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Direct Macrolactonization of Seco Acids via Hafnium(IV) Catalysis

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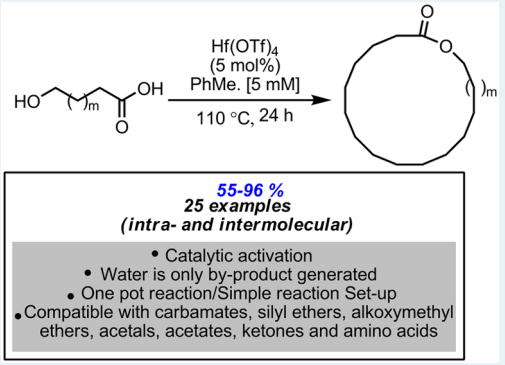
Supporting Information

ABSTRACT: Efficient direct macrolactonization of seco acids can be catalyzed by $Hf(OTf)_4$ in high yields, forming water as the sole byproduct. The $Hf(OTf)_4$ catalyst possesses unique reactivity characteristics relative to other Lewis acids, as it promotes macrolactonization over hydrolysis even in the presence of excess water. In addition to forming a variety of macrolactones and benzolactones (55−90%), intermolecular direct esterifications of carboxylic acids and alcohols were also possible and demonstrated compatibility with common carbamate, silyl ether, alkoxymethyl ether, and acetal protecting groups. All of the macrolactonization and esterification processes developed are operationally simple, "one-pot" reactions that exploit a commercially available catalyst without the need for slow addition or azeotropic techniques.



KEYWORDS: *macrolactonization, hafnium, esterification, macrocyclization, Lewis acids, catalysis*

Macrolactones are one of the most common cyclic motifs found in Nature. In addition to their application in pharmaceuticals,[1] macrolactones have had a tremendous impact on the cosmetic industry.[2−4] Macrocyclic musks have attracted increased attention from the perfume industry, as they do not exhibit the toxicity or bioaccumulation properties associated with traditional nitro-aromatic and polycyclic musks.[5] In 2011, it was estimated that the market for flavors and fragrances was worth over 21 billion dollars.[6] The production of macrocyclic musk is of considerable industrial impact; for example, in 2008 the production of the 16-membered Exaltolide (**2**)[7] was on the order of ∼1000 tons.[8] Consequently, synthetic chemists in both academia and industry have continued to develop new strategies to prepare macrolactones, where Exaltolide and its derivatives have often served as targets for new methodologies. Olefin metathesis,[9] most recently employing *Z*-selective catalysts,[10] and C−H functionalization have recently been explored for the synthesis of macrocyclic musk-like structures.[11] Surprisingly, catalysis has rarely been examined for macrocyclization from the commonly occurring seco acids.[12,13] Macrolactones formed via condensation of the corresponding seco acid are equilibrium-controlled processes, where the reverse hydrolysis reaction can be problematic. While in an analogous intermolecular esterification the alcohol can be added in large excess (often as the solvent) in order to push unfavorable equilibria toward the formation of the desired ester,[14] the stoichiometry of the alcohol and acid functionalities in macrolactonization remains fixed in a 1:1 ratio. In 1936,[13a] Carothers reported a Lewis acid catalyzed transesterification process for the formation of macrolactone **2**. Following thermal polymerization of the seco acid **1**, $MgCl_2$ was used to promote "back-biting" of the oligomer to afford macrolactone **2**, which was concurrently distilled away from the reaction mixture as it formed, thus controlling any unfavorable equilibria.

Current strategies to promote macrolactonization from seco acids involve stoichiometric activation of the carboxylic acid,[15] which is eventually eliminated as a thermodynamically favorable leaving group (Figure 1). Some of the more popular strategies employing this concept for macrolactone synthesis include the Corey−Nicolaou,[16] Boden−Keck,[17] Mitsunobu,[18] and Yamaguchi lactonizations.[19] In each of the above examples, reactions are normally all conducted under high-dilution conditions and the stoichiometric byproducts can be toxic and difficult to remove even via chromatographic separation. The Yamaguchi macrolactonization has been particularly favored among synthetic chemists since its inception in 1979, as almost 200 examples of the macrolactonization protocol have been reported.[20] Recently, modified anhydride reagents inspired by the Yamaguchi method have attracted increased attention for the synthesis of naturally occurring macrolactones.[21] Surprisingly, efficient catalytic direct macrolactonization of seco acids is rare and underdeveloped.[8] Herein, we report on a hafnium-catalyzed macrolactonization protocol for the formation of macrolactones that produces water as the only byproduct.

DISCOVERY OF A HF(IV)-CATALYZED MACROLACTONIZATION

In developing an ideal direct macrolactonization of seco acids, several goals were identified. First, an operationally simple, "one-pot" process was desired which avoided the use of azeotropic techniques (drying tubes, Dean−Stark traps) and

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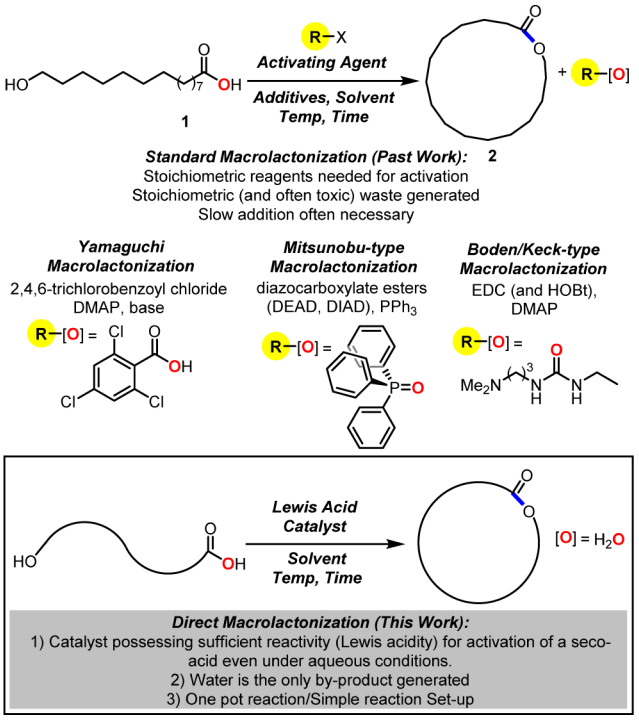

Figure 1. Traditional macrolactonization strategies.

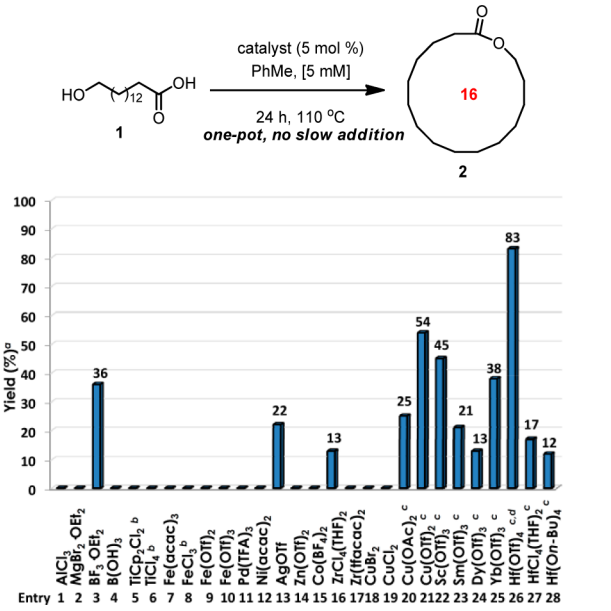

Figure 2. Optimization of a Lewis acid catalyzed macrolactonization process. Footnotes for the entries are as follows. (a) Isolated yields following silica gel chromatography; the remaining mass balance was unreacted **1** unless otherwise noted. (b) No trace of **1** was isolated. (c) Polymerization of **1** was observed. (d) Lower catalyst loadings provided lower yields. When 2.5 mol % $Hf(OTf)_4$ was used, 72% of **2** and 27% reisolated **1** were obtained. At a concentration of 10 mM, 32% of **2** was obtained along with a complex mixture of cyclic and acyclic dimers. Lowering the temperature resulted in low conversions, even when the catalyst loading was increased.

slow-addition/high-dilution apparatus (syringe pumps). Second, the direct macrolactonization would produce water as the only byproduct. These goals present significant challenges for catalysis, as a suitable Lewis acid must not only possess sufficient acidity to activate the macrocyclization but must also retain that reactivity even as the reaction media becomes increasingly "contaminated" by water. An additional requirement is that the Lewis acid must also refrain from catalyzing hydrolysis of the desired macrolactone. Although a thorough investigation surveying a wide variety of Lewis acids from across the periodic table was envisioned, particular focus in the present study was placed on lanthanide-based Lewis acids, including Lewis acids based on elements of groups III and IV that have demonstrated the ability to promote Lewis acid catalysis in aqueous media.[22] The macrolactonization of seco acid **1** to provide Exaltolide **2** was selected as a model substrate for cyclization (Figure 2). The investigations began with various oxophilic Lewis acid catalysts. Although these Lewis acids are known to react readily with water, no precautions to exclude water (such as adding drying tubes or molecular sieves) were taken and no slow-addition techniques were exploited (Figure 2).[23] As expected, titanium, iron, magnesium, boron, and aluminum catalysts in general did not afford any of the desired macrolactone **2** (entries 1−10), and either quantitative recovery of the starting material **1** was observed or the highly acidic conditions caused decomposition of **1**. Some productive macrocyclization was observed copper-based catalysts were used. While $CuCl_2$ and $CuBr_2$ did not promote any macrolactonization, both $Cu(OAc)_2$ and $Cu(OTf)_2$ resulted in unsatisfactory yields of macrocycle **2** (25 and 54% yields, respectively). While AgOTf and $ZrCl_4(THF)_2$ did provide low yields of the macrolactone **2** (22 and 13%, respectively), other transition-metal-based Lewis acids displayed little reactivity even with other electrophilic complexes of Zr, Zn, Pd, Ni, and Co.

Next, Lewis acids from groups III and IV, including lanthanide-based Lewis acids, were investigated. Given the success of electrophilic triflate catalysts for macrocyclization of **1**, $Sc(OTf)_3$ (45%), $Sm(OTf)_3$ (21%), $Dy(OTf)_3$ (13%), and $Yb(OTf)_3$ (38%) were evaluated and showed encouraging but low yields (Figure 2, entries 22−25). Interestingly, when $Hf(OTf)_4$ was used, an 83% yield of the macrolactone **2** was isolated.[24] Yamamoto and co-workers reported that efficient direct intermolecular esterifications using low loadings of $HfCl_4(THF)_2$ were possible, albeit under azeotropic reflux.[25,26] Disappointingly, when the hafnium-based catalysts $HfCl_4(THF)_2$ and $Hf(O\text{-}n\text{-}Bu)_4$ were investigated in the protocol without the use of azeotropic techniques, only low yields were obtained (entries 26 and 27). Given the success of the $Hf(OTf)_4$ complex, the possibility of catalysis via in situ formed HOTf was investigated. In a control reaction, it was found that HOTf did catalyze the macrolactonization (**1** → **2**), albeit in much lower yield (39% vs 83% with $Hf(OTf)_4$). Consequently, macrolactonization using $Hf(OTf)_4$ with added $(i\text{-}Pr)_2NEt$ (50 mol % or 10 equiv of base with respect to $Hf(OTf)_4$) to quench traces of protic acids was performed. In the macrolactonization with added base, the desired macrolactone **2** was isolated in 79% yield.[27] The almost identical yields obtained in either the presence or absence of added base suggests that successful macrolactonization is due to catalysis via the Hf-based Lewis acid.

As stated previously, no precautions were taken to exclude or remove water from the reaction media during the macrolactonization reactions. Hence, efficient Lewis acid catalysis not only must be able to promote macrolactonization in high yields but must also be able to do so in the presence of water without

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catalyzing the reverse hydrolysis reaction. Consequently, all Lewis acid catalysts that displayed some activity for macrocyclization were re-evaluated in two additional control reactions. First, the macrolactonization was performed under the identical reaction conditions utilized in the catalyst survey, but the reaction solvent (PhMe) was pretreated with an excess of water (200 equiv). Under these conditions, the majority of the complexes which demonstrated some measure of activity for direct macrolactonization were now significantly inhibited (isolated yields in **2** shown in red; Figure 3). Gratifyingly, the

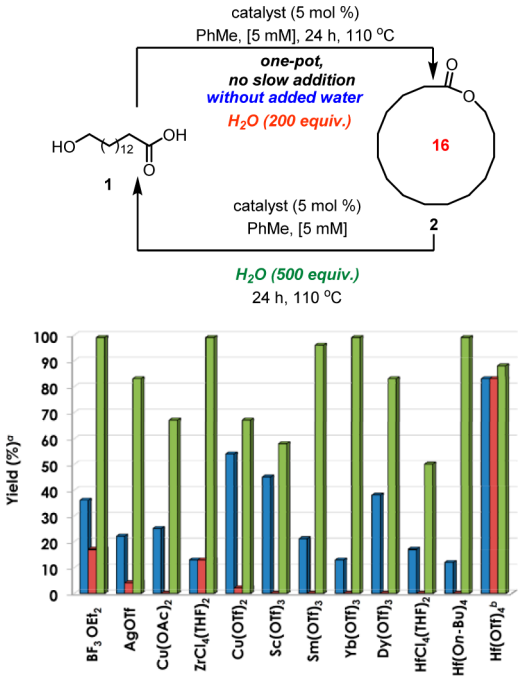
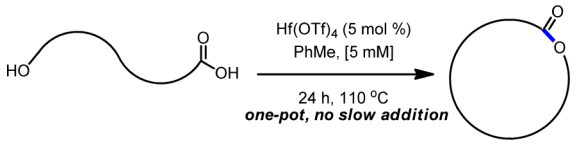


Figure 3. Evaluation of various Lewis acids for a catalytic macrolactonization strategy. The most efficient complex is judged to have yields of macrocyclization under the optimized conditions (blue) and under the optimized reaction conditions in the presence of excess water (red) and provide high recovered yields of macrolactone **2** under hydrolysis conditions (green). Footnotes are as follows. (a) All entries represent isolated yields following silica gel chromatography. (b) The reisolated yield of **2** remained high (>80%) even when 1000 equiv of added H_2O was used.

$Hf(OTf)_4$ catalyst maintained the same level of reactivity (83% yield of macrolactone **2**). Second, all active Lewis acid catalysts were evaluated for their ability to catalyze the hydrolysis of macrolactone **2**. Exaltolide **2** was resubmitted to the macrocyclization conditions with added excess water (500 equiv) for 24 h, and then the remaining macrolactone was isolated (isolated yields of recovered **2** in green; Figure 3). In general, most catalysts promoted some degree of hydrolysis of the macrolactone **2**. Once again, the Hf-based Lewis acids demonstrated ideal reactivity patterns for direct macrolactonization, as they were poor hydrolysis catalysts and greater than 80% of **2** could be reisolated, even when 1000 equiv of excess water was added.

Given the unique ability of $Hf(OTf)_4$ to catalyze the macrolactonization reaction, the synthesis of various macrolactones was investigated under the optimized conditions (Table 1). The medium 13-membered macrolactone **4** was prepared in 55% yield[28] (the smaller 11-membered macrocycle **3** could not be formed under the optimized conditions). Larger

Table 1. Substrate Scope of the $Hf(OTf)_4$-Catalyzed Macrolactonization



	Macrocycle	Yield (%)[a]		Macrocycle	Yield (%)[a]
1	**3** n = 1	<5	10	**11**	73
2	**4** n = 3	55			
3	**2** n = 6	83			
4	**5** n = 7	87			
5	**6** n = 1	90	11	**12**	86
6	**7** n = 3	84			
7	**8** n = 1	56	12	**13**	74
8	**9** n = 11	72			
9	**10**	72	13	**14**	57

[a]Isolated yields following flash chromatography.

rings such as the 16- and 17-membered macrolactones **2** and **5** were isolated in higher yields (83%[29] and 87%, respectively). The yields of the macrolactones obtained via Hf catalysis are either comparable to or higher than those obtained using stoichiometric methods. Cardenas and co-workers prepared the 13-, 16-, and 17-membered macrolactones using a Boden–Keck-type method in 69–78% yield, but stoichiometric amounts of EDC, HOBt, and DMAP and high-dilution/slow-addition techniques were required.[30] Recently, Zhang and co-workers reported a hypervalent iodine(III) reagent for the preparation of macrolactones **2**, **3**, and **5** in 56–94% yields.[31] Although the iodine-based reagent was recyclable, the procedure still required stoichiometric DMAP and PPh_3 as coreagents and subsequent purification/separation of the associated byproducts (PPh_3O) was necessary. Given the abundance and biological activity of benzolactone natural products,[32] the synthesis of four different macrocycles with benzoic acid cores was investigated. The 14- and 16-membered macrolactones **6** and **7** were each isolated in good yields (90% and 84%, respectively). The presence of an alkyne spacer in the analogous macrolactone **8** was well tolerated, although the product was isolated in a lower yield (56%). When the ring size was increased, the 26-membered ring **9** was isolated in 72% yield. The synthesis of other 17-membered macrolactones

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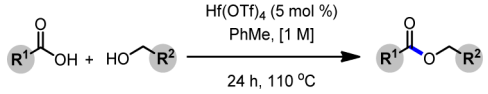
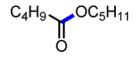
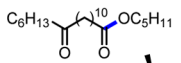
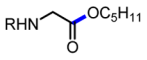
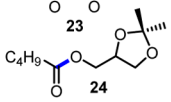
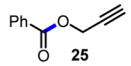
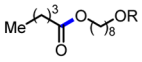
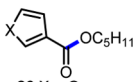
related to the isoambrettolide[33] family of musks was also investigated (entries 9 and 10). Macrolactonization afforded (9*Z*)-isoambrettolide **10** in good yield (72%) without any isomerization of the *cis*-olefin. Protection of the diol moiety of *erythro*-aleuritic acid as its bis-pivaloate ester and subsequent macrocyclization afforded the macrolactone **11** in 73% yield. Finally, macrolactonization of more strained rings, such as the 1,3-diyne containing 21-membered macrolactone **12**, also proceeded in high yield (86%). The $Hf(OTf)_4$-catalyzed protocol also evaluated in the cyclization of structures has enolizable stereocenters and steric bulk adjacent to the reacting carboxylic acid. The 19-membered macrolactone **13** derived from *iso*-leucine was cyclized in 74% yield. Similarly, the 22-membered dipeptide macrocycle **14** was formed in 57% yield. Both macrocycles **13** and **14** were obtained without any observed epimerization.

To further probe the functional group tolerance of the $Hf(OTf)_4$-catalyzed macrolactonization, several intermolecular esterifications were performed (Table 2). The esterification of a

Table 2. Evaluation of Functional and Protecting Group Compatibility in the $Hf(OTf)_4$-Catalyzed Esterifications



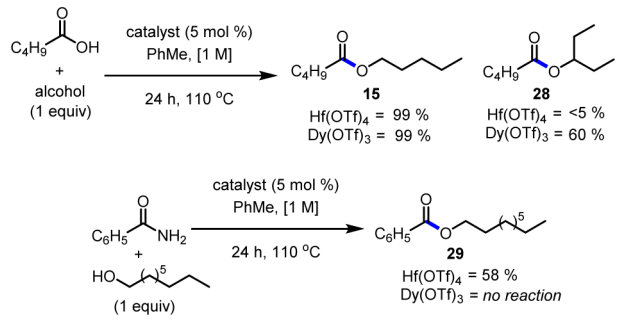
	Macrocycle	Yield (%)[a]		Macrocycle	Yield (%)[a]
1	 **15**	99	9	 **23**	92
			10	 **24**	60[b]
2	**16** R = Boc	72			
3	**17** R = Ts	75			
4	**18** R = Cbz	79	11	 **25**	78
					
5	**19** R = TBS	66[b]			
6	**20** R = TIPS	62[b]			
7	**21** R = MOM	77[b]	12	 **26** X = O	75
8	**22** R = Ac	89[b]	13	**27** X = S	89

[a]Yields following flash chromatography. [b]With added Hünig's base (50 mol %).

simple aliphatic acid and alcohol to provide the ester **15** occurred in quantitative yield (99%, entry 1). Esterification provided Boc-, tosyl-, and Cbz-protected glycine derivatives in good yields (72%). Both TBS- and TIPS-protected silyl ethers were utilized in the esterification to afford the corresponding esters **19** and **20** in 66 and 62% yields, respectively (entries 5 and 6). The addition of Hünig's base (50 mol %) was necessary to avoid cleavage of the TBS and TIPS groups. Similarly, MOM- and acetate-protected alcohols were also tolerated and esterification afforded the corresponding esters **21** and **22** in 77 and 89% yields, respectively. Both acetonide-protected diols and ketone groups were tolerated, and the esters **24** and **23** were obtained in 77 and 92% yields, respectively. The propargyl ester **25** was compatible with the esterification protocol and was isolated in 78% yield.[34] Additionally, carboxylic acids bearing furan and thiophene heterocycles were easily esterified and the *n*-pentyl esters **26** and **27** were isolated in 75 and 89% yields, respectively (entries 10 and 11). The esterification protocol also demonstrated selectivity for condensation with primary alcohols over secondary or tertiary alcohols or primary amines to provide the ester **15**.[35]

In an effort to understand the reactivity of the $Hf(OTf)_4$ complex in direct macrolactonization, several control experiments were performed (Scheme 1). The intermolecular

Scheme 1. Investigations into the Mechanism of the Hf(IV)-Catalyzed Esterification



esterification of 1-pentanoic acid with 1-pentanol was performed with both $Hf(OTf)_4$ and $Dy(OTf)_3$. The stability and catalytic activity of $Dy(OTf)_3$ in water are largely attributed to the cation's large ionic radii and favorable hydrolysis constants.[22c] Although Hf-derived Lewis acids do not possess the same hydrolytic stability as the lanthanide triflates, both $Hf(OTf)_4$ and $Dy(OTf)_3$ provided identical yields of the ester **15** (~99%). Interestingly, when the esterification of benzamide with 1-nonanol was examined under identical reaction conditions, only $Hf(OTf)_4$ promoted the formation of the ester **29** (58% yield).[36] The useful Lewis acidity of Hf-based complexes for a variety of transformations is well documented.[37] Finally, esterification of 1-pentanoic acid was carried out with a secondary alcohol (3-pentanol). While $Hf(OTf)_4$ did afford any of the desired product, $Dy(OTf)_3$ provided a 60% yield of ester **28**. As a whole, these preliminary studies suggest that the direct esterification/macrolactonization is influenced by the Lewis acidity, hydrolytic stability, and steric bulk of the catalyst.

A protocol for an efficient direct Hf(IV)-catalyzed macrolactonization of seco acids has been described. Following a survey of >25 various Lewis acids, $Hf(OTf)_4$ was identified as the most efficient catalyst, promoting macrolactonization in high yields at relatively high concentrations (5 mM). Further investigations into the activity of the $Hf(OTf)_4$ complex demonstrated that (1) $Hf(OTf)_4$ is significantly more efficient relative to other Lewis acids in catalyzing direct macrolactonization, even in the presence of excess water, and (2) $Hf(OTf)_4$ is a poor catalyst for the hydrolysis of macrolactones. A variety of macrolactone and benzolactone skeletons could be prepared, including important macrocycles for the perfume industry. Intermolecular direct esterifications of carboxylic acids and alcohols were also possible and demonstrated compatibility with common carbamate, silyl ether, alkoxymethyl ether, and acetal protecting groups. All of the macrolactonization processes developed are operationally simple, use commercially available catalysts, and are "one-pot" reactions without the need for slow-addition or azeotropic techniques. Importantly, the catalytic process forms environmentally benign water as the only byproduct. Preliminary investigations demonstrate that the Lewis acidity, hydrolytic stability. and steric bulk of the catalyst play important roles in the macrolactonization. The effective-

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ness of the Hf(IV)-catalyzed macrolactonization should be highly useful, given the prevalence of macrolactone structures in pharmaceutically and biologically active products and current interest in sustainability in reagent selection for industrially relevant processes.[38,39]

■ ASSOCIATED CONTENT

Supporting Information

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00082.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(34) Curiously, an esterification with allyl alcohol was not productive and afforded a black reaction mixture with numerous products.

(35) See the Supporting Information for additional experiments involving secondary alcohols.

(36) The activation of primary amides to form esters may suggest that the macrolactonizations proceed via carboxylic acid activation. For

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