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PAPER

Cross-Metathesis approach to α, ω-Bifunctional Compounds from Methyl Oleate and *cis*-2-Butene-1,4-diol

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Abstract: The cross metathesis (CM) of methyl oleate (1) and *cis*-2-butene-1,2-diol (2) was investigated to access *α, w*-bifunctional compounds. The optimal CM conditions involve Stewart-Grubbs catalyst at 0 °C, delivering CM product 3 in excellent yield. 3 was converted, in a single step and in >90% yields, to alcohol 7, aldehyde 8, and olefin 10, the useful synthetic intermediates for many specialty chemicals, including PA11 precursor. A tandem CM/isomerization process was also demonstrated for the first time.

New approaches for industrially important biofuels, surfactants, and other commodity/specialty chemicals from renewable resources, such as naturally derived lipids, are attracting interests in recent years.[1] In this context, an approach in which cross-metathesis (CM) of renewable unsaturated fatty acids and simple olefins providing α, ω-bifunctional compounds as polymer precursors is widely appreciated and researched.[1a, 2] Among the natural fatty acids, oleic acid and its derivatives have been the focus of these studies due to its abundance from plant-based biomass.

In continuation with our studies on efficient and economic polyamide (PA) precursor synthesis from biomass,[2a, 3] we became interested in the use of *cis*-2-butene-1,4-diol (**2**) as CM partner of methyl oleate (**1**), recognizing that its product allyl alcohol (Figure 1) provides multiple pathways to amine functional group. In addition to its availability and low cost, the symmetrical structure and internal olefin of *cis*-2-butene-1,4-diol minimizes formation of self-metathesis products and unstable ruthenium methylidines.[4] Furthermore, directing effect of allylic hydroxyl group has been reported to aid productive CM pathway when ruthenium dichloride was used as a catalyst.[5]

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Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of products, catalyst screening and attempted isomerization data.

However, previously studied CM using **2** or primary allyl alcohols reported low reaction conversion and/or needed a high catalyst loading, that were attributed to catalyst decomposition and resulting side-reactions.[6] Thus, the protected variant of **2** is frequently employed as its surrogate.[7] Hoveyda and co-workers have recently developed a ruthenium disulfide catalyst that promotes the CM delivering 68% of the product in high (*Z*) stereoselectivity.[8] Although the high stereoselectivity was a noteworthy achievement, use of high catalyst loading (3–5 mol%) was not appealing for our project in which the olefin stereochemistry would ultimately be destroyed. Herein we present our study on identifying critical parameters that led to fruitful CM of **1** and **2**. Several pathways to PA11 precursor from the CM product were also established, one of which involves a tandem CM/isomerization sequence in one-pot, demonstrated for the first time[9, 7d] in this work.

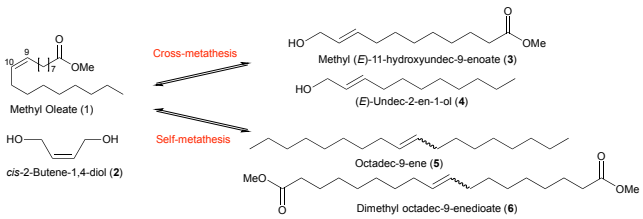


Figure 1. Self-metathesis of methyl oleate (**1**) and cross-metathesis with *cis*-2-butene-1,4-diol (**2**).

We begin our study on the CM of **1** and **2** (Figure 1) using the most used Hoveyda-Grubbs II catalyst (Figure 2, **C1**). Initial examination using chlorobenzene, the optimal solvent in our previous work,[2a] as a solvent at 40 °C provided desired **3**, albeit in a low yield (Table 1, entry 1). A recent report on the use of green solvents for metathesis[10] prompted us to test several alternative solvents; this solvent screening showed that ethyl acetate provided clean and selective reaction (entries 1–3 vs 5; 4 vs 6). *As opposed to typical CM,[11] higher reaction conversions were achieved at lower temperatures.* Thus, the best conversion and selectivity was obtained at 0 °C (entries 3–6) whereas at >40 °C the reaction stalled. This observation may be due to the aforementioned catalyst decomposition.[6b, 6c] Additionally, we found 5 equiv of **2** was necessary for optimal conversion, and the reaction parameters of [**1**:**2** = 1:5; ethyl acetate; 0 °C] were selected for further studies.

Table 1. Solvent and temperature effect on CM of methyl oleate (**1**) and diol **2**[a]

Entry	Solvent	Temp. /°C	Conv. /%[b][c]	3 /%[b]	4 /%[b]	6 /%[b]
1	PhCl	40	65.6	24.4	31.6	17.0
2	DMC	Rt	77.1	44.7	53.7	11.1
3	THF	Rt	70.9	40.7	50.0	9.8
4	THF	0	87.5	52.9	65.6	9.5
5	EtOAc	Rt	89.5	51.2	66.2	9.9
6	EtOAc	0	92.1	59.6	74.7	8.1

[a]To a flask containing methyl oleate (**1**, 1 eq) and *cis*-2-butene-1,4-diol (**2**, 5 eq) at a designated temperature was added a solution of **C1** (2 mol%**)** in a solvent (2 mL) over 1 h. The reaction mixture was stirred at the said temperature and analyzed at 2, 4, 6, and 24 h. [b]At 6 h when the maximum conversion was reached. [c]Determined by GC using methyl palmitate as internal standard.

With the suitable reaction conditions in hand, multiple ruthenium-based metathesis catalysts (Figure 2) were evaluated that best promote the productive CM (Chart 1).[12] Several studies had proven that each catalyst shows unique reactivity towards particular reaction, and efforts to establish a selection guideline has been reported.[11a, 13] Since one of our goals is to achieve a high catalyst turnover, we have excluded the phosphine-based catalysts as well as those without *N*-heterocyclic carbene (NHC) ligand because of their lower stability.[14] Ultimately, the following ruthenium complexes were selected for screening (Figure 2). (a) Bench-mark: Hoveyda-Grubbs II catalyst (**C1**),[15] (b) Fast initiating/highly active: Grela catalyst (**C2**);[16] Umicore M7 series:[17] M71SiPr (**C6**), M72SiPr (**C7**), M73SiPr (**C8**), M74SiPr (**C9**), (c) For hindered olefins: Stewart-Grubbs catalyst (**C4**),[11b, 18] (**C5**).[18] (d) Others: Tagged catalyst: (**C3**);[19] GreenCat (**C10**).[20]

The catalyst examination (Chart 1) showed that **C1** was near optimal, and the catalysts appear to lose their activity as they become structurally distinct.[12] The bulkiness and rigidity of the aromatic ring substituents attached to NHC ligands would determine the catalyst stability,[11a, 13a] or accessibility to substrates.[11b, 18] While our system (Figure 1) is not sterically challenging, the catalysts having NHC ligands with less bulky substituents clearly resulted in higher conversion and selectivity to the productive CM than those with bulkier substituents (**C1–4** vs **C5–9**). Electron-withdrawing groups on the benzylidene ligands, which affect the rate of catalyst initiation, however, have a variable effect (**C6–9**). Overall, **C4** provided the best conversion and selectivity, closely followed by **C1** and **C2** catalysts.

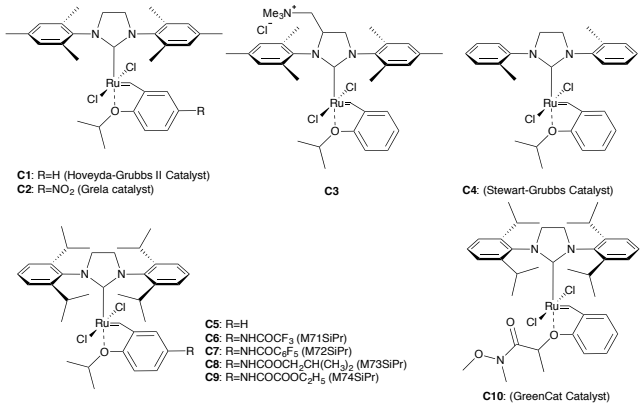
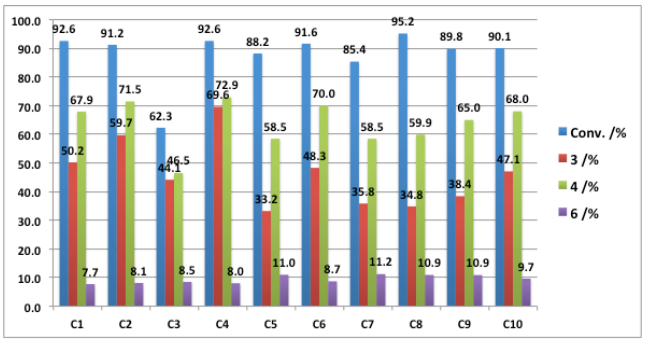


Figure 2. Metathesis catalysts examined in this study.

Chart 1. Metathesis catalyst screening.[12]



With the best performing catalyst identified, the reaction conditions were tuned to improve the process economy (Table 3). First, solvent-free conditions were examined, that resulted in low conversion (entries 1 vs 2).[21] Next, the catalyst loading was minimized: Although the conversion and selectivity obtained by catalysts **C1** and **C4** were small at high (2 mol%) catalyst loading (entries 1, 4), **C4** retained its activity better at lower catalyst loadings (entries 3 vs 7). The catalyst loading of **C4** could be lowered up to 0.2 mol% without sparing the yield (entries 4–8), although the reaction conversion rapidly decreased below this amount.[22] Using the optimal conditions, the CM reaction was successfully conducted on 2 g (input) scale.[12]

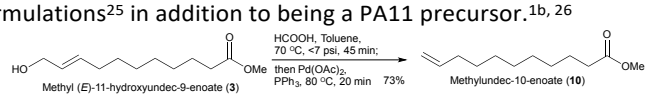
Table 3: Reaction optimization of CM of **1** and diol **2**[a]

Entry	Catalyst /mol%	Time /h	Temp. /°C	Conv. /%[c]	Yield /%[d]	3 /%[e]	6 /%[e]
1	**C1** (2)	15	0→RT	80.2	71	60.0	6.0
2[b]	**C1** (2)	24	0→RT	39.0	–	19.4	15.8
3	**C1** (0.25)	24	0→RT	72.4	52	44.5	12.6
4	**C4** (2)	6	0	91.8	84	70.2	12.8
5	**C4** (1)	22	0→RT	90.0	76	66.3	6.5
6	**C4** (0.4)	24	0→RT	85.9	73	61.3	11.6
7	**C4** (0.25)	24	0→RT	85.8	72	64.0	10.7
8	**C4** (0.2)	24	0→RT	85.3	72	62.9	10.7

[a]Reaction conditions: To a flask containing methyl oleate (**1**, 1 eq) and *cis*-2-butene-1,4-diol (**2**, 5 eq) in ethyl acetate at 0 °C

was added a catalyst solution (2.2 mg/mL) over 1 h. The reaction was kept at this temperature for over 6 h and then was warmed to RT. [b]Neat; The catalyst was added in one portion as solid. [c]Calc. by GC area% of **1**. [d]Isolated yield. [e]GC area%.

With the CM conditions established, we next turned to the conversion of CM product **3** to PA11 precursor, **11**. We have first studied an approach that involves conversion of **3** to terminal olefin **10**, an intermediate used in the current production of PA11 (Scheme 1). First, allyl alcohol **3** was condensed with formic acid under reduced pressure that quantitatively provided an allyl formate.[23, 24] The formate was then subjected to palladium-catalyzed reductive de-formylation (Table 4). The desired olefin **10** was accompanied with other unsaturated by-products, however their formation was suppressed when the reaction was conducted at low temperature (entries 1–3). The best results were obtained at 80 °C that provided a good balance of reaction rate and selectivity (entries 4–7). With the optimal conditions, the desired terminal olefin can be isolated in >95% yield (entry 7). Notably, olefin **10** is a versatile compound that finds applications in cosmetics, pharmaceuticals, and anti-odor formulations[25] in addition to being a PA11 precursor.[1b, 26]



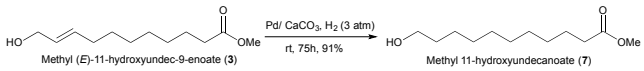
Scheme 1: Synthesis of terminal olefin from **3**.

Table 4. Optimization of the reductive de-formylation[a]

Entry	Pd cat. /mol%	PPh_3 /mol%	Temp. /°C	Time	**1**/By-product[b]
1	5	26	120	1.5 h	66/44
2	5	31	80	1 h	82/18
3	2	30	80	3 h	82/18
4	2	30	50	19 h	–
5	2	30	80	10 min	92/8
6	5	30	50	2 h	86/14
7	2	15	80	10 min	96/4

[a]Reaction conditions: To a mixture of PPh_3 and the formate of **3** in toluene at the indicated temperature was added a solution of $Pd(OAc)_2$ in DME under an argon atmosphere. After the reaction completion, the solution was passed through a pad of silica gel with ethyl acetate and concentrated. [b]By ^1H NMR.

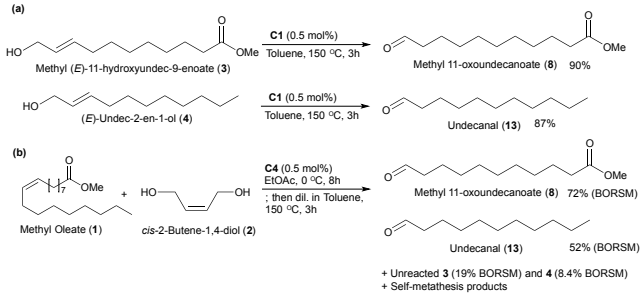
Alternatively, conversion of allyl alcohol 3 to aldehyde generates a useful intermediate that can be converted to an amine through reductive amination.27 A conventional approach to convert allyl alcohol to aldehyde involves hydrogenation of the olefin and oxidation of the alcohol. Hydrogenation of allyl alcohol 3 under standard conditions was unsuccessful due to π-allyl palladium formation that led to olefin 10 and the saturated ester.12 Fortunately, less reactive Lindlar catalyst suppressed the side reactions to deliver the desired saturated alcohol 7 in 91% yield (Scheme 2). Although alcohol 7 could be converted to 8 biocatalytically,27a its chemical oxidation unexpectedly provided low yield in our hand.12



Scheme 2: Conversion of allyl alcohol (**3**) to saturated alcohol (**7**).

The same transformation should be possible simply by olefin isomerization and tautomerization without involving redox chemistry. After unsuccessful attempts using known procedures,[12] we turned to a report by Finnegan in which allyl alcohol was isomerized using metathesis catalysts during the CM,[6a] however, their method was proved incompatible with primary allyl alcohols. Meier and co-workers reported a similar two-stage procedure wherein isolated allyl alcohol, the metathesis product, was isomerized to aldehydes upon heating.[28] Apart from the desired aldehyde (67.5%), they have observed 27% of oligomers.

We studied the possibility of using and optimizing Meier's procedure with **3**. When isomerization was attempted using **C1** in dichloromethane at 70 °C, a mixture of products including the desired aldehyde (**8**, 54 % by GC area) and saturated alcohol (**7**, 36 % by GC area) were observed after 21 h.[6a, 28] Fortunately, after testing the same conditions at various temperature, clean conversion was observed at high temperature to the desired aldehyde, providing >85% yield (Scheme 3 (a)). Finally, it was demonstrated that using a single catalyst dose, the CM and isomerization/tautomerization reactions can be accomplished in (auto)tandem process.[29] Thus, by conducting the reaction of **1** and **2** first at 0 °C, and then at 150 °C, a clean conversion with high selectivity to the desired **8** were observed based on GC analysis (Scheme 3(b)).[12, 30]



Scheme 3: (a) Allyl alcohol isomerization using metathesis catalysts. (b) Tandem cross-metathesis (CM)/allyl alcohol isomerization.

Conclusions

We have identified mild reaction conditions for the previously elusive CM of methyl oleate (**1**) and *cis*-2-butene-1,4-diol (**2**) which reliably provides 72–84% yield of the CM product. In contrast to typical CM, use of low temperature (0 °C) was essential. Employing Stewart-Grubb's catalyst (**C4**) enabled an excellent reaction conversion at low catalyst loading (0.2

mol%) in nearly solvent-free conditions (final concentration: 0.8 M) using environmentally benign solvent (EtOAc).

The product **3** was converted to alcohol **7**, aldehyde **8**, and olefin **10**, in either a single step or in a tandem process**.** Conversion to alcohol **7** was accomplished by hydrogenation using Lindlar catalyst in 91% yield; that of olefin **10**, a manufacturing intermediate for PA11 (Nylon 11) **11**, was achieved by allyl alcohol formylation/deformylation, in over 90% yield. A new method from **3** to aldehyde **8** was developed by isomerization of allyl alcohol **3** using either **C1** or **C4** metathesis catalyst in 90% yield. A tandem CM/isomerization process was also demonstrated using catalyst **C4**, which shows complete selectivity towards the desired aldehyde. Conversion of **8** to **11** has been demonstrated either using biocatalyts[27c] or by conventional reductive amination.[27b] Of note, compounds **7**, **8**, and **10** are all useful synthetic intermediates that have been utilized for various specialty chemical productions, in addition to PA11 precursor (**11**).

Supporting Information

The Electronic Supporting Information (ESI) is available: Experimental details, characterization data, and catalysis screening information (file type, PDF).

Conflicts of Interest

There are no conflict of interest to declare.

Acknowledgement

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