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Communication

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Mechanochemical ruthenium-catalysed olefin metathesis

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Supporting Information Placeholder

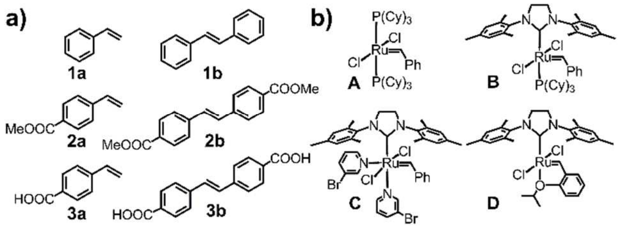
ABSTRACT: We describe the proof-of-principle development of a mechanochemical approach for ruthenium-catalyzed olefin metathesis, including cross-metathesis (CM) and ring-closing metathesis (RCM). The described procedures utilize commercially available catalysts to achieve high-yielding, rapid and room-temperature metathesis of solid or liquid olefins, on multi-gram scale, using either no or only a catalytic amount of a liquid.

Olefin metathesis is one of the most versatile and powerful tools for the formation and interconversion of carbon-carbon double bonds.[1] Ruthenium-based metathesis, brought to the forefront of organic and materials synthesis with the introduction of well-defined ruthenium 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 sustainability of olefin metathesis remain dynamic and challenging research areas.[4] In that context, the solid state has remained almost unexplored as a medium for olefin metathesis.

We now describe the development of the first mechanochemical 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 to olefin metathesis and permits high-yielding, scalable transformations using commercial ruthenium catalysts.[5] Mechanochemical 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 difficult to achieve under conventional conditions,[11] and achieve excellent stoichiometric control and stereoselectivity.[12] Organic mechanochemistry has reached an advanced stage[13] which permits multi-step and one-pot reaction sequences[14-16] and the development of entirely solvent-free synthesis.[17] So far, the exploration of mechanochemical metal-catalyzed processes has focused mostly on condensation[18] and coupling reactions.[19-23] Thus, the present study makes a new range of metal-catalyzed reactions available to mechanosynthesis. Whereas olefin metathesis 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 ruthenium 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 jar,[27] 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] Jars were sealed, but not hermetically, allowing loss of ethylene. We first compared the reactivity of a liquid (**1a**) to that of a low-melting solid (37 °C) methyl 4-vinylbenzoate (**2a**) and a high-melting solid (144 °C) 4-vinylbenzoic acid (**3a**) (Scheme 1a).

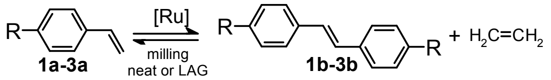
Scheme 1. (a) Substrates, products and (b) catalysts explored for mechanochemical CM reactions.



We compared the performance of the 1st (A) and 2nd generation (B) Grubbs catalysts, the fast-initiating catalyst (C) and the 2nd generation Hoveyda-Grubbs catalyst (D) (Scheme 1b).[30] Products were characterized by powder X-ray diffraction, Fourier transform infrared attenuated total reflectance (FTIR-ATR), ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.[31-33]

The reactivity screen (Table 1) reveals clear differences between liquid and solid olefins. Based on earlier work on metathesis of

Table 1. Exploration of CM by neat milling and LAG[a]



R = -H (**1a,b**); -COOCH$_3$ (**2a,b**); -COOH (**3a,b**)

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]

a) unless otherwise noted, catalyst was added in 2-4 equal portions; b) reaction was cooled using ice water; c) catalyst was added all at once; d) reactivity was not strongly affected by liquid choice, as demonstrated by screening toluene, acetone, ethanol, ethyl acetate or dimethylcarbonate for CM of **2a**, see SI; e) difficult to reproduce, only the highest yield is given here.

neat liquids,[24] we anticipated that CM of styrene should proceed readily. Indeed, as long as teflon jars were used, **1b** was obtained in high yields within 30 min (Table 1, entries 2-4). In contrast, **2a** took 1.5 hours milling to provide **2b** in 30% yield (Table 1, entries 5-11), while **3a** gave no product even after 5 hours (Table 1, entries 12-15). Overall, D was the most efficient of all explored catalysts,[30] while A was ineffective in all experiments and C required cooling during milling (*e.g.* compare entries 8 and 9, Table 1). Adding the catalysts in 2-4 equal portions gave higher yields, indicating that catalyst degradation slowly took place upon milling (*e.g.* compare entries 6 and 7, or 10 and 11, Table 1). Next, we attempted LAG, a technique which utilizes a substoichiometric liquid additive to improve reactivity (Table 1, entries 16-24). LAG reactions are characterized by η, the ratio of added liquid volume to reactant weight, of 0.1-1 µL mg^{-1}.[34] Although LAG (50 µL THF,[36] η~0.16 µL mg^{-1}) did improve the yield of **2b** and enabled the metathesis of **3a**, yields remained mediocre and difficult to reproduce. However, we noted that reaction mixtures formed a thick shell around the ball (Figure 1a,b), suggesting low yields and irreproducibility might be due to poor mixing.

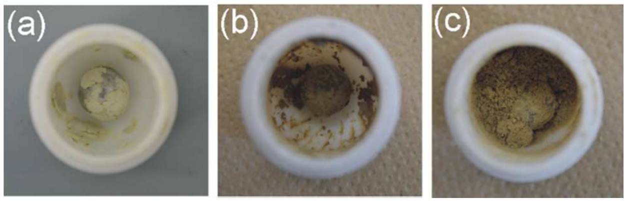


Figure 1. Reaction mixture (**3a**, 2 mol% D) after LAG with and without a solid auxiliary: (a) aggregation on the milling ball after 15 min; (b) after 5 h and (c) after 2h milling with NaCl (34% yield).

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

Table 2. Exploration of CM by LAG with a solid auxiliary using the 2nd generation Hoveyda-Grubbs 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_2SO_4	1.5	92
7	**3a**	D (2)	-	NaCl	5	-
8	**3a**	D (2)	-	NaBr	5	-
9	**3a**	D (2)	-	NaI	5	-
10	**3a**	D (2)	-	KCl	5	-
11	**3a**	D (2)	-	K_2SO_4	5	-
12	**3a**	D (2)	EtOAc(75)	NaCl	5	73
13	**3a**	D (2)	EtOAc(75)	NaBr	5	70
14	**3a**	D (2)	EtOAc(75)	NaI	5	71
15	**3a**	D (2)	EtOAc(75)	KCl	5	74
16	**3a**	D (2)	EtOAc(75)	K_2SO_4	5	71

a) reactions were performed using 2 mmol reactant and 450 mg of the salt b) catalyst was added in 2-4 equal portions during milling.

With conditions for CM of solid olefins established, we addressed the RCM, starting with the liquid **4a** (Scheme 2). Consistent with CM of the liquid reactant styrene, cyclopentene **4b** was obtained in 94% yield after 30 min using 0.25 mol% catalysts D.[31-33] For 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 >93% yield.[31-33]

Scheme 2. Substrates and products of mechanochemical RCM using catalyst D.

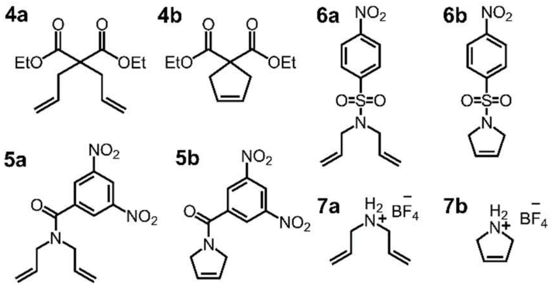
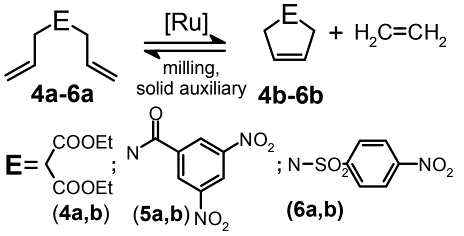


Table 3. Mechanochemical RCM using 0.5 mol% D.[a]



Entry	olefin	liquid[b]	solid auxiliary[c]	yield (%)
1	**5a**	-	-	-
2	**5a**	EtOAc	-	33
3	**5a**	EtOAc	NaCl	92
4	**5a**	EtOAc	NaBr	90
5	**5a**	EtOAc	NaI	93
6	**5a**	EtOAc	KCl	90
7	**5a**	EtOAc	K_2SO_4	91
8	**6a**	-	-	-
9	**6a**	EtOAc	-	39
10	**6a**	EtOAc	NaCl	94
11	**6a**	EtOAc	NaBr	94
12	**6a**	EtOAc	NaI	90
13	**6a**	EtOAc	KCl	91
14	**6a**	EtOAc	K_2SO_4	89

a) catalyst was added in 2-4 portions over 3 hours, using 1 mmol reactant; b) 75 µL; c) 450 mg salt (~150% of reactant weight).

Dihydropyrrole formation was confirmed by single crystal X-ray crystallographic analysis (Figure 2). Synthesis of **5b** is particularly notable, as an earlier attempt at RCM of solid **5a** gave only 3.2% of **5b** after 1 day at 45 °C.[26]

Finally, we addressed the ionic reactant **7a** (Scheme 2, Table 4), to determine if mechanochemical RCM would be tolerant to ammonium salts as protected amine reactants.[37]

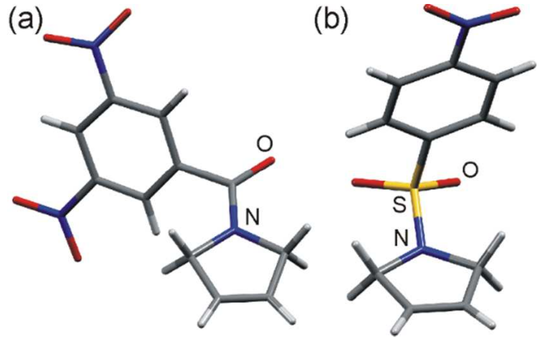
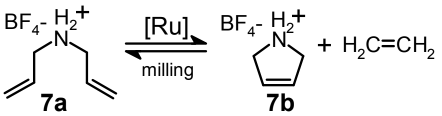


Figure 2. Molecular structures of (a) **5b** and (b) **6b** based on single crystal X-ray diffraction; for the structure of **5a**, see SI.

The RCM of **7a** was not achieved by neat milling or most LAG experiments, except those involving highly polar propylene carbonate (PC) or 1-butyl-3-methylimidazolium tetrafluoroborate ($BMIMBF_4$). Again, combining LAG with a solid auxiliary gave excellent results, affording **7b** in >91% isolated yield for different salt auxiliaries combined with PC (Table 4, Entries 9-13).[31-33]

Table 4. Mechanochemical RCM of 7a using 2 mol% D.[a,b]



Entry	liquid[c]	solid auxiliary[d]	time (h)	yield (%)
1	-	-	1.5	-
2	THF	-	1.5	-
3	Toluene	-	1.5	-
4	EtOAc	-	1.5	-
5	acetone	-	1.5	-
6	DMC	-	1.5	-
7	$BMIMBF_4$	-	1.5	15
8	PC	-	1.5	13
9	PC	NaCl	1.5	96
10	PC	NaBr	1.5	92
11	PC	NaI	1.5	95
12	PC	KCl	1.5	94
13	PC	K_2SO_4	1.5	91

a) catalyst was added in three portions; b) 1 mmol of reactant; c) 75 µL liquid; d) 300 mg salt (~150% of the weight of **7a**)

We also explored mechanochemical CM and RCM of **1a**-**3a** and **5a** on a 10-fold (3 gram) scale. 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**, **2a**, **3a**, **5a** and **7a** by milling with a single alumina ball of 20 mm diameter (8 grams), albeit for smaller amounts of starting material (1 gram) due to less space in the milling vessel.

Table 5. Mechanochemical CM and RCM on 3 gram (steel media) and 1 gram scale (alumina media).[a,b]

olefin	milling media	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

(a) catalyst was added in 2-4 equal portions; (b) NaCl was used as the solid auxiliary (4.5 g or 1.5 g, ca. 150% of the reactant weight).

In summary, we described the first, potentially general and scalable, application of mechanochemistry to olefin metathesis,.[38] The broad importance of olefin metathesis and industrial demands for developing cleaner, sustainable synthetic techniques[39] render the presented approach to metathesis of solid olefins an important step in developing industrially attractive solvent-free organic synthesis.[17] Whereas metathesis of neat liquids takes place readily, as long as steel-based equipment is avoided, reactions of solids presented challenges that were resolved by readily implemented methodologies, without modifications of commercial catalysts. Systematic screening of catalytic liquids and/or solid auxiliaries offers a rapid, simple route to induce and optimize reactions, as illustrated by optimizing RCM of initially non-reactive 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 10- or 100-fold excess of bulk solvent. The reactions have been conducted on a scale of several grams and, as long as completely steel-based equipment is avoided, it is likely they could be further scaled up in a planetary mill[40] or an extruder.[41] We are currently investigating the use of mechanochemistry for olefin metathesis polymerizations.

ASSOCIATED CONTENT

Supporting Information

Selected ^1H and ^{13}C NMR, FTIR-ATR, MS and PXRD data. Crystallographic data for **5a**, **5b** and **6b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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