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

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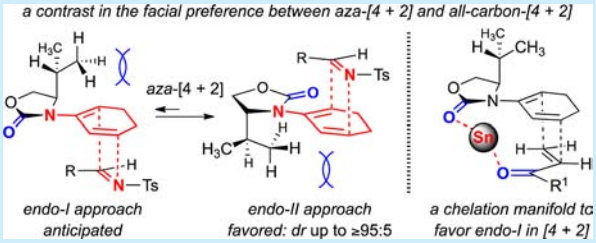
Supporting Information

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.



The isoquinuclidine [or 2-azabicyclo[2.2.2]octane] core is a prevalent motif among biologically active natural products.[1] Catharanthine, an iboga-alkaloid, is a biosynthetic precursor of dimeric vinca alkaloids such as vinblastin and vincristine, which are being used as antitumor agents for treatment of a number of human cancers (Figure 1).[2]

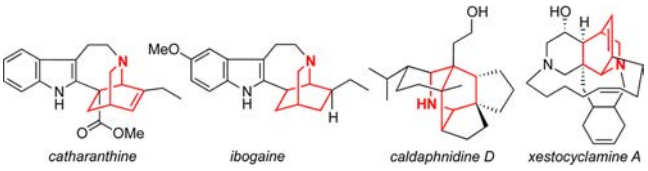
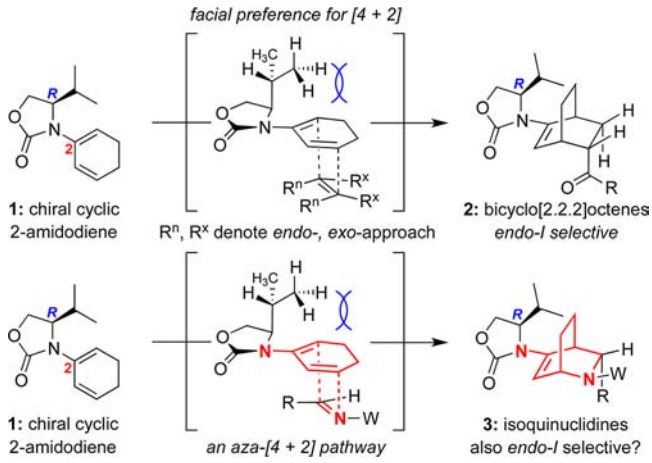


Figure 1. Bioactive natural products with isoquinuclidine core.

Moreover, *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 PKCβ (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, we[5] 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

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



mostly been synthesized through [4 + 2] cycloadditions of 1,2-dihyropyridines.[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 $SnCl_4$, 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 cyclo-

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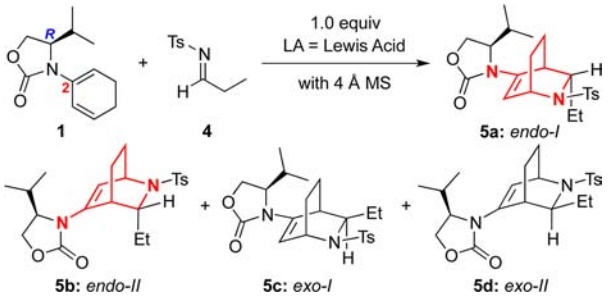
Table 1. Identifying of a Suitable Lewis Acid



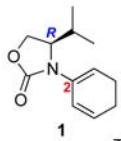
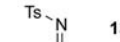
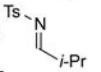
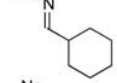
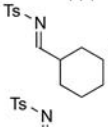
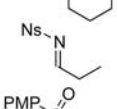
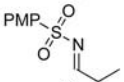
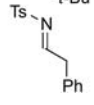
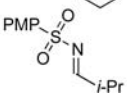
entry	LA	solvent	temp (°C)	time (h)	yield[a] (%)	dr ratio[b]
1	$EtAlCl_2$	CH_2Cl_2	−78	12	14	N.D.[c]
2	$AlCl_3$	CH_2Cl_2	−78	12	38	60:(20:20)
3	BF_3−OEt_2	CH_2Cl_2	−78	12	33	N.D.
4	TMSOTf	CH_2Cl_2	−78	12	48	34:(33:33)
5	$SnCl_4$	CH_2Cl_2	−78	12	60	68:(16:16)
6	$TiCl_4$	CH_2Cl_2	−78	12	52	68:(16:16)
7	$MgBr_2$	THF	rt	14	no rxn[d]	
8	$Zn(OTf)_2$	CH_2Cl_2	rt	18	no rxn	
9	$Yb(OTf)_3$	CH_2Cl_2	rt	15	no rxn	
10	$La(OTf)_3$	CH_2Cl_2	rt	15	no rxn	

[a]Isolated yields; in all cases, 1.0 equiv of Lewis acid was used. [b]Ratios denote *endo*:*exo* with *exo-I*:*exo-II* ratios shown in parentheses. All ratios determined using ^{1}H and/or ^{13}C NMR. [c]N.D. = not determined. [d]Complete recovery of the starting diene **1**.

adduct. While $TiCl_4$ afforded comparable diastereoselectivity but gave a lower yield (entry 6), $MgBr_2$ 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 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 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

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

cyclic diene	imines	yield [%] and *dr*[a,b]	imines[c]	yield [%] and *dr*
 1		**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]
		0[g]		**16:** 58 [≥95:5]
		**12:** 81 [≥95:5]		**17:** 49 [≥95:5]

[a]Reaction conditions followed those described for entry 5 in Table 1. All are isolated yields. [b]Ratios denote *endo*:*exo* [**a**/**b**:**c**/**d**] with the *exo-I*:*exo-II* ratio [**c**:**d**] shown in parentheses. They are determined using ^{1}H and/or ^{13}C NMR. [c]PMP = *p*-methoxyphenyl. [d]Stereochemistry of each isomer was not unambiguously assigned. [e]This ratio implies a single isomer is observed here. [f]Only one *exo*-cycloadduct was seen but unassigned whether it is *exo-I* or *exo-II*. [g]Decomposition of starting diene **1** with no observable desired cycloadduct.

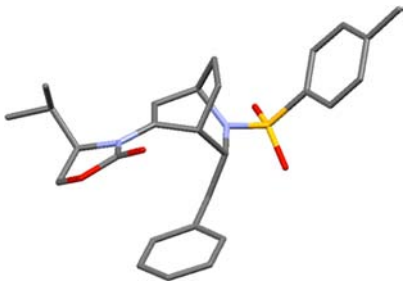
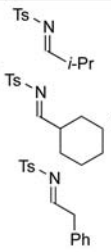
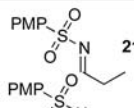
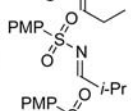
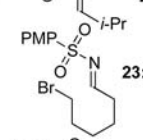
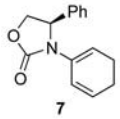
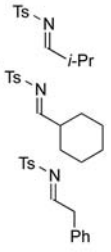
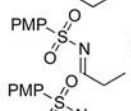
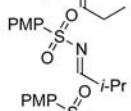
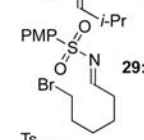
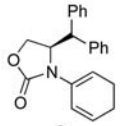
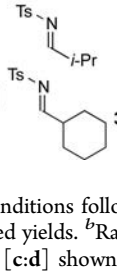
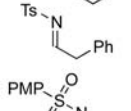
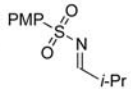


Figure 2. X-ray structure of *endo-II* cycloadduct **12b**.

Table 3. Cycloadditions of Other Cyclic 2-Amidodienes

cyclic dienes	imines	yield [%] and *dr*[a,b]	imines[c]	yield [%] and *dr*
 6		**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)]
 7		**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)]
 8		**30:** 43 [≥95:5]		**32:** 83 [≥95:5]
		31: 60 [89:(11:0)][e]		**33:** 35 [≥95:5]

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

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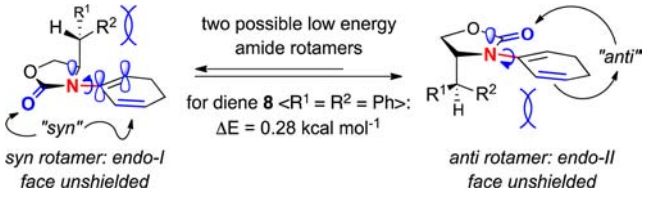
obtained including the usage of Sibi's auxiliary (see diene **8**).[22] These results demonstrate that this cycloaddition can be useful for constructing optically enriched isoquinuclidines.

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

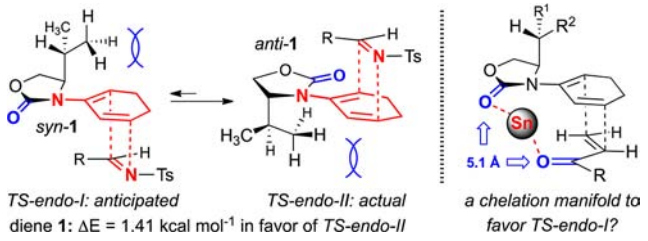
Scheme 2. Two Rotameric Conformations of the Diene



rotameric 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., ΔE = −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

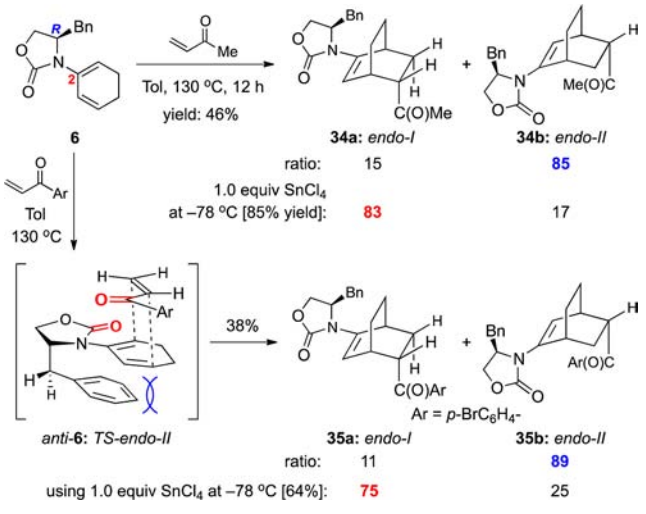
Scheme 3. Unexpected Switch in the Facial Preference



that *TS-endo-II* is actually lower in energy than *TS-endo-I* (1.41 kcal mol^{-1} for diene **1**).[23] This energetic different 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

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



were 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.

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REFERENCES

(1) For reviews, see: (a) Khan, M. O. F.; Levi, M. S.; Clark, C. R.; Ablordeppey, S. Y.; Law, S.-J.; Wilson, N. H.; Borne, R. *Stud. Nat. Prod. Chem.* **2008**, *34*, 753. (b) Sundberg, R. G.; Smith, S. Q. In *The Alkaloids*; Cordell, G. A., Ed. Academic Press: New York, 2002; Vol. *59*.

(2) For isolation of catharanthine, see: (a) Gorman, M.; Neuss, N.; Svoboda, G. H.; Barnes, A. J.; Cone, N. J. *J. Am. Pharm. Assoc. (Sci. Ed.)* **1959**, *48*, 256. (b) Gorman, M.; Neuss, N.; Svoboda, G. H. *J. Am. Chem. Soc.* **1959**, *81*, 4745. For a review on synthesis of iboga-alkaloids, see: (c) Goutam, K. J.; Sibasish, P.; Surajit, S. *Org. Prep. Proced. Int.* **2011**, *43*, 541. For selected examples on the total synthesis of catharanthine, see: (d) Reding, M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973. (e) Raucher, S.; Bray, B. L.; Lawrence, R. F. *J. Am. Chem. Soc.* **1987**, *109*, 442. (f) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236.

(3) For isolation of caldaphnidine D, see: (a) Zhan, Z.-J.; Zhang, C.-R.; Yue, J.-M. *Tetrahedron* **2005**, *61*, 11038. For a review on daphniphyllum alkaloids, see: (b) Jun'ichi, K.; Takaaki, K. *Nat. Prod. Rep.* **2009**, *26*, 936. For selected examples on the total syntheses of daphniphyllum alkaloids, see: (c) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650. (d) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575. (e) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501. (f) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679.

(4) For isolation and biological study of xestocyclamine A, see: (a) Rodriguez, J.; Peters, B. M.; Kurz, L.; Schatzman, R. C.; McCarley, D.; Lou, L.; Crews, P. *J. Am. Chem. Soc.* **1993**, *115*, 10436. (b) Rodrìguez, J.; Crews, P. *Tetrahedron Lett.* **1994**, *35*, 4719. For synthetic studies toward xestocyclamine A, see: (c) Gagnon, A.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1581. (d) Yun, H.; Gagnon, A.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 5311.

(5) Fang, L.-C.; Hsung, R. P.; Ma, Z.-X.; Presser, W. R. *Org. Lett.* **2013**, *15*, 4842.

(6) For leading reviews on allenamide chemistry, see: (a) Lu, T.; Lu, Z.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2013**, *130*, 4862. (b) Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773. (c) Standen, P. E.; Kimber, M. C. *Curr. Opin. Drug Discov. Dev.* **2010**, *13*, 645.

(7) For reviews on chemistry of 2-amino- or 2-amidodienes, see: (a) Enders, D.; Meyer, O. *Liebigs Ann.* **1996**, 1023. (b) Krohn, K. *Angew. Chem., Int. Ed.* **1993**, *32*, 1582. (c) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421. (d) Petrzilka, M. *Synthesis* **1981**, 753. (e) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.

(8) For a review on the synthesis of enamides, see: Tracey, M. R.; Hsung, R. P.; Antoline, J. E.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformation*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, 2005; Chapter 21.4.

(9) For some rare examples of cyclic amidodienes, see: (a) Martínez, R.; Jiménez-Vázquez, H. A.; Delgado, F.; Tamariz, J. *Tetrahedron* **2003**, *59*, 481. (b) Wallace, D. J.; Klauber, D. J.; Chen, C. Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (c) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem.—Eur. J.* **2004**, *10*, 484.

(10) For a study related to an intramolecular cycloaddition mode, see: (a) Hayashi, R.; Feltenberger, J. B.; Hsung, R. P. *Org. Lett.* **2010**, *12*, 1152. (b) Hayashi, R.; Ma, Z.-X.; Hsung, R. P. *Org. Lett.* **2012**, *14*, 252.

(11) For reviews, see: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869. (b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (c) Boger, D. L.; Weinreb, S. M. In *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987. (d) Boger, D. L.; Patel, M. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Scriven, E. F. V., Eds.; Pergamon: London, 1989; Vol. *1*. (e) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. *5*.

(12) For reviews, see: (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Waldmann, H. *Synthesis* **1994**, 535. (e) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (f) Waldmann, H. *Synlett* **1995**, 133. (g) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *190*, 1. (h) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

(13) For leading examples of isoquinuclidine synthesis via Diels–Alder cycloaddition of 1,2-dihydropyridines with alkenes, see: (a) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2013**, *15*, 444. (b) Harrison, D. P.; Iovan, D. A.; Myers, W. H.; Sabat, M.; Wang, S.; Zottig, V. E.; Harman, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 18378. (c) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 13873. (d) Graham, P. M.; Delafuente, D. A.; Lui, W.; Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **2005**, *127*, 10568. (e) Taylor, S. J.; Taylor, A. M.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1681.

(14) For some examples of asymmetric syntheses of isoquinuclidines via Diels–Alder cycloadditions, see: (a) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827. (b) Hirama, M.; Kato, Y.; Maysuyama, H.; Oshikiri, N.; Iyoda, M. *Chem. Lett.* **2008**, *37*, 924.

(15) For leading examples of the preparation of isoquinuclidines from Diels–Alder cycloadditions of cyclohexadienes with imines, see: (a) Maison, W. *Eur. J. Org. Chem.* **2007**, 2276. (b) Ray, C. A.; Risberg, E.; Somfai, P. *Tetrahedron* **2002**, *58*, 5983. (c) Shi, Z.-D.; Yang, B.-H.; Wu, Y.-L.; Pan, Y.-J.; Ji, Y.-Y.; Yeh, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2321. (d) Bailey, P. D.; Wilsona, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337. (e) Lucchini, V.; Prato, M.; Scorrano, G.; Tecillat, P. *J. Org. Chem.* **1988**, *53*, 2251.

(16) For synthesis of isoquinuclidines via conjugate additions, see: (a) Rassat, A.; Rey, P. *Tetrahedron* **1972**, *28*, 741. (b) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2011**, *52*, 2024.

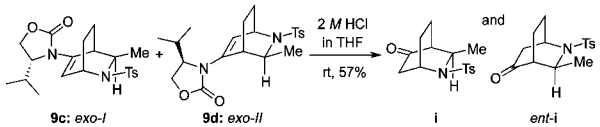
(17) For synthesis of isoquinuclidines from cyclization of silyl enol ethers onto iminium ions, see: Larouche-Gauthier, R.; Bélanger, G. *Org. Lett.* **2008**, *10*, 4501.

(18) For synthesis of these cyclic 2-amidodienes, see: (a) Hayashi, R.; Hsung, R. P.; Feltenberger, J. B.; Lohse, A. G. *Org. Lett.* **2009**, *11*, 2125. (b) Hayashi, R.; Walton, M. C.; Hsung, R. P.; Schwab, J.; Yu, X. *Org. Lett.* **2010**, *12*, 5768. (c) Hayashi, R.; Feltenberger, J. B.; Lohse, A. G.; Walton, M. C.; Hsung, R. P. *Beil. J. Org. Chem.* **2011**, *7*, 410.

(19) See the Supporting Information.

(20) (a) Chen, Z.; Lin, L.; Chen, D.; Li, J.; Liu, X.; Feng, X. *Tetrahedron Lett.* **2010**, *51*, 3088. (b) Cheng, K.; Lin, L.; Chen, S.; Feng, X. *Tetrahedron* **2005**, *61*, 9594. (c) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621. (d) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233.

(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.



(22) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163.

(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.