Amino Alcohols:
Stereoselective Synthesis
and Applications in
Diversity-Oriented Synthesis

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Abstract

This thesis is divided into three separate parts with amino alcohols as the common feature.

The first part describes the development of a novel three-component approach to the synthesis of α-hydroxy-β-amino esters. Utilizing a highly diastereoselective Rh(II)-catalyzed 1,3-dipolar cycloaddition of carbonyl ylides to various aldimines, *syn*-α-hydroxy-β-amino esters formed in high yields and excellent diastereoselectivities. This methodology was also applied in a short enantioselective synthesis of the C-13 side-chain of Taxol.

The second part of the thesis describes a total synthesis of D-*erythro*-Sphingosine based on a cross-metathesis approach to assemble the polar head group and the aliphatic chain.

The last part deals with the application of amino alcohols as scaffolds in a diversity-oriented protocol for the development of libraries of small polycyclic molecules. The design of the libraries is based on the iterative use of two powerful ring-forming reactions; a ring-closing metathesis and an intramolecular Diels-Alder reaction, to simultaneously introduce structural complexity and diversity.

Keywords: amino alcohol, carbenoid, carbonyl ylide, cross-metathesis, diastereoselective, 1,3-dipolar cycloaddition, sphingosine, diversity-oriented synthesis, intramolecular Diels-Alder, oxazolidine, ring-closing metathesis.

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Abbreviations

BHT	2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene)
BINOL	1,1-bi-2-naphthol
CM	cross-metathesis
Cy	cyclohexyl
DCE	1,2-dichloroethane
(DHQ)$_2$PHAL	hydroquinine 1,4-phtalazinediyl diether
(−)-DIPT	(−)-diisopropyl tartrate
DMI	1,2-dimethylimidazole
DOS	diversity-oriented synthesis
EDA	ethyl diazoacetate
FMO	frontier molecular orbital
IMDA	intramolecular Diels-Alder
KHMDS	potassium hexamethyldisilazane
NaHMDS	sodium hexamethyldisilazane
p-TSA	*p*-toluene sulfonic acid
Pybox	pyridine bis(oxazoline)
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
RCM	ring-closing metathesis
Rh$_2$(hfb)$_4$	rhodium hexafluorobutyrate
Rh$_2$(*S*-DOSP)$_4$	dirhodium tetrakis(S-(N-dodecyl benzenesulfonyl)prolinate)
SAE	Sharpless asymmetric epoxidation
TOS	target oriented synthesis

List of Publications

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. **1,3-Dipolar Cycloadditions of Carbonyl Ylides to Aldimines: A Three Component Approach to *syn*-α-Hydroxy-β-Amino Esters**
Staffan Torssell, Marcel Kienle and Peter Somfai
Angew. Chem. Int. Ed. in press

II. **A Practical Synthesis of D-*erythro*-Sphingosine Using a Cross-Metathesis Approach**
Staffan Torssell and Peter Somfai
Org. Biomol. Chem. **2004**, *2*, 1643-1646

1. Introduction

"Fashions come and go both in ladies' apparel and in scientific research"

- Rolf Huisgen

During the last decades, organic chemists have achieved spectacular progress in the synthesis of complex molecules. The synthesis of Brevetoxin A and B by K. C. Nicolaou and co-workers, a project that took 16 years to finish, still stands as a milestone in total synthesis (Figure 1).[1]
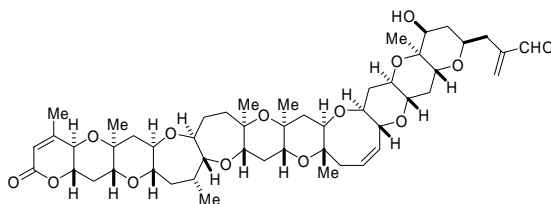

Figure 1. *Brevetoxin B*

Although Nicolaou, Kishi and others have clearly shown, by their amazing work, that chemists are capable of synthesizing almost any compound imaginable, there is a growing demand for new discoveries in the field of organic chemistry since the synthetic methods existing today are still far from satisfactory. The challenge in organic chemistry today, lies not so much in the synthesis of monstrous natural products, which can evidently be achieved with enough manpower, time and money, as in the development of new, straightforward methodologies for the construction of complicated targets and sub-structures. One interesting example is the four-step enzymatic synthesis of the anti-cancer agent Epothilone C by Khosla and co-workers.[2] New areas like click-chemistry, developed by Sharpless and co-workers,[3] and organocatalysis,[4] developed by the MacMillan and List groups, are two examples where the chemists have moved away from the more "traditional" way of thinking about organic chemistry. Instead they are recognizing what could be looked upon as simple, but still brilliant solutions to many of the problems existing in modern organic chemistry, such as hazardous byproducts, expensive and complicated metal-catalysts, just to name a few. Other areas like diversity-oriented synthesis, described by Schreiber and co-

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[1] Nicolaou, K. C.; Tiebes, J.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Koide, K.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1994**, *116*, 9371-9372; Nicolaou, K. C.; Yang, Z.; Shi, G.-S.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264-269; Nicolaou, K. C. *Tetrahedron* **2003**, *59*, 6683-6738.

[2] Boddy, C. N.; Hotta, K.; Tse, M. L.; Watts, R. E.; Khosla, C. *J. Am. Chem. Soc.* **2004**, *126*, 7436-7437.

[3] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

[4] Rouhi, A. M. *C & EN* **2004**, *82*, 41-45; Special issue *Acc. Chem. Res.* **2004**, *37*, 487-631.

workers,[5] have opened new opportunities for chemists to use small molecules to perturb and gain new understanding of functions required in living organisms. These are just a few of the new revolutionizing areas within the organic chemistry community that will set the standard for future developments.

1.1. *vic*-Amino Alcohols

The β-amino alcohol and α-hydroxy-β-amino acid moieties are found in a large variety of biologically important compounds, e.g. natural products and peptides, as well as in a growing number of ligands and chiral auxiliaries for asymmetric synthesis. Amino alcohols are mainly divided into three general subgroups; 1) naturally occurring amino alcohols, 2) synthetic, pharmacologically active amino alcohols and 3) chiral catalysts and auxiliaries containing the amino alcohol motif.[6]

Hydroxy amino acids is the most common class of naturally occurring compounds containing the β-amino alcohol subunit. For example, the vancomycin[7] class of antibiotics contains an arylserine moiety (Figure 2) and the antifungal agent sphingofungin (Figure 7, Chapter 3) contains a hydroxy amino acid moiety in the polar head group. Another large group of biologically active natural products is the cyclic amino alcohols, for example quinine that is used for malaria treatment. One important class of cyclic amino alcohols is the polyhydroxylated alkaloids, also known as aza-sugars, e.g. castanospermine[8] that was found to be a potent inhibitor of α- and β-glucosidases.

Vancomycin fragment

Quinine

(+)-Castanospermine

Saquinavir

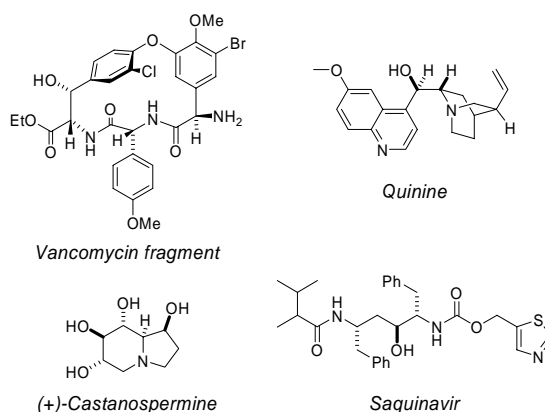**Figure 2.** *Biologically Active β-Amino Alcohols*

[5] Schreiber, S. L. *Science* **2000**, *287*, 1964-1969.

[6] Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561-2576.

[7] Nicolaou, K. C.; Boddy, C. N. *J. Am. Chem. Soc.* **2002**, *124*, 10451-10455.

[8] Michael, J. P. *Natural Product Reports* **1999**, *16*, 675-696; Michael, J. P. *Natural Product Reports* **2001**, *18*, 520-542.

Peptidomimetics constitutes a large group of synthetically produced pharmacologically active amino alcohols, most commonly Renin and HIV-1 protease inhibitors, for example Saquinavir (Figure 2).[6,9]

β-Amino alcohols also play an important role as chiral ligands and chiral auxiliaries in asymmetric catalysis, most commonly derived from natural sources. The amino alcohols are generally derivatized to improve their chelating ability or to increase their steric directing effect.[10] Figure 3 depicts common β-amino alcohol derivatives used in asymmetric synthesis.[11]
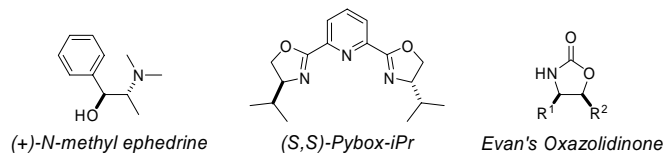

(+)-N-methyl ephedrine   *(S,S)-Pybox-iPr*   *Evan's Oxazolidinone*

Figure 3. *Examples of β-Amino Alcohol-containing Chiral Ligands and Auxiliaries*

1.2. Synthesis of *vic*-Amino Alcohols

Synthetic routes towards enantiopure *vic*-amino alcohols have traditionally mainly relied on derivatization of the chiral pool of amino acids, with the inherent limitation of accessible targets.[12] To circumvent these drawbacks, considerable efforts have been made to develop asymmetric routes to β-amino alcohols, which can be divided into two strategically different approaches. Most commonly, the amino alcohol functionality can be introduced on a pre-existing carbon skeleton. A more efficient approach is the concomitant formation of a new carbon-carbon bond and one or two of the vicinal stereogenic centers in one single step.

1.2.1. Amino Alcohols from a Pre-Existing Carbon Skeleton

The most common approach to stereoselective synthesis of β-amino alcohols starts from a pre-existing carbon skeleton. Alkenes or alkene derivatives are frequently used as substrates for these transformations that often proceed stereospecifically. In addition, these reactions are often accompanied by regioselectivity issues. Although this is a major concern, it can be circumvented if the substrate contains a regio-directing group.

Probably the most investigated route towards enantiomerically pure β-amino alcohols is opening of epoxides with nitrogen nucleophiles. Since both *cis*- and *trans*-epoxides are available in high enantiomeric purity, this approach can be utilized in the synthesis of both *syn*- and *anti*-β-amino alcohols. The regioselectivity of epoxide openings is often poor but can be controlled by introduction of conjugating groups, *e.g.* phenyl or vinyl, the attack of hard

[9] Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277-3284.

[10] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835-875.

[11] Frantz, D. E.; Fässler, R.; Carriera, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807; Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227-2302; Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3-12.

[12] Reetz, M. T. *Angew. Chem. Int. Ed.* **1991**, *30*, 1531-1546.

nucleophiles usually proceeds at the activated benzylic and allylic carbon, respectively (Scheme 1).[13,14]

Scheme 1. *Aminolysis of Vinylepoxides*

78 - 100%
dr 2:1 - 100:0
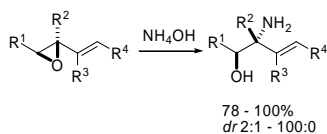
β-Amino alcohols can also be obtained through ring-opening of other cyclic substrates such as aziridines,[14,15] sulfates[16] and carbonates.[17]

The most direct approach toward enantioselective synthesis of β-amino alcohols is the Sharpless asymmetric aminohydroxylation of alkenes. The chiral catalyst utilized in this reaction is the same as in the asymmetric dihydroxylation reaction. α,β-Unsaturated esters and phosphonates have proven to be the most suitable substrates for this reaction (Scheme 2).[18] Although this transformation is an attractive approach to the direct enantioselective synthesis of amino alcohols, the yields are often moderate due to regioselectivity problems.

Scheme 2. *Sharpless Asymmetric Aminohydroxylation*

55 - 90%
ee 90 - 99%
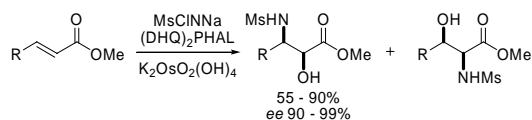
1.2.2. Amino Alcohols from C-C Bond Forming Reactions

The amino alcohol moiety can also be constructed by coupling two fragments, one containing the oxygen functionality and one containing the nitrogen functionality, with a concomitant formation of a new carbon-carbon bond and two vicinal stereogenic centers that requires both enantio- and diastereocontrol. Generally, this approach is limited to certain types of substrates. There are mainly two different strategies employed for enantioselective synthesis of amino alcohols based on C-C bond forming

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[13] Jaime, C.; Ortuno, R., M.; Font, J. *J. Org. Chem.* **1988**, *53*, 139-141.

[14] Olofsson, B.; Somfai, P. *J. Org. Chem.* **2002**, *67*, 8574-8583.

[15] Hwang, G.-I.; Chung, J.-H.; Lee, W. K. *J. Org. Chem.* **1996**, *61*, 6183-6188.

[16] Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett.* **1989**, *30*, 2623-2626; Chang, H.-T.; Sharpless, B. *Tetrahedron Lett.* **1996**, *37*, 3219-3222.

[17] Cho, G. Y.; Ko, S. Y. *J. Org. Chem.* **1999**, *64*, 8745-8747.

[18] Li, G.; Chang, H.-T.; Sharpless, B. K. *Angew. Chem. Int. Ed.* **1996**, *35*, 451-454.

reactions; Mannich-type reactions[19] and addition of glycine derived enolates to aldehydes, which will be discussed below.[20]

One elegant example on a highly stereoselective Mannich-type reaction is based on a nucleophilic additions of α-alkoxy enolates to imines affording amino alcohols with high to excellent enantioselectivity (Scheme 3).[21] Depending on the choice of enolate, both *syn* (R^2 = TBS) and *anti* (R^2 = Bn) amino alcohols can be formed with high diastereoselectivity.

Scheme 3. *Enantioselective Mannich-type Approach*

41 - 100%
syn:anti >99:1 - 6:94
ee 76 - 98%
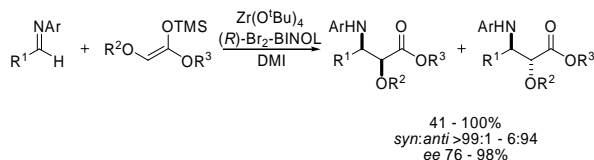
The amino alcohols could also be synthesized using Lewis acid-catalyzed aldol reactions. Zirconium/BINOL-catalyzed reactions of glycine derived silyl ketene acetals to aldehydes furnishes *anti*-β-hydroxy-α-amino acids in excellent yields and enantioselectivities (Scheme 4).[22]

Scheme 4. *Enantioselective Aldol Approach*

71 - 93%
anti:syn 78:22 - 92:8
ee 85 - 97%
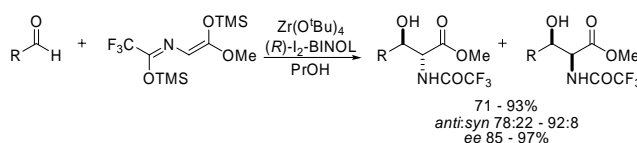
Another approach would be to utilize the stereodirecting effect of a pre-existing stereogenic center. This could be done by nucleophilic additions to α-amino aldehydes, which usually proceed with good diastereoselectivity. One recent example on a divergent protocol for substrate-controlled diastereoselective synthesis of aminodiols based on nucleophilic Mukaiyama aldol additions to α-amino-β-silyloxy aldehydes is depict in Scheme 5.[23] The stereochemical outcome of these reactions is dependent both on the inherent stereochemistry of the aldehyde, *i.e. syn* or *anti*, and the substitution pattern on the nitrogen, *i.e.* chelation- or Felkin-Anh control.

[19] List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827-833; Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842-1843; Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338-339; Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712-4713.

[20] Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843-3846; Yoshikawa, N.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 8289-8298; Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4542-4544.

[21] Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431-432.

[22] Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192-9193.

[23] Restorp, P.; Somfai, P. *Org. Lett.* **2005**, *7*, 893-895.

Scheme 5. *Aminodiols from Diastereoselective Mukaiyama Aldol Additions*

| Chelation-control	Felkin-Anh control
91 - 94%	81 - 92%
dr 92:8 - 98:2	*dr* >98:2
88 - 89%	49 - 91%
dr 88:12 - 98:2	*dr* 44:56 - 47:53

R^2 = H or Bn
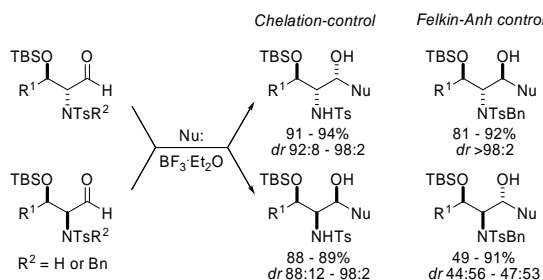
1.3. 1,3-Dipolar Cycloaddition Reactions

The 1,3-dipolar cycloaddition reaction is a five-atom equivalent of the Diels-Alder reaction for the formation of five-membered rings (Scheme 6). The reacting components in the 1,3-dipolar cycloaddition are a 4π-electron component (1,3-dipole or ylide **A**) and a 2π-electron component (dipolarophile **B**), which reacts in a $[4\pi_s+2\pi_s]$-fashion to form the five-membered heterocycle **C**. The reaction is mechanistically related to the Diels-Alder reaction, in which a four-atom, 4π-electron component (diene **D**) and a 2π-electron component (dienophile **E**) also react in a $[4\pi_s+2\pi_s]$-fashion to yield a six-membered ring **F** (Scheme 6). The 1,3-dipolar cycloaddition reaction is a powerful method to generate complex five-membered heterocycles containing multiple stereogenic centers from simple starting materials with high level of stereocontrol. Consequently, the reaction is often included as key step in the synthesis of many complex natural products and biologically active compounds.

Scheme 6. *1,3-Dipolar Cycloaddition and the Diels-Alder Reaction*
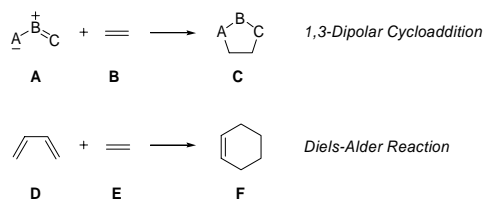
The asymmetric 1,3-dipolar cycloaddition of various 1,3-dipoles and dipolarophiles using different chiral catalysts and auxiliaries has emerged as a relatively new area of research during recent years. Considerable progress has been made, resulting in novel routes to enantiomerically enriched heterocycles. Although these results have provided valuable synthetic tools there are still unexplored aspects of 1,3-dipolar cycloaddition reactions.

1.3.1. 1,3-Dipoles
The 1,3-dipole, or ylide, is a three-atom, 4π-electron system consisting of two filled and one empty orbital. 1,3-Dipoles can be divided into two main groups

and they have at least one zwitterionic resonance structure where the charges are located in a 1,3-fashion (Figure 4):[24]

Propargyl anion-type: 1,3-dipoles in which one of the resonance structures has a double bond on the sextet atom and the other resonance structure has a triple bond on that atom.

Allyl anion-type: 1,3-dipoles where one of the resonance structures has a single bond on the sextet atom and the other structure has a double bond.
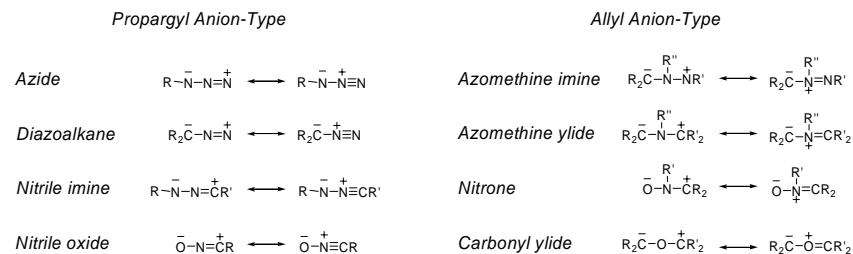
Propargyl Anion-Type

Allyl Anion-Type

Azide   R–N̄–N=N⁺ ⟷ R–N̄–N⁺≡N

Azomethine imine   R₂C̄–N⁺(R")–NR' ⟷ R₂C–N⁺(R")=NR⁻

Diazoalkane   R₂C̄–N=N⁺ ⟷ R₂C̄–N⁺≡N

Azomethine ylide   R₂C̄–N⁺(R")–CR'₂ ⟷ R₂C–N⁺(R")=CR'₂⁻

Nitrile imine   R–N̄–N=C⁺R' ⟷ R–N̄–N⁺≡CR'

Nitrone   Ō–N⁺(R')–CR₂ ⟷ Ō–N⁺(R')=CR₂

Nitrile oxide   Ō–N=C⁺R ⟷ Ō–N⁺≡CR

Carbonyl ylide   R₂C̄–O⁺–CR'₂ ⟷ R₂C̄–O⁺=CR'₂

Figure 4. Common 1,3-Dipoles

1.3.2. Dipolarophiles

The dipolarophile is a 2π-electron moiety that readily reacts with 1,3-dipoles in 1,3-dipolar cycloadditions. Most commonly, electron deficient alkenes are used as dipolarophiles, *e.g.* α,β-unsaturated carbonyl functionalities, but allylic alcohols, allylic halides, vinylic ethers and alkynes are also frequently employed (Figure 5). However, other 2π-electron species such as carbonyl groups and imines have also shown to be excellent dipolarophiles when combined with certain 1,3-dipoles.[25]
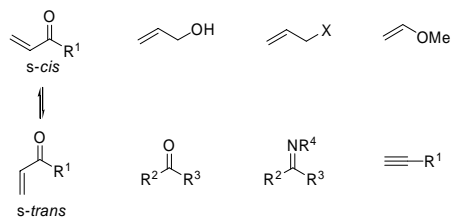

**Figure 5.** Various C-C Dipolarophiles Used in 1,3-Dipolar Cycloadditions

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[24] Smith, M. B.; March, J. *March's Advanced Organic Chemistry*; 5 ed.; John Wiley & Sons, Inc.: New York, 2001.
[25] Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223-269; Mehta, G.; Muthusamy, S. *Tetrahedron* **2002**, *58*, 9477-9504.

1.3.3. Stereo- and Regioselectivity in 1,3-Dipolar Cycloadditions

Generally, 1,3-dipolar cycloadditions are regarded as concerted processes. As a consequence, when 1,3-dipoles react with 1,2-substituted alkenes, the two newly formed stereogenic centers are created in a stereospecific manner due to the *syn*-attack of the dipole, *i.e.* a *trans*-alkene gives rise to a *trans*-substituted five-membered heterocycle (Scheme 7).[26] In the case of a non-concerted, step-wise mechanism one terminus of the dipole adds first to the *trans* alkene dipolarophile, which results in an intermediate where a rotation around the C-C bond in the dipolarophile part of the intermediate would yield the isomeric *cis*-five-membered heterocycle (Scheme 7).

Scheme 7. Concerted vs. Non-Concerted 1,3-Dipolar Cycloadditions
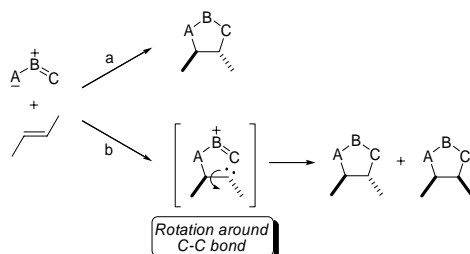
a) Concerted mechanism b) Non-concerted mechanism

The transition state in 1,3-dipolar cycloadditions can be rationalized with the FMO-theory. The reaction can either be controlled by $HOMO_{dipole}$-$LUMO_{dipolarphile}$ interactions or $LUMO_{dipole}$-$HOMO_{dipolarphile}$ interactions. Sustmann has categorized 1,3-dipolar cycloaddition reactions into three types based on the relative FMO energies of the dipoles and the dipolarophiles.[27] For Type I reactions, the dominant interaction is between the HOMO of the dipole and the LUMO of the dipolarophile, *e.g.* reactions with azomethine ylides and carbonyl ylides. For Type II reactions, the reactants have similar FMO energies and consequently the HOMO-LUMO interactions of both dipole-dipolarophile and dipolarophile-dipole are important. For Type III reactions, the dominant interaction is between the LUMO of the dipole and the HOMO of the dipolarophile. This classification of the 1,3-dipolar cycloaddition reaction is also dependent on the dipolarophile. Substituents on the dipole and the dipolarophile influence and perturb the FMO-energies, which can have dramatic effect on the reactivity, the regio- and the diastereoselectivity of the reaction.

The regioselectivity in the reaction is governed by both steric and electronic effects. The addition of dipoles to terminal olefins usually proceeds with addition of the most sterically encumbered dipole functionality to the terminal

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[26] Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, Inc: New York, 1984; Vol. 1, pp 1-176.

[27] Sustmann, R. *Tetrahedron Lett.* **1971**, 2717-2720; Sustmann, R. *Pure Appl. Chem.* **1974**, *40*, 569-593.

olefin carbon.[28] However, these steric effects can be overruled by strong electronic effects, for example reactions with olefins substituted with strong electron-withdrawing or electron-donating groups. When the electronic properties of the substrates are dictating the selectivity, the atom with the largest FMO coefficient in the dipole will interact with the atom with the largest FMO coefficient in the dipolarophile (Scheme 8).[28]

Scheme 8. *Regioselectivity in the 1,3-Dipolar Cycloaddition*
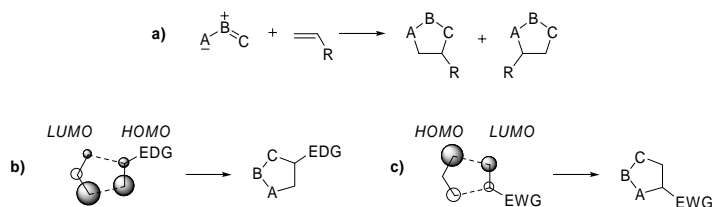
When an allyl anion-type dipole reacts with a dipolarophile the reaction could either go through an *endo*- or an *exo*-transition state producing diastereomeric products. In contrast to the Diels-Alder reaction, where the *endo*-TS can be stabilized by secondary π-orbital interactions, the interaction between the LUMO$_{dipole}$ and the HOMO$_{dipolarophile}$ in the *endo*-TS is usually small (Type II and III). In the case of a Type I reaction, the secondary π-orbital interaction is absent due to the node in the dipole molecular orbital (Scheme 8c). The diastereoselectivity is consequently primarily controlled by steric interactions of the reactants (Scheme 9).[29]

Scheme 9. *Diastereoselectivity in the 1,3-Dipolar Cycloaddition*

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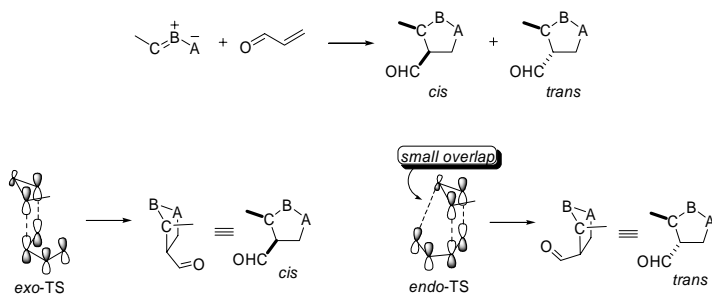
[28] Houk, K. N.; Yamaguchi, K. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley & Sons, Inc: New York, 1984; Vol. 2, pp 407-450.

[29] Gothelf, K. V.; Hazell, R.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346-355; Gothelf, K. V. In *Cycloaddition Reaction in Organic Chemistry*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2001, pp 211-247.

2.
1,3-Dipolar Cycloadditions
of Carbonyl Ylides to Aldimines:
# Synthesis of syn-α-Hydroxy-β-Amino Esters

(Paper I)

2.1. Introduction

As the structural complexity of synthetic targets originating both from natural and synthetic sources increases, there is a growing demand for methodologies for their construction. As such, there is a constant development of new procedures and refinement of already established procedures and methodologies to meet these demands. Cycloaddition chemistry has always been one of the key transformations in modern synthetic organic chemistry for the construction of mono- and polycyclic systems, since it results in increased molecular complexity with high level of stereocontrol from often relatively simple and readily available precursors.

2.1.1. 1,3-Dipolar Cycloadditions of Carbonyl Ylides

Carbonyl ylides are highly reactive dipoles that have been used as key intermediates in a variety of reactions since the 1960s. The structural analysis of a carbonyl ylide reveals that it is a 1,3-dipole **G** (Scheme 10) and can therefore undergo different reaction pathways; internal cyclization reactions forming epoxides **H** or concerted rearrangements and internal proton transfers to neutralize the charged ylide yielding substituted ethers **I**. The synthetically most useful transformation is the 1,3-dipolar cycloaddition reactions, where the carbonyl ylides readily react with double- and triple-bonds yielding the corresponding five-membered oxacycles **J**.[30]

***Scheme 10**. Reactions of Carbonyl Ylides*
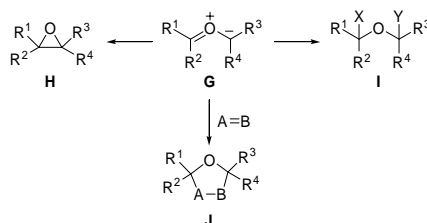
Transition metal-catalyzed diazo decomposition in the presence of aldehydes is an attractive method for the formation of stabilized carbonyl ylides (Scheme 11). Decomposition of diazo compounds leads to formation of highly

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[30] McMills, M. C.; Wright, D. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Towards Heterocycles and Natural Products*; Padwa, A., Pearson , W. H., Eds.; John Wiley & Sons, Inc.: New York, 2002, pp 253-314.

electrophilic metallocarbenoids. These electrophilic compounds can then interact with nonbonding electrons contributed by a Lewis base. If the Lewis base is an uncharged compound, this interaction leads to the formation of an ylide. Nucleophilic species are known to trap carbenes, *e.g.* ethers, amines and halides, as well as sp^2- or sp-hybridized heteroatoms, *e.g.* aldehydes, esters, ketones and imines.[31]

Scheme 11. *Metal-catalyzed Diazo Decomposition*
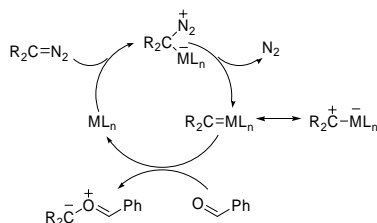
Diazo decomposition and subsequent carbonyl ylide formation

Intramolecular 1,3-dipolar cycloaddition reactions of diazo-derived ylides have been used as key-steps in the synthesis complex natural products by Padwa and others,[25] while examples of intermolecular 1,3-dipolar cycloadditions of carbonyl ylides have been scarce.[32,33,34] Doyle and co-workers have recently investigated the reactivity of carbonyl ylides and thereby increased the understanding of substituent effects on the product outcome.[35] Suga and co-workers have developed the first example of a highly enantioselective 1,3-dipolar cycloaddition of a carbonyl ylide with various dipolarophiles catalyzed by chiral Lewis acids (Scheme 12).[34]

Scheme 12. *Lanthanide/Pybox-catalyzed Asymmetric Carbonyl Ylide Cycloaddition*

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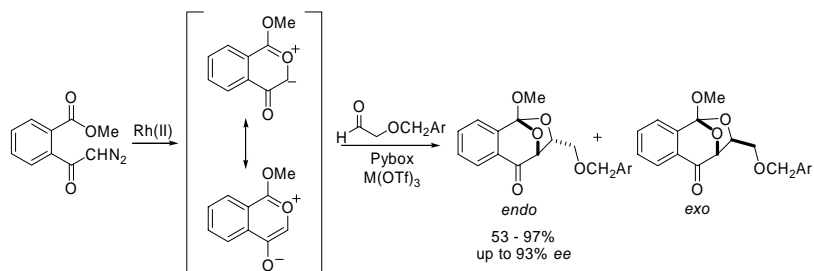
[31] Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263-309.

[32] Huisgen, R.; de March, R. *J. Am. Chem. Soc.* **1982**, *104*, 4953-4954; Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100-3109; Jiang, B.; Zhang, X.; Luo, Z. *Org. Lett.* **2002**, *4*, 2453-2455.

[33] Lu, C.-D.; Chen, Z.-Y.; Liu, H.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2004**, *6*, 3071-3074.

[34] Suga, H.; Inoue, K.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47-56.

[35] Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269-5274.

### 2.1.2. 1,3-Dipolar Cycloadditions of Azomethine Ylides

One of the most important classes of 1,3-dipolar cycloadditions involves azomethine ylides. 1,3-Dipolar cycloadditions using azomethine ylides is the conceptually most simple and efficient method for the construction of saturated, nitrogen-containing, five-membered heterocycles. Ylide generation, often performed *in situ*, followed by cycloaddition with suitable dipolarophiles furnishes pyrrolidines and pyrrolines in only one step from simple starting materials. Since the azomethine ylide is inherently achiral, the chiral induction must come from either a chiral auxiliary on the dipole/dipolarophile or from a chiral catalyst. Schreiber and co-workers have recently developed an elegant approach using a silver(I) acetate/QUINAP-catalyzed [3+2] azomethine ylide cycloaddition of α-imino esters and acrylates furnishing 3-substituted pyrrolidines in excellent yields and enantioselectivities (Scheme 13).[36] The azomethine ylides are formed by deprotonation in the α-position followed by a bidentate complexation of the chiral catalyst to the imine nitrogen and the enolate oxygen.

Scheme 13. *Ag(I)-catalyzed Asymmetric Azomethine Ylide Cycloaddition*

89 - 95%
89 - 96% *ee*

(S)-QUINAP
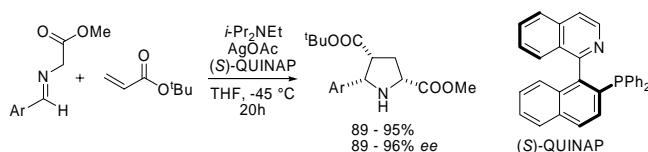
Another attractive mild method for azomethine ylide formation is the combination of a metallocarbene and an imine. The 1,3-dipole intermediate generated *in situ* could then be reacted with a variety of dipolarophiles, most commonly alkene or alkyne moieties (Scheme 14).[37,38,39]

Scheme 14. *Metal-catalyzed Three-Component Formation of Pyrrolidines*
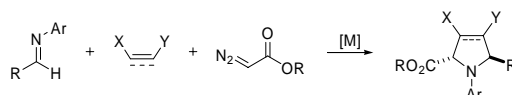
2.1.3. Aim of the Study and Synthetic Strategy

The aim of this study is to develop a novel entry to *vic*-amino alcohols using a 1,3-dipolar cycloaddition reaction. We envisioned that amino alcohols **1** could be obtained by hydrolysis of the corresponding oxazolidines **2**, and that these heterocycles could be available by a 1,3-dipolar cycloaddition reaction of either a carbonyl ylide **3** to an imine **4a** (Scheme 15, disconnection **A**) or by a 1,3-dipolar cycloaddition of an azomethine ylide **5** to an aldehyde **6b** (Scheme 15, disconnection **B**). The carbonyl ylides are derived from carbene insertion of **7a** on aldehyde **6a** and the azomethine ylides are prepared by

[36] Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174-10175.

[37] Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1995**, *34*, 676-678.

[38] Jørgensen, K. A.; Rasmussen, K. G. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1287-1291; Li, G.-Y.; Chen, J.; Yu, W.-Y.; Hong, W.; Che, C.-M. *Org. Lett.* **2003**, *5*, 2153-2156.

[39] Galliford, C. V.; Beenan, M. A.; Nguyen, S. T.; Scheidt, K. A. *Org. Lett.* **2003**, *5*, 3487-3490.

carbene insertion of **7b** on imine **4b**. This approach might suffer from potential chemoselectivity problems since both pathways start from the same types of starting materials and both aldehydes and imines could potentially react with carbenes forming the corresponding ylides (*vide infra*).

Multi-component cycloadditions involving carbonyl ylides[33,35] and azomethine ylides[37,39,40] as well as ammonium[41] and oxonium ylides[42] derived from transient carbenoid intermediates have received a lot of attention in the literature lately. Judging from what has been reported there are no given answers whether a metallocarbene would react with an aldehyde forming a carbonyl ylide, or if it would react with an imine to form an azomethine ylide. It has been reported that the substituent on the imine nitrogen has a large impact on the azomethine ylide formation; electron-donating substituents usually work better than electron-withdrawing substituents.[38,39]

Scheme 15. *Retrosynthetic Analysis of vic-Amino Alcohol Synthesis*
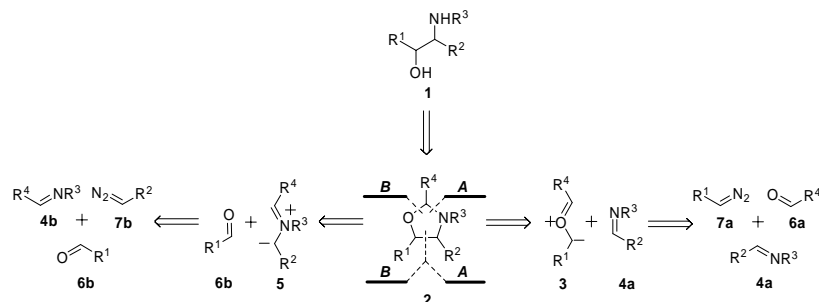
2.2. 1,3-Dipolar Cycloadditions

In our initial investigation, commercially available benzylidene benzylamine (**8a**) and benzaldehyde (**9a**) were chosen as the imine and aldehyde components together with ethyl diazoacetate (EDA, **10**) and $Rh_2(OAc)_4$ as catalyst (Scheme 16). Reaction using literature conditions[34] (rt and addition of EDA over 1 h) afforded the desired cycloadduct **11**, which upon hydrolysis yielded *vic*-amino alcohol **12** (*dr* 93:7) in 82% yield.

Scheme 16. *1,3-Dipolar Cycloaddition; Carbonyl Ylide vs. Azomethine Ylide*

R[1] = CO_2Et R[2] = Ph via carbonyl ylide
R[1] = Ph R[2] = CO_2Et via azomethine ylide
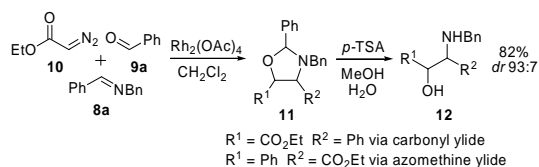
[40] Yan, M.; Jacobsen, N.; Hu, W.; Gronenberg, L. S.; Doyle, M. P.; Colyer, J. T.; Bykowski, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 6713-6716.
[41] Wang, Y.; Zhu, Y.; Chen, Z.; Mi, A.; Hu, W.; Doyle, M. P. *Org. Lett.* **2003**, *5*, 3923-3926.
[42] Lu, C.-D.; Liu, H.; Chen, Z.-Y.; Hu, W.-H.; Mi, A.-Q. *Org. Lett.* **2005**, *7*, 83-86.

14

In order to determine the regiochemistry and the relative stereochemistry of the amino alcohol and thereby elucidate the reaction pathway, *i.e.* azomethine ylide or carbonyl ylide intermediate, the product had to be further derivatized. The relative stereochemistry of *vic*-amino alcohols is most easily confirmed by converting the compound into the corresponding oxazolidinone (**13**) using standard conditions[14] followed by ^{1}H NMR analysis of the geminal 4,5 coupling constant (Scheme 17). The coupling constant was 5.1 Hz, which is consistent with a 4,5-*trans* stereochemistry.[43]

Scheme 17. *Determination of Relative Stereochemistry*

R[1] = CO_2Et R[2] = Ph via carbonyl ylide
R[1] = Ph R[2] = CO_2Et via azomethine ylide
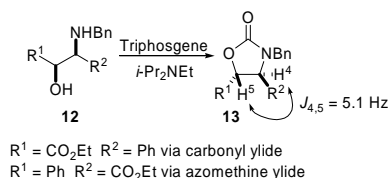
The regiochemistry was verified by converting amino alcohol **12** into the known compound **14** by reduction of the ester functionality to the corresponding primary alcohol with LAH followed by tri-acylation of the aminodiol using acetic anhydride. This chemical correlation proved the structure as shown in Scheme 18,[44] derived from a 1,3-dipolar cycloaddition of a carbonyl ylide to imine **8a**.

Scheme 18. *Determination of Regiochemistry*
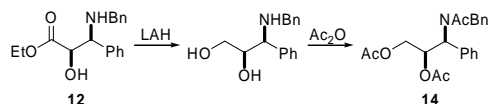
With working reaction conditions at hand, it was of interest to optimize the key components of the reaction (Table 1). First, different metal catalysts were evaluated. $Cu(OTf)_2$ is known to be a suitable catalyst for the decomposition of EDA (**10**) but unfortunately it only led to recovery of **8a** (entry 2), probably due to coordination of the metal to the basic imine nitrogen, which would inhibit the carbenoid formation.[37,39,45] As a consequence, when both $Rh_2(OAc)_4$ and $Cu(OTf)_2$ were employed simultaneously, the desired product was isolated in slightly decreased yield and with 2:1 *syn*:*anti* selectivity (entry 3). In this case, the Rh(II)-catalyst generates the metallocarbene, while the Cu(II)-catalyst acts as a Lewis acid and coordinates to the imine, which consequently influences the diastereoselectivity of the reaction.[45] Next, the substituent on the imine was varied to investigate if this would influence the reaction outcome. When using imine **8b** together with $Rh_2(OAc)_4$ as catalyst, a complex reaction mixture was obtained with no trace of the desired product (entry 4). Attempts with $Cu(OTf)_2$ gave aziridine **15** (2:1 *cis*:*trans* selectivity, entry 5) through either an intramolecular ring-closure of the corresponding

[43] Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548-1562.
[44] Akai, S.; Tsuzuki, Y.; Matsuda, S.; Kitagaki, S.; Kita, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2813-2820.
[45] For comparison of Cu(I)- and Rh(II)-catalyzed diazo decomposition in the presence of an imine, see; Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692-4693.

azomethine ylide (Scheme 19, path a) or a Lewis acid activation of the imine followed by a nucleophilic addition of the diazo ester (path b) with S_N2 displacement of N_2 in an aza-Darzen-type reaction.[37,45] Attempts with imine **8c** only gave recovered starting material when using either $Rh_2(OAc)_4$ or $Cu(OTf)_2$ (entry 6 and 7). Finally, the aldehyde component was varied using *p*-MeO-benzaldehyde (**9b**) and *p*-NO$_2$-benzaldehyde (**9c**) but this led to decreased yields and diastereoselectivities and consequently the remaining experiments were performed with **9a** (entry 8, 9). The acetal-substituent is only of minor interest since it is removed in the hydrolysis step.

Table 1. *Optimization of 1,3-Dipolar Cycloaddition*[a]

Entry	**8** (Ar)	**9** (Ar')	Cat.	*dr* (*syn*:*anti*)[b]	Yield *syn*-**12** (%)[c]
1	**a** (Bn)	**a** (Ph)	$Rh_2(OAc)_4$	93:7	**a** 82
2	**a** (Bn)	**a** (Ph)	$Cu(OTf)_2$	n.a.	**a** 0[d]
3[e]	**a** (Bn)	**a** (Ph)	$Rh_2(OAc)_4$	67:33	**a** 67[f]
4	**b** (Ph)	**a** (Ph)	$Rh_2(OAc)_4$	n.a.	**b** 0[g]
5	**b** (Ph)	**a** (Ph)	$Cu(OTf)_2$	n.a.	**b** 0[h]
6	**c** (4-MeOPh)	**a** (Ph)	$Rh_2(OAc)_4$	n.a.	**c** 0[d]
7	**c** (4-MeOPh)	**a** (Ph)	$Cu(OTf)_2$	n.a.	**c** 0[d]
8	**a** (Bn)	**b** (4-MeOPh)	$Rh_2(OAc)_4$	80:20	**a** 67[f]
9	**a** (Bn)	**c** (4-NO$_2$Ph)	$Rh_2(OAc)_4$	85:15	**a** 47[f]

[a] The reaction was carried out with imine **8** (1.0 equiv), aldehyde **9** (1.5 equiv), $Rh_2(OAc)_4$ (2.0 mol%) or $Cu(OTf)_2$ (5 mol%) and powdered 4Å MS in CH_2Cl_2 (Rh-cat.) or THF (Cu-cat.) at rt with addition of ethyl diazoacetate **10** (1.5 equiv) over 1 h. Hydrolysis was performed with *p*-TSA (2 equiv) in MeOH:H_2O (95:5). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture after hydrolysis. [c] Isolated yields. [d] Recovered starting material. [e] $Cu(OTf)_2$ (5 mol%) added. [f] Yield for *syn* + *anti*. [g] Complicated reaction mixture. [h] Aziridine **15** formed (*cis*:*trans* 2:1).

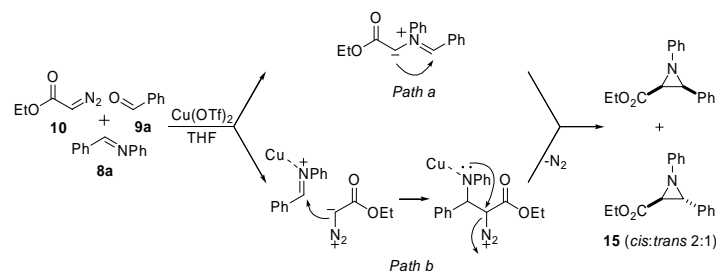**Scheme 19.** *Aziridine Formation from Intramolecular Ring-Closure*

Table 2. 1,3-Dipolar Cycloadditions to Various Aldimines[a]

Entry	**8** (R)	dr (syn:anti)[b]	Yield syn-**12** (%)[c]
1	**a** (Ph)	93:7	**a** 82
2[d]	**d** (4-NO$_2$C$_6$H$_4$)	91:9	**d** 61
3	**e** (4-ClC$_6$H$_4$)	98:2	**e** 75
4	**f** (4-FC$_6$H$_4$)	97:3	**f** 78
5	**g** (3-MeOC$_6$H$_4$)	98:2	**g** 77
6	**h** (4-MeC$_6$H$_4$)	97:3	**h** 87
7[d]	**i** (4-MeOC$_6$H$_4$)	94:6	**i** 78
8	**j** (2-Naphthyl)	98:2	**j** 83
9[d,e]	**k** (2-Furyl)	92:8	**k** 75
10[d,e]	**l** (CO$_2$Et)	83:17	**l** 64

[a] The reaction was carried out with imine **8** (1.0 equiv), benzaldehyde (1.5 equiv), Rh$_2$(OAc)$_4$ (2.0 mol%) and powdered 4Å MS in CH$_2$Cl$_2$ at rt with addition of ethyl diazoacetate (1.5 equiv) over 1 h. Hydrolysis was performed with p-TSA (2 equiv) in MeOH:H$_2$O (95:5). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture after hydrolysis, syn- and anti-diastereomers separable with flash chromatography. [c] Isolated yield. [d] 10 h addition time. [e] Reaction performed at 0 °C.

The performance of other imines under the optimized reaction conditions is summarized in Table 2. In all cases, the reactions proceeded cleanly to provide the desired syn-α-hydroxy-β-amino esters in high yield and excellent diastereoselectivity.[46] Several benzylidene benzylamine derivatives containing electron withdrawing (entries 2-5) or donating substituents (entries 6-8) in meta- or para-position gave comparable yields and diastereoselectivities irrespective of the steric and electronic properties of the aryl substituent. Also the furfural-derived imine **8k** afforded the corresponding product **12k** in high yield and diastereoselectivity (entry 9), which is of interest since the furan moiety can be readily derivatized into several useful functional groups (Scheme 20).[47,48] The reaction of ethyl glyoxalate imine **8l** gave syn-β-hydroxyaspartate **12l**, a potent blocker of the glutamate transporters,[49] in high yield and good diastereoselectivity (entry 10). This indicates that the

[46] The syn- and anti-diastereomers where readily separated with flash chromatography for all substrates.

[47] For examples of oxidative cleavage of the furan moiety, see; Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987-3990 and references therein.

[48] For examples of the aza-Achmatowicz reaction, see; Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401-404 and references therein.

[49] Shimamoto, K.; Shigeri, Y.; Yasuda-Kamatani, Y.; Lebrun, B.; Yumoto, N.; Nakajima, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2407-2410.

reaction is not only restricted to aromatic imines, thus widening the scope of the transformation.

Scheme 20. *Possible Transformations of Furan-substituted Amino Alcohol* **12k**
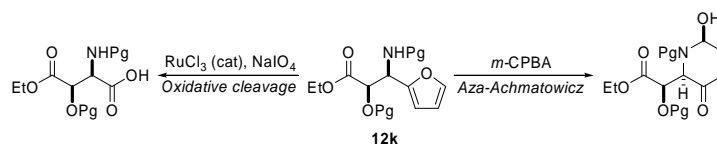
2.3. Mechanistic Aspects of the 1,3-Dipolar Cycloaddition

Mechanistically, the reaction is believed to proceed through a chemoselective insertion of the metallocarbene on the lone-pair of benzaldehyde (**9a**) forming either a metal-free[33,50] or a metal-associated ylide[50,51,52] (Scheme 21).

Scheme 21. *Metal-Free and Metal-Associated Ylides*
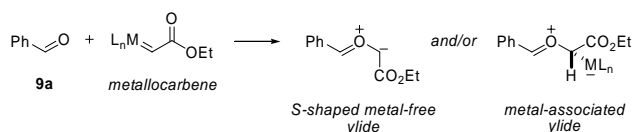
If a metal-free ylide is formed, it has been suggested that the reaction could occur via the thermodynamically most stable S-shaped ylide,[50] which then reacts with the imine in an *endo*-selective cycloaddition favoring the formation of *trans*-oxazolidine **11**.[53] The *endo*-transition state is favored over the *exo*-transition state due to the steric interactions between the ester functionality on the ylide and the benzylidene substituent on the imine (Scheme 22).

In the case of a metal-associated ylide, the choice of catalyst would influence the stereochemical outcome of the reaction, since the catalyst is associated to the transition state. The only proposed mechanistic pathway for 1,3-dipolar cycloadditions of carbonyl ylides deals with their reaction with aldehydes (Scheme 23).[50,52] A stepwise mechanism is suggested where a nucleophilic attack of the aldehyde lone pair on ylide **16** (Scheme 23) is followed by orientation of the aldehyde in such way that the steric interaction between the aldehyde substituent (Ar') and the carbenic proton is minimized. Catalyst decomplexation and ring-closure then affords *cis*-dioxolane **17** as the major product.
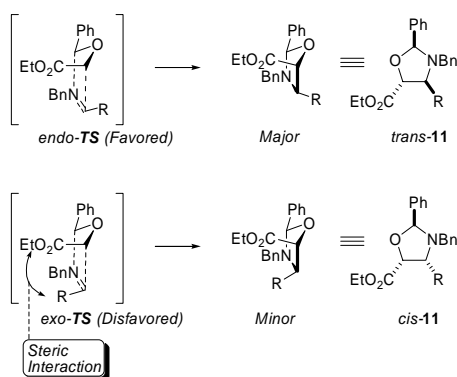
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[50] Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210-7215.

[51] Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S.-I. *J. Am. Chem. Soc.* **1999**, *121*, 1417-1418; Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M.; Expósito-Castro, M. Á. *J. Org. Chem.* **2003**, *68*, 6153-6159.
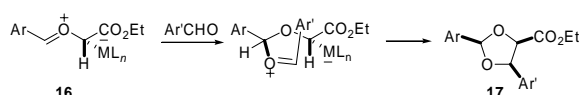
[52] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50-61.

[53] It should be noted that it is not the difference in free-energy between the ylide conformers (ΔG) that dictates which conformer that reacts, it is the difference in transition state energy (ΔG*), according to the Curtin-Hammett principal.

Scheme 22. *Proposed Mechanism for 1,3-Dipolar Cycloadditions of Metal-Free Ylides*

*endo-**TS** (Favored)* *Major* *trans-**11***

*exo-**TS** (Disfavored)* *Minor* *cis-**11***

Steric Interaction

**Scheme 23.** *Proposed Mechanism for Metal-associated Carbonyl Ylides*

16 **17**

To address whether the carbonyl ylide is metal-associated, its generation and subsequent reaction with imine **8a** was performed with $Rh_2(hfb)_4$ and $Rh_2(S$-DOSP)$_4$, respectively. With $Rh_2(hfb)_4$ **12a** was obtained in only 13% yield with decreased diastereoselectivity (*syn*:*anti* 88:12, compared to Table 2, entry 1) and with $Rh_2(S$-DOSP)$_4$ **12a** was obtained in 62% yield with high diastereoselectivity (*syn*:*anti* 94:6) and modest enantioselectivity (24% ee). These preliminary results support a metal-associated ylide in this case. It is interesting to note that no products derived from formation of azomethine ylides, by combination of **10** with the benzyl-substituted imines, was observed in these reactions.[37,39]

2.4. Asymmetric 1,3-Dipolar Cycloadditions

It was also of interest to develop an asymmetric protocol based on a chiral auxiliary for the synthesis of enantiomerically enriched *syn*-α-hydroxy-β-amino esters. (−)-8-Phenyl menthyl diazoacetate (**18**) has successfully been employed as the carbene source in asymmetric cyclopropanation reactions.[54] Diazo ester **18** was synthesized from (−)-8-phenyl menthol in 50% yield through a three-step procedure.[54] Unfortunately, the reaction of **18** with **8a** and **9a** gave none of the desired product (Scheme 24).

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[54] Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518-2526.

**Scheme 24.** *Asymmetric 1,3-Dipolar Cycloadditions Using Chiral Diazo Ester*
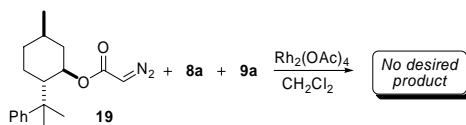
An alternative approach would be to employ a chiral imine derived from (+)-α-methylbenzylamine. Gratifyingly, reaction of the enantiomerically pure imine **8m** with **9a** and **10** gave, after hydrolysis, the desired *syn*-amino alcohol **19** in good yield (77%) and selectivity (*syn*:*syn*:*anti* 8:1:1) (Scheme 25). Compound **19** was readily isolated from the two minor isomers by flash chromatography.

Scheme 25. *Asymmetric 1,3-Dipolar Cycloadditions Using Chiral Imines*
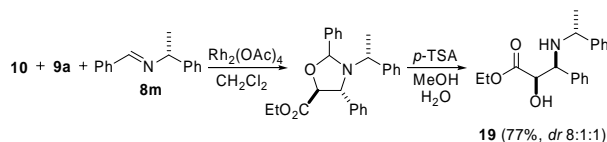
Having established this asymmetric transformation, the utility was demonstrated in a short synthesis of the Taxol C-13 side chain **21** (Scheme 26),[18] which is known to be important for the anti-tumor activity of Taxol.[47,55] Catalytic hydrogenolysis of amino alcohol **19** followed by benzoylation under Schotten-Baumann conditions afforded amide **20** (77% yield, 2 steps). Finally, hydrolysis of **20** using LiOH yielded the Taxol side chain **21** as a white solid in 5 steps from **8m** and 42% overall yield. Analytic data of **21** were in all aspects identical to those previously reported.[18,47,55]

Scheme 26. *Asymmetric Synthesis of C-13 Side Chain of Taxol*
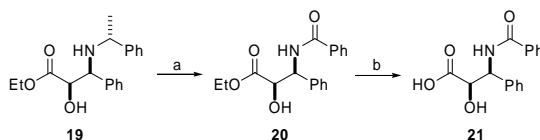
Reagents and conditions: (a) (i) H_2, Pd(OH)$_2$, EtOH, 3M HCl, rt; (ii) PhCOCl, NaHCO$_3$, EtOAc, 0 °C, 77% over 2 steps; (b) LiOH·H$_2$O, THF:MeOH:H$_2$O (10:5:4), rt, 89%.

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[55] Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320-4323; Gou, D.-M.; Liu, Y.-C.; Chen, C.-S. *J. Org. Chem.* **1993**, *58*, 1287-1289; Aggarwal, V. K.; Vasse, J.-L. *Org. Lett.* **2003**, *5*, 3987-3990. For the shortest synthesis of **21**, see reference 18.

20

3.
Total Synthesis of
D-*erythro*-Sphingosine

(Paper II)

3.1. Introduction

Glycosphingolipids are ubiquitous constituents of cell membranes, located abundantly in all plasma membranes as well as in intracellular organelles in all eukaryotic cells. The recent discovery of their biologically active metabolites e.g. sphingosine, ceramide and lysosphingolipids has generated interest in the physiological role of these molecules. The backbone of the sphingolipids consists of a long aliphatic chain connected to a polar 2-amino-1,3-diol head group. D-*erythro*-Sphingosine (**22**, Figure 6) and related compounds have been shown to inhibit protein kinase C, which affects cell regulation and signal transduction, and exhibit anti tumor promoter activities in various mammalian cells. In addition, these compounds may function as modulators of cell function and possibly also as secondary messengers.[56] Due to the biological importance of **22** and its derivatives many synthetic routes to enantiopure sphingolipids have been described, most commonly utilizing starting materials from the chiral pool, e.g. L-serine or carbohydrates.[57] Other investigations have employed asymmetric reactions such as Sharpless asymmetric epoxidations or aldol reactions with chiral auxiliaries to install the two vicinal stereogenic centers.[58,59] Recently Kobayashi and co-workers developed an elegant approach to the synthesis of L-*erythro*-Sphingosine based on a highly enantioselective zirconium catalyzed aldol reaction of a glycine-derived silicon enolate with aldehydes (Scheme 5, Chapter 1).[22]

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[56] Karlsson, K.-A. *Trends Pharm. Sci.* **1991**, *12*, 265-272; Hannun, Y.; Bell, R. M. *Science* **1989**, *243*, 500-507; Hannun, Y. *Science* **1996**, *274*, 1855-1859.

[57] Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075-1091; Gargano, J. M.; Lees, W. J. *Tetrahedron Lett.* **2001**, *42*, 5845-5847; Nakamura, T.; Shiozaki, M. *Tetrahedron* **2001**, *57*, 9087-9092; van der Berg, R. J. B. H. N.; Korevaar, C. G. N.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron Lett.* **2002**, *43*, 8409-8412; Lee, J.-M.; Lim, H.-S.; Chung, S.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 343-347.

[58] Nugent, T. C.; Hudlicky, T. *J. Org. Chem.* **1998**, *63*, 510-520; He, L. L.; Byun, H. S.; Bittman, R. *J. Org. Chem.* **2000**, *65*, 7627-7633; Corey, E. J.; Choi, S. *Tetrahedron Lett.* **2000**, *41*, 2765-2768.

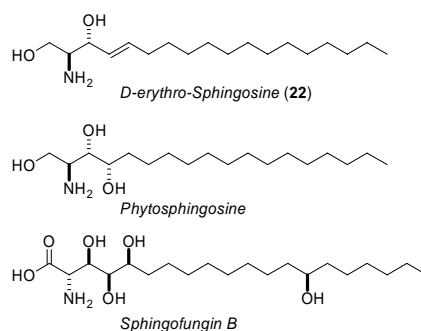[59] Olofsson, B.; Somfai, P. *J. Org. Chem.* **2003**, *68*, 2514-2517.

D-erythro-Sphingosine (**22**)

Phytosphingosine

Sphingofungin B

Figure 6. *Various Sphingoid Bases*

3.2. Synthetic Strategy

The formation of the (*E*)-olefin moiety of **22** has traditionally been accomplished by either an (*E*)-selective C-C double bond forming reaction, *e.g.* Wittig-Schlosser, Julia-Kocienski and Horner-Wadsworth-Emmons-type olefination, or stereoselective reductions of alkynes. We became interested in assembling **22** by using an alkene cross-metathesis reaction to introduce the required *E* olefin moiety (Scheme 27). Such a strategy would be convenient compared to alternatives using more traditional C-C double bond forming reactions, since the required catalyst is commercially available and the metathesis usually proceeds with low amount of byproduct formation.[60,61] This approach would also allow for a convergent route towards Sphingosine analogs by simply changing the cross-metathesis partners. The polar head group **23** should be available from epoxide **24**, which, in turn, is readily prepared from divinylcarbinol (**25**). The realization of this strategy yields a practical synthesis of **22** as outlined below.

***Scheme 27***. *Retrosynthetic Analysis of D-erythro-Sphingosine*

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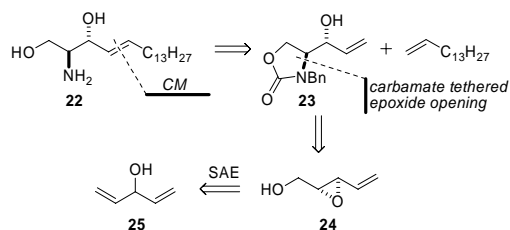
[60] Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900-1923.

[61] Chatterjee, A.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

3.3. Oxazolidinone Synthesis

Sharpless asymmetric epoxidation of commercially available divinylcarbinol **25** afforded epoxide **26**, followed by base-induced Payne rearrangement to give **24** in high yield (65% over 2 steps) and excellent enantiomeric purity (>99% ee), as previously reported (Scheme 28).[62,63] It was expected that intermolecular reaction of **24** with various nitrogen nucleophiles would, for electronic reasons, result in a preferential ring-opening in the allylic position.[13,64] To circumvent this, the C-2 amino functionality was introduced through a two-step procedure using an intramolecular epoxide-opening *via* a tethered carbamate. Alkyl isocyanates have previously been used as nitrogen nucleophiles to give regioselective attack at the C-2 position of epoxy alcohols.[65,66] Consequently, when epoxy alcohol **24** was treated with benzyl isocyanate and Et$_3$N in a sealed tube, benzyl carbamate **27** was obtained in excellent yield with complete regioselectivity. The subsequent deprotonation of **27** using NaH followed by intramolecular epoxide opening proceeded sluggishly and gave a poor yield of oxazolidinone **23**.[65,67] Gratifyingly, when using NaHMDS in THF at low temperature **23** was obtained in 88% yield.[68] As expected the product derived from the favored *5-exo-tet* cyclization was the only detected product; the product derived from the *6-endo-tet* cyclization being disfavored according to the Baldwin rules.[69]

Scheme 28. *Synthesis of Oxazolidinone* **23**
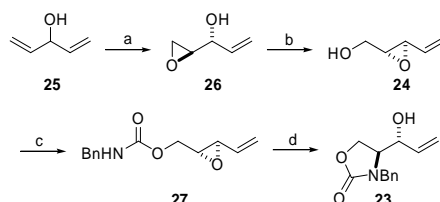
Reagents and conditions: (a) (-)-DIPT, Ti(O^{i}Pr)$_4$, cumene hydroperoxide, CH$_2$Cl$_2$, -35 °C, 77%, >99% ee; (b) NaOH (0.5 M), rt, 85%; (c) BnNCO, Et$_3$N, Et$_2$O, 60 °C, 98%; (d) NaHMDS, THF, -15 °C, 88%.

3.4. Cross-Metathesis and Completion

Due to the lipid chain and the hydrophilic head group, Sphingosine exhibits surfactant-like properties, *e.g.* low solubility in organic solvents at low temperature, and problematic flash chromatography due to aggregation of the material on the silica gel column.[59] The late introduction of the aliphatic chain

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[62] Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525-1529; Jäger, V.; Schröter, D.; Koppenhoefer, B. *Tetrahedron* **1991**, *47*, 2195-2210.

[63] Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264-8268.

[64] Olofsson, B.; Khamrai, U.; Somfai, P. *Org. Lett.* **2000**, *2*, 4087-4089.

[65] Roush, W. R.; Adam, W. A. *J. Org. Chem.* **1985**, *50*, 3752-3757.

[66] Jäger, V.; Stahl, U.; Hummer, W. *Synthesis* **1991**, 776-782.

[67] Jäger, V.; Hummer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769-776.

[68] Martin, R.; Moyano, A.; Pericas, M. A.; Riera, A. *Org. Lett.* **2000**, *2*, 93-95.

[69] Smith, M. B. *Organic Synthesis*; McGraw-Hill, Inc.: New York, 1994.

by a cross-metathesis reaction overcomes many of these problems and has advantages over several of the existing strategies towards **22**, in which the lipid chain is introduced at an early stage of the synthesis.

Compound **28** was synthesized by an olefin cross-metathesis reaction of allylic alcohol **23** and 1-pentadecene in the presence of Ru-catalysts **29**-**31** (Figure 7 and Table 3).
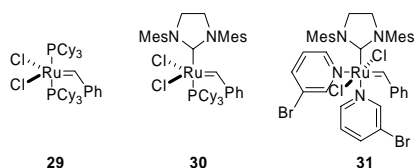
Figure 7. Ru-catalyst used in cross-metathesis reaction

Table 3. Cross-Metathesis

Entry	Cat.	mol %	Conditions[a]	Product (%)[b]	E:Z[c]
1	**29**	5	40 °C, 43 h	n.r.	n.a.
2	**30**	5	rt, 3 days	**28** (35)	14:1
3	**30**	5	40 °C, 24 h	**28** (49)	5:1
4[d]	**30**	10	50 °C, 1.5 h	**28** (7) / **32** (57)	12:1 / E
5[e]	**30**	10	40 °C, 0.75 h	**28** (52)	16:1
6	**31**	10	40 °C, 1.5 h	**28** (59)	17:1

[a] 1-pentadecene (2 equiv.) in CH$_2$Cl$_2$. [b] Isolated yields. [c] Determined by crude ^{1}H-NMR analysis. [d] 1-pentadecene (2 equiv.) in PhMe. [e] Ti(O^{i}Pr)$_4$ (2 equiv.) was added prior to the catalyst.

The initial coupling attempts under standard cross-metathesis conditions,[61] using the commercially available Grubbs' ruthenium carbene catalysts **29** and **30**, resulted in no reaction or required prolonged reaction time, giving **28** in moderate yield and E:Z selectivity (Table 3, entries 1-3). When the reaction was conducted in toluene instead of CH$_2$Cl$_2$ homodimer **32** precipitated from the reaction mixture as a white solid, thereby shifting the equilibrium towards this undesired dimerization (entry 4). The low chemical yield encountered with catalyst **29** or catalyst **30** in CH$_2$Cl$_2$ at room temperature, or low E:Z selectivity encountered with catalyst **30** in refluxing CH$_2$Cl$_2$, could be circumvented by addition of 2 equivalents of Ti(O^{i}Pr)$_4$ to the reaction mixture and **28** was isolated in 52% yield (78% based on recovered starting material) with 16:1 E:Z selectivity (entry 5). The E:Z isomers were readily separated by flash chromatography. The need for Ti(O^{i}Pr)$_4$ could be explained by the

24

heteroatom density in **23**, as Ru-catalyst **30** can form inactive chelates with Lewis-basic sites in the substrate.[70] The presence of Ti(O^{i}Pr)$_4$ decreases this chelation and increases the amount of desired product.[70,71] When employing Grubbs' phosphine-free 3-bromopyridine catalyst **31**[72] (Figure 7), the yield and *E*:*Z* selectivity were increased to 59% (82% based on recovered starting material) and 17:1 respectively (entry 9). Catalyst **31** was readily available in one step from commercially available **30** and has shown increased reactivity in various cross-metathesis reactions (Scheme 29).[72,73] The increased reactivity of catalyst **31** is due to the absence of phosphine ligands. The 3-bromopyridine ligands lead to a faster ligand-dissociation from the precatalysts and a decreased tendency for ligand re-association. Consequently, the concentration of the active catalytic-species in the reaction mixture is higher, hence the increased reactivity.

Scheme 29**. Synthesis of Bispyridine Catalyst **31
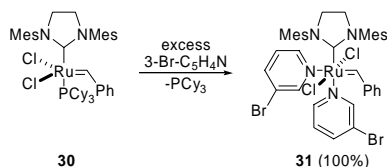
Removal of the benzyl group in **28** with sodium in liquid ammonia proceeded cleanly to afford oxazolidinone **33**, which was then hydrolyzed without further purification with 1M KOH in refluxing EtOH:H$_2$O to yield the desired D-*erythro*-sphingosine (**22**) as a white solid over seven steps from commercially available **25** in 33% overall yield (Scheme 30). Analytical data of **22** were in all aspects identical to those previously reported.[57-59]

***Scheme 30**. Deprotection of D-erythro-Sphingosine*
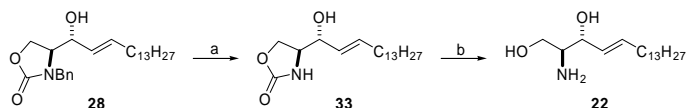
Reagents and conditions: (a) Na, NH$_3$ (l), -78 °C, quant.; (b) 1M KOH, H$_2$O:EtOH 1:1, 100 °C, quant.

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[70] Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130-9136.

[71] Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651-4654; Rodríguez, S.; Castillo, E.; Carda, M.; Marco, J. A. *Tetrahedron* **2002**, *58*, 1185-1192.

[72] Love, J. A.; Morgan, J. P.; Trnka, T. M.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 4035-4037.

[73] Kang, B.; Kim, D.-H.; Do, Y.; Chang, S. *Org. Lett.* **2003**, *5*, 3041-3043; Kanemitsu, T.; Seeberger, P. H. *Org. Lett.* **2003**, *5*, 4541-4544.

4.
Diversity-Oriented Synthesis

"There should be no problem with biology driving science unless perhaps you happen to be a chemist!"

- Stuart L. Schreiber

4.1. Introduction

Modern drug discovery often involves screening of large collections of small molecules against different protein targets in order to find new drug candidates. These small molecules are usually synthesized using target-oriented synthesis (TOS). When small molecules are used for interacting with biological functions, regardless of any target, it is more beneficial to employ a collection of structurally complex and diverse small molecules derived from a diversity-oriented synthesis (DOS) protocol.[5]

4.1.1. TOS and Retrosynthetic Analysis

TOS is primarily used to access well-defined compounds, often complex natural products known for specific biological properties. The most effective tool when planning the synthesis of complex natural products is retrosynthetic analysis; a problem solving technique involving recognition of key structural elements in the product that code for specific reaction transformations. This approach is then applied repetitively in order to dissect a complex product into simple starting materials (Scheme 31).

Scheme 31. *Dissection of a Complex Target using Retrosynthetic Analysis.*
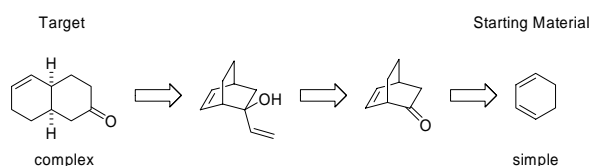
4.1.2. DOS and Forward-Synthetic Analysis

DOS is a divergent, branched strategy not aimed for a specific target molecule, and consequently retrosynthetic analysis cannot be applied directly. The synthetic pathway is instead analyzed in the direction of the chemical reactions, *i.e.* from reactants to product. The key feature of a forward-synthetic analysis is to recognize powerful complexity-generating reactions that can be used pair-wise in an iterative fashion, in which the product of the first reaction acts as the substrate for the second. This allows the synthesis of collections of complex and diverse small molecules in only 3 to 5 steps.[5,74]

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[74] Schreiber, S. L. *C & EN* **2003**, *81*, 51-61.

4.1.3. Synthetic Strategies in DOS

The most common and often very effective approach when planning a DOS protocol is to use a reagent-encoded strategy. Starting from a common substructure or functionality, different complexity-generating reactions can be applied for the formation of the first layer of diverse molecular skeletons. Most importantly, the newly created compounds must themselves also be able to undergo other complexity-generating reactions, thus creating the second or third layer of diverse compounds. This approach could then be widened when adding different sets of diverse building blocks to the newly created molecular skeletons. This building block based approach, one synthesis-one skeleton strategy, has proven to be very effective and general but has also some limitations; compounds derived from a common molecular core-structure are likely to exhibit similar chemical properties, thereby limiting the diversity of the compound collection.[75] More effectively, the appended building blocks can be replaced with skeletal information elements (σ-elements, substrate-encoded approach), which are defined as appendages with pre-encoded reactivity that will react with a common core-structure forming products with different skeletons under a set of common reaction conditions.[75,76]

One example of a σ-element based diversity protocol utilizes a relatively unreactive furan core-structure that can be oxidized under mild conditions to a more reactive, electrophilic *cis*-enedione intermediate (Scheme 32).[75] Three substrates containing a σ-element; two, one or zero nucleophilic hydroxyl groups adjacent to the furan ring, were subjected to the same oxidative (NBS) and acidic (PPTS) reaction conditions affording three products with distinct molecular skeletons.

Scheme 32. *σ-Element Based DOS Pathway*
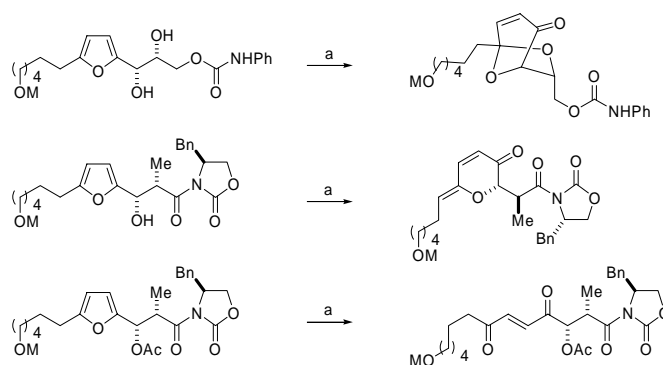
Reagents and conditions: (a) NBS, NaHCO$_3$, NaOAc, THF:H$_2$O, rt; PPTS, CH$_2$Cl$_2$, 40 ° to 45 °C, 33-81%.

[75] Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613-618.

[76] Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58; Burke, M. D.; Berger, E. M.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 14095-14105.

4.1.4. Aim of the Study

The aim of this study was to develop diversity-oriented libraries of small polycyclic organic molecules based on a readily available vinylic *vic*-amino alcohol scaffold. The design of the libraries is based on the iterative use of two powerful ring-forming reactions to simultaneously introduce structural complexity and diversity. Since the vinylic *vic*-amino alcohols are available in all eight stereoisomers they will serve as ideal substrates for both reagent- and stereochemical-encoded diversity protocols (Scheme 33).

**Scheme 33.** *Regio- and Stereodivergent Synthesis of Vinylic vic-Amino Alcohols*
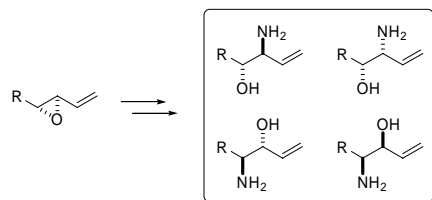
Only one enantiomer of vinylepoxide shown

4.1.5. Synthetic Strategy

Construction of the first generation library starts by alkylation of the vinylic *vic*-amino alcohol **34** (one stereoisomer arbitrarily selected) followed by a ruthenium catalyzed ring-closing metathesis (RCM) to give cyclic amine **35** (Scheme 34, n = 1-3). Alkylation of **35** sets the stage for an intramolecular Diels-Alder reaction to yield tricycle **36** (m = 1,2). The tricyclic core **36** could then be further derivatized at the C-C double bond, *e.g.* by epoxidation, dihydroxylation or cyclopropanation. Substituents R' and R'' could be used as handles for Pd-catalyzed coupling reactions, *e.g.* Heck or Suzuki reactions. Substituent R could also be used for attachment to solid support, a common strategy in DOS. This strategy would lead to 48 different polycyclic core structures when using all eight amino alcohol isomers.

**Scheme 34.** *First Generation Library Using an RCM-IMDA Sequence*
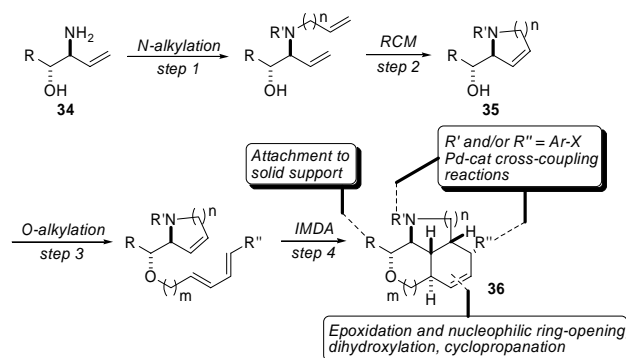
4.2. First Generation Library

4.2.1. Amino Alcohol Synthesis

The substrates used in the DOS library synthesis have to be available from generally applicable synthetic routes with the requirements of commercially available starting materials and flexible, predictable and highly regio- and diastereoselective reactions. The vinylic *vic*-amino alcohols used as substrates for these libraries of polycyclic small molecules were synthesized from the corresponding vinylepoxides, which can be ring opened regioselectively in the allylic position by nitrogen nucleophiles.[64] The aminolysis of vinylepoxides using neat ammonia with *p*-TSA as catalyst,[77] or using aqueous ammonium hydroxide has previously been developed in our group.[78] The reaction proceeds stereospecific and regioselectively *via* a S$_N$2 attack at the allylic position affording the vicinal *anti*-amino alcohol. Pyne and co-workers have developed a Lewis acid promoted aminolysis approach of vinylepoxides using a 1:1 molar ratio of the vinyl epoxide and the primary amine with LiOTf in acetonitrile.[79] This methodology gives the same excellent regioselectivity affording the vicinal *anti*-amino alcohol.

Benzylation of vinylepoxide **24** using benzyl bromide and sodium hydride with a catalytic amount of tetrabutylammonium iodide afforded the benzyl-protected vinyl epoxide **37** in 53% yield (Scheme 35). Aminolysis of vinylepoxide **37** using allylamine with a catalytic amount of *p*-TSA afforded the desired *anti*-amino alcohol **38** as single detected regioisomer in high yield. Protection of allylic amine **38** using *p*-TsCl gave the corresponding RCM precursor **39**. Aminolysis of vinylepoxide **37** using ammonium hydroxide afforded the desired *anti*-amino alcohol **40** as single detectable regioisomer in excellent yield. Protection of amino alcohol **40** as the corresponding oxazolidinone **41** by *N*-alkylation with 4-bromo-1-buten gave RCM precursor **42** in 49% over 2 steps.

Scheme 35. *Synthesis of Vinylic vic-Amino Alcohols*
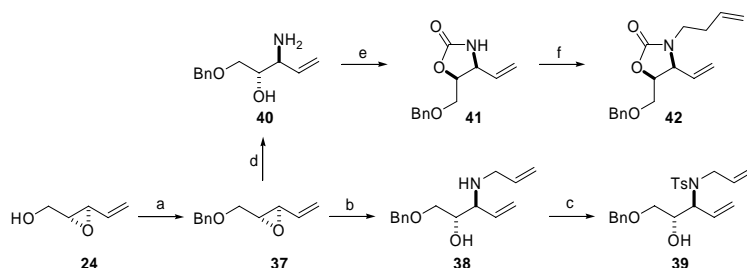
Reagents and conditions: (a) BnBr, NaH, Bu$_4$NI (0.1 equiv), THF, rt, 53%. (b) Allylamine, p-TSA (0.1 equiv), 110 °C, 81%. (c) p-TsCl, Et$_3$N, DMAP, THF, -15 °C, 80%. (d) NH$_4$OH (25%), 140 °C, 98%. (e) (Cl$_3$CO)$_2$CO, ^{i}Pr$_2$NEt, CH$_2$Cl$_2$, rt, 95%. (f) 4-bromo-1-buten, NaH, LiI (cat), DMF, 0 °C → rt, 53%.

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[77] Lindström, U. M.; Franckowiak, R.; Pinault, N.; Somfai, P. *Tetrahedron Lett.* **1997**, *38*, 2027-2030.

[78] Lindström, U. M.; Olofsson, B.; Somfai, P. *Tetrahedron Lett.* **1999**, *40*, 9273-9276.

[79] Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731-734; Lindsay, K. B.; Pyne, S. G. *Synlett* **2004**, 779-782.

4.2.2. Ring-Closing Metathesis

The first complexity-generating transformation used in this DOS protocol was the ruthenium catalyzed ring-closing metathesis.

RCM-precursors **39** and **42** were ring-closed under standard RCM conditions using 5 mol % of Grubbs' second-generation ruthenium catalyst **30** (Scheme 36). Reaction of diene **39** in refluxing CH_2Cl_2 proceeded sluggishly and required prolonged heating and increased catalyst loading to yield **43**. This could be circumvented with increased reaction temperature. When the reaction was run in toluene at 80 °C **43** was obtained in 95% yield.[80] RCM of diene **42** proceeded cleanly at room temperature in CH_2Cl_2 to afford **44** in 94% yield.

Scheme 36. *Ring-Closing Metathesis of vic-Amino Alcohols*
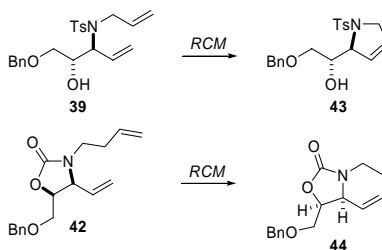
Reagents and conditions: **43**; *Ru-catalyst* **30** *(5 mol%), PhMe, 80 °C, 1h, 95%.* **44**; *Ru-catalyst* **30** *(5 mol%), CH_2Cl_2, rt, 94%.*

### 4.2.3. Intramolecular Diels-Alder

The second complexity-generating reaction in this DOS sequence was planned to be an intramolecular Diels-Alder (IMDA) reaction with simultaneous formation of two C-C bonds and three stereogenic centers in one single step.

Oxazolidinone **44** was hydrolyzed to amino alcohol **45**, which was then subjected to a selective *O*-alkylation protocol[81] with (*E*)-5-bromo-1,3-diene using KHMDS at –78 °C to afford the enediene **46** in only 36% yield (Scheme 37). The reaction suffered from low conversion and the *O*-alkylation was accompanied with some undesired *N*-alkylation (13%). Protection of the *N*-H moiety of **45** gave the corresponding sulfonamide **47** followed by *O*-alkylation with (*E*)-5-bromo-1,3-diene using NaH in DMF gave the Ts-protected enediene **48**. The five-membered *p*-toluenesulfonamide **43** was subjected to the same *O*-alkylation procedure to afford enediene **49** in excellent yield.

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[80] RCM reactions in toluene are substantially faster than in CH_2Cl_2. This increased reactivity is not only an effect of increased reaction temperatures, see: Furstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204-2207.

[81] Somfai, P.; Marchand, P.; Torsell, S.; Lindström, U. M. *Tetrahedron* **2003**, *59*, 1293-1299.

Scheme 37. *Synthesis of IMDA Precursors*
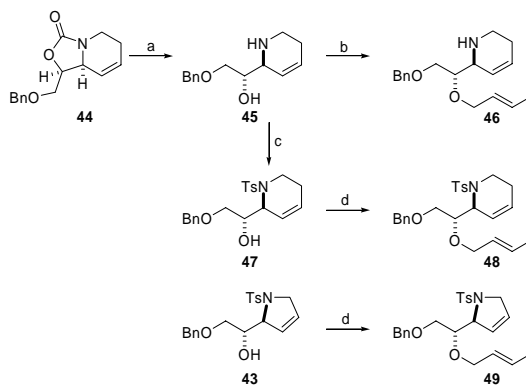
*Reagents and conditions: (a) 1M KOH, EtOH:H$_2$O (1:1), 100 °C, 72%. (b) (E)-5-bromo-penta-1,3-diene, KHMDS, THF, -78 °C, 36%. (c) p-TsCl, Et$_3$N, CH$_2$Cl$_2$, -15 °C, 92%. (d) (E)-5-bromo-penta-1,3-diene, NaH, Bu$_4$NI (0.1 equiv), DMF, 0 °C → rt, **48**: 85%, **49**: 92%.*

Enediene **46** (R = H) was unreactive under to standard Diels-Alder conditions, reflux in toluene. The temperature was then increased to 160, 190 and 215 °C, respectively, but unfortunately no reaction occurred according to ^{1}H NMR of the crude reaction mixture (Scheme 38). When **46** was heated to 250 °C using a microwave oven the starting material decomposed. When enediene **48** (R = Ts) was subjected to 200 °C in toluene for 24 h no product was detected and **48** was recovered along with 36% of alcohol **47**. This undesired side-product, probably formed from a homolytic cleavage of the ether bond, initiated by traces of peroxides, could be suppressed by addition of a small amount of a radical inhibitor, 2,6-di-*tert*-butyl-4-methylphenol (butylated hydroxytoluene, BHT)[82] to the reaction mixture. Thermolysis of enediene **48** in the presence of BHT at 215 °C in toluene lead to the formation of the unidentified product **50** in considerable amount (1.5:1 ratio of two diastereomers) along with unreacted starting material (19%). Structure elucidation of compound **50** has not been possible.

Scheme 38. *Thermal IMDA (R = H or Ts)*
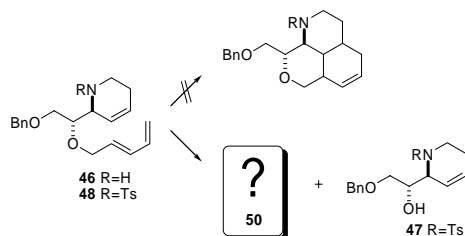

*Reagents and conditions: **46**; PhMe, Δ, 0%. **48**; PhMe, 200 °C, **47**, 36%; BHT (20 w%), PhMe, 215 °C, **50**, **47**, 19%.*

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[82] Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361-4368.

These major setbacks lead us to investigate the IMDA reaction using an inverse electron-demand system, *i.e.* electron-rich dienophile and electron-poor diene. The enediene **51** was chosen since the same DOS sequence could be applied with only minor alterations of the original synthetic route. Consequently the reversed electron-demand IMDA precursor **51** was prepared from secondary alcohol **47** in 68% yield using 2,4-pentadienoyl chloride (Scheme 39). Unfortunately, none of the desired product was detected when **51** was subjected to thermolysis in the presence of BHT.

**Scheme 39.** *Reversed Electron-Demand IMDA*
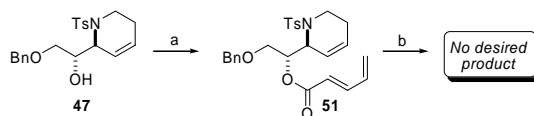
Reagents and conditions: (a) 2,4-Pentadienoyl chloride, Et₃N, DMAP (cat.), CH₂Cl₂, rt, 68%. (b) BHT (15 mol%), m-Xylene, 168 °C.

4.2.4. Rhodium(I)-Catalyzed [4+2]-Cycloadditions

Electronically unactivated IMDA precursors frequently require harsh thermal conditions in order to form the desired [4+2]-cycloadduct, usually accompanied with poor level of stereocontrol. Rh(I)-based catalysts can mediate intramolecular [4+2]-cycloadditions under mild conditions with excellent yields and selectivities even for substrates that normally cannot undergo Diels-Alder reactions under thermal conditions.[83] The stereochemical outcome of these Rh(I)-catalyzed reactions is consistent with the stepwise mechanism depicted in Scheme 40. First, Rh(I) coordinates to the enediene forming π-complex **52**, which leads to the initial bond forming event affording Rh(III)-allyl complex **53**, which is in equilibrium with Rh(III)-σ complex **54**. Regeneration of the active Rh(I)-complex from **54** by reductive elimination then completes the catalytic cycle, resulting in the formation of [4+2]-cycloadduct **55**.[83]

Scheme 40. *Rh(I)-Catalyzed IMDA*

X=CH₂, O or NTs.
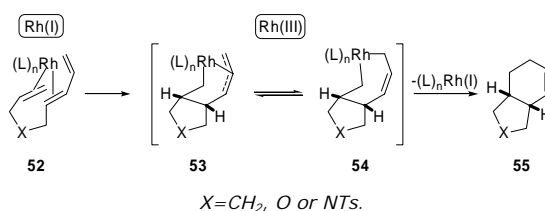
Several fruitless attempts were made to react IMDA precursor **49** with different Rh(I)-catalysts (Table 4). Rh(I)-catalyst **56**, which is known to catalyze [4+2]-cycloadditions of various enedienes adjacent to a *p*-toluenesulfonamide moiety,[83] gave no conversion under standard conditions (Table 4, entry 1). When both the catalyst loading and the temperature were increased the only detected product was alcohol **43** (entry 3). When

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[83] O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Org. Biomol. Chem.* **2003**, *1*, 2038-2040.

employing the more reactive cationic Rh(I)-catalyst **57**[84] only a complicated mixture of byproducts was obtained (entry 2). The cationic Rh-catalyst **58**, which have been successfully employed in [4+2]- and [5+2]-cycloadditions[85] as well as enyne cycloisomerizations,[86] was tested in this reaction without success. Reaction in 1,2-dichloroethane at room temperature gave no conversion, and when the temperature was increased to 85 °C only alcohol **43** was obtained along with unreacted starting material (entry 4).

Table 4. *Rhodium(I)-Catalyzed [4+2]-Cycloaddition*
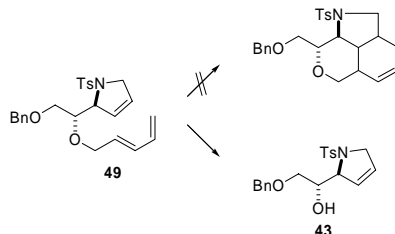
Entry	Catalyst	mol %	Conditions	Result
1	**56** P$_3$RhCl^a [84]	2	THF, 55 °C, 26 h	S.M
2	**56** P$_3$RhCl^a	10	THF, 100 °C, 17 h	S.M, **43**
3	**57** (PPh$_3$)$_3$Rh$^+$SbF$_6^-$ [85]	5	PhMe, 80 °C, 16 h	S.M, byprod
4	**58** [Rh(dppb)]$^+$SbF$_6^-$ [86]	5	DCE, rfx, 3 d	S.M, **43**

^{a} P = P(O^{i}C$_3$HF$_6$)$_3$

4.2.5. Conclusions

Several Diels-Alder conditions were screened, both thermal and Rh(I)-catalyzed, without success. These results imply that the enediene system used for this DOS-library does not fulfill the criteria for a successful DOS-strategy. The reason for the failure of this transformation is probably that the system is electronically disfavored, *i.e.* energy gap between HOMO and LUMO of the reacting components is too big. Preferably, electron-poor dienophiles should be reacted with electron-rich dienes or the opposite, *i.e.* inverse-electron demand Diels-Alder.

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[84] O'Mahony, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443-445.

[85] Wang, B.; Cao, P.; Zhang, X. *Tetrahedron Lett.* **2000**, *41*, 8041-8044.

[86] Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 6370-6371.

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Acknowledgements

Appendix A

The following is a description of my contribution to Publications I and II, as requested by KTH.

Paper I: I performed the majority of the lab work and supervised the diploma worker Marcel Kienle, who prepared and reacted substrate **8k**. I wrote the article.

Paper II: I performed all lab work and wrote the article.

Unpublished results (Chapter 4): I performed all lab work.

Appendix B

This appendix contains experimental procedures and analytical data of compounds **37**-**51**.

B 1. **Diversity-Oriented Synthesis Project (Chapter 4)**.

(2*R*,3*R*)-2-((benzyloxy)methyl)-3-vinyloxirane (37). To a solution of NaH (1.69 g, 70.3 mmol) in dry THF (130 mL) was added **24** (3.52 g, 35.1 mmol) in dry THF (5 mL) at rt. The mixture was stirred for 20 min, BnBr (4.63 mL, 38.9 mmol) and Bu$_4$NI (1.31 g, 3.51 mmol) was then added in quick succession. The reaction mixture was stirred overnight at rt under N$_2$, quenched with H$_2$O (150 mL) and extracted with CH$_2$Cl$_2$ (3*100 mL). The combined organic phases were dried (MgSO$_4$) and concentrated giving a yellow oil. Flash chromatography of the residue (pentane:EtOAc 20:1→15:1) gave **37** (3.501 g, 52%) as a pale yellow oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.40-7.24 (m, 5H), 5.64-5.55 (m, 1H), 5.49 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dd, *J* = 10.0, 1.5 Hz, 1H), 3.77 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.54 (dd, *J* = 11.5, 5.4 Hz, 1H), 3.28 (dd, *J* = 7.4, 2.0 Hz, 1H), 3.11 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.0, 135.1, 128.6, 127.9, 120.0, 73.5, 70.0, 58.8, 56.2.

(2*S*,3*S*)-3-(allylamino)-1-(benzyloxy)pent-4-en-2-ol (38). To a solution of **37** (102.1 mg, 0.54 mmol) in freshly distilled allylamine (0.805 mL, 10.7 mmol) was added *p*-TSA (14.3 mg, 0.075 mmol). The resultant mixture was heated to 110 °C in a sealed glass reactor for 3 days. The reaction mixture was cooled to rt and the solvent was removed under reduced pressure. Flash chromatography (pentane:EtOAc 1:2 + 1% NH$_3$ → EtOAc) of the residue gave **38** (107 mg, 81%) as a pale orange/brown solid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38-7.25 (m, 5H), 5.87 (m, 1H), 5.69 (ddd, *J* = 17.3, 10.2, 8.6 Hz, 1H), 5.16 (m, 4H), 4.54 (s, 2H), 3.83 (q, *J* = 4.8 Hz, 1H), 3.54 (d, *J* = 5.0 Hz, 2H), 3.29 (m, 1H), 3.23 (dd, *J* = 8.4, 4.5 Hz, 1H), 3.10 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 138.0, 136.7, 136.4, 128.3, 127.6, 118.2, 115.8, 73.4, 71.9, 71.3, 63.0, 49.4.

(2*S*,3*S*)-3-(*N*-allyl-*N*-tosylamino)-1-(benzyloxy)pent-4-en-2-ol (39). To a solution of **38** (197 mg, 0.80 mmol) in THF (15 mL) containing Et$_3$N (445 μL, 3.19 mmol) and DMAP (4.9 mg, 0.040 mmol) was added *p*-TsCl (151.8 mg, 0.80 mmol). The resultant mixture was stirred at 0 °C for 2 h and then at rt for 48 h. To the reaction mixture was added HCl (0.1M) and the aqueous layer was extracted with CH$_2$Cl$_2$ (3*15 mL), dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (pentane:EtOAc 3:1) of the residue gave **39** (256 mg, 80%) as a clear oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, *J* = 8.3Hz, 2H), 7.38-7.24 (m, 7H), 5.79 (m, 2H), 5.17 (m, 2H), 5.10 (ddd, *J* = 10.1, 2.0, 1.1 Hz, 1H), 4.97 (m, 1H), 4.60 (d, J_{AB} = 11.7 Hz, 1H), 4.52 (d, J_{AB} = 11.7 Hz, 1H), 4.27 (t, *J* = 7.3 Hz, 1H), 4.07 (m, 1H), 3.97 (tdd, *J* = 16.2, 5.4, 1.4 Hz, 1H), 3.69 (m, 2H), 3.55 (dd, *J* = 9.7, 6.9 Hz, 1H), 2.57 (d, *J* = 4.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.3, 137.8, 137.5, 135.3, 131.9, 129.5, 128.4, 127.8, 127.4, 120.7, 118.1, 73.3, 71.3, 71.0, 62.0, 48.7, 21.5.

(2*S*,3*S*)-3-amino-1-(benzyloxy)pent-4-en-2-ol (40). Vinylepoxide **37** (538 mg, 2.83 mmol) in NH_4OH (10 mL) was heated in a sealed glass tube at 140 °C for 1.5 h. The mixture was extracted with CH_2Cl_2 (3*20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **40** (0.572 g, 98%), which was used in the next step without further purification. Characterization has been previously reported by the group.[87]

(4*S*,5*S*)-5-((benzyloxy)methyl)-4-vinyloxazolidin-2-one (41). Preparation and characterization has been previously reported by the group.[87]

(4*S*,5*S*)-5-((benzyloxy)methyl)-3-(but-3-enyl)-4-vinyloxazolidin-2-one (42). To a solution of NaH (37.0 mg, 3.26 mmol) in DMF (3.0 mL) was added oxazolidinone **41** (300 mg, 1.286 mmol) in DMF (0.60 mL) at 0 °C and the resultant solution was stirred allowing to warm to rt. After 1 h 4-bromo-1-butene (0.196 mL, 1.929 mmol) was added dropwise over 20 min at rt followed by a catalytic amount of LiI. The resultant mixture was stirred for an additional 14 h, cooled to 0 °C and carefully quenched with water and extracted with ether. The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (pentane:EtOAc 2:1) of the residue gave **42** (193 mg, 53%) as a viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.11 (m, 0.5H), 5.07 (m, 1H), 5.04 (m, 0.5m), 4.65 (dt, J = 8.5, 5.3 Hz, 1H), 4.55 (d, J_{AB} = 11.9 Hz, 1H), 4.53 (d, J_{AB} = 11.9 Hz, 1H), 4.29 (t, J = 8.7 Hz, 1H), 3.62 (d, J = 5.3 Hz, 2H), 3.52 (dt, J = 14.1, 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8. 138.0, 135.3, 132.1, 128.3, 128.2, 122.4, 117.7, 75.9, 74.1, 68.7, 61.5, 41.7, 32.4.

(*R*)-2-(benzyloxy)-1-((*R*)-2,5-dihydro-1-tosyl-1*H*-pyrrol-2-yl)ethanol (43). To a solution of **39** (36.8 mg, 0.092 mmol) in PhMe (8 mL) was added Ru-catalyst **30** (4.2 mg, 5 μmol). The resultant mixture was heated to 80 °C for 1 h and then cooled to rt. The solvent was removed *in vacuo* and flash chromatography (pentane:EtOAc 1:1) of the residue gave **43** (32.6 mg, 95%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.28-7.17 (m, 7H), 5.57 (m, 2H), 4.54 (d, J_{AB} = 11.9 Hz, 1H), 4.48 (m, 1H), 4.46 (d, J_{AB} = 11.9 Hz, 1H), 4.04 (m, 2H), 3.57 (d, J = 5.7 Hz, 2H), 2.70 (m, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.0, 133.9, 129.8, 128.4, 127.72, 127.68, 127.5, 126.7, 126.5, 73.5, 72.6, 71.3, 70.03, 56.2, 21.5.

(1*S*,8a*S*)-1-((benzyloxy)methyl)-5,6-dihydro-1H-oxazolo[3,4-a]pyridin-3(8aH)-one (44). To a solution of **42** (25.5 mg, 0.090 mmol) in CH_2Cl_2 (5.0 mL) was added Ru-catalyst **30** (4.5 mg, 5.3 μmol) and the resultant mixture was stirred for 2.5 h at rt. The solvent was removed *in vacuo* and flash chromatography (pentane:EtOAc 1:1) of the residue gave **44** (22.2 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.96 (m, 1H), 5.69 (m, 1H), 4.73 (m, 1H), 4.55 (d, J_{AB} = 11.8 Hz, 1H), 4.51 (d, J_{AB} = 11.8 Hz, 1H), 4.47 (m, 1H), 3.91 (m, 1H), 3.59 (d, J = 6.1 Hz, 2H), 3.03 (m, 1H), 2.26-2.39 (m, 1H), 1.99 (m, 1H).

[87] Lindström, U. M.; Somfai, P. *Synthesis* **1998**, 109-117.

(*S*)-2-(benzyloxy)-1-((*S*)-1,2,5,6-tetrahydropyridin-2-yl)ethanol (45).
Compound **44** (217 mg, 0.836 mmol) was refluxed in 1M KOH (8 mL, EtOH:H$_2$O 1:1) for 2 h. EtOH was removed under reduced pressure and 2 M NaOH (4 mL) was added. The mixture was extracted with diethyl ether (3*20 mL). The combined organic phases were washed with brine, dried (MgSO$_4$) and concentrated giving a pale yellow solid. The crude product was recrystallized in diethyl ether giving **45** (140.5 mg, 72.0 %) as a white solid: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41-7.32 (br m, 5H), 5.90 (m, 1H), 5.65 (dd, *J*=10.2, 1.5 Hz, 1H), 4.56 (s, 2H), 3.84 (dd, *J*=10.7, 4.5 Hz, 1H), 3.63 (m, 3H), 3.12 (ddd, *J*=11.9, 5.8, 2.2 Hz, 1H), 2.88 (ddd, *J*=12.0, 10.3, 4.3 Hz, 1H), 2.66 (br s, 2H), 2.24-2.16 (br m, 1H), 1.96 (m, 1H).

(*S*)-2-((*S*)-1-((*E*)-penta-2,4-dienyloxy)-2-(benzyloxy)ethyl)-1,2,5,6-tetrahydropyridine (46). To a solution of **45** (50 mg, 0.21 mmol) and (*E*)-5-bromopenta-1,3-diene[82] (31.5 mg, 0.21 mmol) in dry THF (5 mL) was added KHMDS (0.5 M in toluene, 0.943 mL, 0.47 mmol) at -78 °C under N$_2$. The reaction mixture was stirred overnight in a cooling bath allowed to reach rt. The reaction was quenched with aq. Na$_2$CO$_3$ (10 mL) and extracted with ether. The combined organic extracts were dried (MgSO$_4$) and concentrated giving a orange oil. Flash chromatography (CH$_2$Cl$_2$:MeOH 9:1 → 4:1) of the residue gave **46** (23.9 mg, 37%) as an orange oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34-7.26 (m, 5H), 6.39-6.22 (m, 2H), 5.87-5.76 (m, 2H), 5.67 (m, 1H), 5.19 (m, 1H), 5.09 (m, 1H), 4.54 (s, 2H), 4.23 (dd, *J* = 13.0, 6.2 Hz, 1H), 4.14 (dd, *J* = 12.9, 6.3 Hz, 1H), 3.66 (m, 3H), 3.53 (m, 1H), 3.09 (ddd, *J* = 8.1, 5.8, 2.4 Hz, 1H), 2.84 (ddd, *J* = 11.9, 10.0, 4.4 Hz, 1H), 2.77 (br s, 1H), 2.22-2.14 (m, 1H), 1.98-1.93 (m, 1H).

(*S*)-2-(benzyloxy)-1-((*S*)-1,2,5,6-tetrahydro-1-tosylpyridin-2-yl)-ethanol (47). To a solution of **45** (20.0 mg, 0.086 mmol) and *p*-TsCl (16.3 mg, 0.086 mmol) in dry CH$_2$Cl$_2$ (1.5 mL) was added Et$_3$N (24 μL, 0.17 mmol) at -78 °C under N$_2$. The reaction mixture was stirred for 1 h at -78 °C and 1.5 h at -15 °C and H$_2$O (1 mL) was added. Extrelut® workup and removal of solvent gave a pale yellow oil. Flash chromatography (pentane:EtOAc 2:1) of the residue gave **47** (31.4 mg, 92%) as a clear oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.37-7.31 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.76 (m, 2H), 4.62 (d, *J*$_{AB}$ = 11.6 Hz, 1H), 4.56 (d, *J*$_{AB}$ = 11.6 Hz, 1H), 4.34 (m, 1H), 3.94-3.86 (m, 2H), 3.76 (dd, *J*$_{AB}$ = 9.7, 3.7 Hz, 1H), 3.63 (dd, *J*$_{AB}$ = 9.7, 6.8 Hz, 1H), 3.25 (m, 1H), 2.61 (d, *J* = 5.2 Hz, 1H), 2.40 (s, 3H), 1.70 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 143.4, 138.2, 138.0, 129.7, 128.6, 128.0, 127.9, 127.1, 127.0, 124.5, 73.6, 73.5, 72.0, 54.9, 40.0, 22.5, 21.6.

(*S*)-2-((*S*)-1-((*E*)-penta-2,4-dienyloxy)-2-(benzyloxy)ethyl)-1,2,5,6-tetrahydro-1-tosylpyridine (48). To a solution of NaH (10.7 mg, 0.45 mmol) in dry THF (1.5 mL) was added **47** (86.4 mg, 0.22 mmol) in dry THF (0.5 mL). The mixture was stirred for 20 min at rt and (*E*)-5-bromopenta-1,3-diene (36.1 mg, 0.25 mmol) and Bu$_4$NI (8.2 mg, 0.022 mmol) were added in quick succession. The resultant mixture was stirred for 3 days. The reaction was quenched with water (5.5 mL), extracted with ether, dried (MgSO$_4$) and concentrated *in vacuo*. Flash chromatography (pentane:EtOAc 10:1 → 5:1) of the residue gave **48** (85.8 mg, 85%) as a pale yellow oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.37-7.22 (m, 7H), 6.32 (dt, *J* = 16.8, 10.2 Hz, 1H), 6.20 (dd, *J* = 15.1, 10.6 Hz, 1H), 5.74 (m, 3H), 5.19 (d, *J* = 16.3 Hz, 1H), 5.09 (d, *J* = 9.4 Hz, 1H), 4.57 (dd, *J* = 30.8, 11.9 Hz, 2H), 4.41 (d, *J* =

5.1 Hz, 1H), 4.23 (dd, J = 12.8, 6.3 Hz, 1H), 4.10 (dd, J = 12.8, 6.0 Hz, 1H), 3.90 (dt, J = 14.1, 5.4 Hz, 1H), 3.79 (q, J = 5.6 Hz, 1H), 3.70 (dd, J = 10.3, 5.0 Hz, 1H), 3.61 (dd, J = 10.3, 6.2 Hz, 1H) 3.33 (m, 1H), 2.40 (s, 3H), 1.75 (m, 2H).

(*S*)-2-((*S*)-1-((*E*)-penta-2,4-dienyloxy)-2-(benzyloxy)ethyl)-2,5-dihydro-1-tosyl-1*H*-pyrrole (49). To a solution of NaH (20.5 mg, 0.51 mmol, 60 wt% washed with 3*pentane) in dry DMF (4 mL) was cannulated **43** (95.8 mg, 0.26 mmol) in DMF (1 mL). The mixture was stirred at 0 °C for 5 min, then 5-bromopenta-1,3-diene (56.6 mg, 0.39 mmol) and Bu_4NI (9.5 mg, 0.026 mmol) were added in quick succession. The resultant mixture was stirred at rt for 1 h, quenched with H_2O (4 mL) and extracted with Et_2O (4*10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (pentane:EtOAc 5:1) of the residue gave **49** (103.7 mg, 92%) as a pale yellow oil: [^1]H NMR (400 MHz, CDCl_3) δ 7.67 (d, J = 8.3 Hz, 2H), 7.37-7.23 (m, 7H), 6.29 (m, 2H), 5.75 (td, J = 15.0, 6.1 Hz, 1H), 5.65 (m, 2H), 5.15 (m, 2H), 4.61 (d, J_{AB} = 11.8 Hz, 1H), 4.60 (m, 1H), 4.53 (d, J_{AB} = 11.8 Hz, 1H), 4.25 (d, J = 6.0 Hz, 2H), 4.11 (m, 3H), 3.58 (ddd, J = 16.5, 10.3, 5.8 Hz, 2H), 2.41 (s, 3H); [^13]C NMR (100 MHz, CDCl_3) δ 143.5, 138.1, 136.5, 134.3, 133.0, 130.4, 129.7, 128.4, 127.65, 127.63, 127.5, 126.5, 126.2, 117.4, 79.8, 73.3, 72.1, 70.3, 69.0, 55.7, 21.5.

Unknown cycloaddition product (50). Compound **48** (53.3 mg, 0.12 mmol) and BHT (10, 7 mg, 20 w%) in dry toluene (2.5 mL) was degassed under vacuum in a sonic bath. The reaction mixture was heated to 215 °C for 9 days. The solvent was evaporated to give a brown oil. Flash chromatography (pentane:EtOAc 8:1) of the residue gave **50** (19 mg) as a mixture of two diastereomers (diastereomeric ratio 1.5:1) and **47** (10.2 mg, 19%) as a clear oil. The diastereomers were separated on a HP 1100 system with a Zorbax semi-preperative column, hexane:*i*PrOH 99.5:0.5 mobile phase and 5mL/min flow rate. R_T(major) = 10.38 min, R_T(minor) = 12.09 min: Major diastereomer: [^1]H NMR (400 MHz, CDCl_3) δ 7.56 (d, J = 8.2 Hz, 2H), 7.38-7.24 (m, 7H), 6.07 (d, J = 10.2 Hz, 1H), 5.47 (dt, J = 10.2, 2.8 Hz, 1H), 5.02 (m, 1H), 4.70 (d, J_{AB} = 12.0 Hz, 1H) 4.57 (d, J_{AB} = 12.0 Hz, 1H), 4.45 (d, J = 10.5 Hz, 1H), 3.93 (dd, J = 10.8, 4.0 Hz, 1H), 3.75 (m, 2H), 3.39 (dd, J = 5.9, 1.1 Hz, 1H) 2.43 (s, 3H), 2.22 (m, 1H), 2.01 (m, 1H), 1.89 (m, 1H) 1.70-1.53 (m, 3H), 1.03 (d, J = 7.4 Hz, 3H); [^13]C NMR (100 MHz, CDCl_3) δ 144.0, 138.6, 133.4, 132.0, 129.7, 128.7, 128.1, 127.7, 126.8, 86.2 73.9, 73.0, 71.0, 48.6, 43.6, 36.7, 36.4, 27.8, 22.5, 21.7; Minor diastereomer: [^1]H NMR (400 MHz, CDCl_3) δ 7.63 (d, J = 8.2 Hz, 2H), 7.38-7.31 (m, 5H), 7.21 (d, J = 8.2 Hz, 2H), 5.88 (dt, J = 10.0, 3.2 Hz, 1H), 5.51 (d, J = 10.1 Hz, 1H), 4.78 (dd, J = 10.2, 3.7 Hz, 1H), 4.56 (d, J_{AB} = 12.1 Hz, 1H) 4.51 (d, J_{AB} = 12.1 Hz, 1H), 4.29 (m, 1H), 3.93 (m, 1H), 3.63 (m, 1H), 3.50 (dd, J_{AB} = 10.2, 3.3 Hz, 1H), 3.45 (dd, J_{AB} = 10.2, 5.4 Hz, 1H), 3.27 (ddd, J = 12.1, 7.5, 2.9 Hz, 1H), 2.60 (m, 1H), 2.40 (s, 3H), 2.25 (m, 1H), 1.65-1.46 (m, 3H), 0.98 (d, J = 7.5 Hz, 3H).

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(2*E*)-(*S*)-2-(benzyloxy)-1-((*S*)-1,2,5,6-tetrahydro-1-tosylpyridin-2-yl)ethyl penta-2,4-dienoate (51). To a solution of **47** (74.6 mg, 0.19 mmol) and 2,4-pentadienoylchloride[88] (1.45 mL, 0.29 mmol, 0.2 M in CH_2Cl_2) in dry CH_2Cl_2 (4 mL) was added Et_3N (40.3 μL, 0.29 mmol) and DMAP (cat.). The reaction mixture was stirred over night. Cold water was added, the aqueous phase was made basic with $NaHCO_3$ (sat.) and extracted twice with ether. The combined organic phases were washed with 0.1 M HCl, 0.5 M NaOH and water, dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (pentane:EtOAc 5:1 → 2:1) of the residue gave **51** (60.8 mg, 68%) as a bright yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.34-7.22 (m, 8H), 6.46 (m, 1H), 5.93 (d, *J* = 15.5 Hz, 1H), 5.73-5.60 (m, 3H), 5.51 (m, 1H), 5.26 (m, 1H), 4.65 (m, 1H), 4.59 (d, J_{AB} = 11.9 Hz, 1H), 4.55 (d, J_{AB} = 11.9 Hz, 1H), 3.88 (dt, *J* = 3.5 Hz, 1H), 3.79 (dd, J_{AB} = 10.8, 4.2 Hz, 1H), 3.75 (dd, J_{AB} = 10.8, 6.1 Hz, 1H), 3.19 (m, 1H), 2.40 (s, 3H), 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.6, 138.2, 134.9, 129.7, 128.5, 127.9, 127.7, 127.5, 127.3, 126.1, 123.5, 121.9, 74.4, 73.3, 69.1, 52.5, 39.7, 22.5, 21.7.

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[88] Freshly prepared from pentadienoic acid and oxalylchloride in CH_2Cl_2 with a cat. amount of DMF, see; Dauben, W. G.; Bridon, D. P.; Kowalczyk, B. A.; *J. Org. Chem.* **1989**, *54*, 6101-6106.