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(4 + 3) Cycloadditions of Nitrogen-Stabilized Oxyallyl Cations

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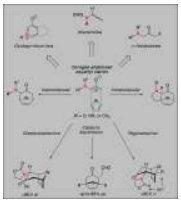
Abstract



The use of heteroatom-substituted oxyallyl cations in (4 + 3) cycloadditions has had a tremendous impact on the development of cycloaddition chemistry. Extensive efforts have been exerted toward investigating the effect of oxygen-, sulfur-, and halogen-substituents on the reactivity of oxyallyl cations. Most recently, the use of nitrogen-stabilized oxyallyl cations has gained prominence in the area of (4 + 3) cycloadditions. The following article will provide an overview of this concept utilizing nitrogen-stabilized oxyallyl cations.

Keywords

oxyallyl; (4 + 3); cycloaddition; nitrogen atom; heterocyclic compounds; regioselectivity

Introduction

(4 + 3) cycloadditions employing oxyallyl cations **1** and dienes represent a powerful approach for constructing seven-membered carbocycles **2**.[1] While this process has been known for almost 50 years, the utility of heteroatom-stabilized oxyallyl cations [**Figure 1**] has become increasingly prominent in the realm of (4 + 3) cycloadditions because of the ability of the heteroatom to provide an electronically-biased oxyallyl cation that can lead to highly regioselective and stereoselective cycloadditions.[2,3]

The use of oxygen-[4], sulfur-[5], and halogen-substituted[6] oxyallyl cations in (4 + 3) cycloadditions has been extensively studied and applied in a number of elegant natural product syntheses.[7] However, nitrogen-stabilized oxyallyl cations offer distinct advantages over other heteroatom systems. The trivalency of the nitrogen atom allows: (1) Tethering of a chirality-inducing unit [**R***] to generate new stereocenters, (2) inclusion of a coordinating unit [**W**] to provide conformational rigidity, (3) greater flexibility in designing intramolecular reactions, (4) the ability to tune the electron-donating ability toward the oxyallyl cation, and (5) the amino group can serve as the nitrogen atom source for accessing *N*-heterocycles and complex natural alkaloids. These remarkable features represent attractive advantages for developing highly stereoselective (4 + 3) cycloadditions.

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Recent developments making use of nitrogen-stabilized oxyallyl cations have emerged in the past decade sparking a renewed interest in the field of (4 + 3) chemistry. In this concept article, we will focus specifically on (4 + 3) cycloadditions involving nitrogen-stabilized oxyallyl cations and the application of such methodology.

Oxidopyridinium Ions in (4 + 3) Cycloadditions

The use of oxidopyridinium ions in dipolar cycloadditions has been well-established since the early 1970s.[8] While commonly used in (5 + 2) cycloadditions[9], Katritzky was one of the first to demonstrate that such intermediates could also undergo a (4 + 3) cycloaddition with dienes [**Scheme 1**].[10] Katritzky found substituted oxidopyridinium ions, obtained through the thermal decomposition of its dimer **3**, could be used in a (4 + 3) cycloaddition with 2,3-dimethylbutadiene to give cycloadduct **4** in 75% yield. Although oxidiopyridium ions are cyclic aromatic species, they can also be considered stabilized oxyallyl cations.

At the same time, Mok and Nye reported similar results using the quinolinium species **5** [**Scheme 1**].[11] A variety of dienes could be used, giving cycloadducts with high *exo* selectivity. However, when using unsymmetrical dienes, mixtures of regioisomers were obtained.

Over 20 years later, Cha and co-workers utilized Katritzky's method as an approach to the core of sarain A [**Scheme 2**].[12] Slow addition of triethylamine to a mixture of **6** and cyclopentadiene provided the desired *endo* cycloadduct **7a** in 58% yield along with a small amount of the *exo* product **7b** and the (5 + 2) product **8**. The *endo* product **7a** was then further functionalized to give the core structure of sarain A.

Amino-Stabilized Oxyallyl Cations in (4 + 3) Cycloadditions

To the best of our knowledge, there has been only one report of amino-stabilized oxyallyl cations used in a (4 + 3) cycloaddition by Myers and Barbay.[13] They showed that oxidation of **10** led to the unstable α-amino-α′-fluoro ketone **11**, which decomposed to generate an amino-stabilized oxyallyl cation and underwent a (4 + 3) cycloaddition in the presence of cyclopentadiene affording cycloadduct **12** in 35% yield.

Diastereoselective (4 + 3)

In the same report, Myers and Barbay showed that use of a chiral imidazolidinone auxiliary could provide diastereoselectivity in the cycloaddition [**Scheme 4**]. Reaction of **13** with cyclopentadiene in hexafluoroisopropanol gave a mixture of cycloadducts favoring *endo* product **15** with a diastereoselectivity of 6.8:1. The observed selectivity of the major product was proposed to come from the chiral vinyliminium **14**, which favors approach of the diene from the top face as the bottom face is blocked by the benzyl group.

Amido-Stabilized Oxyallyl Cations in (4 + 3) Cycloadditions

By far, amides have been utilized most frequently in cycloadditions involving nitrogen-stabilized oxyallyl cations. The prevalent use of amides in this area is likely due to the stability and ease of preparing such precursors to the oxyallyl cation as well as the ease at which one can control the donating ability of the nitrogen atom toward the oxyallyl cation, thereby affecting its reactivity.

Intermolecular (4 + 3)

Walters was the first to report the use of amido-stabilized oxyallyl cations in a (4 + 3) cycloaddition.[14] The reaction of phthalimide-substituted dibromide **16** with furan using

Föhlisch's conditions[15] afforded cycloadduct **18a** in 60% yield via the amido-stabilized oxyallyl cation **17** [**Scheme 5**]. Some solvolysis product was also observed in the reaction. Interestingly, when using $LiClO_4$, a mixture of two cycloadducts was obtained. Similar results were also found when using cyclopentadiene under varying reaction conditions. The authors proposed that an association of lithium with the oxyallyl species may be responsible for the results.

Furthermore, Walters examined the regioselectivity of the cycloaddition when using 2-methyl and 2-methoxyfuran [**Table 1**].[16] In all cases, the *anti* regiochemistry (**19a** and **19b**) was favored having the phthalimide and furan substituent on opposite sides of the cycloadduct. A small amount of the *exo* (extended)[17] product was obtained in each case. However, using $LiClO_4$ provided the highest overall selectivity for the *anti*, *endo* (compact)[17] product **19a** in reasonable yields, consistent with Föhlisch's results using $LiClO_4$ with an oxygen-stabilized oxyallyl system.[18]

Although it is not entirely clear if the nitrogen or bromine provides a stronger electronic bias on the oxyallyl cation leading to the stereochemical outcome, the results are not in stark contrast with recent studies carried out on similar systems (*vide infra*). Semi-empirical calculations and FMO analysis were unable to provide an adequate mechanistic explanation for these results, but the reaction was predicted to occur through a stepwise process.

We reported using oxazolidinone-substituted allenamides[19] as precursors to nitrogen-stabilized oxyallyl cations in order to gain access to (4 + 3) cycloadducts.[20] As shown in **Scheme 6**, epoxidation of allenamide **20** with dimethyldioxirane (DMDO) generates the allene oxide **21**, which can open to give the nitrogen-stabilized oxyallyl cation **22**. The resulting oxyallyl cation was reacted with cyclopentadiene or furan affording cycloadducts **23** and **24**, respectively, in good yields.

Diastereoselective (4 + 3)

Using the same method with various chiral oxazolidinone auxiliaries, we were able to obtain high levels of diastereoselectivity in the intermolecular (4 + 3) cycloaddition [**Scheme 7**].[20] Oxidation of chiral allenamide **25** in the presence of furan led to a mixture of exclusively *endo* isomers **26a** and **26b** in 80% yield with a ratio of 75:25 favoring the *endo-I* isomer. In most cases, the diastereselectivity could be increased to favor essentially one isomer when using $ZnCl_2$.

Based on these results, a stereochemical model was proposed in which chelation of the oxygen atoms to zinc would increase the conformational rigidity of the oxyallyl cation, thereby providing greater facial discrimination and enhanced diastereomeric induction. Thus, the resulting stereochemistry of **26a** (confirmed by X-ray) would arise via a steric-driven approach of furan to the less hindered face of the oxyallyl cation.

Select examples using different auxiliaries without $ZnCl_2$ are shown in **Figure 2**. The diastereoselectivities were found to vary greatly depending on the R group of the chiral auxiliary, but high diastereoselectivities were achieved even without the use of $ZnCl_2$ as with **28** and **29**. The stereochemistry of the cycloadducts was originally assigned based on the stereochemical assignment made for **26a**. However, several of the cycloadducts have since been reassigned based on recent studies (*vide infra*).

This methodology was subsequently applied by Kozlowski and Hsung toward the synthesis of new chiral ligands used for the asymmetric alkylation of aldehydes.[21] As shown in **Scheme 8**, the chiral ligand **33** was prepared from cycloadducts **31** through a 4 step sequence involving hydrogenation, reduction of the ketone, cleavage of the auxiliary to give

the amino alcohol **32** and finally alkylation of the primary amine. Reaction of benzaldehyde with $ZnEt_2$ and 5 mol% of the chiral ligands provided the desired alcohol **34** in excellent yields and enantiomeric excess. Predictive 3D-QSSR calculations were also performed which correlated closely with the experimental results.

We also explored the use of chiral enamides as an alternative approach toward chiral nitrogen-stabilized oxyallyl cations [**Scheme 9**].[22] Epoxidation of chiral enamide **35** followed by acidic methanolysis led to a mixture of aminals **36a** and **36b**. Oxidation and subsequent enol ether formation of the major isomer led to the cycloaddition precursor **37** in 64% yield. Upon treatment with catalytic TMSOTf and 10 equivalents of furan, **37** underwent the (4 + 3) cycloaddition affording **38** in a modest 30% yield but with good diastereoselectivity favoring the *endo-I* isomer. An equal amount of product with only single bond formation to furan was also obtained. No other examples using this methodology have since been reported.

MaGee and Walters also reported a diastereoselective (4 + 3) cycloaddition using their methodology with chiral oxazolidinone auxiliaries.[23] As shown in **Table 2**, reaction of chiral bromoketone **39** with furan or cyclopentadiene under the standard conditions gave cycloadducts **40a** and **40b** in approximately a 2:1 ratio favoring the *endo-I* product.

When using $MgBr_2$, they observed a remarkable improvement in diastereoselectivity, obtaining almost exclusively one *endo* product with furan, although the yield was somewhat diminished. Similar results were also found when using cyclopentadiene under the Lewis acid conditions.

The resulting stereochemistry of the major product was proposed to arise from oxyallyl cation **41**, in which the solvent or a Lewis acid can chelate [**Figure 3**]. An *endo* approach of furan away from the phenyl substituent on the oxazolidinone would then lead to the observed product. It is worth noting that these findings agreed closely with the results reported by us.[19]

Interestingly, when employing a bulkier oxazolidinone derived from camphanic acid, Walters and MaGee observed a complete reversal in stereochemistry of the cycloadduct [**Scheme 10**]. Reaction of **42** under the reaction conditions led to a 90% yield of the *endo-II* cycloadduct **43**, consistent with a non-chelated transition state. Attempts to reverse the stereochemical outcome through a chelation pathway using Lewis acids were unsuccessful.

A similarly unexpected reversal in stereochemistry was also reported by us in the (4 + 3) cycloaddition of allenamides with substituted furans [**Scheme 11**].[24] Oxidation of allenamide **25** in the presence of 2-methylfuran and $ZnCl_2$ led to the predicted cycloadduct **44**, consistent with the *endo-I* pathway previously observed. However, when the reaction was run in the presence of 2-methyl furoate, a complete reversal in selectivity was observed in favor of the *endo-II* product **45**. The use of $ZnCl_2$ had little effect on the diastereoselectivity with 2-methyl furoate.

These intriguing results prompted Houk and Hsung to examine the (4 + 3) cycloaddition of several chiral nitrogen-stabilized oxyallyl cations in hopes of providing an improved rationale for the observed outcomes.[25] In the originally proposed model (**Scheme 7**), it was thought that the oxyallyl cation possessed a *Z* configuration with the two oxygen atoms on the same side of the C_α-N double bond. Thus, the stereoselectivity was believed to be controlled by steric repulsion between furan and the phenyl group, leading to the major product observed experimentally. Moreover, the *Z*-oxyallyl cation had a suitable geometry for forming a chelate, thus explaining the increased stereoselectivity in the presence of $ZnCl_2$.

However, DFT calculations revealed that the *E*-oxyallyl cation was actually the preferred configuration [**Figure 4**]. Transition state structures of the *E*-oxyallyl cation with furan were also calculated to be lower in energy than the *Z*-oxyallyl cation. Furthermore, while the presence of $ZnCl_2$ was found to lower the activation barrier for the ensuing cycloaddition, there was no change in the preferred configuration of the oxyallyl species and thus, no chelation would be involved.

Perhaps most surprising was the preference found for the reaction of furan from the more hindered face of the oxyallyl cation when calculated for the phenyl-substituted oxazolidinone [**46**, **Figure 5**]. This was attributed to a stabilizing CH−π interaction between the C3 hydrogen on furan and the phenyl substituent. Thus, the stereoselectivity leading to **26a** was controlled not by steric repulsion, but by "steric attraction". This is also in agreement with work done by Harmata and Houk involving alkoxy-substituted siloxyallyl cations.[26]

Further investigation into some of the other previously reported cycloadducts also led to a revision of their initially assigned stereochemistry. As the benzyl group in **47** is unable to participate in a CH−π interaction, a steric-driven approach would be expected to control the stereochemistry, thereby leading to the *endo-II* cycloadduct **27**. This was confirmed through X-ray analysis of the major isomer.

Furthermore, in the case of the diphenyl isopropyl oxazolidinone, the stereochemistry of the major product **29** (confirmed by X-ray) can be attributed to both steric and CH−π interactions. The favored transition state **48** benefits from minimization of repulsive interactions with the isopropyl group as well as a stabilizing CH−π interaction with one of the C5-phenyl substituents leading to excellent selectivity for one isomer.

It is worth noting that with the isopropyl-substituted oxazolidinone, the diastereoselectivity was only 45:55 (*vide supra*), thereby accentuating the impact that non-bonding CH−π interactions can have on the stereochemical outcome of such cycloadditions. This rationale using only an *E*-oxyallyl cation with steric versus CH−π interactions would also explain the reversal in selectivity observed by Walters and MaGee in their system.[22]

We also reported the diastereoselective (4 + 3) cycloaddition with pyrroles as an approach to tropinone alkaloids.[27] As shown in **Scheme 12**, reaction of allenamide **25** with the Boc-protected pyrrole under DMDO oxidation led to the desired cycloadduct **49** in 76% and a ratio of 82:18 favoring the *endo-I* product. Slow addition of DMDO via a syringe pump was required for the chemoselective oxidation of the allenamide over the pyrrole. Similar diastereoselectivities were obtained with pyrrole using various chiral oxazolidinones as was reported with furan.[20] Cycloadduct **50** was derivatized from **51** in order to confirm the stereochemistry by X-ray analysis.

In light of the new mechanistic insights involving CH−π interactions,[25] some of the structures of the tropinone adducts have been revised. Presumably, the stereochemistry of **49** and **51** resulted from CH−π interactions, **52** and **54** resulted from steric repulsions, and the excellent selectivity obtained for **53** and **55** would be due to an integration of both interactions as observed with furan.

The cycloaddition with pyrroles was also applied in an approach toward the core of parvineostemonine [**Scheme 13**].[27] Starting from **51**, hydrogenation and Boc deprotection gave amine **56** in 73% yield. *N*-allylation and subsequent allylation at the α-substituted position afforded diene **58** which was finally subjected to ring-closing metathesis to give the core of parvineostemonine **59** in 36% yield.

Intramolecular (4 + 3)

Nitrogen-Tethered—Intramolecular (4 + 3) cycloadditions allow for an increased level of complexity in the resulting product with the ability to make polycyclic ring systems in a single step.[1,2] We were the first to demonstrate the use of nitrogen-stabilized oxyallyl cations in an intramolecular (4 + 3) cycloaddition.[28] The initial report focused on the use of *N*-tethered allenamides in which the diene is tethered through the nitrogen atom. As shown in **Scheme 14**, DMDO oxidation of allenamides **60** and **61** afforded the desired cycloadducts **62** and **63**, respectively, as single diastereomers. Slow addition of DMDO via syringe pump was critical to prevent competing oxidation of furan. A small amount of the epoxidized cycloadduct **64** was also obtained from the reaction of **60**.

A mechanistic model was presented based on the preferred conformations of substituted oxyallyl cations [**Figure 6**]. While two possible approaches, **65**-*endo* and **65**-*exo*, would both lead to the observed stereochemistry, it was proposed that **65**-*exo* should dominate because it possesses a preferred W-conformation, whereas **65**-*endo* would experience more $A^{1,3}$ strain.[1,2]

Longer tethered allenamides were also tolerated under the reaction conditions, although diminished stereoselectivity was observed. However, when cyclic-tethered allenamides **66** were employed, excellent diastereoselectivities were achieved regardless of tether length [**Scheme 15**]. The observed stereochemistry was rationalized based on a similar **67**-*exo* approach. The proposed model also agrees with the recent studies which suggest a preferred *E*-oxyallyl cation (*vide supra*).[25]

Most recently, we examined a new class of *N*-sulfonyl substituted allenamides and their improved reactivity in the intramolecular (4 + 3) cycloaddition.[29] As shown in **Scheme 16**, allenamide **69** was prepared in six steps starting from furfural. Reaction with DMDO at -78 °C led to the desired cycloadduct **70** with four stereocenters in 94% yield and a diastereomeric ratio of ≥95:5 for the major isomer shown. The use of *N*-sulfonyl allenamides allowed a more practical and expedient approach for obtaining diastereoselectivity in the cycloaddition.

Carbon-Tethered—The (4 + 3) cycloaddition has also been reported with dienes tethered onto the allene itself and could serve as a potential route to the aromadendrane alkaloids [**Scheme 17**].[30] We demonstrated that DMDO oxidation of α-tethered allenamide **71** afforded the cycloadduct **73**, containing a quaternary stereocenter, in 75% yield and with excellent disastereoselectivity. An *E*-oxyallyl cation **72** and *endo* approach of furan was proposed to lead to the major isomer, although it is unclear as to whether or not CH−π interactions play a role.

In the same report, we also explored the use of γ-tethered allenamides in the (4 + 3) cycloaddition [**Scheme 18**]. Treatment of γ-tethered allenamide **71** with DMDO led to cycloadduct **72a** as the major isomer when n was equal to 1 or 2 carbons. While the stereochemistry of the protected alcohol seemed to have an effect on the resulting stereochemistry of the products, the axial chirality of the allene did not play a role since its stereochemistry is scrambled upon formation of the oxyallyl cation.

Interestingly, when the tether length was increased to n = 3, the stereochemical outcome was reversed in favor of **72b**. Other examples using butadiene also displayed a reversal in stereochemistry. These intriguing results suggested an overall change in the preferred conformation of the oxyallyl cation depending on the tether length or the diene used. While models were proposed to rationalize the stereochemical outcome, further work will need to

be done to provide a better mechanistic understanding. Computational studies have not yet been reported on these intramolecular systems.

Catalytic Asymmetric (4 + 3) Cycloadditions

Surprisingly, there have only been two reports of catalytic asymmetric (4 + 3) cycloadditions[31] using nitrogen-stabilized oxyallyl cations, but the potential for future development in this area is promising and merits further exploration.

Harmata was the first to report the catalytic asymmetric (4 + 3) cycloaddition utilizing a chiral organocatalyst with pentadienals.[32] As shown in **Scheme 19**, reaction of pentadienal **73** with 2,5-disubstituted furans in the presence of 20 mol% chiral amine catalyst and trifluoroacetic acid afforded the cycloadducts **75** with good yields and up to 89% enantiomeric excess. The reaction presumably proceeds through the vinylogous nitrogen-stabilized oxyallyl cation **74** in which the top face is blocked by the benzyl substituent of the catalyst thereby leading to an *endo* approach of furan from the bottom face.

The only other catalytic asymmetric (4 + 3) cycloaddition was reported by Hsung using chiral Lewis acid catalysts [**Scheme 20**].[33] Reacting achiral allenamide **20** with DMDO and various dienes in the presence of catalytic CuOTf and the chiral bisoxazoline ligand shown afforded the desired cycloadducts **76a/b** in good yields and up to 99% enantiomeric excess. The use of molecular sieves and $AgSbF_6$ was found to increase the overall yield and selectivities.

A working model was proposed based on previous studies for asymmetric catalysis using C_2-symmetric ligands.[34] Chelation of the oxyallyl cation to the copper catalyst would create four quadrants. Out of the two productive front quadrants, the top *endo* approach would be favored as the bottom approach would have unfavorable steric interactions with the phenyl substituent. While the model correctly predicts the observed enantioselectivity, its validity is unclear in light of our recent computational work suggesting the preference for the *E*-oxyallyl cation. Further mechanistic studies would prove useful in this regard.

The reaction also displayed interesting regioselectivity with unsymmetrical furans. Depending on the position of the substituents on furan, regioselectivities were found to favor either the *syn* or the *anti* products **76a** and **76b**, respectively. Regioselectivities were high in most cases, although certain furans were found to give diminished enantioselectivities. While an ade quate explanation for the regioselectivity was unclear at the time, a mechanistic study on the observed regiochemistry has since been reported (*vide infra*).[35]

First Regiochemical Models In Oxyallyl Cation (4 + 3) Cycloadditions

The use of nitrogen-stabilized oxyallyl cations with unsymmetrical dienes in (4 + 3) cycloadditions has been reported to provide high levels of regioselectivity in many cases.[16,23,24] However, there have been few systematic studies concerning the regioselectivity of oxyallyls and the influence of substituents on the diene.[3e,23] Furthermore, there had not been any coherent let alone predictive model reported for the regioselectivities in (4 + 3) cycloadditions.

Houk and Hsung reported the first systematic study on the regioselectivity between furans and nitrogen-stabilized oxyallyl cations using the oxazolidinone-substituted system.[35] As shown in **Scheme 21**, reaction of allenamide **20** with 3-methylfuran or ethyl 3-furoate gave predominantly the *anti* product **77** having the oxazolidinone and furan substituent on opposite sides of the cycloadduct. However, when using 2-methylfuran or methyl 2-furoate,

the regiochemistry reversed giving predominantly the *syn* cycloadduct **78**. Inclusion of a Lewis acid generally increased the yield, but did not alter the regioselectivity.

The reaction was calculated to be a concerted process, although the transition states showed slightly more bonding at the ω enolate terminus. Furthermore, only the *E*-oxyallyl cation was involved in the reaction, consistent with our previous computational work.[25] DFT calculations on the regioselectivities predicted the correct major product for each furan and a predictive set of regiochemical models were proposed as shown in **Figure 7**. With electron-withdrawing ester groups, the regiochemical preference was consistent with electronic effects as a conjugate addition type of approach. In contrast, steric effects likely governed the regioselectivities for methylfurans in which the oxyallyl attacks the less substituted position with 2-methylfuran or avoids steric hindrance with the oxazolidinone for 3-methylfuran.

Other donor-substituted oxyallyl cations have often been calculated to undergo (4 + 3) cycloadditions in a stepwise process, with the oxyallyl cation exhibiting electrophilic behaviour [**Figure 8**].[4a,16,26,36.] In contrast, nitrogen-substituted oxyallyl cations are a distinct class of oxyallyl displaying ambiphilic properties and thus, are truly stabilized oxyallyl cations. These features provide oxazolidinone-substituted oxyallyls with well-defined and unique regiochemical properties, allowing a coherent and predictive set of models to be established. These models can also serve as useful guidelines for future studies in other (4 + 3) cycloadditions.

Summary and Outlook

The chemistry of heteroatom-stabilized oxyallyl cations remains a fertile ground for continued exploration. Within this realm, nitrogen-stabilized oxyallyl cations represent of unique class of allylic cations that have allowed for the development of highly stereoselective (4 + 3) cycloadditions.

The use of nitrogen-stabilized oxyallyl cations in (4 + 3) cycloadditions offers distinct adva ntages for the construction of nitrogen heterocycles and complex natural alkaloids. From the development of new reaction methodology to its application in asymmetric catalysis and natural product synthesis, the utility of (4 + 3) cycloadditions with nitrogen-stabilized oxyallyl cations has grown tremendously. It is our hope that this concept article will stimulate further growth and development in this field.

Acknowledgments

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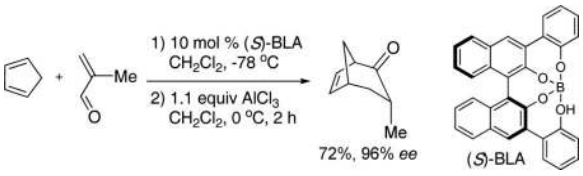

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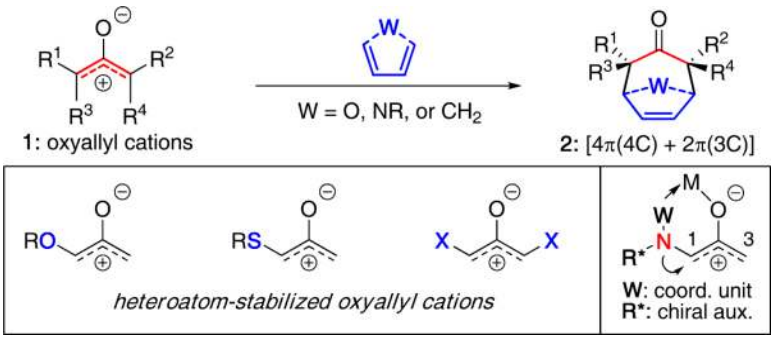
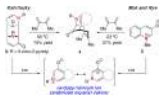
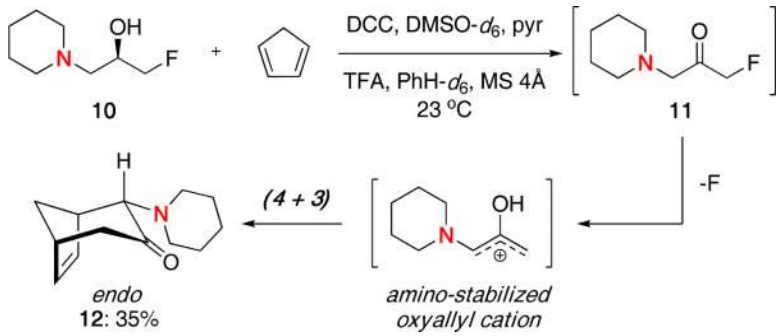


Figure 1.
Types of Oxyallyl Cations in (4 + 3) Cycloadditions.

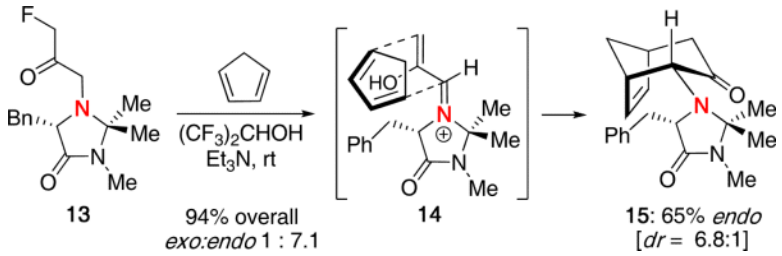


Scheme 1.
Oxidopyridinium Ions in (4 + 3) Cycloadditions.

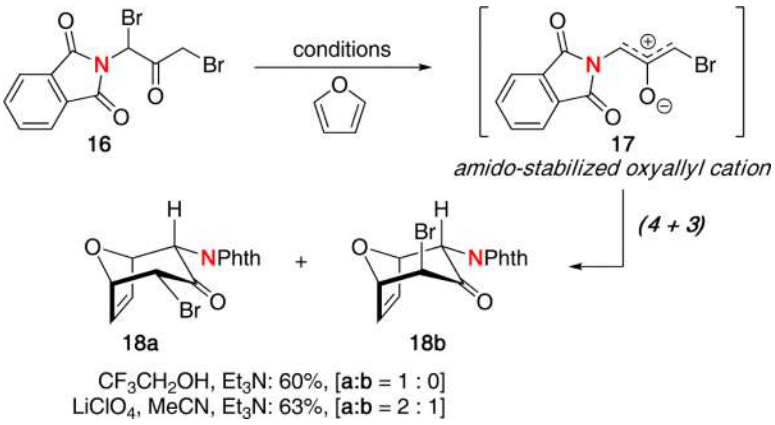
Scheme 2.
Application Toward Sarain A.



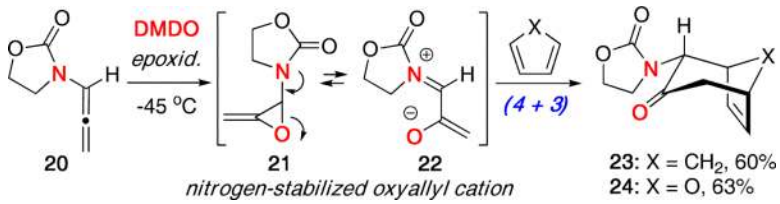
Scheme 3.
Generation of an Amino-Stabilized Oxyallyl Cation .



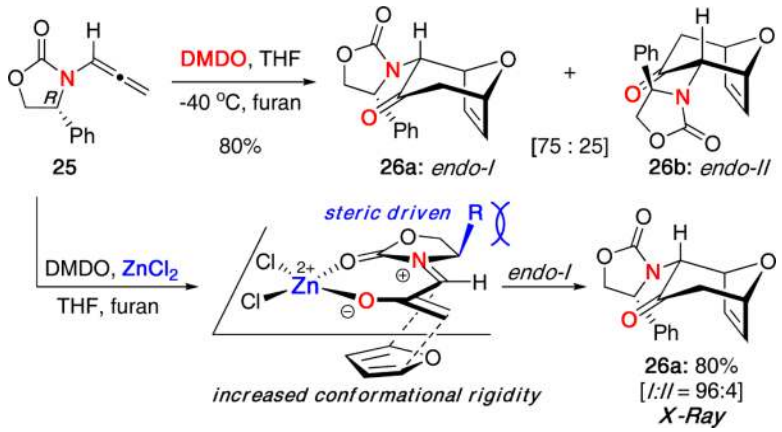
Scheme 4.
Diastereoselective (4 + 3) Cycloaddition.



Scheme 5.
(4 + 3) Cycloaddition of Amido-Stabilized Oxyallyl Cations.



Scheme 6.
(4 + 3) Cycloaddition of Allenamides.



Scheme 7.
Diastereoselective (4 + 3) Cycloaddition of Chiral Allenamides.

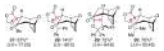
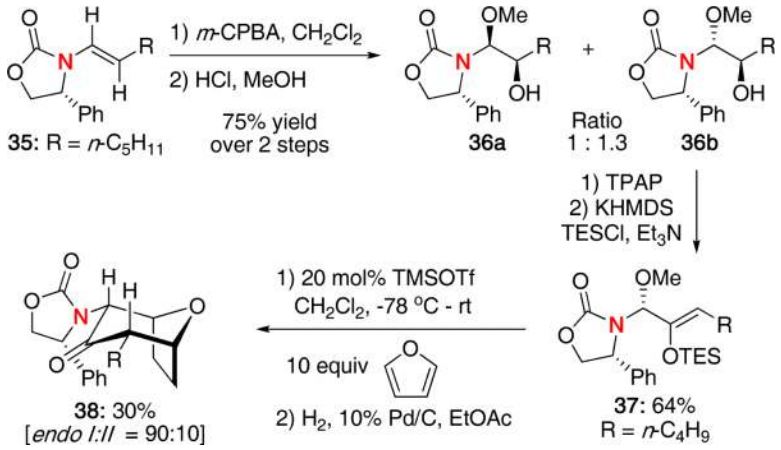


Figure 2.
(4 + 3) Cycloadducts Derived from Chiral Allenamides.

Scheme 8.
Synthesis of Chiral Ligands from (4 + 3) Cycloadducts.



Scheme 9.
Diastereoselective (4 + 3) Cycloaddition Derived from Enamides.

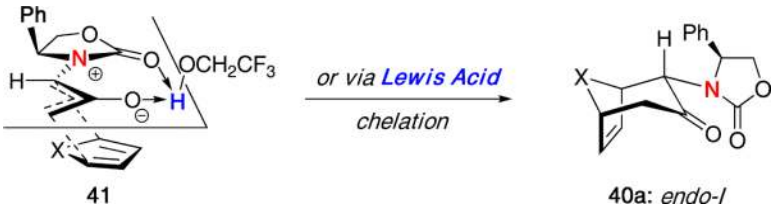


Figure 3.
Proposed Model for Diastereoselective (4 + 3) Cycloaddition.

Scheme 10.
Reversal in Stereochemistry for (4 + 3).

Scheme 11.
Reversal in Stereochemistry with Substituted Furans.

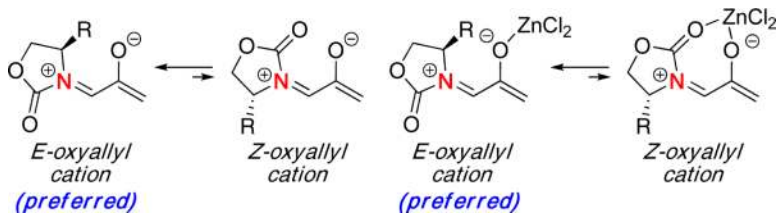


Figure 4.
Preferred Geometries of Nitrogen-Stabilized Oxyallyl Cations.

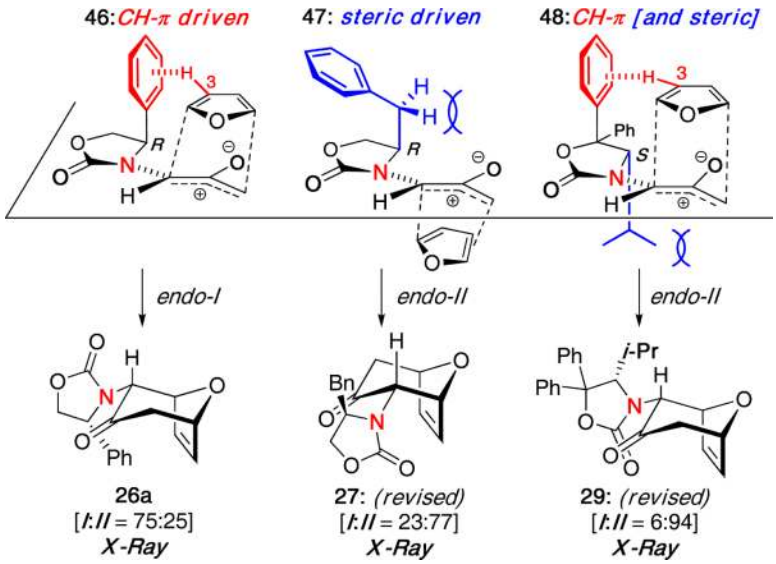
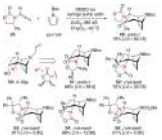
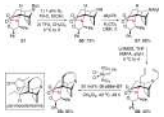


Figure 5.
Revised Models for Oxyallyl-Furan (4 + 3) Cycloadditions.



Scheme 12.
(4 + 3) Cycloaddition with Pyrroles



Scheme 13.
An Approach Toward Parvineostemonine.

Scheme 14.
N-Tethered Intramolecular (4 + 3) Cycloaddition.

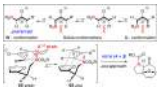
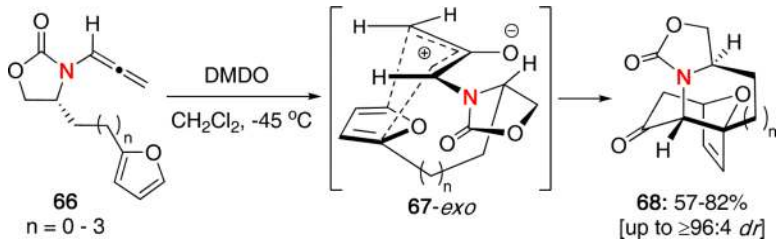


Figure 6.
Model for *N*-Tethered Intramolecular (4 + 3) Cycloaddition.

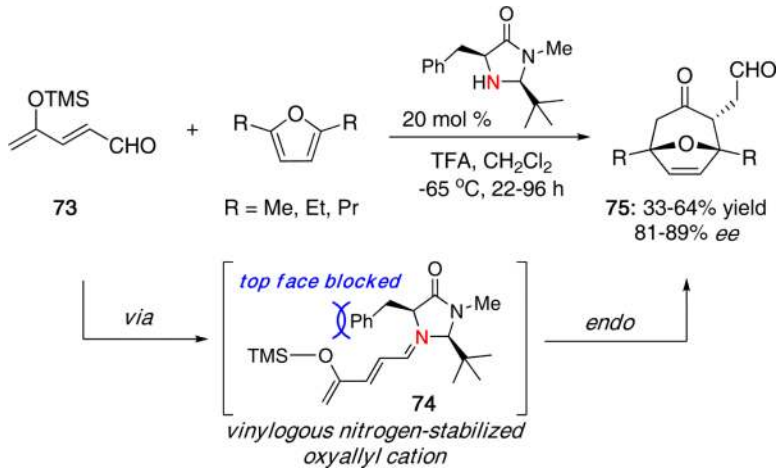


Scheme 15.
(4 + 3) Cycloaddition of Cyclic-Tethered Allenamides.

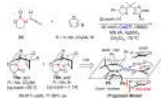
Scheme 16.
(4 + 3) Cycloaddition of *N*-Sulfonyl Allenamides.

Scheme 17.
α-Tethered Intramolecular (4 + 3) Cycloaddition

Scheme 18.
γ-Tethered Intramolecular (4 + 3) Cycloadditions.



Scheme 19.
Organocatalytic Asymmetric (4 + 3) Cycloaddition.



Scheme 20.
Catalytic Asymmetric (4 + 3) Cycloaddtion of Allenamides

Scheme 21.
Regioselective (4 + 3) Cycloaddition.

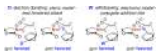


Figure 7.
Summary of Regioselectivity with Unsymmetrical Furans.

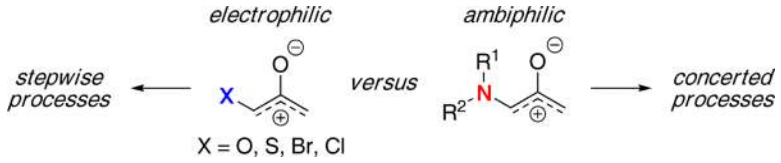
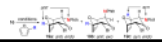


Figure 8.
Heteroatom- vs. Nitrogen-Stabilized Oxyallyl Cations.

Table 1

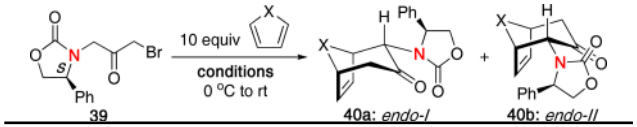
Regioselectivity in Walters' (4 + 3) Cycloaddition.



entry	conditions	R	*anti, endo*	*anti, exo*	*syn, endo*	yield [%]
1	CF_3CH_2OH, Et_3N	Me	3.5	1	2.7	77
2	CF_3CH_2OH, Et_3N	OMe	3	3	1	60
3	$LiClO_4$, MeCN, Et_3N	Me	6.5	1.4	1	73
4	$LiClO_4$, MeCN, Et_3N	OMe	17	1	0	57

Table 2

Diastereoselective (4 + 3) Cycloaddition of α-Bromoketones.



39 40a: *endo-I* 40b: *endo-II*

entry	conditions	X	*endo / exo*	*endo 1:11*	yield [%]
1	CF_3CH_2OH, Et_3N	0	93:7	66:34	70
2	CF_3CH_2OH, Et_3N	CH_2	93:7	66:34	65
3	$MgBr_2$, MeCN, Et_3N	0	98:2	98:2	40
4	$MgBr_2$, MeCN, Et_3N	CH_2	86:14	86:14	45