

Stereoselective Synthesis of Isoquinuclidines through an Aza-[4 + 2] Cycloaddition of Chiral Cyclic 2-Amidodienes

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S Supporting Information

ABSTRACT: A highly stereoselective aza-[4 + 2] cycloaddition of chiral cyclic 2-amidodienes with *N*-sulfonyl aldimines is described. While this Lewis acid promoted heterocycloaddition provides an efficient strategy for constructing optically enriched isoquinuclidines, it is mechanistically intriguing. The cycloaddition favored the *endo-II* pathway in the absence of a viable bidentate coordination. This represents an unexpected switch from the anticipated *endo-I* selectivity obtained in the all-carbon cycloaddition.

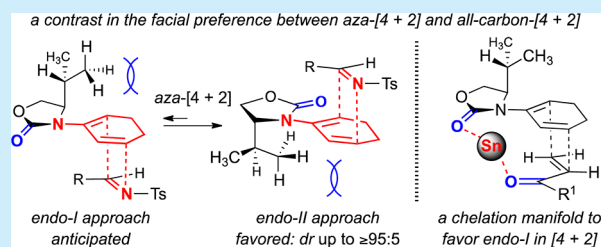
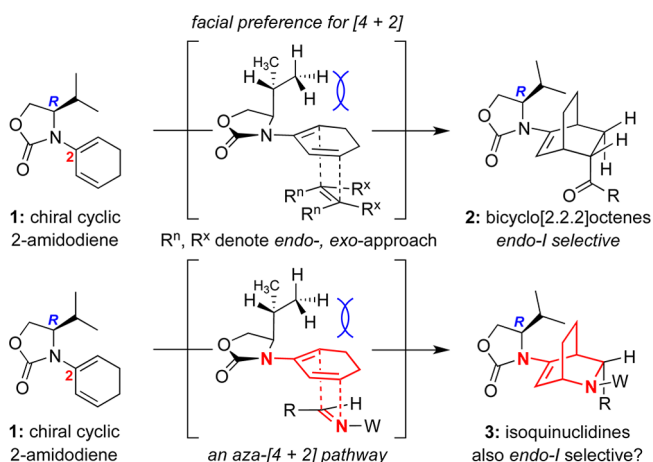


Figure 1. Bioactive natural products with isoquinuclidine core.

Daphniphyllum alkaloids such as caldaphnidine D have shown a variety of pharmacological activities such as cytotoxicity and antioxidative activity.³ Xestocyclamine A, a polycyclic alkaloid isolated from a marine sponge, exhibits potent inhibitory property of PKC β (PKC = protein kinase C).⁴ Given such potential significance in cancer therapeutic development, designing efficient methods to access the isoquinuclidine core represents an important endeavor not only for constructing these natural products but also advancing biological studies that can lead to possible drug discovery.^{2–4}

Recently, we⁵ reported a highly regio- and stereoselective Diels–Alder cycloaddition featuring de novo chiral cyclic 2-amidodienes **1** (Scheme 1) derived from allenamides.⁶ This cycloaddition provides a facial entry to optically enriched [2.2.2]bicyclic manifolds [**1**→**2** in Scheme 1]. Despite a rich history of amino and amido dienes,^{7,8} cyclic 2-amidodienes are rare,⁹ and there certainly is a lack of overall systematic exploration of their reactivities.¹⁰ Given the significance of isoquinuclidine, we envisioned that an aza-[4 + 2] cycloaddition^{11,12} employing imines as heterodienophiles could prove to be an efficient strategy for stereoselective constructions of optically enriched isoquinuclidines that have mostly been

Scheme 1. Cyclic 2-Amidodienes in [4 + 2] Cycloadditions



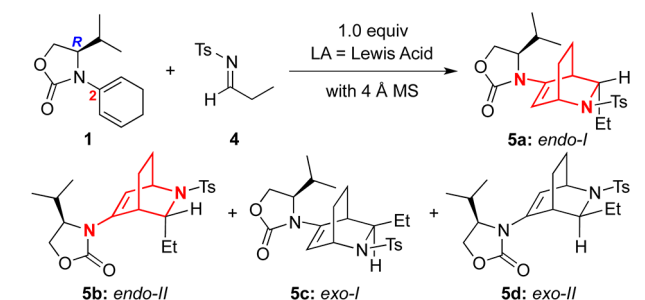
synthesized through [4 + 2] cycloadditions of 1,2-dihydropyridines.^{13–17} We wish to report here our success in developing a highly stereoselective aza-[4 + 2] cycloaddition of cyclic 2-amidodienes with *N*-sulfonyl aldimines and finding of an unexpected switch in the selectivity.

We commenced our investigation by screening Lewis acid conditions using cyclic 2-amidodiene **1**¹⁸ with *N*-Ts aldimine **4** serving as the dienophile. As shown in Table 1, although aluminum- and boron-based Lewis acids were less effective (entries 1–3) and TMSOTf is only marginal (entry 4), the best promoter for this reaction appeared to be SnCl₄, leading to the desired cycloadduct **5**¹⁹ in 60% yield (entry 5). There are three isomers found in this reaction with the major isomer being the *endo-II* product (**5b**) and the two minor isomers being *exo-I* and *exo-II* products **5c** and **5d**, respectively. The actual stereochemical assignments were made using another cycloadduct.

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Table 1. Identifying of a Suitable Lewis Acid



| entry | LA | solvent | temp (°C) | time (h) | yield ^a (%) | dr ratio ^b |
|-------|-----------------------------------|---------------------------------|-----------|----------|------------------------|-----------------------|
| 1 | EtAlCl ₂ | CH ₂ Cl ₂ | -78 | 12 | 14 | N.D. ^c |
| 2 | AlCl ₃ | CH ₂ Cl ₂ | -78 | 12 | 38 | 60:(20:20) |
| 3 | BF ₃ ·OEt ₂ | CH ₂ Cl ₂ | -78 | 12 | 33 | N.D. |
| 4 | TMSOTf | CH ₂ Cl ₂ | -78 | 12 | 48 | 34:(33:33) |
| 5 | SnCl ₄ | CH ₂ Cl ₂ | -78 | 12 | 60 | 68:(16:16) |
| 6 | TiCl ₄ | CH ₂ Cl ₂ | -78 | 12 | 52 | 68:(16:16) |
| 7 | MgBr ₂ | THF | rt | 14 | no rxn ^d | |
| 8 | Zn(OTf) ₂ | CH ₂ Cl ₂ | rt | 18 | no rxn | |
| 9 | Yb(OTf) ₃ | CH ₂ Cl ₂ | rt | 15 | no rxn | |
| 10 | La(OTf) ₃ | CH ₂ Cl ₂ | rt | 15 | no rxn | |

^aIsolated yields; in all cases, 1.0 equiv of Lewis acid was used. ^bRatios denote *endo:exo* with *exo-I:exo-II* ratios shown in parentheses. All ratios determined using ¹H and/or ¹³C NMR. ^cN.D. = not determined. ^dComplete recovery of the starting diene 1.

While TiCl₄ afforded comparable diastereoselectivity but gave a lower yield (entry 6), MgBr₂ and Zn(OTf)₂ were ineffective in promoting the cycloaddition (entries 7 and 8). Neither were rare earth metal triflates such as Yb(OTf)₃ and La(OTf)₃ useful in this context (entries 9 and 10), although they have been successfully utilized in aza-[4 + 2] reactions.²⁰

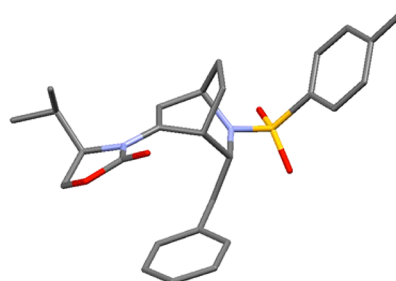
Having identified a suitable Lewis acid, a series of *N*-Ts-aldimines were examined as summarized in Table 2: (1) The

Table 2. Examining the Scope of *aza*-Dienophiles

| cyclic diene | imines | yield [%] and <i>dr</i> ^{a,b} | imines ^c | yield [%] and <i>dr</i> |
|--------------|--------|--|---------------------|----------------------------------|
| | | 9: 81 [72:(14:14)] | | 13: 51 [(50:30:20)] ^d |
| | | 10: 40 [≥95:5] ^e | | 14: 26 [≥95:5] |
| | | 11: 36 [86:(14:0)] ^f | | 15: 50 [(60:40)] ^d |
| | | 12: 81 [≥95:5] | | 16: 58 [≥95:5] |
| | | | | 17: 49 [≥95:5] |
| | | | | 19: 46 [89:(11:0)] ^e |

^aReaction conditions followed those described for entry 5 in Table 1. All are isolated yields. ^bRatios denote *endo:exo* [a/b:c/d] with the *exo-I:exo-II* ratio [c:d] shown in parentheses. They are determined using ¹H and/or ¹³C NMR. ^cPMP = *p*-methoxyphenyl. ^dStereochemistry of each isomer was not unambiguously assigned. ^eThis ratio implies a single isomer is observed here. ^fOnly one *exo*-cycloadduct was seen but unassigned whether it is *exo-I* or *exo-II*. ^gDecomposition of starting diene 1 with no observable desired cycloadduct.

minor isomers of cycloadducts 9 were cleanly isolated as a mixture and could be concisely assigned as a pair of *exo*-cycloadducts, more specifically 9c and 9d, after its hydrolysis.²¹ (2) The *tert*-butyl-substituted imine was unfortunately not tolerated likely due to the steric hindrance of the *t*-Bu group, and aryl aldimines appear to be inferior substrates in terms of selectivity (see 13). (3) With respect to nitrogen substitutions, methane sulfonyl and Ns groups were not ideal (see 14 and 15, respectively). In contrast, Ts- and PMP-sulfonyl groups were very effective (see 16 and 17). (4) Lastly and most importantly, the single-crystal X-ray structure the major isomer of cycloadducts 12 reveals that it is 12b, therefore unambiguously confirming the *endo-II* selectivity (Figure 2). Cycloadditions of

Figure 2. X-ray structure of *endo-II* cycloadduct 12b.

other chiral cyclic 2-amidodienes with *N*-sulfonyl aliphatic aldimines were also examined (Table 3). Depending on the imine, in general, good selectivities as well as yields were obtained

Table 3. Cycloadditions of Other Cyclic 2-Amidodienes

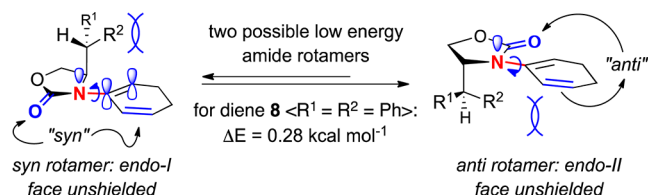
| cyclic dienes | imines | yield [%] and <i>dr</i> ^{a,b} | imines ^c | yield [%] and <i>dr</i> |
|---------------|--------|--|---------------------|-------------------------|
| | | 18: 62 [≥95:5] ^d | | 21: 75 [72:(14:14)] |
| | | 19: 46 [89:(11:0)] ^e | | 22: 36 [≥95:5] |
| | | 20: 75 [≥95:5] | | 23: 80 [72:(14:14)] |
| | | 24: 55 [≥95:5] | | 27: 74 [84:(8:8)] |
| | | 25: 39 [≥95:5] | | 28: 44 [≥95:5] |
| | | 26: 78 [≥95:5] | | 29: 76 [80:(10:10)] |
| | | 30: 43 [≥95:5] | | 32: 83 [≥95:5] |
| | | 31: 60 [89:(11:0)] ^e | | 33: 35 [≥95:5] |

^aReaction conditions followed those described for entry 5 in Table 1. All are isolated yields. ^bRatios denote *endo:exo* [a/b:c/d] with the *exo-I:exo-II* ratio [c:d] shown in parentheses. They are determined using ¹H and/or ¹³C NMR. ^cPMP = *p*-methoxyphenyl. ^dThis ratio implies a single isomer is observed here. ^eOnly one *exo*-cycloadduct was seen but unassigned whether it is *exo-I* or *exo-II*.

including the usage of Sibi's auxiliary (see diene **8**).²² These results demonstrate that this cycloaddition can be useful for constructing optically enriched isoquinuclidines.

Mechanistically, we became intrigued because the stereochemical outcome is opposite from what we had anticipated. As shown in Scheme 2, there are two possible low energy rotameric

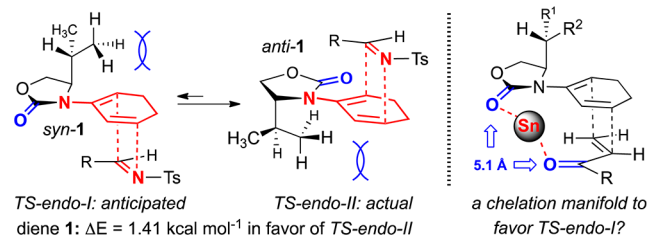
Scheme 2. Two Rotameric Conformations of the Diene



conformations for these cyclic 2-amidodienes, *syn* and *anti*, which can be defined by the position of the carbamate carbonyl relative to the blue-colored olefin with respect to the red C–N bond (see wavy arrows in Scheme 2). In both rotamers, the nitrogen lone pair is coplanar and fully delocalized into the diene motif. In our previous all-carbon cycloaddition,⁵ the observed *endo-I* selectivity suggests that the *syn* rotamer is operative because its substituent on the chiral auxiliary shields the top *endo-II* face. Although Spartan B3LYP/6-31G* calculations reveal that the *anti* rotamer is more favored, the energetic difference is sufficiently small (i.e., $\Delta E = -0.28$ kcal mol⁻¹ for diene **8**) that it should not preclude the possibility of the *syn* rotamer being the more reactive conformer.

Consequently, we expected *endo-I* selectivity also for the current aza-[4 + 2] cycloadditions, but instead, these are *endo-II* selective processes, thereby implying a facial preference switch with the *anti* rotamer being operative. Furthermore, as shown in Scheme 3, Spartan B3LYP/6-31G* calculations demonstrate

Scheme 3. Unexpected Switch in the Facial Preference

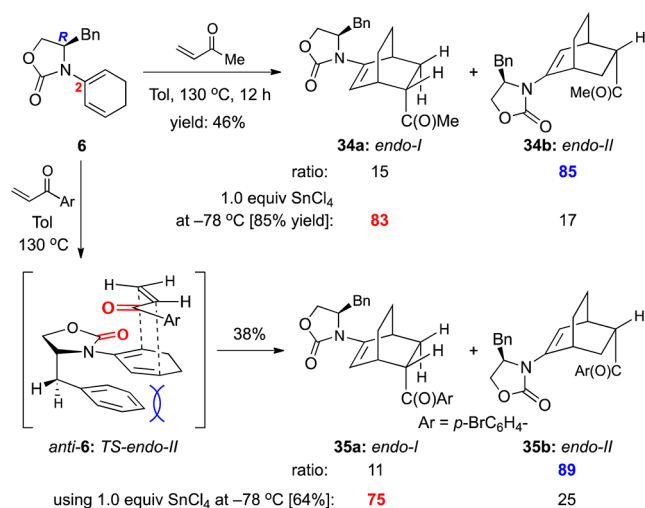


that *TS-endo-II* is actually lower in energy than *TS-endo-I* (1.41 kcal mol⁻¹ for diene **1**).²³ This energetic difference in the transition states agrees quite well with our observed stereochemical outcome. To reconcile these differences, we suspect that the previous cycloaddition involved a highly organized transition-state through a long distance chelation with the tin metal coordinating to both carbonyl oxygen atoms (right-hand side in Scheme 3). This bidentate coordination is likely only feasible with *TS-endo-I* ($d = 5.1$ Å) given the much longer distance between the same two oxygen atoms in *TS-endo-II* ($d = 6.0$ Å, not shown).

To provide support for this proposal, we examined the all-carbon cycloaddition in the absence of any Lewis acids. We had previously avoided this condition because these cyclic 2-amidodienes tend to undergo isomerization via a 1,5-H shift at high temperatures over an extended period of time, leading to the more stable 1-amidodienes.¹⁸ With some trepidation, we

carefully carried out cycloadditions of diene **6** with two enones at high temperature as shown in Scheme 4. Although yields were

Scheme 4. Reversal to the *Endo-II* Selectivity



not particularly high, we managed to isolate the desired cycloadducts **34a/b** and **35a/b** with complete reversal of selectivity from those obtained under Lewis acid conditions. These results provide rather strong support for our assertion that the cycloaddition prefers the energetically more favored *TS-endo-II* (0.28 kcal mol⁻¹ for diene **6**)²³ through the *anti* rotamer and that, in the presence of a viable bidentate coordination,²⁴ this selectivity can be altered and/or completely reversed.

In summary, we have developed a highly stereoselective aza-[4 + 2] cycloaddition of 2-amidodienes and *N*-sulfonyl aldimines. This Lewis acid promoted heterocycloaddition provides an efficient strategy for constructing optically enriched isoquinuclidines. Mechanistically, we uncovered an unexpected switch from the anticipated *endo-I* selectivity. In the absence of a chelation-dictated transition state, these aza-[4 + 2] cycloadditions favored the *endo-II* pathway through the *anti* rotamer. Further mechanistic study through calculation and its applications in total synthesis of relevant alkaloids are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as NMR spectra, characterizations, and X-ray structural files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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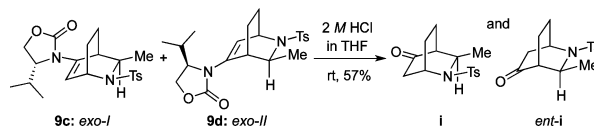
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(19) See the Supporting Information.

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(21) Hydrolysis of **9c** and **9d** as a mixture using 2 M HCl and THF provided a pair of enantiomers **i** and **ent-i**, which are indistinguishable in NMR spectroscopy. Given that the major cycloadduct is *endo-II* and that if it were an inseparable pair of *endo* and *exo* cycloadducts hydrolysis would have given two diastereomers, we can confidently assign the two minor isomers as *exo-I* and *exo-II* cycloadducts.



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(23) We thank one of the reviewers for suggesting a “dipole minimization” argument as to why *TS-endo-II* is preferred. In this transition state, the dipole for the carbonyl and imine of *anti-1* in Scheme 3 and for the two carbonyls of *anti-6* in Scheme 4 are pointed in opposite directions, thereby leading to a stabilizing factor to *TS-endo-II*.

(24) Intriguingly, in the context of *aza-[4 + 2]* cycloadditions, the carbamate carbonyl appears to be well within the reach of the imino nitrogen atom (*d* = 4.6 Å for *TS-endo-I* of *syn-1*). We think the potential chelation here with the tin metal is likely not effective sterically because the nitrogen lone pair is tucked away underneath the diene. Thus, considerations purely based on net distances may not be sufficient. We are currently investigating this issue further.

NOTE ADDED AFTER ISSUE PUBLICATION

The received date was corrected to read February 6, 2014 on October 28, 2014.