

Asymmetric Catalysis

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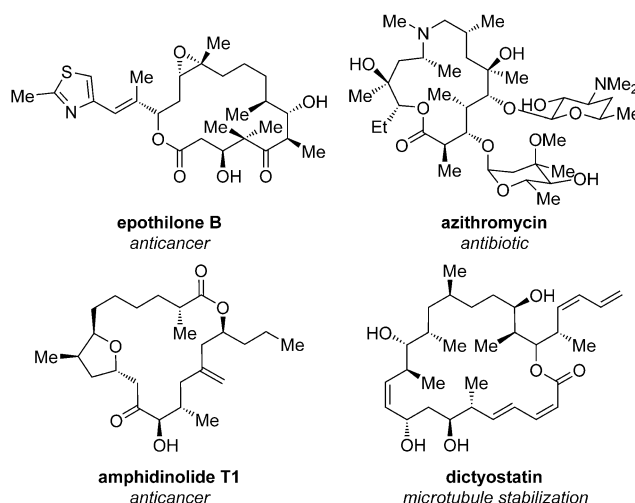
Enantioselective Rhodium-Catalyzed Atom-Economical Macrolactonization

Stephanie Ganss and Bernhard Breit*

Abstract: A highly attractive route toward macrolactones, which form the cyclic scaffold of a multitude of diverse natural compounds, is described. Although many chemical approaches to this structural motif have been explored, an asymmetric variant of the cyclization is unprecedented. Herein we present an enantioselective macrolactonization through an intramolecular atom-economical rhodium-catalyzed coupling of ω -allenyl-substituted carboxylic acids. The use of a modified diop ligand, chiral DTBM-diop, led to high enantioselectivity (up to 93 % ee). The reaction tolerated a large variety of functionalities, including α,β -unsaturated carboxylic acids and depsipeptides, and provided the desired macrocycles with very high enantio- and diastereoselectivity.

Macrocyclic natural products are captivating owing to their often complex molecular architecture of a large ring combined with a broad diversity of functional groups and high stereochemical complexity.^[1] In particular, macrocyclic scaffolds of the macrolactone family are present in numerous natural compounds^[2] exhibiting intriguing fungicidal and insecticidal bioactivity,^[3] as well as olfactory^[4] and medicinal properties (Scheme 1).^[5]

Over the past decades, many different methods have been developed to close macrocyclic ring systems,^[1c,2] for example, ring-closing metathesis,^[6] Diels–Alder macrocyclization,^[7] intramolecular cross-coupling,^[8] metal-catalyzed coupling reactions,^[9] and Horner–Wadsworth–Emmons-type olefination reactions.^[10] However, the macrolactonization of ω -seco acids by activation of either the acid or the alcohol moiety still remains the most prevalent method with a variety of reliable and high-yielding procedures.^[2] Unfortunately, these procedures are rather unattractive in terms of the modern demands for resource efficiency in organic synthesis with regard to step economy,^[11] redox economy,^[12] atom economy,^[13] and protecting-group-free synthesis.^[14] Furthermore, the often harsh and basic conditions lead to isomerization, double-bond migration, and epimerization.^[2] Additionally, the introduction of the required stereochemical information during the ring closure would render a preceding installation step unnecessary. Hence, the development of improved access toward (macro-)lactones remains a highly challenging and active field. Transition-metal-catalyzed reactions for C–O bond



Scheme 1. Selected examples of naturally occurring macrolactones.

formation have great potential as a powerful new strategy to form macrolactones.^[15]

In 2006, White and co-workers reported an elegant and general procedure for the macrolactonization of ω -alkenyl-substituted carboxylic acids through a sulfoxide-promoted palladium-catalyzed allylic C–H oxidation.^[16] However, the use of more than a stoichiometric amount of an external oxidant is mandatory for this cyclization, the enantio- and diastereoselectivity of which can to date not be controlled by the catalyst. Intramolecular transition-metal-catalyzed addition reactions of carboxylic acids to multiple bonds are well-known^[17] and represent a new approach to (macro-)lactonization. In fact, the asymmetric intramolecular hydroxycarbonylation of ω -allenyl-substituted carboxylic acids was reported most recently by Toste and co-workers,^[18] who used a bifunctional heterogeneous molecular gold catalyst, and by Lipshutz and co-workers,^[19] who employed a micellar gold catalyst. Another iridium-catalyzed asymmetric lactonization of alkenyl-substituted carboxylic acids was reported by Nagamoto and Nishimura.^[20] Each reaction type proceeded with mostly high enantioselectivity but was limited to γ - and δ -lactones.

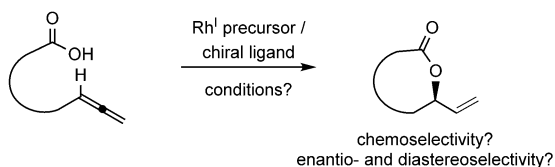
Our research group is interested in the atom-economical rhodium-catalyzed addition of pronucleophiles to alkynes^[21] and allenes.^[22] In this context, a hydroxycarbonylation to form branched allylic esters^[21b] was developed and serves as an attractive alternative to allylic substitution^[23a–c] and allylic oxidation^[23d,e] for the synthesis of valuable allylic intermediate structures.^[24] When the achiral ligand DPEphos was used, a broad range of racemic branched allylic esters were obtained. This system was also performed in an intramolec-

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ular manner to provide a racemic atom-economical (macro)-lactonization method.^[25] However, a general atom-economical and enantioselective macrolactonization based on transition-metal catalysis remains unknown.

Thorough investigations of the mechanism provided evidence that this transformation proceeds via an intermediate allene.^[26] In fact, we were able to report a general intermolecular hydroxycarbonylation of allenes with (–)-diop ((–)-**L1**).^[22a] The branched allylic esters with various functionalities were obtained not just in high yields but also with excellent enantioselectivity. These results encouraged us to investigate the potential of this reaction for the first enantioselective and atom-economical macrolactonization by the intramolecular addition of carboxylic acids to terminal allenes (Scheme 2).



Scheme 2. General reaction scheme for the rhodium-catalyzed intramolecular asymmetric coupling of carboxylic acids with terminal allenes.

The optimization process was performed for the conversion of the model substrate hexadeca-14,15-dienoic acid (**1**) into the 15-membered macrolactone **2**. In first reactivity assays, we reevaluated the previously reported conditions and optimized the different reaction parameters. The preliminary optimal results were obtained at room temperature with $[\text{Rh}(\text{cod})\text{Cl}]_2$ and (+)-diop ((+)-**L1**) in DCE at a 0.01 M substrate concentration (Table 1, entry 1), which gave the *R*-configured macrolactone **2**.^[27,28] Besides the desired product lactone **ML**, the formation of the endo- and exocyclic enol lactones **EL** as well as the corresponding diolide **DL** was observed. Further screening of different rhodium precursors revealed $[\text{Rh}(\text{cod})\text{acac}]$ as a suitable alternative catalyst, which improved the *ee* value of **2** to 85 % (Table 1, entry 2).^[29] To further improve the enantioselectivity, we tested different privileged ligands. Since ligands containing a diop-analogue backbone still proved to be the most suitable for the reaction, various diop derivatives were tested with either an altered acetal backbone (Table 1, entries 3 and 4) or varying aromatic moieties with different steric and electronic properties (entries 5–7). To our delight, product **2** was obtained with high enantioselectivity (91 % *ee*) with DTBM-diop (**L3**).

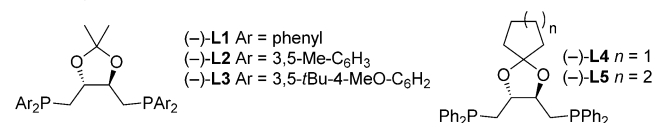
Having optimized the reaction conditions, we turned our focus to the scope of the reaction for the synthesis of macrolactones with different ring sizes, from a medium-sized 13-membered lactone up to a large 21-membered macrolactone (Scheme 3). All targeted macrolactones, **2–6**, were obtained in good yield and with good *ee* values of up to 93 %.

To demonstrate the potential of this procedure for more complex systems, we examined various functionalized ω -allenyl-substituted carboxylic acid substrates (Scheme 4). We found that aromatic acids can be used, as exemplified by the

Table 1: Screening of different diop derivatives in the rhodium-catalyzed macrolactonization.

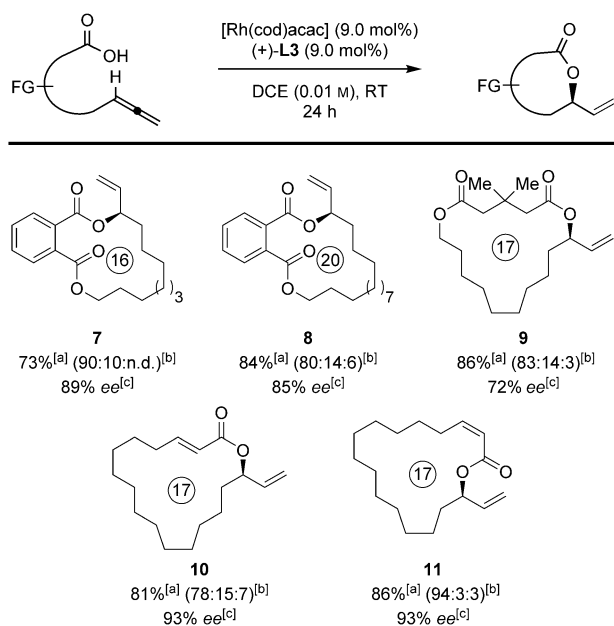
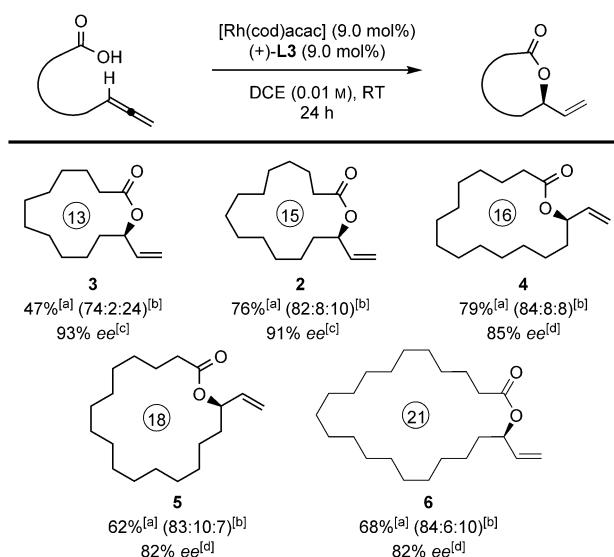
Entry ^[a]	Ligand	Combined yield [%] ^[b] (ML/EL/DL) ^[c]	<i>ee</i> [%] ^[d]
1 ^[e]	(+)-diop (L1)	85 (90:4:6)	74 (<i>R</i>)
2	(+)-diop (L1)	81 (86:6:8)	85 (<i>R</i>)
3	(–)-Cp-diop (L4)	69 (88:6:6)	86 (<i>S</i>)
4	(–)-Cy-diop (L5)	< 5	85 (<i>S</i>)
5	(–)-DM-diop (L2)	8 (76:–:24)	84 (<i>S</i>)
6	(–)-DTBM-diop (L3)	86 (80:9:11)	91 (<i>S</i>)
7	(+)-DTBM-diop (L3)	76 (82:8:10)	91 (<i>R</i>)

[a] Reaction conditions: $[\text{Rh}(\text{cod})\text{acac}]$ (9.0 mol %), ligand (9.0 mol %), **1** (0.5 mmol), DCE (0.01 M), room temperature, 24 h. [b] Combined yield of the product mixture. [c] Product ratio determined by ^1H NMR spectroscopy. [d] The *ee* value was determined by GC on a chiral stationary phase. [e] The reaction was performed with $[\text{Rh}(\text{cod})\text{Cl}]_2$ (4.5 mol %). acac = acetylacetonate, cod = 1,5-cyclooctadiene, DCE = 1,2-dichloroethane.



synthesis of the benzolactones **7** and **8**, which were formed in good yield with 89 and 85 % *ee*, respectively. With the synthesis of the dimethyl-substituted macrolactone **9**, the tolerance of a second ester functionality could be proved, thus opening up the possibility of forming symmetrical and unsymmetrical diolides. Under common basic macrolactonization conditions, the isomerization or migration of the alkene of α,β -unsaturated carboxylic acids is a frequently occurring problem.^[2] Fortunately, the cyclization to **10** and **11** proceeded successfully with retention of the alkene configuration, and both products were obtained with 93 % *ee*.

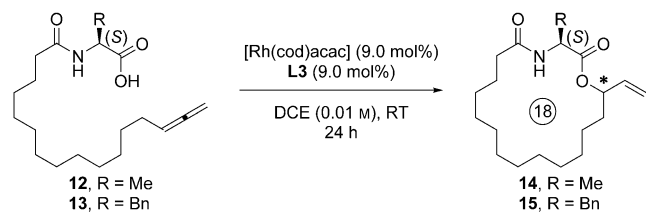
Next, we were curious to investigate the diastereoselectivity of the macrolactonization of substrates with inherent stereochemical information. We first examined the cyclization of the linear precursors **12** and **13**, containing a chiral amino acid moiety, with racemic DTBM-diop to assess the diastereoselectivity in terms of substrate control (Table 2, entries 1 and 4). A certain degree of diastereoselectivity in favor of the *S,S*-configured products was observed. At this point, the assignment of the configuration of the formed diastereomers was confirmed by X-ray crystallographic analysis of (*S,S*)-**14** and (*S,R*)-**14**.^[28] We were pleased to observe almost perfect diastereoselectivity in the formation of the alanine- and phenylalanine-containing macrolactones **14** and **15** when ligands (–)- and (+)-**L3** were used.



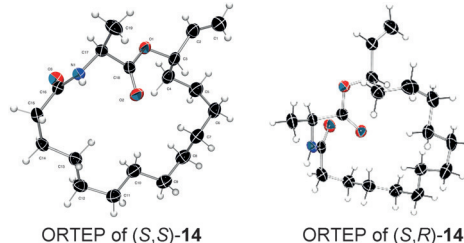
Scheme 4. Synthesis of functionalized macro-lactones by the intramolecular rhodium-catalyzed addition of carboxylic acids to allenes. Reaction conditions: [Rh(cod)acac] (9.0 mol %), (+)-L3 (9.0 mol %), substrate (0.5 mmol), DCE (0.01 M), room temperature, 24 h. [a] Combined yield of the product mixture. [b] Product ratio determined by ^1H NMR spectroscopy. [c] The *ee* value was determined by HPLC on a chiral stationary phase. n.d. = not detected.

In summary, we have described a highly atom-economical rhodium-catalyzed intramolecular coupling of carboxylic

Table 2: Synthesis of depsipeptides **14** and **15** through the intramolecular rhodium-catalyzed addition of carboxylic acids to allenes.^[a]



[a] Reaction conditions: [Rh(cod)acac] (9.0 mol %), (+)-L3 (9.0 mol %), substrate (0.5 mmol), DCE (0.01 M), room temperature, 24 h. [b] Combined yield of the product mixture. [c] Diastereomeric ratio determined by ^1H NMR spectroscopy. Bn = benzyl.



acids with terminal allenes for the synthesis of enantiomerically enriched macrolactones. This first direct enantioselective synthesis of macrolactones gives the desired products in good yields with high enantio- and diastereoselectivity. The presented conditions were applied to the formation of many different ring sizes and a broad range of functionalities, in particular, ester, amide, and olefinic groups. Future studies will elucidate the potential for a general asymmetric homodimerization strategy. Applications of this methodology in the target-oriented synthesis of natural products are being pursued in our laboratory.

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Keywords: asymmetric catalysis · hydrooxycarbonylation · ligand design · macrolactonization · rhodium

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