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Enantioselective Rhodium-Catalyzed Dimerization of ω-Allenyl Carboxylic Acids: Straightforward Synthesis of C_2-Symmetric Macrodiolides

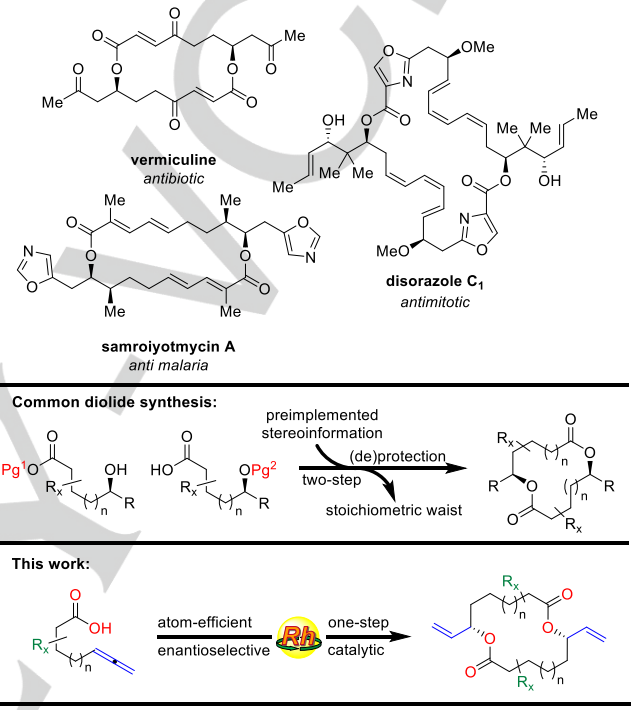
*Philip Steib and Bernhard Breit**

Abstract: *Herein, we report on the first enantioselective and atom-efficient, catalytic one-step dimerization methodology to selectively transform ω-allenyl carboxylic acids into C_2-symmetric, 14- to 28-membered bismacrolactones (macrodiolides). This convenient asymmetric access serves as an attractive route towards multiple naturally occuring homodimeric, macrocyclic scaffolds and demonstrates the excellent efficiency to construct the complex, symmetric core structures. Utilizing a rhodium catalyst with a modified chiral cyclopentylidene-diop ligand, the desired diolides were obtained in good to high yields, high diastereo- and excellent enantioselectivity.*

In recent decades, dimeric structures of polyketide origin have gained increasing scientific attention, as they show a manifold of unique structural features and a great potential to constitute a large number of novel medicinally relevant substances.[1,2] Aside from unsymmetrical, heterogeneous dimers, a group of complex C_2-symmetrical oxacyclic diolides comprise a large number of biologically active compounds (Scheme 1). In this spectrum, immuno-suppressives,[3a] antibiotics,[3b] anthelmintics,[3c] herbicides and fungicides,[3d,e] as well as active agents against cancer,[3f] HIV and the tropical disease malaria can be found.[3g,h] As a consequence these compounds have gained great interest as synthetic targets.[4]

By theory, this C_2-symmetry element should allow for a highly convergent dimerization strategy of an appropriate monomer. However, known synthetic strategies towards diolides follow more linear approaches, which result in multistep synthesis, with the need for orthogonally protected building blocks and/or previously implemented stereogenic centers.[5] Today, the most frequently applied method to construct macrolactones and diolides is the lactonization of the corresponding *seco* acid with stoichiometric amounts of coupling reagents.[6] However, only a few examples using the convergent direct dimerization strategy have been developed, such as a one-pot double MITSUNOBU reaction,[7] double trans-esterification,[8a,b] double SAKURAI allylation,[9] double SUZUKI or STILLE cross-coupling and alkyne metathesis.[10a,b;11] Nevertheless, direct enantioselective diolide formation ideally employing catalyst control remains unknown.

Transition metal catalyzed C-O bond formation could target this issue next to modern demands for resource efficiency and has been investigated throughout the past years in our group.[12,13] Thus, our research has developed methods for coupling carboxylic acids,[14a,b,c] next to other diverse pronucleophiles,[15] to allenes and alkynes in an inter-, as well as intramolecular manner to form branched allylic products.



Scheme 1: Selected examples of biologically active diolides in nature, common synthetic strategies and the concept of this report.

However, when attempting the formation of lactones of the medium size range, dimeric diolides were observed as major products.[14b] This let us speculate whether such a rhodium-catalyzed dimerization reaction of allenyl-carboxylates could be developed towards a general enantioselective catalytic macrodiolide synthesis.[16]

We herein report such a general method for the enantio-, diastereo- as well as regioselective rhodium-catalyzed dimerization of allenyl-carboxylic acids for the formation of C_2-symmetric macrodiolides.

Building upon prior experiences of allene/carboxylic acid addition reactions from our group,[14a,b] we started optimization by using undeca-9,10-dienoic acid (**9g**) as model substrate. Employing $[Rh(cod)Cl]_2$ and diop (**L1**) at room temperature in DCE at a 0.01 M substrate concentration (Table 1, entry 1) with a reaction time of 48 h a good yield of the macrodiolide dimer was obtained albeit only in poor diastereoselectivity. The latter could be significantly improved by lowering the reaction temperature (Table 1, entry 1-4). Best results balancing yield and diastereoselectivity were obtained at 0 °C (Table 1, entry 2). A further screening of ligands proved the cyclopentylidene-modified Cp-diop **L2** as most suitable.[17] The increased activity of this catalyst system allowed to lower the catalyst loading for the reaction at 0 °C (Table 1, entry 6).

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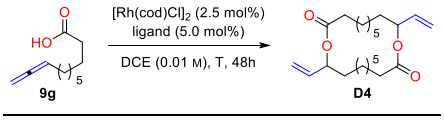
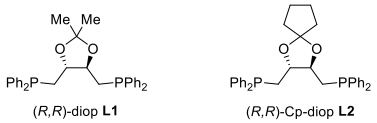
***Table 1**:* Screening of diop derivatives at different temperatures.





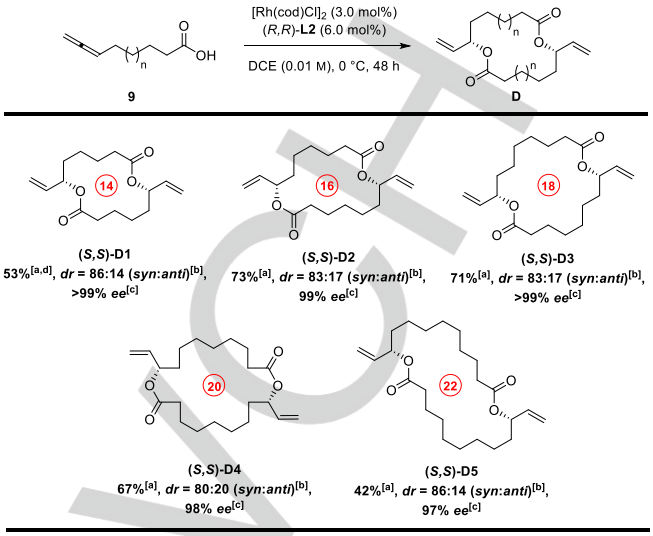
Entry	Ligand[a]	T [°C]	Yield [%][b]	*d.r.* (*syn:anti*)[c]
1	diop (**L1**)	r.t.	70	57:43
2[d]	diop (**L1**)	0	67	78:22
3[d,e]	diop (**L1**)	-5	26	81:19
4[d,f]	diop (**L1**)	-10	19	81:19
5	Cp-diop (**L2**)	r.t.	84	63:37
6[g]	Cp-diop (**L2**)	0	67	80:20

[a] Chiral variants of all ligands were used. [b] Isolated yield. [c] Diastereomeric ratio determined by ^{1}H NMR of the vinylic signals. [d] 5.0 mol% $[Rh(cod)Cl]_2$ and 10 mol% of ligand were used. [e] 64% conversion. [f] 47% conversion. [g] 3.0 mol% $[Rh(cod)Cl]_2$ and 6.0 mol% ligand were used. DCE=1,2-dichloroethane. cod=1,5-cyclooctadiene.

With these conditions at hand, our focus turned to the scope of the reaction. We started by investigating ω-allenyl carboxylic acids with saturated carbon chain spacers of different lengths.[18,19] Indeed, 14- to 22-membered aliphatic macrodiolides **D1**-**D5** were obtained in moderate to high yields, good diastereoselectivities and excellent enantioselectivities up to >99% *ee* (Table 2).[20] The very high enantioselectivities of the *syn*-diastereomers relate to the statistical asymmetric amplification, known as the HOREAU principle.[21] Erosion of the stereogenic center over time was excluded. When aiming at larger, aliphatic ring sizes, we found increasing evidence that diolide formation competes with the formation of higher oligomers. When attempting to prepare 24-membered diolides the corresponding 12-membered monolactone became the major product.[14g]

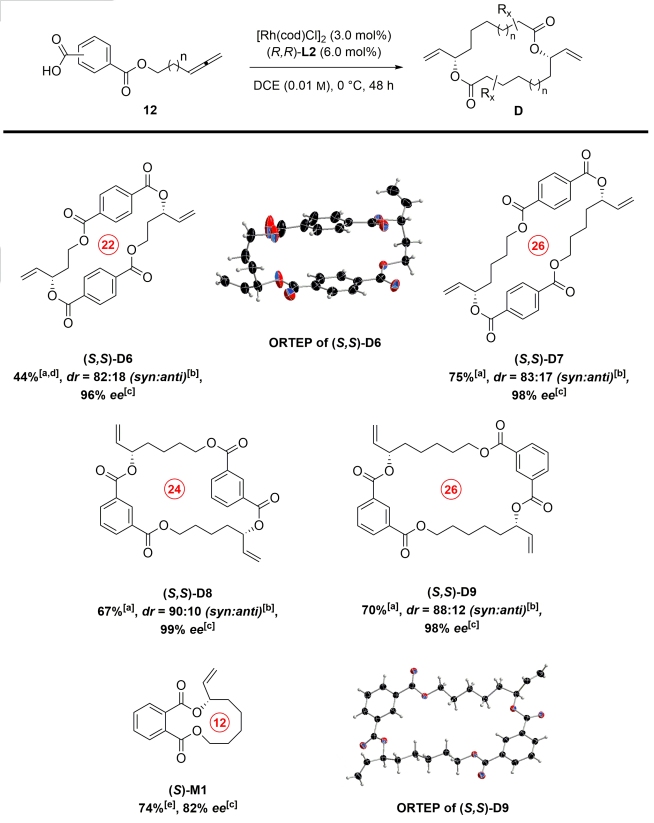
Next, the dimerization of conformationally more restricted ω-allenyl benzoic acid derivatives with either an *ortho*-, *meta*- and *para*-substitution pattern was studied. The reaction of the *para*-substituted allenyl acid **12e** (Table 3, n=1) produced a rather strained diolide **D6** (see crystal structure of **D6**).[22] In this case the addition of Cs_2CO_3 as a co-catalyst was found to be beneficial to achieve full conversion. Accordingly, using a substrate with elongated alkyl chain providing increased conformational flexibility furnished a higher yield for diolide formation **D7**. Good yields from 67 to 76% were obtained for the *meta*-substituted products **D8** and **D9**. In every case enantioselectivities were excellent. However, the *ortho*-substituted phthalic ester derivative reacted in a different fashion: The main product was found to be the 12-membered monolactone **M1**, indicating that a conformationally more proximate orientation of the reacting functional groups induces monolactone formation.

Table 2: Synthesis of unfunctionalized 14- to 22-membered diolides by rhodium-catalyzed dimerization of ω-allenyl carboxylic acids.



[a] Combined, isolated yield of diolides. [b] Ratio determined by ^{1}H NMR of vinyl-H atoms. [c] Determined by HPLC on a chiral phase. [d] 10 mol% Cs_2CO_3 were added.

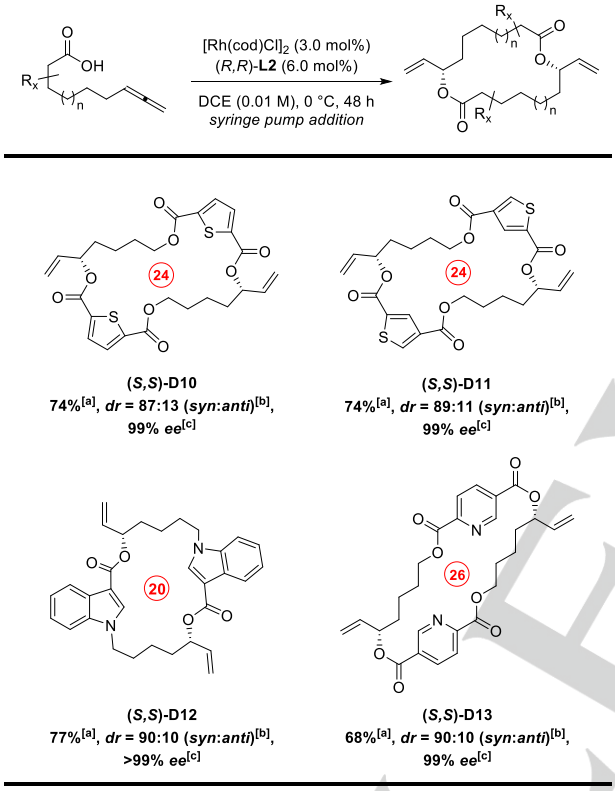
Table 3: Synthesis of terephthalic and isoterephthalic acid derived 22- to 26-membered diolides by rhodium-catalyzed dimerization of ω-allenyl carboxylic acids.



[a] Combined, isolated yield of diolides. [b] Ratio determined by ^{1}H NMR of arylic-H atoms. [c] Determined by HPLC on a chiral phase. [d] 4.5 mol% $[Rh(cod)Cl]_2$, 9.0 mol% ligand and 10 mol% Cs_2CO_3 were used. [e] Syringe pump technique was applied.

We also looked into the preparation of macrodiolides, functionalized with several different heterocyclic systems. Such heterocyclic diolides might serve as receptors for differently charged ions and neutral molecules.[23] We were delighted to see that thiophene- and indole-based substrates provided the corresponding diolides **D10** to **D12** with good yields. Even basic, potentially metal-coordinating pyridines (**D13**) were tolerated. In addition to excellent enantioselectivities, improved diastereoselectivities up to 90:10 were observed. Such pyridine-containing macrocycles may become of use as attractive chiral ligands in asymmetric homogeneous catalysis, with the feature of being readily functionalized by modification of the vinyl group.

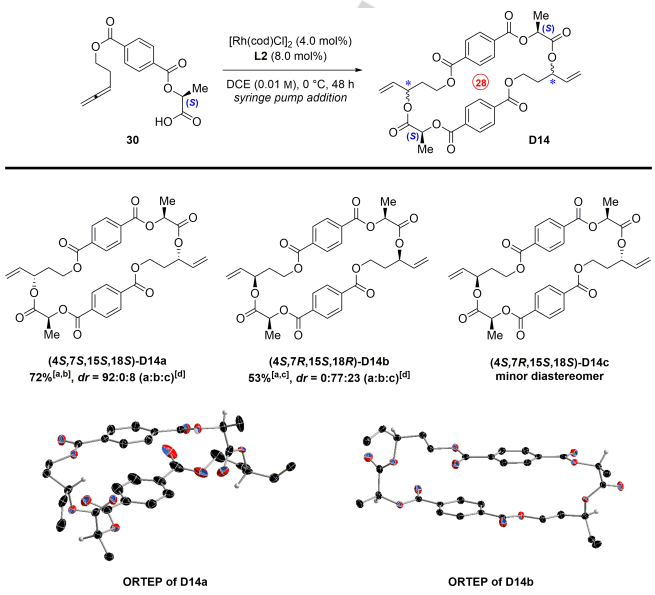
Table 4: Synthesis of diolides with divers heteroaryl-groups.



[a] Combined, isolated yield of diolides. [b] Ratio determined by ^{1}H NMR of arylic-H atoms. [c] Determined by HPLC on a chiral phase.

Having managed to construct diolides enantioselectively, we pursued with addressing the question whether catalyst control of diastereoselectivity can be achieved using allenic caboylic acid substrates with preexisting stereoinformation. To this aim, *para*-substituted benzoic acid derived allene **12e** was elongated with a (*S*)-lactic acid moiety, providing the possibility to form three diolidic diastereoisomers **D14a-c** (Table 5). Indeed, we were delighted to observe perfect catalyst control of diastereoselectivity forming either of the C_2-symmetric diolides **D14a** and **D14b**, when employing (−)-**L2** or (+)-**L2** as chiral ligands, respectively. Assignment of the configuration was confirmed by X-ray analysis for the *all*-(*S*) diastereomer **D14a** and the (*S,R,S,R*)-diastereomer **D14b**.

Table 5: Catalyst control upon rhodium-catalyzed dimerization of an α-chiral ω-allenyl carboxylic acid. Determination of the configuration of the three possible diastereomers.



[a] Combined, isolated yield of diolides. [b] (−)-**L2** was used. [c] (+)-**L2** was used. [d] Ratio determined by ^{1}H NMR of arylic-H atoms after filtration through silica. Non stereogenic H-Atoms are omitted for clarity regarding the ORTEP drawings.

In conclusion, we herein developed a highly atom-efficient, enantioselective, one-step rhodium-catalyzed dimerization strategy of ω-allenyl carboxylic acids, furnishing C_2-symmetrical homodiolides and generating two stereogenic centers concomitantly. Aside from good yields, the 14- to 28-membered symmetric diolides were obtained in high diastereo- and excellent enantioselectivity. This methodology represents a valuable alternative over existing two-step *seco* acid coupling procedures. Functionalization within the ring system and late stage modification of the allylic moiety could grant a convenient access to this important class of natural products and to a field of new complexing macrocycles, chiral ligand classes as well as interesting organic materials when polymerized.

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Keywords: asymmetric catalysis • macrolactones • diolide • rhodium • allenes

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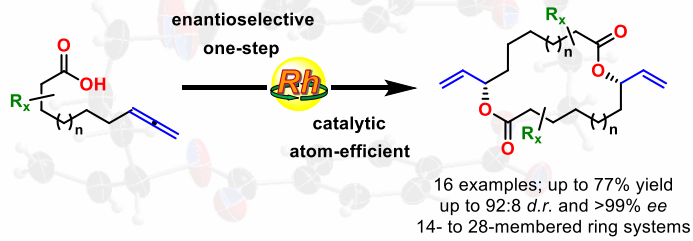

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Enantioselective Rhodium-Catalyzed Dimerization of ω-Allenyl Carboxylic Acids: Straightforward Synthesis of C_2-Symmetric Macrodiolides

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A highly atom-efficient, enantioselective, one-step rhodium-catalyzed dimerization strategy of ω-allenyl carboxylic acids, furnishing C_2-symmetrical homodiolides, a structural motif found in numerous natural products, has been developed. The method features high enantioselectivies generating two stereogenic centers concomitantly.