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Ethyl lactate: A green solvent for olefin metathesis

Sebastian Planer,[a] Anupam Jana[a] and Karol Grela*

Abstract: Compatibility of selected, commercially available ruthenium olefin metathesis catalysts with ethyl lactate as solvent was evaluated using a range of substrates and conditions. In addition, the preparation of a metathesis catalyst in simplified manner by using the advantages of ethyl lactate was accomplished. The application of ethyl lactate facilitates product isolation (also allowing for lower Ru-contamination in crude metathesis products) and improves the overall green angle of olefin metathesis.

Introduction

Lactic acid esters (LE), produced commercially from a range of agricultural residues and food byproducts, have found a considerable interest as eco-friendly alternatives to petrochemical solvents.[1-3] Recently, chemical recycling of polylactide from disposable packaging materials, developed by Du Pont and others, became an important alternative source of lactic esters.[4-6] In this context, Sobota *et al.* reported a simple and convenient solvothermal alcoholysis method for large-scale recycling of polylactide residues.[1,7] Such lactic esters can be used as diluents for various oils and resins, solvents for dyes, paints, inks and pigments, as well as degreasing fluids for machinery and as cleaning agents to remove graffiti.[1,8-10]

However, according to our knowledge, there are very few reports on the application of LE as solvents in chemical synthesis.[11] Therefore, we decided to test ethyl lactate (EL), one of the simplest and cheapest lactic esters, in catalytic olefin metathesis. Olefin metathesis is a selective and atom-economic chemical transformation that offers a great promise in pharmaceutical and fine-chemical industries.[12-14] Unfortunately, environmentally unfriendly solvents like dichloromethane (DCM) or toluene are typically used in metathesis reactions, also at pilot-plants and even in production processes.[15,16] Other commonly employed solvents include 1,2-dichloroethane, fluorinated aromatic solvents,[17,18] and benzene.[12-14] The exploration of alternative “green solvents” for olefin metathesis has recently become of interest in order to minimize the environmental pollution resulting from the use of hazardous solvents in traditional chemical production.[19] Despite the numerous mechanistic and computational studies in olefin metathesis,[20,21] only a limited number of publications focus on “green” solvents as a means of reducing environmental impact.[22] These include water,[23] acetic acid,[24] methyl *tert*-butyl ether (MTBE),[25] dimethyl carbonate (DMC),[26] glycerol,[27] polyethylene glycol,[28] methyl decenoate,[29] 2-methyltetrahydrofuran (2-MeTHF),[30] and ethyl acetate (AcOEt).[21] Additionally, ionic liquid toluene binary mixtures and supercritical carbon dioxide (scCO$_2$) have also been used in metathesis as a substitute for organic solvents.[17,32]

However, there is no report on the use of ethyl lactate as solvent for olefin metathesis reaction. This green solvent can be produced from renewable sources or even recycled from human generated wastes and used safely without affecting the environment.[33-36] EL exhibits very favourable toxicological properties being nonteratogenic and readily undergoing metabolic hydrolysis to ethyl alcohol and lactic acid by enzymatic esterase activity (lactic acid being a natural metabolite in humans).[37] The hydroxyl group of ethyl lactate makes it miscible and compatible with water or aliphatic alcohols, while its intrinsic high-boiling point (T_{bp} = 151 °C) allows its use at high temperatures, if needed. These advantageous properties encouraged us to explore the use of ethyl lactate as a greener substitute for more environmentally detrimental solvents used typically in olefin metathesis.

Results and Discussion

Although a wide variety of olefin metathesis catalysts are now available, their effectiveness can vary greatly from one application to another making the judicious choice of the most optimal one a daunting challenge.[38] As such, we chose to examine the effect of EL on the performance of selected representative commercially available catalysts using a variety of functionalised substrates (Figure 1). Grubbs and Hoveyda-Grubbs catalysts **[Ru]-1**, **[Ru]-2** and **[Ru]-6** have transformed the metathesis reaction into a tremendously powerful synthetic tool and are among the most popular 2nd generation catalysts.[39a] Variants of these include the fast initiating Apeiron Nitro-catalyst **[Ru]-3**, activated by a strong electron withdrawing group in *para*-position to the chelating isopropoxy-benzylidene ligand.[39b] The indenylidene-based **[Ru]-4** represents another class of reliable Ru catalysts.[29c] Last but not least, the commercially available AquaMet™ complex **[Ru]-5** was selected due to its favourable water-solubility.[29d]

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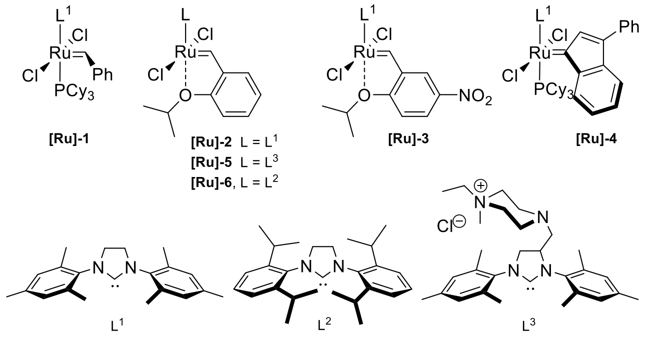
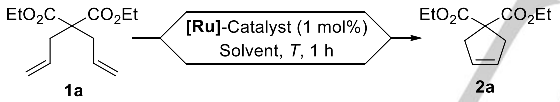


Figure 1. Commercially available metathesis complexes used in this study.

Initial studies and condition optimization. We began our investigation by examining the RCM reaction of the standard model substrate diethyl diallymalonate (**1a**) in solvents, typically employed in metathesis, toluene and dichloromethane (DCM) as well as in ethyl lactate (EL) at 40 °C (Table 1). In a representative experiment, a mixture of substrate **1a** (1.0 mmol, 0.1 mM) and the catalyst (1.0 mol%) in the appropriate solvent (10 mL) was stirred at 40 °C for 1 h under an argon atmosphere using durene (1 equiv.) as an internal standard (Scheme 1). Upon cooling, the reaction was quenched with ethyl vinyl ether and the conversion determined by GC analysis.



Scheme 1. Model RCM reaction used in comparative study.

Table 1. Solvent comparison for the model RCM reaction of **1a** at 40 °C.[a,b]

Solvent	Catalyst	Conversion [%]
Ethyl lactate	**[Ru]-1**	38
	[Ru]-2	61
	[Ru]-3	63
	[Ru]-4	12
Toluene	**[Ru]-1**	99
	[Ru]-2	99
	[Ru]-3	99
	[Ru]-4	99
Dichloromethane	**[Ru]-1**	99
	[Ru]-2	63
	[Ru]-3	99
	[Ru]-4	90

[a] Catalyst 1 mol%, *C* = 0.1 M, under Ar. [b] Conversion determined by GC, durene was used as internal standard. [c] Ethyl lactate "synthetic" grade was distilled prior to use.

In EL, catalysts **[Ru]-2** and **[Ru]-3** achieved 61% to 63% conversion. Surprisingly, **[Ru]-1** and **[Ru]-4** showed rather poor results (Table 1). In contrast, under the same conditions, RCM of **1a** in dichloromethane and toluene provided product **2a** in excellent yields regardless of the chosen catalyst. The results summarized in Table 1 show cleanly that at 40 °C the metathesis reaction in ethyl lactate proceeds rather tardily, while toluene and DCM were proven to be superior.
To check the temperature influence on the reactivity of various Ru catalysts in ethyl lactate, the experiments were repeated at 70 °C maintaining the catalyst loading and reaction time (Table 2). However, the low boiling DCM was replaced by 2-MeTHF. At this modified conditions, all catalysts exhibited improved activity in ethyl lactate. Starting with **[Ru-1]**, good conversion to RCM product **2a** in ethyl lactate was recorded without the appearance of undesired side products.

Table 2. Solvent comparison for the model RCM reaction of **1a** at 70 °C .[a,b]

Solvent	Catalyst	Conversion [%]
Ethyl lactate	**[Ru]-1**	60
	[Ru]-2	91
	[Ru]-3	95
	[Ru]-4	97
	[Ru]-5	91
Toluene	**[Ru]-1**	99
	[Ru]-2	99
	[Ru]-3	99
	[Ru]-4	99
2Me-THF	**[Ru]-1**	96
	[Ru]-2	88
	[Ru]-3	80
	[Ru]-4	96

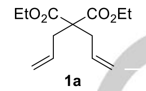
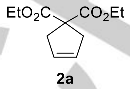
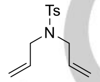
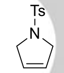
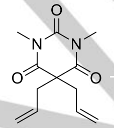
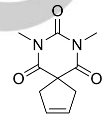
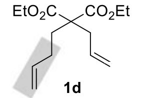
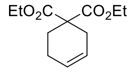
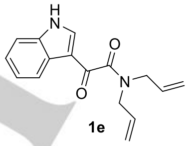
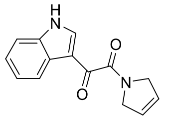
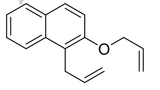
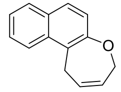
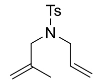
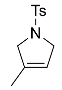
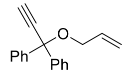
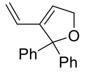
[a] Catalyst 1 mol%, *C* = 0.1 M, under Ar. [b] Conversion determined by GC, durene was used as internal standard. [c] Ethyl lactate "synthetic" grade was distilled prior to use. For better insight, please find a time depending conversion plot comparing toluene and ethyl lactate in the SI.

The conversion observed in the presence of **[Ru]-2** was fully comparable with the one obtained in toluene and even better than the conversion in 2-MeTHF. **[Ru]-4** showed similar activity independent from the choice of solvent. To our surprise, the RCM reaction in presence of **[Ru]-3** catalyst in ethyl lactate indicated 95% conversion, which was higher than carried out in 2-MeTHF (80%). Encouraged by these results, we focused on the water-soluble complex **[Ru]-5** to check its compatibility with ethyl lactate. Also in this case diethyl diallylmalonate **1a** reacted smoothly at 70 °C to form the corresponding product **2a** in 91% yield.[40]

Scope and limitation studies and product isolation. The results obtained so far encouraged us to test the compatibility of this solvent with a broader spectrum of substrates.[41] Thus, a number of various unsaturated substrates were employed following the same experimental procedure. A mixture of the respective substrate (1 mmol, C = 0.1 M) and catalyst (1 mol%) dissolved in distilled "synthetic" grade EL (≥98%; distilled without drying agent and non-degassed) was heated up to 70 °C to afford the expected products (Table 3). In addition, we envisaged to use the favourable physicochemical properties of EL (T_{bp} = 151 °C, water solubility) to enable easy product-separation from the reaction mixture. Therefore, we decided to check if we could isolate the crude products not only by evaporation of the solvent *in vacuo*, but also by diluting the reaction mixture with water and using biphasic extraction technique (Further information provided in SI).

A wide range of substrates underwent reactions in EL leading to diversely substituted carbo- and heterocyclic derivatives (also of pharmaceutical interest) as shown in Table 3. For example, diethyl diallylmalonate **1a** led to the cyclopentene derivative **2a** in the presence of 1 mol% nitro-Hoveyda-Grubbs catalyst **[Ru]-3** after 1 h in 85% isolated yield (crude product isolated by extraction, entry 1). The yield of the reaction remained unchanged when the catalyst was substituted by **[Ru]-4** (entry 2). Next, the RCM reaction of model diene **1b** was investigated. Both catalysts **[Ru]-3** and **[Ru]-4** led to product **2b** in good isolated yields (80% and 86%). Notably, the same catalysts **[Ru]-4** and **[Ru]-3** showed similar efficiency in the case of barbituric acid derivative **1c**. The RCM reaction of **1c** in the presence of **[Ru]-3** afforded 92% isolated yield of **2c**, whereas **[Ru]-4** provided 99% yield. In case of **1d**, cyclohexene derivative **2d** was isolated in 88% yield in presence of **[Ru]-3** (**[Ru]-2** led to lower yield; cf. entry 7 and 8). Next, we decided to check the performance of **[Ru]-2** and **[Ru]-3** in RCM of *N*,*N*-diallyl-2-(1*H*-indol-3-yl)-2-oxoacetamide (**1e**). Again, the expected product **2e** was isolated in very good isolated yield using **[Ru]-3** as catalyst, while **[Ru]-2** gave slightly lower yield (72%, entry 10). Also, the RCM reaction of naphthalene derivative **1f** resulted in the isolation of the desired 7-membered cyclic ether with good yield and excellent selectivity (similar substrates tend to undergo unwanted C–C double bond isomerisation).[42] Interestingly, although catalyst **[Ru]-3** shows good overall efficiency, the RCM reaction of more challenging trisubstituted diene **1g** was accomplished in 64% isolated yield only. Furthermore we were pleased to see that the enyne cycloisomerization of **1h** gave the expected product **2h** in 98% isolated yield. The results presented in Table 3 encouraged us to test the possibility of using more challenging substrates (e.g. volatile alkenes) in cross-metathesis reactions (CM) in ethyl lactate (Table 4). At first, allylbenzene **3a** and three equivalents of (*Z*)-but-2-ene-1,4-diol diacetate **4a** were dissolved in ethyl lactate and heated at 70 °C for 2 h in presence of 1 mol% of **[Ru]-3**. As a result, product **5a** was obtained in 88% yield as a mixture of *E*-

Table 3. RCM and enyne-cycloisomerization in ethyl lactate at optimised conditions. [a,b]

Entry	Substrate	Product	[Ru]	Isolated yield [%]
1[c]	 **1a**	 **2a** 	**[Ru]-3**	85
2[c]			**[Ru]-4**	85
3	 **1b**	 **2b**	**[Ru]-3**	80
4			**[Ru]-4**	86
5	 **1c**	 **2c**	**[Ru]-3**	92
6			**[Ru]-4**	99
7	 **1d**	 **2d**	**[Ru]-3**	88
8			**[Ru]-2**	50
9	 **1e**	 **2e**	**[Ru]-3**	93
10			**[Ru]-2**	72
11	 **1f**	 **2f**	**[Ru]-3**	69
12	 **1g**	 **2g**	**[Ru]-3**	64
13	 **1h**	 **2h**	**[Ru]-3**	98

[a] Reactions carried out in prior distilled "synthetic" grade ethyl lactate under Ar at 70 °C. [b] *C* = 0.1 M, **[Ru]** = 1 mol%. [c] Crude product isolated by simple biphasic extraction after addition of water to the reaction mixture (see the SI for details).

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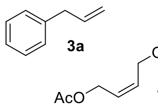
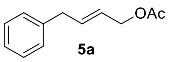
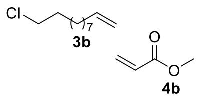
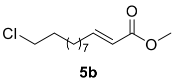
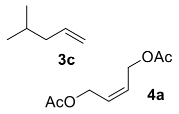
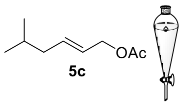
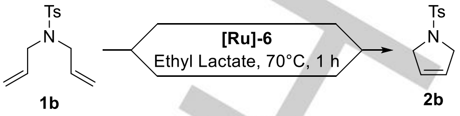
Table 4. CM scope in ethyl lactate[a,b]

Entry	Substrate	Product	[Ru]	Isolated yield [%] (*E*/*Z*)
1	 3a 4a	 5a	**[Ru]-3**	88 (8:1)
2			**[Ru]-4**	76 (8:1)
5	 3b 4b	 5b	**[Ru]-3**	76 (18:1)
6			**[Ru]-4**	93 (22:1)
7[d]	 3c 4a	 5c	**[Ru]-3**	65 (6:1)
8[c,d]			**[Ru]-4**	71 (6:1)
9[c,d]			**[Ru]-5**	65 (5:1)

[a] Reactions carried out in prior distilled "synthetic" grade ethyl lactate under Ar at 70 °C. *E*/*Z* ratio calculated by ^{1}H NMR. [b] **[Ru]** = 1 mol%, *C* = 0.5 M and 3 equiv. of crosspartner (**4a** and **4b**) were used. [c] *C* = 1 M. [d] Crude product isolated by simple biphasic extraction after addition of water to the reaction mixture (see the SI for details).

and *Z*-isomers in 8:1 ratio. The same CM reaction promoted by **[Ru]-4** also afforded product **5a** in good yield (76%, entry 2). Importantly, CM proceeded efficiently also in case of electron poor alkenes, such as methyl acrylate **4b**, in presence of **[Ru]-3** leading to the corresponding disubstituted *α,β*-unsaturated ester **5b** in 76% isolated yield. We were pleased to see that under these conditions, catalyst **[Ru]-4** afforded **5b** in 93% isolated yield (entry 4). Notably, CM of the volatile alkene **3c** and **4a** leads to the corresponding product **5c** in good yields (65-71%), in presence of various Ru-catalysts (entry 5-7), by applying biphasic extraction technique (see SI).

Catalyst low-loading experiments. To quantify the activity of **[Ru]-3** in EL, a selected metathesis reaction was performed using gradually reduced catalyst loading (Table 5). The RCM reaction of diallyltosylamide **1b** was performed in prior distilled and additionally degassed ethyl lactate ("synthetic" grade) under a protective atmosphere of argon (Scheme 2). The reaction conversion was checked after 1 hour using GC analysis. Catalyst loadings from 2500 (0.25 mol%) down to 250 ppm resulted in excellent conversions, whilst a catalyst loading of only 100 ppm led to decreased conversion (51%). In these experiments catalyst **[Ru]-3** provided a maximal turnover number (TON) of 5100.



Scheme 2. Model RCM reaction used for catalyst loading study.

Table 5. Low catalyst loading experiment for the model RCM reaction of 1b[a]

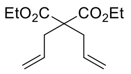
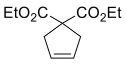
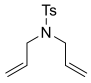
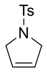
Entry	C [M]	**[Ru]-6** loading [mol%]	Conversion [%]	TON	TOF [min^{-1}]
1	0.1	0.25	99	396	6.6
2	0.1	0.10	87	870	14.5
3	0.5	0.025	82	3280	54.7
4	0.5	0.010	51	5100	85.0

[a] Conversion determined by GC, durene was used as internal standard.

Reactions without protective argon atmosphere. Next, we proved the possibility of performing olefin metathesis in ethyl lactate sacrificing the protective atmosphere of argon to make this methodology more convenient from a practical point of view.[43] At first, we run the model RCM reaction of **1a** and **1b** to check the difference in isolated yield between the reaction conducted under argon (Table 3) and in air (see Table 6). Gratifyingly, both these conditions gave similar isolated yields proving the tolerance of Ru-catalyst **[Ru]-3** in EL towards air. Similarly, the CM reaction between allylbenzene and (*Z*)-but-2-ene-1,4-diol diacetate proceeded with the same effectiveness (entry 3).

Facile isolation of products by precipitation. The miscibility of EL with water is in this context an important feature, because the metathesis product can be isolated more conveniently by simple decantation (in case of an oily product) or by filtration (in case of a solid material) followed by distillation or crystallization.

Table 6. Metathesis reactions in ethyl lactate in open air[a]

Entry	Substrate	Product	[Ru]	Isolated yield [%]
1	 1a	 2a	**[Ru]-3**	85[b]
2	 1b	 2b	**[Ru]-5**	88[c]

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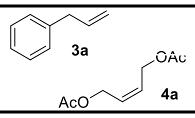
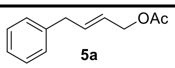
3	 **3a** **4a**	 **5a**	**[Ru]-3**	88[d]

[a] Reactions carried out in prior distilled "synthetic" grade ethyl lactate without protective atmosphere of argon at 70 °C, **[Ru]** = 1 mol%. [b] C = 0.1 M. [c] C = 0.2 M, product isolated by precipitation and filtration (see SI and Figure 2). [d] *C* = 0.5 M, 3 equiv. of crosspartner **4a** were used.

In order to demonstrate that extraction with organic solvents and column chromatography can be completely avoided in larger scale metathesis, we decided to run RCM of **1b** on a gram-scale (for the reaction conditions, see: Table 6, entry 2). We carried out a metathesis reaction using 2 mmol of **1b** in the presence of water-soluble catalyst **[Ru]-5** while again sacrificing the protective atmosphere of argon in order to design a reaction as simplified and handy as possible. After the reaction was completed, water (150 mL) was added to the reaction mixture in order to precipitate product **2b** as a solid material (Fig 2A). The solid product was then collected on a sintered-glass funnel (Fig 2B) and washed with water and dried to get analytically pure product **2b** (Fig 2C) in 88% yield, which is fully comparable to the previously obtained results (86%, Table 3, entry 4).

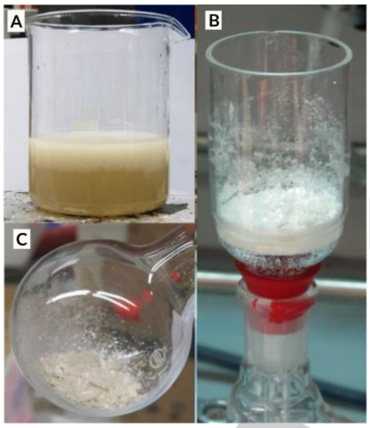
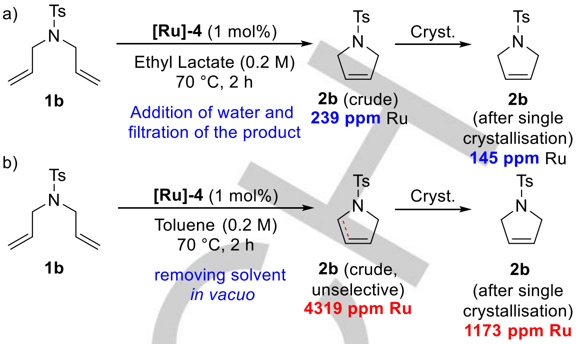


Figure 2. Isolation of the RCM product **2b** without column chromatography. (A) Water added to the reaction mixture to precipitate **2b**. (B) Filtration through sintered glass funnel. (C) Isolated product **2b** in 88% yield.

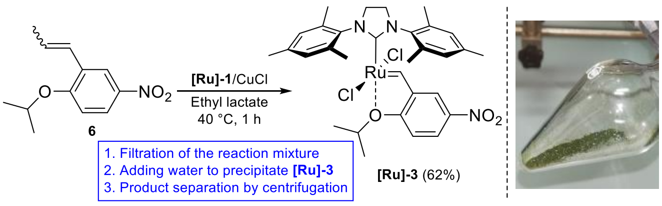


Scheme 3. Ruthenium contamination of product **2b** obtained in metathesis reaction carried out in (a) ethyl lactate and in (b) toluene. Ru content (in ppm) determined by ICP-MS.

Apparently, the same precipitation/filtration procedure is not possible in the case of "classic" solvents as for example toluene, where the solvent must be evaporated *in vacuo* leading to more contaminated crude product **2b** (Scheme 3).

In addition, the RCM reaction of **1b** in toluene at 70 °C (Scheme 3) was found to be less selective under chosen conditions, as the formation of by-products was observed,[22] making column chromatography or recrystallisation inevitable to obtain pure product **2b** (see SI for details).

Green metrics and outlook. Finally, comparing the RCM reaction of **1b** in EL and in toluene allowed us to approximate some Green Metrics, such as the EcoScale parameter,[44] which was 20 Penalty Points higher in the case of toluene (for details see SI). To show some other possible uses of this solvent in the context of transition metal-catalysed olefin metathesis, we attempted the synthesis of Apeiron's Nitro Catalyst **[Ru]-3** in EL (Scheme 4). As the result, we found that this complex, typically prepared in dichloromethane,[45] can be obtained in EL. Furthermore, the beneficial miscibility of EL and water enabled isolation of the formed **[Ru]-3** by simple precipitation caused by addition of water followed by centrifugation, thus allowing for easier isolation (for more details, see SI).



Scheme 4. Synthesis of catalyst **[Ru]-3** in ethyl lactate followed by product precipitation with water and centrifugation.

Conclusions

We have successfully demonstrated that olefin metathesis proceeds well in the environmentally friendly ethyl lactate (EL) solvent, promoted by a number of Ru catalysts (1.0-0.02 mol%). Both, RCM and CM proceed with high conversions at elevated temperature (70 °C) with or without the protective atmosphere of argon. Furthermore, the use of distilled EL is sufficient to provide good yields for a range of substrates, while the catalyst loading can be reduced to a hundred ppm level. Water miscibility of EL allows easier isolation of some products that are, in comparison, less contaminated with catalyst's traces. Finally, the preparation of the organometallic complex **[Ru]-3** was conducted for the first time in EL. The advantages demonstrated herein, coupled with the benign nature of ethyl lactate, which can be obtained from biomass or from polylactide wastes in an economically viable and environmentally sustainable method, should persuade researchers in both industry and academia to seriously consider alternate solvents for environmentally friendly olefin metathesis processes.

Experimental Section

*General Procedures for RCM and enyne cycloisomerization reactions (**1a**-**1h**)*

Procedure 1A: Ethyl lactate removed by evaporation

To a solution of substrate (1 equiv., 1.0 mmol, C = 0.1 M) in prior distilled ethyl lactate (10 ml) the catalyst (1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C, until TLC monitoring showed a complete or no progressing conversion. The reaction mixture was cooled to room temperature and the 1,4-bis(3-isocyanopropyl)-piperazine scavenger (4 mol%) was added and stirred for 30 minutes. The solvent was removed in vacuo and the residue was subjected to flash chromatography (SiO_2) to afford the product.

Procedure 1B: Ethyl lactate removed by extraction (RCM of **1a**)

To a solution of substrate(1 equiv., 1.0 mmol, C = 0.1 M) in prior distilled ethyl lactate (10 ml) the catalyst (1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C, until TLC monitoring showed a complete or no progressing conversion. The reaction mixture was cooled to room temperature and the 1,4-bis(3-isocyanopropyl)piperazine scavenger (4 mol%) was added and stirred for 30 minutes. 20 ml of diethyl ether were added to the reaction mixture and the mixture was extracted with water (4×10 ml). The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo the residue was subjected to flash chromatography (SiO_2) to afford the product.

Procedure 1C: RCM of **1b** and product isolation without column chromatography

To a solution of substrate **1b** (0.5 g, 2.0 mmol, 1 equiv.) in 10 ml prior distilled ethyl lactate (C = 0.2 M, synthetic grade) **[Ru]-5** (16.1 mg, 0.02 mmol, 1 mol%) was added. The reaction mixture was stirred at 70 °C for 2 hours before 150 ml of dest. water were added at RT. The resulting suspension was stirred for 30 minutes and the precipitate filtered through a sintered-glass funnel and dried in vacuo to afford product **2b** (0.39 g, 1.75 mmol, 88%).

*General Procedures for CM (**3a**-**3c**)*

Procedure 2A: Ethyl lactate removed by evaporation

To a solution of substrate (1 equiv., C = 0.5 M) and methyl acrylate resp. (2Z)-2-Butene-1,4-diyl diacetate (3 equiv.) in prior distilled ethyl lactate the catalyst (1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C, until TLC monitoring showed a complete or no progressing conversion. The reaction mixture was cooled to room temperature and the 1,4-bis(3-isocyanopropyl)piperazine scavenger[10] (4 mol%) was added and stirred for 30 minutes. The solvent was removed in vacuo and the residue was subjected to flash chromatography (SiO_2) to afford the product.

Procedure 2B: Ethyl lactate removed by extraction (CM of **3c**)

To a solution of substrate (1 equiv., C = 0.5 M) and methyl acrylate resp. (2Z)-2-Butene-1,4-diyl diacetate (3 equiv.) in prior distilled ethyl lactate the catalyst (1 mol%) was added under protective atmosphere of argon. The reaction mixture was stirred at 70 °C, until TLC monitoring showed a complete or no progressing conversion. The reaction mixture was cooled to room temperature and the 1,4-bis(3-isocyanopropyl)piperazine scavenger (4 mol%) was added and stirred for 30 minutes. The solvent was removed in vacuo and the residue was subjected to flash chromatography (SiO_2) to afford the product.

*Synthesis of **[Ru]-3** in ethyl lactate*

A flame-dried schlenk flask was charged with **[Ru]-1** (0.08 mmol, 69.3 mg, 1 equiv.) and suspended in 7 ml ethyl lactate (natural grade, prior distilled over Al_2O_3 under argon). CuCl (0.08 mmol, 8.0 mg, 1 equiv.) and 1-Isopropoxy-4-nitro-2-(prop-1-en-1-yl)benzene **6** (0.08 mmol, 17.7 mg, 1 equiv.) were added to the suspension and stirred for 1 h at 40 °C until TLC monitoring indicated full conversion. The reaction mixture was filtered over a pad of celite and washed with ethyl acetate (2 ml). Distilled water (10 ml) was added and the resulting green suspension was stirred for 20 minutes at 0 °C and separated by centrifugation (10 minutes, 5000 rotations/minute). The organic-aqueous phase was removed and the remaining solid dried *in vacuo* and recrystallized from DCM/methanol (1:2) to afford **[Ru]-3** in 62% isolated yield (33 mg, 0.08 mmol).

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Keywords: Metathesis • Green Chemistry • Environmental Chemistry • Renewable Resources • Catalysis

[1] a) R. Petrus, D. Bykowski and P. Sobota, *ACS Catal*., **2016**, *6*, 5222; b) D. Bykowski, A. Grala and P. Sobota, *Tetrahedron Let*., **2014**, *55*, 5286.
[2] Galaster, Galasolv, PURASOLV, and VertecBio EL are examples of commercial lactate ester based solvents produced by Galactic, Purac, or Vertec Biosolvents.
[3] a) S. M. Nikles, M. Piao, A. M. Lane and D. E. Nikles, *Green Chem.* **2001**, *3*, 109; b) C. S. M. Pereira, V. M. T. M. Silva and A. E. Rodrigues*, Green Chem*., **2011**, *13*, 2658.
[4] a) L. D. Brake, *Recovery of polyhydroxy acids*. U.S. Patent 5,264,614, November 23, **1993**, SciFinder Scholar 1994:77892; b) L. D. Brake, *Preparation of alkyl esters by depolymerization of poly(hydroxyl acids.* U.S. Patent 5,264,617, November 23, **1993**, SciFinder Scholar 1994:78004.
[5] a) X. Song, H. Wang, X. Yang, F. Liu, S. Yu and S. Liu, *Polym. Degrad. Stab.,* **2014**, *110*, 65; b) A.-F. Mohd-Adnan, H. Nishida and Y. Shirai, *Polym. Degrad.Stab.*, **2008**, *93*, 1053; c) M. Yagihashia and T.Funazukuri, *Ind. Eng. Chem. Res*. **2010**, *49*, 1247−1251; d) K. Hirao, Y. Shimamoto, Y. Nakatsuchi and H. Ohara, *Polym. Degrad. Stab*. **2010**, *95*, 86; e) V. Piemonte and F. Gironi, *J. Polym. Environ*., **2013**, *21*, 275; f) H. Tsuji, H. Daimon and K. Fujie, *Biomacromolecules*, **2003**, *4*, 835; g) L. D. Brake and N. S. Subramanian, *Rapid depolymerization of polyhydroxy acids*. U.S. Patent 5,264,626, November 23, **1993**, SciFinder Scholar 1994:78003; h) P. Coszach, J.-C. Bogaert and J. Willocq, *Chemical recycling of poly(lactic acid) by hydrolysis*. WO Patent 2010118954A1, October 21, **2010**, SciFinder Scholar 2010:1310693; i) M. Faisal, T. Saeki, H. Tsuji, H. Daimon and K. Fujie, *Trans. Ecol. Environ.* **2006**, *92*, 225.
[6] a) E. M. Filachione, J. H. Lengel and C. H. *Fisher, Ind. Eng. Chem*. **1945**, *37*, 388; b) E. M. Filachione and C. H. Fisher, *Volatile esters of hydroxycarboxylic acids*. U.S. Patent 2,405,646, August 13, **1946**, SciFinder Scholar 1947:807.
[7] According to specification provided in Ref. 1a, such solvothermally de-polymerised and distilled ethyl lactate is of high purity, comparable to the commercially available EL samples. See Supporting Information for more details.
[8] a) M.-L. C. Adolfsson, A. K. Saloranta, M. K. Silander, S. A. Varila and M. V. Wikstedt, *Colorant composition for solvent-borne paint products*. WO Patent 9,708,255 A1, March 6, **1997**, SciFinder Scholar 1997:290107; b) H. R. Bakker and M. T. C. Kranz, *Paint composition based on a chemical cross linking system and/or oxidative drying, with lactates as solvent and thinner*. WO Patent 9914280A1, March 25, **1999**, SciFinder Scholar 1999:216978.
[9] a) H. J. Weltman and T. L. Phillips, *Nonflammable mild odor solvent cleaner with (m)ethyl lactate and propylene glycol propyl ether*. U.S. Patent 5,604,196, February 18, **1997**, SciFinder Scholar 1997:169108; b) H. J. Weltman and T. L. Phillips, *Nonflammable mild-odor low-toxic solvent cleaner.* U.S. Patent 5,437,808, August 1, **1995**, SciFinder Scholar 1995:792920; c) J. Muse, *Environmentally friendly solvent containing isoamyl lactate*. U.S. Patent 2007/0155644A1, July 5, **2007**, SciFinder Scholar 2007:733124; d) J. Julemont, I. Leonard and D. Dormal, *Antibacterial cleaning composition impregnated non-woven wipe*. WO Patent 2003/050228A1, June 19, **2003**, SciFinder Scholar 2003:472587; e) B. Laux, *VOC-free solvent blends for cleaning surfaces.* U.S. Patent 2005/0209123 A1, September 22, **2005**, SciFinder Scholar 2005:1026591.
[10] J. E. Opre, *Environmentally friendly ink cleaning preparation*. U.S. Patent 6,284,720B1, September 4, **2001**, SciFinder Scholar 2001:650486.
[11] S. Paul, K. Pradhan and A. R. Das, *Current Green Chemistry,* **2016***, 3,* 111.
[12] R. H. Grubbs, A. G. Wenzel, D. J. O'Leary, E. Khosravi in *Handbook of Metathesis*, Vol. 1-3, Wiley-VCH, Weinheim, **2015**.
[13] K. Grela, *Olefin Metathesis Theory and Practice*; John Wiley & Sons, Inc.: Hoboken, **2014**, pp. 523-537.
[14] a) C. A. Busacca, D. R. Fandrick, J. J. Song and C. H. Senanayake, *Adv. Synth. Catal*., **2011**, *353*, 1825; b) J. Magano and J. R. Dunetz, *Chem. Rev*., **2011**, *111*, 2177; c) J. C. Mol, *J. Mol. Catal. A: Chem*., **2004**, *213*, 39.
[15] Philip Wheeler, John H. Phillips, and Richard L. Pederson, *Org. Process Res. Dev*. **2016**, *20*, 1182.
[16] a) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehadad and P. J. Dunne, *Green Chem*., **2016**, *18*, 288; b) D. Prat, J. Haylerb and A. Wells, *Green Chem*., **2014**, *16*, 4546.
[17] a) C. Samojłowicz, M. Bieniek, A. Zarecki, R. Kadyrov and K. Grela, *Chem. Commun*., **2008**, 6282; b) C. Samojłowicz, M. Bieniek, A. Pazio, A. Makal, K. Wozniak, A. Poater, L. Cavallo, J. Wojeik, K. Zdanowski and K. Grela, *Chem.–Eur. J.*, **2011**, *17*, 12981.
[18] K. Grela, M. Bieniek. R. Kadyrov, "*Verfahren zur Metathese in elektroarmen aromatischen Lösungsmitteln*" DE Patent Application 102007018148.7 (Degussa AG, **2007**).
[19] a) R. A. Sheldon, *Chem. Soc. Rev*., **2012**, *41*, 1437; b) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. S. P. Sherwood, Binks and A. D. Curzons, *Green Chem*., **2011**, *13*, 854. For information on environmental and life cycle assessment of green solvents see: c) P. G. Jessop, *Green Chem*., **2011**, *13*, 1391; d) E. S. Beach, Z. Cui and P. T. Anastas, *Energy Environ. Sci*., **2009**, *2*, 1038; e) C. Capello, U. Fischer and K. Hungerbuhler, *Green Chem.*, **2007**, *9*, 927; f) R. Hofer and J. Bigorra, *Green Chem*., **2007**, *9*, 203; g) R. A. Sheldon, *Green Chem*., **2005**, *7*, 267; h) W. M. Nelson, *Green solvents for chemistry*: *perspectives and practice,* Oxford University Press, New York, **2003**.
[20] a) P. E. Romero and W. E. Piers, *J. Am. Chem. Soc*., **2007**, *129*, 1698; b) C. E. Webster, *J. Am. Chem. Soc*., **2007**, *129*, 7490; c) A. Correa and L. Cavallo, *J. Am. Chem. Soc*., **2006**, *128*, 13352; d) V. F. Kuznetsov, K. Abdur-Rashid, A. J. Lough and D. G. Gusev, *J. Am. Chem. Soc*., **2006**, *128*, 14388; e) G. Occhipinti, H. R. Bjorsvik and V. R. Jensen, *J. Am. Chem. Soc*., **2006**, *128*, 6952; f) D. Benitez and W. A. Goddard III, *J. Am. Chem. Soc*., **2005**, *127*, 12218; g) A. C. Tsipis, A. G. Orpen and J. N. Harvey, *Dalton Trans*., **2005**, 2849; h) C. Adlhart and P. Chen, *J. Am. Chem. Soc.*, **2004**, *126*, 3496; i) S. Fomine, S. M. Vargas and M. A. Tlenkopatchev, *Organometallics*, **2003**, *22*, 93; j) L. Cavallo, *J. Am. Chem. Soc*., **2002**, *124*, 8965; k) S. F. Vyboishchikov, M. Buhl and W. Thiel, *Chem.–Eur. J.*, **2002**, *8*, 3962.
[21] M. S. Sanford, J. A. Love R. H. Grubbs, *J. Am. Chem. Soc*., **2001**, *123*, 6543.

[22] K. Skowerski, J. Białecki, A. Tracz, T. K. Olszewski *Green Chem*., **2014**, *16*, 1125.

[23] a) K. Grela, Ł. Gułajski and K. Skowerski, *Alkene Metathesis in Water*, in *Metal-Catalyzed Reactions in Water* (Eds. P. Dixneuf and V. Cadierno) Wiley-VCH, **2013**, ch. 8, pp. 291–333; b) J. Schatz and J. Tomasek, *Green Chem*., **2013**, *15*, 2317; c) K. Skowerski, G. Szczepaniak, C. Wierzbicka, Ł. Gułajski, M. Bieniek and K. Grela, *Catal. Sci. Technol*., **2012**, *2*, 2424; d) D. Burtscher and K. Grela, *Angew. Chem., Int. Ed.*, **2009**, *48*, 442; e) L. Gulajski, P. Sledz and A. Lupa, *Green Chemistry*, **2008**, *10*, 279; f) J. P. Jordan and R. H. Grubbs, *Angew. Chem. Int. Ed.,* **2007**, *46*, 5152.

[24] C. S. Adjiman, A. J. Clarke, G. Cooper and P. C. Taylor, *Chem. Commun*., **2008**, 2806.

[25] K. M. Kuhn, T. M. Champagne, S. H. Hong, W.-H. Wei, A. Nickel, C. W. Lee, S. C. Virgil, R. H. Grubbs, R. L. Pederson, *Org. Let*., **2010**, *12*, 984.

[26] a) H. Bilel, N. Hamdi, F. Zagrouba, C. Fischmeister and C. Bruneau, *Green Chem*., **2011**, *13*, 1448; b) X. Miao, C. Fischmeister, C. Bruneau and P. H. Dixneuf, ChemSusChem, **2008**, *1*, 813; c) K. Żukowska, Ł. Pączek, K. Grela, *ChemCatChem* **2016**, *6*, 2817.

[27] N. Bakhrou, F. Lamaty, J. Martinez and E. Colacino,*Tetrahedron Let*., **2010**, *51*, 3935.

[28] X. Bantreil, M. Sidi-Ykhlef, L. Aringhieri, E. Colacino, J. Martinez and F. Lamaty, *J. Catal*., **2012**, *294*, 113.

[29] M. Kniese, M. A. R. Meier, *Green Chem*., **2010**, *12*, 169.

[30] a) M. Smoleń, M. Kędziorek and K. Grela, *Catal. Commun*., **2014**, *44*, 80; b) M. Smoleń, W. Kośnik, R. Gajda, K. Woźniak, A. Skoczeń, A. Kajetanowicz, K. Grela, *Chem. Eur. J.* **2018**, *24*, 15372; c) M. Smoleń, A. Marczyk, W. Kośnik, B. Trzaskowski, A. Kajetanowicz, K. Grela, *Eur. J. Org. Chem*. **2019**, 640.

[31] M. Sledź, M. Mauduit and K. Grela, *Chem. Soc. Rev*., **2008**, *37*, 2433.

[32] a) A. Fürstner, L. Ackermann, K. Beck, H. Hori, D. Koch, K. Langemann, M. Liebl, C. Six and W. Leitner, *J. Am. Chem. Soc*., **2001**, *123*, 9000; b) R. Martin, C. Murruzzu, M. A. Pericas and A. Riera, *J. Org. Chem*., **2005**, *70*, 2325; c) J. Song, M. Hou, G. Liu, J. Zhang, B. Han and G. Yang, *J. Phys. Chem. B*, **2009**, *113*, 2810.

[33] Henneberry, M. Green Solvents: Agrochemicals in Place of Petrochemicals, PCI Magazine - Paint & Coatings Industry, **2002**, *18*, 84; http://www.pcimag.com/articles/84078-green-solvents-agrochemicals-in-place-of-petrochemicals (accessed February 19, **2016**).

[34] M. Dusselier, P. Van Wouwe, A. Dewaele, E. Makshina, B. F. Sels, *Energy Environ. Sci*., **2013**, *6*, 1415.

[35] a) Y. Gu and F. Jerome, *Chem. Soc. Rev*., **2013**, *42*, 9550; b) C. Estevez, *Sustainable Solutions – Green Solvents for Chemistry*, in Sustainable Solutions for Modern Economies, *RSC Green Chem. No. 4*, ed. R. Höfer, *RSC Publ., Cambridge*, **2009**, 407.

[36] a) R. Petrus, D. Bykowski, and P. Sobota *ACS Catal*. **2016**, *6*, 5222; b) Y. L. Kua, S. Gan, A. Morris, H. K. Ng *Sustainable Chemistry and Pharmacy*, **2016**, *4*, 21; c) C. S. M. Pereira, V. M. T. M. Silva and A. E. Rodrigues *Green Chem*., **2011**, *13*, 2658; d) S. Aparicio and R. Alcalde *Green Chem*., **2009**, *11*, 65.

[37] J. J. Clary, V. J. Feron and J. A. van Velthuijsen, *Regul Toxicol. Pharmacol.*, **1998**, *27*, 88.

[38] a) M. Bieniek, A. Michrowska, D. L. Usanov, K. Grela, *Chem. Eur. J.* **2008**, *14*, 806; b) A. Michrowska and K. Grela, *Pure Appl. Chem.*, **2008**, *80*, 31.

[39] For general reviews on catalysts **[Ru]-1** to **[Ru]-5**, see: a) O. M. Ogba, N. C. Warner, D. J. O'Leary and R. H. Grubbs, *Chem. Soc. Rev*., **2018**, *47*, 4510; b) T. K. Olszewski, M. Bieniek, K. Skowerski, K. Grela, *Synlett*, **2013**, *24*, 903; c) F. Boeda, H. Clavier and S. P. Nolan, *Chem. Commun*. **2008**, 2726; d) A. Jana and K. Grela, *Chem. Commun.,* **2018**, *54*, 122.

[40] In our study we had access to two grades of ethyllactate ("synthetic" and "natural", ≥98% each) purchased from Sigma-Aldrich. As we checked, both of these grades give virtually the same results in a model RCM reaction of **1b** (97 and 98% of conversion, respectively), assured that they were purified (distilled) in the same way. Such distilled solvent exhibits the same purity level as the waste recycled EL described by Sobota [Ref. 1a] (for details, see SI).

[41] For behaviour of these and similar model substrates with other catalysts and conditions, see e.g. a) P. Małecki, K. Gajda, O. Ablialimov, M. Malinska, R. Gajda, K. Wozniak, A. Kajetanowicz, K. Grela, *Organometallics* **2017***, 36,* 2153*; b)* H. Clavier, F. Caijo, E. Borré, D. Rix, F. Boeda, S. P. Nolan, M. Mauduit, *Eur. J. Org. Chem*., **2009**, *29*, 4254; c) A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, *J. Am. Chem. Soc.* **2004***, 126,* 9318*.*

[42] A. A. Rajkiewicz, K. Skowerski, B. Trzaskowski, A. Kajetanowicz and K. Grela, *ACS Omega*, **2019**, *4*, 1831 and references cited therein.

[43] For a review, see: L. Piol, F. Nahra and S. P. Nolan, *Beilstein J. Org. Chem*. **2015**, *11*, 2038.

[44] K. Van Aken, L. Strekowski, L. Patiny, *Beilstein J. Org.Chem.* **2006**, *2*, 1.

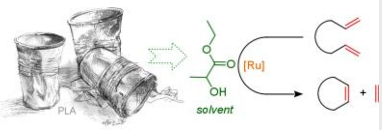
[45] For preparation of **[Ru]-3** in DCM, see: a) K. Grela, S. Harutyunyan, A. Michrowska, *Angew. Chem. Int. Ed.* **2002**, *41*, 4038; b) A. Michrowska, R. Bujok, S. Harutyunyan, V. Sashuk, G. Dolgonos, K. Grela, *J. Am. Chem. Soc.* **2004**, *126*, 9318.

Entry for the Table of Contents

Layout 1:

FULL PAPER

From used plastic cups to a solvent for olefin metathesis: Ethyl lactate was introduced as a green alternative for classic solvents in olefin metathesis due to its advantageous properties. A wide range of commercially available ruthenium metathesis catalysts were tested towards their compatibility with ethyl lactate in a rich substrate scope.



*Sebastian Planer, Anupam Jana, Karol Grela**

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Ethyl Lactate: A green solvent for olefin metathesis

Layout 2:

FULL PAPER

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Title

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