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Cross-Metathesis of Biosourced Fatty Acid Derivatives: A Step Further Toward Improved Reactivity

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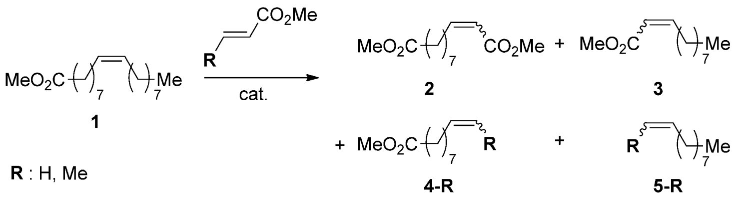
The improved catalytic conversion of bioresources, namely unsaturated fatty acid derivatives, is presented. The targeted reaction is ruthenium-catalyzed cross-metathesis with functionalized olefins (α,β-unsaturated esters), that affords shorter diesters. These can be used as biosourced (pre)monomers for the production of polyesters. It is demonstrated that switch from terminal to internal cross-metathesis partners (that is, from methyl acrylate to methyl crotonate) allows use of ppm-level catalyst loadings, while retaining high productivity and selectivity. This was exemplified on a commercial biosourced fatty acid methyl esters mixture, using minimal purification of the substrate, on a 50 g scale. We propose that this improved catalytic behavior is due to the sole presence of more stable alkylidene intermediates, as the notoriously unstable ruthenium methylidene species are not formed using an internal functionalized olefin.

The use of renewable raw materials by the chemical industry is nowadays increasingly important, as exemplified by the emerging concept of the biorefinery.[1] Synthetic chemists are pushed towards a change of paradigm from petroleum- to biomass-derived chemicals. Thus, triglycerides extracted from plant oils are a source of fatty acid derivatives, such as their methyl esters [fatty acid methyl esters (FAMEs)].[2] Depending on the selected crop, these can comprise a given degree of unsaturation, which provides a handle for chemical transformation and for their further upgrade into higher value chemicals.[3] Due to the above-mentioned need for improved biomass transformation, constant efforts have been devoted to the functionalization of the FAME derivatives. In this context, olefin metathesis plays a key role as a powerful, versatile reaction, mostly thanks to the spectacular development of ruthenium catalysts.[4] These combine high activity and selectivity along with tolerance toward impurities, a most crucial feature when considering their use in biomass-derived chemicals, the purity of which is occasionally problematic. Self-metathesis of FAMEs was probed very early on,[5] and over the years, much effort was devoted into their upgrading by cross-metathesis with ethylene.[6] Following on seminal work,[7] further improvement in catalytic systems design triggered the use of electron-deficient cross-metathesis partners such as acrylates or acrylonitrile: when applied to fatty acid derivatives, this affords an efficient entry into α,ω-bifunctional molecules, such as diesters,[8] ester-nitrile[9] or ester-amine[10] that have found application as monomers for polyesters or polyamides production.[11]



Scheme 1. Cross-metathesis of methyl oleate (**1**) with terminal and internal functionalized olefin.

It was shown by Bruneau's team that efficient cross-metathesis with such substrates as methyl acrylate (Scheme 1, R = H) or acrylonitrile implies the use of second generation metathesis catalysts with low catalysts loadings, provided that slow addition of the catalyst was carried out.[12] With these terminal olefins as cross-partners, ruthenium-methylidene fragments are formed during metathesis. Most often, the formation of such fragments leads to the degradation of the catalyst.[13] It may thus be of interest to overcome such a problem through the use of internal olefin derivatives (Scheme 1, R = alkyl). Indeed, this strategy was successfully followed by Patel and co-workers for non-functionalized alkenes: switching from ethylene to internal olefin such as 2-butene has a most beneficial influence on productivity toward cross-metathesis of biosourced fatty acid derivatives.[14] In this contribution we will demonstrate how a switch from terminal to internal electron-deficient olefin derivatives can afford bifunctionalized products with improved yields from a biosourced FAMEs mixture.

Our investigations were initiated on the benchmark methyl oleate substrate (**1**), prior to extension to actual biosourced FAME mixtures. Even though reactant purification was shown to have a major impact on conversion,[15] we chose to merely

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degas and percolate **1** over activated alumina to remain close to industry-relevant conditions.

The cross-metathesis of methyl oleate **1** with an excess of methyl acrylate (4 equiv) was performed in toluene at 60 °C with Umicore catalysts **M31** and **M51** (Figure 1) to give four products as a mixture of *E* (major) and *Z* isomers (Scheme 1). Among these four products, two originate from the cross-metathesis reaction (CM, **2** and **3**, Scheme 1), and two from self-metathesis (SM) of methyl oleate and of **4-H** and **5-H** (**6** and **7**, Scheme 2). As previously reported, vinylidene-terminated products **4-H** and **5-H** are not detected.[8]

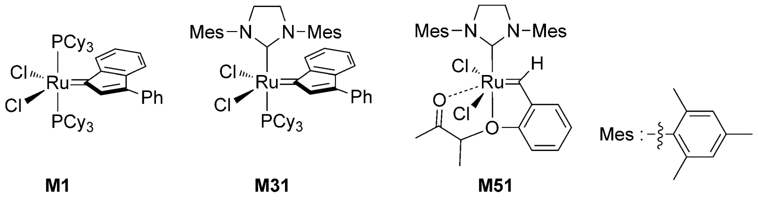
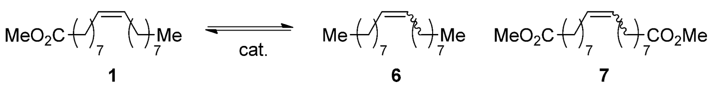


Figure 1. Commercially available ruthenium catalysts **M1**, **M31**, and **M51**.



Scheme 2. Self-metathesis of methyl oleate.

M51 is more effective than **M31**, achieving higher conversion and selectivity (Table 1). Even at a low catalyst loading, such as 260 ppm (0.026 %), **M51** afforded almost complete conversion with selectivity for cross-metathesis products over 90 % (Table 1, entry 5). However, lower loadings of catalyst lead to a decrease in both conversion and selectivity, showing the limits of these catalysts in our conditions (Table 1, entries 7 and 8). Worth mentioning is that 3 ppm of catalyst were able to achieve a productive turnover number (TON) of approximately 19 000, that is into cross-metathesis products (entry 8), which indicates the robustness of this system. Additionally, we checked that first generation catalyst **M1** does not afford any cross-metathesis products, as reported in the literature.

Table 1. Cross-metathesis between **1** and methyl acrylate.[a]

Entry	Catalyst loading	C[b,c] [%]	Selectivity [%] CM[c,d]	SM[c,e]	TON	Productive TON[f]
1	**M31** 0.29 %	74	63	37	260	160
2	**M31** 290 ppm	63	40	60	2170	870
3	**M31** 29 ppm	58	30	70	20 000	6000
4	**M31** 3 ppm	11	13	87	36 600	4770
5	**M51** 0.26 %	99	96	4	380	365
6	**M51** 260 ppm	96	92	8	3690	3400
7	**M51** 26 ppm	69	52	48	26 500	13 800
8	**M51** 2.6 ppm	33	15	85	127 000	19 000

[a] Conditions: 0.51 mmol **1**, 4 equiv of MA, 60 °C, 4 h, 2 mL toluene. [b] Conversion of **1**. [c] Determined by GC using tetradecane as internal standard. [d] Selectivity in cross-metathesis products. [e] Selectivity in self-metathesis products. [f] Turnover numbers in cross-metathesis products.

To assess the influence of the double-bond substitution, we probed the use of methyl crotonate as the cross-metathesis partner. Thus, cross-metathesis of **1** with methyl crotonate in excess (4 equiv) was performed under the same conditions than previously with catalysts **M31** and **M51**.

In the first place, we observed that switching to an internal olefin has no detrimental effect on reactivity for both catalysts. Significant beneficial effects are even obtained for catalyst **M31** on both conversion and selectivity (Table 2, entries 1–3). About 5 times higher productive TON is achieved by switching from methyl acrylate to methyl crotonate using 29 ppm of **M31** (Table 2, entry 3). Decreasing the loading to 3 ppm leads to low conversion of methyl oleate, with poor selectivity (Table 2, entry 4).

Regarding **M51**, there again, the beneficial effect appears at low catalyst loading. Higher loadings afford good catalytic performances as observed with methyl acrylate (Table 2, entries 5 and 6). However at 26 ppm loading, a productive TON of more than 35 000 is reached (Table 2, entry 7), which is significantly better than with methyl acrylate (TON of 13 800 , Table 1, entry 7). Decreasing the loading to 3 ppm again leads to a drop in conversion leading mainly to self-metathesis products before the occurrence of the cross reaction,[9] though this still corresponds to a productive TON of approximately 28 300 (Table 2, entry 8). Regarding the underlying mechanistic issues, these results indicate a better tolerance of the ruthenium ethylidene towards decomposition in comparison the methylidene derivative, whether intrinsic to the stability of these species[16] or due to impurities within the substrates and reagents.

Having demonstrated the interest of cross-metathesis with an internal functionalized olefin, we moved on to a biosourced substrate, namely Lubrirob 201.01, provided by Novance. This fatty methyl esters mixture is composed of saturated compounds (8.6 %), along with methyl linoleate (7.3 %) and methyl oleate as the major unsaturated species (83.6 %). Under metathesis conditions, the last two substrates will give rise to their respective self- and cross-metathesis products (See Supporting Informa-

Table 2. Cross-metathesis between **1** and methyl crotonate.[a]

Entry	Catalyst loading	C[b,c] [%]	Selectivity [%] CM[c,d]	SM[c,e]	TON	Productive TON[f]
1	**M31** 0.29%	96	97	3	330	320
2	**M31** 290 ppm	97	97	3	3300	3200
3	**M31** 29 ppm	96	97	3	33 000	31 100
4	**M31** 3 ppm	26	4	96	88 500	3470
5	**M51** 2600 ppm	96	97	3	420	360
6	**M51** 260 ppm	95	99	1	3640	3600
7	**M51** 26 ppm	96	96	4	37 000	35 450
8	**M51** 3 ppm	53	16	84	177 700	28 300

[a] Conditions: 0.51 mmol **1**, 4 equiv methyl crotonate, 60 °C, 4 h, 2 mL toluene. [b] Conversion of **1**. [c] Determined by GC using tetradecane as internal standard. [d] Selectivity in cross-metathesis (CM) products. [e] Selectivity in self-metathesis (SM) products. [f] Turnover numbers in cross-metathesis products.

Table 3. Cross-metathesis between Lubrirob and methyl acrylate (MA) or methyl crotonate (MC).[a]

Entry	Catalyst loading	Partner	Conversion [%][b,c]	Selectivity [%] CM[c,d]	SM[c,e]	TON	Productive TON[f]
1	260 ppm	MA	78	59	38	3000	1770
2	26 ppm	MA	1	0	100	390	0
3	260 ppm	MC	94	97	5	3615	3400
4	100 ppm	MC	95	96	4	9500	9120
5	26 ppm	MC	9	0	100	3620	0

[a] Conditions: 150 mg Lubrirob 201.01, **M51** catalyst, 4 equiv methyl acrylate or methyl crotonate, 60 °C, 4 h, 2 mL toluene. [b] Conversion of methyl oleate and methyl linoleate. [c] Determined by GC using tetradecane as internal standard [d] Selectivity in cross-metathesis products. [e] Selectivity in self-metathesis products. [f] Turnover numbers in cross-metathesis products.

tion for expected metathesis products). However, these will eventually comprise the same functionalized products **2** and **4-R**, resulting from the $=CH(CH_2)_7CO_2Me$ fragment they hold in common. To ease analytical issues, methyl linoleate self- and cross-metathesis products have been identified from dedicated metathesis reactions (see Supporting Information).

Our study focused on **M51** as this is the most efficient catalyst for the considered cross-metathesis reactions. The conversion of Lubrirob indicated thereafter will concern methyl oleate and methyl linoleate substrates. Self- and cross-metathesis of the other minor unsaturated compounds may occur, leading to a small amount of several products, which have only been detected as traces in the reaction mixtures. In the presence of 4 equivalents of methyl acrylate and using **M51** at a loading of 260 ppm, Lubrirob is as efficiently converted as **1**, with a productive TON of about 1800. However, the use of lower catalyst loading results in severe conversion and selectivity drop, which was less obvious with pure methyl oleate (Table 3, entries 1 and 2). Switching to methyl crotonate for the cross-metathesis cleavage again proved to be beneficial: 260 ppm of **M51** afford excellent conversion and selectivity of Lubrirob, up to the levels obtained with pure methyl oleate (Table 3, entry 3). Further decrease in catalyst loading down to 100 ppm is still possible without compromise in catalytic performances, as productive TON reaches about 9100 (Table 3, entry 4). The use of lower catalyst loading leads to a drastic decrease in conversion and selectivity (Table 3, entry 5).

On these grounds, we demonstrated the efficiency of our approach in a large scale synthesis using 50 g of Lubrirob, with 100 ppm of **M51** (11 mg), under similar reaction conditions (4 equivalents of methyl crotonate, 60 °C, 4 h). The reaction was performed in bulk, as avoiding use of solvent is beneficial in terms of green chemistry. The substrate was converted up to 96% (**1** and methyl linoleate), with high selectivity toward cross-metathesis products (97%). Separation of diester **2** (*E* isomer) was achieved by automated chromatography, affording the compound in 84% isolated yield based on the initial content in **1** and methyl linoleate. The identity and purity of **2** was checked by GC, GC-MS and NMR (see Supporting Information). As a comparison, under identical reaction conditions, the use of methyl acrylate only afforded a productive TON of about 1700 for cross-metathesis products compared to 9100 when methyl crotonate was used.

In conclusion, we have shown that cross-metathesis of methyl oleate with a functionalized olefin can be improved by a switch from terminal to internal alkene cross-partner. We also have demonstrated that cross-metathesis of biosourced compounds that have been subjected to minimal purification can be efficiently carried out with this approach, to achieve a productive TON of approximately 9100. Thus, a valuable diester compound can be accessed with high purity in high yield, using low catalyst loading and solvent free-conditions, from a commercial biosourced FAME mixture.

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Keywords: cross-metathesis · fatty acid methyl esters · methyl crotonate · methyl oleate · ruthenium catalyst

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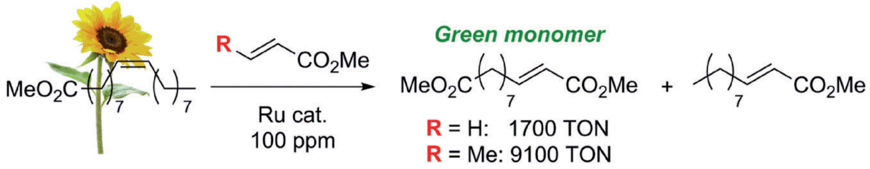

Howdy, partner! The use of internal functionalized olefins as partners in the cross-metathesis of biosourced fatty acid methyl esters affords a monomer for polyester synthesis with high efficiency, despite low catalytic loading and minimal substrate purification.

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