	D (1)	—	NaBr	1.5	92
4	2a	D (1)	—	NaI	1.5	92
5	2a	D (1)	—	KCl	1.5	91
6	2a	D (1)	—	K ₂ SO ₄	1.5	92
7	3a	D (2)	EtOAc (75)	NaCl	5	73
8	3a	D (2)	EtOAc (75)	NaBr	5	70
9	3a	D (2)	EtOAc (75)	NaI	5	71
10	3a	D (2)	EtOAc (75)	KCl	5	74
11	3a	D (2)	EtOAc (75)	K ₂ SO ₄	5	71

^aReactions were performed using 2 mmol of reactant and 450 mg of the salt. ^bCatalyst was added in 2–4 equal portions during milling.

Scheme 2. Substrates/Products of MC RCM Using Catalyst D



RCM of solid olefins, we attempted the synthesis of dihydropyrroles **5b** and **6b** from protected diallylamines **5a** and **6a** (Table 3). Again, LAG with a solid auxiliary gave excellent results, affording **5b** and **6b** in >92% yield.^{31–33} Dihydropyrrole formation was confirmed by single-crystal XRD (Figure 2). The

Table 3. MC RCM Using 0.5 mol % D^a

entry	olefin	liquid ^b	solid auxiliary ^c	yield (%)
1	5a	—	—	—
2	5a	EtOAc	—	33
3	5a	EtOAc	NaCl	92 ^d
4	5a	EtOAc	KCl	90
5	5a	EtOAc	K ₂ SO ₄	91
6	6a	—	—	—
7	6a	EtOAc	—	39
8	6a	EtOAc	NaCl	94 ^d
9	6a	EtOAc	KCl	91
10	6a	EtOAc	K ₂ SO ₄	89

^aCatalyst was added in 2–4 portions over 3 h using 1 mmol of reactant. ^b75 μL . ^c450 mg of salt (~150% of reactant weight). ^dSimilar results were obtained with NaBr and NaI.

synthesis of **5b** is particularly notable, as an earlier attempt at RCM of **5a** gave only a 3.2% yield of **5b** after 1 day at 45 °C.²⁶

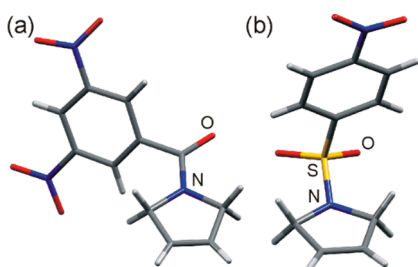
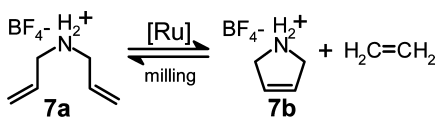


Figure 2. Structures of (a) **5b** and (b) **6b** (for **5a**, see the SI).

Finally, we addressed the ionic reactant **7a** (Scheme 2 and Table 4) to determine whether MC RCM would be tolerant to

Table 4. MC RCM of **7a** Using 2 mol % D^{a,b}



entry	liquid ^c	solid auxiliary ^d	time (h)	yield (%)
1	—	—	1.5	—
2	THF ^e	—	1.5	—
3	BMIMBF ₄	—	1.5	15
4	PC	—	1.5	13
5	PC	NaCl	1.5	96
6	PC	NaBr	1.5	92
7	PC	NaI	1.5	95
8	PC	KCl	1.5	94
9	PC	K ₂ SO ₄	1.5	91

^aCatalyst was added in three portions. ^b1 mmol of reactant. ^c75 μL of liquid. ^d300 mg of salt (~150% of the weight of **7a**). ^eSimilar results were obtained with toluene, EtOAc, acetone, and dimethyl carbonate.

ammonium salts as protected amine reactants.³⁷ The RCM of **7a** was not achieved by neat milling or by LAG experiments, except those involving highly polar propylene carbonate (PC) or 1-butyl-3-methylimidazolium tetrafluoroborate (BMIMBF₄). Again, combining LAG with a solid auxiliary gave excellent results, affording **7b** in >91% isolated yield for different salt auxiliaries combined with PC (entries 5–9).^{31–33}

We also explored mechanochemical CM and RCM of **1a–3a** and **5a** on a 10-fold (3 g) scale. The optimized reactions were readily adapted to this scale by increasing the catalyst loading by only 50% and using two stainless steel balls (Table 5).³⁸ Excellent conversions were also achievable for **1a–3a**, **5a**, and **7a** by milling with a single 20 mm diameter alumina ball (8 g), albeit for smaller amounts of starting material (1 g) because of the decreased space in the mill.

In summary, we have described the first potentially general and scalable application of mechanochemistry to OM. The broad importance of OM and industrial demands for developing cleaner, sustainable synthetic techniques³⁹ render the presented approach to metathesis of solid olefins an important step in the development of industrially attractive solvent-free organic syntheses.¹⁷ Whereas metathesis of neat liquids took place readily as long as steel-based equipment was avoided, reactions of solids presented challenges that were resolved by readily implemented methodologies without modifications of commer-

Table 5. CM/RCM on a 3 g (Steel) or 1 g (Alumina) Scale^{a,b}

olefin	milling medium	catalyst (%)	liquid (mL)	time (h)	yield (%)
1a	steel	D (0.75)	—	0.5	95
2a	steel	D (1.5)	—	1	89
3a	steel	D (3)	EtOAc (0.5)	5	67
5a	steel	D (0.75)	EtOAc (0.5)	3	90
1a	alumina	D (0.75)	—	0.5	96
2a	alumina	D (1.5)	—	1.5	91
3a	alumina	D (3)	EtOAc (0.25)	5	70
5a	alumina	D (0.75)	EtOAc (0.25)	3	91
7a	alumina	D (3)	PC (0.25)	1.5	92

^aCatalyst was added in 2–4 equal portions. ^bNaCl was used as the solid auxiliary (4.5 or 1.5 g, ca. 150% of the reactant weight).

cial catalysts. Systematic screening of catalytic liquids and/or solid auxiliaries offers a rapid, simple route to induce and optimize reactions, as illustrated by the optimization of RCM of initially nonreactive solids to almost quantitative level. It is notable that the amount of solid auxiliary used remains comparable to that of reactant (150% by weight), in contrast to conventional solution reactions, which often use a 10- or 100-fold excess of bulk solvent. The reactions were conducted on a scale of several grams, and it is likely that as long as completely steel-based equipment is avoided, they could be further scaled up in a planetary mill^{38a} or an extruder.^{38c} We are currently studying the use of mechanochemistry for OM polymerizations.

■ ASSOCIATED CONTENT

📄 Supporting Information

Methods and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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