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Tandem Olefin Metathesis/Oxidative Cyclization: Synthesis of Tetrahydrofuran Diols from Simple Olefins

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Supporting Information

ABSTRACT: A tandem olefin metathesis/oxidative cyclization has been developed to synthesize 2,5-disubstituted tetrahydrofuran (THF) diols in a stereocontrolled fashion from simple olefin precursors. The ruthenium metathesis catalyst is converted into an oxidation catalyst in the second step and is thus responsible for both catalytic steps. The stereochemistry of the 1,5-diene intermediate can be controlled through the choice of catalyst and the type of metathesis conducted. This olefin stereochemistry then controls the THF diol stereochemistry through a highly stereospecific oxidative cyclization.

Assisted tandem catalysis is an attractive synthetic strategy where a single catalyst is added at the outset of the reaction and is intentionally converted into a new species via a change in reaction conditions for a second catalytic step.[1] Ruthenium alkylidene catalysts have been frequently used in assisted tandem catalysis in order to couple a metathesis step with other transformations, including but not limited to dihydroxylation, hydrogenation, and isomerization, showcasing the versatility of these complexes.[2] We sought to further explore the dual nature of these alkylidene complexes in tandem catalysis.

The Ru- or Os-catalyzed oxidative cyclization of 1,5-dienes is a convenient method to prepare 2,5-disubstituted tetrahydrofuran (THF) diols in a stereocontrolled manner.[6] Furthermore, these THF diols are present in a wide variety of complex natural products (Figure 1). While olefin metathesis could be envisioned as a practical way to assemble the 1,5-diene substrate, there have been no reports of utilizing alkylidene catalysts for oxidative cyclization. Herein we report the development of a tandem metathesis/oxidative cyclization capable of assembling a diverse set of THF diols, where the diol stereochemistry is determined from the intermediate olefin geometry set in the metathesis step.

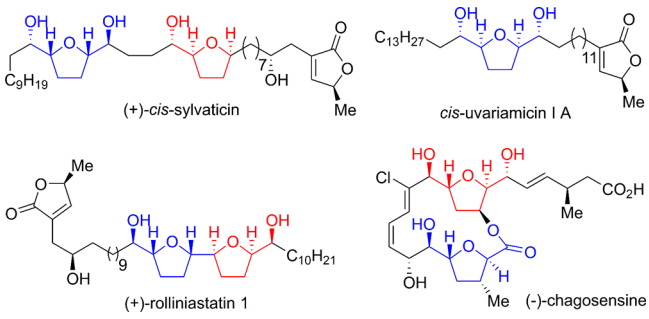

Figure 1. Natural products[3] containing the THF diol motif from the Annonaceous acetogenin[4] and macrolide families.[5]

The oxidative cyclization of 1,5-dienes mediated by permanganate was discovered in 1965 by Klein and Rojahn.[7] Later, it was found that RuO_4[8] or OsO_4[9] can catalyze this transformation in the presence of a suitable oxidant, such as $NaIO_4$ (Figure 2A). In 1979, Baldwin and Walba independently demonstrated the stereospecificity of the oxidative cyclization with respect to olefin geometry.[10] The currently accepted mechanism involves initial [3 + 2]-cycloaddition with one of the olefins.[6] Subsequently, the metallo ester intermediate undergoes a second [3 + 2]-cycloaddition with the pendant olefin, followed by hydrolysis, furnishing a THF diol. Each olefin dioxygenation step is *stereospecific* with respect to olefin geometry, analogous to olefin dihydroxylation. The cyclization step is also *stereoselective* with respect to the facial approach of the olefin and generally favors the *cis*-2,5-disubstituted THF.

Ruthenium alkylidene complexes have been shown to be converted into dihydroxylation catalysts upon treatment with $NaIO_4$, and this has been used in the development of tandem metathesis/dihydroxylation.[11] While the precise nature of the oxidized ruthenium species has not been firmly established, if this species is also capable of catalyzing oxidative cyclization, then 1,5-dienes accessible via olefin metathesis could be transformed into 2,5-disubstituted THF diols in a stereocontrolled fashion (Figure 2B).

We envisioned that olefin metathesis could be a powerful approach to synthesizing the requisite 1,5-dienes necessary for oxidative cyclization with control of olefin geometry (Figure 2C). Cross metathesis is well studied and can achieve high E-selectivity through thermodynamic control for many substrate classes, including acrylates and bulky terminal olefins.[12] Additionally, considerable effort in recent years has focused on metathesis catalysts capable of achieving high kinetic Z-selectivity.[13] More recently, stereoretentive cross metathesis has also been developed.[14]

In order to test whether ruthenium alkylidene complexes are competent in oxidative cyclization, we chose to study the oxidation of bisacrylate **1**. Using conditions optimized for ruthenium catalyzed dihydroxylation ($NaIO_4$, catalytic $CeCl_3$, 3:3:1 EtOAc/MeCN/H_2O),[15] first generation, second generation, and cyclometalated alkylidene complexes **Ru-1**−**5** (Figure 3) all catalyzed the desired oxidative cyclization to give THF diol

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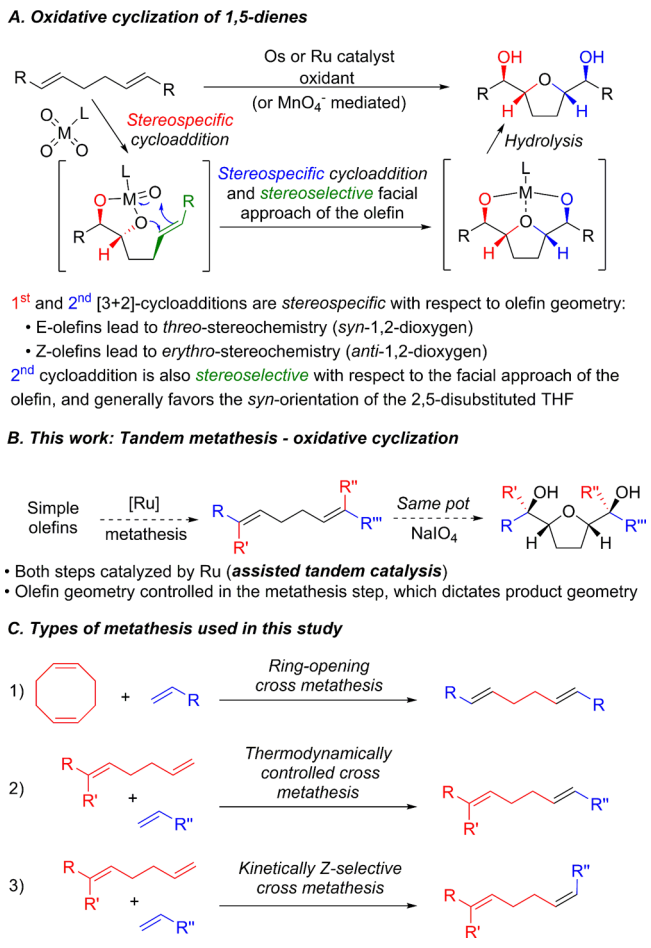


Figure 2. (A) Oxidative cyclization of 1,5-dienes catalyzed by Ru or Os or mediated by Mn. (B) Proposed tandem metathesis/oxidative cyclization. (C) Types of olefin metathesis used in this study to generate the intermediate 1,5-dienes with control of olefin geometry.

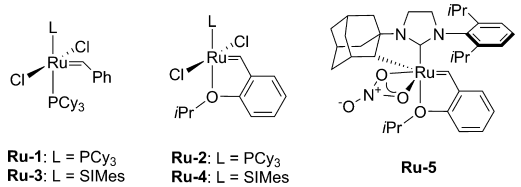


Figure 3. Ruthenium alkylidene catalysts examined in this study.

2a (Table 1). While full conversion of **1** was observed in all cases, first generation complexes **Ru-1,2** produced significantly more byproducts, leading to lower yields of **2a**. Second generation catalysts **Ru-3,4** gave comparable yields (64% and 63%, entries 3 and 4). $CeCl_3$ has been proposed to facilitate hydrolysis of ruthenate ester intermediates via acid catalysis as well as increase the redox potential.[14c,16] In the absence of $CeCl_3$, THF diol **2a** was still obtained, albeit in lower yield (42%, entry 6). A control experiment in the absence of ruthenium led to complete recovery of bisacrylate **1**, indicating that ruthenium is necessary for oxidation to occur (entry 7).

E,E-Bisacrylates such as **1** can be conveniently synthesized by ring-opening cross metathesis of 1,5-cyclooctadiene (**3**) with an *α,β*-unsaturated ester in the presence of a second generation catalyst such as **Ru-3** or **Ru-4**.[17] A tandem metathesis/oxidative cyclization was thus examined using 1,5-cyclooctadiene (**3**) as a 1,5-diene precursor. Ring-opening cross metathesis of **3** with a

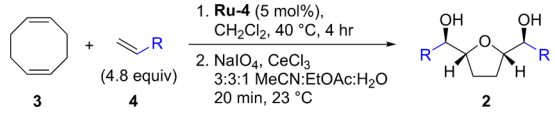
Table 1. Comparison of Various Ru Alkylidene Catalysts in the Oxidative Cyclization of Bisacrylate 1

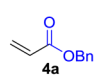
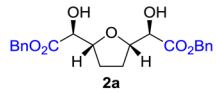
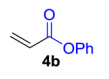
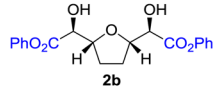
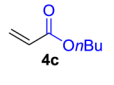
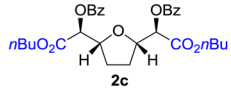
entry	catalyst	deviation from above	**1** (%)[a]	**2a** (%)[a]
1	**Ru-1**	–	0	36
2	**Ru-2**	–	0	37
3	**Ru-3**	–	0	64
4	**Ru-4**	–	0	63
5	**Ru-5**	–	0	36
6	**Ru-4**	no $CeCl_3$	0	42
7	none	–	100	0

[a]Determined by ^{1}H NMR using mesitylene as an internal standard.

series of acrylates, followed by sequential treatment of the crude solution with $NaIO_4$ and catalytic $CeCl_3$, produced the desired *meso*-THF diols **2** (Table 2). Both aryl and alkyl acrylates were

Table 2. Tandem Ring-Opening Cross Metathesis/Oxidative Cyclization of 1,5-Cyclooctadiene with Terminal Olefins



Entry	Terminal olefin	Product	Isolated Yield (%)[a]
1	 **4a**	 **2a**	50
2	 **4b**	 **2b**	57% (52%)[b]
3	 **4c**	 **2c**	41%[c]

[a]Isolated as a single diastereomer. [b]Using 2.5 mmol of **3** (964 mg **2b** isolated). [c]Isolated yield after benzoylation (for ease of purification).

effective. Upon scale-up to 2.5 mmol of **3**, phenyl acrylate derived THF diol **2b** was obtained in 52% yield (964 mg, entry 2). While the yields are moderate, we feel that the high degree of molecular complexity that can be achieved with a single catalyst renders the method highly attractive.[18,19]

We next wondered whether polybutadiene could be used in place of 1,5-cyclooctadiene (**3**) in the metathesis step, since the 1,5-olefin units in this polymer are expected to undergo cross metathesis to lead to the same *E,E*-bisacrylate intermediate as is formed with **3**. The tandem sequence was performed using phenyl acrylate and polybutadiene (M_n = 3000, *cis*-1,4 content = 75%, *trans*-1,4 content = 24%, vinyl content = 1%), and THF diol **2b** was obtained in 35% yield (Scheme 1). This result is valuable since polybutadiene is an inexpensive and widely available 1,5-diene building block. The molecular structure of **2b** was determined by X-ray crystallography, as illustrated in Figure 4. The vicinal dioxygen stereocenters are *threo*, as expected for a *syn*

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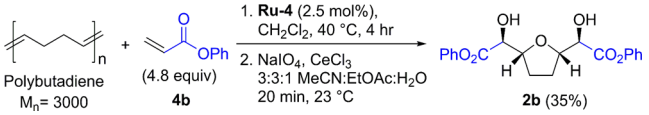
Scheme 1. Cross Metathesis/Oxidative Cyclization Using Polybutadiene As a Source of 1,5-Diene



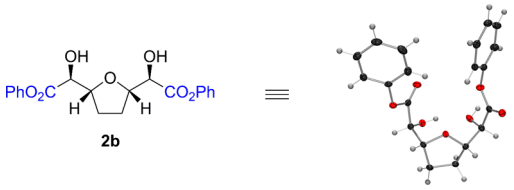


Figure 4. Molecular structure of **2b** determined by X-ray crystallography.

dioxgenation of an *E*-olefin, and the THF ring substituents are oriented in a *syn* arrangement. This observed stereochemistry is consistent with previous reports on oxidative cyclization with RuO_4.[6]

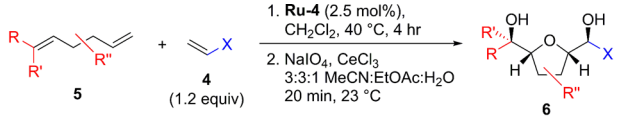
Next we examined cross metathesis/oxidative cyclization with unsymmetrical 1,5-dienes containing one hindered olefin (expected to be a spectator in the metathesis step) and one terminal olefin (capable of cross metathesis).[12] *E*-**5a** underwent cross metathesis with benzyl acrylate followed by oxidative cyclization in sequential fashion to give THF diol **6a** in 65% yield (Table 3, entry 1).[20] Phenyl acrylate **4b** and butyl acrylate **4c** reacted in a similar fashion to produce **6b** and **6c** in 66% and 60% yields, respectively. *Z*-1,4-Diacetoxy-2-butene **4d** also underwent cross metathesis with **5a** followed by oxidative cyclization to give monoacetate **6d** in 59% yield.

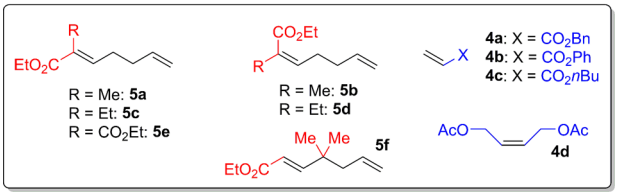
If the geometry of the trisubstituted olefin is inverted, the resulting tertiary alcohol stereochemistry is also expected to invert. When *Z*-diene **5b** was used with benzyl or phenyl acrylate, THF diols **6e** and **6f** were obtained in 69% and 73% yield, respectively. Hydrogenolysis of benzyl ester **6e** yielded the monocarboxylic acid **7a**, which provided crystals suitable for X-ray diffraction (Figure 5). The THF 2- and 5-substituents were found to be in a *syn* configuration, and the vicinal dioxygenation geometries are consistent with a *syn*-dioxygenation of the olefins. This is in agreement with expectations from previous reports on oxidative cyclization of 1,5-dienes with ruthenium catalysts[6] (see Figure 2A).

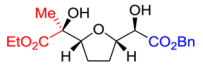
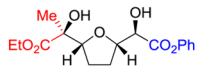
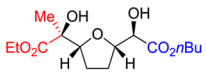
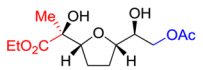
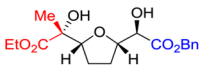
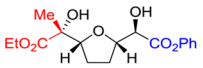
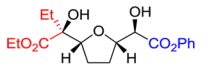
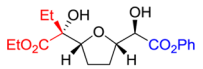
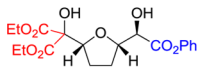
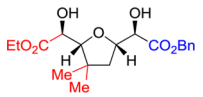
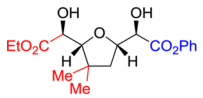
E- and *Z*-ethyl substituted olefins **5c** and **5d**, as well as *α,β*-unsaturated-1,3-diester **5e**, also underwent tandem cross metathesis/oxidative cyclization to provide THF diols **6g–i** in 42–73% yield (entries 7–9). Geminal dimethyl substitution on the diene linker was tolerated, as **5f** underwent reaction with **4a** and **4b** to give **6j** and **6k** in 76% and 63% yield, respectively. The allylic quaternary center presumably provided enough steric hindrance to prevent reversible metathesis of the ethyl acrylate moiety.

Having demonstrated that the hydroxyl stereochemistry of the THF diol depends on the olefin geometry of the 1,5-diene intermediate, we sought to use Z-selective metathesis in order to generate *Z*-diene intermediates in a catalytic fashion. Given the activity of cyclometalated alkylidene **Ru-5** in the oxidative cyclization of **1** (Table 1), and the use of **Ru-5** in tandem Z-selective cross metathesis–dihydroxylation,[11d] we anticipated that this complex would also be able to catalyze the oxidative cyclization of *Z*-diene intermediates in a stereospecific fashion.

Table 3. Tandem Cross Metathesis/Oxidative Cyclization of 1,5-Dienes with Terminal Olefins





Entry	5	4	Product	6	Yield (%)[a]
1	5a	4a		6a	65
2	5a	4b		6b	66
3	5a	4c		6c	60
4	5a	4d		6d	59[b]
5	5b	4a		6e	69
6	5b	4b		6f	73
7	5c	4b		6g	73
8	5d	4b		6h	60
9	5e	4b		6i	42
10	5f	4a		6j	76
11	5f	4b		6k	63

[a]Isolated as a single diastereomer. [b]1.25 of equiv of **4d**, 5 mol % **Ru-4**; see Supporting Information for details.

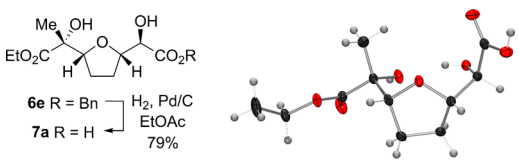


Figure 5. Molecular structure of **7a** determined by X-ray crystallography.

Using **Ru-5** as catalyst, diene **5a** and **5g** underwent cross metathesis with an excess of allyl benzoate (5 equiv), to give an *E,Z*-diene intermediate, which then underwent oxidative cyclization upon exposure to the oxidative conditions to provide diol **6l** and **6m** in 45% and 30% yield,[21] respectively (Scheme 2).

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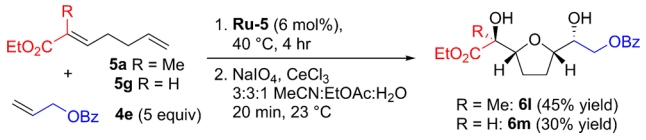
Scheme 2. Z-Selective Cross Metathesis/Oxidative Cyclization



In conclusion, a tandem olefin metathesis/oxidative cyclization has been developed to generate 2,5-disubstituted THF diols in a stereocontrolled fashion. The stereochemistry of the intermediate 1,5-dienes can be controlled by the choice of catalyst in the metathesis step, and this stereochemistry is translated to the product in the oxidative cyclization. We are currently exploring mechanistic aspects of this process. It is envisioned that this methodology will provide a concise route to biologically important THF diol motifs as well as contribute to a greater understanding of tandem catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b02653.

Experimental details, characterization data (PDF)
X-ray crystallography data for **2b**; CIF file also available from the CCDC (No. 1465061) (CIF)
X-ray crystallography data for **7a**; CIF file also available from the CCDC (No. 1465062) (CIF)

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Notes

The authors declare no competing financial interest.

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(18) The ring-opening cross metathesis was optimized independently (see Supporting Information for details) and generally results in >95% conversion under optimized conditions. The oxidation step is primarily responsible for the moderate yields, due to byproduct formation (the intermediate dienoate is fully consumed). Ongoing studies are directed at identifying byproducts.

(19) The minor diastereomer with respect to the 2- and 5-substituents on the THF ring was not identified, and thus a diastereoselectivity for the oxidative cyclization cannot be reported. In the literature, diastereoselectivity is generally high when the 1,5-diene contains a H substituent at the 2- and 5-positions (see ref 6).

(20) As was the case for Table 2, yields in Table 3 are primarily limited by the oxidation step. Conversion after the cross metathesis step was generally >95% when investigated independently.

(21) The moderate yields are due in part to the statistical nature of the Z-selective cross metathesis, byproduct formation in the oxidation step, and difficulty in removing the 1,2-diol byproduct derived from the allyl benzoate homodimerization intermediate.

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