ORGANIC LETTERS

2008
Vol. 10, No. 24
5613−5615

Substrate Encapsulation: An Efficient Strategy for the RCM Synthesis of Unsaturated ϵ-Lactones

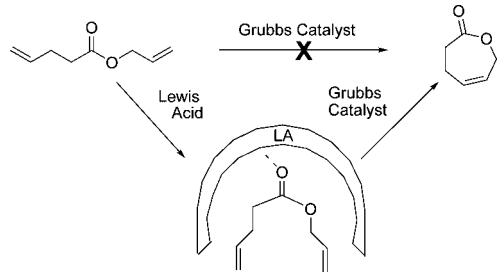
Emily B. Pentzer, Tendai Gadzikwa, and SonBinh T. Nguyen*

Department of Chemistry and International Institute of Nanotechnology, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113

stn@northwestern.edu

Received October 23, 2008

ABSTRACT



A facile substrate-encapsulated RCM-based synthesis of 7-membered lactones is reported. Coordination of the α,ω-dienyl ester precursor to the bulky Lewis acid (LA) aluminum tris(2,6-diphenylphenoxide) (ATPH) provides a protective extended steric pocket to the olefin moieties, thereby favoring intramolecular RCM over intermolecular ADMET oligomerization. The LA-encapsulated esters undergo ring-closure in the presence of Ru-based olefin metathesis catalysts to give previously difficult-to-access 7-membered β,γ- and γ,δ-unsaturated lactones in good yields.

Ring-closing metathesis (RCM) is rapidly evolving into a major strategy in the synthesis of numerous cyclic natural products and fine chemical intermediates. As a high-yielding synthetic method with few side products, it is an ideal route to otherwise difficult-to-make cyclic molecules.[1−3] The popularity of RCM as a synthetic tool can be attributed to the wide availability of well-defined olefin metathesis catalysts (Figure 1) and the emerging understanding of conditions that favor intramolecular ring-closure.[4] Unfortunately, RCM must often be carried out under highly dilute conditions to suppress undesirable acyclic diene metathesis (ADMET) oligomerizations. Some RCM substrates are further plagued by conformational biases that prevent ring closure and therefore require covalent modification before the desired reactivity can be realized.[2,5] Herein, we present a substrate-encapsulated methodology that enables, for the first time, the ring-closure of RCM-unfavorable α,ω-dienyl

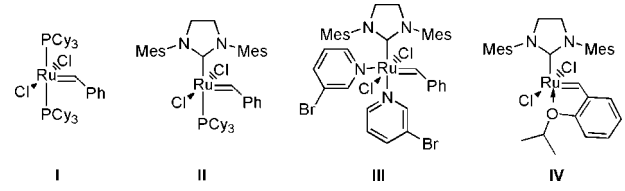


Figure 1. Commonly used Ru-based metathesis catalysts: first-generation Grubbs (**I**), second-generation Grubbs (**II**), third-generation Grubbs (**III**), second-generation Hoveyda−Grubbs (**IV**).

(1) Brenneman, J. B.; Martin, S. F. *Curr. Org. Chem.* **2005**, *9*, 1535–1549.
(2) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122–5128.
(3) Sieck, S. R.; Hanson, P. R. *Chemtracts: Org. Chem.* **2006**, *19*, 280–294.
(4) Han, S.-Y.; Chang, S. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 5−22.
(5) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838–3844.

10.1021/ol8022227 CCC: $40.75
Published on Web 11/17/2008

esters to occur without covalent substrate modification and demonstrate its use in the preparation of previously inaccessible 7-membered unsaturated lactones.

Although β,γ- and γ,δ-unsaturated 7-membered lactones are important intermediates in medicinal, natural product, and polymer chemistry, their syntheses are often low yielding[6] or cumbersome.[7,8] We believe that RCM would be an excellent modular route to these compounds, which can serve as new synthons bearing orthogonal, noninteracting olefin/ester functionalities. While RCM has been used to synthesize conjugated 7-membered lactones,[9−11] its use in the synthesis of other unsaturated ϵ-lactones has been met with only limited success.[12−15] This can be partially attributed to an unfavorable geometry of the starting acyclic esters, which are well-known to exist almost exclusively in the *Z* conformation, opposite of the required *E* ester geometry[16,17] of the ϵ-lactone product. This geometry places the two olefins of the substrate far apart and intermolecular ADMET is favored over intramolecular RCM.

We hypothesize that the aforementioned RCM-unfavorable conformational bias can be overcome by coordination of the carbonyl functionality of α,ω-dienyl esters to a cone-like, bulky LA. Such coordination could "encapsulate" the substrate (Figure 2, right), prevent intermolecular reactivity,

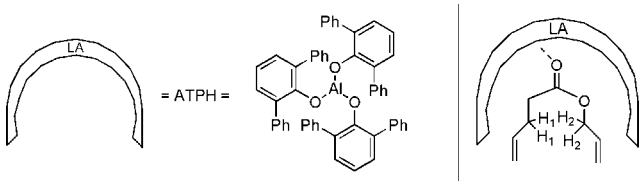
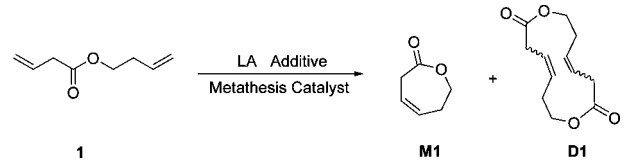


Figure 2. Aluminum tris(2,6-diphenyl)phenoxide (left) and proposed encapsulation of α,ω-dienyl ester (right).

and allow the desired RCM to occur, even at concentrations much higher than those used in conventional RCM. We selected the bulky LA aluminum tris(2,6-diphenyl)phenoxide (ATPH, Figure 2, left) given that Yamamoto and co-workers have elegantly employed it to selectively encapsulate conjugated carbonyl systems and control their regio-reactivities.[18]

Under conventional RCM concentrations (30−40 mM) the metathesis of **1** by catalyst **II** yields exclusively cyclic dimer **D1**; the desired β,γ-unsaturated ϵ-lactone **M1** can only be obtained under extremely dilute conditions (0.5 mM, see the Supporting Information). Thus, it is remarkable that in the presence of ATPH, **M1** can be readily obtained from **1** at 0.1 M (Table 1, entry 6), *200 times more concentrated*. The

Table 1. Optimization of RCM Conditions To Form 7-Membered Lactones



entry[a]	catalyst (loading)	LA additive (equiv)	*T* (°C)	M_1:D_1[b]
1	II (10 mol %)	none	45	0:100
2	II (10 mol %)	$Ti(O^iPr)_4$ (1.05)	45	0:100
3	II (10 mol %)	ATMP (1.05)	45	0:100
4	II (10 mol %)	ATIP (1.05)	45	0:100
5	II (10 mol %)	ATPH (1.05)	45	87:13
6[c]	II (10 mol %)	ATPH (1.05)	45	90:10
7	II (10 mol %)	ATPH (0.1)	45	31:79

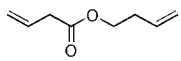
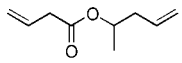
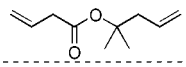
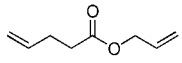
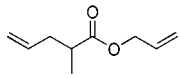
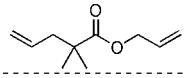
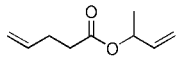
[a] Reactions performed at 20 mM substrate concentration in refluxing methylene chloride for 5 h. [b] Product distribution determined by GC(FID). [c] Reaction performed at 0.1 M substrate concentration. ATMP = aluminum tris(2,6-dimethylphenoxide). ATIP = aluminum tris(2,6-diisopropylphenoxide). ATPH = aluminum tris(2,6-diphenylphenoxide).

^{1}H NMR spectrum of a mixture of **1** and ATPH clearly indicates a single complex, supporting our encapsulation hypothesis. The extended steric pocket of ATPH is important as the RCM of **1** yielded only **D1** in the presence of the less-shielding $Ti(O^iPr)_4$, aluminum tris(2,6-dimethyl)phenoxide, and aluminum tris(2,6-diisopropyl)phenoxide LAs (Table 1, entries 2−4). Catalysts **I**−**IV** all afford the ϵ-lactone **M1** in the presence of ATPH, though catalyst **I** is the least efficient (Table S1, Supporting Information). While ATPH can act catalytically (Table 1, entry 7), the best yields are observed with a slight stoichiometric excess, consistent with the observations of Yamamoto and co-workers.[19]

Our substrate-encapsulated RCM strategy can be readily extended to synthesize several β,γ- and γ,δ-unsaturated ϵ-lactones in excellent yield, regardless of substitution pattern (Table 2). Although ATPH can be prepared and stored before use, it is more conveniently made in situ and used directly for RCM in a one-pot method (Table 2, entry 2). In addition, 2,6-diphenylphenol can easily be recovered in over 80% yield and

(6) Lou, X.; Detrembleur, C.; Lecomte, P.; Jerome, R. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2286–2297.
(7) Oka, T.; Murai, A. *Tetrahedron* **1998**, *54*, 1–20.
(8) Kido, F.; Kazi, A. B.; Yoshikoshi, A. *Chem. Lett.* **1990**, 613–616.
(9) Briggs, T. F.; Dudley, G. B. *Tetrahedron Lett.* **2005**, *46*, 7793–7796.
(10) Choi, T.-L.; Grubbs, R. H. *Chem. Commun.* **2001**, 2648–2649.
(11) Nakashima, K.; Imoto, M.; Miki, T.; Miyake, T.; Fujisaki, N.; Fukunaga, S.; Mizutani, R.; Sono, M.; Tori, M. *Heterocycles* **2002**, *56*, 85–89.
(12) Agrawal, D.; Sriramurthy, V.; Yadav, V. K. *Tetrahedron Lett.* **2006**, *47*, 7615–7618.
(13) Dirat, O.; Vidal, T.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 4801–4802.
(14) Christoffers, J.; Oertling, H.; Fischer, P.; Frey, W. *Tetrahedron* **2003**, *59*, 3769–3778.
(15) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.
(16) Jones, G. I. L.; Owen, N. L. *J. Mol. Struct.* **1973**, *18*, 1–32.
(17) The rotational barrier (~10 kcal/mol) between the *E* and *Z* isomers of open-chain esters can easily be overcome at room temperature, but the 5 kcal/mol difference in ground-state energy between these two isomers is heavily biased towards the RCM-unfavorable *Z* conformation See Eliel et al. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; p 618.
(18) Yamamoto, H.; Saito, S. *Pure Appl. Chem.* **1999**, *71*, 239–245.
(19) Saito, S.; Yamamoto, H. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; pp 33−42.

Table 2. RCM Results for the Synthesis of Various 7-Membered Unsaturated Lactones

entry[a]	substrate		RCM product	conversion (%)	M:D[b,f]
1[c]		(1)		100	90:10
2[c,d]				100	90:10
3[c]		(2)		100	98:2
4[c]		(3)	R, R` = H or Me	100	100:0
5[e]		(4)		100	97:3
6[e]		(5)		100	99:1
7[e]		(6)	R, R` = H or Me	100	88:12
8[e]		(7)		100	93:7

[a] All reactions performed at 10 mM substrate concentration in methylene chloride with 10 mol% catalyst and solid ATPH (see the Supporting Information). [b] Product distribution determined by GC(FID). [c] Catalyst **II** was used, 4 h. [d] ATPH was prepared in situ from recycled 2,6-diphenylphenol. [e] Catalyst **IV** was used, 8 h. [f] Isolated yields can be found in the Supporting Information.

reused without detriment to reaction yield or selectivity (Table 2, entry 2). While catalyst **II** can be used in the synthesis of all β,γ-unsaturated ϵ-lactones, catalyst **IV** is preferred for the γ,δ-unsaturated isomers to avoid their rearrangement to the more thermodynamically stable γ-lactones (see the Supporting Information). Presumably, this undesirable process is catalyzed by a decomposition side product of **II**.[20]

The encapsulation effects of ATPH on α,ω-dienyl esters can readily be seen in the crystal structure of the ATPH•**4** complex (Figure 3), where the binding pocket of ATPH extends over

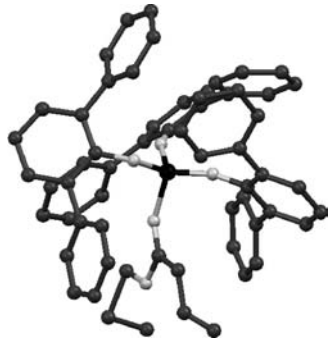


Figure 3. Ball-and-stick depiction of the crystal structure of the ATPH−(*Z*)-**4** complex.

the ester moiety and forces the two olefins closer together than would be expected in the unbound state (Figure S5, Supporting Information). Assuming that the solution conformation of ATPH•**4** does not deviate significantly from this structure, coordination of the dienyl ester to ATPH would enhance its intramolecular RCM reactivity due to steric confinement. The ROESY spectrum of ATPH•**4** complex (Figure S3, Supporting Information) reveals an off-diagonal peak corresponding to a proximal interaction between protons $\mathbf{H_1}$ and $\mathbf{H_2}$ (Figure 2, right) that was not observed in the analogous spectrum of the free ester **4** (Figure S2, Supporting Information). This data clearly shows the presence of the ATPH-(*E*)-**4** isomer in solution,[21] and suggests that coordination may provide the added benefit of an increased population/prolonged lifetime of the *E* ester isomer necessary for intramolecular RCM.

In conclusion, by exploiting steric interactions between an encapsulating LA and an ester-containing substrate, intramolecular ring-closure of RCM-unfavorable dienyl esters can now be achieved in excellent conversions. In contrast to the analogous α,ω-dienyl secondary amides, which must be *N*-modified to be RCM-reactive,[5] our strategy requires no covalent modification of the substrate. We emphasize that the results presented here demonstrate the first use of encapsulation to alter substrate reactivity in RCM, in contrast to the well-explored use of LA additives to prevent substrate coordination to metathesis catalysts.[22,23] Our results stress the critical importance of substrate conformation,[24] which must be taken into account in the RCM of problematic precursors. Efforts are currently underway to expand this methodology to include other carbonyl-containing 7- and 8-membered rings (see the Supporting Information).

Acknowledgment. Financial support was provided by the NSF (Grant No. DMR-0094347), the AFOSR (MURI Grant No. FA9550-07-1-0534), and the NIH CCNE program (Grant No. NCI 1U54 CA119341-01). We thank Prof. Deryn Fogg (U. Ottawa), Prof. Joseph B. Lambert (NU), and Dr. Yuyang Wu (NU) for helpful discussions, Mr. Byungman Kang for the calculated structure of **1**, and the reviewers for excellent suggestions that helped to improve the current manuscript. We thank Dr. Richard Pedersen (Materia, Inc.) for his advice and for the gifts of catalysts **II** and **IV**. E.B.P. is an NSF Graduate Research Fellow.

Note Added after ASAP Publication. Due to a production error, various galley corrections were not included in the version published ASAP November 17, 2008; the correct version was published on the Web December 11, 2008.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8022227

(20) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

(21) Unfortunately, repeated attempts to obtain crystallographic structural information for this isomer resulted only in the isolation of the ATPH-(*Z*)-**4** isomer (see Figure 3 and the Supporting Information), most likely due to crystal packing forces.

(22) Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871–874.

(23) Fuerstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

(24) Paquette, L. A.; Basu, K.; Eppich, J. C.; Hofferberth, J. E. *Helv. Chim. Acta* **2002**, *85*, 3033–3051.