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Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis

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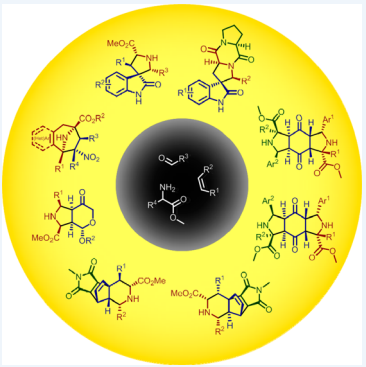
CONSPECTUS: Cycloaddition reactions are among the most powerful methods for the synthesis of complex compounds. In particular, the development and application of the 1,3-dipolar cycloaddition, an important member of this reaction class, has grown immensely due to its powerful ability to efficiently build various five-membered heterocycles. Azomethine ylides are commonly used as dipoles for the synthesis of the pyrrolidine scaffold, which is an important motif in natural products, pharmaceuticals, and biological probes. The reaction between azomethine ylides and cyclic dipolarophiles allows access to polycyclic products with considerable complexity. The extensive application of the 1,3-dipolar cycloaddition is based on the fact that the desired products can be obtained with high yield in a regio- and stereocontrolled manner. The most attractive feature of the 1,3-dipolar cycloaddition of azomethine ylides is the possibility to generate pyrrolidines with multiple stereocenters in a single step. The development of enantioselective cycloadditions became a subject of intensive and impressive studies in recent years. Among many modes of stereoinduction, the application of chiral metal−ligand complexes has emerged as the most viable option for control of enantioselectivity.



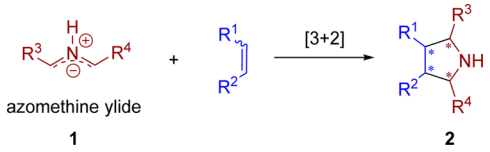
In chemical biology research based on the principle of biology-oriented synthesis (BIOS), compound collections are prepared inspired by natural product scaffolds. In BIOS, biological relevance is employed as the key criterion to generate hypotheses for the design and synthesis of focused compound libraries. In particular, the underlying scaffolds of natural product classes provide inspiration for BIOS because they define the areas of chemical space explored by nature, and therefore, they can be regarded as "privileged". The scaffolds of natural products are frequently complex and rich in stereocenters, which necessitates the development of efficient enantioselective methodologies.

This Account highlights examples, mostly from our work, of the application of 1,3-dipolar cycloaddition reactions of azomethine ylides for the catalytic enantioselective synthesis of complex products. We successfully applied the 1,3-dipolar cycloaddition in the synthesis of spiro-compounds such as spirooxindoles, for kinetic resolution of racemic compounds in the synthesis of an iridoid inspired compound collection and in the synthesis of a nitrogen-bridged bicyclic tropane scaffold by application of 1,3-fused azomethine ylides. Furthermore, we performed the synthesis of complex molecules with eight stereocenters using tandem cycloadditions. In a programmable sequential double cycloaddition, we demonstrated the synthesis of both enantiomers of complex products by simple changes in the order of addition of chemicals. Complex products were obtained using enantioselective higher order [6 + 3] cycloaddition of azomethine ylides with fulvenes followed by Diels−Alder reaction. The bioactivity of these compound collections is also discussed.

INTRODUCTION

The 1,3-dipolar cycloaddition reaction is among the most prominent reactions in organic synthesis.[1−3] It involves various 1,3-dipoles and alkenes to build five-membered heterocycles in a single step[4] and may generate up to four stereocenters.[1] For efficient steering of regio-, diastereo-, and enantioselectivity, chiral metal complexes have proven very versatile.[1−3] Among the dipoles, azomethine ylides **1** have been extensively used,[2,3] and the development of novel azomethine ylide precursors, dipolarophiles, and chiral catalysts has enabled the highly enantioselective[5−7] synthesis of substituted pyrrolidines with multiple stereocenters (Scheme 1).

Scheme 1. 1,3-Dipolar Cycloaddition Reaction between Azomethine Ylides and Alkenes



We have actively pursued chemical biology research through biology-oriented synthesis (BIOS).[8−14] According to the BIOS reasoning, the molecular scaffolds of natural products are highly conserved in nature, and many natural products that share a

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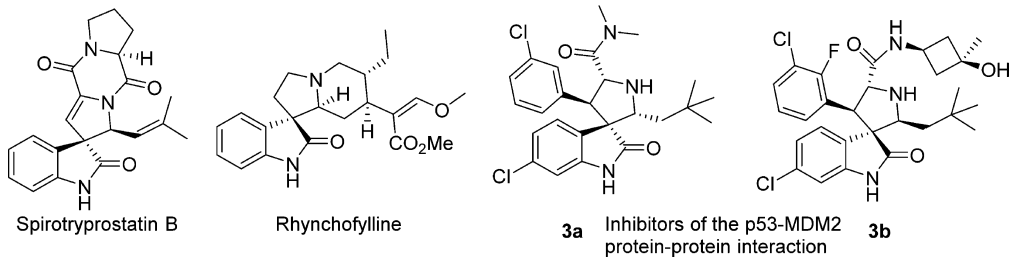
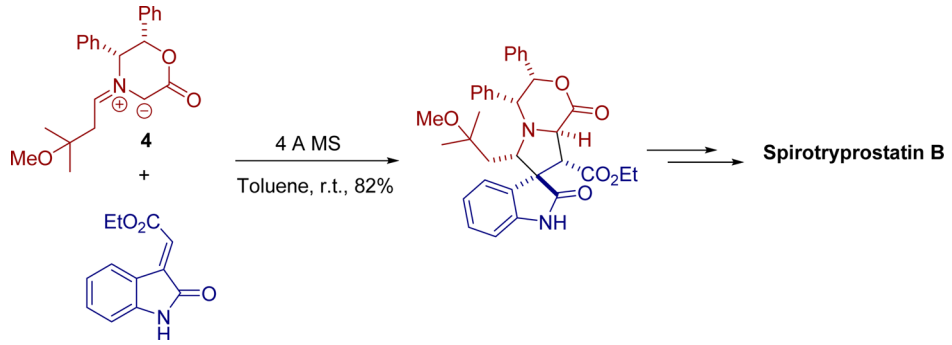
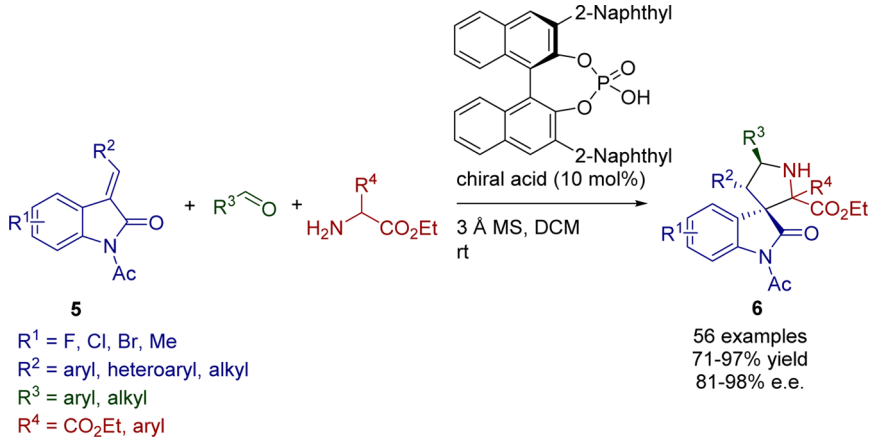


Figure 1. Representative examples of bioactive and naturally occurring spirooxindoles.

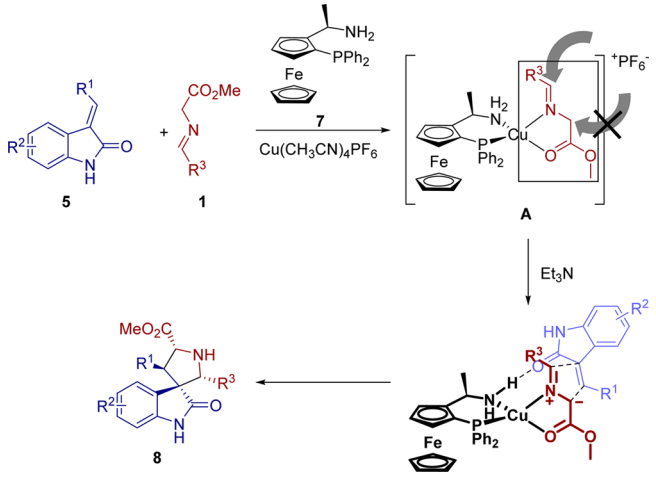
Scheme 2. William's Use of the 1,3-Dipolar Cycloaddition in the Synthesis of Spirotryprostatin B



Scheme 3. Organocatalytic Enantioselective Synthesis of Spirooxindoles



Scheme 4. Proposed Mechanistic Model for the Enantioselective Spirooxindole Synthesis



common scaffold, but have different substituent patterns, display diverse bioactivity profiles. Therefore, the scaffolds of natural products can be defined as "privileged structures" as chosen in evolution.[9] Following this logic, their privileged structures can be considered as good starting points for compound collection development. Because natural product scaffolds often are complex and contain multiple stereocenters, the development of efficient catalytic enantioselective synthesis methods is an integral part of BIOS.

In this Account, we highlight the development of catalytic enantioselective 1,3-dipolar cycloaddition reactions to obtain natural-product-inspired compound libraries. Recent advances have made this reaction type one of the most efficient stereocontrolled methods to obtain molecules with multiple stereocenters. We have attempted to harness the power of 1,3-dipolar cycloaddition for advanced synthetic applications such as generation of molecules with quaternary spirocenters and programmable sequential double cycloadditions to generate molecules with eight stereocenters in a single step. We have also developed higher order [6 + 3] cycloadditions of

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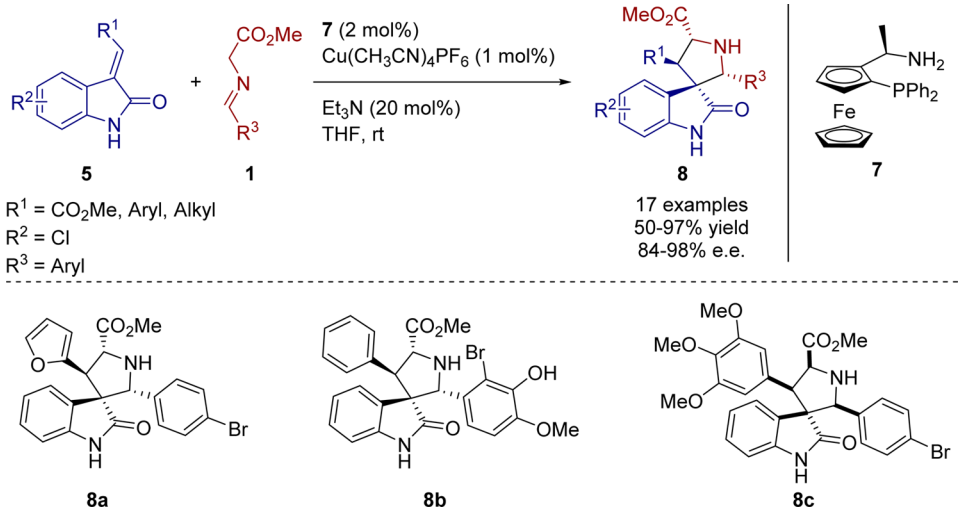
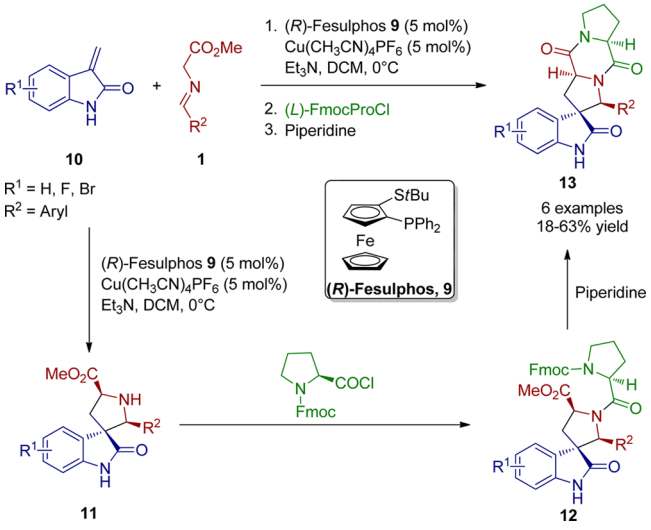
Scheme 5. Catalytic Enantioselective [3 + 2] Cycloaddition for the Synthesis of Spirooxindoles



Scheme 6. One-Pot Enantioselective Synthesis of Spirotryprostatin A Analogues



azomethine ylides with fulvenes in tandem with the Diels–Alder reaction to obtain complex molecular scaffolds, and the 1,3-dipolar cycloaddition strategy has been utilized for the kinetic resolution of substituted oxopyranes. A direct synthesis of a N-bridged bicyclic tropane inspired scaffold was achieved using 1,3-fused cyclic azomethine ylides. This Account encompasses these advanced transformations along with similar developments contributed by other groups.

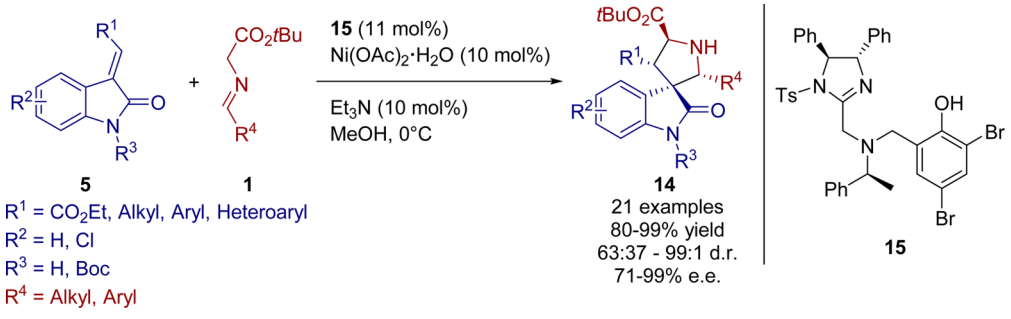
Catalytic Enantioselective Synthesis of 3,3′-Pyrrolidinyl Spirooxindoles

Spirooxindole alkaloids with a spiro ring fusion at the 3-position of the oxindole backbone with a pyrrolidinyl moiety have pronounced and diverse bioactivity (Figure 1).[15] Spirotryprostatin B arrests the cell-cycle at G2/M phase. Importantly, even non-natural spirooxindoles (compounds **3a** and **3b**, Figure 1) inhibit the cell-cycle and are nonpeptidic inhibitors of the p53-MDM2 protein–protein interaction which is critical for the tumor-suppressing activity of the p53 protein.

The 3,3′-pyrrolidinyl-spirooxindole scaffold has been the subject of many elegant asymmetric syntheses,[16] which usually involve multistep diastereoselective transformations using chiral auxiliaries. The pyrrolidinyl moiety embedded in the spirooxindole may be built up through a highly versatile [3 + 2] cycloaddition strategy. After pioneering studies by Grigg et al.,[17] Williams et al. have successfully used the 1,3-dipolar cycloaddition to install the 3,3′-pyrrolidinyl-spirooxindole motif in their synthesis of spirotrypostatin B (Scheme 2) making use of a chiral auxiliary embedded in the azomethine ylide **4**.[18] Schreiber et al. later employed this approach for a split-pool synthesis of more than 3000 spirooxindoles.[19]

The first enantioselective access to this heterocycle was reported in 2009 by Gong and co-workers through a chiral phosphoric-acid-catalyzed three-component 1,3-dipolar cycloaddition reaction of methylene–indolinones **5**, aldehydes, and

Scheme 7. Enantioselective Synthesis of *exo*′-Spirooxindoles



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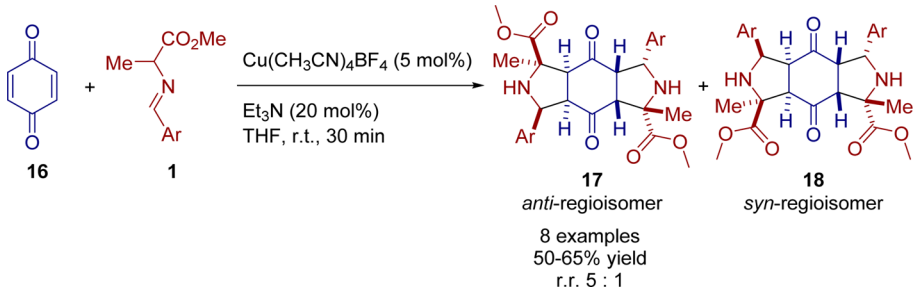
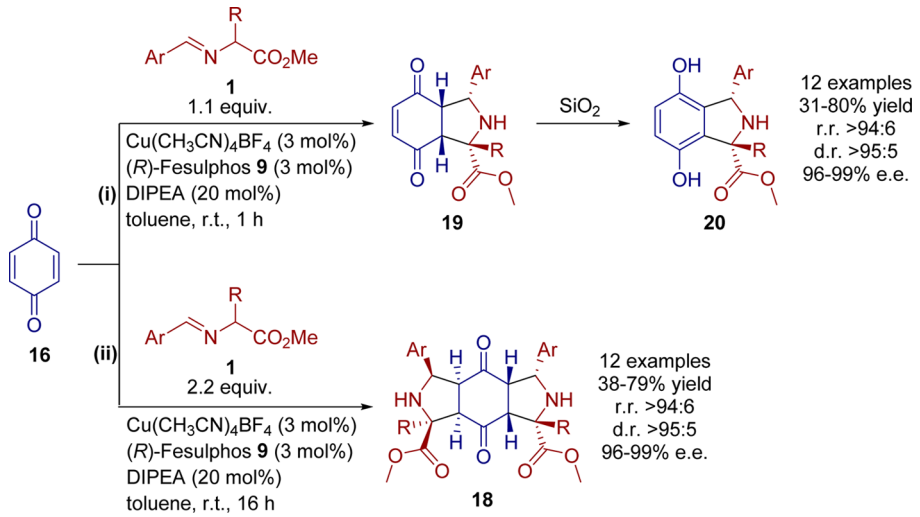
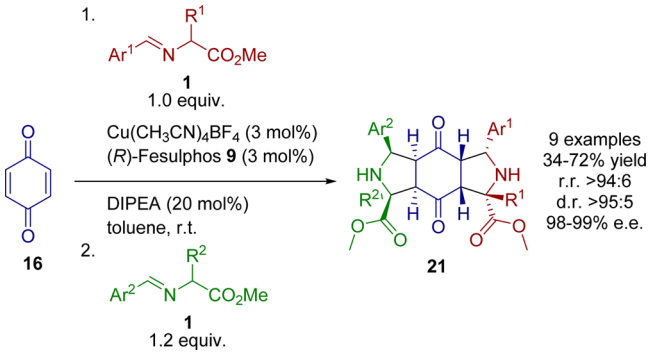
Scheme 8. Double Cycloaddition of Alanine Methyl Ester Imines 1 and *p*-Benzoquinone 16



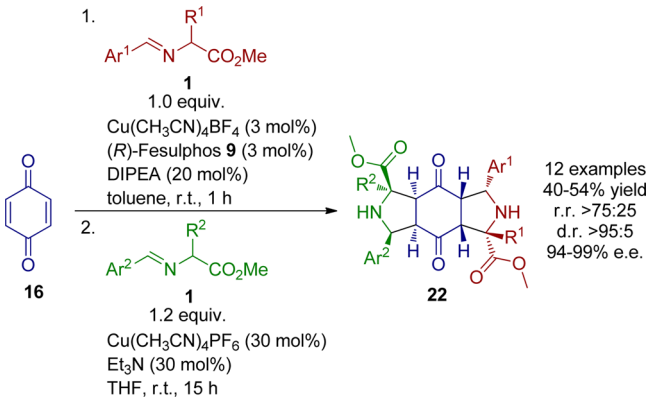
Scheme 9. Catalytic Enantioselective Double Cycloaddition for *syn*-Product Synthesis



Scheme 10. Enantioselective Synthesis of Mixed *syn*-Isomers



Scheme 11. Selective Enantioselective Synthesis of Mixed *anti*-Isomers



amino esters (Scheme 3).[20] The major products **6** were obtained with high enantio- and regioselectivity and unusual regioselectivity, which could be explained on the basis of a favorable $\pi-\pi$ stacking interaction between the 2-oxindole and the conjugate esters in the transition state. This rationale was backed by elaborate theoretical calculations.

Simultaneously, we developed the first Lewis-acid-catalyzed highly enantioselective synthesis of 3,3′-pyrrolidinyl spirooxindoles through a 1,3-dipolar cycloaddition of an azomethine ylide to a 3-arylidene- or alkylidene oxindole[14] (Schemes 4 and 5). The corresponding optimization revealed a nonlinear effect of the ligand/Cu^+ ratio on the enantioselectivity not observed before for 1,3-dipolar cycloaddition reactions. The ee of the product decreased drastically from 90% to 72% when the ratio was changed from 1:1 to 1.1:1. However, the level of enantioselectivity was restored when the ratio was further increased, and lastly the best ee of 98% and d.r. of 15:1 were obtained using a 2:1 ligand/Cu^+ ratio. To rationalize these observations, formation of a 1:1 complex **A** was proposed, which is present together with catalytic Cu^+ not coordinated to any chiral ligand and, therefore, responsible for the racemic background reaction (Scheme 4).

Initially formed complex **A** is deprotonated by base to generate the dipole, and the dipolarophile **5** is directed to the less-hindered back face to avoid unfavorable steric interactions with the two phenyl groups on the phosphorus. The oxindole oxygen may form a hydrogen bond with the amino group of ligand **7** and hence stabilize the proposed transition state. Replacement of the amino group in ligand **7** by a dialkylamino

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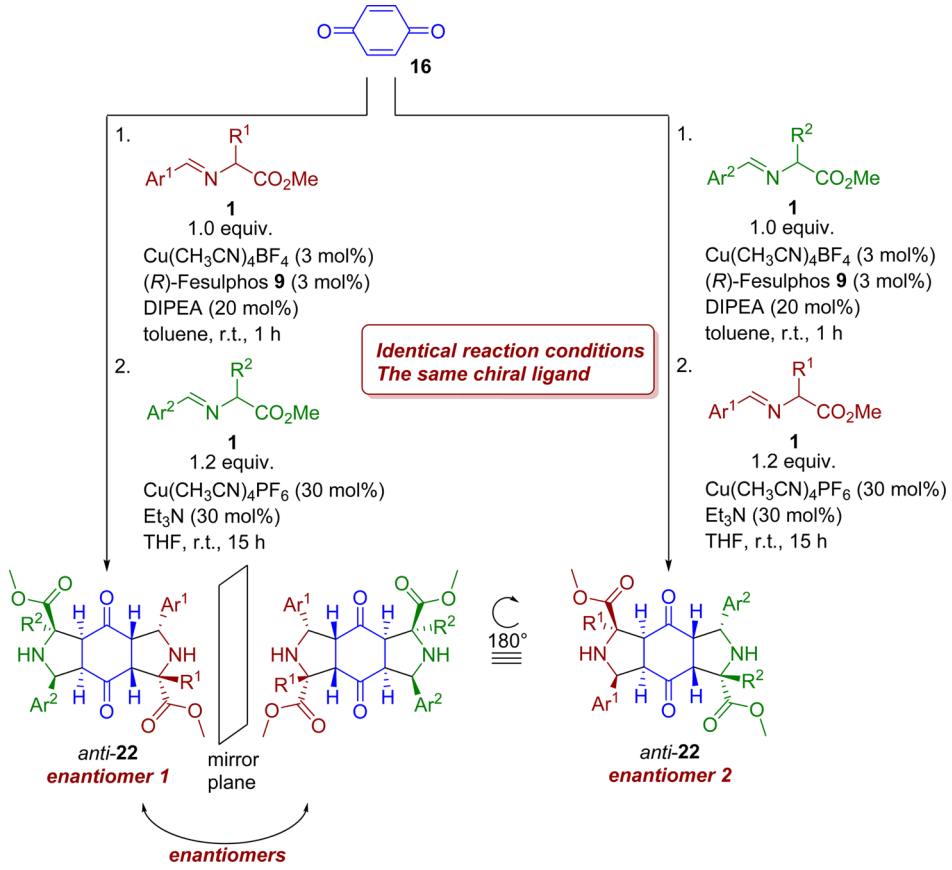
Scheme 12. Selective Synthesis of Enantiomers



group leads to formation of the enantiomer of product **8**, because in this case, the H-bond stabilization is lost. Instead, unfavorable steric interactions with the two alkyl groups direct the incoming oxindole to the front side, which results in reversed enantioselection.

The scope of the reaction is broad (Scheme 5) such that unsaturated indolinones **5** with aromatic, heteroaromatic, and aliphatic substituents react efficiently. Similarly, imino ester **1** could be varied, tolerating electron-withdrawing and electron-donating substituents on the phenyl ring. However, the diastereomeric **8c** was formed from the corresponding (*Z*)-isomer of benzylidene−indolinone in the presence of silver acetate without any ligand possibly by a stepwise Michael−Mannich reaction sequence.

Subsequently, this methodology was applied to assemble the 3,3′-pyrrolidinyl-spirooxindole scaffold embedded in spirotryprostatin A (Scheme 6).[21] In an efficient one-pot synthesis, a Cu^{+}/(*R*)-Fesulphos **9**-catalyzed enantioselective 1,3-dipolar cycloaddition of α,α-disubstituted alkene **10** with the iminoester **1** to form pyrrolidinyl oxindole **11** was followed by acylation to give **12**. Finally, removal of the Fmoc-group triggers diketopiperazine cyclization to establish the pentacyclic core of **13**.

With the knowledge that 3,3′-pyrrolidino-spirooxindoles induce mitotic arrest by interfering with the p53-MDM2 interaction, a focused collection of cycloadducts **8** was screened at a concentration of 30 μM for phenotypic changes associated with mitotic arrest in BSC-1 cells.[22] Only compound **8c** (Scheme 5), which differs from the other compounds by its relative configuration, induced phenotypic changes, such as accumulation of round-shaped cells with condensed DNA, indicating mitotic arrest. Both enantiomers of **8c** were screened separately, which revealed that (−)**8c** and not (+)**8c** caused accumulation of cells in the G2/M phase in BSC-1, HCT116 p53 +/+ and p53 −/−, and HeLa cells. More detailed studies revealed that unlike other 3,3′-spirooxindoles, (−)**8c** does not inhibit the p53-MDM2 interaction but rather interferes with microtubule polymerization. This new mode of action reinstates the BIOS philosophy, which embraces the insight that compound classes modeled on natural products can lead to hitherto unknown bioactivities.

Arai et al. used Ni(II) and chiral imidazoline−aminophenol ligand **15** with Et_3N to selectively obtain the *exo*′-diastereomer of spirooxindole **14** (Scheme 7).[23] The reported procedure is rather versatile with a range of substitutions being tolerated to give the corresponding products with high ee.

The different methodologies highlight the versatility of 1,3-dipolar cycloaddition reactions to generate different diastereomers of the spirooxindole products.

Double 1,3-Dipolar Cycloadditions

The synthesis of structurally and stereochemically complex molecular frameworks is an integral part of chemical biology research according to BIOS. The dipolar cycloaddition is a particularly efficient way to generate cyclic compounds rich in stereocenters, because up to four stereocenters can be generated in a single step. By analogy, up to eight stereocenters can be installed in a single molecule if the product of the first cycloaddition can participate in a second cycloaddition. On the basis of this logic, we developed an asymmetric one-pot tandem synthesis of structurally complex molecular structures by two consecutive cycloadditions of azomethine ylides **1** and *p*-

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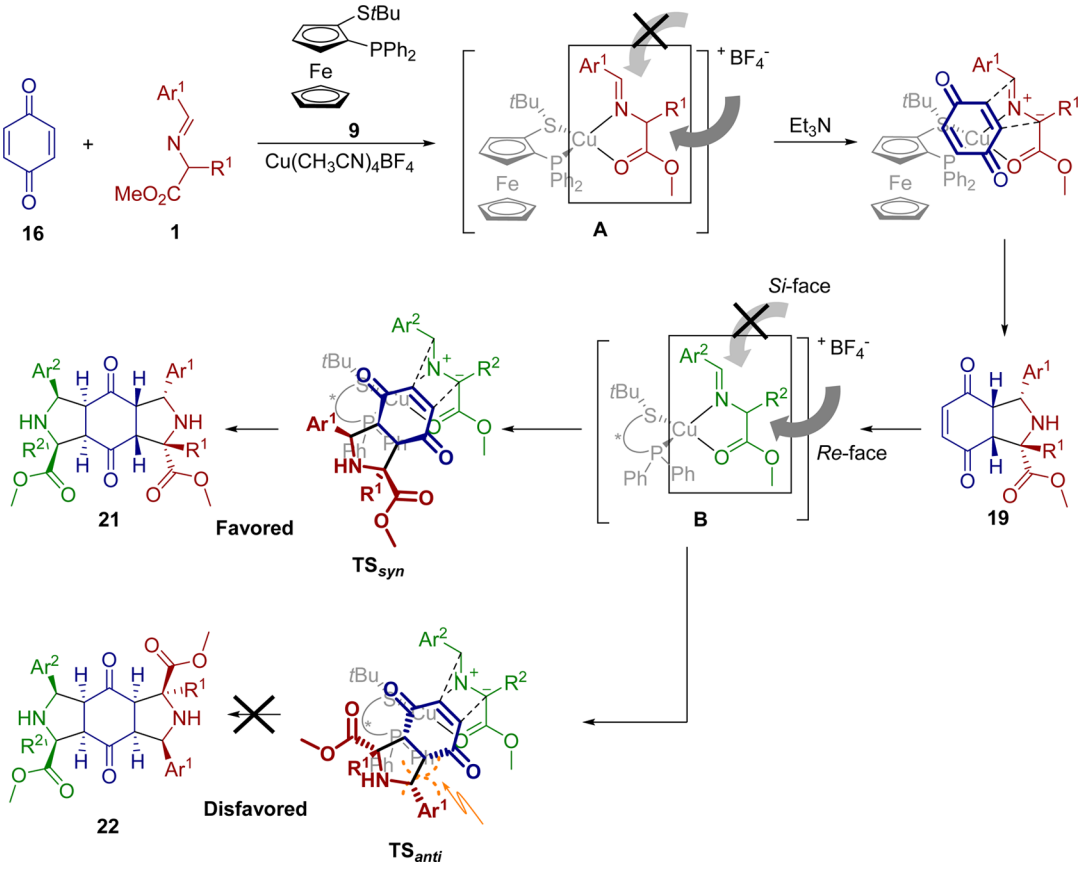
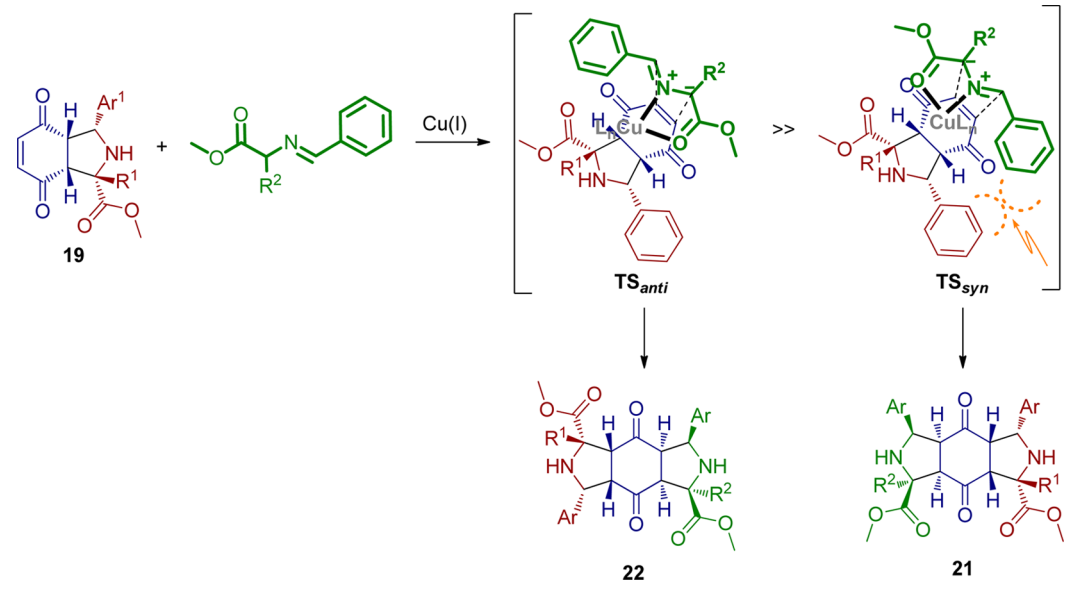
Scheme 13. Stereochemical Rationale for the Selective Formation of Mixed *syn*-Isomers



Scheme 14. Stereochemical Rationale for the Selective Synthesis of *anti*-Isomers



benzoquinone **16** (Scheme 8).[24] Four new C−C bonds and eight stereocenters could be generated with high regio-, diastereo-, and enantioselectivity in a single operation using this methodology. Remarkably, every level of selectivity could be steered by using a common set of reagents and by varying *only* the order of reagents and/or the catalyst. This level of operational efficiency makes the methodology programmable.

For the development of a catalytic double dipolar cycloaddition, *p*-benzoquinone **16** (Scheme 8) was treated with alanine methyl ester imine **1** (R = H) in dichloromethane in the presence of base to yield a 1:1 mixture of *anti*-**17** and *syn*-**18** double cycloaddition products. Thus, the reaction proceeded with high diastereoselectivity but low regioselectivity.

Crystal structure analysis of *anti*-isomer **17** revealed that the central 1,4-cyclohexadione ring adopts a chair conformation

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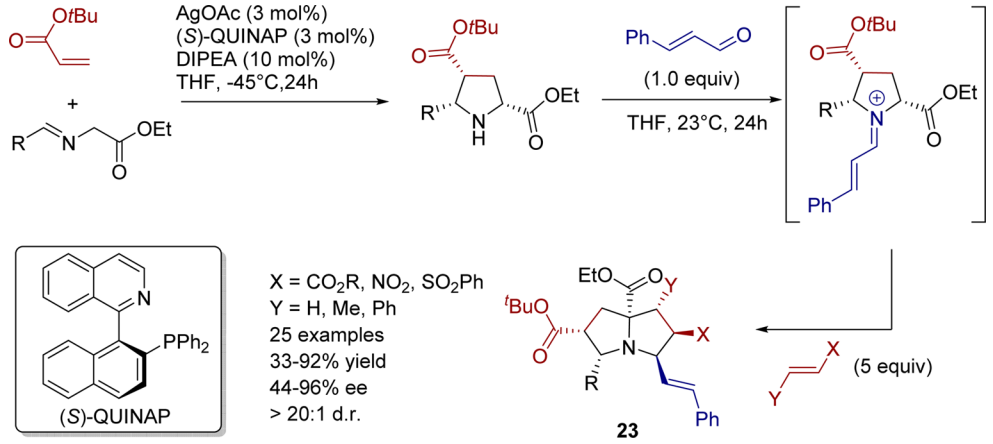
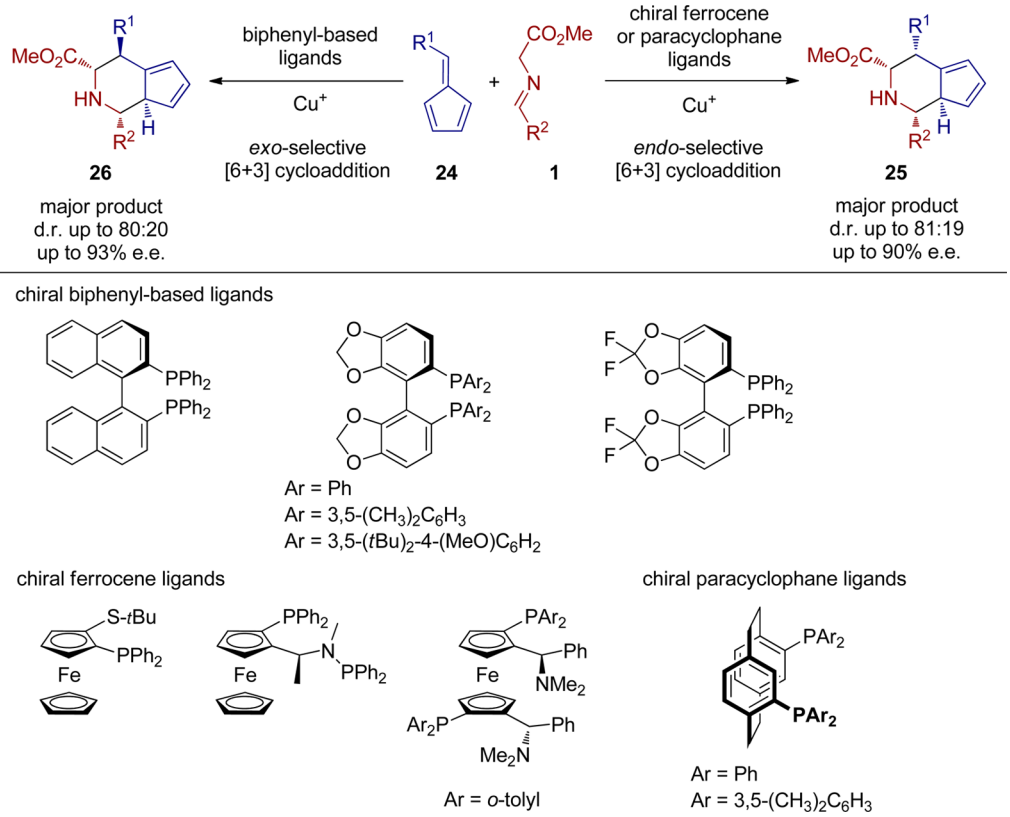
Scheme 15. Synthesis of Pyrrolizidines through Two One-Pot 1,3-Dipolar Cycloaddition



Scheme 16. Stereodivergent [6 + 3] Cycloaddition



such that the molecule has a center of inversion. This transformation tolerates imines derived from aromatic aldehydes with electron-donating as well as electron-withdrawing substituents (Scheme 8). Under optimized reaction conditions, the *anti*-product **17** could be predominantly obtained with a regioselectivity ratio of 5:1. Because *syn*-isomer **18** does not possess any center of inversion, its enantioselective synthesis was developed. Various azomethine ylides derived from variably substituted aromatic aldehydes reacted efficiently in terms of regioselectivity, diastereoselectivity, and enantioselectivity. The same reaction conditions were also used for obtaining hydroquinones **20** via isomerization of monocycloadducts **19** (Scheme 9).

Mixed cycloadducts incorporating two different dipoles can be obtained in the presence of a chiral catalyst bearing a bulky ligand because the second cycloaddition is slower than the first cycloaddition. On the basis of this finding, a sequence was optimized wherein 1,4-benzoquinone **16** was treated with 1 equiv of α-iminoester **1** under catalytic enantioselective reaction conditions for 1 h followed by treatment with a second α-iminoester for 15 h to obtain the mixed double cycloaddition products *syn*-**21** in a one-pot tandem sequence with excellent levels of stereoselectivity (Scheme 10).

Control of the regioselectivity (*anti* vs *syn*) was achieved on the basis of the observation that the regioselectivity of the product can be changed simply by switching from a chiral catalyst to an achiral catalyst. Moreover, it was found that the reaction rate of the second cycloaddition is low in the presence of a chiral catalyst carrying a bulky ligand but high in the presence of a "ligand-free" catalyst. Thus, if the second

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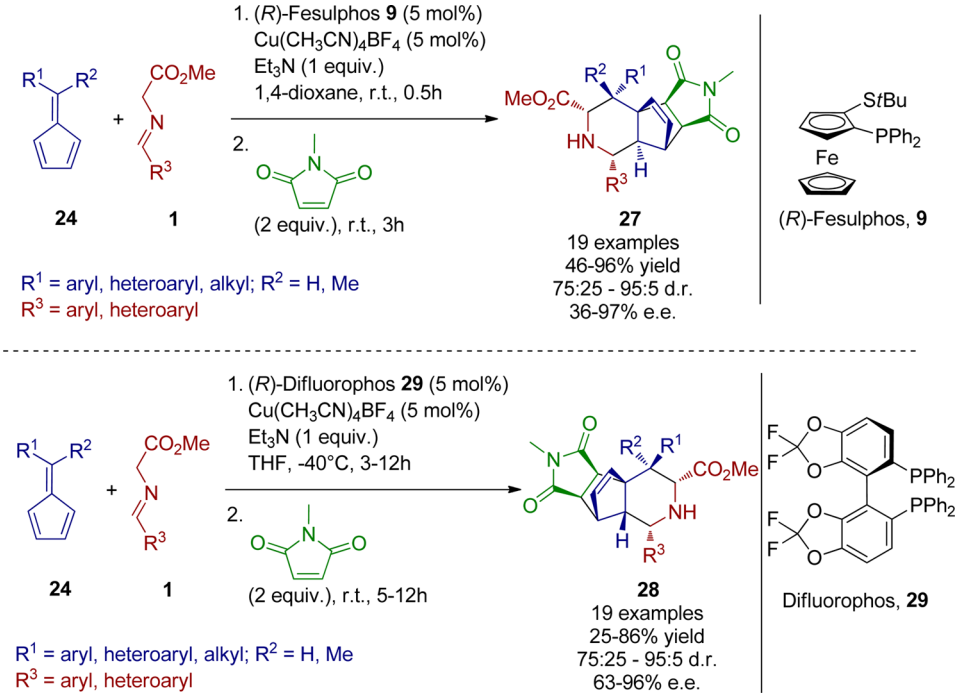
Scheme 17. Scope of the Tandem [6 + 3]/[4 + 2] Cycloaddition



cycloaddition is performed in the presence of a relative excess of ligand-free catalyst, the reaction should give the *anti*-product predominantly. It is important to note that if the second cycloaddition is carried out with a different iminoester, then the mixed *anti*-product **22** would not have a center of inversion and hence would be chiral. Indeed, when 1,4-benzoquinone was treated with 1 equiv of α-iminoester **1** in the presence of catalyst with chiral ligand followed by the addition of a second α-iminoester and ligand-free catalyst upon completion of the first step in a one-pot procedure, the regioselectivity of the product was shifted to 75:25 in favor of the *anti*-isomer **22** (Scheme 11). In addition, THF is critical for the second cycloaddition because it enhances the solubility of Cu-$(CH_3CN)_4PF_6$. By means of this methodology, a variety of mixed *anti*-product **22** could be successfully obtained regardless of the electronic properties and position of the substituents on the aryl group of the iminoester.

Because the enantioselectivity is exclusively determined in the first step of the tandem sequence, reversing the order of the α-iminoester addition gives the opposite enantiomer (Scheme 12).

The stereochemical course of the reaction can be explained by means of the model proposed in Scheme 13. The α-iminoester along with the bidentate chiral ligand **9** forms a tetrahedral arrangement around Cu(I) to generate the catalytic asymmetric intermediate **A**. This complex is deprotonated by the base to generate the azomethine ylide which undergoes the first cycloaddition with benzoquinone through front side attack forming an *endo* transition state to give monocycloadduct **19**. In the next step, this monocycloadduct functions as dipolarophile. Due to the steric hindrance in transition state **B**, the dipolarophile approaches from the front side (*re* face with respect to C═N) where it can orient itself to form either the mixed *syn*-product **21** or the mixed *anti*-product **22**. The transition state leading to the formation of the *anti*-product (TS_{anti}) bears a destabilizing steric interaction between the aryl substituent of the cycloadduct and the phenyl group of the ligand. Hence, the formation of mixed *syn*-product **21** is favored in the presence of chiral ligand.

For the formation of the *anti*-product (Scheme 14), the second cycloaddition has to take place predominantly in the presence of achiral nonbulky ligands; thus, the stereochemistry at the new stereogenic centers is controlled by the stereocenters in monocycloadduct **19**. The aryl group and the *cis*-substituted carboxylate moiety in the pyrrolidine part of the monocycloadduct **19** (shown in brown) effectively block one face of the double bond, thereby predisposing the metal-complexed azomethine ylide (shown in green) to attack from the other side. During this attack, the two reacting species can arrange themselves in *syn*- or *anti*-arrangement (TS_{syn} vs TS_{anti}). *Syn*-attack is disfavored because of the steric interaction between two aromatic moieties in the TS_{syn}. Thus, predominantly *anti*-product **22** is formed under these conditions.

Recently, Reisman and co-workers developed a highly enantioselective synthesis of multiply substituted pyrrolizidine **23** in a one-pot tandem 1,3-dipolar cycloaddition reaction (Scheme 15).[25] An AgOAc/(*S*)-QUINAP catalyst system was used to induce enantioselectivity.[6] Enantioselectivity is determined in the first step of the reaction, whereas the second step is a diastereoselective process. The scope of the reaction is rather broad and tolerates various iminoesters and dipolarophiles to give products **23** with high enantioselectivity (up to 96% ee) and yields (up to 92%).

[6 + 3]/[4 + 2] Tandem Cycloaddition Reaction Sequence

The enantioselective [3 + 2] cycloaddition has been developed into one of the most powerful methods for the synthesis of pyrrolidines. However, catalytic enantioselective higher order cycloadditions have rarely been explored. Fulvenes **24** containing 6 π electrons may serve as dipolarophiles in the cycloaddition with 1,3-dipoles, which is formally called [6 + 3] cycloaddition (Scheme 16), and Hong et al. first utilized this strategy for a synthesis of racemic pentasubstituted piperidine derivatives.[26] We developed the first catalytic enantioselective

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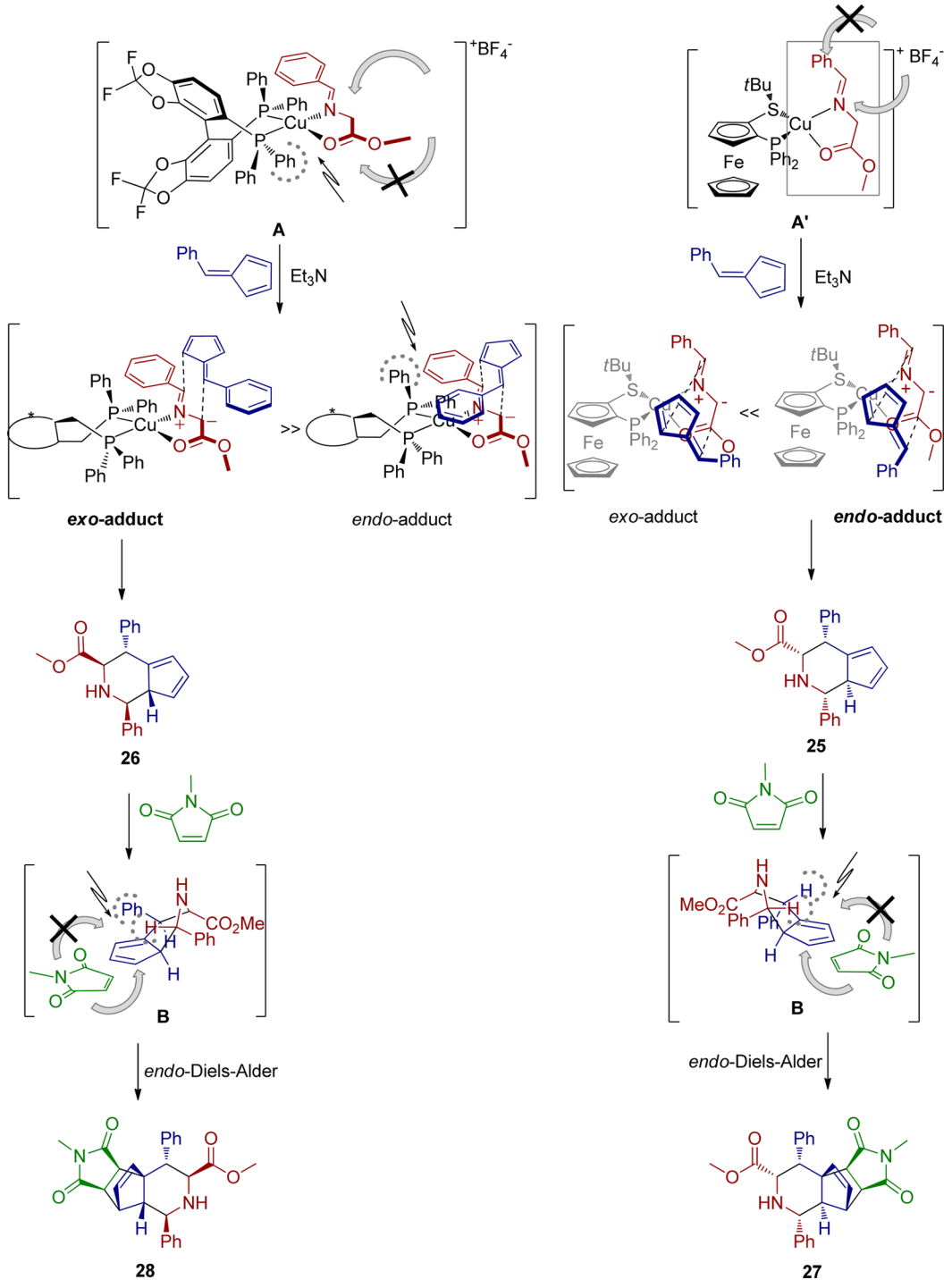
Scheme 18. Mechanistic Rationale for the Stereodivergency in the [6 + 3] Cycloaddition



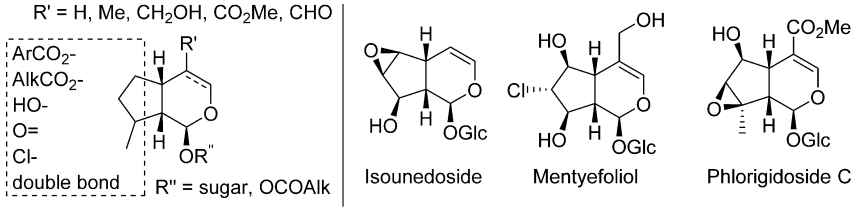


Figure 2. Structure and substitution pattern in the natural iridoids.

[6 + 3] cycloaddition of azomethine ylides with fulvenes to obtain piperidine derivatives with high regio- and enantioselectivity.[27,28] Treatment of azomethine ylide **1** and unsymmetrical fulvene **24** in the presence of a substoichiometric

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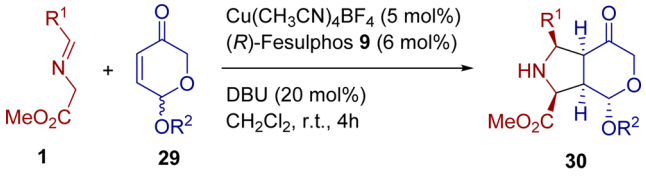
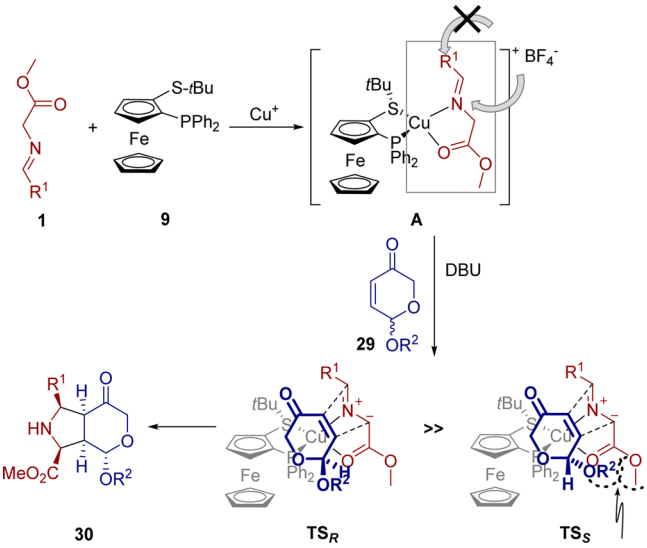
Scheme 19. Scope of the Kinetic Resolution of Racemic Oxopyranes by 1,3-Dipolar Cycloaddition



R^1 = aryl, heteroaryl
R^2 = Bz, Piv, Ac, methoxy acetyl, 4-pentenoyl

Scheme 20. Proposed Transition States for the Kinetic Resolution of Oxopyranes



amount of Cu(I) salt, base, and a chiral ligand led to the formation of two diastereomeric [6 + 3] cycloaddition products **25** and **26**. In the presence of chiral ferrocene and paracyclophane ligands, **25** was formed through *endo*-selective cycloaddition; biphenyl based ligands favor the formation of *exo*-selective diastereomer **26**. Shortly after our report, Wang et al. reported a similar [6 + 3] cycloaddition reaction of iminoesters and fulvenes for the synthesis of piperidine derivatives.[29]

Products **25** and **26** are only moderately stable, and hence, the reactive cyclopentadiene moiety was reacted with *N*-methylmaleimide at ambient temperature to obtain the corresponding stable Diels–Alder products in good yield, with high diastereoselectivity, and without loss of enantiomeric purity. The reaction proceeds smoothly with various dienophiles such as maleic anhydride, benzoquinone, and 1,4-naphthoquinone and, therefore, was established as one-pot sequence to form the tandem [6 + 3]/[4 + 2] products **27** and **28** directly starting from an α-iminoester. Both pathways were separately optimized with respect to various reaction conditions to obtain the products with high levels of selectivity (Scheme 17).[27,28] The tandem transformations proceed efficiently irrespective of the electronic nature of the substituents on imine **1**. Similarly, various substitutions on the fulvenes are tolerated. Alkyl-substituted fulvenes gave the products in good yields but with low enantioselectivity.

The stereochemical course of this stereodivergent reaction can be explained on the basis of the transition state model depicted in Scheme 18. The reaction giving the *exo*-product has been depicted on the *left* and the pathway to the *endo*-product on the *right*. In both cases, the bidentate ligand and the iminoester form a tetrahedral catalytic complex with Cu(I), which is shown as complex **A** for the Difluorophos ligand **29** and complex **A′** for the Fesulphos ligand **9**. The fulvene

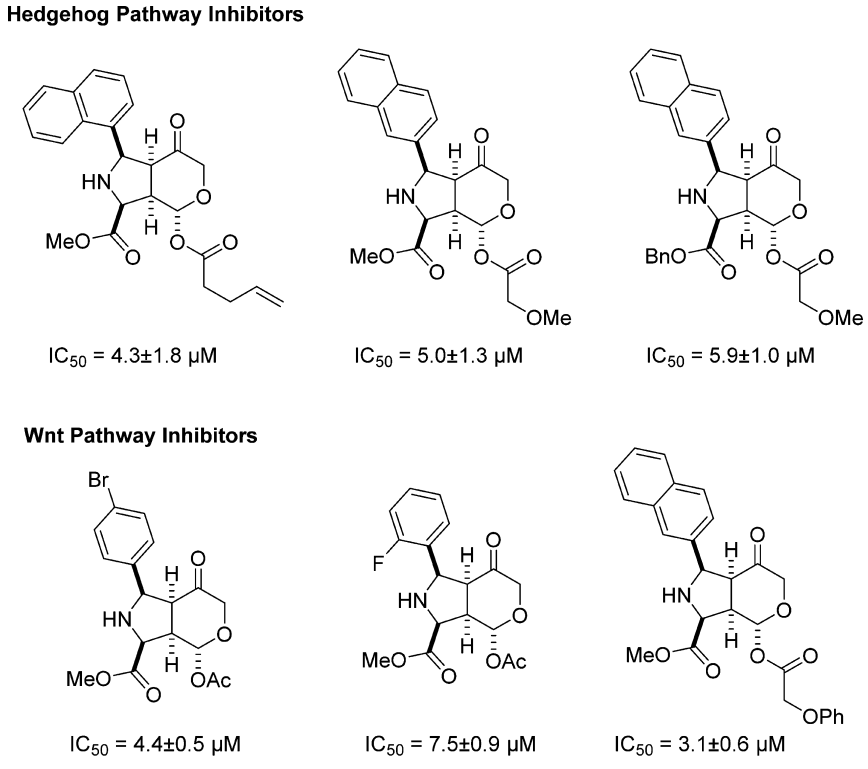


Figure 3. Representative examples of Hedgehog and Wnt pathway inhibitors.

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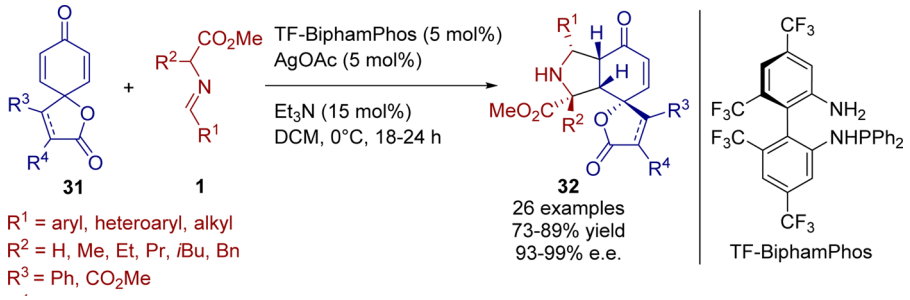
Scheme 21. Catalytic Asymmetric Desymmetrization



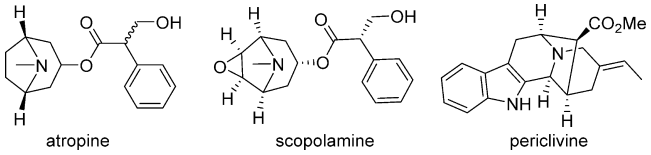


Figure 4. Naturally occurring tropane-based compounds.

approaches the complex either from the front or the back side depending on the steric interaction and space available. In complex **A**, the diphenylphosphine group blocks the front face of the azomethine ylide completely, and hence, the attack of the fulvene is directed to the back side. In the *endo* orientation, the fulvene encounters an unfavorable steric interaction with one of the phenyl groups, and hence, the *exo* orientation is favored to form the corresponding *exo*-product **26**. In complex **A′**, the *tert*-butyl group of the ligand effectively blocks the back side. In this case, there is enough space available for *endo* or *exo* orientation of the fulvene, and the *endo*-product **25** is thermodynamically preferred. Both products **25** and **26** undergo a [4 + 2] cycloaddition with maleimide through *endo*- transition states **B** to form the corresponding diastereomeric tandem [6 + 3]/[4 + 2] cycloaddition products **27** and **28** respectively.

Kinetic Resolution of Pyranones by Means of Asymmetric [3 + 2] Cycloaddition

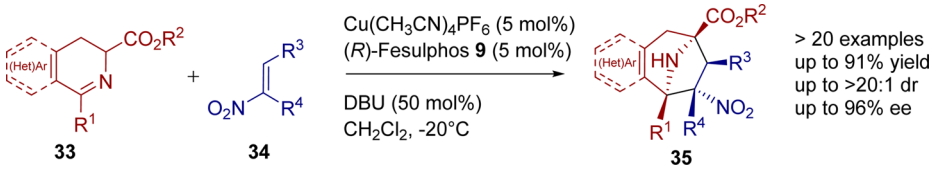
Iridoids are a large group of cyclopentano[*c*]pyran monoterpene secondary metabolites of terrestrial and marine flora and fauna. They are predominantly *cis*-fused bicycles studded with various functional groups and stereocenters (Figure 2) and endowed with a wide range of bioactivities. In order to synthesize an iridoid-inspired compound collection, we investigated a kinetic resolution of racemic 2*H*-pyran-3(6*H*)-ones **29** by means of asymmetric [3 + 2] cycloaddition with *α*-iminoesters (Scheme 19).[30] The optimal reaction conditions for the catalytic enantioselective cycloaddition reaction were established through an elaborate optimization process and once again, the Cu(I)/(*R*)-Fesulphos catalytic system gave the best enantioselectivity (Scheme 19). Notably, the relative configuration of the major product **30** is the same as in the natural analogues.

The reaction is very facile and tolerates a variety of iminoesters irrespective of the electronic properties of the substituents in the aryl part. The products contain five stereocenters and were formed as essentially single diastereomer and with consistently high ee. Similarly, variations in oxopyranes **29** were also tolerated well to give the corresponding products with high levels of stereoselectivity. To rationalize the stereochemical course and the kinetic resolution, we assume that in the first step, the catalytic species **A** is generated through bidentate coordination of the iminoester and the chiral ligand **9** to Cu(I) in a tetrahedral arrangement (Scheme 20). After deprotonation, the dipolarophile approaches from the front side to avoid unfavorable steric interaction with the *tert*-butyl group of the ligand. At this stage, in oxopyrane **29** with the (*R*)-configuration, the bulky OR^2 substituent is oriented away from the ester group of the iminoester, whereas in the (*S*)-configured oxopyrane, OR^2 has a unfavorable steric interaction with the ester group. This results in a more stabilized transition state (TS_R vs TS_S) for the (*R*)-oxopyrane and, consequently, a faster reaction. This model matches the observed selectivity.

A collection of 115 compounds was synthesized and investigated for its ability to modulate biological signaling relevant to developmental processes and tumorigenicity. The corresponding assays monitor the Wnt[31] and the hedgehog pathway.[32]

In the Wnt pathway reporter gene assay, a HEK293 reporter cell line was employed, and compounds for which cell viability remained at >80% in control experiments were used in primary screening. Undesired inhibition of the reporter luciferase, transcription, or translation was ruled out with appropriate controls. Much to our delight, several compounds were identified as potent inhibitors of the Wnt pathway with IC_{50} values in the low micromolar range (Figure 3). Delineation of a structure−activity relationship from the screening results revealed that the R^2 group plays an important role in determining the bioactivity (Scheme 19). Introduction of an acetate (R^2 = Ac) led to the most frequent active compounds, whereas bulky carboxylic residues such as benzoic, pivalic, or *iso*-pentanoic acids as the R^2 group induced lower activity (Scheme 19). Notably, R^1 could be varied widely without loss

Scheme 22. Scope of the Catalytic Enantioselective Tropane Synthesis



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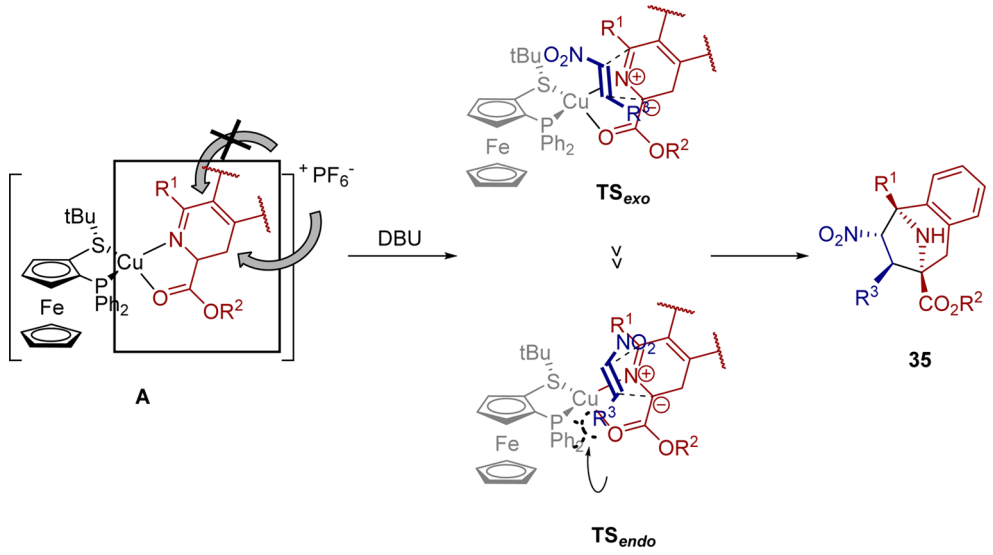
Scheme 23. Mechanistic Proposal for the Stereochemical Course of the Reaction



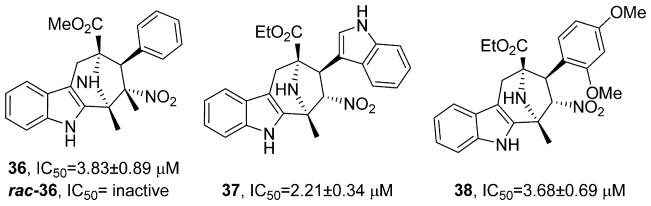


Figure 5. Representative examples of the Hedgehog signaling pathway inhibition.

of activity. Finally, protection of the nitrogen atom of compound **30** by various carboxylic acids resulted in inactive compounds.

Investigation of the hedgehog pathway modulation also revealed inhibitors with IC_{50} values in the low micromolar range (Figure 3). To this end, mouse embryonic mesoderm fibroblast C3H10T1/2 cells were used. During differentiation, osteoblast specific genes such as alkaline phosphatase, which plays an essential role in bone formation, are highly expressed. Activity of alkaline phosphatase can be monitored directly by following substrate hydrolysis yielding a highly luminescent product. Inhibition of the hedgehog pathway results in reduction of luminescence.

These findings support the notion that NP-inspired compound collections may be rich sources for modulators and probes with diverse bioactivity from one given compound collection endowed with biological relevance.

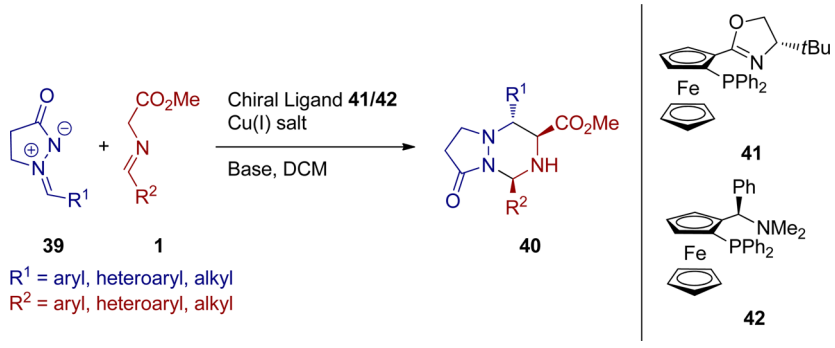
Recently, Wang and co-workers developed an efficient asymmetric desymmetrization of spiro cyclohexadienone lactones **31** through a Ag(I) catalyzed 1,3-dipolar cycloaddition with iminoesters (Scheme 21).[33] TF-BiphamPhos was used as the chiral ligand. The methodology provides an expedient access to spirolactone–pyrrolidine **32** in high yields (up to 89%) with high enantioselectivity (up to 99%).

Catalytic Enantioselective Synthesis of the Tropane Scaffold

The tropane scaffold defines the structural core of >600 alkaloids. Many natural tropane derivatives are used for the treatment of neurological and psychiatric diseases such as Parkinson's, schizophrenia, depression, and so forth (Figure 4). Despite this long-standing importance, no general and efficient methods for the stereoselective synthesis of functionalized tropanes have been developed.[34]

To enantioselectively assemble the bicyclic core of the tropane scaffold, we explored the [3 + 2] cycloaddition of a cyclic 1,3-fused azomethine ylide precursor **33** and the appropriate alkene. Under optimized reaction conditions, the *exo*′-isomer was formed predominantly if nitroalkene **34** was employed as dipolarophile (Scheme 22).[35] The reaction tolerates various substitution patterns in both reaction partners. Remarkably, the products were obtained with at least two fully

Scheme 24. Enantioselective Cross-Cycloaddition



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substituted and two tertiary stereocenters out of a maximum of four contiguous stereocenters in the five-membered ring. This reaction is the first example where a 1,3-fused cyclic azomethine ylide was used successfully in an enantioselective [3 + 2] cycloaddition reaction. Moreover, this was also the first case for selective formation of an *exo*′-product from an *S*-shaped azomethine ylide and a general methodology involving ketimines in an enantioselective [3 + 2] cycloaddition.

The observed stereoselectivity of the product can be rationalized on the basis of the model shown in Scheme 23. (*R*)-Fesulphos and the iminoester form a tetrahedral complex **A** around Cu(I). The nitroalkene approaches from the front side to avoid the bulky *tert*-butyl moiety of the ligand (*R*)-Fesulphos **9** and to form the *exo*-transition state preferably to avoid unfavorable interaction of the β-substituent with the phenyl group of the ligand in the *endo* -approach.

A focused compound collection of 84 compounds was synthesized and screened in a cell-based assay for monitoring hedgehog pathway modulation.[32] In a confirmation of BIOS reasoning, we were delighted to find that the compound collection contained several inhibitors of hedgehog-signaling with IC_{50} values in the low μM range (Figure 5). Delineation of a structure-activity relationship indicated that activity is higher when R^3 is an aryl group (compound **35**, Scheme 22). Among the investigated substituents on the aryl group, methoxy was best. A phenyl group as backbone instead of indole compromises the bioactivity of the compounds.

[3 + 3] Cross-Cycloaddition of Different Ylides

Very recently, the Wang and Guo groups independently developed a cross-cycloaddition of azomethine ylide **1** with azomethine imines **39** to obtain the pyrazolotriazinone scaffold **40** (Scheme 24).[36,37] Wang et al. used 5 mol % of *t*Bu-Phosferrox **41** in combination with $Cu(CH_3CN)_4BF_4$ in the presence of Cs_2CO_3 as base as the optimal reaction conditions. Guo's group used 10 mol % of *P*,*N*-ferrocene based ligand **42** with $Cu(CH_3CN)_4ClO_4$ in the presence of DBU. Both groups reported a broad scope for the cycloaddition. The products were obtained essentially as single diastereomers with high enantiomeric excess.

SUMMARY

Although the 1,3-dipolar cycloaddition has been known for a long time, enantioselective versions of this reaction were developed only recently. Whereas most of the efforts are directed toward simple transformations leading to the pyrrolidine ring system, its application in other valuable transformations was conspicuously absent. We have endeavored to present in this Account our contributions to the application of the Lewis-acid-catalyzed catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides to achieve advanced synthetic transformations. The enantioselective formation of quaternary spirocenters leading to the synthesis of spirooxindoles along with the application of this methodology for the synthesis of the spirotryprostatin A scaffold set the stage and inspired the development of a programmable enantioselective one-pot synthesis of molecules with eight stereocenters, followed by the development of the first catalytic enantioselective [6 + 3] cycloaddition involving fulvenes as dipolarophiles. We employed the 1,3-dipolar cycloaddition for the kinetic resolution of oxopyranes leading to the synthesis of azairidoid and introduced the first general catalytic enantioselective synthesis of the tropane scaffold using 1,3-dipolar cycloadditions of hitherto unknown 1,3-fused cyclic azomethine ylides. This Account is an attempt to showcase the large potential of the catalytic enantioselective 1,3-dipolar cycloaddition with azomethine ylides.

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Notes

The authors declare no competing financial interest.

Biographies

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Marco Potowski was born in Lünen, Germany in 1984. He received his B.Sc. in 2008 and his M.Sc. in 2010 from the Technical University of Dortmund. Presently, he is carrying out research leading towards a PhD degree under the supervision of Prof. H. Waldmann at the Max Planck Institute of Molecular Physiology.

Zhi-Jun Jia was born in Sichuan, China, in 1986. He received his Bachelor of Science in Biology and Bachelor of Management in Marketing from Sichuan University in 2009. Then he joined Prof. Ying-Chun Chen's group at the same university as a master student in Medicinal Chemistry. Since 2012, he has been pursuing his PhD under the supervision of Prof. H. Waldmann in the Department of Chemical Biology at Max Planck Institute for Molecular Physiology.

Andrey P. Antonchick was born in 1976 in Bobruysk, USSR. He received a PhD from the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus (Minsk) and the Max Planck Institute for Chemical Ecology (Jena) under the guidance of Prof. V.A. Khripach and PD Dr. B. Schneider. After a postdoctoral appointment with Prof. M. Rueping at Frankfurt University, he joined the group of Prof. H. Waldmann. In June, 2010 he was appointed group leader at the Max Planck Institute of Molecular Physiology. His research interests lie in the development of new reaction methodologies.

Herbert Waldmann was born on June 11, 1957 in Neuwied, Germany. He received his PhD in 1985 from the University of Mainz under the guidance of Prof. H. Kunz in organic chemistry after which he completed a postdoctoral appointment with Prof. G. Whitesides at Harvard University. He was appointed as Professor of Organic Chemistry at the University of Bonn (1991), full Professor of Organic Chemistry at the University of Karlsruhe (1993), Director at the MPI of Molecular Physiology Dortmund, and Professor of Organic Chemistry at the University of Dortmund (1999). His research interests are focused on various areas of chemical biology research.

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