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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 enlisting a series of nineteen enol ethers bearing chiral auxilaries is reported 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 auxilaries (**18a**, **19a** and **37a**) rationally emerged from the studies and provide remarkable selectivities (for **19a** and **37a**: 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 4π 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 *α*,*β*-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 $LUMO_{diene}$-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 (≥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 one in which the nitrogen lone pair and the σ C–O bond of an enol ether dienophile lie trans periplanar to one another further benefiting from 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

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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 contrast and largely 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 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 diastereoselectivities 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 yet to be 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, eighteen 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 the minor exo adduct was observed as a dt (5.32 ppm, J = 1.8, 8.3 Hz) and both the structure as well as the relative and absolute stereochemistry 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

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the well-defined conformations of the endo (diaxial substituents) versus exo (axial –OR*, equatorial $–CO_2Et$) 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 did so at the expense of the rate of the reaction and with an erosion 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 being 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 (99%) with exceptional endo diastereoselectivity (24:1) and excellent facial selectivity (8–9:1), Figure 6.

The most interesting and useful series **14**–**19** began with an examination of enol ethers derived from α-hydroxy esters and lactones being inspired by the studies of Dujardin.[9] Thus, the mandelate-derived enol ether **14a** analogous 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). Like the preceding hindered enol ethers (e.g. **6a**), the reactivity of **17a** was modest and likely contributing 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 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 auxilaries (**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** deserve 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

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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 provided racemic product. Presumably, this arises through TMSOTf/Et_3N 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 $Hg(O_2CCF_3)_2$ in the presence of Et_3N 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**: $[\alpha]_D^{25}$ –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 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 a s-trans conformation (Figure 8, β = 180°) even though their ground state conformation is typically s-cis (β = 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 sp^3 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 being 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.

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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 a varied 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.

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 of 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 enhancements 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, $CHCl_3$ 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 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 $TiCl_4$, 2.3 equiv Et_3N, CH_2Cl_2, 15 to 0 °C, 60–85%) and their reaction with **19a** compared alongside diene **1**. Represented in Figure 12 are conversions at a single time point under conditions that were suitable to distinguish between 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 increase 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** that was not distinguishable from that of **1** (>20:1 endo, >20:1 facial selectivity).

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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 auxilary 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 auxilaries were often precluded by preferential ring opening reactions of the reactive five-membered lactones and this was more significant with **18b** versus **17b**. Finally, reduction of cycloadduct **22b** (H_2, $Pd(OH)_2$/C, EtOH) followed by acid treatment of the resulting amine led to cyclization to the unique tricyclic heterocycle **38** 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, the role of the free NH of the secondary amide became important to establish. Although the 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** ($[\alpha]_D 25 - 49$ (*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 was 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 in the more nonpolar solvents (toluene) than **19a** 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.

Conclusions

A systematic examination of the [4 + 2] cycloaddition of *N*-sulfonyl-1-aza-1,3-butadienes with enol ethers bearing chiral auxilaries 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 auxilaries (**18a**, **19a** and **37a**) that 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 auxilaries and applications of the azadiene Diels–Alder reaction are in progress and will be reported in due course.

Supplementary Material

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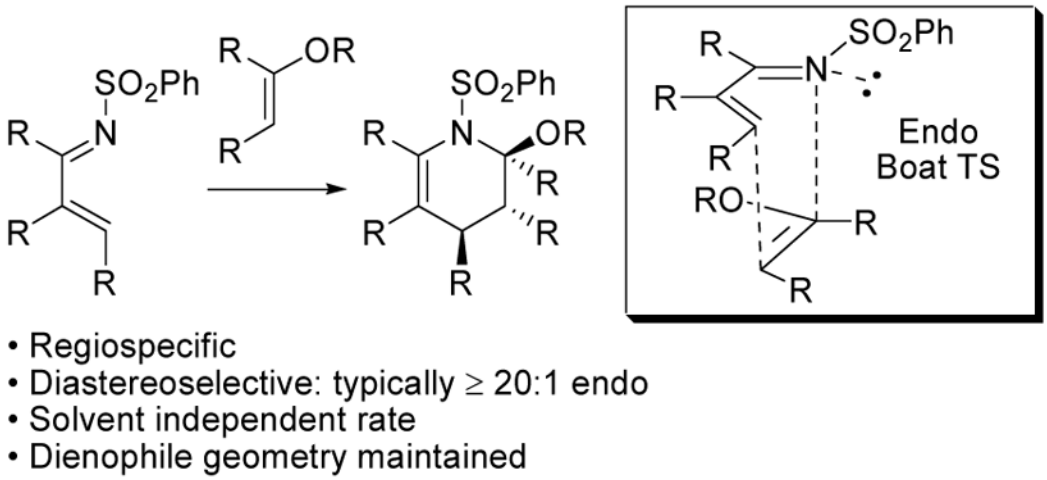

Figure 1 . N
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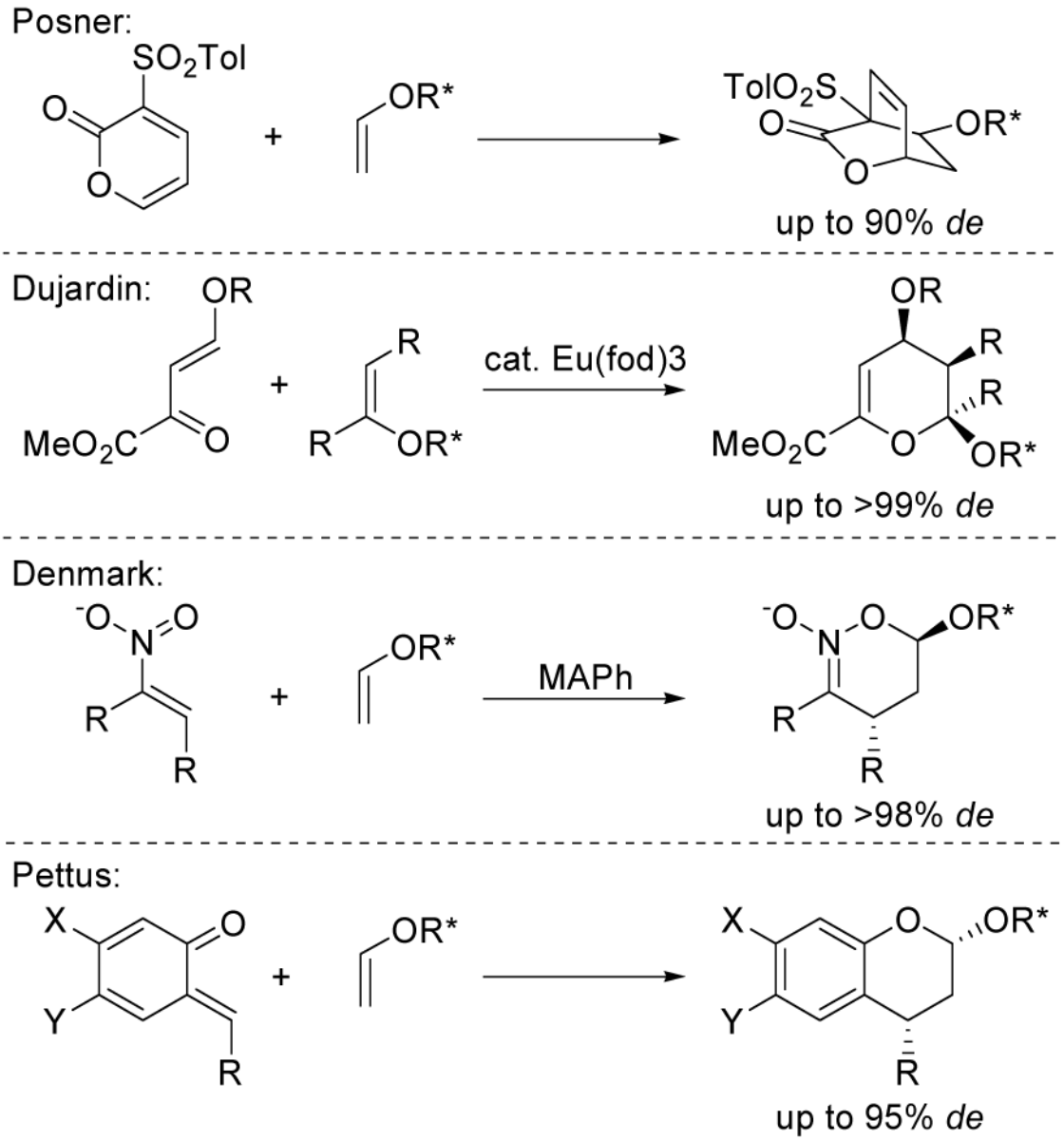

Figure 2.
Cycloadditions of optically active enol ethers.

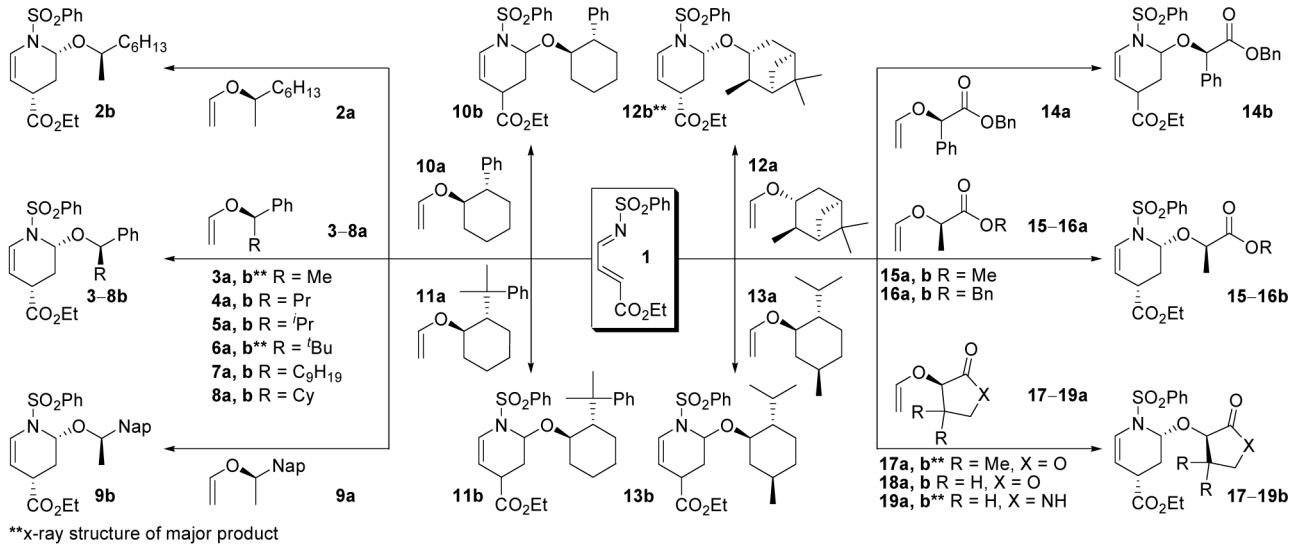

Figure 3.
Survey of optically active enol ethers.

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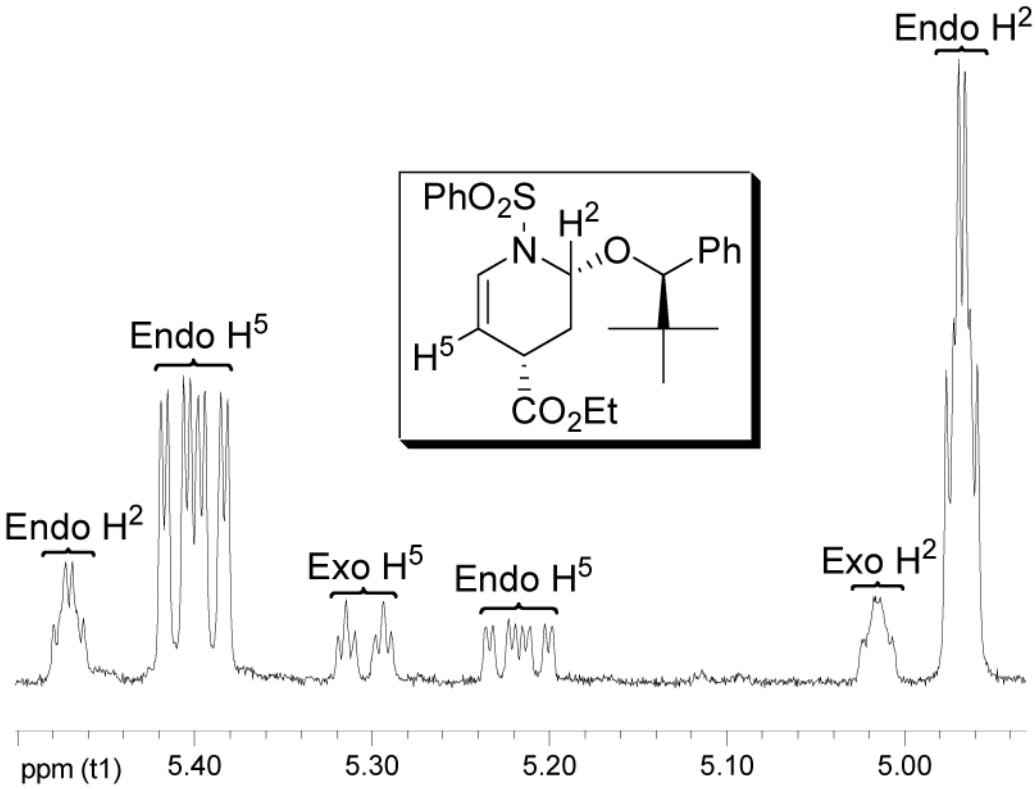

Figure 4.
Diagnostic cycloadduct 1H NMR signals.

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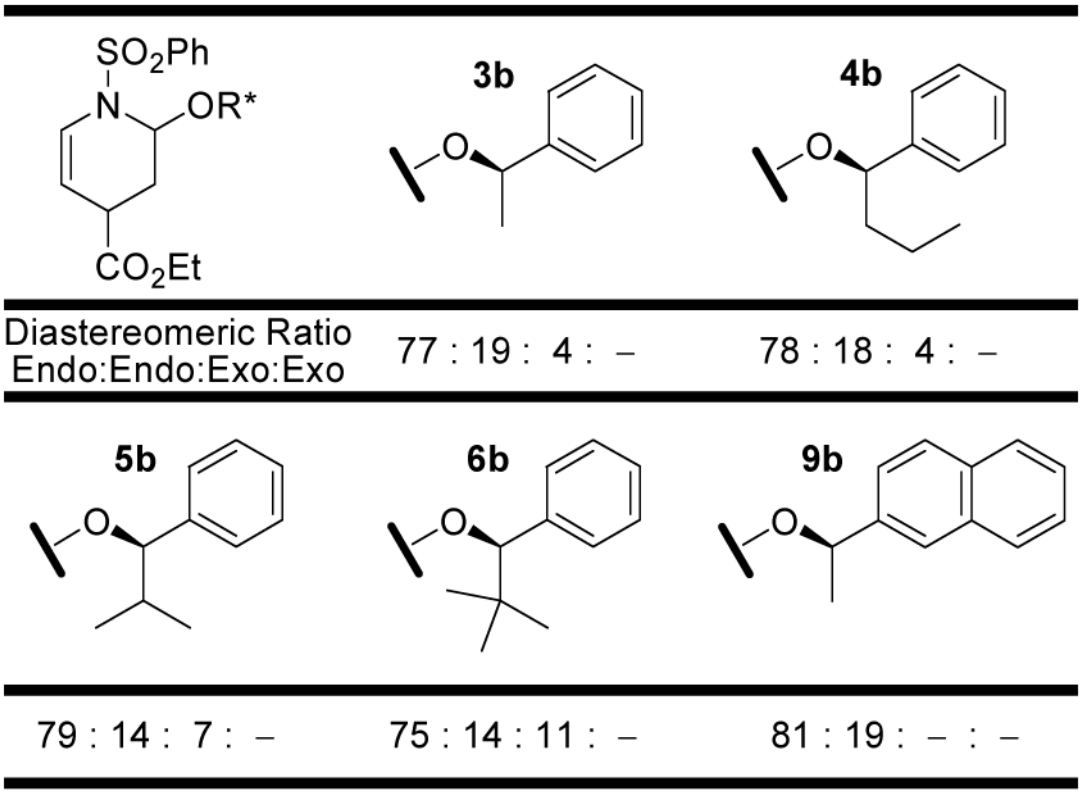

Figure 5.
Dienophile series **3–9.**

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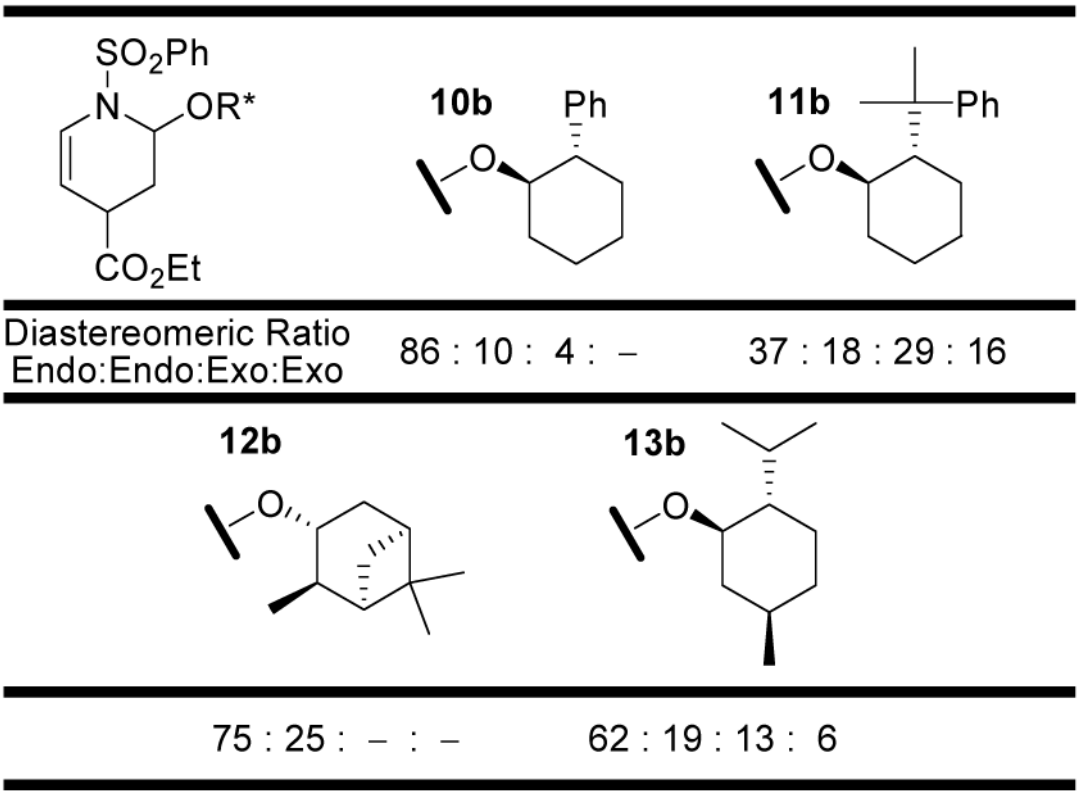

Figure 6.
Dienophile series **10–13.**

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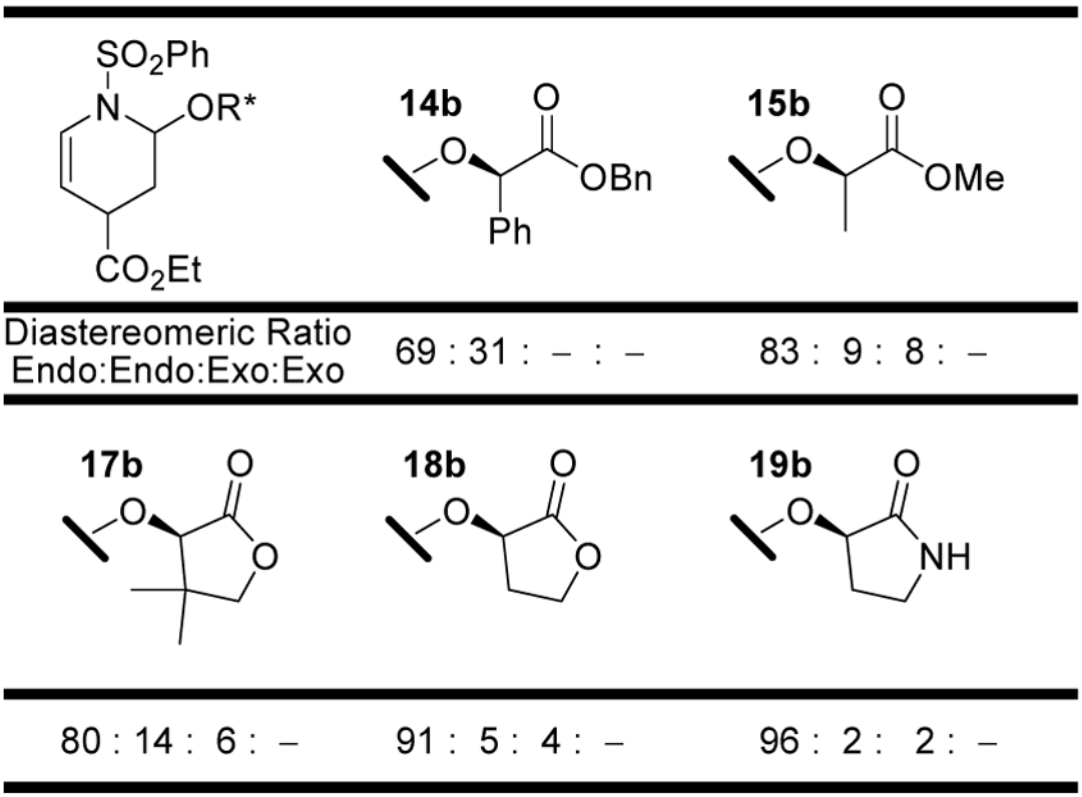

Figure 7.
Dienophile series **14–19.**

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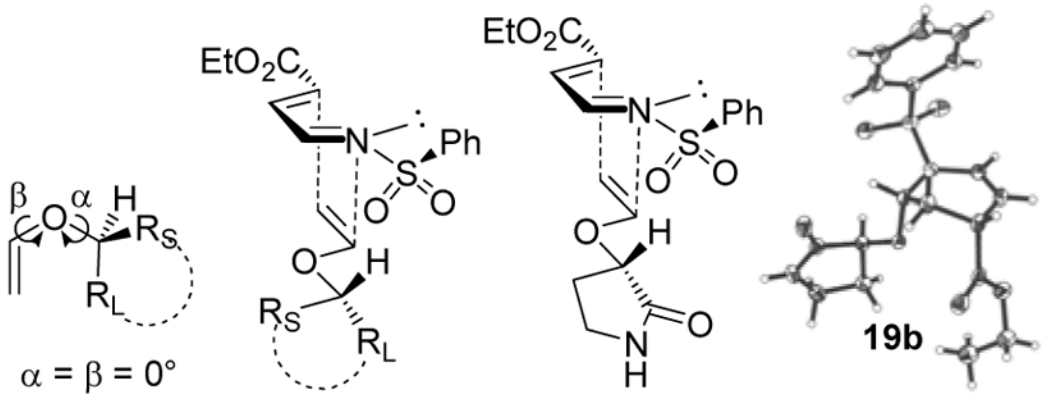
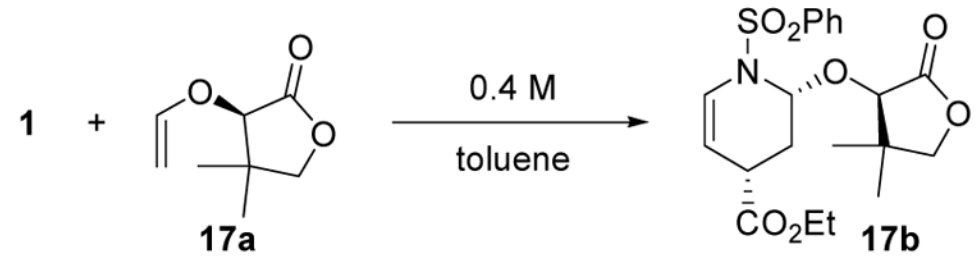
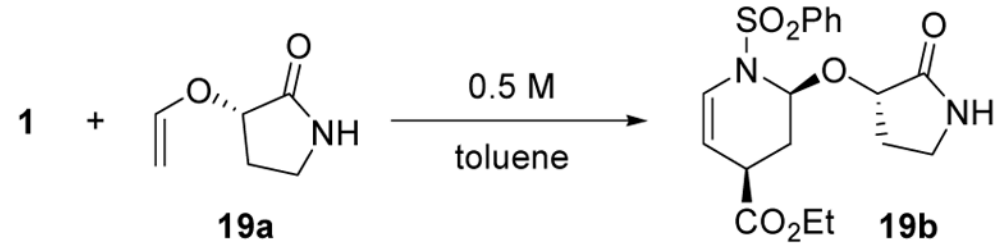


Figure 8.
Transition state model. (S-enantiomer depicted)



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

Figure 9.
Temperature Dependence.

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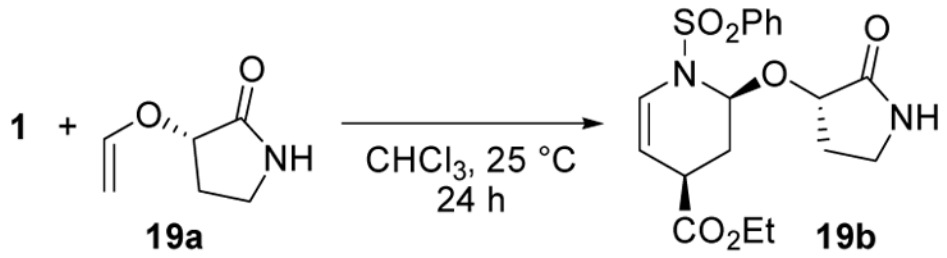

Conc. **1** (M)	% Conversion	
	1.5 equiv **19a**	3 equiv **19a**
0.05	14%	32%
0.1	23%	44%
0.5	63%	89%
1.0	80%	98%
2.0	≥98%	≥98% (15 h)

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

Figure 10.
Concentration Dependence.

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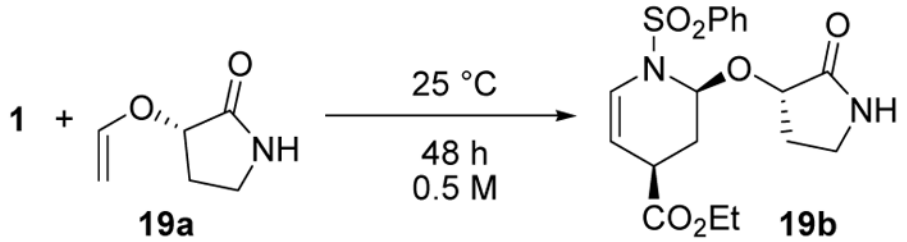

Solvent	% conversion[a]	Rel. Rate	*dr*[b]
CCl_4	>98%	1.0	96 : 2 : 2 : –
C_6H_6	90%	0.90	94 : 3 : 3 : –
toluene	90%	0.90	96 : 2 : 2 : –
THF	85%	0.85	96 : 2 : 2 : –
$CHCl_3$	85%	0.85	96 : 2 : 2 : –
CH_2Cl_2	72%	0.72	94 : 3 : 3 : –
CH_3CN	60%	0.60	94 : 3 : 3 : –

[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 11.
Solvent Effects.

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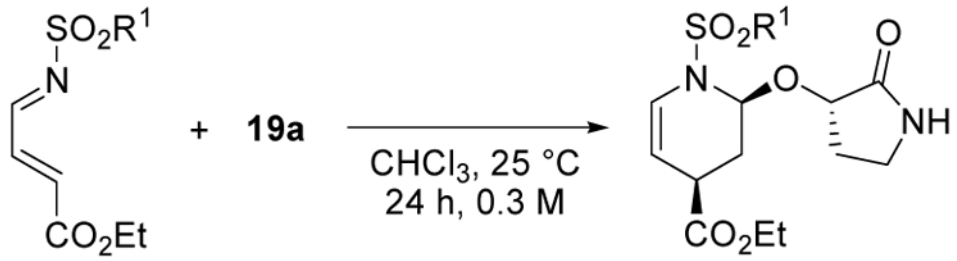

1, 20–25a **19–25b**

Diene	R^1	Time (h)	% Conversion[a]
1	Ph	24	44
20a	Me	24	33
21a	^{t}Bu	24	28
22a	2-NO_2Ph	24	91
23a	4-NO_2Ph	24	95
24a	2-CF_3Ph	24	81
25a	2,4-$(F)_2$Ph	24	76

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

Figure 12.
Sulfonyl Substituent.

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19a (R = H)
37a (R = Me)

19b (R = H)
37b (R = Me)

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.

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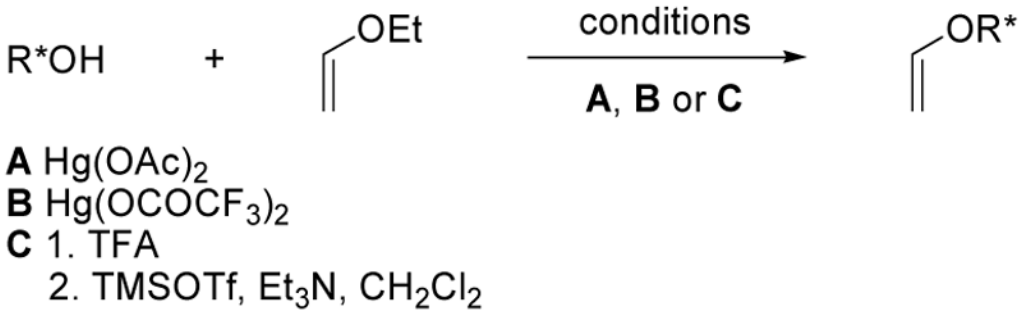

Scheme 1.

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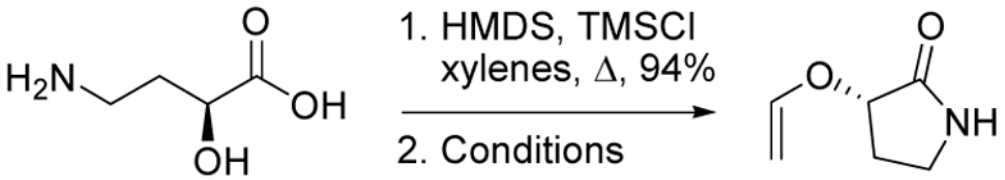

Conditions	Result
1.TFA, ethyl vinyl ether 2.TMSOTf, Et_3N, CH_2Cl_2	66%, racemized
$[Ir(cod)Cl]_2$, vinyl acetate, Na_2CO_3, toluene, 100 °C	No Desired Product
$Hg(OAc)_2$, ethyl vinyl ether	No Reaction
$Hg(OC(O)CF_3)_2$, Et_3N, ethyl vinyl ether	66% (>99% *ee*)

Scheme 2.

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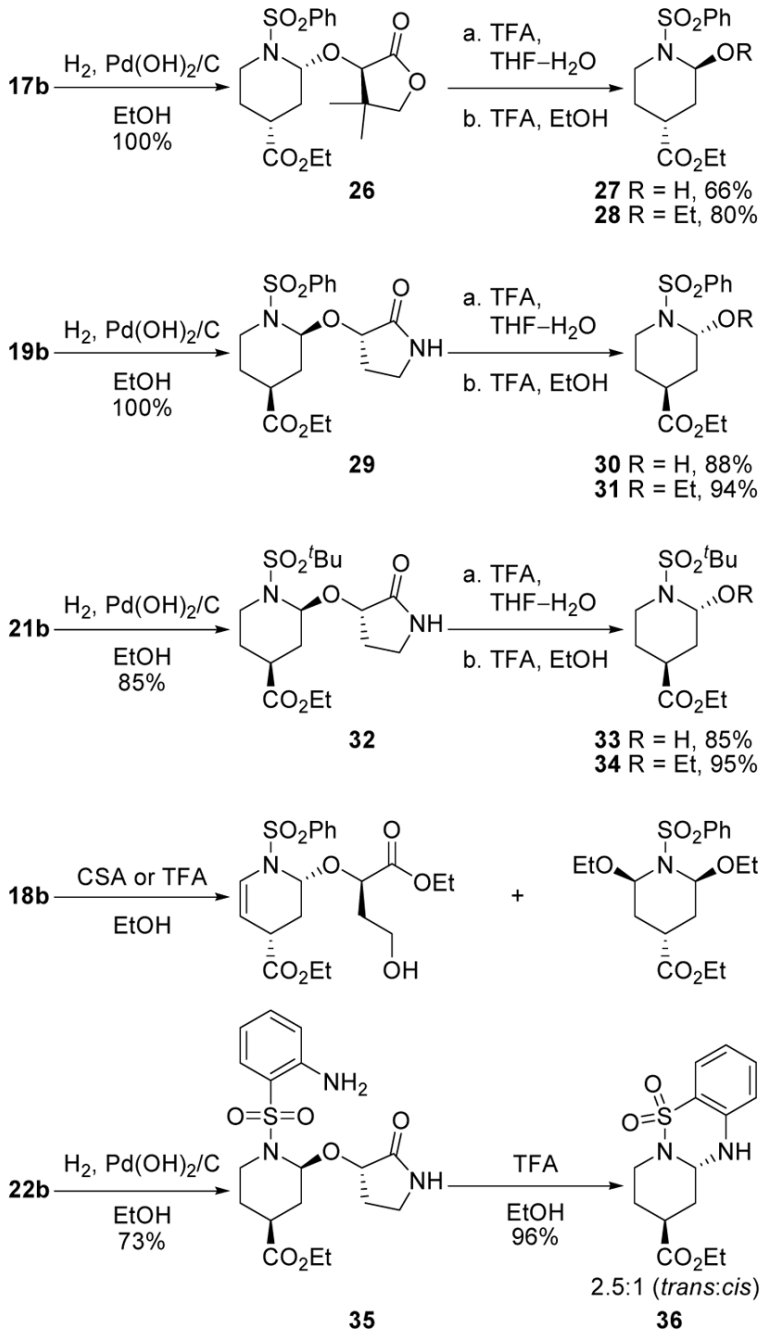

Scheme 3.

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Table 1

Results of Survey of Optically Active Enol Ethers

Dienophile	Time (h)	Major Adduct (% Conversion)[a]	Total Conv (%)	Ratio of Diastereomers[b]			Endo : Exo	Endo Facial Selectivity
				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	—

Reactions performed at RT, 0.3 M with respect to diene in toluene.

[a]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 based on ^{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 $CHCl_3$ as solvent, 1 M with respect to diene.

[e]Yield from reference [1c].