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Asymmetric Synthesis

The Asymmetric Hetero-Diels–Alder Reaction in the Syntheses of Biologically Relevant Compounds

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asymmetric synthesis · chemical biology · cycloaddition · heterocycles · natural products

Dedicated to Professor Roland Winter on the occasion of his 60th birthday

The hetero-Diels–Alder reaction is one of the most powerful transformations in the chemistry toolbox for the synthesis of aza- and oxa-heterocycles embodying multiple stereogenic centers. However, as compared to other cycloadditions, in particular the dipolar cycloadditions and the Diels–Alder reaction, the hetero-Diels–Alder reaction has been much less explored and exploited in organic synthesis. Nevertheless, this powerful transformation has opened up efficient and creative routes to biologically relevant small molecules and different natural products which contain six-membered oxygen or nitrogen ring systems. Recent developments in this field, in particular in the establishment of enantioselectively catalyzed hetero-Diels–Alder cycloadditions steered by a plethora of different catalysts and the application of the resulting small molecules in chemical biology and medicinal chemistry research, are highlighted in this Minireview.

1. Introduction

The hetero-Diels–Alder (HDA) reaction, that is, the [4+2] cycloaddition in which the diene or the dienophile contains at least one heteroatom (Figure 1), is among the most efficient methods for the synthesis of oxa- and aza-heterocycles. However, despite its efficiency, in comparison to the all-carbon Diels–Alder (DA) cycloaddition, it has been far less exploited and explored in organic synthesis. For instance, while major strides have been made in the development of enantioselectively catalyzed DA reactions, efforts to develop asymmetric HDA reactions are relatively few. Interestingly, for several natural products it has been hypothesized that their biosynthesis includes an HDA step.

However, contrary to the recent discovery of Diels–Alderases, enzymes catalyzing DA reactions in vivo for the synthesis of secondary metabolites,[1] there is only little information available about hetero-Diels–Alderases.[2] Nevertheless, this powerful transformation, which constructs six-membered heterocycles in one step, has found its logical use in synthetic strategies designed to yield biologically active small molecules. In many cases, an enantioselective synthesis of a desired heterocycle is the key step in targeting a compound with known biological activity, like natural products. Alternatively the goal of the synthesis may be to get access to a hit or lead structure from a compound collection based on biologically relevant molecular frameworks. By employing either chiral catalysts or chiral auxiliaries embedded in the substrates, diastereo- and enantioselective HDA reactions have successfully enabled the synthesis of small

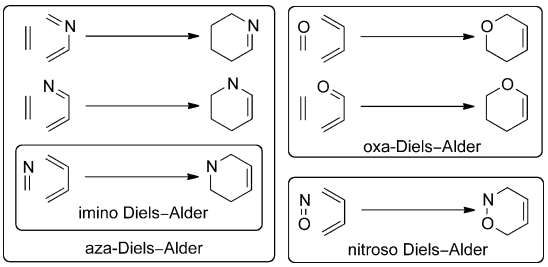

Figure 1. Nomenclature of hetero-Diels–Alder reactions. In the case of an oxygen atom as a heteroatom, the reaction is called an oxa-Diels–Alder reaction and when it is a nitrogen atom, the term aza-Diels–Alder is used. A nitroso-Diels–Alder reaction is a variant where vicinal N and O atoms are implied in the cycloaddition

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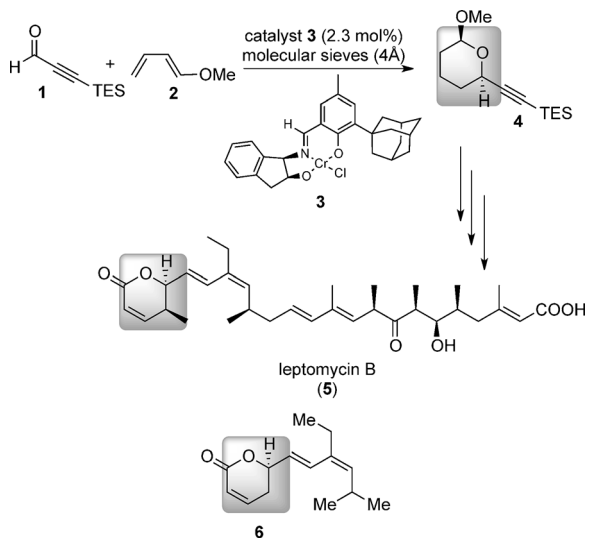
bioactive molecules. Also, different modes of activation that were initially developed for the DA reaction proved efficient for the HDA reaction. For instance, the relative HOMO–LUMO orbital energies of substrates can be modulated by means of the right choice of catalysts, such as a Lewis acid or a nucleophilic organocatalyst, and by varying reaction conditions such as temperature.[3]

In this Minireview, we focus on the applications of asymmetric HDA reactions in the syntheses of biologically relevant molecules reported since 2005, including the synthesis of natural products and natural-product-inspired compound libraries. For more comprehensive discussions about the subject and the application of hetero-Diels–Alder reactions in industrial syntheses of active ingredients, the reader is referred elsewhere.[4–6] Furthermore, the synthesis of biological building blocks, such as sugars, using HDA reactions is analyzed. Finally, asymmetric HDA reactions which make use of biomimetic synthesis and employ biocatalysts are described.

2. Asymmetric Hetero-Diels–Alder Reactions in the Total Syntheses of Natural Products

Hetero-Diels–Alder reactions with aza- or oxa-substituted dienes or dienophiles are powerful methods to assemble heterocycles, in a regio- and stereoselective manner, for the synthesis of natural products. There are many advantages which make HDA transformations an especially useful method in the synthesis of complex molecules. Mild reaction conditions for organocatalyzed or Lewis acid catalyzed reactions, high atom economy, and tolerance of non-interacting functional groups makes the HDA reaction a preferred transformation.[7]

The polyketide natural products anguinomycins, leptomycin B, and their derivatives have been synthesized by using an oxa-Diels–Alder reaction at an early stage.[8] The total synthesis begins with an asymmetric HDA reaction between the aldehyde **1** and diene **2,** and was catalyzed by the Jacobsen chromium(III) catalyst[9] **3** to yield the tetrahydropyran **4** in 86% yield and with 96% *ee* (Scheme 1). The building block **4** is then further processed through functionalization of the alkyne to build the polyketide chain. The stereochemistry introduced by the enantioselective oxa-Diels–Alder reaction of **4** further directs the synthesis of polyketides like leptomycin B (**5**).



Scheme 1. Synthesis of leptomycin B (**5**) using an oxa-Diels–Alder reaction as a key step for heterocycle formation. TES = triethylsilyl.

These polyketides were evaluated for the inhibition of nucleocytoplasmic transport by Gademann et al.[8] Both anguinomycins C and D strongly inhibited Crm1-mediated nucleocytoplasmic transport and may therefore be potential anticancer agents. The truncated δ-lactone **6** (Scheme 1), obtained after two steps from the oxa-Diels–Alder adduct completely blocked Crm1-mediated nuclear export at 50 nM, and led to the accumulation of the Rio2 protein in the nucleus at 25 nM. Structural simplification of complex natural products may retain the desired biological activity of the parent compound and is a promising approach for the development of novel bioactive compounds inspired by natural products.[10,11] The HDA reaction proved its potential in the synthesis of leptomycin analogues, since it was the key

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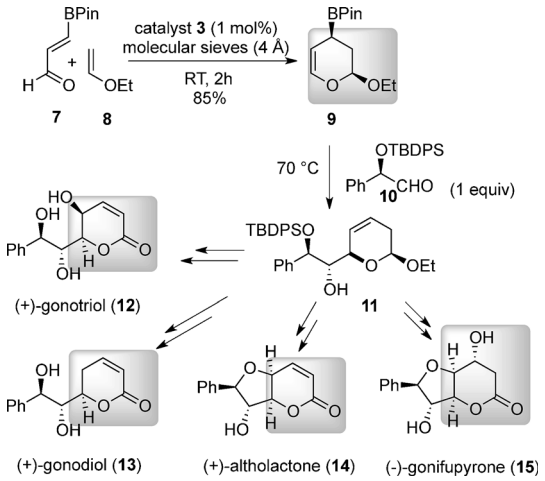
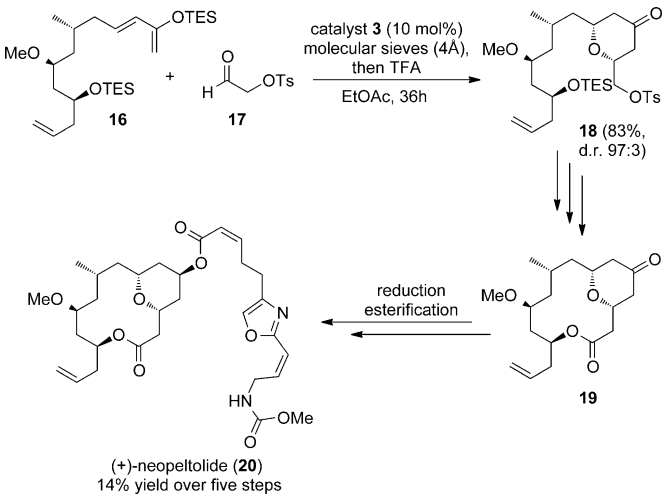
Kamal Kumar was born in Amritsar, India. He studied Pharm. Sciences at Guru Nanak Dev Univ. Amritsar and later completed his PhD in 2000 under the supervision of Prof. M. P. S. Ishar. Since 2006 he has led a group in the department of Chemical Biology at the MPI for Molecular Physiology, Dortmund. His research interests include the development of natural-product-based libraries, cascade reactions, organo- and coinage metal catalyzed annulations, and probing biological functions with small molecules.

Vincent Eschenbrenner-Lux was born in Strasbourg, France where he received his MSc in Chemistry and Biology in 2010 from the University of Strasbourg. He is currently a graduate student in the group of Prof. H. Waldmann and his studies focus on natural-product-inspired compound collection synthesis using hetero-Diels–Alder and cascade reactions.



Scheme 2. Synthesis of (+)-gonotriol and analogues by a hetero-Diels–Alder reaction between oxadiene (**7**) and a dienophile (**8**). Pin = pinacol, TBDPS = *tert*-butyldiphenylsilyl.



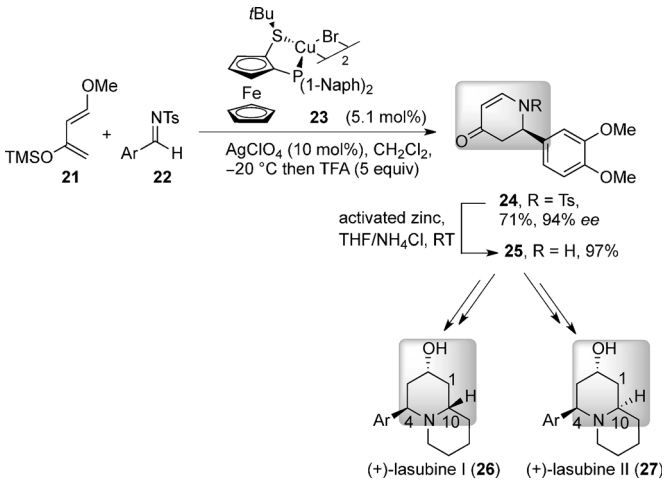
Scheme 3. Synthesis of (+)-neopeltolide (**20**) by an oxa-Diels–Alder reaction catalyzed by the Jacobsen chromium catalyst **3**. TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.

reaction in providing the functionalized core which was used later for the preparation of natural product analogues.

Another example of an oxa-Diels–Alder reaction catalyzed by a chromium(III) catalyst was reported by Carboni et al.[12] An inverse-electron-demand HDA reaction between the oxadiene **7** and vinyl ether **8** as the dienophile proceeded smoothly and set the stereochemistry at an early stage of the synthesis (Scheme 2). The HDA reaction yielded the allylborane **9** which reacted with the aldehyde **10** to provide a common building block (**11**), which in a few steps gave access to (+)-gonotriol (**12**), (+)-gonodiol (**13**), (+)-altholactone (**14**), and (−)-gonifupyrone (**15**). The compounds **12**–**15** were isolated from *Goniothalamus sp.* and have anticancer activity. Annexin staining of HL-60 cells treated with **14** in a flow cytometry experiment indicated a concentration-dependent increase of apoptosis. Pre-treatment of cells with the antioxidant *N*-acetylcysteine (1 mM) led to complete abrogation of apoptosis induced by **14** and indicated involvement of oxidative stress.[13,14]

In a synthesis of (+)-neopeltolide (**20**),[15] the pyrane ring within the macrocycle was synthesized through an oxa-Diels–Alder reaction between the silyloxydiene **16** and aldehyde **17** in the presence of the catalyst **3** to form the intermediate **18** in 83% yield and with good diastereoselectivity (d.r. 97:3; Scheme 3). Additional macrocyclization, reduction, and esterification afforded the potent antiproliferative and cytotoxic agent[16,17] (+)-neopeltolide (**20**) in 14% yield over five steps.

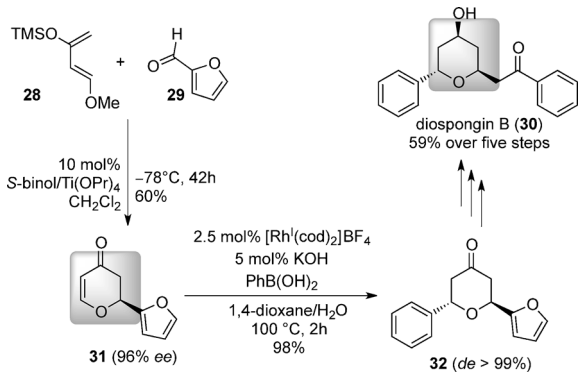
Indolizidine, quinolizidine, and piperidine alkaloids encompass a large group of natural products which display a broad range of biological activities. Lasubines I (**26**) and II (**27**) are two quinolizidine alkaloids isolated from plants of the *Lythraceae* family, and differ only in the configuration at C10 (Scheme 4).[18] An elegant application of the asymmetric HDA reaction was reported in the total synthesis of the lasubines by exploiting a chiral ferrocene catalyst in the key HDA reaction.[19] Thus, the core heterocycle was generated by an imino-Diels–Alder reaction between Danishefsky's diene **21** and the tosylimine **22** in the presence of the Cu/Fesulphos



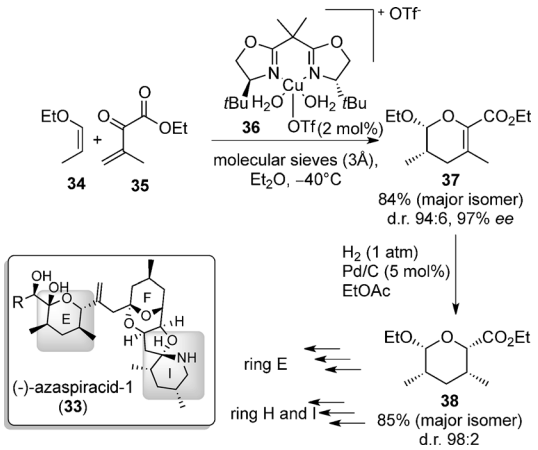
Scheme 4. Synthesis of the lasubines **26** and **27** using an enantioselective imino-Diels–Alder reaction as a key step. THF = tetrahydrofuran, TMS = trimethylsilyl.

bromo dimer complex **23** as the catalyst and $AgClO_4$ in CH_2Cl_2, thus leading to the piperidinone **24** in 71% yield and 94% *ee*. Additional functionalization of **24** yielded **26** and **27** from the common building block **25**.

Diospongins, a new family of diarylheptanoid natural products isolated from *Dioscorea spongiosa* display promising inhibitory activities on bone resorption and are therefore potential therapeutic agents for treating osteoporosis.[20] In an enantioselective total synthesis of diospongins, an oxa-Diels–Alder reaction, catalyzed by a binol/titanium complex,[21] introduced the furyl group enantioselectively (Scheme 5). The stereochemistry established thereby subsequently directed a diastereoselective rhodium-catalyzed arylation.[22] Both enantiomers of the adduct **31** were obtained using *S*- and *R*-binol and subsequently yielded the corresponding *trans*-diastereoisomers **32**. The synthesis of diospongin B (**30**) was then achieved in five additional steps with an overall yield of 59% from **32**. The stereoselective reduction of the ketone to



Scheme 5. Enantioselective synthesis of diospongin (**30**) by means of a key oxa-Diels–Alder reaction. binol = 2,2′-dihydroxy-1,1′-binaphthyl, cod = 1,5-cyclooctadiene.



Scheme 6. Enantioselective oxa-Diels–Alder synthesis of the common building block **37** for the synthesis of the azaspiracid rings E and I. Tf = trifluoromethanesulfonyl.

a secondary alcohol was achieved by employing Noyori's catalyst. The HDA reaction also facilitated the formation of analogues of the natural product having the desired biological activity.

The infamous azaspiracid poisoning incident happened in 1995 when at least eight people in the Netherlands fell ill after consuming blue mussels (*Mytilus edulis*).[23] In 1998, the Yasumoto group isolated the causative toxin for this poisoning as azaspiracid-1 (**33**).[24] Since then, 11 azaspiracid analogues have been described. Biological evaluation of azaspiracids has revealed a number of toxic effects such as cytotoxicity in mammalian cell lines,[25] teratogenic effects in finfish,[26] perturbation of cell adhesion,[27] modulation of the actin cytoskeleton,[28] and inhibitory effects on neuronal transmission.[29] The availability of only minute amounts of azaspiracids from natural sources remains a major hurdle for deeper biological investigations to better understand the cause of their toxicity.[30,31] Therefore, the total synthesis of these natural products was a logical goal so as to gain access to these complex molecules and their analogues.

The E and I rings of azaspiracid-1 (**33**; Figure 2) embody two *syn*-1,3-dimethyl fragments of the same configuration and can be constructed from a common precursor (**38**; Scheme 6).[32] To this end, an enantioselective oxa-Diels–Alder reaction was used to generate the dihydropyran **37**. Diethyl ether was the best solvent for this particular HDA reaction (97% *ee*, d.r. 94:6) and it was scaled up to 10–20 grams to provide **37** in 84% yield as a single isomer. The cycloaddition between the oxadiene **35** and vinyl ether **34** proceeded readily in the presence of the copper complex **36** (2 mol%). A subsequent hydrogenation of the double bond with Pd/C yielded **38** with very high diastereoisomeric ratio

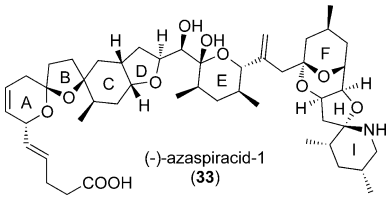
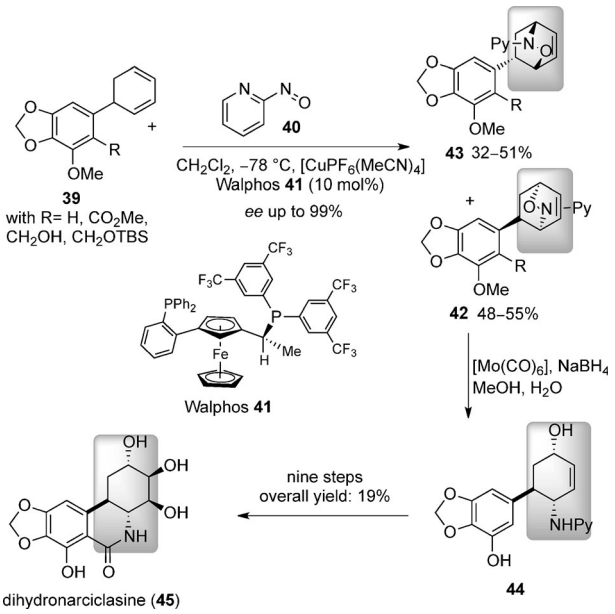


Figure 2. Structure of (−)-azaspiracid-1 (**33**).



Scheme 7. Synthesis of dihydronarciclasine (**45**) with an enantioselective and regioselective nitroso-Diels–Alder reaction as a key step.[31] Py = pyridine, TBS = *tert*-butyldimethylsilyl.

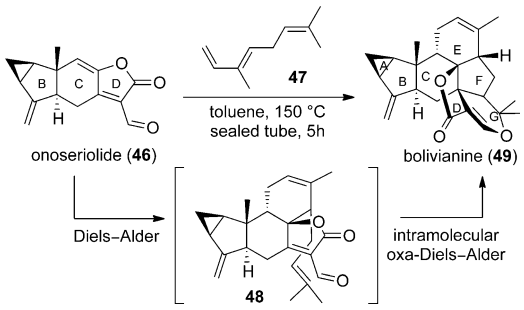
(98:2). The fragment **38** was further used to generate the desired E and I ring systems in the total synthesis of **33**.

An interesting application of an enantioselective nitroso-Diels–Alder reaction was reported in the total synthesis of *trans*-dihydronarciclasine (**45**; Scheme 7).[33] The desired stereochemistry in the target molecule was induced by the key HDA reaction between a decorated cyclohexadiene (**39**) and 2-nitrosopyridine (**40**), thus yielding the regioisomeric bicyclic compounds **42** and **43** with *ee* values of up to 99%.[34] The HDA reaction was catalyzed with the chiral Walphos catalyst **41** in the presence of copper(I). Ring opening of the bicycle in **42** leads to the intermediate **44** which was converted, in nine steps with an overall yield of 19%, into **45**.

(+)-*trans*-Dihydronarciclasine (**45**) is derived from narciclasine, a naturally occurring Amaryllidaceae alkaloid, iso-

lated from *Narcissus pseudonarcissus*, which modulates cell cycle progression. While narciclasine potently inhibits human cytochrome CYP3A4, its dihydro analogue was inactive.

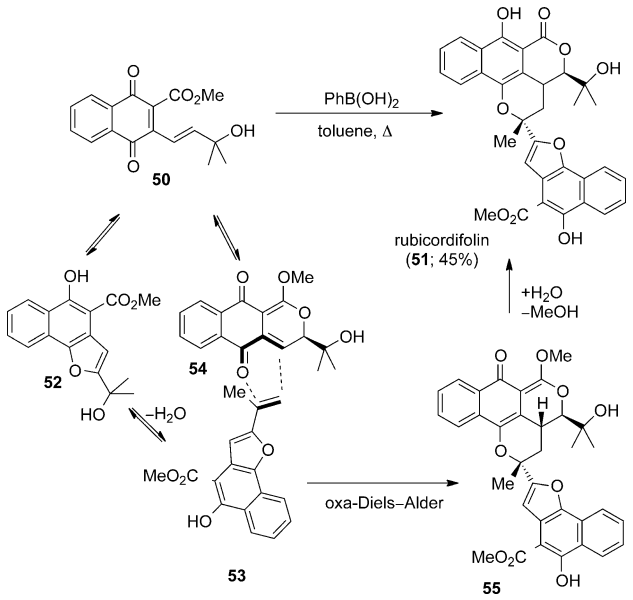
Carbo- or hetero-DA reactions can generate multiple new stereogenic centers, and if the two cycloadditions can be used in tandem or in a cascade, molecular complexity can be rapidly built up. In a total synthesis of bolivianine (**49**) a DA and an intramolecular hetero-Diels–Alder (IMHDA) reaction proceeded as a cascade reaction. This heptacyclic sesquiterpene contains nine stereogenic centers, and was isolated from *Hedyosmum angustifolium*.[35] The DA reaction of onoseriolide (**46**) with β-*E*-ocimene (**47**) led to the intermediate **48** which concomitantly underwent an intramolecular oxa-Diels–Alder reaction between the α,β-unsaturated aldehyde moiety of onoseriolide and the remaining double bond of **47** (Scheme 8).[36] By means of this elegant and ambitious DA/IMHDA cascade, the EFG tricycle of bolivianine (**49**) was formed in one step.



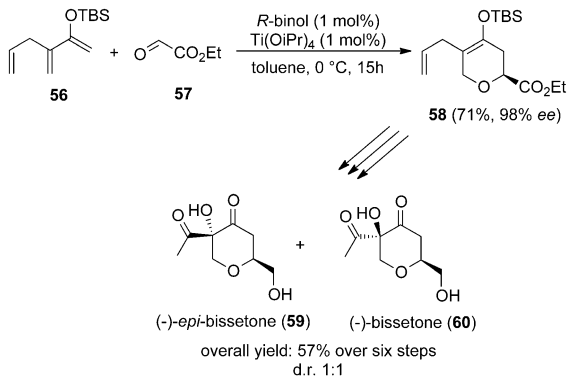
Scheme 8. Synthesis of bolivianine (**49**) through a Diels–Alder/intramolecular hetero-Diels–Alder cascade reaction.

Rubicordifolin (**51**) was isolated from *Rubia cordifolia*.[37] It displayed significant cytotoxicity both in vitro and in vivo, thus inhibiting the growth of sarcoma ascites in mice at low concentrations. In a biomimetic total synthesis of this natural product, Trauner et al. employed a key oxa-Diels–Alder reaction.[38] The diastereoselective dimerization of naphthalenedione (**50**) led to **51** in a single step in 45% yield (Scheme 9). The mechanism of this reaction was thoroughly investigated using theoretical calculations of the energies and geometry of the intermediates.[39] The monomer **50** cyclizes divergently to give the oxadiene **54** and dienophile **53** which undergo an oxa-Diels–Alder reaction to provide the intermediate **55** which undergoes loss of methanol to yield the desired product **51**. The concise, biomimetic synthesis of rubicordifolin not only fully established the structure but also provided hundreds of milligrams of the biologically active natural product which could be easily modified to produce analogues for biological investigations.

(−)-*epi*-Bissetone (**59**) is an antimicrobial pyranone extracted from *Briareum polyanthes*.[40] For its total synthesis, a binol/titanium complex-catalyzed oxa-Diels–Alder cycloaddition reaction was employed as a key step.[41] Under Lewis acid catalysis, the diene **56** and aldehyde **57** reacted in toluene to form the dihydropyran **58** in 71% yield and with 98% enantiomeric excess (Scheme 10). Further modifications of



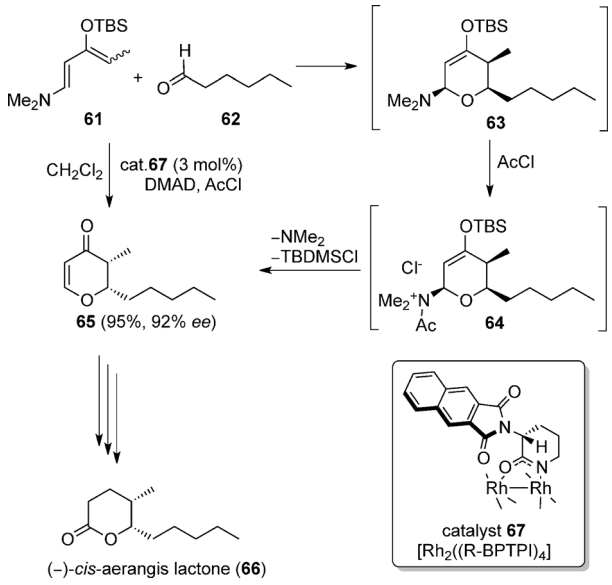
Scheme 9. Diastereoselective oxa-Diels–Alder reaction as the key step in a cascade synthesis of rubicordifolin (**51**).



Scheme 10. A diastereoselective oxa-Diels–Alder reaction as the key step in the synthesis of (−)-bissetone (**60**).

this precursor led to a 1:1 mixture of the diasteroisomers (−)-bissetone (**60**) and *epi*-bissetone (**59**) in 57% overall.

An asymmetric rhodium-catalyzed HDA reaction was employed in the total synthesis of the (−)-*cis*-aerangis lactone (**66**).[42] The methyl-substituted diene **61** underwent an oxa-Diels–Alder reaction with the aldehyde **62** in the presence of a dirhodium catalyst (**67**) in CH_2Cl_2 to form the dihydropyran **63** (Scheme 11). The reaction mixture was subsequently treated with dimethylacetylene dicarboxylate (DMAD) and acetyl chloride for combined elimination of dimethylamine and *tert*-butyldimethylsilyl chloride to yield the dihydropyranone **65** in excellent yield and with high enantioselectivity. DMAD was used to trap the excess **61** which would otherwise react with an oxacarbenium ion generated from **64** and thereby decreased the yield of **65**. Aerangis lactones are fragrances extracted from the white orchid *Aerangis confusa*, and their enantioselective synthesis is of high relevance as different enantiomers smell differently.[43]



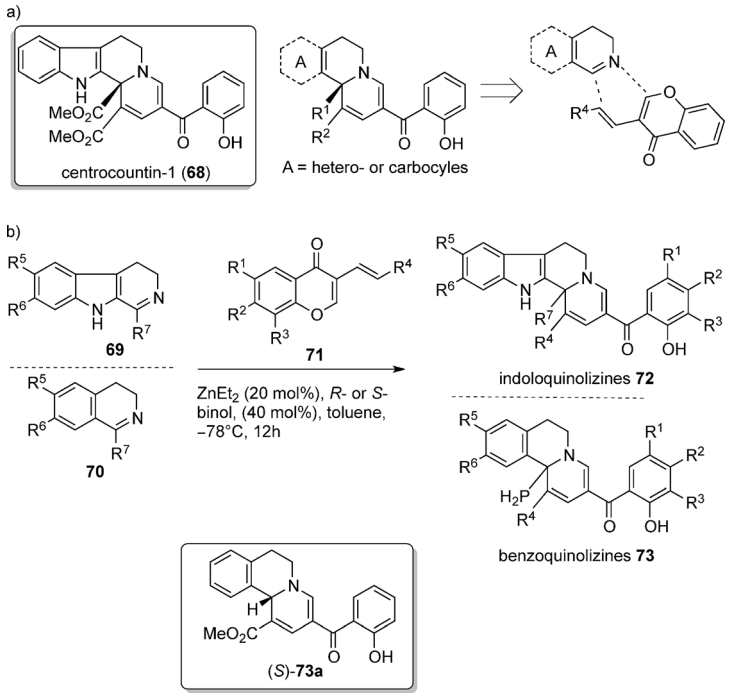
Scheme 11. Rhodium-catalyzed synthesis of (−)-*cis*-aerangis lactone (**66**).

3. Hetero-Diels–Alder Reactions in the Development of Small-Molecule Tools for Chemical Biology

The HDA reaction plays a significant role in the synthesis of complex natural products and the synthesis of small-molecule libraries. Importantly, HDA cycloadditions can provide different heterocyclic scaffolds using suitably substituted heterodienes and dienophiles. However, only in relatively few cases were asymmetric HDA reactions applied in compound-collection synthesis to identify biologically active small molecules.

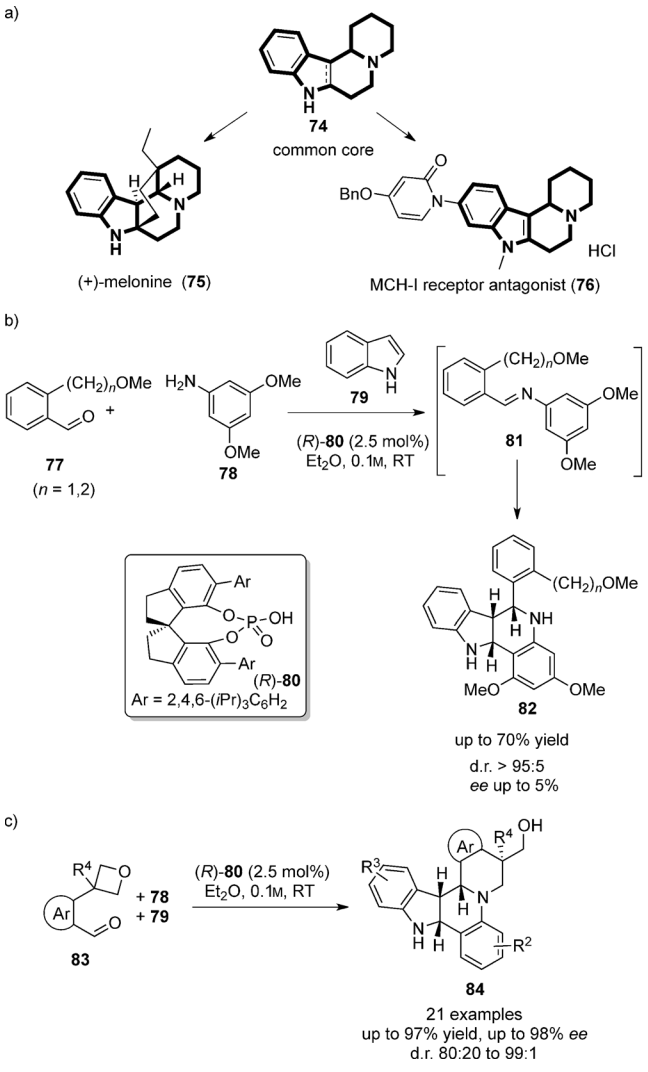
Waldmann et al. discovered modulators of centrosome integrity, termed centrocountins, which caused fragmented and supernumerary centrosomes, chromosome congression defects, multipolar mitotic spindles, acentrosomal spindle poles, and multipolar cell division by targeting the centrosome-associated proteins nucleophosmin and Crm1.[44] The core molecular framework of the centrocountins, that is, the tetrahydro[2,3-*b*]indoloquinolizine was synthesized by means of a cascade reaction sequence which generates a stereogenic center carrying an ester moiety (Scheme 12a).[45,46]

To vary the ester group and to replace the indole moiety with other carbo- and heterocycles (ring A; Scheme 12a), which might provide more potent molecules than centrocountin-1 (**68**), a new synthesis strategy was developed. An enantioselective inverse-electron-demand imino-Diels–Alder (IEDIDA) reaction between various electron-rich cyclic imines (**69** and **70**) and electron-poor chromone dienes (**71**) was developed, thus leading to centrocountin analogues (Scheme 12b). The IEDIDA reaction was catalyzed by a preformed chiral binol/zinc catalyst to yield intermediary cycloadducts which open up to yield either indoloquinolizines (**72**) or benzoquinolizines (**73**). The synthesis provided a compound collection with yields of up to 97% and *ee* values of up to 94%. Subsequently, this compound collection was screened against HeLa cell lines to investigate modulation of the cell cycle. The compound (*S*)-**73a** emerged as a highly potent molecule which blocked mitosis in selected cancer cell lines by inducing chromosome misalignments and formation of tri- and multipolar spindles, thus ultimately leading to apoptotic cell death.



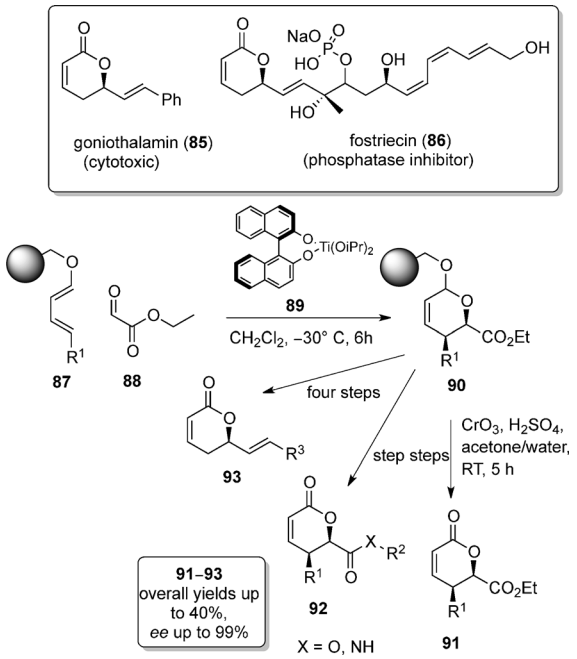
Scheme 12. a) Centrocountin-1 (**68**) and retrosynthetic analysis for analogue synthesis by means of IEDIDA reaction. b) Synthesis of a ring-fused quinolizine compound collection.

Natural products embodying the tetracyclic indole core (**74**; Scheme 13a), such as (+)-melonine (**75**), are used in the treatment of various disorders, including obesity, anxiety, depression, non-alcoholic fatty liver disease, and psychiatric disorders.[47,48] The tetracyclic scaffold of these bioactive molecules has inspired the synthesis of compound collections by means of asymmetric aza-Diels–Alder reactions.[49] For instance, in the synthesis of tetracyclic indoles (**82**), the imines **81** were generated from the aldehydes **77** and aniline **78**, and underwent an aza-Diels–Alder reaction with indole (**79**) in the presence of (*R*)-**80** (Scheme 13b). Introduction of directing ether groups in **77** allowed the installation of three stereogenic centers in **82** with high diastereoselectivity (95:5), however enantioselectivity was low. If the aldehyde was equipped with an oxetane ring as a directing group (see **83**) the reaction proceeded with remarkable diastereo- and enantioselectivity (Scheme 13c). The secondary amine of the cycloadducts induced oxetane ring-opening and thereby the formation of the tetrahydroisoquinoline ring in **84**.



Scheme 13. a) Three-component one-pot hetero-Diels–Alder reaction. b and c) Synthesis of a melonine-inspired compound library consisting of **82** and **84**.

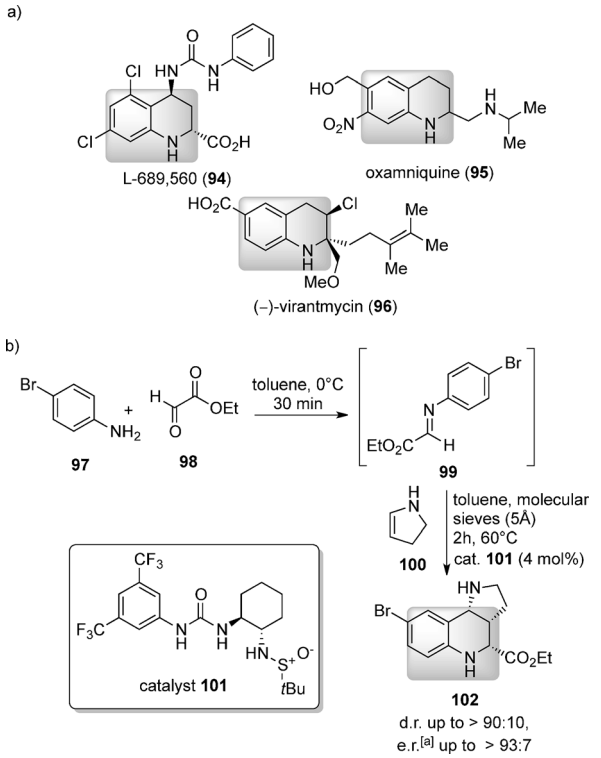
The α,β-unsaturated δ-lactone is a frequently occurring scaffold in natural products[50] which often are antiproliferatives, immunosuppressives, and enzyme inhibitors. For the synthesis of a compound library based on the δ-lactone scaffold, an enantioselective oxa-Diels–Alder reaction on solid support was developed by the group of Waldmann (Scheme 14).[51,52] The resin-bound diene **87** reacted with ethyl



Scheme 14. Solid-phase synthesis of natural-product inspired dehydrolactones (**91**–**93**) through an enantioselective oxa-Diels–Alder reaction.

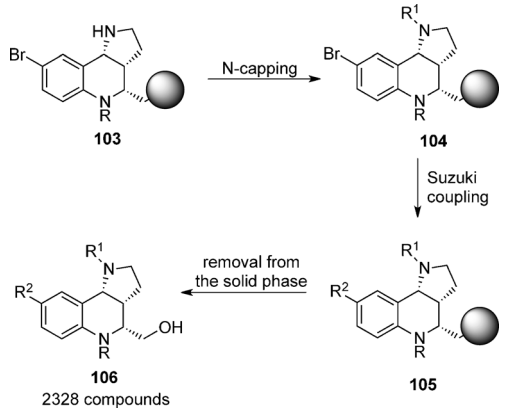
glyoxylate (**88**) in an oxa-Diels–Alder reaction which was catalyzed by the chiral binol/titanium complex **89**. The resin-bound cycloadducts **90**, upon release under oxidative conditions, led to the δ-lactones **91**. The cyloadducts **90** were also transformed into differently substituted δ-lactones (**92** and **93**). Forty compounds were synthesized by this method with up to 40% overall yield and *ee* values of up to 99%. The resulting δ-lactones were evaluated in two phenotype-based screens monitoring cell cycle inhibition and viral entry into cells, and new modulators of both biological events were discovered.

Tetrahydroquinoline (THQ) is a frequently occurring scaffold in natural products and small synthetic molecules endowed with biological activity (Scheme 15a). Highly substituted THQs can be synthesized by means of the Povarov reaction which can simultaneously generate up to three contiguous stereocenters. Different asymmetric versions of this reaction have been developed.[53–58] A library of THQs was synthesized by cooperative catalysis using chiral ureas and in a combination of solution- and solid-phase chemistry. Thus, the aniline **97** and aldehyde **98** formed the imine **99**, which underwent Povarov reaction with the dienophile **100** catalyzed by **101** (Scheme 15b). The THQ **102** was formed with high diastereo- and enantioselectivity. The stereochemically enriched THQ scaffold was further elaborated on solid



Scheme 15. Synthesis of the THQ **102** by an enantioselective Povarov reaction. a) Biologically active natural and synthetic molecules with a THQ scaffold. b) Enantioselective synthesis of a THQ compound library. [a] The enantiomeric excess was measured for the major diastereoisomer **102**.

phase to build a library of THQs.[59] The resin-bound THQ **103**, derived from **102**, was exposed to derivatization by Suzuki coupling and nitrogen capping (N-acylation and N-sulfonylation, amide synthesis, reductive amination, etc.) to introduce diversity into the library (Scheme 16). After removal from the solid phase, 2328 THQ compounds (**106**) were isolated. In silico library design guided the choice of building blocks employed in the production phase and allowed adjustment of the molecular properties of the library members.

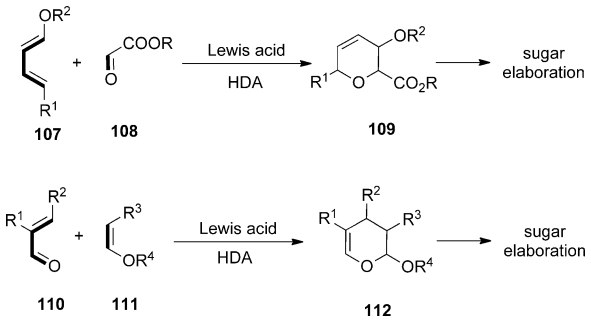


Scheme 16. Solid-phase elaboration of the THQ scaffold for compound library synthesis.

4. Asymmetric HDA Reactions in the Synthesis and Elaboration of Carbohydrates

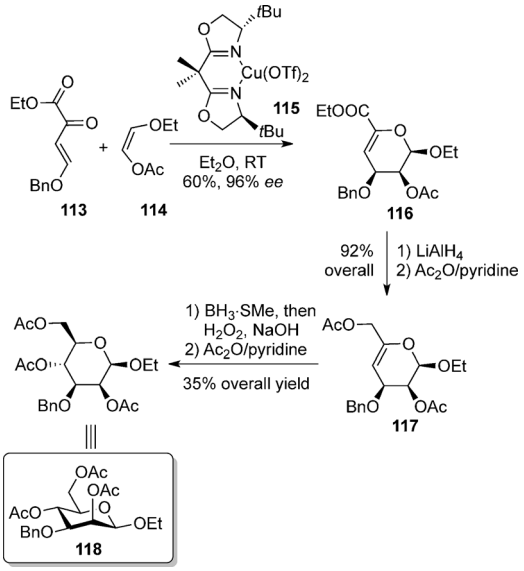
Carbohydrates play important roles in numerous biological processes such as angiogenesis,[60] cancer development,[61,62] immune-system function,[63] and microbial and viral pathogenesis,[64] and increasingly attract attention in pharmaceutical research. Therefore, innovative preparative procedures for carbohydrate synthesis are in high demand.

Chirality plays a crucial role in carbohydrate uptake and function in vivo. Even a single change in a stereocenter can render a carbohydrate biologically inactive.[65] The asymmetric oxa-Diels–Alder reaction can give access to functionalized sugars either by cycloaddition reactions between 1,3-dienes (**107**) and heterodienophiles, like the aldehyde **108**, thus yielding dihydropyrans (**109**) or by reaction between oxa-1,3-dienes (**110**) and vinyl ethers, like **111**, as dienophiles, thus leading to dihydropyrans (**112**; Scheme 17).[66]



Scheme 17. The HDA approach to synthesize and elaborate sugars.

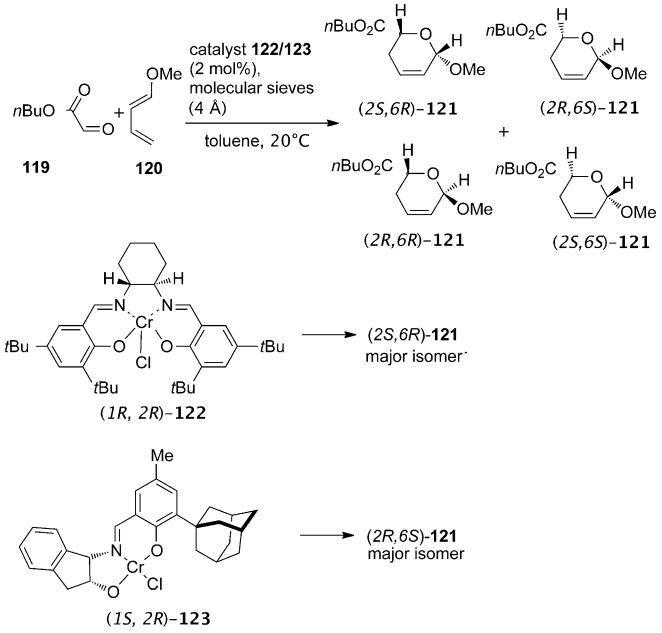
The synthesis of β-D-mannohexopyranoside (**118**) was achieved with an inverse-electron-demand oxa-Diels–Alder (IEDODA) reaction (Scheme 18). The copper complex **115**



Scheme 18. β-D-Mannohexopyranoside (**118**) by HDA of the ketoester **113** and vinyl ether **114**.

catalyzed the IEDODA reaction between the oxadiene **113** and dienophile **114** to yield the dihydropyran **116** in 60% yield and 96% *ee*.[67] Reduction of the ethyl ester with lithium aluminium hydride, and hydroboration with an oxidative workup was followed by O-acetylation, thus leading to **118**.

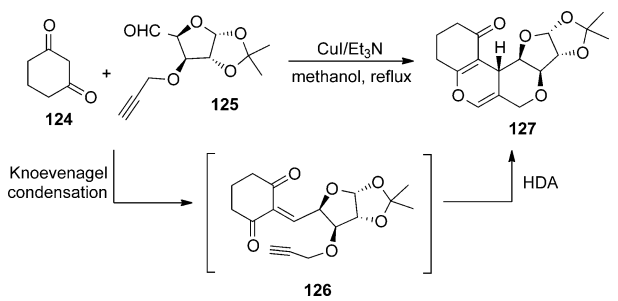
Jurczak et al. employed an alternative oxa-Diels–Alder strategy and used 1-methoxybuta-1,3-diene (**120**) with the glyoxylate **119**[68] in the presence of Jacobsen's chromium(III) catalyst (Scheme 19). While the salen-type complex (1*R*,2*R*)-**122** led to the predominant formation of the cycloadduct (2*S*,6*R*)-**121** in good yield (83%) and with acceptable enantioselectivity (70% *ee*), the tridentate $Cr^{III}Cl$ complex (1*S*,2*R*)-**123** provided the adduct (2*R*,6*S*)-**121** in high yield (96%) and with high enantiomeric excess (88%).



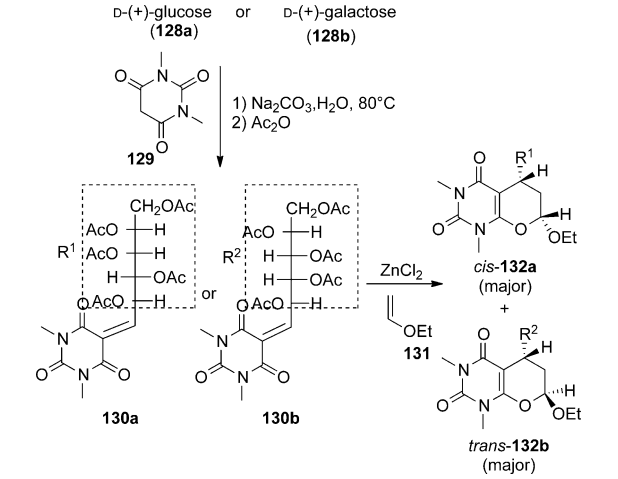
Scheme 19. Asymmetric HDA reaction of **120** with **119** catalyzed by the chromium(III) catalysts **122** and **123**.

Differently ring-fused pyranopyran scaffolds often form the core structures of various natural products. For instance, biscopyran,[69] a phytotoxic hexasubstituted pyranopyran isolated from *Vitex rotundifolia*, suppresses the inflammatory responses related to asthma.[70] Synthetic access to its core scaffold is demanding and often rerquires multistep synthesis sequences. An interesting domino synthesis strategy including an oxa-Diels–Alder reaction was employed to access related carbohydrate analogues. The O-propagyl derivative **125** underwent Knoevenagel condensation with the 1,3-diketone **124**, thus leading to the intermediate **126** which embodies an oxadiene in proximity to an acetylenic moiety (Scheme 20). In the presence of copper iodide, a HDA reaction ensued to form the tetrahydrofuro-pyranopyran **127** in 80% yield[71].

Carbohydrates may also serve as stereodirecting chiral auxiliaries in HDA reactions as shown in a synthesis of pyranopyrimidines (Scheme 21).[72] Knoevenagel condensation of sugars, for instance, D-(+)-glucose (**128a**) or D-(+)-galactose (**128b**) with *N*,*N*-dimethylbarbituric acid in



Scheme 20. Stereoselective domino Knoevenagel/HDA reaction to yield annulated furo[3,2-*b*]pyrano[4,3-*d*]pyrans (**127**).



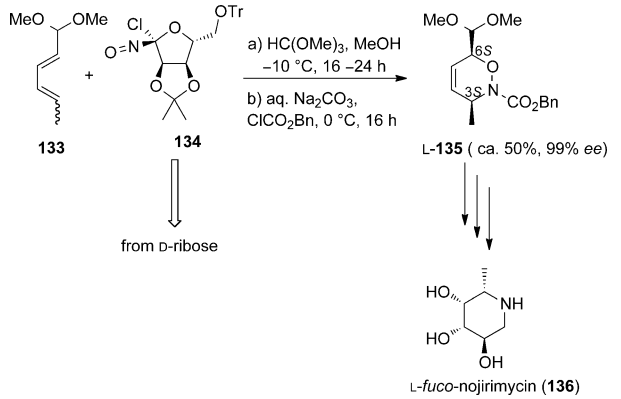
Scheme 21. Sugar-dependent diastereoselective domino Knoevenagel/hetero-Diels–Alder reaction to give the pyranopyrimidines **132**.

water in the presence of a base yielded sodium salts of 5-glycopyranosyl-1,3-dimethylbarbiturates, which after O-acetylation yielded the required oxadienes **130**. The sugar-functionalized barbituric acids **130** reacted with the vinyl ether **131** in an oxa Diels–Alder reaction catalyzed by zinc chloride to yield the pyrano[2,3-*d*]pyrimidines **132**. The sugar moiety influences the diastereoselectivity, that is, D-glucose-derived oxadiene (**130a**) predominantly yielded the *cis*-adduct **132a**, whereas the D-galactose-derived oxadiene **130b** yielded the *trans*-adduct **132b** as a major product.

Iminosugars, like the glycosidase inhibitor[73] L-*fuco*-nojirimycin (**136**), can be synthesized by a nitroso Diels–Alder reaction in which the carbohydrate-derived chiral auxiliary steers the stereochemistry (Scheme 22).[74] Thus, HDA reaction between the diene **133** and nitroso-functionalized sugar **134** (synthesized from D-ribose) followed by N acylation delivered the adduct L-**135** with an enantiomeric excess of 99%.

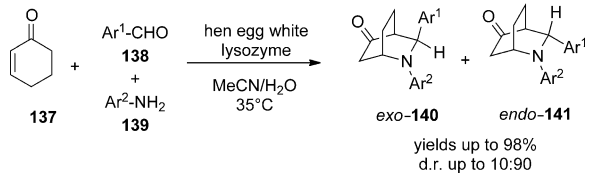
5. Biological Catalysts for Asymmetric HDA Reactions

Although a hetero-Diels–Alderase is yet to be discovered, the example set by the Diels–Alderase enzyme has inspired exploration of biomolecules like antibodies and other pro-



Scheme 22. Synthesis of L-*fuco*-nojirimycin (**136**) employing an enantioselective nitroso-Diels–Alder reaction. Tr = CPh_3.

teins as catalysts for asymmetric HDA cycloadditions.[75–77] Guan et al. described the use of hen egg white lysozyme in a diastereoselective formal aza-Diels–Alder reaction to yield the azabicyclooctanones *exo*-**140** and *endo*-**141** (Scheme 23).

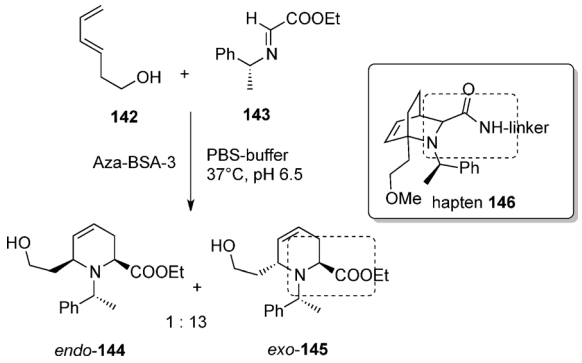


Scheme 23. Diastereoselective aza-Diels–Alder reaction catalyzed with hen egg white lysozyme.

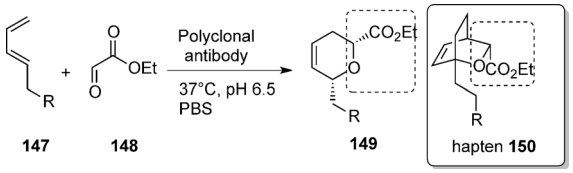
The products were formed with yields of up to 98% and diastereomer ratios up to 90:10. The transformation has broad scope and tolerates different amines and aldehydes.[78] The stereoselectivity of the reaction can be modulated by variation of temperature and solvent. For instance, complete diastereoselectivity in favor of the *exo*-product **140** was observed if the reaction was carried out at 25 °C in pure water. The authors assume that product formation occurs in a Mannich/Michael process which only formally represents an aza-Diels–Alder reaction. Aspartate 52 and glutamate 35 in the enzyme may play significant roles in catalysis. Glu-35 may protonate the carboxy group of the cyclohexenone while Asp-52 may abstract the acidic proton to direct enol addition to an in situ generated imine in a nonconcerted process.

Catalysis of the imino-Diels–Alder reaction was also attempted with polyclonal antibodies. To this end, the azabicyclic hapten **146** was designed to mimic the *exo* transition state of the intended HDA reaction, and used to generate antibodies.[79] Antibody Aza-BSA-3 (Anti-hapten **146**) catalyzed the imino-Diels–Alder reaction between the diene **142** and iminoester **143** in PBS-buffer at 37 °C and pH 7 to yield a mixture of adducts, **144** and **145** (Scheme 24). The *exo*-adduct was formed predominantly and thus validated the design of **146**.

In a related report, polyclonal antibodies raised to the hapten **150**[80] catalyzed the oxa-Diels–Alder reaction be-



Scheme 24. Antibody-catalyzed diastereoselective aza-Diels–Alder reaction.



Scheme 25. Antibody-catalyzed diastereoselective oxa-Diels–Alder reaction.

tween the diene **147** and ethyl glyoxylate **148**, thus leading to the adduct **149** as a single diastereoisomer (Scheme 25).[79]

6. Outlook

Six-membered aza- and oxa-heterocycles frequently occur in both natural products and small bioactive molecules, including drugs endowed with a multitude of biological activities. Although hetero-Diels–Alder reactions provide efficient access to these scaffolds, application of this methodology has not gained as much attention as, for instance, the use of dipolar cycloadditions for heterocycle synthesis and the application of Diels–Alder reactions in carbocycle synthesis. The strategic incorporation of an HDA reaction in the synthesis of complex molecules, for example, natural products, may be complicated on the one hand by the often multistep and tedious synthesis of the required substrates, in particular the heterodienes. On the other hand,[81] reactivity and selectivity problems may frequently be encountered and reaction conditions optimized with model substrates may not be transferable to reactions with more complex starting materials. In general, the development of asymmetric, in particular enantioselectively catalyzed, hetero-Diels–Alder reactions remains highly challenging, and frequently stoichiometric amounts of chiral mediators are required to reach preparatively viable levels of stereoselection.[82] In addition, the substrates for the HDA reactions may be prone to undesired side reactions such as hydrolysis, nucleophilic additions, and/or other cycloadditions,[83] thereby demanding stringent optimization and application of reaction conditions. Recent advances in asymmetric HDA reaction methodology notwithstanding, there remains ample room for further development. In particular, catalytic methods, which employ

readily accessible chiral ligands and catalysts, provide efficient control of diastereo- and enantioselectivity, and tolerate a broad range of substrates are in high demand. Notably, only few inverse electron-demand asymmetric hetero-Diels–Alder reactions have been successfully developed so far. Recently, synthesis methods and pathways employing cascade and domino reactions have found widespread and increasing attention.[84] These reaction sequences could be designed to include asymmetric hetero-Diels–Alder reactions as key steps for the synthesis of complex heterocycles incorporating multiple stereogenic centers.

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[1] H. J. Kim, M. W. Ruszczycky, S.-h. Choi, Y.-n. Liu, H.-w. Liu, *Nature* **2011**, *473*, 109 – 112.
[2] V. Gouverneur, M. Reiter, *Chem. Eur. J.* **2005**, *11*, 5806 – 5815.
[3] G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902 – 923.
[4] J.-A. Funel, S. Abele, *Angew. Chem.* **2013**, *125*, 3912 – 3955; *Angew. Chem. Int. Ed.* **2013**, *52*, 3822 – 3863.
[5] G. B. Rowland, E. B. Rowland, Q. Zhang, J. C. Antilla, *Curr. Org. Chem.* **2006**, *10*, 981 – 1005.
[6] a) M. G. Memeo, P. Quadrelli, *Chem. Eur. J.* **2012**, *18*, 12554 – 12582; b) S. Jayakumar, M. P. S. Ishar, M. P. Mahajan, *Tetrahedron* **2002**, *58*, 379 – 471.
[7] H. Waldmann, *Synthesis* **1994**, 535 – 551.
[8] S. Bonazzi, O. Eidam, S. Güttinger, J.-Y. Wach, I. Zemp, U. Kutay, K. Gademann, *J. Am. Chem. Soc.* **2010**, *132*, 1432 – 1442.
[9] D. E. Chavez, E. N. Jacobsen, *Org. Synth.* **2005**, *82*, 34 – 42.
[10] P. A. Wender, J. L. Baryza, C. E. Bennett, C. Bi, S. E. Brenner, M. O. Clarke, J. C. Horan, C. Kan, E. Lacote, B. Lippa, P. G. Nell, T. M. Turner, *J. Am. Chem. Soc.* **2002**, *124*, 13648 – 13649.
[11] D. S. Kim, C. G. Dong, J. T. Kim, H. B. Guo, J. Huang, P. S. Tiseni, Y. Kishi, *J. Am. Chem. Soc.* **2009**, *131*, 15636 – 15641.
[12] A. Favre, F. Carreaux, M. Deligny, B. Carboni, *Eur. J. Org. Chem.* **2008**, 4900 – 4907.
[13] S. H. Inayat-Hussain, A. B. Osman, L. B. Din, N. Taniguchi, *Toxicol. Lett.* **2002**, *131*, 153 – 159.
[14] C. Wiart, *Evidence-Based Compl. Alt. Med.* **2007**, *4*, 299 – 311.
[15] A. K. Ghosh, K. A. Shurrush, Z. L. Dawson, *Org. Biomol. Chem.* **2013**, *11*, 7768 – 7777.
[16] A. E. Wright, J. C. Botelho, E. Guzman, D. Harmody, P. Linley, P. J. McCarthy, T. P. Pitts, S. A. Pomponi, J. K. Reed, *J. Nat. Prod.* **2007**, *70*, 412 – 416.
[17] H. Fuwa, M. Kawakami, K. Noto, T. Muto, Y. Suga, K. Konoki, M. Yotsu-Yamashita, M. Sasaki, *Chem. Eur. J.* **2013**, *19*, 8100 – 8110.
[18] K. Fuji, T. Yamada, E. Fujita, H. Murata, *Chem. Pharm. Bull.* **1978**, *26*, 2515 – 2521.
[19] O. G. Mancheño, R. G. Arrayás, J. Adrio, J. C. Carretero, *J. Org. Chem.* **2007**, *72*, 10294 – 10297.
[20] J. Yin, K. Kouda, Y. Tezuka, Q. Le Tran, T. Miyahara, Y. J. Chen, S. Kadota, *Planta Med.* **2004**, *70*, 54 – 58.
[21] G. E. Keck, X. Y. Li, D. Krishnamurthy, *J. Org. Chem.* **1995**, *60*, 5998 – 5999.
[22] G. Kumaraswamy, G. Ramakrishna, P. Naresh, B. Jagadeesh, B. Sridhar, *J. Org. Chem.* **2009**, *74*, 8468 – 8471.
[23] M. J. Twiner, N. Rehmann, P. Hess, G. J. Doucette, *Mar. Drugs* **2008**, *6*, 39 – 72.
[24] M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke, T. Yasumoto, *J. Am. Chem. Soc.* **1998**, *120*, 9967 – 9968.
[25] M. J. Twiner, P. Hess, M. Y. B. Dechraoui, T. McMahon, M. S. Samons, M. Satake, T. Yasumoto, J. S. Ramsdell, G. J. Doucette, *Toxicon* **2005**, *45*, 891 – 900.
[26] J. R. Colman, M. J. Twiner, P. Hess, T. McMahon, M. Satake, T. Yasumoto, G. J. Doucette, J. S. Ramsdell, *Toxicon* **2005**, *45*, 881 – 890.
[27] G. Ronzitti, P. Hess, N. Rehmann, G. P. Rossini, *Toxicol. Sci.* **2007**, *95*, 427 – 435.
[28] N. Vilarino, K. C. Nicolaou, M. O. Frederick, E. Cagide, I. R. Ares, M. C. Louzao, M. R. Vieytes, L. M. Botana, *Chem. Res. Toxicol.* **2006**, *19*, 1459 – 1466.
[29] N. V. Kulagina, M. J. Twiner, P. Hess, T. McMahon, M. Satake, T. Yasumoto, J. S. Ramsdell, G. J. Doucette, W. Ma, T. J. O'Shaughnessy, *Toxicon* **2006**, *47*, 766 – 773.
[30] A. Alfonso, M. R. Vieytes, K. Ofuji, M. Satake, K. C. Nicolaou, M. O. Frederick, L. M. Botana, *Biochem. Biophys. Res. Commun.* **2006**, *346*, 1091 – 1099.
[31] C. Vale, K. C. Nicolaou, M. O. Frederick, B. Gomez-Limia, A. Alfonso, M. R. Vieytes, L. M. Botana, *J. Med. Chem.* **2007**, *50*, 356 – 363.
[32] D. A. Evans, L. Kværnø, T. B. Dunn, A. Beauchemin, B. Raymer, J. A. Mulder, E. J. Olhava, M. Juhl, K. Kagechika, D. A. Favor, *J. Am. Chem. Soc.* **2008**, *130*, 16295 – 16309.
[33] J. McNulty, A. Thorat, N. Vurgun, J. J. Nair, E. Makaji, D. J. Crankshaw, A. C. Holloway, S. Pandey, *J. Nat. Prod.* **2011**, *74*, 106 – 108.
[34] C. K. Jana, A. Studer, *Chem. Eur. J.* **2008**, *14*, 6326 – 6328.
[35] L. Acebey, M. Sauvain, S. Beck, C. Moulis, A. Gimenez, V. Jullian, *Org. Lett.* **2007**, *9*, 4693 – 4696.
[36] C. Yuan, B. Du, L. Yang, B. Liu, *J. Am. Chem. Soc.* **2013**, *135*, 9291 – 9294.
[37] H. Itokawa, Z. Z. Ibraheim, Y.-F. Qiao, K. Takeya, *Chem. Pharm. Bull.* **1993**, *41*, 1869 – 1872.
[38] J.-P. Lumb, D. Trauner, *J. Am. Chem. Soc.* **2005**, *127*, 2870 – 2871.
[39] J.-P. Lumb, J. L. Krinsky, D. Trauner, *Org. Lett.* **2010**, *12*, 5162 – 5165.
[40] J. H. Cardellina, R. L. Hendrickson, K. P. Manfredi, S. A. Strobel, J. Clardy, *Tetrahedron Lett.* **1987**, *28*, 727 – 730.
[41] J. Majer, J. Jurczak, P. Kwiatkowski, L. Cotarca, J. C. Caille, *Tetrahedron* **2013**, *69*, 8463 – 8469.
[42] Y. Watanabe, N. Shimada, M. Anada, S. Hashimoto, *Tetrahedron: Asymmetry* **2014**, *25*, 63 – 73.
[43] D. Bartschat, D. Lehmann, A. Dietrich, A. Mosandl, *Phytochem. Anal.* **1995**, *6*, 130 – 134.
[44] H. Dückert, V. Pries, V. Khedkar, S. Menninger, H. Bruss, A. W. Bird, Z. Maliga, A. Brockmeyer, P. Janning, A. Hyman, S. Grimme, M. Schürmann, H. Preut, K. Hübel, S. Ziegler, K. Kumar, H. Waldmann, *Nat. Chem. Biol.* **2012**, *8*, 179 – 184.
[45] V. Eschenbrenner-Lux, H. Dückert, V. Khedkar, H. Bruss, H. Waldmann, K. Kumar, *Chem. Eur. J.* **2013**, *19*, 2294 – 2304.
[46] V. Eschenbrenner-Lux, P. Küchler, S. Ziegler, K. Kumar, H. Waldmann, *Angew. Chem.* **2014**, *126*, 2166 – 2169; *Angew. Chem. Int. Ed.* **2014**, *53*, 2134 – 2137.
[47] S. Baassou, H. M. Mehri, A. Rabaron, M. Plat, *Tetrahedron Lett.* **1983**, *24*, 761 – 762.
[48] P. R. Guzzo, M. D. Surman, A. J. Henderson, M. X. Jiang, *Azinone-substituted azapolycycle mch-1 antagonists, methods of making, and use thereof*, WO 2011003012 A2011003011, **2011**.
[49] Z. Chen, B. Wang, Z. Wang, G. Zhu, J. Sun, *Angew. Chem.* **2013**, *125*, 2081 – 2085; *Angew. Chem. Int. Ed.* **2013**, *52*, 2027 – 2031.
[50] M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl, H. Waldmann, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 17272 – 17277.

[51] T. Leßmann, M. G. Leuenberger, S. Menninger, M. Lopez-Canet, O. Müller, S. Hümmer, J. Bormann, K. Korn, E. Fava, M. Zerial, T. U. Mayer, H. Waldmann, *Chem. Biol.* **2007**, *14*, 443 – 451.
[52] M. A. Sanz, T. Voigt, H. Waldmann, *Adv. Synth. Catal.* **2006**, *348*, 1511 – 1515.
[53] L. He, M. Bekkaye, P. Retailleau, G. Masson, *Org. Lett.* **2012**, *14*, 3158 – 3161.
[54] L. Ren, T. Lei, J. X. Ye, L. Z. Gong, *Angew. Chem.* **2012**, *124*, 795 – 798; *Angew. Chem. Int. Ed.* **2012**, *51*, 771 – 774.
[55] M. S. Xie, X. H. Liu, Y. Zhu, X. H. Zhao, Y. Xia, L. L. Lin, X. M. Feng, *Chem. Eur. J.* **2011**, *17*, 13800 – 13805.
[56] H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. P. Zhu, *J. Am. Chem. Soc.* **2009**, *131*, 4598 – 4599.
[57] T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070 – 13071.
[58] H. Xu, S. J. Zuend, M. G. Woll, Y. Tao, E. N. Jacobsen, *Science* **2010**, *327*, 986 – 990.
[59] B. Gerard, M. W. O'Shea, E. Donckele, S. Kesavan, L. B. Akella, H. Xu, E. N. Jacobsen, L. A. Marcaurelle, *ACS Comb. Sci.* **2012**, *14*, 621 – 630.
[60] R. Kannagi, M. Izawa, T. Koike, K. Miyazaki, N. Kimura, *Cancer Sci.* **2004**, *95*, 377 – 384.
[61] P. Nangia-Makker, J. Conklin, V. Hogan, A. Raz, *Trends Mol. Med.* **2002**, *8*, 187 – 192.
[62] S. F. Slovin, S. J. Keding, G. Ragupathi, *Immunol. Cell Biol.* **2005**, *83*, 418 – 428.
[63] L. Morelli, L. Poletti, L. Lay, *Eur. J. Org. Chem.* **2011**, 5723 – 5777.
[64] J. M. Binley, Y. E. A. Ban, E. T. Crooks, D. Eggink, K. Osawa, W. R. Schief, R. W. Sanders, *J. Virol.* **2010**, *84*, 5637 – 5655.
[65] J. E. Hein, D. G. Blackmond, *Acc. Chem. Res.* **2012**, *45*, 2045 – 2054.
[66] D. D'Alonzo, A. Guaragna, G. Palumbo, *Curr. Org. Chem.* **2009**, *13*, 71 – 98.
[67] H. Audrain, J. Thorhauge, R. G. Hazell, K. A. Jorgensen, *J. Org. Chem.* **2000**, *65*, 4487 – 4497.
[68] P. Kwiatkowski, M. Asztemborska, J. Jurczak, *Synlett* **2004**, 1755 – 1758.
[69] A. Evidente, A. Andolfi, L. Maddau, A. Franceschini, F. Marras, *J. Nat. Prod.* **2005**, *68*, 568 – 571.
[70] S. Park, M.-S. Park, K.-H. Jung, J. Song, Y. A. Kim, H. J. Cho, B.-I. Min, H. Bae, *PLoS One* **2014**, *9*, e87558.
[71] J. S. Yadav, B. V. S. Reddy, A. V. H. Gopal, R. N. Rao, R. Somaiah, P. P. Reddy, A. C. Kunwar, *Tetrahedron Lett.* **2010**, *51*, 2305 – 2308.
[72] A. Pałasz, J. Kalinowska-Tluscik, M. Jablonski, *Tetrahedron* **2013**, *69*, 8216 – 8227.
[73] E. T. Reese, F. W. Parrish, M. Ettlinge, *Carbohydr. Res.* **1971**, *18*, 381 – 388.
[74] M. Dubernet, A. Defoin, C. Tarnus, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1172 – 1174.
[75] M. S. Humble, P. Berglund, *Eur. J. Org. Chem.* **2011**, 3391 – 3401.
[76] A. Babtie, N. Tokuriki, F. Hollfelder, *Curr. Opin. Chem. Biol.* **2010**, *14*, 200 – 207.
[77] O. P. Ward, A. Singh, *Curr. Opin. Biotechnol.* **2000**, *11*, 520 – 526.
[78] Y.-H. He, W. Hu, Z. Guan, *J. Org. Chem.* **2012**, *77*, 200 – 207.
[79] Z.-D. Shi, B.-H. Yang, Y.-L. Wu, Y.-J. Pan, Y.-Y. Ji, M. Yeh, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2321 – 2324.
[80] Y.-J. Hu, Y.-Y. Ji, Y.-L. Wu, B.-H. Yang, M. Yeh, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1601 – 1606.
[81] A. K. Ghosh, K. Xi, *J. Org. Chem.* **2009**, *74*, 1163 – 1170.
[82] K. Ishihara, M. Miyata, K. Hattori, T. Tada, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 10520 – 10524.
[83] C. H. Krauch, S. Farid, G. O. Schenck, *Chem. Ber./Recl.* **1965**, *98*, 3102 – 3117.
[84] V. Eschenbrenner-Lux, H. Waldmann, K. Kumar, *Domino Reactions* (Ed.: L. F. Tietze), Wiley-VCH, Weinheim, **2013**, pp. 497 – 522.