# Diastereoselective Diels−Alder Reactions of *N*-Sulfonyl-1-aza-1,3-butadienes with Optically Active Enol Ethers:  An Asymmetric Variant of the 1-Azadiene Diels−Alder Reaction

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***Abstract:*** The first detailed study of a room-temperature asymmetric Diels−Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes is reported enlisting a series of 19 enol ethers bearing chiral auxiliaries, with many providing highly diastereoselective (endo and facial diastereoselection) reactions, largely the result of an exquisitely organized [4+2] cycloaddition transition state. Three new, readily accessible, and previously unexplored auxiliaries rationally emerged from the studies and provide remarkable selectivities (two of these give 49:1 endo:exo and 48:1 facial selectivity) that promise to be useful in systems beyond those detailed.

## Introduction

In a series of studies, we introduced and have explored the $4\pi$ participation of electron-deficient *N*-sulfonyl-1-aza-1,3-butadienes in intermolecular Diels−Alder reactions with electron-rich dienophiles.[1] The complementary N1 substitution of an $\alpha,\beta$-unsaturated imine with an electron-withdrawing substituent ($-SO_2R$) accentuates the inherent electron-deficient nature of the 1-aza-1,3-butadiene, accelerating its participation in [4+2] cycloaddition reactions with electron-rich dienophiles in LUMO$_{\text{diene}}$-controlled Diels−Alder reactions. Further, a bulky electron-withdrawing N1 substituent decelerates competitive 1,2-imine addition relative to [4+2] cycloaddition and stabilizes the [4+2] cycloaddition product (deactivated enamine) to the reaction conditions while enhancing the electron-deficient character of the diene. Based on theses features, the *N*-sulfonyl-1-aza-1,3-butadienes that were explored were found to participate in regiospecific and diastereoselective inverse electron demand Diels−Alder reactions with characteristics of a concerted [4+2] cycloaddition reaction (Figure 1).[2]

Moreover, the reactions exhibited an unusually high endo diastereoselectivity ($\geq 20:1$) that could be attributed to a [4+2] cycloaddition transition state which benefits not only from a conventional stabilizing secondary orbital interaction but also from one in which the nitrogen lone pair and the C−O $\sigma$ bond of an enol ether dienophile lie trans periplanar to one another,



- Regiospecific
- Diastereoselective: typically ≥ 20:1 endo
- Solvent independent rate
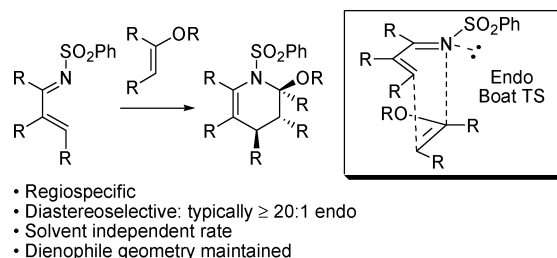- Dienophile geometry maintained

***Figure 1.*** *N*-Sulfonyl-1-azadiene Diels−Alder reaction.

providing the further benefit of a transition-state anomeric effect. A bonus of the *N*-sulfonyl-1-aza-1,3-butadienes was that they proved to be stable imine derivatives capable of simple isolation and purification (SiO$_2$ or Florisil chromatography), resistant to tautomerization to the corresponding stabilized enamine, and still remarkably reactive in prototypical [4+2] cycloadditions that were found to proceed under unusually mild conditions (25−100 °C). The utility of these reactions has been exploited in the total synthesis of several natural products, including streptonigrone,[3] fredricamycin A,[4] nothapodytine B and (−)-mappicine,[5] (+)-camptothecin,[6] and (−)-piericidin A1.[7]

Throughout the course of these studies, we have periodically examined approaches to conducting asymmetric variants of this [4+2] cycloaddition reaction. To date, we have not been successful in identifying Lewis acid catalysts (chiral or achiral) that can accelerate the [4+2] cycloaddition; rather they promote the nonproductive consumption of the reacting partners. By

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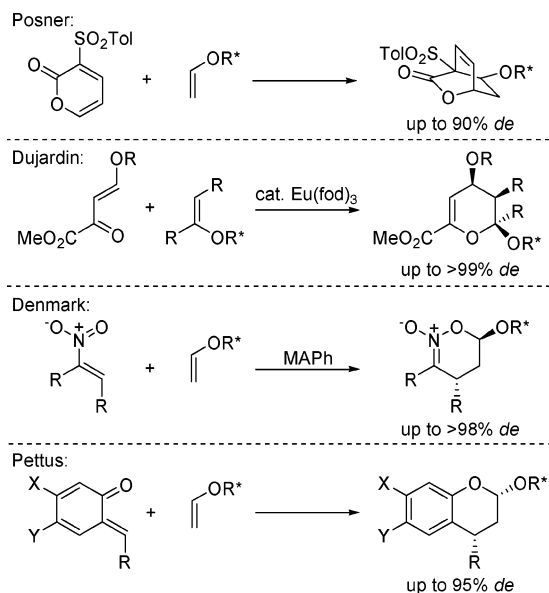(7) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704.
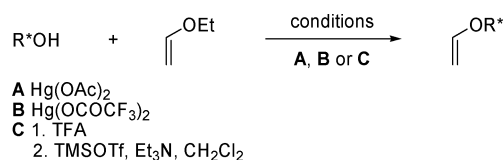
**Figure 2.** Cycloadditions of optically active enol ethers.

lectivities in the Lewis acid-catalyzed reactions of a series of chiral enol ethers with nitroalkenes,[11] and Pettus has extended their use in uncatalyzed cycloaddition reactions with *o*-quinone methides (Figure 2).[12]

**Dienophile Preparation.** Several methods were enlisted for the preparation of the vinyl ethers examined (Scheme 1). Typically, they were prepared from ethyl vinyl ether by Hg-(OAc)$_2$-catalyzed exchange with the alcohol corresponding to the desired vinyl ether (method A).[13] A variant of this approach utilizes mercury(II) trifluoroacetate, although few examples of its use in transetherification reactions have been detailed (method B).[14] Dujardin developed a two-step procedure for vinyl ether formation involving acid-catalyzed mixed acetal formation from the chiral alcohol and ethyl vinyl ether, followed by a TMSOTf-promoted elimination to the desired vinyl ether (method C).[15] More recently, Ishii reported an iridium-catalyzed transetherification ([Ir(cod)Cl]$_2$),[16] and Schlaf reported analogous reactions catalyzed by palladium (Pd(DPP)(OCOCF$_3$)$_2$).[17] In our hands, their effectiveness was found to be substrate dependent.

**Survey of Dienophile Chiral Auxiliaries.** Initially, 18 optically active enol ethers were examined with the prototypical *N*-sulfonyl-1-aza-1,3-butadiene **1** (Figure 3 and Table 1). The distribution of cycloaddition products and their quantitation were determined by ^{1}H NMR of the reaction mixtures which typically displayed distinguishable signals for each of the four possible products. Thus, the initial assignments and the quantitation were made by examination and integration of the C2−H and C5−H ^{1}H NMR signals of the cycloadducts. The C5−H splitting was diagnostic of endo (ddd, $J = 8.3, 5.1, 1.6$ Hz) versus exo (dt, $J = 8.3, 1.8$ Hz) addition, and both the C5−H and C2−H integrations were used for the quantitations. Representative of this, the results with dienophile **6a** are illustrated in Figure 4, where C5−H of the two endo adducts are each observed as a clear ddd (5.40 and 5.26 ppm, $J = 1.6, 5.1, 8.3$ Hz), whereas

contrast and largely as the result of the exquisitely organized [4+2] cycloaddition transition state, we have found and herein detail that their reactions with enol ether dienophiles bearing chiral auxiliaries provide highly diastereoselective (endo and facial diastereoselection) Diels−Alder cycloadditions. Three new, readily accessible, and previously unexplored auxiliaries, which rationally emerged from these studies, proved highly selective (>20:1 endo and >20:1 facial selectivity) and promise to be useful in systems beyond those that we detail.

At the onset of the studies, we explored enol ethers bearing chiral auxiliaries that have been disclosed in preceding cycloaddition reactions. Posner has shown that modest to good diastereomeric excesses are observed when chiral vinyl ethers derived from benzylic secondary alcohols undergo [4+2] cycloadditions with 3-sulfinyl- and 3-sulfonyl-2-pyrones both in the presence and in the absence of a Lewis acid catalyst.[8] Dujardin utilized chiral enol ethers derived from mandelate or pantalactone to prepare enantiopure hexose derivatives and *β*-benzamido aldehydes via their reaction with *β*,*γ*-unsaturated *α*-keto esters.[9,10] Denmark has observed excellent diastereose-
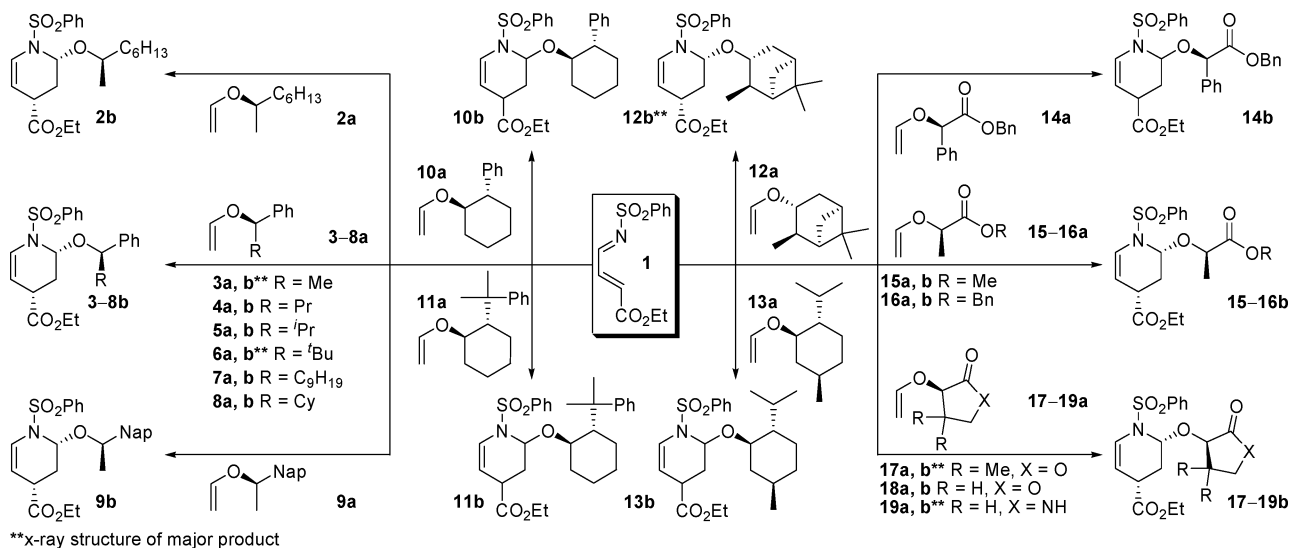


**Figure 3.** Survey of optically active enol ethers.

***Table 1.*** Results of Survey of Optically Active Enol Ethers

| dienophile | time (h) | major adduct (% conversion)[a] | total conv (%) | ratio of diastereomers[b] | | | endo facial selectivity |
|---|---|---|---|---|---|---|---|
| | | | | endo | exo | endo:exo | |
| **2a** | 60 | **2b** (52)[c] | 97 | 54:40 : | 3:3 | 16:1 | 1.4:1 |
| **3a** | 60 | **3b** (72) | 94 | 77:19 : | 4:— | 19:1 | 4:1 |
| **4a** | 60 | **4b** (49) | 63 | 78:18 : | 4:— | 24:1 | 4:1 |
| **5a** | 60 | **5b** (63) | 80 | 79:14 : | 7:— | 13:1 | 6:1 |
| **6a** | 72 | **6b** (48) | 64 | 75:14 : | 11:— | 8:1 | 5:1 |
| **7a** | 60 | **7b** (71) | 91 | 78:18 : | 4:— | 24:1 | 4:1 |
| **8a** | 60 | **8b** (53) | 69 | 77:15 : | 8:— | 12:1 | 5:1 |
| **9a** | 60 | **9b** (71) | 88 | 81:19 : | —:— | >25:1 | 4:1 |
| **10a** | 60 | **10b** (85) | 98 | 86:10 : | 4:— | 24:1 | 9:1 |
| **11a** | 48 | **11b** (12)[c] | 31 | 37:18 : | 29:16 | 1:1 | 2:1 |
| **12a** | 60 | **12b** (41) | 55 | 75:25 : | —:— | >25:1 | 3:1 |
| **13a** | 60 | **13b** (55) | 86 | 62:19 : | 13:6 | 4:1 | 3:1 |
| **14a** | 60 | **14b** (12) | 18 | 69:31 : | —:— | >25:1 | 2:1 |
| **15a** | 60 | **15b** (27) | 45 | 83:9 : | 8:— | 12:1 | 11:1 |
| **16a** | 60 | **16b** (32) | 38 | 85:9 : | 6:— | 16:1 | 9:1 |
| **17a** | 60 | **17b** (54)[d] | 68 | 80:14 : | 6:— | 16:1 | 6:1 |
| **18a** | 60 | **18b** (59)[d] | 65 | 91:5 : | 4:— | 24:1 | 18:1 |
| **19a** | 48 | **19b** (96)[d] | ≥98 | 96:2 : | 2:— | 49:1 | 48:1 |
| ethyl vinyl ether | 46 | (82)[e] | — | — | — | >25:1 | — |

[a] Reactions performed at room temperature, 0.3 M with respect to diene in toluene. Major adduct % conversion based on integration of major product C2−H versus minor diastereomer C2−H's and diene C2−H. Some hydrolysis of diene ocassionally observed (<5%). [b] Ratios based on $^1$H NMR integration of C2−H of products unless otherwise noted. Endo and exo compounds assigned on the basis of $^1$H NMR splitting patterns. Some peaks could not be located due to overlap, small size, or low conversion. [c] Integration based on C5−H. [d] Anhydrous CHCl₃ as solvent, 1 M with respect to diene. [e] Yield from ref 1c.
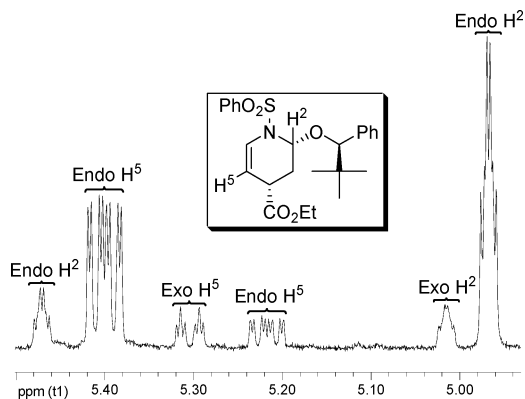


***Figure 4.*** Diagnostic cycloadduct $^1$H NMR signals.

the minor exo adduct was observed as a dt (5.32 ppm, $J = 1.8$, 8.3 Hz), and both the structure and the relative and absolute stereochemistries of the major product were established by a single-crystal X-ray structure determination.[18] The diagnostic C5−H coupling in the $^1$H NMR spectra arises from the well-defined conformations of the endo (diaxial substituents) versus exo (axial −OR*, equatorial −CO₂Et) cycloadducts and the resulting C5−H/C4−H coupling constants of ca. 5 Hz (C4−H$_{eq}$) versus ca. 2 Hz (C4−H$_{ax}$). In an analogous fashion, the structures of the major products derived from **3** and **6** (representative of **2**−**9**), **12**, and **17** and **19** (representative of **14**−**19**) were established by X-ray.[18]

Clear trends emerged in the examination of the series **2**−**9a**, inspired by the Posner studies, where the role of the aryl ring was probed with **2** versus **3** and the size of the dienophile alkyl substituent was systematically increased with **3**−**6**. As the size of the alkyl group was increased (**3a**→**6a**), the facial selectivity of the cycloaddition increased modestly (6:1 vs 4:1), but it did so at the expense of the rate of the reaction and with an erosion
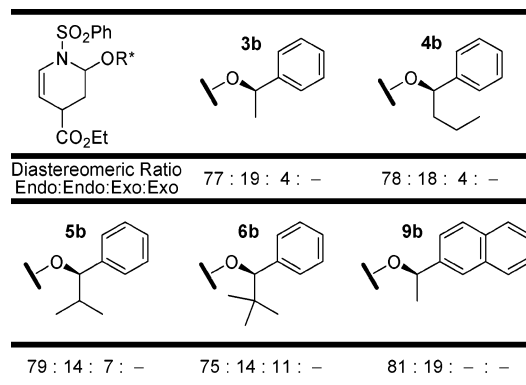


***Figure 5.*** Dienophile series **3**−**9**.

of the superb endo diastereoselectivity (8:1 vs 19:1). Replacing the aryl ring with a saturated alkyl group (**2a**) or a larger naphthyl ring (**9a**) did not significantly impact the endo diastereoselection, and the latter did not improve the cycloaddition facial selectivity. Within this series, the amount of the major diastereomer approached the respectable level of 80% of the product for each of the dienophiles, with the enhanced facial selectivity of the larger alkyl derivatives being offset by a larger proportion of exo adduct(s). As such, and because of their enhanced rates of reactions, **3a** and **9a** emerge as the most useful dienophiles in this series (Figure 5).

Several enol ethers, **10**−**13a**, bearing chiral six-membered rings were examined, inspired by the work of Denmark and Swindell (**10**−**12a**)[19−21] or Posner (**13a**).[8] Whereas the most hindered of these (**11a** and **12a**) exhibited poor reactivities, poor endo diastereoselectivities (**12a**) and/or modest to poor facial selectivities, **13a** and especially **10a** exhibited good chemical reactivity (% conversions), outstanding (**10a**, 24:1) or modest (**13a**, 4:1) endo diastereoselectivity, and good (**10a**, 9:1) or modest (**13a**, 3:1) facial selectivity. Of these, the dienophile **10a** proved most satisfactory, providing conversions that slightly exceed 85% for the major diastereomer in a reaction that provides superb conversions (98%) with exceptional endo diastereoselectivity (24:1) and excellent facial selectivity (9:1) (Figure 6).

The study of the most interesting and useful series, **14**−**19**, began with an examination of enol ethers derived from α-hydroxy esters and lactones, inspired by the studies of Dujardin.[9] Thus, the mandelate-derived enol ether **14a**, analo-

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(12) Pettus, T. R. R.; Selenski, C. *J. Org. Chem.* **2004**, *69*, 9196.
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(14) Tan, D. S.; Schreiber, S. L. *Tetrahedron Lett.* **2000**, *41*, 9509.
(15) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653.
(16) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590.
(17) Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225.
(18) Atomic coordinates for the major cycloadducts derived from the reaction of **1** with **3a** (**3b**, CCDC286828), **6a** (**6b**, CCDC286829), **12a** (**12b**, CCDC286826), **17a** (**17b**, CCDC286830), and **19a** (**19b**, CCDC286827, (*S*)-enantiomer) and for the major cycloadduct from the reaction of **19a** with **21a** (**21b**, CCDC287011, (*S*)-enantiomer) have been deposited with the Cambridge Crystallographic Data Center.
(19) Denmark, S. E.; Schnute, M. E. *J. Org. Chem.* **1991**, *56*, 6738.
(20) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1996**, *61*, 6727.
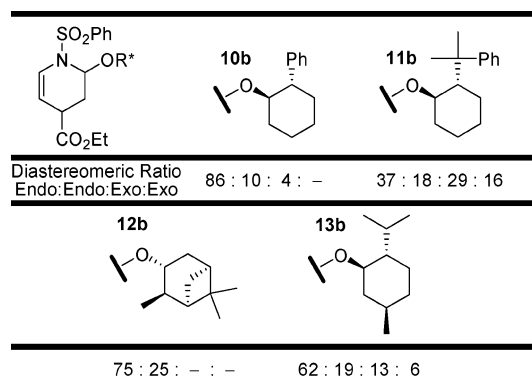(21) Swindell, C. S.; Tao, M. *J. Org. Chem.* **1993**, *58*, 5889.
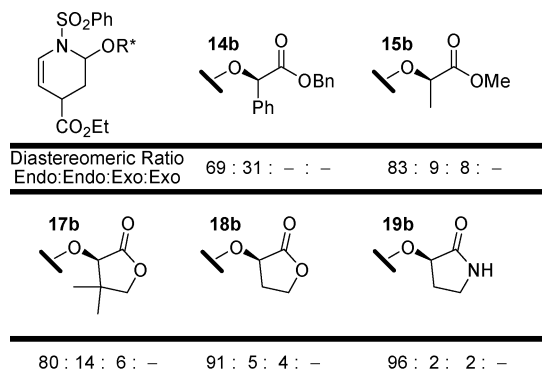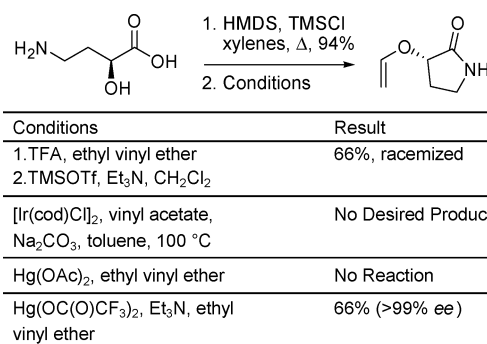
**Figure 6.** Dienophile series **10**−**13**.



**Figure 7.** Dienophile series **14**−**19**.

**Scheme 2**



| Conditions | Result |
|---|---|
| 1.TFA, ethyl vinyl ether<br>2.TMSOTf, Et$_3$N, CH$_2$Cl$_2$ | 66%, racemized |
| [Ir(cod)Cl]$_2$, vinyl acetate,<br>Na$_2$CO$_3$, toluene, 100 °C | No Desired Product |
| Hg(OAc)$_2$, ethyl vinyl ether | No Reaction |
| Hg(OC(O)CF$_3$)$_2$, Et$_3$N, ethyl<br>vinyl ether | 66% (>99% *ee*) |

gous to those explored by Dujardin,[22] exhibited superb endo diastereoselection but poor facial selectivity (2:1) and low conversions, whereas Dujardin's pantalactone-derived enol ether **17a**[9] maintained the excellent endo diastereoselection (16:1) and exhibited a substantially improved facial selectivity (6:1). As was observed with the preceding hindered enol ethers (e.g., **6a**), the reactivity of **17a** was modest and likely contributed to the erosion of the endo diastereoselection. Consequently, we examined **18a** with removal of the *gem*-dimethyl substitution of **17a**, which has not been previously explored, and found that it was more reactive, exquisitely endo diastereoselective (24:1), and remarkably facial selective (18:1). The lactate-derived enol ethers **15a** and **16a** were subsequently examined to define the importance of cyclic structure of **18a** and were found to be both less reactive and less selective than **18a**. Finally, the corresponding lactam **19a**, which proved both synthetically more accessible and more stable to subsequent transformations, was examined and found to exhibit a higher reactivity and an even greater level of endo (49:1) and facial (48:1) diastereoselection than **18a** (Figure 7). Thus, it is from these latter studies that two of the new and most impressive auxiliaries (**18a** and **19a**) rationally emerged, exhibiting remarkable endo (>20:1) and facial (>20:1) selectivities for the [4+2] cycloaddition reactions with **1** which promise to be useful in systems beyond those that we detail.

**Preparation of 18a and 19a.** The preparation of **18a** and **19a** deserves a more detailed discussion as a result of their utility. Although we have not yet examined this in depth, the preparation of **18a** was conducted from ethyl vinyl ether and (+)-(R)-2-hydroxy-γ-butyrolactone (both enantiomers are commercially available) utilizing Dujardin's two-step protocol[15] (20%) or Ishii's [Ir(cod)Cl]$_2$-catalyzed[16] alcohol exchange (20%), whereas the Hg(II)-catalyzed reactions led only to side product formation. This difficulty in the preparation of **18a** (low conversions), coupled with its propensity to undergo competitive lactone ring-opening reactions (hydrolysis, esterification) in subsequent transformations, led to the examination and preferential use of the corresponding lactam **19a**. The preparation of **19a**, which eventually proved straightforward, also provided unexpected initial observations (Scheme 2). (−)-(S)-3-Hydroxy-2-pyrrolidinone, which is commercially available or readily prepared from (−)-(S)-4-amino-2-hydroxybutanoic acid (HMDS, TMSCl, xylenes, 94%)[23] and is readily available in both enantiomeric forms,[24] could be cleanly converted to **19a** using ethyl vinyl ether and Dujardin's two-step protocol, but unexpectedly it provided racemic product. Presumably, this arises through TMSOTf/Et$_3$N silylation of the amide (*O*-silyl imidate formation) and subsequent racemization.[25] Although the iridium and Hg(OAc)$_2$-catalyzed exchange with ethyl vinyl ether did not cleanly provide **19a**, the reaction catalyzed by Hg(O$_2$CCF$_3$)$_2$ in the presence of Et$_3$N effectively provides **19a** (66%) without evidence of competitive racemization.[25] Significantly, **19a** provides beautiful, large white prisms upon recrystallization from EtOAc−hexanes, providing a convenient stage and manner for ensuring its chemical and optical purity (for (S)-**19a**, [α]$^{25}$$_D$ −78 (*c* 0.77, CHCl$_3$)).[25]

**Cycloaddition Model.** We have suggested that the exceptional endo diastereoselection observed with the *N*-sulfonyl-1-aza-1,3-butadienes results from not only a conventional stabilizing secondary orbital interaction but also a transition-state anomeric effect in which the nitrogen lone pair and the C−O σ bond of the dienophile enol ether lie trans periplanar to one another in the endo boat transition state.[1] Regardless of the origin of stabilization for an anomeric effect (n−σ* stabilization or avoidance of electrostatic repulsion),[26] the endo boat transition state embodies its trans periplanar lone pair/C−O bond arrangement, whereas the exo boat transition state places them proximal and gauche to one another. We have suggested that it is the

(22) (a) Prapansiri, V.; Thornton, E. R. *Tetrahedron Lett.* **1991**, *32*, 3147. (b) Dujardin, G.; Molato, S.; Brown, E. *Tetrahedron: Asymmetry* **1993**, *4*, 193.

(23) Sarairi, D.; Maurey, G. *Bull. Soc. Chim. Fr.* **1987**, 297.

(24) Perhaps the most expedient approach to either enantiomer of 3-hydroxy-2-pyrrolidinone is Amano PS-C lipase-mediated alcoholysis of racemic 3-acetoxy-2-pyrrolidinone (>99% ee of either enantiomer at 50% conversion, er = 1057): Kamal, A.; Ramana, K. V.; Ramana, A. V.; Babu, A. H. *Tetrahedron: Asymmetry* **2003**, *14*, 2587.

(25) The two enantiomers of **19a** are readily separable by chiral phase HPLC: 2 × 25 cm Chiralcel OD, 10% i-PrOH/hexanes, 1 mL/min, $t_R$ = 15.3 (3R) and 17.0 (3S) min, α = 1.11.

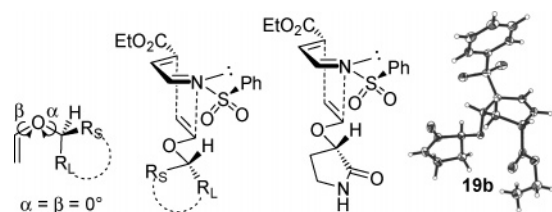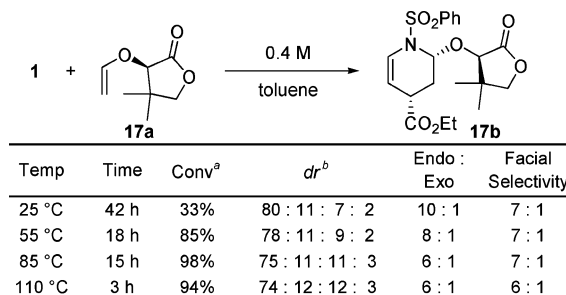(26) Juarist, E.; Cuervas, G. *Tetrahedron* **1992**, *48*, 5019.

**Figure 8.** Transition-state model (*S*-enantiomer depicted).

superimposition of this transition-state anomeric effect on top of the conventional stabilizing secondary orbital interaction that provides the exceptional endo diastereoselection.[1] Any erosion of this endo diastereoselectivity with **2**−**19a** is derived from destabilizing steric interactions present in the endo transition state, which then result in a slower rate of reaction.
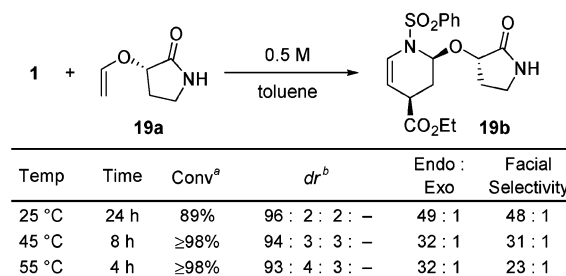
Houk has shown computationally and experimentally that vinyl ethers prefer to react in inverse electron demand Diels−Alder and 1,3-dipolar cycloadditions through an s-trans conformation (Figure 8, $\beta = 180°$), even though their ground-state conformation is typically s-cis ($\beta = 0°$).[27] Enlisting the s-trans conformation, the cycloadditions provide products consistent with reaction through a conformation in which α is approximately 60°, providing the transition state illustrated in Figure 8, with the dienophile H oriented toward the diene and with its large group oriented away from the diene. When the dienophile approaches the diene in this s-trans conformation, the chiral auxiliary comes into proximity of the sterically demanding and electronegative sp³ sulfonyl moiety, requiring that the sulfonyl phenyl group orient itself on the diene face opposite the approaching dienophile. This places the electronegative sulfonyl oxygens on the same diene face as the approaching dienophile, accounting for the observation that the electronegative ester, lactone, or lactam carbonyls of **14**−**19**, although sterically undemanding, are similarly directed away from the sulfonyl group and behave as the most effective $R_L$. Notably, the X-ray crystal structures of the cycloadducts,[18] albeit being ground-state structures of the reaction products, embody each of these features (Figure 8).

**Reaction Parameters.** A series of reaction parameters were examined to identify those that might significantly impact the cycloaddition. As anticipated, increasing the reaction temperature lowers the reaction diastereoselectivity. However, the *N*-sulfonyl-1-aza-1,3-butadienes typically possess an intrinsic reactivity that permits their use at 25 °C. Nonetheless, the reaction of **1** with **19a** was examined at a range of reaction temperatures, and both the endo selectivity and the facial diastereoselectivity of the cycloaddition diminished as the reaction temperature increased. However, the detected changes were very small and almost within the limits of error of the detection method (NMR) (Figure 9). The more sterically hindered pantalactone-derived dienophile **17a**, which reacts more slowly with **1**, exhibited a more discernible trend with varying reaction temperature. Thus, as the reaction temperature was increased to drive the sluggish reaction to completion, the endo diastereoselection dropped more significantly than the endo facial selectivity (Figure 9).

(27) Liu, J.; Niwayama, Y. Y.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064.

| Temp | Time | Conv[a] | dr[b] | Endo : Exo | Facial Selectivity |
|---|---|---|---|---|---|
| 25 °C | 42 h | 33% | 80 : 11 : 7 : 2 | 10 : 1 | 7 : 1 |
| 55 °C | 18 h | 85% | 78 : 11 : 9 : 2 | 8 : 1 | 7 : 1 |
| 85 °C | 15 h | 98% | 75 : 11 : 11 : 3 | 6 : 1 | 7 : 1 |
| 110 °C | 3 h | 94% | 74 : 12 : 12 : 3 | 6 : 1 | 6 : 1 |

[a] Based on ¹H NMR integrations of product C2-H versus diene C2-H.
[b] Based on ¹H NMR integration of product C2-H.



| Temp | Time | Conv[a] | dr[b] | Endo : Exo | Facial Selectivity |
|---|---|---|---|---|---|
| 25 °C | 24 h | 89% | 96 : 2 : 2 : − | 49 : 1 | 48 : 1 |
| 45 °C | 8 h | ≥98% | 94 : 3 : 3 : − | 32 : 1 | 31 : 1 |
| 55 °C | 4 h | ≥98% | 93 : 4 : 3 : − | 32 : 1 | 23 : 1 |

[a] Based on ¹H NMR integrations of product C2-H versus diene C2-H.
[b] Based on ¹H NMR integration of product C2-H.

**Figure 9.** Temperature dependence.



| Conc. **1** (M) | % Conversion | |
|---|---|---|
| | 1.5 equiv **19a** | 3 equiv **19a** |
| 0.05 | 14% | 32% |
| 0.1 | 23% | 44% |
| 0.5 | 63% | 89% |
| 1.0 | 80% | 98% |
| 2.0 | ≥98% | ≥98% (15 h) |
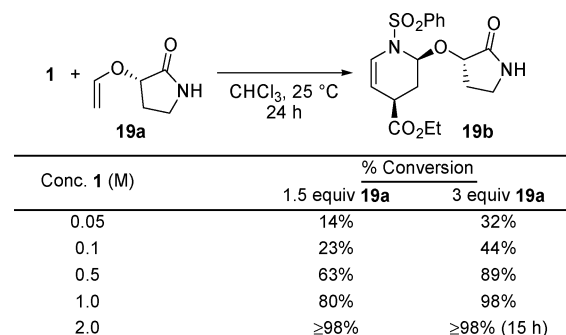
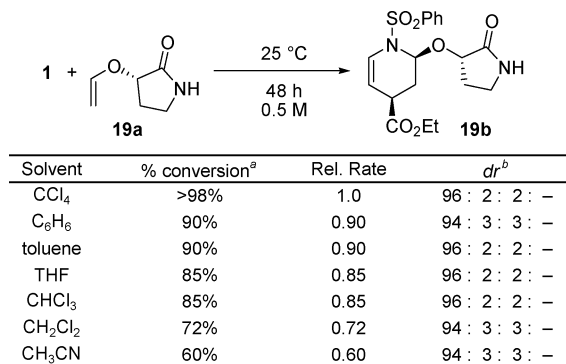[a] Based on ¹H NMR integrations of product C2-H versus diene C2-H.

**Figure 10.** Concentration dependence.

As anticipated, the reactions exhibit a pronounced dependence on the concentration, with satisfactory rates observed at 25 °C at reactant concentrations ≥0.5 M (Figure 10).

Consistent with expectations for a concerted [4+2] cycloaddition reaction, the rate of the reaction of diene **1** with dienophile **19a** as well as the diastereoselectivity exhibited little solvent dependency (Figure 11). In fact, slightly faster rates of reaction were observed as the solvent polarity decreased, not increased, consistent with little or no charge buildup in the transition state of the reaction. Moreover, the slight rate enhancement as the solvent polarity decreases is consistent with the nonpolar solvent enhancement of a preferential cycloaddition transition state involving the s-trans versus s-cis enol ether conformation.[27] Of all the solvents explored, CHCl₃ consistently provided the cleanest reactions, proceeding at good rates with outstanding diastereoselectivities, accommodating a range of substrate solubilities.

***N*-Sulfonyl Substituent: Impact on Reactivity and Diastereoselectivity.** Although the reactivity of the *N*-phenylsulfonyl azadiene **1** is excellent at 25 °C and its reaction diastereoselectivity with **19a** is outstanding, alternative sulfonyl substituents were examined in efforts to establish their impact and potential
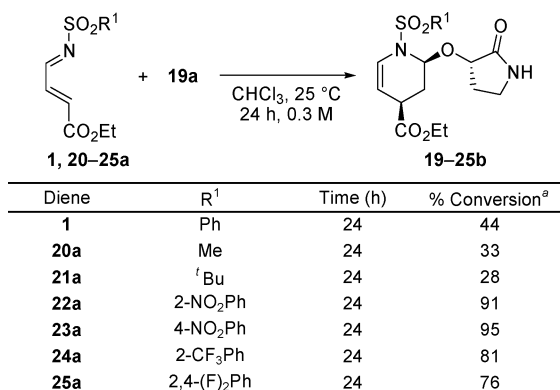
| Solvent | % conversion[a] | Rel. Rate | dr[b] |
|---------|----------------|-----------|-------|
| CCl₄ | >98% | 1.0 | 96 : 2 : 2 : – |
| C₆H₆ | 90% | 0.90 | 94 : 3 : 3 : – |
| toluene | 90% | 0.90 | 96 : 2 : 2 : – |
| THF | 85% | 0.85 | 96 : 2 : 2 : – |
| CHCl₃ | 85% | 0.85 | 96 : 2 : 2 : – |
| CH₂Cl₂ | 72% | 0.72 | 94 : 3 : 3 : – |
| CH₃CN | 60% | 0.60 | 94 : 3 : 3 : – |

[a] Based on ¹H NMR integrations of product C2-H versus diene C2-H.
[b] Based on ¹H NMR integration of product C2-H.

**Figure 11.** Solvent effects.



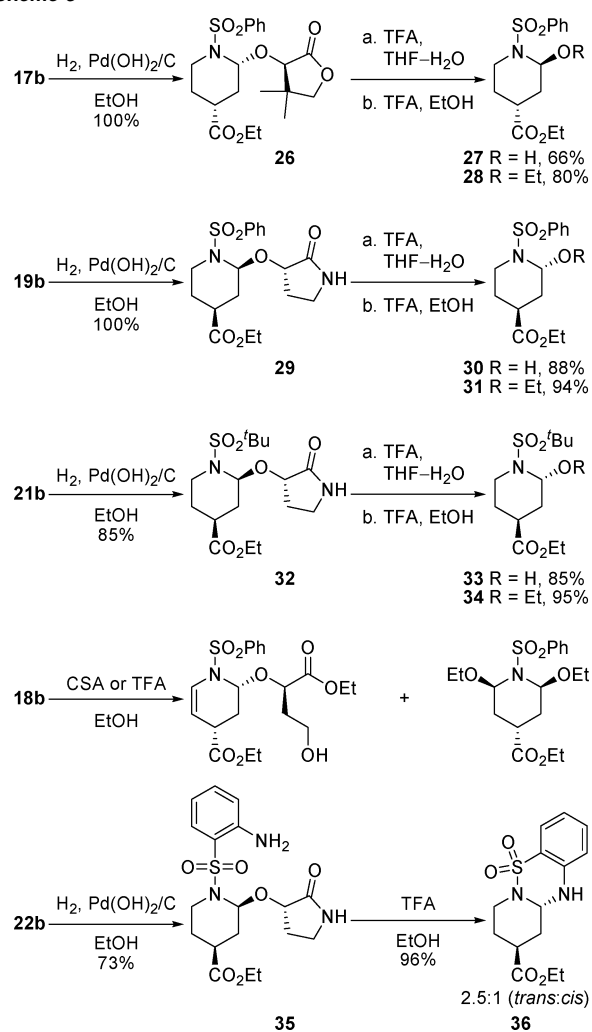| Diene | R¹ | Time (h) | % Conversion[a] |
|-------|-----|----------|-----------------|
| 1 | Ph | 24 | 44 |
| 20a | Me | 24 | 33 |
| 21a | ᵗBu | 24 | 28 |
| 22a | 2-NO₂Ph | 24 | 91 |
| 23a | 4-NO₂Ph | 24 | 95 |
| 24a | 2-CF₃Ph | 24 | 81 |
| 25a | 2,4-(F)₂Ph | 24 | 76 |

[a] Based on ¹H NMR integrations of product C2-H versus diene C2-H.

**Figure 12.** Sulfonyl substituent.

importance. Moreover, in addition to a predictable impact that their electron-withdrawing properties might have on reactivity or that their steric size might have on the facial diastereoselectivity, the additional methods available for their deprotective removal (e.g., **21a**/H⁺ or **22a** and **23a**/RS⁻)[28,29] further extend the scope of the *N*-sulfonyl-1-aza-1,3-butadiene Diels−Alder reactions. Thus, dienes **20−25a** were prepared by direct condensation of ethyl *trans*-4-oxo-2-butenoate with the corresponding sulfonamide (0.6 equiv of TiCl₄, 2.3 equiv of Et₃N, CH₂Cl₂, −15 to 0 °C, 60−85%), and their reaction with **19a** was compared alongside diene **1**. Represented in Figure 12 are conversions at a single time point under conditions that were suitable to distinguish among all seven dienes. Consistent with expectations, both **20a** and **21a**, bearing aliphatic sulfonyl substituents, were slightly less reactive than the phenylsulfonyl diene **1**. Notably, the reactivity and reaction diastereoselectivity (>20:1 endo:exo; >20:1 facial selectivity) of **20a** and **21a** were comparable, suggesting that the size of the sulfonyl substitutent has little impact on the reaction, consistent with the transition-state model (Figure 8). The addition of electron-withdrawing phenyl substituents (**22−25a**) predictably and significantly increases the diene reactivity. This smooth, predicable, and tunable reactivity of the substituted phenylsulfonyl derivatives allows the extension of these studies to 1-aza-1,3-butadienes that might possess an intrinsic lower reactivity. Each of the dienes exhibited a cycloaddition diastereoselectivity with **19a**

(28) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604.
(29) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

**Scheme 3**



that was not distinguishable from that of **1** (>20:1 endo, >20:1 facial selectivity).

**Cycloadduct Transformations.** Catalytic hydrogenation of the cycloadduct double bond, followed by acid-catalyzed (TFA) removal of the chiral auxiliary in the presence of water or an alcohol, cleanly provides the 2-alkoxy or 2-hydroxy derivatives, and this is illustrated in Scheme 3 with **17b**, **19b**, and **21b**. Limited attempts to remove (exchange) the auxiliary without prior reduction (or reaction) of the double bond led to preferential and additional alkoxy addition at C5, providing the 2,5-dialkoxy derivative. Unlike the lactam **19b**, reactions of the cycloadducts **17b** and **18b** bearing the lactone auxiliaries were often precluded by preferential ring-opening reactions of the reactive five-membered lactones, and this was more significant with **18b** than with **17b**. Finally, reduction of cycloadduct **22b** (H₂, Pd(OH)₂/C, EtOH), followed by acid treatment of the resulting amine, led to cyclization to the unique tricyclic heterocycle **36** in superb conversions.

**Dienophile *N*-Substitution.** With the emergence of **19a**, bearing a chiral cyclic amide auxiliary, as the most effective dienophile for use with the *N*-sulfonyl-1-azadienes, it became important to establish the role of the free NH of the secondary amide. Although comparison of **18a** (the corresponding lactone) with **19a** suggested little role for the amide free NH, the latter did exhibit a greater endo diastereoselectivity (49 vs 24:1) and

a significantly better endo facial selectivity (48 vs 18:1). Moreover, and on occasion, competitive dimerization addition of the amide NH of **19a** or its cycloadducts with the *N*-sulfonyl-1-aza-1,3-butadiene or dienophile enol ether was observed in the slower reactions when one of the reaction partners was enlisted in larger excesses at higher reaction concentrations or at increased reaction temperatures. As a consequence, we examined the corresponding *N*-methyl derivative **37a**, possessing a cyclic tertiary amide, as the chiral auxiliary which lacks the free NH of **19a**. Thus, *N*-methylation of **19a** (1.0 equiv of NaH, 1.5 equiv of MeI, THF, 25 °C, 8 h, 95%) cleanly provided **37a** ([α]$^{25}_D$ −49 (*c* 0.58, CHCl$_3$, >99% ee). Enol ether **37a** reacted with the prototypical *N*-sulfonyl-1-azabutadiene **1** to provide **37b**, with an endo diastereoeselectivity (49:1) and endo facial selectivity (48:1) that were indistinguishable from those of **19a** (Figure 13). Thus, the free NH of **19a** does not contribute to the diastereoselectivity of its cycloaddition reactions, and the behavior of **37a** along with the transition-state model in Figure 8 suggests that a wide range of amide substitutions might be accommodated. Moreover, **37a** proved much more soluble than **19a** in the more nonpolar solvents (toluene), where it exhibited a comparable or perhaps slightly enhanced reactivity, and, unlike **19a**, it is not susceptible to competitive dimerization reactions entailing reactions of the free NH.

## Conclusion

A systematic examination of the [4+2] cycloaddition of *N*-sulfonyl-1-aza-1,3-butadienes with enol ethers bearing chiral auxiliaries led to the delineation and optimization of factors that influence the facial selectivity of the Diels−Alder reaction while maintaining the intrinsically superb endo diastereoselectivity. The emerging transition-state model of the [4+2] cycloaddition (Figure 8) led to the examination of three readily available but previously unexplored auxiliaries (**18a**, **19a**, and **37a**) that
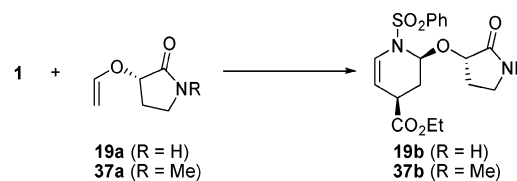


| Dienophile (equiv) | Solvent (M) | Temp. | Time | % conversion[a] (% yield) | dr[b] |
|---|---|---|---|---|---|
| **19a** (1.5) | CHCl$_3$ (1.0) | 23 °C | 48 h | 96 (80) | 96 : 2 : 2 : − |
| **37a** (1.5) | CHCl$_3$ (1.0) | 23 °C | 48 h | 95 (93) | 96 : 2 : 2 : − |
| **19a** (1.5) | CHCl$_3$ (0.5) | 23 °C | 48 h | 85 | 96 : 2 : 2 : − |
| **37a** (1.5) | CHCl$_3$ (0.5) | 23 °C | 48 h | 90 | 96 : 2 : 2 : − |
| **19a** (1.5) | toluene (0.5) | 23 °C | 48 h | 90 | 96 : 2 : 2 : − |
| **37a** (1.5) | toluene (0.5) | 23 °C | 48 h | 95 | 96 : 2 : 2 : − |
| **19a** (1.5) | toluene (0.5) | 75 °C | 3 h | >98 (51) | 90 : 4 : 6 : − |
| **37a** (1.5) | toluene (0.5) | 75 °C | 3 h | >98 (95) | 90 : 4 : 6 : − |

[a] Based on $^1$H NMR integrations of product C2-H versus diene C2-H.
[b] Based on $^1$H NMR integration of product C2-H.

***Figure 13.*** Dienophile *N*-substitution.

provided remarkable selectivities (for **19a** and **37a**, 49:1 endo and 48:1 facial diastereoselectivity) for an uncatalyzed Diels−Alder reaction that proceeds at room temperature. Additional uses of the new vinyl ether auxiliaries and applications of the azadiene Diels−Alder reaction are in progress and will be reported in due course.

**Supporting Information Available:** Full experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.