

# Modern Macrolactonization Techniques

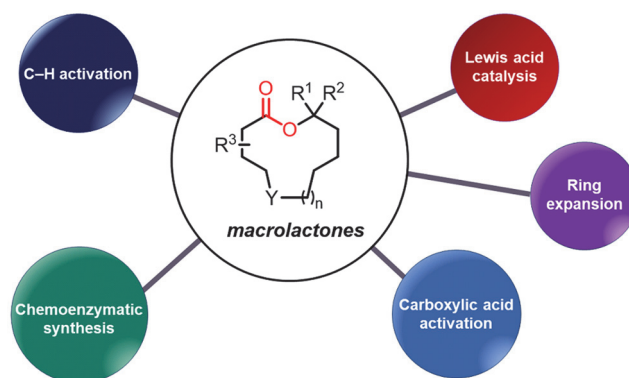
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**Abstract** The study of macrolactonization processes has been a steady endeavor for synthetic chemists to access macrocycles that are fundamental in the development of numerous high-added-value compounds, notably drugs and fragrances. This field of research is essential as macrolactonizations usually take place at the end of manifold syntheses and chemists need reliable, efficient, and versatile tools to avoid unpredictable results that would lead them to completely redesign their synthetic plan. Here, we highlight the recent methods reported to achieve macrolactonizations towards the formation of both macrolactones and macrodiolides, which feature either Lewis acids, transition metals or organic molecules as activating agents.

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**Key words** macrolactone, macrodiolide, coupling agent, Lewis acid, C–H activation, ring expansion, chemoenzymatic

## 1 Introduction

Macrolactones are found across a broad range of pharmaceuticals, agrochemicals, and cosmetics. Classical examples include erythromycin (antibiotic), epothilone B (anticancer), amphotericin B (antifungal), spinosyn A (insecticide), and exaltolide<sup>®</sup> and musk T<sup>®</sup> (fragrances) (Figure 1).<sup>1–4</sup> Since exaltolide has a rather simple chemical structure, it can effectively be produced on 1000-ton-scale annually for the perfume industry, which is in stark contrast with the structurally complex erythromycin and spinosyn A. Currently, their syntheses remain very lengthy,<sup>5–7</sup> and their

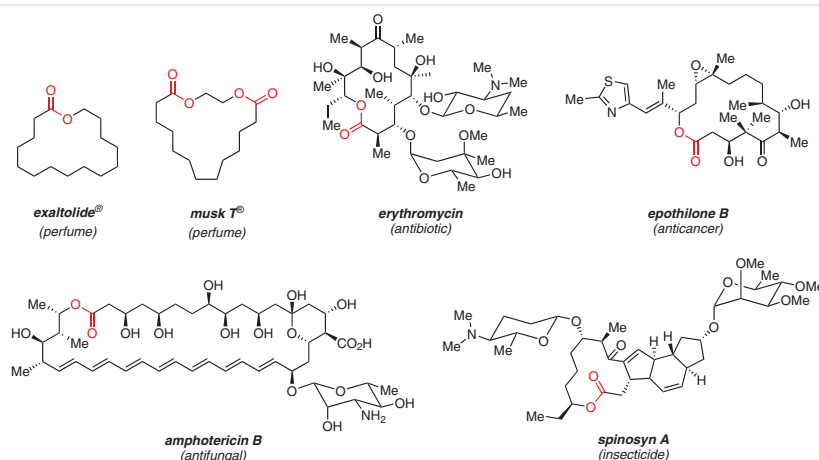


**Max Van Hoof** (left) obtained his Master's degree in chemistry in 2018 and his Ph.D. at KU Leuven in 2023 supervised by Prof. Wim Dehaen and Dr. Steven De Jonghe. He is currently a postdoctoral fellow at the University of Strasbourg under the guidance of Dr. David Lebœuf. His research focuses on the development of new catalytic synthetic methodologies, with a specific focus on exploiting the unique solvent properties of hexafluoroisopropanol (HFIP).

**Guillaume Force** (center) received his Master's degree in chemistry in 2017 and his Ph.D. from Université Paris-Saclay in 2021 under the supervision of Dr. David Lebœuf. During his Ph.D. studies, his research focused on the use of supramolecular chemistry in organic synthesis and homogeneous catalysis. He is currently a postdoctoral fellow at the CEA-Saclay in the group of Dr. Frédéric Taran.

**David Lebœuf** (right) obtained his Ph.D. in organic chemistry in 2009 under the guidance of Prof. Max Malacria (UPMC, Paris VI). After completing two postdoctoral periods, at the University of Rochester with Prof. Alison J. Frontier (2010–2012) and at the ICIQ with Prof. Antonio M. Echavarren (2012–2013), he was appointed as a CNRS researcher at Université Paris-Saclay in 2013. In 2019, he joined the ISIS institute (Université de Strasbourg), where his research interests focus on the application of supramolecular chemistry to catalysis, notably cultivating the use of hexafluoroisopropanol in synthesis.

production typically relies on fermentation of *Streptomyces erythreus* and *Saccharopolyspora spinosa*.<sup>1,2</sup> This clearly points to the great challenge that the synthesis of complex macrolactones represents to this day. However, there are noticeable exceptions, such as the efficient and versatile



**Figure 1** Selected examples of macrolactones of interest

fully synthetic routes developed by Myers and co-workers via a convergent assembly of simple chemical building blocks towards macrolide antibiotic analogues.<sup>8,9</sup>

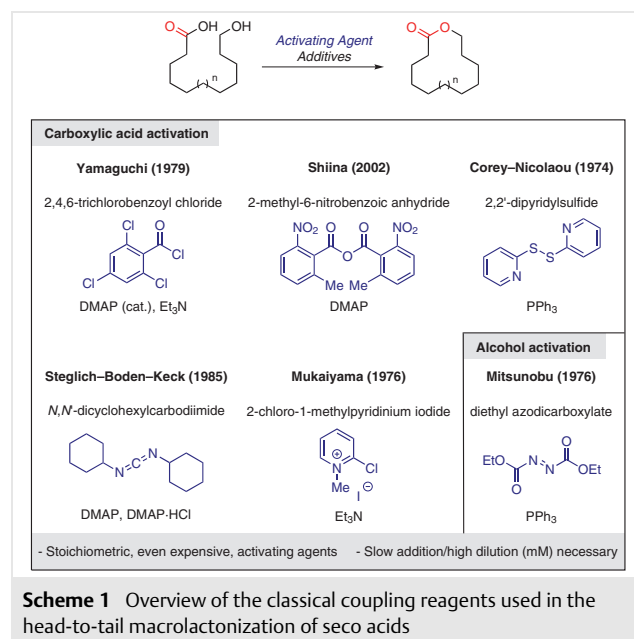
Given the continual need for increasingly sophisticated molecules to efficiently bind to drug targets when small molecules prove inefficient, the interest in complex macrocyclic molecules will likely continue to grow.<sup>10,11</sup> Consequently, the development of innovative strategies for their synthesis will remain of high interest to the synthetic community.

Countless methods can be found in the literature to generate the macrolactone framework.<sup>12–20</sup> To cite but a few examples, macrocyclizations involving ring-closing metathesis, intramolecular cross-coupling reactions, and olefinations have been devised. In this short review, we will focus on the advances made to forge the lactone motif for macrolactones and macrodiolides over the past twenty years. When this is the case, the ability of the described methods to additionally generate medium-ring sizes will be mentioned given the challenges associated with their synthesis. These different strategies include new modes of activation for the carboxylic acid, C–H activation, ring expansion, chemoenzymatic synthesis and other variants. These procedures will first be discussed, along with their mechanism. Whenever possible, their performance will be compared with the classical conditions.

## 2 Stoichiometric Carboxylic Acid Activation

Currently, macrolactonization via head-to-tail cyclization of seco acids using stoichiometric amounts of a coupling agent to activate either the carboxylic acid or the alcohol is the method of choice. Classical methods for carboxylic acid activation have been developed by Yamaguchi (2,4,6-trichlorobenzoyl chloride),<sup>21</sup> Shiina (2-methyl-6-nitroben-

zoic anhydride),<sup>22,23</sup> Corey–Nicolaou (2,2'-dipyridyldisulfide),<sup>24,25</sup> Steglich–Keck–Boden (*N,N'*-dicyclohexylcarbodiimide),<sup>26,27</sup> and Mukaiyama (2-chloro-1-methylpyridinium iodide).<sup>28</sup> Regarding alcohol activation, the Mitsunobu reaction (diethyl azodicarboxylate) is the most prominent strategy (Scheme 1).<sup>29</sup> While truly innovative, most of these methods are subject to different drawbacks—practical and fundamental—that can limit their utility, including highly dilute conditions and/or slow addition protocols to prevent oligomerizations, generating several by-products, even toxic ones, which can make the purification of the target product challenging, without mentioning their cost-effectiveness and their lack of versatility.

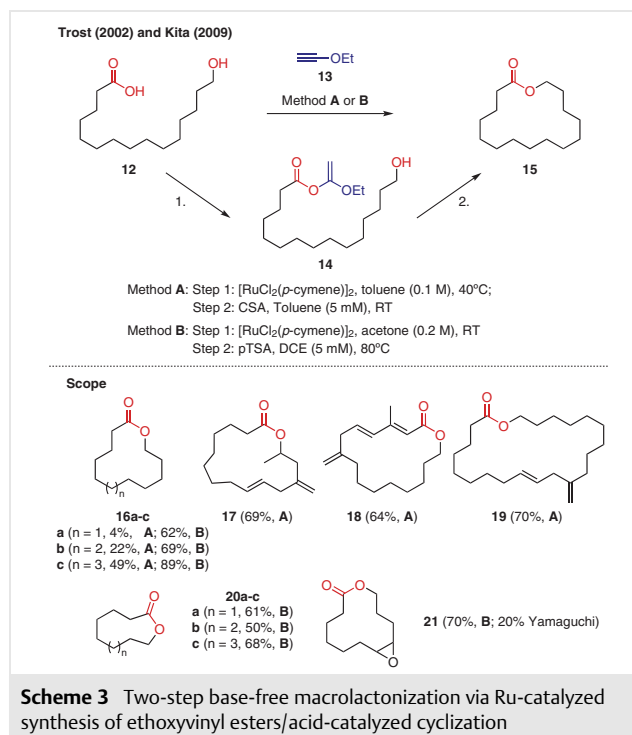
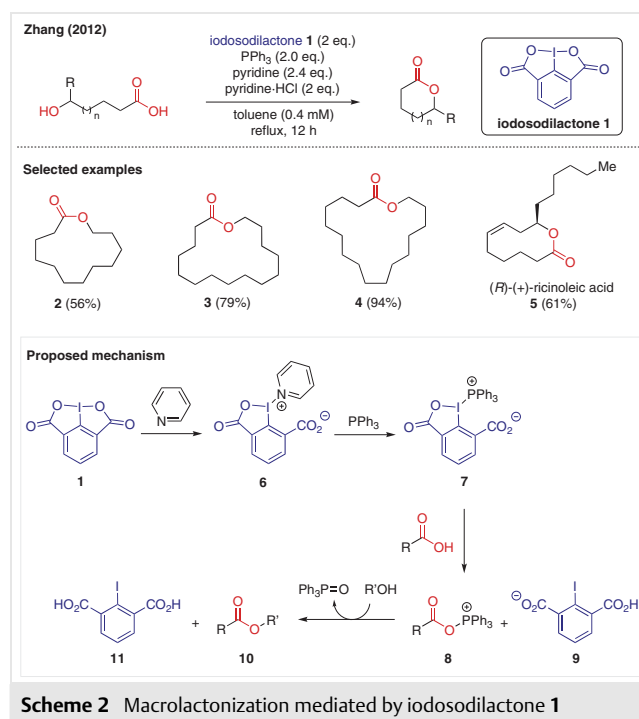


As a result, several original strategies have recently emerged in the literature to overcome these challenges, including new modes of activation for the carboxylic acid, C–H activation, ring expansion and other variants. These procedures will first be discussed, along with their mechanisms. Whenever possible their performance will be compared with the classical conditions.

As mentioned in the introduction, a variety of strategies have been developed to activate the carboxylic acid through the stoichiometric formation of a more electrophilic species with coupling agents. To offset the use of stoichiometric amounts of activating agent, Zhang and co-workers reported a combination of iodosodilactone **1**—a hypervalent iodine reagent—triphenylphosphine, pyridine and pyridine-HCl to promote the macrolactonization reaction.<sup>30</sup> The advantage of this method is the use of a mild and environmentally benign hypervalent iodine oxidant, which is easily regenerated by reoxidation of the by-product **11** with NaOCl (Scheme 2). Regarding the mechanism, the authors proposed, as a first step, the formation of arylodine(III) species **6** resulting from the nucleophilic addition of pyridine on iodosodilactone **1**, thereby increasing its reactivity towards triphenylphosphine. The authors substantiated their proposal for this mode of activation by the observation that the one-pot reaction resulted in an approximately 20% reduced yield compared with the two-step procedure involving the prior reaction of pyridine with iodosodilactone **1** under reflux. The generated phosphonium zwitterion **7** (detected by ESI-MS) would then react with the carboxylic acid to afford acyloxyphosphonium salt **8**. Proof for the acti-

vation at the carboxylic acid was obtained through <sup>18</sup>O-labeling studies. This promoter system enabled the formation of 13- to 17-membered rings **2–5** in yields ranging from 56 to 94%. In comparison to classic coupling reagents, this strategy allows the retention of configuration for the alcohol **5**. However, highly dilute conditions (0.4 mM) and stoichiometric amounts of additives are used, which offsets the supposed sustainability associated with the use of a benign and recycled oxidant.

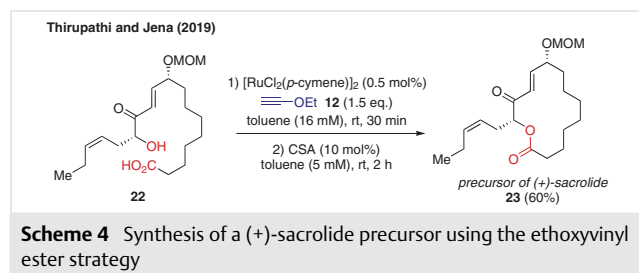
One potential issue shared by the classical conditions and the method developed by Zhang is the use of a large excess of base which can trigger unwanted side reactions, such as the isomerization of unsaturated carboxylic acid derivatives. For this reason, the Trost group set out to circumvent this issue by developing base-free conditions (Scheme 3, method A).<sup>31</sup> They envisioned a two-step cyclization method involving an ethoxyvinyl ester intermediate **13**, formed from a reaction with ethoxyacetylene (**12**), which has the advantage of only forming ethyl acetate as a by-product. Seminal studies by the group of Dixneuf showed that carboxylic acids and alkynes react smoothly towards alkoxyvinyl esters using Ru(II) catalysis,<sup>32</sup> which was exemplified by Wasserman and Kita in acid-catalyzed intermolecular esterifications.<sup>33–35</sup> When applying this two-step sequence to the preparation of macrolactones (**14** and **15**, 12- and 14-membered rings), a competition between macrodiolide formation and macrolactonization was observed, leading to low and moderate yields (4% and 49%, respectively). However, in the case of larger ring sizes (15-



to 22-membered rings), the proportion of macrodiolide diminished, leading to the target macrolactones in yields varying between 60 and 70%. Importantly, preventing base-mediated side reactions was successful since unsaturated seco acids gave high yields, despite being highly sensitive to base-mediated isomerization. A notable example is macrolactone **16**, for which no isomerization was observed. This is in sharp contrast to the Yamaguchi conditions where isomerizations contributed to 50% of the mass balance.

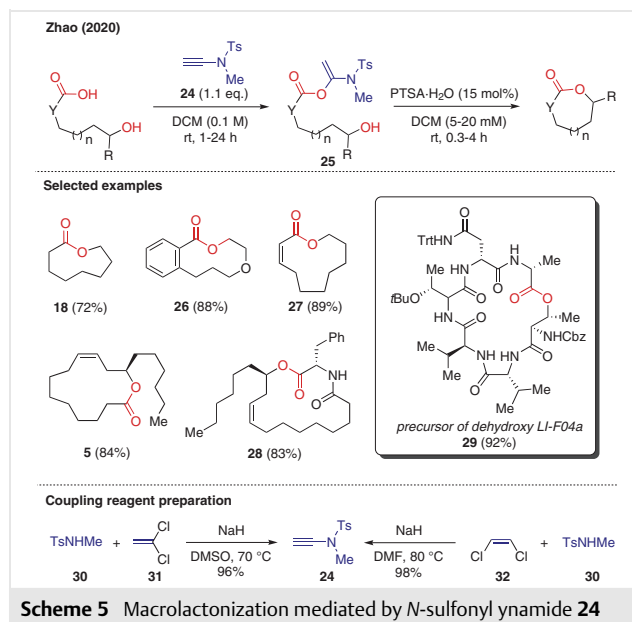
The group of Kita later succeeded in improving the overall yields by limiting macrodiolide formation, while simultaneously expanding the scope of the reaction to include previously inaccessible lactones with short chains (**18** and **19**, 9- and 11-membered rings).<sup>36</sup> This required changing the solvent for the formation of ethoxyvinyl esters (from toluene to acetone), followed by a controlled addition of the active ester to a solution of *p*-toluenesulfonic acid (*p*TsOH) in 1,2-DCE (Scheme 3, method B). Using this modified procedure, the yields ranged from 50 to 89% for 9- to 14-membered rings. Additionally, the lactone **21** bearing an epoxide functionality was obtained in 70% yield, while the Yamaguchi method performed poorly (20%).

The macrolactonization using ethoxyvinyl esters has found application in numerous total syntheses, which were discussed in detail in a recent review from the Kita group.<sup>37</sup> The most recent example was reported in 2019 by Thirupathi and Jena, who adapted this strategy for a late-stage macrolactonization for the total synthesis of (+)-sacrolide (Scheme 4). Here, cyclization of the MOM-protected precursor of sacrolide **22** proceeded in 60% yield.<sup>38</sup>



More recently, the Zhao group developed a transition-metal-free variant of this two-step coupling, employing *N*-sulfonyl ynamide **24** instead of ethoxyacetylene (**12**). After exploring the synthesis<sup>39,40</sup> and application of sulfonyl ynamides in amide/peptide and thioamide coupling,<sup>41,42</sup> they applied this approach to macrolactonization, notably in the synthesis of cyclodepsipeptides (Scheme 5).<sup>43</sup> The activation occurs via nucleophilic addition of the carboxylic acid, resulting in the formation of an  $\alpha$ -acyloxyenamide active ester **25**, which smoothly reacts with alcohols under acid-catalyzed conditions to provide the corresponding macrolactone. Of note, in some cases, CuCl must be used as a catalyst to achieve the first step. This method is mild and

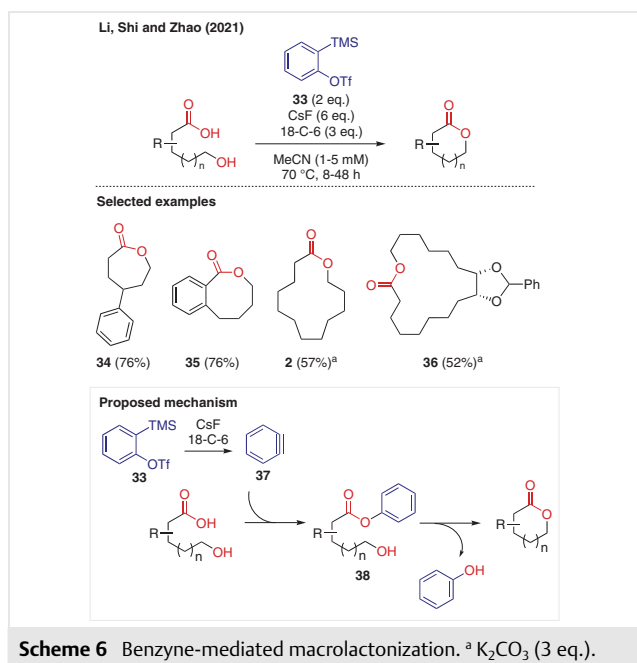
practical since both the activation and cyclization steps occur at room temperature without loss of selectivity for the macrolactone that could result from the formation of macrodiolides or higher oligomers. In all, this method stands out from most macrolactonization protocols, which generally require high temperatures. Additionally, this transformation exhibits a broad scope of macrolactones (7- to 19-membered rings) that were obtained in high yields without observing any racemization. Remarkably, even challenging medium-sized rings (8- to 11-membered rings) gave high yields. To showcase the utility of their method, the authors compared their acyloxyenamide-mediated macrocyclization with other methods for the synthesis of dehydroxy LI-F04a. The acyl-enamide-mediated cyclization occurred in 92% yield to afford **29** over two steps. In comparison, the Steglich–Boden–Keck, Yamaguchi, Corey–Nicolaou, Shiina, and Mitsunobu methods only gave yields between 6 and 52%, all accompanied by epimerization. It is worth mentioning that the possibility to prepare ring sizes larger than 19-membered rings was not evaluated.



However, we must point out that, unlike traditional approaches, *N*-sulfonyl ynamide **24** presents the disadvantage of being a rather expensive reagent. While its synthesis is straightforward and high yielding, the 1,1- and 1,2-dichloroethylene starting materials **31** and **32** are relatively expensive and have few commercial suppliers. This currently limits the broader application of this highly efficient coupling agent in macrolactonization.

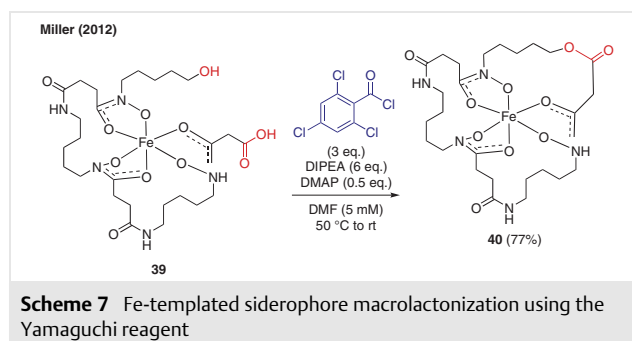
Besides the cost associated with its utilization, the use of reagent **24** leads to an additional limitation, namely the generation of by-products that must be separated from the target product. More recently, Li, Shi and Zhao reported a

method that can bypass the challenging removal of the activating group by-product by only forming phenol (Scheme 6).<sup>44</sup> They used the formation *in situ* of benzyne **37** from 1-(trifluoromethyl)-2-(trimethylsilyl)benzene (**43**), which can react with carboxylic acids to give the corresponding phenyl esters **38**. Following transesterification, macrolactones were obtained in good yields (up to 76%). Notable drawbacks for this benzyne-mediated coupling are the requirement of large excesses of the various reagents and additives for obtaining high yields, which significantly adds to the cost of this coupling method.



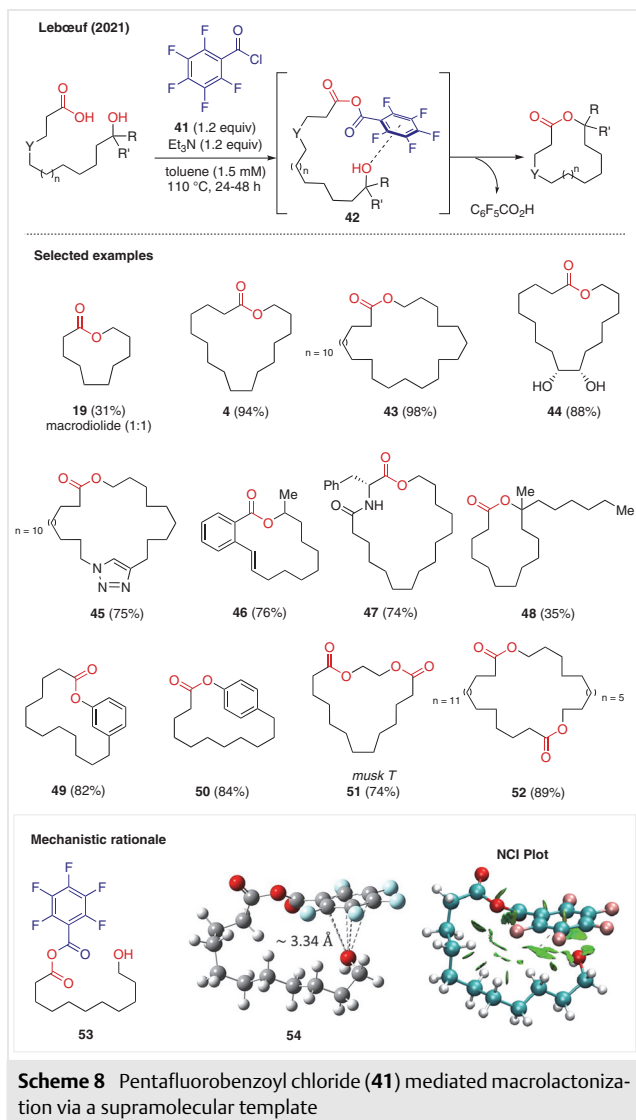
Another elegant example of direct macrolactonization is the bioinspired iron(III)-templated macrolactonization of siderophores (Scheme 7).<sup>45,46</sup> Siderophores are a class of low-molecular weight compounds that are potent Fe(III) chelators used by bacteria to accumulate iron. The natural macrocyclic analogues, which have been discovered thus far, possess an iron-binding efficiency approximately 300 times greater than linear examples. Miller and co-workers reasoned that the strong iron chelation should pre-organize the system to favor the Yamaguchi macrolactonization. Indeed, this proved highly successful since macrolactones were obtained in yields ranging from 74 to 96%. In turn, the absence of a siderophore template did not provide any cyclized product when Keck and Yamaguchi conditions were used. The removal of iron by treatment with EDTA occurred in 95% yield. However, the application is unfortunately limited as it requires specific substrates to realize the template.

In this context, the goal of our group was to combine the best aspects of the various approaches used for the activation of carboxylic acids to achieve a general method for



macrolactonizations. Based on their respective efficacy, we judged that the formation of a mixed anhydride was still the most convenient and efficient method to access macrolactones. But, in contrast to Yamaguchi, our idea was to introduce a supramolecular template to bring the reactive sites close to each other. Pentafluorobenzoyl chloride (**41**) was selected as the reagent because of its ability to create  $\pi$ -lone pair interactions in solution.<sup>47</sup> The hypothesis was that such interactions could bring both reactive sites in proximity to favor the intramolecular macrolactonization over oligomerization processes. In addition, because of the strong nucleofugality of the pentafluorobenzoate group, it was anticipated that a superior activation of the reacting carbonyl group for the cyclization step would take place. Other advantages of this approach are that pentafluorobenzoyl chloride is inexpensive and the highly water-soluble by-product, pentafluorobenzoic acid, can be easily removed by aqueous treatment, facilitating the purification of the corresponding macrolactone. Overall, this method proved particularly effective for large ring sizes (from 17- to 29-membered rings with yields up to 98%), without observing the formation of the corresponding macrodiolides (Scheme 8).<sup>48</sup> On the other hand, the proportion of macrodiolide increased with smaller ring sizes. While the yields remained high for 13- and 15-membered rings, the ratio between macrolactone and macrodiolide reached 1:1 with 10-hydroxydecanoic acid (**19**). The reaction was compatible with various functional groups, including unprotected diol (**44**), alkene, strained 1,3-butadiene and triazole (**45**). The framework of resorcylic lactones and a cyclodepsipeptide were generated in 76% and 74% yields (**46** and **47**), respectively. The method could also be applied to secondary aliphatic alcohols and carboxylic acids. Even underdeveloped tertiary aliphatic alcohols were tolerated, albeit in a moderate yield (**48**, 35%). In the same vein, it was assumed that this approach could be applied to less reactive phenol derivatives via  $\pi$ - $\pi$  interactions. Under the standard conditions, the target compounds were obtained in high yields, even arduous *meta*- and *para*-cyclophanes **49** and **50**. However, reactions with phenols proved to be slower as they required 48 hours to reach full conversion. This method is also efficient for the formation of macrodiolides. Of note, none of the

classical strategies mentioned in Scheme 1 worked for such transformations. For instance, 16- to 34-membered macrolides could be rapidly assembled in high yields (up to 89%). In addition, musk T<sup>®</sup> (**51**), a compound with major industrial applications, was generated in a single step within 48 hours in 74% yield. Importantly, the NMR spectra of the crude products did not show any traces of pentafluorobenzoic acid after a basic aqueous treatment. While the process does not require any slow addition, performing the reaction in dilute solution is mandatory to avoid a significant decrease in yield because of the formation of oligomers.



To gain insight on the role of potential non-covalent interactions in the macrolactonization, a computational analysis was performed to identify stable conformers of mixed anhydride **53**. In particular, conformer **54**, which is stabilized by  $\pi$ -lone pair interactions, was found, confirming that  $\pi$ -lp interactions can engineer the preorganization of the system. Besides, non-covalent interaction (NCI) analysis also showed  $\pi$ -lp interactions between the lone pair of the oxygen and the pentafluorophenyl group in the case of conformer **54**, which is key for the macrolactonization. Another important point is that the atomic Mulliken charges computed for the mixed anhydride incorporating a pentafluorophenyl moiety show that the reacting carbonyl has a partial positive charge ( $\delta^+ = 0.32$  |e-|), making it prone to undergo nucleophilic addition from the alcohol. All these data were in agreement with the initial hypotheses.

For their part, Feng, Dong and co-workers exploited a phenyl thioester activating group in the one-pot two-step synthesis of enantioenriched macrolactonides (Scheme 9).<sup>49</sup> In contrast to previous examples, in which the carboxylic acid was activated in the presence of the reactive alcohol nucleophile, a thiophenol was preinstalled, and the reacting phenol was initially masked in the form of *o*-quinone methide **55**. Following an enantioselective scandium(III)-catalyzed Friedel–Crafts alkylation of indolyl alkylthioester **56** with **55**, the formed seco acid **57** underwent a base-mediated ( $\text{Cs}_2\text{CO}_3/\text{DIPEA}$ ) dimerization towards the thermodynamically and kinetically favored 18-membered diolide **58**, which is favored over the macrolactonization towards a 9-membered lactone. The Friedel–Crafts reaction is nearly quantitative with an *ee* of 93%. Regarding the overall sequence, the yield is high (70%) and both the diastereoselectivity and enantioselectivity are excellent (93:7 d.r., 99% *ee*).

Feng and Dong (2021)

**55**

**56**

1)  $\text{Sc}(\text{OTf})_3/\text{L}^*$  (1:1; 5 mol%)  
DCM (0.1 M), 35 °C, 4 h

2)  $\text{Cs}_2\text{CO}_3$  (1.5 eq.)  
DIPEA (0.5 eq.)  
35 °C, 12 h

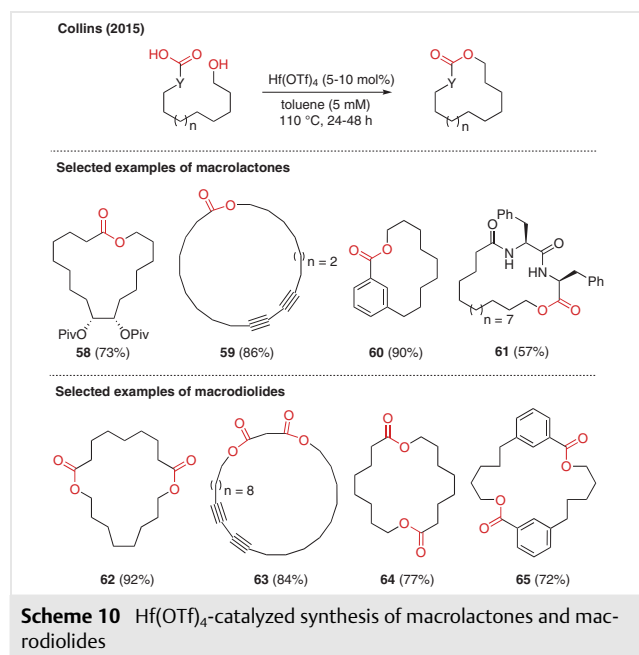
**57** (99%, 93% *ee*)

**58** (70%, 93:7 d.r., 99% *ee*)

**Scheme 9** Scandium-catalyzed enantioselective Friedel–Crafts alkylation of indoles with an *o*-quinone methide and base-mediated dimerization

### 3 Lewis Acid Catalyzed Reaction

While employing easily removable stoichiometric activating groups greatly facilitates the purification process (vide supra), Lewis acid catalyzed macrocyclizations of seco acids have the potential to significantly improve the atom economy and entirely circumvent the need for by-products separation all together, water being the only by-product formed. To this end, Collins achieved a highly efficient  $\text{Hf}(\text{OTf})_4$ -catalyzed activating-group-free macrolactonization of seco acids (Scheme 10).<sup>50,51</sup> Prior work by Mukaiyama had proven  $\text{Hf}(\text{OTf})_4$  to be an efficient catalyst for obtaining small and medium macrolactones that are generally challenging.<sup>52</sup> However, their procedure used an activated ester derived from di-2-thienyl carbonate, and was not evaluated in the direct cyclization of seco acids.



A key feature observed with this hafnium catalyst was its sufficient Lewis acidity and oxophilicity for mediating the lactonization, while being tolerant to the presence of water and not facilitating lactone hydrolysis. As a result, no specific measures for excluding water from the reaction mixture were required, and even addition of excess water had a negligible influence. A variety of seco acids with chain lengths between 13 and 26 could be cyclized in high yields, in the same range as those obtained when using stoichiometric activating groups. The presence of esters, alkenes, alkynes, and amides along the seco acid chain was tolerated, as demonstrated by the synthesis of macrolides **58** and **59**, as well as depsipeptide **61**. However, the reaction performed poorly in the presence of secondary aliphatic alcohols and the reactivity of tertiary alcohols nor phenols was mentioned. In another vein, identical conditions were suc-

cessfully adapted to the preparation of macrodiolides from the reaction of diols with diacids, and from seco acids, by slightly changing the catalyst loading (5 to 10 mol%).<sup>51</sup>

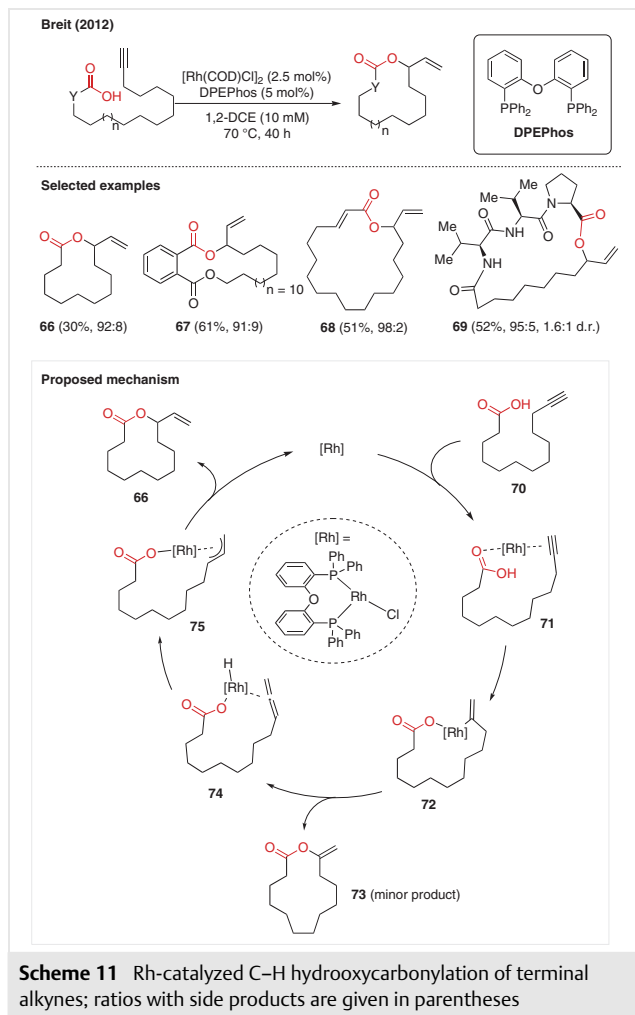
### 4 C–H Activation

While the cyclization of seco acids remains the most explored pathway for preparing macrolactones, this strategy suffers from several drawbacks, such as the need for highly dilute conditions or slow addition protocols to prevent dimerization and oligomerization. To these issues should also be added the limited availability of seco acid starting materials that often require multistep syntheses with additional protection and deprotection steps, and the generation of stoichiometric by-products which may not be easily separable from the target product. In this context, transition-metal-catalyzed C–H activation strategies not only improve the step efficiency, but also minimize the amount of by-products generated during the macrolactonization,<sup>53</sup> making them an attractive alternative to the use of the stoichiometric activating agents discussed above.

In 2012, the Breit group developed a macrolactonization procedure via Rh-catalyzed C–H hydroxycarbonylation of terminal alkynes towards cyclic branched allyl esters (Scheme 11),<sup>54</sup> which relied on prior findings on intermolecular processes.<sup>55</sup> This Rh-catalyzed reaction is redox-neutral as the alkyne acts as an internal oxidant. Consequently, it is an atom-economic alternative to the seminal work by the group of White on Pd(II)-catalyzed allylic C–H oxidation using stoichiometric amounts of benzoquinone.<sup>56</sup> The mechanism follows a carboxylate-directed, Markovnikov-selective hydrometalation of the alkyne to give complex **72**. Extensive mechanistic studies, including DFT computations, support that this oxidative addition is initiated by an intramolecular proton transfer from the carboxylic acid to the  $\text{C}_{\text{sp}}$  carbon in complex **71**.<sup>57</sup> Next,  $\beta$ -hydride elimination from **72** would lead to a terminal allene coordinated to Rh-hydride species **74**. Subsequent hydrometalation of the allene towards an  $\eta^3$ -allyl complex **75** and reductive elimination would finally yield the allyl ester **66**, simultaneously regenerating the Rh active species. It should be noted that reductive elimination can occur from **72** as an off-cycle process to give the carboxylate Markovnikov adduct **73**. This exocyclic enol lactone is observed as a minor product in ratios varying between 2:98 and 20:80 with respect to the allyl esters.

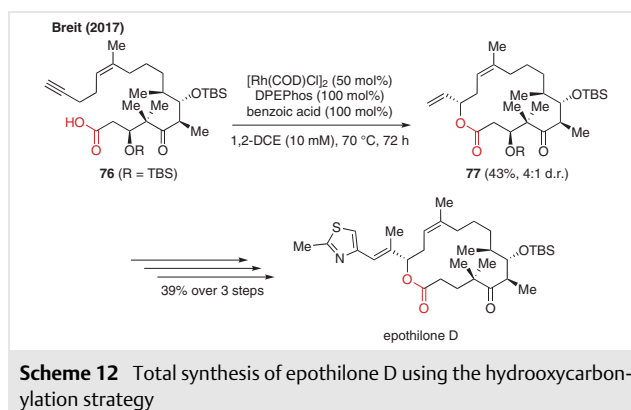
Overall, the yields of the allyl lactone range from 55 to 74% for 14- to 23-membered rings. However, the more challenging 12-membered macrolactone **66** could only be obtained in 30% yield. The main side products included exocyclic enol lactone **73** and a macrodiolide. In general, the selectivity for allyl versus enol product exceeds a 95:5 ratio and the amount of macrodiolide is negligible. In contrast to

the classic coupling conditions, isomerization of unsaturated carboxylic acids/esters was not observed, as exemplified by macrolactone **68**.



Furthermore, the utility of this cyclization was demonstrated in the synthesis of depsipeptide **69** in 52% yield, and in the total synthesis of epothilone D (Scheme 12).<sup>58</sup> In the latter, the allyl functionality in **77** could be introduced stereoselectively under substrate control (4:1 d.r.), and was used as a synthetic handle to introduce the thiazolyl-olefin moiety through a Tsuji–Wacker oxidation to the ketone followed by a Wittig olefination.

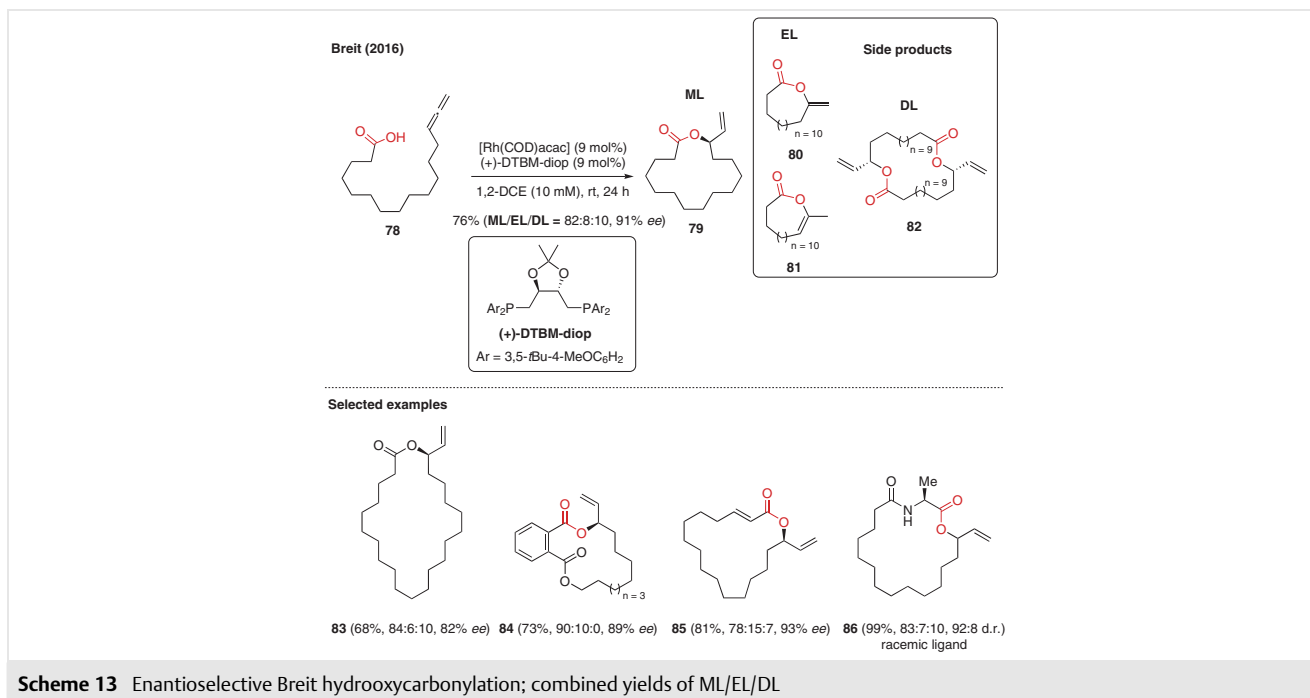
However, limiting factors for a broader application of this method in the total synthesis of natural products were the absence of an asymmetric version and the difficulty in controlling the diastereoselectivity of the process. Therefore, the next challenge tackled by the Breit group was the development of an asymmetric variant of this reaction (Scheme 13).<sup>59</sup> In this case, more reactive terminal allenes were used in the Rh-catalyzed lactonization in place of



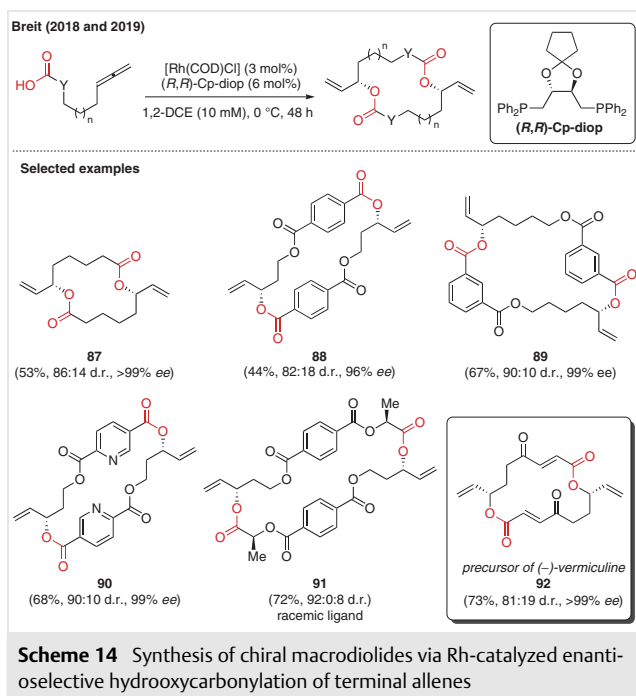
alkynes, as the authors anticipated a better control over the stereoselectivity. Regarding the macrolactonization, the choice of rhodium catalyst precursor was critical for the success of the reaction. The use of  $[\text{Rh}(\text{COD})\text{Cl}]_2$  resulted in the formation of a macrodiolide along with endo/exocyclic enol formation, while the use of  $[\text{Rh}(\text{COD})\text{acac}]$  favored the macrolide formation. Among the various ligands screened, diop-type ligands were found to be the most efficient for the catalytic activity. In particular, the combination  $[\text{Rh}(\text{COD})\text{acac}]/\text{DTBM-diop}$  at room temperature proved optimal. The vinyl lactones were isolated in comparable yields to those of the previous work (50–80%) with *ee* values of 73–93%. Nevertheless, all products were isolated as mixtures with endo- and exocyclic enol lactones as well as macrodiolides (16–26% yields). As before, no isomerization of unsaturated carboxylic acids/esters was observed. Additionally, diastereomeric depsipeptide **86** could be prepared with a good d.r. of 92:8 and a 99% overall yield.

Furthermore, the hydroxycarbonylation of terminal alkenes was adapted to the enantioselective synthesis of macrodiolides with equal success after turning back to  $[\text{Rh}(\text{COD})\text{Cl}]_2$  and using a Cp-diop ligand at 0 °C (Scheme 14).<sup>60</sup> Overall, the dimerization products could be obtained in yields ranging from 42 to 73%, with high *ee* values (92 to 99%) and with high control of the diastereoselectivity (90:10 to 80:20 d.r.). The reaction was also applied to terephthalic- and isoterephthalic-containing substrates to give products **88** and **89**. Replacing the phenyl ring by a coordinating heteroaromatic cycle had no impact on the reactivity either (**90**). Remarkably, in the case of a substrate possessing a chiral center, complete control of the diastereoselectivity was observed in the formed product **91**. To illustrate the potential of this method, the asymmetric dimerization was applied to the synthesis of the vermiculine precursor **92** (81:19 d.r. (*syn/anti*) and >99% *ee*).<sup>61</sup> This total synthesis was efficiently achieved in 7 steps with a 20% overall yield.

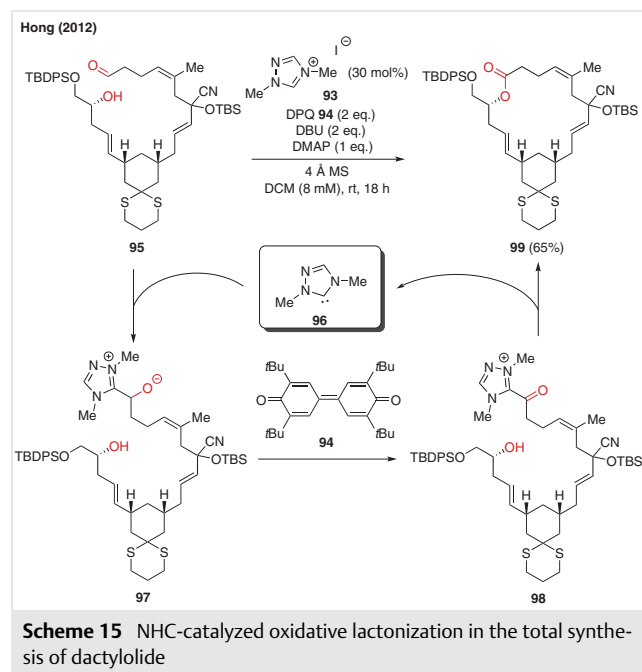
In a different approach, dactylolide<sup>62</sup> was prepared by Hong and co-workers using an efficient 1,2,4-triazolium *N*-heterocyclic carbene (NHC)-catalyzed oxidative lactonization of aldehydes,<sup>63</sup> which was inspired by previous work



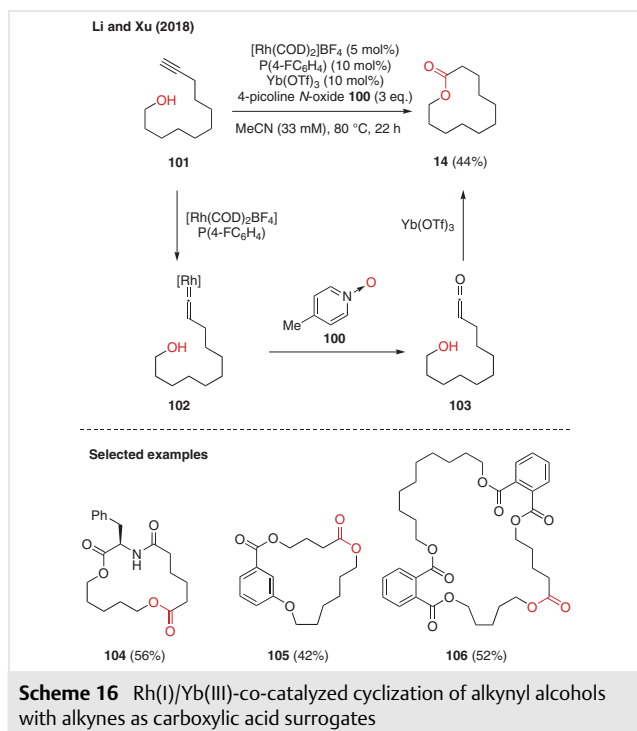
on NHC-catalyzed oxidative esterification of aldehydes (Scheme 15).<sup>64,65</sup> The authors took this initiative in response to the low yields reported for previous syntheses of this molecule using classical macrolactonization conditions.<sup>66,67</sup> The aldehyde C–H activation occurs via formation of



Breslow intermediate **97**, which can be oxidized to acyl heterazolium ion **98** using a mild oxidant such as 3,3',5,5'-*tert*-butyl diphenylquinone (DPQ) (**94**). This acyl heterazolium ion **98** is a strong electrophile that smoothly undergoes lactonization. The cyclization towards the 18-membered dactylole precursor **99** proceeded in 65% yield.



In 2018, Li, Xu and co-workers reported another method involving the use of an alkyne as a surrogate for the carboxylic moiety (Scheme 16).<sup>68</sup> Compared to other strategies, this synthesis bypasses the tedious preparation of the key carboxylic acid precursor, notably regarding protection/deprotection steps. They proposed an oxidative macrolactonization of alkynyl alcohol **101** via cooperative catalysis between a transition metal (Rh(I)) and a Lewis acid (Yb(III)). This reaction relies on the formation of rhodium vinylidene **102** and its subsequent oxygenation into ketene **103** via the use of picoline *N*-oxide **100**, a mechanism that was supported by deuterium-labelling experiments. Here, the role of the Lewis acid is to harness the electrophilicity of the ketene intermediate to favor the addition of the alcohol, thus delivering the corresponding macrolactones. Of note, neither slow addition nor high dilution ( $c = 33$  mM) were required. This method allows access to 12- to 33-membered rings in yields not exceeding 72%.



In 2022, the Gnanaprakasam group pushed the boundaries for minimal by-product formation through a cross-dehydrogenative coupling of diphenyldimethanols using a ruthenium(II)-PNP-type pincer catalyst (Ru-MACHO) (Scheme 17). Here, only  $H_2$  is generated as a by-product.<sup>69</sup> The authors proposed the following reaction mechanism: First, the Ru-MACHO pre-catalyst is deprotonated by  $CS_2CO_3$  to form the catalytically active species **116**, to which the alcohol coordinates.  $\beta$ -Hydride elimination results in the formation of monoaldehyde intermediate **119** and Ru-H species **120**. The corresponding hemiaminal **121** would then

coordinate to the active Ru-catalyst **116** and a subsequent  $\beta$ -hydride elimination would deliver macrolactone **107**. Meanwhile, reductive elimination from **120** would regenerate the active catalyst. This mechanism was supported by isolation of monoaldehyde **119**, and detection of hemiaminal-Ru complex **122** by HMRS. In general, the yields for the macrolactonization ranged between 30 and 80%, the major side products being attributed to decarbonylation and macrolactone formation. Interestingly, when using a substrate with both a benzyl alcohol and a  $\beta$ -phenylethanol unit, the latter was oxidized in preference to the more reactive benzylic alcohol to give product **112**, which can be explained by a lower steric hindrance. Importantly, the reaction could also be extended to diphenylethanols to provide, for example, compound **113** in 58% yield. The authors stated that the yield obtained for macrolactones depends predominantly on three factors. First, sufficiently high dilution is required, and within the tested concentration range, product yields continued to increase with higher dilution. Second, the spacer length is critical for the macrolactonization, with ring sizes between 12 and 16 seeming ideal for *ortho*-substituted diphenyldimethanols. Regarding *meta*-substituted derivatives, ring sizes larger than 15 all worked smoothly (**114** and **115**). Third, the substituents on the phenyl seem to have an influence on the reactivity, although only methoxy and bromo substituents were mentioned.

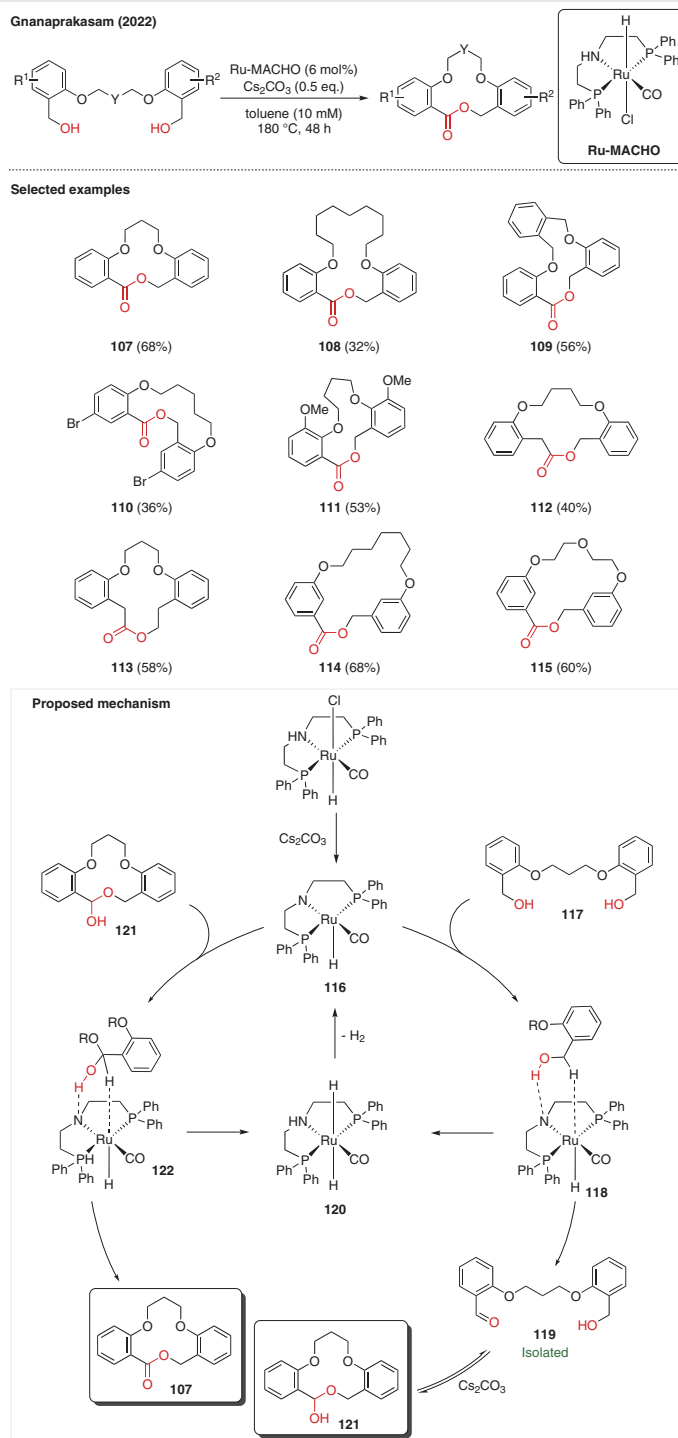
## 5 Ring-Expansion Strategy

All the previously described macrolactonizations involved an end-to-end macrocyclization step, which generally requires high temperatures and high dilution to prevent competitive reactions. This results in low sustainability, practicality and scalability for these methods. Additionally, when end-to-end cyclizations are used, a *de novo* synthesis of fully functionalized acyclic starting materials is typically required. Since these cyclizations are sensitive to subtle structural and conformational variation of the precursors, the chemical space that can be explored is drastically restricted. Remarkably, ring-expansion approaches ingeniously circumvent several of the issues associated with long-chain end-to-end macrolactonization by combining an existing cycle to a linear fragment that can readily form a small fused ring. In a subsequent step, a simple rearrangement can lead to a larger ring-expanded cycle.<sup>70–74</sup> In most cases, none of these transformations necessitate highly dilute conditions.

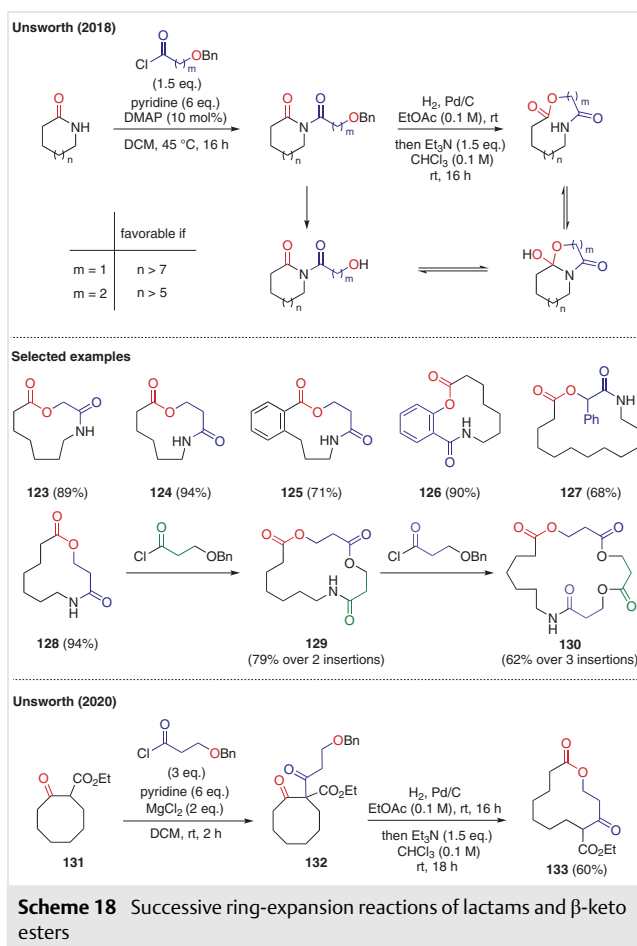
Following seminal strategies by Shemyakin and co-workers,<sup>75</sup> the Unsworth group pioneered the development of a specific class of ring-expansion strategy that they have coined as successive ring expansions of lactams and  $\beta$ -keto esters (Scheme 18).<sup>76–78</sup> This is a multistep procedure allowing hydroxy acid side-chain insertion reactions in lactams and cyclic keto esters, using  $\alpha$ - and  $\beta$ -benzyloxy acyl

chlorides (glycolic and hydracrylic acid derivatives). The first step involves the acylation of the lactam or keto ester to generate the corresponding imide or tricarbonyl, while the second step entails hydrogenolysis of the benzyl group.

In the case of the isomerization of an imide into a cyclol, ring-opening reactions are less favorable and a third reaction step—treatment with  $\text{Et}_3\text{N}$  in chloroform—is thus required.<sup>77</sup>



**Scheme 17** Ru-MACHO-catalyzed cross-dehydrogenative coupling of diphenyldimethanols



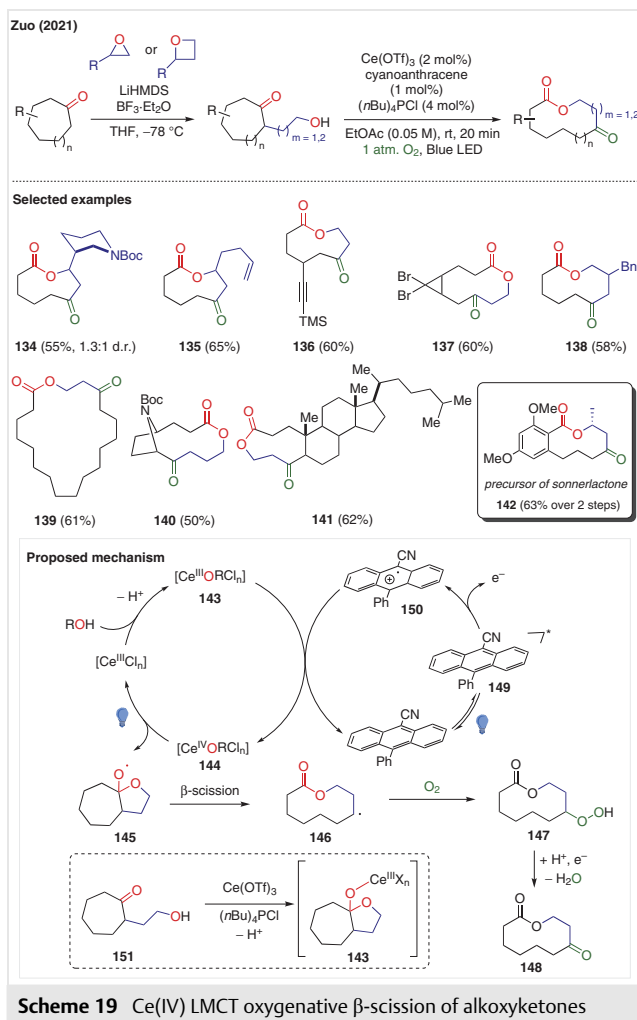
Based on the relative stability of the isomeric imides/cyclols/lactones and tricarbonyl/cyclols/lactones, which were determined by DFT calculations, and the observed reaction outcome, the authors propose that the insertion takes place under thermodynamic control, favorably unfolding as long as the ring-expanded isomer is lowest in energy by 3 kcal/mol.<sup>77,78</sup> This explains why the insertion of glycolic acid derivatives ( $m = 1$ ) does not occur for 4- to 7-membered lactams, since the resulting medium-sized lactones suffer from high ring and transannular strain. However, in the case of 8- to 12-membered lactams, the insertion of glycolic acid proceeded smoothly, affording products in yields of 83–89%, as the ring and transannular strain in the lactam is relieved. With respect to hydracrylic acid derivatives ( $m = 2$ ), the insertion in lactams occurred smoothly for ring sizes  $\geq 6$  (Scheme 18). Interestingly, the successive ring-expansion reaction was successively applied to the same substrate, in most cases without significant loss of efficiency, enabling the synthesis of second- and third-generation side-chain-inserted macrolactones.

In turn, in the case of hydracrylic acid derived tricarbonyls, the isomerization and ring opening were favorable for all tested ring sizes ( $\geq 5$ ) since the lactones were at least 9

kcal/mol more stable. For instance, macrolactone **133** was obtained in a good yield (60%) (Scheme 18).<sup>78</sup>

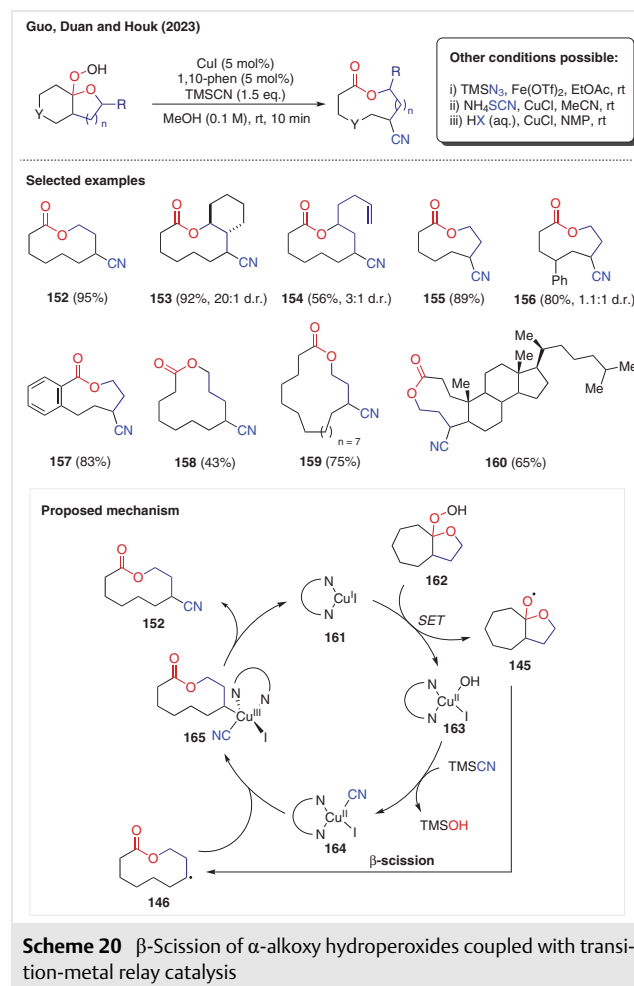
Another class of ring-expansion reactions relies on the  $\beta$ -scission of alkoxy radicals derived from lactol (a cyclic hemiketal) or their derived  $\alpha$ -alkoxy hydroperoxides.<sup>79</sup> Seminal studies in this field date back to the 1980s, when the groups of Schreiber, Suginome, and Suarez performed these ring expansions using stoichiometric  $\text{FeSO}_4/\text{Cu}(\text{OAc})_2$ ,<sup>80</sup>  $\text{HgO}/\text{I}_2$ ,<sup>81</sup> and  $\text{PhI}(\text{OAc})_2/\text{I}_2$ .<sup>82</sup> While this ring-expansion strategy has found some applications in the total synthesis of macrocyclic lactones such as (+)-*cis*-lauthisan,<sup>83</sup> modern variants were only recently developed, aiming to avoid the use of stoichiometric oxidants and highly toxic metals to provide more sustainable approaches.

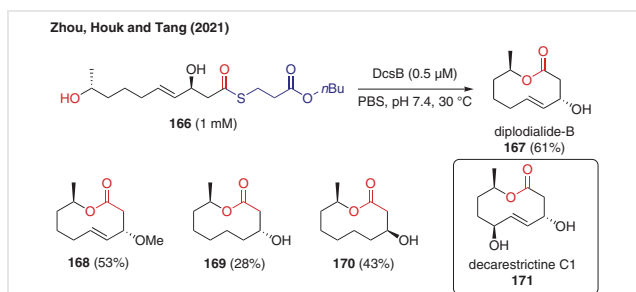
Thus, in parallel to the work of the group of Unsworth, the Zuo group developed an aerobic  $\text{Ce}(\text{OTf})_3/9$ -phenyl-10-anthronitrile photocatalytic oxidative ring expansion of alkoxyketones (or cyclic hemiketals) under blue LED irradiation (Scheme 19),<sup>84</sup> building on previous work using a light-to-metal charge transfer (LMCT) excitation of  $\text{Ce}(\text{IV})$  complexes in the  $\beta$ -scission of C–H and C–C bonds of alcohols, aldehydes and carboxylic acids.<sup>85</sup> Here, this  $\text{Ce}(\text{IV})$  LMCT  $\beta$ -scission was used to generate macrolactones directly from alkoxyketones via tautomerization to a lactol followed by C–C bond cleavage. The alkoxyketone starting materials for this ring expansion are easily accessible by LiHMDS-mediated alkylation of cyclic ketones with oxiranes and oxetanes. The authors proposed the following dual catalytic cycle: First, the formation of a lactol would be favored in the presence of a  $\text{Ce}(\text{III})$  Lewis acid, which would lead to  $\text{Ce}(\text{III})$ -lactol complex **143**. Upon oxidation by anthracene radical cation **150**,  $\text{Ce}(\text{IV})$  species **144** would be obtained. Subsequent photoexcitation of **144** would produce an O-centered radical **145** that would undergo  $\beta$ -scission. The alkyl radical **146** formed would then be trapped by oxygen to generate a peroxy radical **147**. Quenching of this radical by the photoexcited cyanoanthracene **149** would lead to the formation of ketolactone **148** and radical cation **150**. There are several advantages to this methodology. First, full conversion occurs within only 20 minutes of irradiation by virtue of the cyanoanthracene co-photocatalyst enabling the cerium turnover. Second, the need for harsh oxidants is avoided, significantly increasing the substrate tolerance for this reaction. To demonstrate the versatility of this reaction, the authors prepared over 100 macrolactones in yields ranging from 37 to 81%. This included ring sizes ranging from 9- to 19-membered rings, possessing Boc-amines (**134** and **140**), alkenes (**135**), alkynes (**136**), cyclopropanes (**137**) or sulfones. Additionally, this methodology was applied to the 4-step total synthesis of (3*R*,5*S*)-sonnerlactone. The alkylation and photocatalytic oxidative ring expansion gave **142** in 63% yield (over two steps), after which an  $\text{AlCl}_3$ -mediated demethylation and asymmetric transfer hydrogenation were performed to obtain sonnerlactone in a 35% overall yield.



The main drawback associated with this method is the inability of introducing functionality other than ketones on the carbon radical formed after the ring expansion. Guo, Duan, Houk and co-workers recognized this issue as an opportunity,<sup>86</sup> and combined the  $\beta$ -scission of  $\alpha$ -alkoxy hydroperoxides, developed by Schreiber, with iron- and copper-catalyzed radical relay catalysis.<sup>87,88</sup> In this manner, they were able to develop four sets of conditions for introducing nitrile, azide, thiocyanate, and halides using TMSCN, TMSN<sub>3</sub>, NH<sub>4</sub>SCN, and hydrohalic acids on the ring-expanded products (Scheme 20). The reaction mechanism for the Cu-catalyzed introduction of cyanide was studied by DFT and supported by radical inhibition and trapping experiments, as well as by HRMS detection of several reactive intermediates. First, oxidation of Cu(I) species **161** by the hemiketal peroxide **162** would generate Cu(II) hydroxide **163** and alkoxy radical **145** that can undergo  $\beta$ -scission to give

**146**. The latter was trapped by TEMPO and diphenyl ethylene. Ligand exchange with TMSCN on the Cu(II) hydroxide species **163** would generate copper complex **164** that can undergo oxidative addition with alkyl radical **146** towards **165**. Finally, reductive elimination would give the macrocyclic lactone carbonitrile **152** while regenerating Cu(I) active catalyst **161**. With the exception of Cu(III) intermediate **165**, all the proposed Cu species were detected by HRMS. Naturally, regarding the other three reaction conditions (i–iii), a different mechanistic pathway might be followed, without involving the intermediacy of Cu(III). For instance, a direct coupling between radical **146** and the ligand of **164** could be envisioned, Cu(I) being regenerated by accepting one electron via an outer-sphere mechanism. Using these mild conditions, a broad variety of macrocyclic lactones with sizes ranging from 10- to 19-membered rings could be assembled in high yields (40–98%) with concomitant introduction of nitrile, azide, thiocyanate, and halide functionalities.



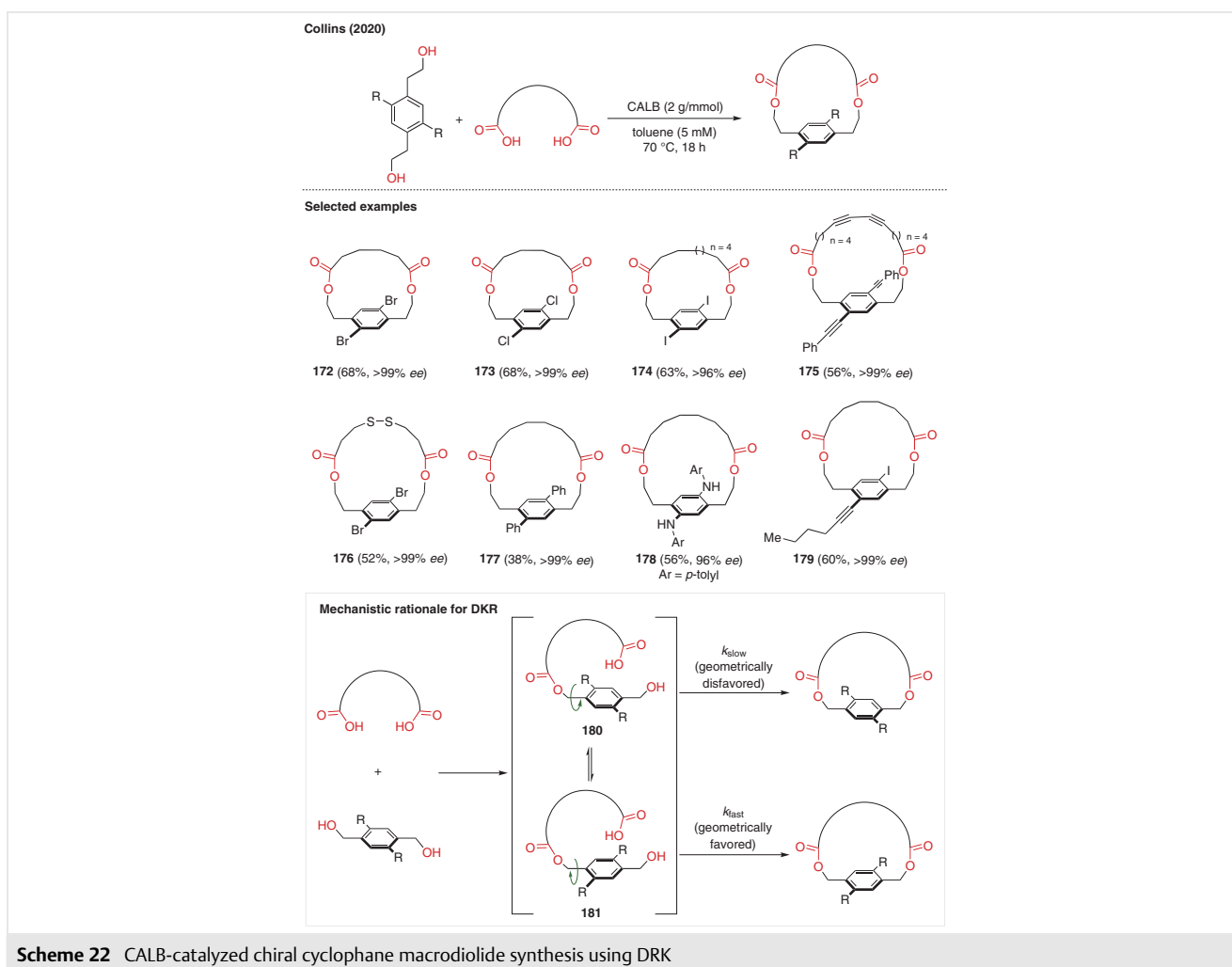


**Scheme 21** Macrolactonization of thioesters catalyzed by the thioesterase enzyme DcsB; PBS = phosphate buffer saline

## 6 Chemoenzymatic Synthesis

With the emergence of chemoenzymatic synthesis, a thioesterase enzyme (DcsB), which can promote the formation of medium-sized rings and macrocycles (up to a 13-membered ring), was identified by Zhou, Houk, Tang and

co-workers while elucidating the synthesis of decarestrictine C1 from *Beauveria bassiana* ARSEF 2860 (Scheme 21).<sup>89</sup> Since decarestrictine C1 is derived from a polyketide, the authors expected the lactonization to occur from the polyketide bound to the acyl carrier unit of polyketide synthase. To transpose this biosynthetic macrolactonization to broader synthetic applications, the ACP-polyketide was structurally simplified towards more simple acyl thioester analogues, which were meant to resemble the ACP-tethered acyclic precursor. In the DcsB-catalyzed macrolactonization, a positive trend between the lipophilicity of the acyl thioesters and the yield of the macrolactone diploidalide-B was observed. Using the most promising acyl thioester, which was derived from butyl 3-mercaptopropanoate, macrolactonizations were performed for both modified polyketide substrates and short-chain seco acids, which are generally challenging substrates. Given that even these simple seco acids could be cyclized in yields ranging from 49 to 82%, the thioesterase enzyme DcsB clearly holds significant potential in the chemoenzymatic preparation of lactones.



Recently, the Collins group also developed an elegant chemoenzymatic synthesis of planar chiral cyclophane macrodiolides using simple aliphatic diacids or diesters and dialcohols,<sup>90</sup> taking inspiration from biocatalytic dynamic kinetic resolution (DKR), which combines a transition-metal complex that catalyzes substrate racemization with an enzyme that selectively acylates a single enantiomer.<sup>91</sup> To achieve their goal, they selected the commercially available lipase enzyme serine hydrolase *Candida antarctica* lipase B (CALB) since it possesses both a high thermal stability and a proven track-record in the DKR of secondary alcohols with high enantioinduction.<sup>92</sup> In contrast to classical DKRs, the ester precursor is achiral, and free rotation of the aromatic ring allows interconversion between the two acyclic monoester intermediates **180** and **181** that give macrolactones with opposite planar chirality (Scheme 22).

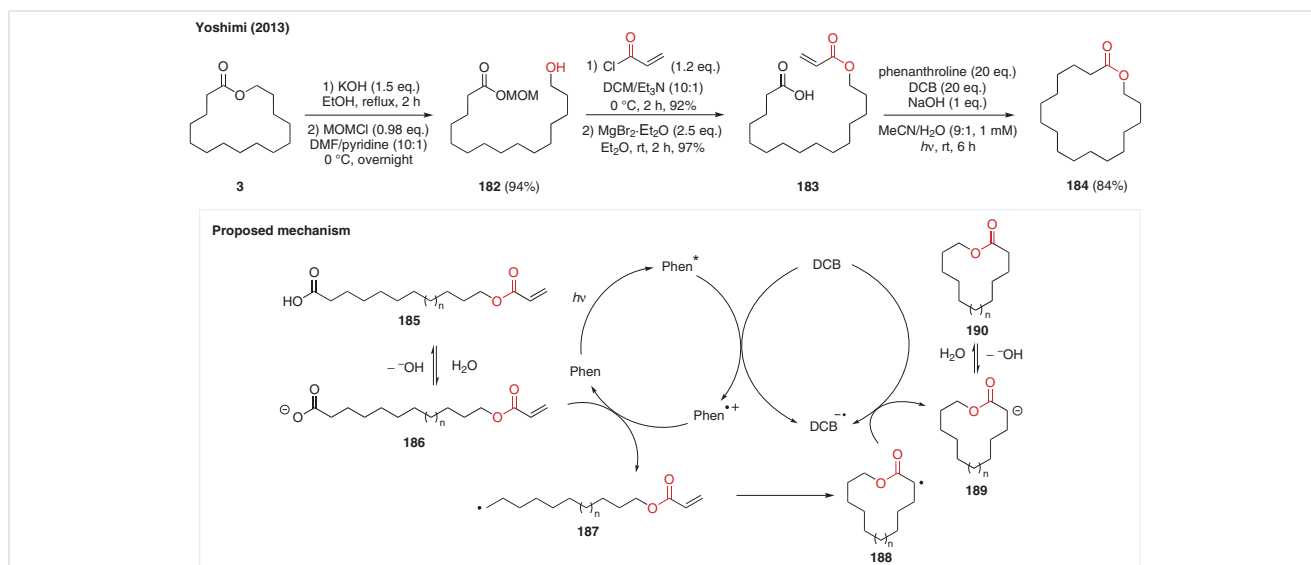
First, the catalytic competence of CALB was evaluated in the diolide synthesis from 1,4-phenylenedimethanol and nonanedioic acid, giving the corresponding achiral cyclophane in a moderate yield (Scheme 22). However, this could not be successfully extended to substituted 1,4-phenylenedimethanols, which gave low yields along with a low barrier to thermal racemization. On the other hand, transposing the reaction to 2,2'-(1,4-phenylene)bisethanol substrates with diacids proved successful, delivering the corresponding cyclophanes in high yields (up to 88%) and excellent enantioselectivities (>95%). A broad variety of arene substituents were tolerated, including halide, aryl, alkynyl and aniline substituents, delivering products **172–179**. In the alkyl linker, 1,3-butadiyne (**175**) and disulfide (**176**) moieties could be introduced. Docking studies gave clear insights into the origin of the enantioselectivity, since only the major product and its monoester were appropriately

oriented with the carboxylic acid near the catalytic serine, making only their cyclization geometrically favorable.

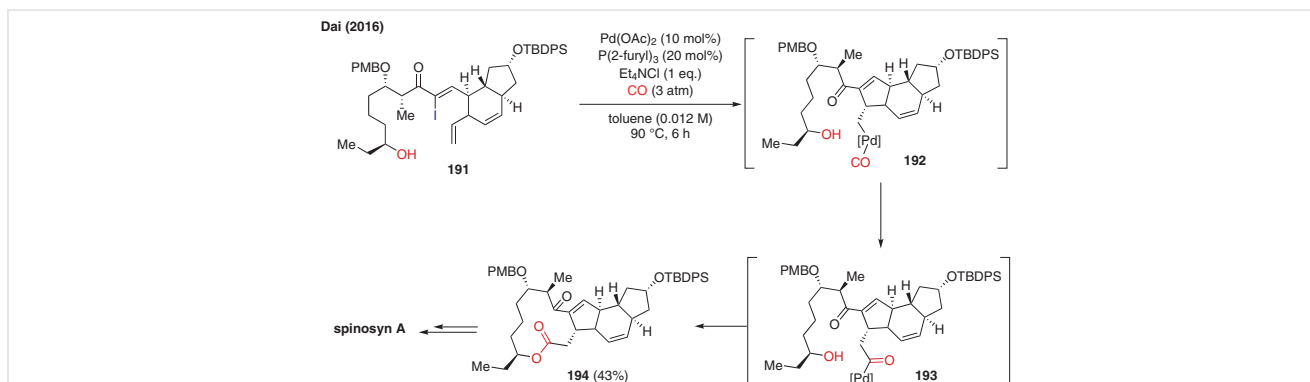
## 7 Other Macrolactonization Variants

In the past decade, other alternative strategies have emerged to construct macrolactones using less conventional tactics. As an example, Yoshimi and co-workers developed a ring-closing macrolactonization via a decarboxylative intramolecular photoinduced electron transfer (PET) reaction of carboxylic acid tethered acrylate ester (Scheme 23).<sup>93,94</sup> This reaction sequence is formally a ring expansion as it starts with the hydrolysis of macrolactone **3** to form the corresponding seco acid, which is then protected with methoxymethyl chloride (MOMCl) to give **182**. After reaction with acryloyl chloride and deprotection of the MOM group to give **183**, the head-to-tail radical macrolactonization is performed. This intramolecular cyclization was based on their previous work involving the intermolecular reaction of electron-deficient alkenes with carboxylate-derived alkyl radicals, which was achieved by using a high-pressure mercury lamp and phenanthroline as a photocatalyst in combination with *p*-dicyanobenzene (DCB) as an electron acceptor.<sup>95</sup>

The authors proposed the following mechanism: Upon excitation of phenanthroline, electron transfer to DCB generates a phenanthroline radical cation, which is a sufficiently strong oxidant to trigger decarboxylation of primary alkyl carboxylates. This single-electron transfer (SET) process results in the formation of a primary alkyl radical **187**, with concomitant regeneration of phenanthroline. Following alkyl radical addition to the acrylate, the formed radical



**Scheme 23** The reaction sequence for the ring expansion of macrolactones involving decarboxylative intramolecular photoinduced electron transfer (PET)



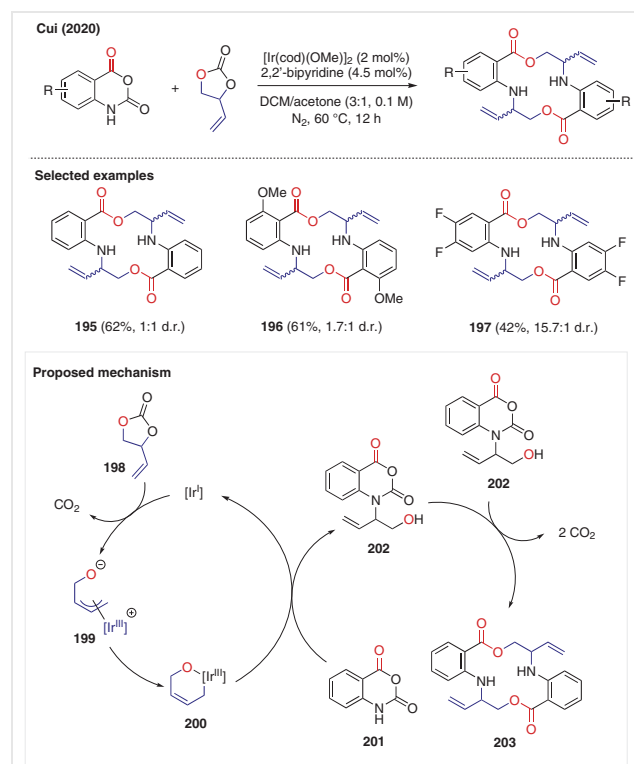
**Scheme 24** Palladium-catalyzed carbonylative Heck macrolactonization as a key step in the total synthesis of spinosyn A

**188** is reduced via SET from the DCB radical anion. Finally, protonation delivers product **190** (Scheme 23). Here, one of the issues is the use of superstoichiometric amounts of promoters, which limits the appeal of the method, especially on large scale.

The Dai group developed a spinosyn A total synthesis using a palladium-catalyzed carbonylative Heck macrolactonization (Scheme 24).<sup>96</sup> Interestingly, carbopalladation in **191** precedes CO insertion due to preorganization of the vinyl iodide and alkene, contrary to what would be expected for an intermolecular carbonylative Heck reaction. One can appreciate how the 5-membered ring and the 12-membered macrolactone are both elegantly introduced in a single step to give the product in 43% yield as a single diastereomer.

In 2020, Cui and co-workers developed a synthesis of benzo-fused 14-membered aza-macrodilides via an iridium-catalyzed reaction of vinyl ethylene carbonate **198** with isatoic anhydrides (Scheme 25).<sup>97</sup> Vinyl ethylene carbonates (VECs) can undergo transition-metal-catalyzed decarboxylation to serve as dipole precursors for the formation of zwitterionic  $\pi$ -allyl metal intermediates. As such, they have been applied in a variety of Pd-catalyzed annulation reactions for the construction of a large variety of heterocycles via allylic substitutions and formal cycloadditions.<sup>98</sup> Here, a decarboxylative allyl-amination/macrolactonization cascade was investigated. In the proposed mechanism, the authors suggest that the reaction is initiated by a decarboxylative oxidative addition of vinyl ethylene carbonate (**198**) to Ir<sup>I</sup>, generating a zwitterionic  $\pi$ -allyl Ir<sup>III</sup> intermediate **199**. This intermediate would then tautomerize into the highly electrophilic iridacycle **200** by analogy with palladium-catalyzed reactions. Nucleophilic addition of the nitrogen of isatoic anhydride **201** would give a branched allylic alcohol **202** intermediate and regenerate the Ir<sup>I</sup> catalyst. Finally, the allylic alcohol intermediate **202** would dimerize via an intermolecular transesterification with a concomitant decarboxylation to deliver macrodilide **203**. This mechanism was supported by two control experiments. First, the reac-

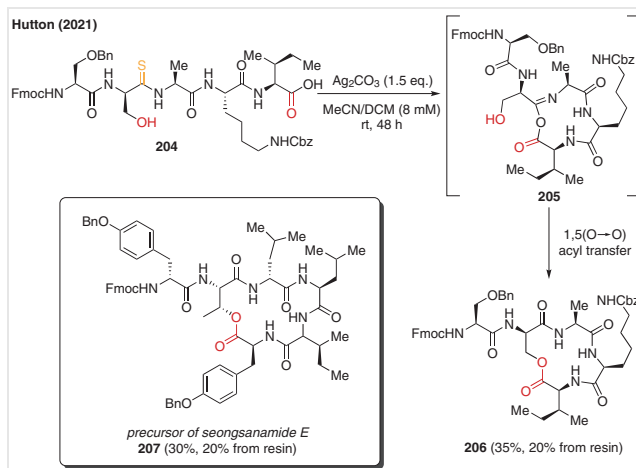
tion of *N*-methylisatoic anhydride gave no conversion. Second, the reaction of 3,4-dihydro-(1*H*)-quinolin-2-one provided the branched allylic alcohol. During their investigations of the reaction scope, the presence of both electron-donating and electron-withdrawing substituents on the isatoic anhydride phenyl ring were well-tolerated, delivering the corresponding macrolactones in yields ranging from 36 to 66%. However, no control of the diastereoselectivity was observed. This issue was later tackled during the development of an asymmetric variant of this reaction by Wang,



**Scheme 25** Iridium-catalyzed hydroxyallylation of vinyl ethylene carbonate (**198**) with isatoic anhydrides and decarboxylative dimerization

Dong and co-workers<sup>99</sup> using an Ir complex with a chiral phosphoramidite and dibenzo[*a,e*]cyclooctene ligand in combination with Et<sub>3</sub>N in DCM, furnishing all the products in yields practically identical to the racemic variant, but with diastereomeric ratios superior to 20:1 and *ee* values greater than 99%.

The Hutton group investigated a unique cascade for the synthesis of a depsipeptide, relying on their previous report on the epimerization-free synthesis of imides via a Ag(I)-promoted reaction of amino acids or C-terminal peptides with thioamides (Scheme 26).<sup>100,101</sup> Here, silver plays a dual role in the imide formation, acting both as a base and a thiophilic sulfide-sequestering agent. When using this reaction for the macrocyclization of N-terminally unprotected peptides, a subsequent 1,4(O→N) acyl transfer from a cyclic isoimide intermediate was observed.<sup>101</sup> In the case of macrolactonization, this cascade process was rationally implemented by using N-terminally protected serine- or threonine-derived thioamide peptides such as **204**.<sup>102</sup> In this way, silver-promoted intramolecular coupling affords cyclic isoimide intermediate **205**, which then smoothly undergoes an intramolecular 1,5(O→O) acyl transfer with the serine/threonine side chain OH. It is noteworthy that protection or functionalization of the serine/threonine N-terminus with one additional residue was required to prevent competitive 1,4(O→N) acyl transfer. This macrolactonization was applied in the synthesis of a variety of depsipeptides, notably seongsanamide E.



**Scheme 26** Macrolactonization by Ag(I)-promoted reactions of peptides with thioamides

## 8 Conclusion and Outlook

Over the last decades, significant progress has been made in the development of creative and efficient macrolactonization protocols, including catalytic and enantioselective versions. They are increasingly versatile, tolerating more and more functional groups. Overall, these methods

are often complementary, enabling access to various ring sizes depending on the approach chosen. However, a major hurdle remains to be overcome, namely the issue of the high dilution that limits the appeal of most of these methods. Ring expansion represents a solution, but it usually leads to highly specific scaffolds. In this context, it is noteworthy that examples featuring modern technologies such as flow chemistry, photocatalysis and electrochemistry are still rare, but which may represent interesting pathways to follow to solve this challenge in the near future.

## Conflict of Interest

The authors declare no conflict of interest.

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