Synthetic Methods

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Diversity-Oriented Synthesis of Drug-Like Macrocyclic Scaffolds Using an Orthogonal Organo- and Metal Catalysis Strategy**

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Dedicated to Professor Dieter Enders on the occasion of his retirement

Abstract: *Small-molecule modulators of biological targets play a crucial role in biology and medicine. In this context, diversity-oriented synthesis (DOS) provides strategies toward generating small molecules with a broad range of unique scaffolds, and hence three-dimensionality, to target a broad area of biological space. In this study, an organocatalysis-derived DOS library of macrocycles was synthesized by exploiting the pluripotency of aldehydes. The orthogonal combination of multiple diversity-generating organocatalytic steps with alkene metathesis enabled the synthesis of 51 distinct macrocyclic structures bearing 48 unique scaffolds in only two to four steps without the need for protecting groups. Furthermore, merging organocatalysis and alkene metathesis in a one-pot protocol facilitated the synthesis of drug-like macrocycles with natural-product-like levels of shape diversity in a single step.*

In biology and medicine, small molecules are critical, for example, in the study of signaling pathways and as potential therapeutics.[1–6] However, the identification of small-molecule modulators for a particular protein target, especially if its structure is unknown, is nontrivial. The enormous size of chemical space (estimated as more than 10^{60} stable small molecules)[7] precludes the testing of all possible compounds in a screening campaign, and the absence of structural guidelines leads to debate over suitable selection criteria for small-molecule libraries. In this respect, scaffold diversity,[8–11] structural complexity,[6,8,12] and the fraction of sp^3-hybridized carbon atoms (Fsp^3)[12–15] have been identified as important selection. The efficient access to such structurally diverse small molecules has been termed diversity-oriented synthesis (DOS).[2–6,9,16]

Since the pioneering work of Schreiber,[16] many groups have focused on the development of novel DOS strategies—demonstrating a variety of concepts and hit discoveries.[17–24] Recent work in this field has sought to increase the scaffold diversity of libraries, as this is considered the most significant principle component of diversity (others being appendage, functional group, and stereochemical diversity).[8,9] In this regard, the build/couple/pair (B/C/P) algorithm has been established as a popular strategy[25–29] for the generation of diverse scaffolds, while other methods such as oxidative ring expansion,[30,31] fragment-based domain shuffling,[32] two-directional synthesis,[33] and multi-dimensional coupling have also been reported.[34] Very recently, these strategies have been applied to the synthesis of macrocycles,[26–28,31–34] which constitute attractive and underrepresented targets in drug discovery. Macrocycles exhibit unique properties such as conformational pre-organization as well as higher affinity and selectivity for biological targets.[35]

In the outlined work, we report a new B/C/P-based strategy (Scheme 1a) toward natural-product-like macrolactones **5**, utilizing building blocks **6**–**11** with self-orthogonal handles for organo- and metal catalysis (Schemes 1b and 2).

We envisaged that the aldehydes and their organocatalytic coupling partners (termed "alophile" building blocks) could be prepared in one or two steps from commercially available starting materials (Scheme 2). In this context, each "alophile" group of molecules sharing a building block core was synthesized from the same aldehyde precursor, introducing structural diversity in the outlined synthetic approach as early as in the build phase (Scheme 2a). For example, aldehyde **10** was transformed into enal **11**, alcohol **13**, β-ketoester **15**, and chalcone derivative **16** in moderate to excellent yields (55–99%). In the build phase, six different classes of building blocks were synthesized, ranging from aromatic (**10**–**11**, **13**, **15**, and **16**) and heteroaromatic (**17**–**20**, and **23**) to aliphatic core structures (**21** and **22**).

In the couple phase, considering the extensive number of reported methodologies in the field of organocatalysis,[36] we chose to focus on the use of N-heterocyclic carbenes (NHCs) **34**–**36** as organocatalysts. NHCs exhibit some unusual properties, enabling the "umpolung" of functional groups, for example the conversion of the carbon atom in α or γ position of an aldehyde into a nucleophile.[37] Using this transformation to our advantage, ten unique coupling motifs were accessible from aldehyde **10** or enal **11**, as is demonstrated for the phenolate building block (Scheme 3), which was subjected to single-step transformations such as benzoin (**24**),[38] Stetter (**25**),[39] or different redox-esterification reactions (**27**–**29**, **32**, and **33**)[40–44] and cascade processes (**30** and **31**).[45,46] We found that all coupling reactions gave the desired products in

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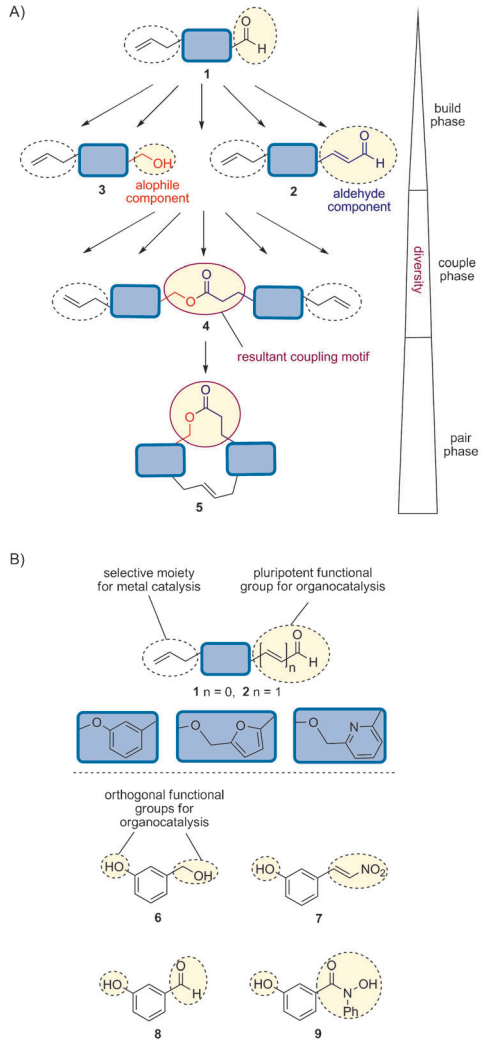
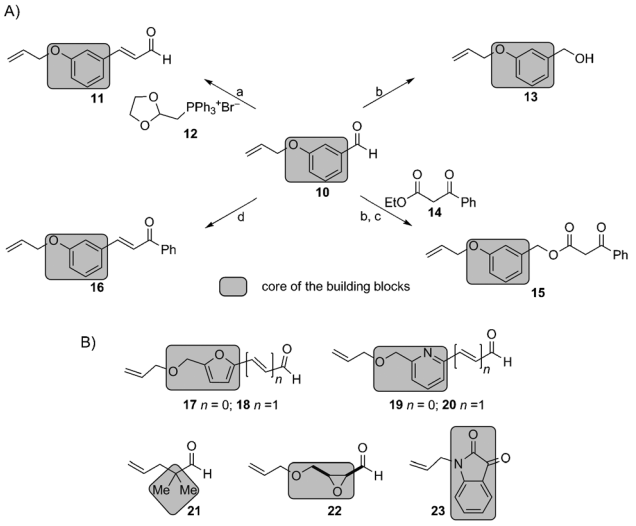
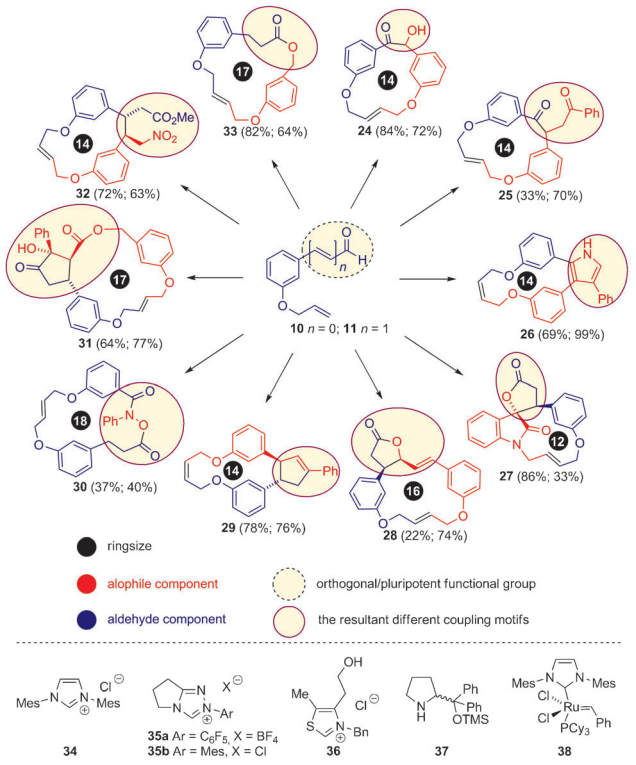


Scheme 1. Diversity through organo- and metal catalysis. A) The B/C/P algorithm in the proposed strategy. B) Building blocks with pluripotent and orthogonal functional groups.



Scheme 2. Building blocks. A) Diversification of aldehyde **10** toward "alophile" components. B) Building blocks with different cores. Reaction conditions: a) **12** (3 equiv), NaOMe, DMF/MeOH 2:1, reflux, 55%; b) $NaBH_4$, $NaHSO_4$, H_2O, CH_3CN, 81%; c) **14** (1 equiv), 4-NO_2-C_6H_4-$B(OH)_2$ (2.5 mol%), toluene, 79%; d) acetophenone, EtOH/$SOCl_2$ 10:1, 99%. DMF = *N*,*N*-dimethylformamide.



Scheme 3. Macrocycles with different coupling motifs accessible through organocatalysis followed by ring-closing metathesis. For clarity, only examples with the phenolate core and the major stereoisomer are presented. Yields are shown of the purified product (organocatalytic coupling; ring-closing metathesis). Mes = mesityl. TMS = trimethylsilyl.

synthetically useful yields (22–86%) prior to the optimization of reaction conditions.

In order to access macrocycles that possess larger ring sizes and hence, higher skeletal diversity in the DOS library, self-orthogonal building blocks were used as branching points (Scheme 4). In this context, diol **6**, nitrostyrene **7**, and aldehyde **8** were modified regioselectively under NHC catalysis and thus without the need for protection. Therefore, after installation of the first coupling motif, the building block chains in the intermediates **39**, **42**, and **9** were directly extended according to a formal B/C/C algorithm. Moreover, in the particular case of hydroxamic acid **9**, the outlined protocol was repeated a third time demonstrating a B/C/C/C algorithm.

Finally, in the pair phase, the macrocyclization of the constructed linear precursors was achieved through alkene metathesis in moderate to excellent yield (33-99%), constructing 51 distinct polyether macrolactones.[47]

The synthesized DOS library of 51 macrocyclic compounds was analyzed statistically in order to evaluate the

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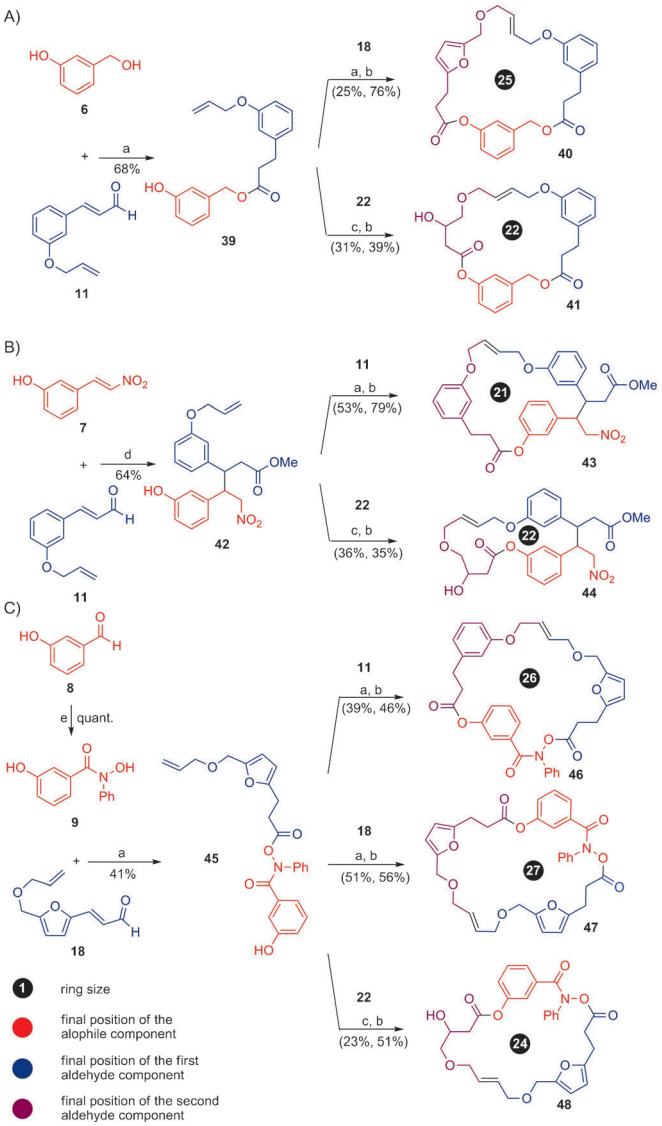


Scheme 4. Synthesis of macrocyclic scaffolds using B/C/C/P (A,B) and B/C/C/C/P (C) algorithms. Reaction conditions: a) **35a** (10 mol%), NaOAc, CH_2Cl_2, 40°C; b) **38** (10 mol%), CH_2Cl_2, reflux; c) PhNO (1.0 equiv), **35a** (10 mol%), TMEDA, CH_2Cl_2, RT; d) **35b** (30 mol%), $KHCO_3$, toluene/MeOH 10:1, RT; e) **35a** (10 mol%), TMEDA, CH_2Cl_2, RT. Yields of isolated products (organocatalytic coupling; ring-closing metathesis) after column chromatography are given in brackets. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine

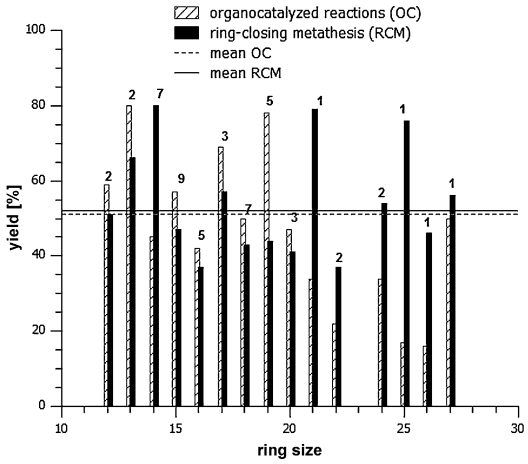
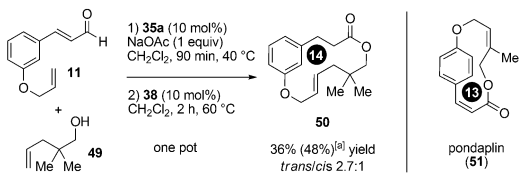


Figure 1. Mean yields with respect to ring size for organocatalysis and ring-closing metathesis steps. Numbers above the bars represent the number of macrocycles of the corresponding ring size in the library.

efficiency and diversity achieved using the demonstrated strategy. First, the yields of all organocatalytic coupling and alkene metathesis reactions were plotted in a histogram (Figure 1). These yields were dependent on both the ring size and functional groups present, with mean yields for each step in excess of 50%, exemplifying the synthetic utility of the presented methodology. Subsequently, the shape and chemo-physical diversity of the DOS library was visualized in the form of a principal moment-of-inertia plot (PMI; Supporting Information, Figure S1) and a principal component analysis plot (PCA; Figure S2) featuring 15 calculated chemo-physical properties, respectively. In both instances, we compared our set of macrocycles with two reference collections: an established set of 40 top-selling drugs and 60 natural products.[31,34] In the PMI analysis, our DOS library exhibited broad shape diversity and more prominent spherical characteristics (comparable to that of the natural product reference set) than the drug reference set, which is mostly confined to rod- and disc-like shapes. In addition, PCA illustrated the pronounced drug-like properties of our DOS library.

To further increase the step economy of the proposed B/C/P methodology, we envisaged that under certain circumstances, the NHC-catalyzed coupling and alkene metathesis steps could be combined in one pot.[48] However, it is known that NHCs react quickly with late transition metals, thereby decreasing their reactivity, and thus this combination of catalyst types was very rarely investigated previously.[49,50] Fortunately, we found that the Grubbs II catalyst **38** showed no appreciable loss in activity in the presence of the NHCs used. Therefore, we combined the NHC-catalyzed redox-esterification and Ru-catalyzed alkene metathesis steps in one pot (Scheme 5) to furnish macrocyclic lactone **50** smoothly and with comparable efficiency to the step-wise protocol (36% versus 48% overall yield, respectively). It is noteworthy that **50** strongly resembles natural products, for example pondaplin (**51**), a phenyl propanoid with anti-cancer properties.[51,52]

In summary, we have demonstrated the efficient synthesis of a DOS library of macrocyclic compounds using an



Scheme 5. One-pot synthesis of macrolactone **50** through a combination of NHC-catalyzed redox-esterification and Grubbs II catalyzed alkene metathesis. a) Yield of isolated product **50** as a mixture of *E*/*Z* isomers after column chromatography. Comparative yields over two steps using a stepwise protocol are given in brackets.

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orthogonal organo- and metal catalysis strategy. The key to this approach was the exploitation of the pluripotency of aldehydes for NHC organocatalysis in the couple phase as part of a classical B/C/P algorithm. A mean yield of 50% was achieved across all reactions performed. Cheminformatic analysis illustrated that the created DOS library possesses drug-like chemo-physical properties and significantly higher three-dimensionality than the reference drug library. Finally, a very rare combination of organo- and metal catalysis in one pot was shown in the synthesis of macrocycles.

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[47] An overview of all macrocyclic structures in the presented DOS library is given in the supporting information (pS3-pS6).

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[52] In a preliminary phenotypic screen, compound **50** indicated activity against several bacterial strains. Results will be reported in due course.

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