Organic Syntheses

Discussion Addendum for:

Practical Synthesis of Novel Chiral Allenamides: (*R*)-4-Phenyl-3-(1,2-propadienyl)oxazolidin-2-one

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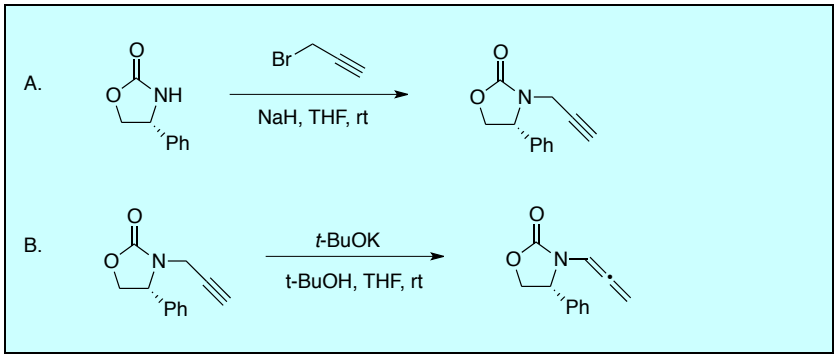

Allenamides, especially chiral allenamides, are important synthetic intermediates and exist as key structural motifs in many natural products. We recently reported an efficient route to the formation of chiral allenamides that relied upon the isomerization of chiral propargylic oxazolidinones for the introduction of the chiral allenamide functionality.[2] More recently, the stereospecific amidation of optically enriched allenyl iodides using catalytic copper(I) salt and *N*,*N*-dimethylethylene-diamine as ligands has emerged as a facile strategy to access chiral allenamides[3] (Scheme 1) In recent years, major advances in allenamide chemistry have been concerned with the applications of chiral allenamides

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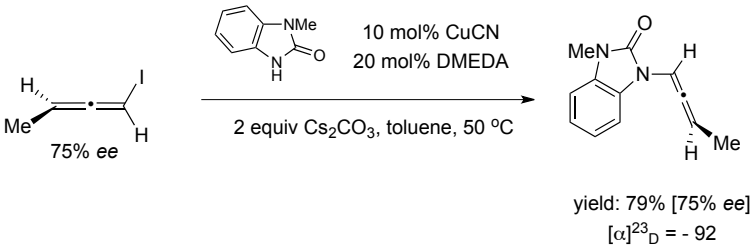
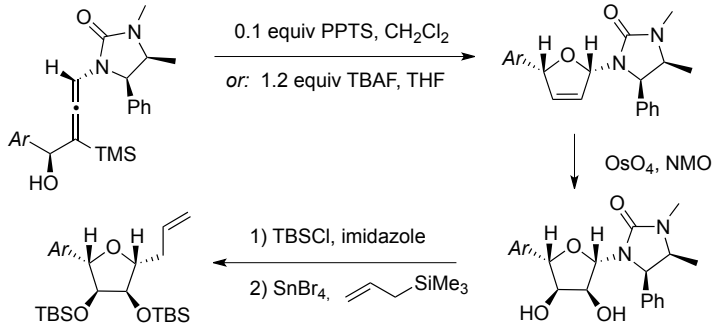


Scheme 1. Synthesis of chiral allenamides promoted by CuCN/dmeda catalyst

to stereoselective synthesis. These advances will be summarized in this article.

(I) CYCLIZATION REACTIONS

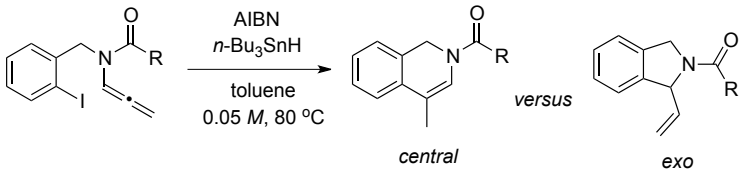
The ability of γ-substituted allenamides to undergo cyclization reactions[4] using either stoichiometric TBAF or catalytic PPTS affords stereodivergent syntheses of 2,5-disubstituted dihydrofurans (Scheme 2). The resulting products were then subjected to stereoselective dihydroxylations demonstrating the synthetic utility of chiral allenamides in the stereoselective synthesis of complex molecules.



Scheme 2. Intramolecular ring cyclization reactions of γ-substituted allenamides

Cyclization of allenamides can also proceed via a radical mechanism[5] using a combination of AIBN and *n*-Bu_3SnH (Scheme 3). The radical addition reactions are highly selective for the *central* carbon of the allene, leading to an efficient preparation of nitrogen heterocycles such as

isoquinolines, and carbocycles such as indane and naphthalene derivatives. The *exo*-cyclization mode could also be achieved in some cases, leading to the synthesis of isoindoles.

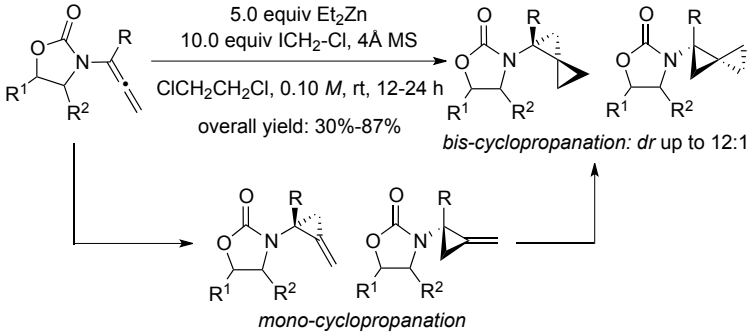


Scheme 3. Radical mediated intramolecular cyclization reactions

(II) CYCLOADDITION REACTIONS

A) [2π + 1π] CYCLOADDITIONS

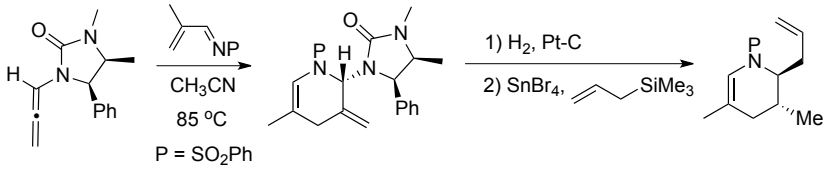
The Simmons-Smith cyclopropanations[6] of chiral allenamides provides a viable strategy to obtain optically enriched amido-spiro [2.2] pentanes (Scheme 4). This reaction was efficient with good substrate generality, and represents the most direct synthesis of both chemically and biologically interesting amido-spiro [2.2] pentane systems. However, it suffers from poor diastereoselectivities for unsubstituted chiral allenamides. For α-substituted allenamides, the diastereoselectivity was improved, but both mono- and bis-cyclopropanation products were observed.



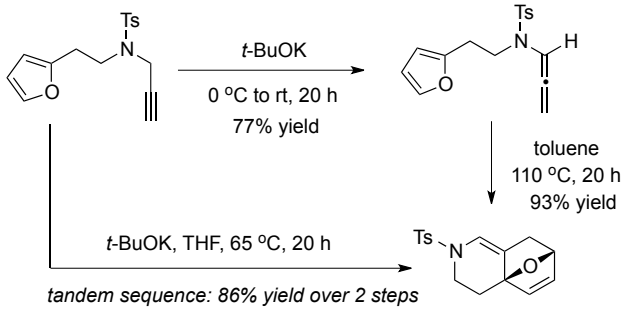
Scheme 4. Cyclopropanation reactions of chiral allenamides

B) [4π + 2π] CYCLOADDITIONS

An inverse electron-demand *aza* [4π + 2π] cycloaddition[7] was observed in the reaction of chiral allenamides with 1-azadienes (Scheme 5). In addition, it was also possible to promote a stereoselective intramolecular normal demand [4π + 2π] cycloaddition[8] under thermal conditions without the need for metal catalysts (Scheme 6). Both of these works are applicable for the construction of highly functionalized *aza*-sugars and related nitrogen heterocycles synthesis.



Scheme 5. Inverse electron-demand aza-[4π + 2π] cycloaddition

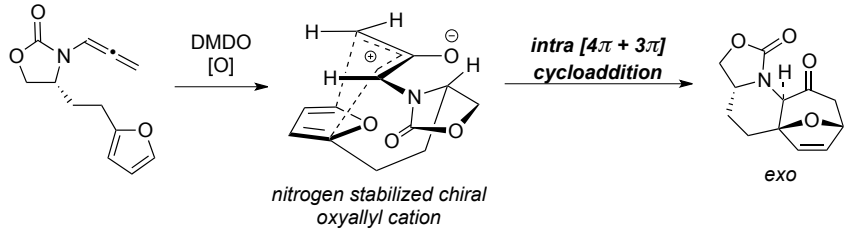


Scheme 6. Intramolecular [4π + 2π] cycloaddition

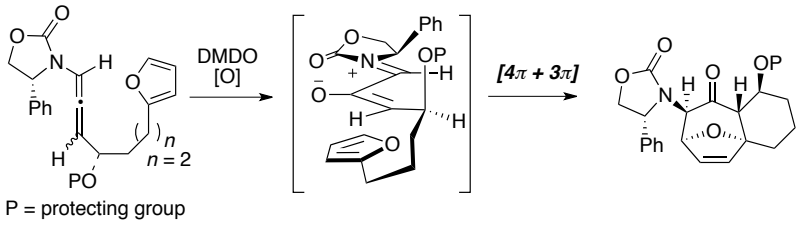
C) [4π + 3π] CYCLOADDITIONS

The first intramolecular [4π + 3π] cycloaddition[9] using nitrogen-stabilized chiral oxyallyl cations[10] was observed in the epoxidation of *N*-tethered allenamides (Scheme 7). The origin of the high selectivities for the oxyallyl cycloadditions was postulated to originate from structure of the nitrogen-stabilized chiral oxyallyl cation intermediate. This strategy was expanded to include the chemoselective epoxidation of allenamides

tethered to either α or γ carbon atom of dienes[11] followed by the tandem [4π + 3π] cycloaddition step (Scheme 8).

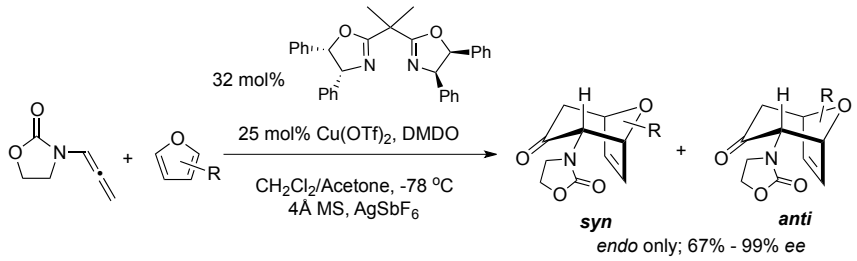


Scheme 7. Intramolecular [4π + 3π] cycloaddition via a nitrogen-stabilized chiral oxyallyl cation



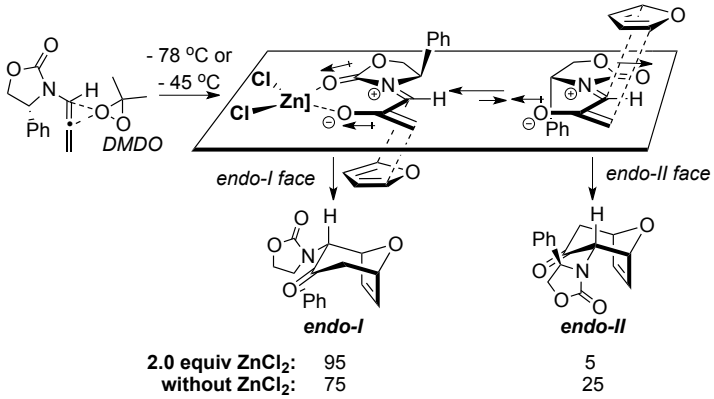
Scheme 8. Epoxidation of α or γ tethered allenamides in tandem with intramolecular [4π + 3π] cyclocycloaddition

A highly enantioselective version of this [4π + 3π] cycloaddition was promoted by catalytic amounts of a chiral Lewis acid complex generated from $Cu(OTf)_2$ and C_2-symmetric bisoxazolines as ligands.[12] High enantioselectivities were obtained when either unsubstituted or substituted furans were employed as the dienes (Scheme 9).



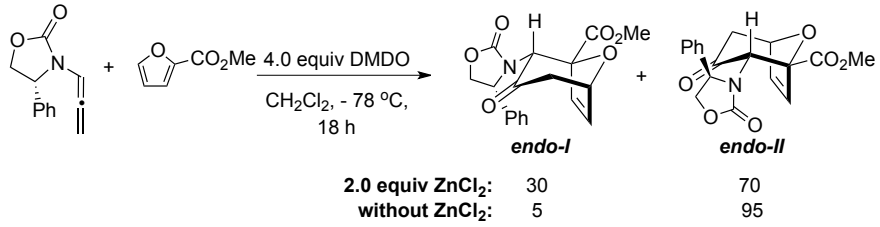
Scheme 9. Enantioselective [4π + 3π] cycloaddition promoted by chiral copper catalysts

Mechanistically, it had been rationalized that the observed stereoselectivity for the intermolecular [4π + 3π] cycloaddition between nitrogen-stabilized oxyallyl cation and furan is a result of the furan approaching in a favorable *endo* manner from the less hindered bottom or *endo-I* face of the oxyallyl cation. This preference can be further enhanced with a bidentate metal cation such as Zn that can chelate to both the oxyallyl oxygen atom and the oxazolidinone carbonyl oxygen (Scheme 10).



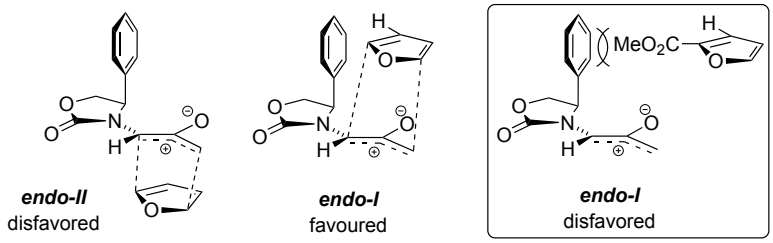
Scheme 10. Intermolecular [4π + 3π] cycloaddition in favor of *endo*-I facial attack with furans as dienes

However, an unexpected reversal of diastereoselectivity was observed when methyl 2-furoate was employed as the diene with nitrogen-stabilized oxyallyl cation.[13] This intriguing reversal in favor of the *endo-II* cycloaddition pathway is likely a result of the transition state minimizing the dipole interaction between the oxyallyl cation and ester carbonyl of methyl 2-furoate (Scheme 11).



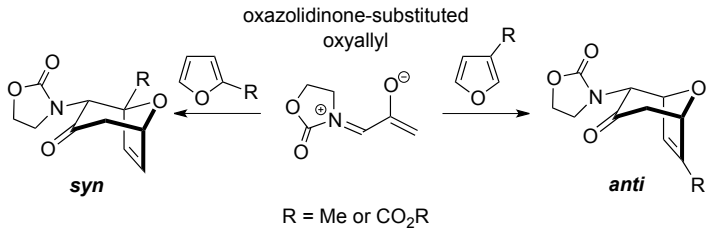
Scheme 11. Reversal of diastereochemistry in preference for *endo*-II facial attack with methyl-2-furoate as diene

Based on density functional theory calculations, it was further established that the stereo-induction for the [4π + 3π] cycloaddition between oxyallyl cation and unsubstituted furan is due to the stabilizing CH-π interactions between the incoming furan and the Ph group on the oxyallyl isomer (Scheme 12). These CH-π interactions cause the cycloaddition to take place preferentially via the more crowded face of the oxazolidinone to afford the product with the stereochemistry resulting from the addition via *endo* I-face.[14] In the case of methyl-2-furoate, the reversal of stereoselectivity can be ascribed to the repulsive interactions between the Ph group and the 2-COOMe group which outweighs the stabilizing effect of the CH-π interactions. As such, cycloaddition takes place preferentially through the less crowded transition state affording a product with stereochemistry that can be explained by *endo* II-facial attack.



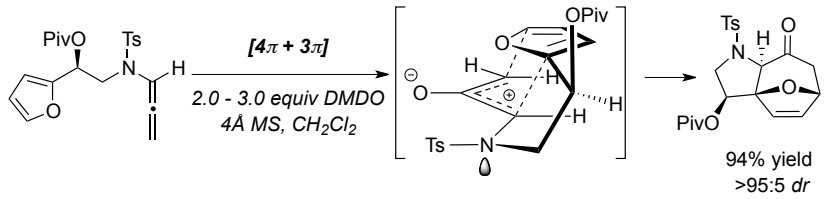
Scheme 12. CH- π interactions between furan and Ph group on the oxyallyl cation favours product with *endo* I-stereochemistry

This [4π + 3π] cycloaddition reaction was further expanded to include the reactions between oxazolidinone-substituted oxyallyl groups and unsymmetrically substituted furans.[15] *Syn* regioselectivity was observed when the furan has a 2-Me or 2-COOR substituent, while *anti* regioselectivity is obtained with a 3-Me or 3-COOR group (Scheme 13).



Scheme 13. Intermolecular [4π + 3π] cycloadditions between oxazolidinone-substituted oxyallyls and unsymmetrically-substituted furans

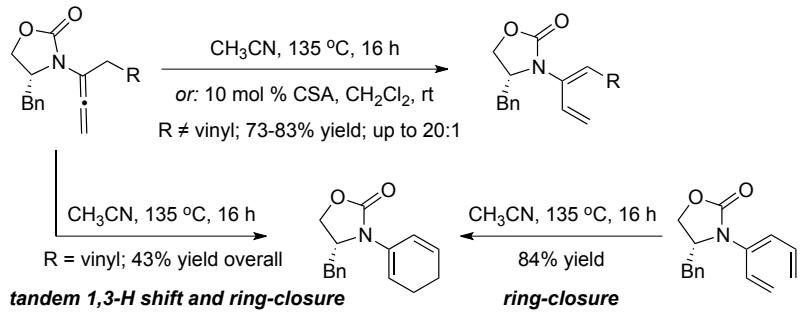
Finally, a practical and diastereoselective intramolecular [4π + 3π] cycloaddition of *N*-sulfonyl substituted oxyallyl cations with furans was also reported (Scheme 14). Selectivity is found to depend on the tethering length as well as the stability of the oxyallyl cation intermediate, whether generated from *N*-carbamoyl- or *N*-sulfonyl-substituted allenamides.[16] The use of chiral *N*-sulfonyl-substituted allenamide provided minimal diastereoselectivity in the cycloaddition, while high diastereoselectivity can be achieved with a stereocenter present on the tether.



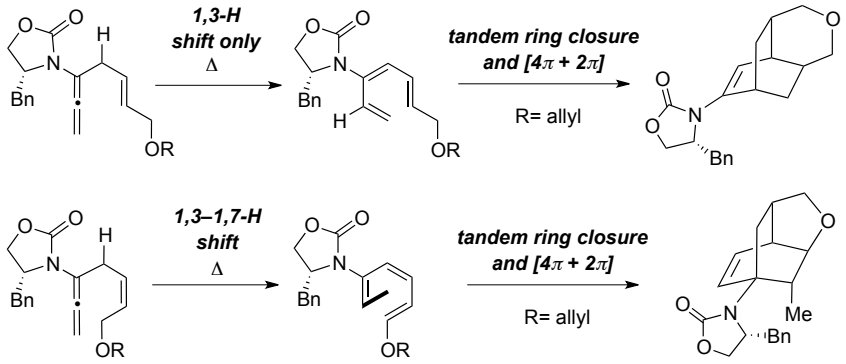
Scheme 14. Intramolecular [4π + 3π] cycloaddition of *N*-sulfonyl substituted oxyallyl cations with furans as dienes

III. ISOMERIZATION REACTIONS

The ability of allenamides to undergo regio- and stereoselective 1,3-hydrogen shift under both acidic and thermal conditions, leads to the *de novo* preparations of 2-amido-dienes.[17] This process could be rendered in tandem with a 6π -electron pericyclic ring closure to access cyclic 2-amido-dienes in good overall yields directly from the respective allenamides (Scheme 15). Further broadening of the scope of this isomerization reaction leads to the development of a new torquoselective ring-closure of chiral amide-substituted 1,3,5-hexatrienes and its application in tandem with [4π + 2π] cycloaddition[18] (Scheme 16). The trienes were derived via either a 1,3-hydrogen or 1,3-H–1,7-hydrogen shift of a-substituted allenamides, and the entire sequence through the [4π + 2π] cycloaddition could be promoted in tandem.

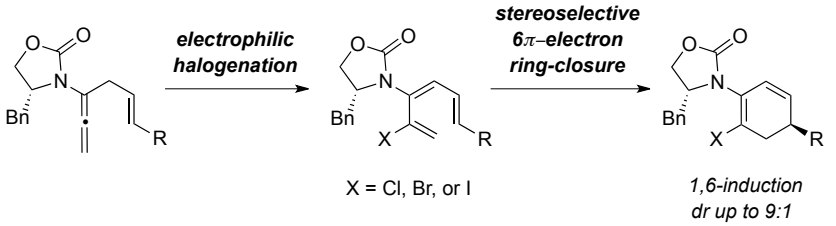


Scheme 15. Stereoselective isomerizations of chiral allenemides in tandem with a 6π -electron pericyclic ring closure



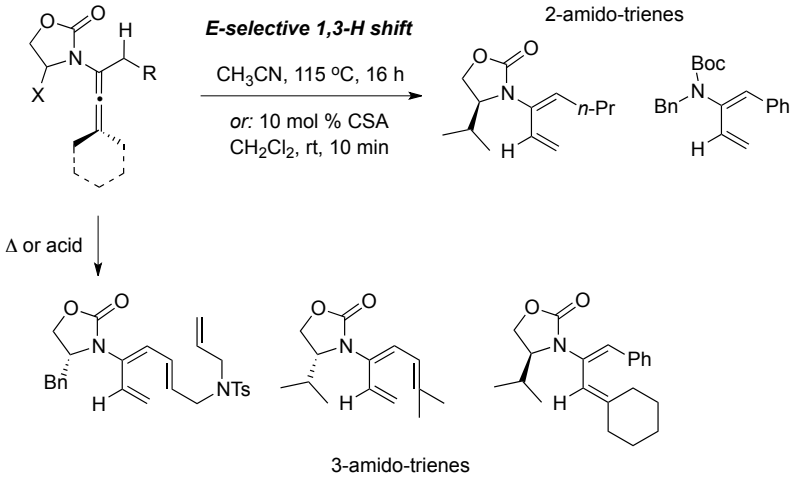
Scheme 16. Isomerizations of allenamides to chiral amide-substituted 1,3,5-hexatrienes in tandem with [4π + 2π] cycloaddition

The efforts reported thus far unveiled an invaluable opportunity not only to develop a new and attractive template for conducting stereoselective 6π-electrocyclic ring-closures, but also to achieve a highly challenging 1,6-asymmetric induction. Indeed, a diastereoselective 6π-electrocyclic ring-closure employing halogen-substituted 3-amidotrienes via a 1,6-remote asymmetric induction was subsequently reported[19] (Scheme 17). This new asymmetric manifold for pericyclic ring-closure further underscores the significance of the allenamide chemistry.



Scheme 17. Isomerizations of allenamides to chiral halogen-substituted 3-amido-triene in tandem with 6π-electron electrocyclic ring-closure

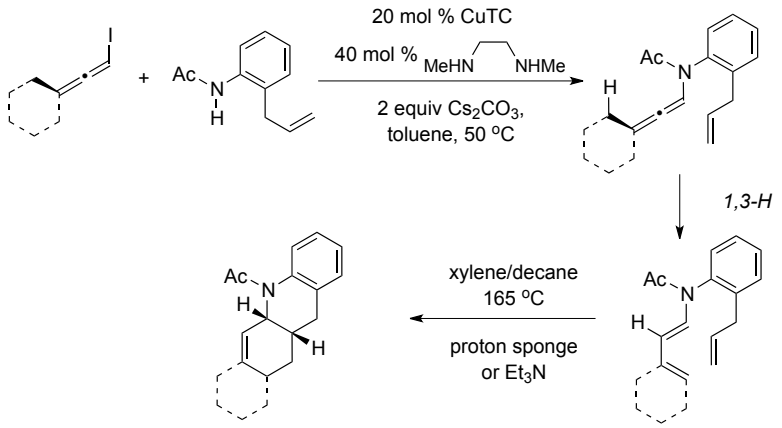
In addition, 1,3-hydrogen shifts using allenamide[20] is also applicable to the preparation of acyclic 2-amido-dienes and 3-amido-trienes. Additionally, 6π-electron electrocyclic ring-closure could be carried out using 3-amido-trienes to afford cyclic 2-amido-dienes, and such electrocyclic ring-closure could be rendered in tandem with the 1,3-hydrogen shift, thereby constituting a facile construction of synthetically rare cyclic 2-amido-dienes (Scheme 18).



Scheme 18. Isomerizations of chiral allenamides to either 2- or 3-amido-trienes

Finally, a new approach to Oppolzer's intramolecular Diels-Alder cycloaddition [IMDA] through γ-isomerization[21] of readily available *N*-tethered allenamides is described. These IMDA reactions are carried out in

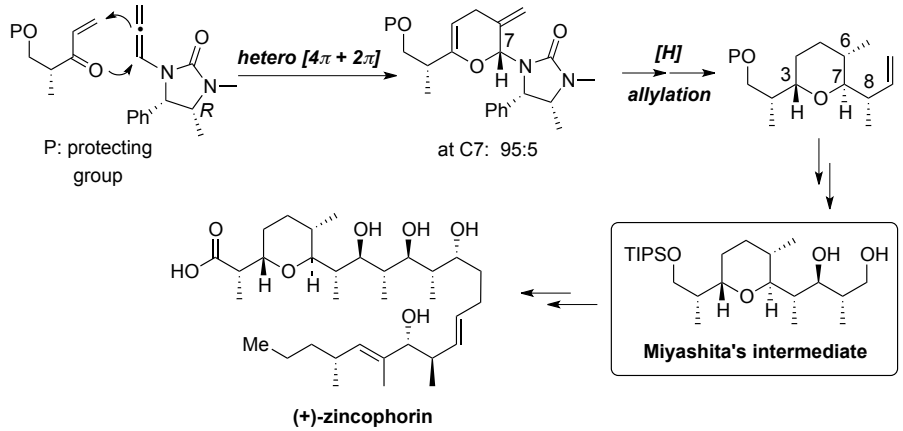
tandem with the allenamide isomerization or 1,3-hydrogen shift, leading to complex nitrogen heterocycles in a highly stereoselective manner (Scheme 19).



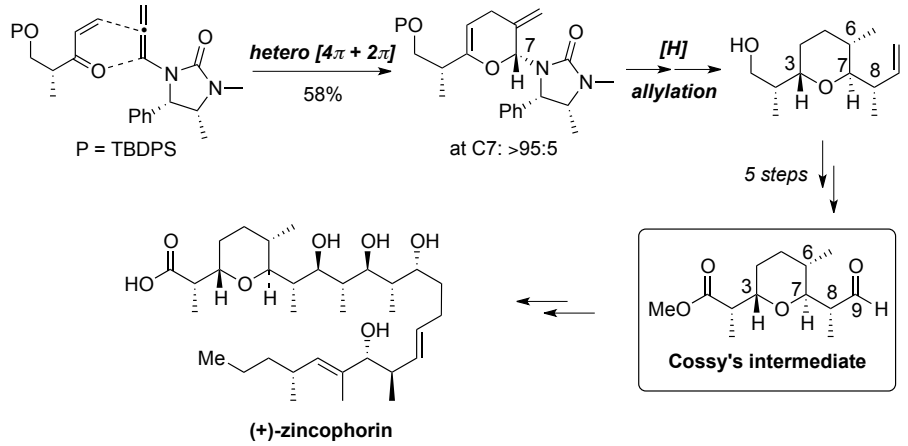
Scheme 19. Oppolzer's intramolecular Diels-Alder cycloaddition [IMDA] via γ-isomerization of *N*-tethered allenamides

(IV) NATURAL PRODUCT SYNTHESIS

The synthetic usefulness of the stereoselective inverse electron-demand [4π + 2π] cycloaddition using chiral allenamide was demonstrated in the formal synthesis of (+)-zincophorin. This effort describes the preparation of the Miyashita's intermediate which features the first synthetic application of a stereoselective inverse electron demand hetero [4π + 2π] cycloaddition of a chiral allenamide and an interesting urea directed Stork-Crabtree hydrogenation (Scheme 20).[22] This approach was subsequently applied for the construction of the Cossy's C1-C9 subunit of (+)-zincophorin[23], which also led to the observation of an unusual urea directed Stork-Crabtree hydrogenation (Scheme 21). It is noteworthy that these works represent the first application of chiral allenamides in natural product synthesis.

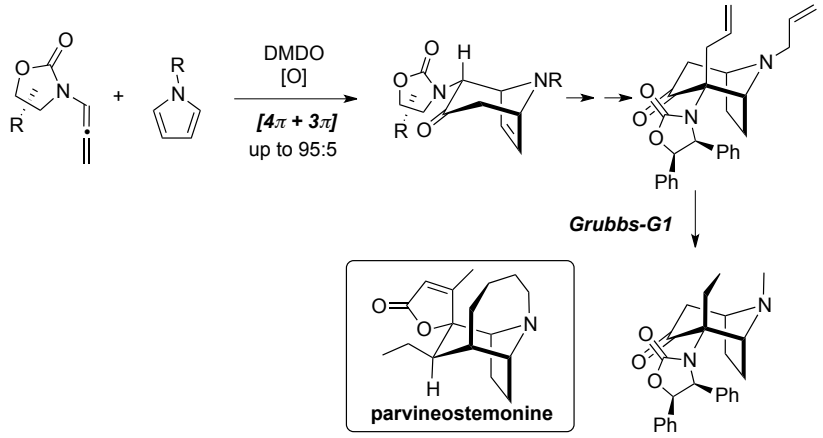


Scheme 20. Stereoselective inverse electron demand hetero [4π + 2π] cycloaddition for the synthesis of (+)-Zincophorin via the Miyashita's intermediate



Scheme 21. Stereoselective inverse electron demand hetero [4π + 2π] cycloaddition for the synthesis of (+)-Zincophorin via the Cossy's intermediate

Finally, a highly stereoselective [4π + 3π] cycloaddition of *N*-substituted pyrroles with allenamide-derived nitrogen-stabilized chiral oxyallyl cations was reported which could serve as a useful approach towards the construction of the *aza*-tricyclic core of parvineostemonine[24] (Scheme 22).



Scheme 22. Stereoselective [4π + 3π] cycloaddition of *N*-substituted pyrroles with allenamides for the synthesis of parvineostemonine

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Richard P. Hsung went to Calvin College for his B.S. in Chemistry and Mathematics, and attended The University of Chicago for his M.S. and Ph.D. degrees in Organic Chemistry, respectively, under supervisions of Professors Jeff Winkler and Bill Wulff. After post-doctoral research at Chicago with Professor Larry Sita, and as an NIH post-doctoral fellow with Professor Gilbert Stork at Columbia University, he began his independent career at University of Minnesota before moving to University of Wisconsin in 2006. He is the recipient of an NSF Career Award and The Camille Dreyfus Teacher-Scholar Award. He has co-authored over 250 publications, delivered over 200 invited lectures, and supervised over 160 students and post-doctoral fellows with research interests in developing cycloadditions and annulations to natural product total syntheses and stereoselective methods using allenamides, ynamides, enamides, and cyclic acetals.

Teo Yong Chua received both his B.Sc. and Ph.D. degrees at the National University of Singapore. He pursued his graduate studies on the design of chiral indium complexes for asymmetric catalysis, under the supervision of Professor Loh Teck Peng. In 2006, he joined the faculty at the National Institute of Education, Nanyang Technological University as an Assistant Professor. His current research interests include the development of new asymmetric catalytic systems and transition-metal-catalyzed methodologies for applications in organic synthesis.