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Tandem Radical Reactions and Ring-Closing Metathesis. Application in the Synthesis of Cyclooctenes

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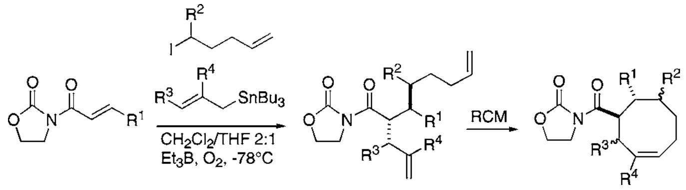
ABSTRACT



Fumarate- and acrylate-substituted oxazolidinones undergo tandem radical reaction to form dienes in moderate to good yields. The resulting dienes provide cyclooctenes in moderate to good yields after ring-closing metathesis (RCM). The role of the carbon backbone substituents and other variables in the efficiency of the eight-membered ring formation is discussed.

Radical reactions allow for the formation of multiple carbon−carbon bonds in a single synthetic operation.[1] We have recently shown that enoates undergo highly diastereoselective tandem radical addition/allylation reactions.[2] We have been interested in taking advantage of the diene products that can be readily prepared from these tandem reactions in the synthesis of cyclooctenes via ring-closing metathesis (RCM) reactions. RCM has emerged as a novel strategy for the synthesis of carbo- and heterocycles.[3] The formation of small rings is often shown to be very efficient via RCM reactions.[4] However, the formation of medium-sized rings still remains difficult using this methodology.[5] Our goal in this program was to identify structural features on the 1,9-decadiene backbone and reaction conditions that would lead to efficient formation of the eight-membered ring using RCM. Numerous ruthenium-based catalysts (**1**−**8**, Figure 1) have been developed in the past few years that provide a large reactivity range for optimization of the cyclooctene formation.[6] The synthesis of the precursor dienes through radical reactions and optimization of the RCM reaction for cyclooctene formation are the focus of the paper.

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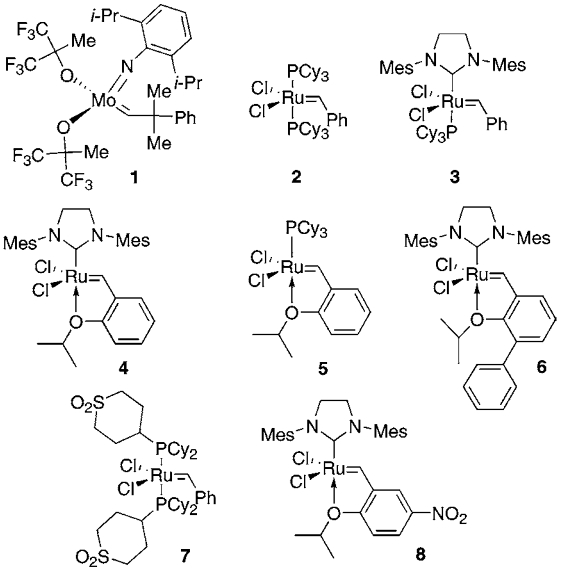
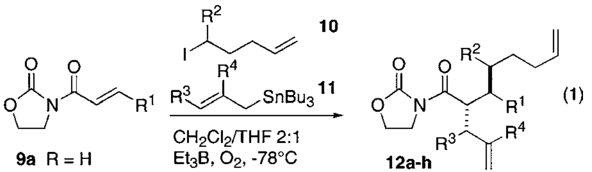


Figure 1.

Our experiments began with the synthesis of the desired dienes by tandem radical addition/trapping experiments. Our group has previously reported that enoates undergo tandem radical reactions to provide products in moderate to good yields and high diastereoselectivities. Several dienes (**12a**–**h**) were synthesized from the acrylate or fumarate oxazolidinone (**9**) as the substrate (eq 1). Previous work showed that lanthanide Lewis acids were the best for carrying out radical addition–trapping experiments. Thus, our choice of Lewis acid was either ytterbium triflate or yttrium triflate. All reactions were carried out with alkyl iodide (**10**) (10 equiv), allyl stannanes (**11**) (5 equiv), either 30 mol % or a stoichiometric amount of the Lewis acid, and triethylborane, under an atmosphere of oxygen. The results of these tandem radical reactions are summarized in Table 1 (entries 1–8). Addition/trapping experiments with the less nucleophilic primary radicals were marginally efficient, yielding products in only 40–50% yield (entries 1, 3, 4, 5, 7, and 8). Reactions with the secondary radicals were slightly more efficient, furnishing dienes in 51% and 72% yields (entries 2 and 6). In these two examples where R^2 = Me, the dienes **12b** and **12f** were obtained as a 1:1 mixture of diastereoisomers (entries 2 and 6). When crotyl stannane was used as the trap (R^3 = Me), the resulting products **12c** and **12g** were obtained in a 2:1 diastereomeric ratio (Table 1, entries 4 and 7).

With all the dienes in hand, we then evaluated ring-closing metathesis reactions to synthesize cyclooctenes. On the basis of literature precedents, initial reactions were performed using the second-generation Grubbs catalyst (**3**). The results of these RCM reactions are summarized in Table 2. Our standard reaction condition was the treatment of the diene in the presence of 10 mol % of **3** under high dilution (1 mM) in refluxing dichloromethane for 18 h. Six of the dienes

Table 1. Synthesis of Dienes by Addition/Trapping[a]

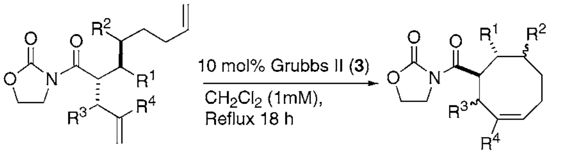


9a R = H
9b R = CO_2Et
12a-h

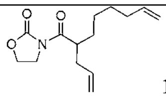
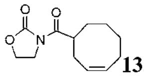
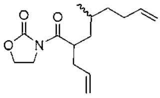
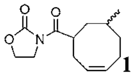
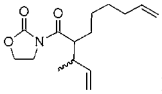
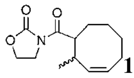
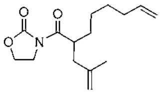
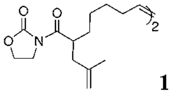
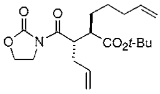
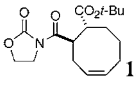
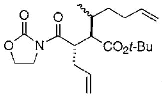
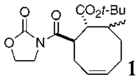
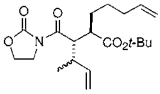
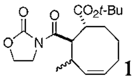
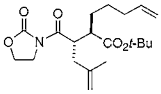
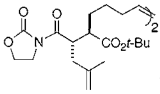
entry	Lewis acid/ equiv	R^1	R^2	R^3	R^4	product	% yield[b]
1	$Y(OTf)_3$/0.3	H	H	H	H	**12a**	49
2	$Yb(OTf)_3$/1.0	H	CH_3	H	H	**12b**	51
3	$Y(OTf)_3$/0.3	H	H	CH_3	H	**12c**	50
4	$Y(OTf)_3$/0.3	H	H	H	CH_3	**12d**	47
5	$Y(OTf)_3$/0.3	CO_2tBu	H	H	H	**12e**	40
6	$Yb(OTf)_3$/1.0	CO_2tBu	CH_3	H	H	**12f**	72
7	$Y(OTf)_3$/0.3	CO_2tBu	H	CH_3	H	**12g**	49
8	$Y(OTf)_3$/0.3	CO_2tBu	H	H	CH_3	**12h**	47

[a] For reaction conditions see Supporting Information. [b] Isolated yields after chromatography. Diastereomer ratio was determined by NMR.

Table 2. Synthesis of Cyclooctenes Using RCM Reactions[a]



12a-h **13a-h**

entry	diene	product	% yield[b]
1	 **12a**	 **13a**	43
2	 **12b**	 **13b**	88
3	 **12c**	 **13c**	33
4	 **12d**	 **13d**	60
5	 **12e**	 **13e**	70
6	 **12f**	 **13f**	70
7	 **12g**	 **13g**	19
8	 **12h**	 **13h**	63

[a] For reaction conditions see Supporting Information. The diastereomeric ratios for the products were the same as of those for the starting dienes. [b] Isolated yields after column chromatography.

cyclized to afford the corresponding cyclooctenes (**13**) in moderate to excellent yield. In general substrates that contain substituents on the carbon backbone but at a distant location from the reaction centers gave high yields in the cyclization. For example, dienes **12b** and **12f** with R^2 = Me underwent a smooth ring-closing metathesis reaction and provided the best yields for **13b** and **13f** (88% and 70%, entries 2 and 6).[7] In contrast, substrates with substituents allylic to the reaction center gave low yields for the cyclized products (**13c** and **13g**, 33% and 19%, respectively, entries 3 and 7). Substrates with 1,1-disubstitutents (**12d** and **12h**) did not undergo ring-closing metathesis. These two dienes gave dimers **13d** and **13h** in 60% and 63% yield, respectively (entries 4 and 8).

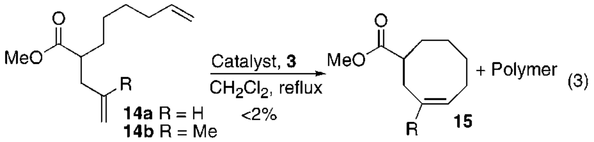
The poor reactivity of the dienes **12d** and **12h** led us to explore alternative catalysts for cyclization. Diene **12d** was subjected to several catalysts (**1**, **3**, **4**, and **5**) using standard reaction conditions. Unfortunately all the reactions with several different catalysts resulted in either recovered starting material or dimer formation. The results from these reactions are summarized in Table 3. For example, Hoveyda−Grubbs catalyst (**4**) afforded dimer in 66% along with 22% recovered starting material. This is not too surprising because this catalyst is more often used for cross-metathesis reactions than cyclizations.[8] In an effort to determine if these alternate catalysts are effective for cyclooctene formation, we carried out a brief study using **12a** as a substrate. As observed before, reaction of **12a** using most of the catalysts resulted in recovered starting material. To our surprise, 10 mol % of Grubbs I (**2**) resulted in a 1:1 inseparable mixture of product and starting material, with an overall yield of 60%. The only two other successful cyclizations using an alternate catalyst were from **12a** using 25 mol % of **2** (49% yield, entry 10) and the conversion of diene **12e** to **13e** in 27% yield using **8**, the recently described catalyst of Grela. Since an increased catalyst loading of **2** provided the cyclooctene **12a** in similar yield to that from catalyst **3**, the dienes **12d** and **12g** were reacted under these conditions. Unfortunately, these dienes also did not undergo any cyclization with Grubbs I catalyst (**2**).

Table 3. Evaluation of Different Catalysts.

entry	sm	product	cat. (mol %)	concn (mM)	time	% yield^b
1	**12d**	**13d**	**1** (10)	1	28	sm
2	**12d**	**13d**	**1** (10)	10	72	sm
3	**12d**	**13d**	**3** (10)	1	18	60
4	**12d**	**13d**	**4** (10)	1	36	sm
5	**12d**	**13d**	**4** (10)	10	36	66^b
6	**12b**	**13d**	**5** (10)	10	46	sm
7	**12a**	**13a**	**1** (10)	1	28	sm
8	**12a**	**13a**	**2** (10)	1	24	60^c
9	**12a**	**13a**	**2** (25)	1	40	49
10	**12a**	**13d**	**3** (10)	1	18	43
11	**12a**	**13a**	**4** (10)	1	28	sm
12	**12a**	**13a**	**5** (10)	10	48	sm
13	**12a**	**13a**	**1** (10)	1	28	sm
14	**12e**	**13e**	**8** (10)	1	36	27

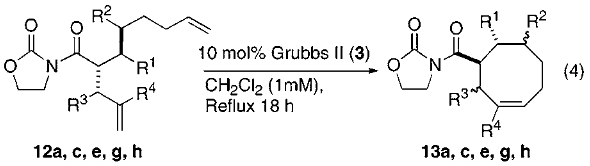
[a] Isolated yields after column chromatography. [b] 22% recovered starting material was also isolated. [c] 1:1 mixture of starting material and product

To investigate if steric bulk of the oxazolidinone played a role in the unsuccessful cyclization from substrates **12d** or **12h**, we converted **12d**,**h** into their corresponding methyl esters **14** using $MgBr_2$ or $Sm(OTf)_3$ in methanol.[9] The resulting esters **14** were subjected to our standard cyclization conditions using 10 mol % of Grubbs II catalyst (**3**) (eq 3). Unfortunately, they resulted in mostly recovered starting material, some polymeric material, and none of cyclooctene **15**.



Temperature has been shown to have an impact on dimer formation in RCM reactions.[10] To evaluate this variable, we performed the RCM reaction at room temperature. Several of the dienes were reacted at room temperature in the presence of catalyst **3** for several days in order for them to cyclize (eq 4, Table 4). These reactions are very slow at room temperature but gave similar or slightly better yields as compared to reactions under reflux conditions (entries 1−5). However, substrates **12d** and **12g**, containing a 1,1-disubstituted alkene, failed to undergo RCM reaction at room temperature.

Table 4. Room-Temperature Reactions^a



entry	R^1	R^2	R^3	R^4	product	time, d	% yield (sm)^b
1	H	H	H	H	**13a**	7	53 (20)
2	H	H	CH_3	H	**13c**	10	39
3	CO_2tBu	H	H	H	**13e**	7	60 (30)
4	CO_2tBu	H	CH_3	H	**13g**	10	34
5	CO_2tBu	H	H	CH_3	**13h**	10	37 dimer

[a] For reaction conditions see Supporting Information. [b] Isolated yields after column chromatography.

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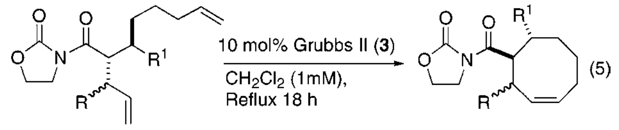
(6) Catalysts **1**, **2**, **3**, and **4** are commercially available. Catalyst **5**: Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791. Catalyst **6**: Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794. Catalyst **7**: Rolle, T.; Grubbs, R. H. *Chem. Commun.* **2002**, 1070. Catalyst **8**: Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.

(7) Crimmins has shown that conformational effects play a key role in the RCM reactions leading to eight-membered rings. See: Crimmins, M. T.; Choy, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 5653. A detailed analysis of conformational effects on cyclization in our work will be presented in a full paper.

(8) Randl, S.; Gessler, S.; Wakamatsu, H.; Blechert, S. *Synlett* **2001**, 430.

While our work was near completion, Kim and co-workers reported that yields for RCM reactions can be improved by a simple modification of the workup procedure using activated carbon, which effectively removes the catalyst and byproducts derived thereof.[11] Two substrates, **12c** and **12g**, which gave marginal yields in cyclization were chosen to evaluate the new workup procedure (eq 5, Table 5). For example, the yield for **13c** increased from 33% to 48% (compare entry 1 with entry 2) using the modified workup. A similar enhancement was also seen for **13g** (19% to 44%, compare entry 4 with entry 5). Further improvements in yield could be achieved by conducting the reaction at higher dilution and using the modified workup protocol (compare entries 2 with 3 and 5 with 6).

Table 5. Workup and Concentration Studies



12c R = CH$_3$, R^1 = H
12g R = CH$_3$, R^1 = CO$_2$t-Bu

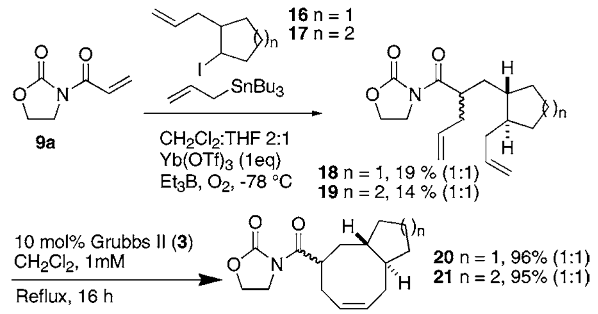
13c R = CH$_3$, R^1 = H
13g R = CH$_3$, R^1 = CO$_2$t-Bu

entry	compd	concn (mM)	workup[a]	% yield[b]
1	**12c**	1	A	33
2	**12c**	1	B	48
3	**12c**	0.5	B	78
4[c]	**12g**	1	A	19
5	**12g**	1	B	44
6	**12g**	0.5	B	65

[a] Method A: column chromatography. Method B: treatment with carbon followed by column chromatography. [b] Isolated yields after chromatography. [c] A 2:1 diastereomeric mixture of **12g** was used. The product **13g** was also a 2:1 diastereomeric mixture.

The ophiobolin and fusicoccin family of natural products contains a fused 5,8,5-ring system, and several members from this class have been popular targets.[12] We were interested in extending our methodology to the synthesis of bicyclic systems. To this end we attempted preparing the 5,8- and 6,8-bicyclic ring systems (Scheme 1). Addition of the iodo allylcyclopentane (**16**) and the iodo allylcyclohexane (**17**) to **9a** afforded the corresponding dienes **18** and **19** in 19% and 14% yield, respectively. Attempts to improve the yields have so far proven unsuccessful, although complete optimization studies have not been carried out. However, the subsequent RCM reactions proceeded smoothly and afforded 96% and 95% yield of the bicyclic compounds **20** and **21**. The relative stereochemistry of the cyclic compounds were determined by NOE analysis of **18**−**21**. The trans stereochemistry at the ring junction is established during radical addition and is consistent with observations in the literature.[13]

Scheme 1



In conclusion, we have shown that simple as well as complex cyclooctenes can be synthesized using radical reactions in combination with RCM technology. Variables such as substitution, catalyst, concentration, and temperature that impact on cyclization efficiency have been investigated. Overall, the cyclizations are efficient with substituents at remote locations to the olefinic center and become more difficult or unsuccessful when the substituents are close to or at the reaction center. Extension of the methodology in target synthesis is underway.

Acknowledgment. This work was supported by a grant (GM-54656) from the National Institute of Health.

Supporting Information Available: Characterization data for compounds **1**−**21** and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297.

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