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A Journal of ChemPubSoc Europe

# Accepted Article

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**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.201801009

**Link to VoR:** http://dx.doi.org/10.1002/ejoc.201801009

**Supported by** ACES Asian Chemical Editorial Society

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10.1002/ejoc.201801009


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# Diazepane Carboxylates as Organocatalysts in the Diels-Alder Reaction of α-Substituted Enals

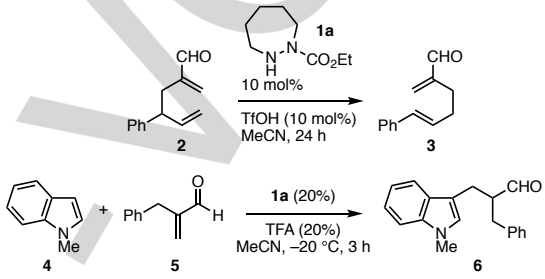
Nicklas O. Häggman, Benjamin Zank, HyunJune Jun, Dainis Kaldre and James L. Gleason*[a]

**Abstract:** Ethyl diazepane carboxylate efficiently catalyzes the Diels-Alder cycloaddition of α-substituted-α,β-unsaturated aldehydes via iminium ion organocatalysis. The reaction is applicable to a range of dienes and dienophiles and generally proceeds at room temperature in the presence of 5 mol% catalyst and 2.5 mol% triflic acid co-catalyst. The incorporation of a stereogenic center on the diazepane backbone in combination with a menthyl carbamate produces a catalyst which affords enantioselectivities of 70-95% ee for the cycloaddition of cyclopentadiene with a range of dienophiles. The enantioselectivity is rationalized via a transition state in which electrostatic stabilization by the carboxylate directs the diene to the more hindered face of the dienophile.

The Diels-Alder cycloaddition is one of the most fundamental reactions in organic synthesis. The ability to unite two fragments and set up to four stereocenters in a fully atom-economical process makes it a powerful synthetic transformation. The prevalence of six-membered rings in natural products has resulted in its employment in countless total syntheses.[1] Given its high synthetic utility, the Diels-Alder reaction is among the most well studied in the area of asymmetric catalysis.[2] Recent work has mainly focused on organocatalytic methods, including both iminium catalysis and chiral Brønsted acid catalysis.[3] In the former class, seminal work by MacMillan showed that imidazolidinones could catalyze the cycloadditions of α,β-unsaturated aldehydes and ketone dienophiles with high enantioselectivity.[4]

A significant challenge in the organocatalytic Diels-Alder, and in iminium ion catalysis of enals in general, are substrates bearing α-substitution. [5] While simple enals such as acrolein or cinnamaldehyde are excellent substrates with most catalysts, significant A-1,3 strain in the iminium ions formed from secondary amines and α-substituted enals severely limits their formation. In the context of the Diels-Alder reaction, only a single example of chiral secondary amine catalysis of an α-substituted enal, using the Jørgensen/Hayashi prolinol catalyst, has been reported.[6] Examples of secondary amine catalysis are likewise limited in other functionalizations of α-substituted enals.[7] The most common solution to this low reactivity is the employment of primary amine catalysts, as these relieve A-1,3 strain.[8]

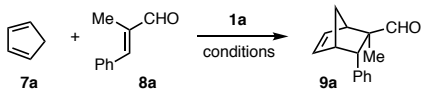
In the course of developing an organocatalytic Cope rearrangement, we identified ethyl diazepane carboxylate **1a** as a highly effective catalyst with the unusual ability to form iminium ions from α-substituted enals, including substrates bearing quaternary centers at the alpha position (Scheme 1).[9] We subsequently found that **1a** was also effective in catalyzing the Michael addition of indoles and other electron rich aromatics to α-substituted enals.[10] Both cyclic and acyclic hydrazides have been previously developed as catalysts for the Diels-Alder reaction of simple α-unsubstituted enals.[11] In this Communication, we show that **1a** is an outstanding catalyst for the Diels-Alder reaction of the more challenging α-substituted enals.[12] Moreover, we show that development of highly enantioselective catalysts is possible and relies on weak electrostatic interactions to induce asymmetry.




**Scheme 1.** Organocatalytic Cope and Michael addition of α-substituted enals using ethyl diazepane carboxylate (**1**).

We began our study by screening the effects of catalyst **1a** in the Diels-Alder addition of cyclopentadiene to α-methylcinnamaldehyde. This dienophile is very unreactive, with only one example its use in a Diels-Alder, with 2,3-dimethylbutadiene, occurring in low yield under forcing conditions.[13] Employing 50 mol% of **1a** as catalyst with an equivalent amount of HCl as co-catalyst in $CD_3CN$ at room temperature for 24 h resulted in only low conversion (13%) to the cycloadduct as judged by $^1H$ NMR (Table 1). As observed in our Cope rearrangement chemistry, the reaction was significantly faster with triflic acid as co-catalyst, providing >95%

**Table 1.** Screening of catalyst **1a** in the Diels-Alder Cycloaddition of cyclopentadiene with α-methylcinnamaldehyde.




| Catalyst Loading | Acid co-catalyst (mol%) | Solvent | Conversion[a] | Exo/Endo |
|---|---|---|---|---|
| 50% | HCl (50%) | $CD_3CN$ | 13% | n.d. |
| 50% | TfOH (50%) | $CD_3CN$ | >95% | 16:1 |
| 20% | TfOH (10%) | $CD_3CN$ | 81% | 17:1 |
| 5% | TfOH (2.5%) | $CD_3CN$ | 76% | 13:1 |
| **5%** | **TfOH (2.5%)** | **$CD_3NO_2$** | **>95% (92%)[b]** | **14:1** |
| 5% | TfOH (2.5%) | $CD_3OD$ | 18% | n.d. |
| 5% | TfOH (2.5%) | $CDCl_3$ | 20% | n.d. |
| 5% | TfOH (2.5%) | toluene-$d_8$ | - | N.A |

[a] Conversion measured by $^1H$ NMR. [b] Isolated yield.

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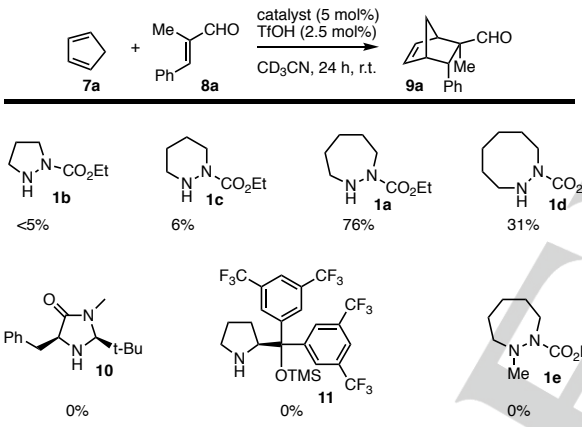
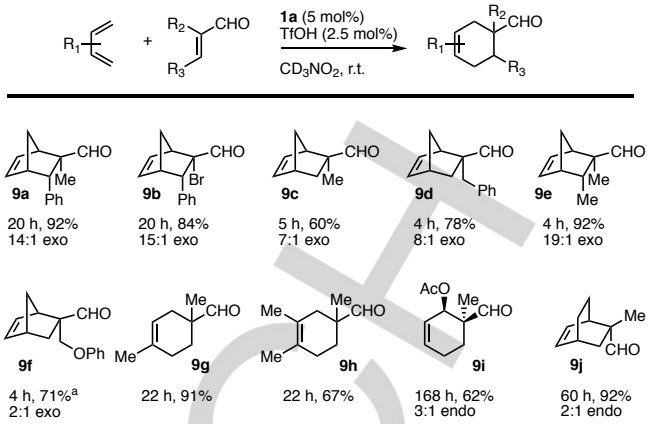
conversion to the cycloadduct as a 16:1 ratio of exo to endo isomers. The loading of the catalyst could be lowered to as little as 5%, with 2.5% TfOH, although this resulted in moderately attenuated conversion. Advantageously, we found that switching solvent to $d_3$-nitromethane re-established high conversion rates and allowed **9a** to be isolated in 92% yield. Other solvents such as $CD_3OD$ or $CDCl_3$ were not as effective as reactions in either acetonitrile or nitromethane.

We compared catalyst **1a** with its homologues in the cycloaddition of **7a** + **8a** in $CD_3CN$ and found, as previously, that seven-membered ring catalyst **1a** was more efficient than the five- (**1b**) and six-membered ring (**1c**) catalysts (Scheme 2). We also assessed eight-membered ring catalyst **1d** and found that it was not as effective as **1a**, in contrast to results in the Cope rearrangement where **1d** was more efficient. Known secondary amine catalysts such as MacMillan's imidazolidinone **10**[14] and Jorgensen/Hayashi catalyst **11**[6, 15] were unreactive with **8a** under our reaction conditions, highlighting the exceptional reactivity of **1a**. Finally, **1e,** the N-methylated analog of **1a**, also failed to catalyze the reaction, supporting an iminium-catalyzed reaction mechanism instead of proton catalysis.




**Scheme 2.** Comparison of organocatalysts in the Diels-Alder Cycloaddition of cyclopentadiene with α-methylcinnamaldehyde.

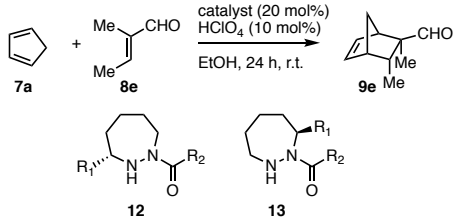
With an optimized set of conditions in hand, we examined the scope of catalyst **1a** with a range of dienophiles and dienes (Scheme 3). In reactions with cyclopentadiene, we found that α-bromocinnamaldehyde was similarly reactive to α-methylcinnamaldehyde. The reaction was complete within 20 h and the product **9b** could be isolated in 84% yield as a 15:1 exo/endo mixture. Dienophiles lacking the β-phenyl group were significantly more reactive. The reaction with methacrolein was complete within 5 h and the adduct **9c** was isolated in 60% yield as a 7:1 exo/endo mixture. Other dienophiles such as α-benzylacrolein, tiglic aldehyde and α-benzyloxyacrolein were similarly reactive, with reactions complete within 4 h and cycloadducts **9d-f** being isolated in excellent yields. Surveying other dienes, we found that cycloadditions between methacrolein and simple acyclic alkenes such as isoprene or 2,3-dimethylbutadiene were complete within 22 h, affording cycloadducts **9g** and **9h** in 91% and 67% yield. Other less reactive dienes such as cyclohexadiene or 1-acetoxybutadiene required longer reaction times, but proceeded in good to excellent yields. In contrast to reactions with cyclopentadiene, these latter examples were slightly endo selective.




**Scheme 3.** Diels-Alder scope with catalyst **1a**. a) reaction conducted in EtOH, using $HClO_4$ as acid co-catalyst.

The excellent reactivity of **1a** suggested its possible use as a scaffold for chiral catalyst development. In the Cope rearrangement, we briefly examined C3 and C7-substituted catalysts **12a** and **13a** and noted the surprising finding that the latter afforded higher enantioselectivity even though the stereogenic center was not next to the position of iminium ion formation.[9] We assessed **12a** and **13a** and their derivatives in the cycloaddition of cyclopentadiene with tiglic aldehyde. While reactions in nitromethane were poorly selective, we observed that reactions in ethanol afforded **9e** in 57% and 39% ee using **12a** and **13a**, respectively (Table 2).[16-18] Notably, **12a** was more effective, in contrast to the results in the Cope rearrangement. Intriguingly, we observed only small changes in ee upon

**Table 2.** Screening of chiral catalysts in the Diels-Alder Cycloaddition of cyclopentadiene with α-methylcinnamaldehyde. [a]



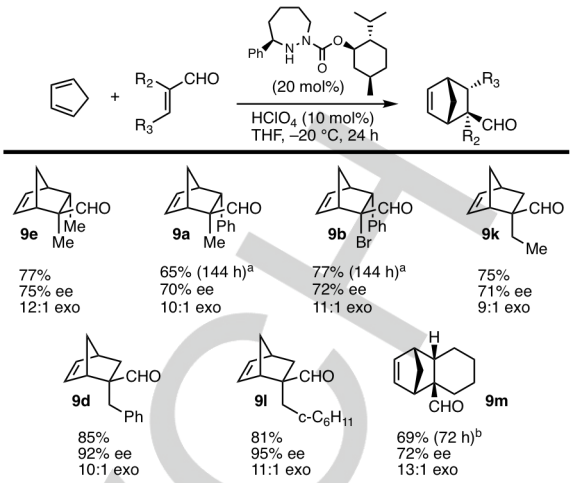

| Catalyst | $R_1$ | $R_2$ | ee (exo)[b] | exo/endo |
|---|---|---|---|---|
| **12a** | Ph | OEt | 57% | 8:1 |
| **13a** | Ph | OEt | 39% | 19:1 |
| **ent-12b** | $CH_2OH$ | OEt | -51% | 19:1 |
| **ent-12c** | Np | OEt | -40% | 10:1 |
| **12d** | Ph | OBn | 62% | 9:1 |
| **12e** | Ph | NHBn | 20% | 18:1 |
| **12f** | Ph | Ph | -5%[c] | 13:1 |
| **12g** | Ph | tBu | -43%[c] | 19:1 |
| **12h** | H | *O*-(–)-menthyl | 15% | 11:1 |
| **12i** | H | *O*-(*S*)-2-PhEt | 11% | 12:1 |
| **12i** | Ph | *O*-(–)-menthyl | 71% | 8:1 |
| **12k** | Ph | *O*-(+)-menthyl | 46% | 8:1 |

[a] All reactions proceeded to >90% conversion. [b] Product ee's are adjusted for the ee of the catalysts, which were typically 90-95%. [c] Negative ee values indicate the enantiomer of **9e** was the major product.

modification of the group adjacent to the secondary amine, with small groups like hydroxymethyl (e.g. ent-**12b**) and larger groups such as naphthyl (ent-**12c**) affording only minor changes in enantioselectivity. In contrast, more significant changes were observed upon modification of the electron withdrawing group. While a Cbz group (**12d**) slightly increased the ee to 62%, changing to a benzyl urea (**12e**) dropped the ee significantly. Intriguingly, the presence of benzoyl (**12f**) and pivaloyl (**12g**) groups inverted the sense of enantioinduction even though the configuration of the stereogenic center remained constant.

Given the significant impact of the electron withdrawing group on the ee of the reaction, we explored the use of chiral carbamates. Very modest selectivity was observed for menthyl (**12h**, 15% ee), and phenethyl (**12i**, 11% ee) carbamates. However, we found that the combination of a menthyl carbamate with a C3 phenyl group displayed classical matched/mismatched behaviour. [19] Catalyst **12j** bearing a (–)-menthyl group produced the cycloadduct in 71% ee while the (+)-menthyl carbamate (**12k**) resulted in 46% ee, in both cases in 8:1 exo/endo diastereoselectivity. Moreover, reaction at –20 °C in THF with **ent-12j** proceeded in only 24 h to afford a 77% isolated yield and further improved the selectivity to 75% ee and 12:1 exo/endo (Scheme 4).

Catalyst ent-**12j** displayed good to excellent reactivity and enantioselectivity for reaction of cyclopentadiene with a number of dienophiles.[20] α-Methylcinnamaldehyde and α-bromocinnamaldehyde required longer reaction times (144 h) but afforded cycloadducts **9a** and **9b** in good yields and 70-72% ee. More impressively, α-benzylacrolein and α-cyclohexylmethylacrolein both displayed higher reactivity and outstanding enantioselectivity, affording **9d** and **9l** in 92 and 95% ee, respectively.




**Scheme 4.** Enantioselective organocatalytic Diels-Alder reaction of α-substituted enals with cyclopentadiene. a) Reactions run in $CH_3CN$. b) Reaction run in EtOH.

The diazepane carboxylate is a new platform for asymmetric catalysis and we sought to understand the origins of stereoinduction, including the significant influence of the electron withdrawing group. We conducted a DFT study using the methyl carbamate analogue of **12a** at the M06-2X/6-311+G**//M06-2X/6-311G* level. The most stable conformation of the iminium ion formed with methacrolein possessed the s-*trans*-(*Z*)-iminium geometry[21] with the phenyl group anchoring the diazepane in an equatorial position and with the carbamate positioned

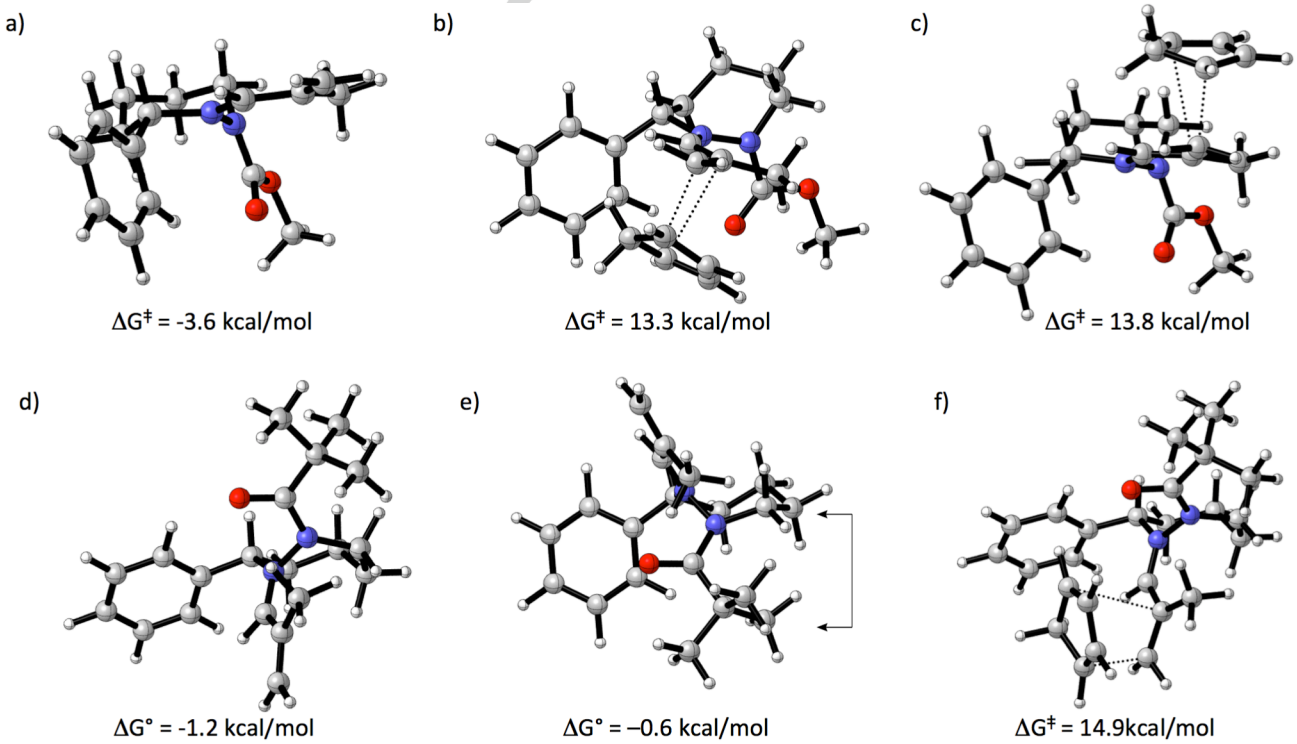



**Figure 1.** DFT modelling at the M06-2X/6-311+G**//M06-2X/6-311G* level, including SMD solvation model for EtOH. a) The most stable conformations of the iminium ion of the methyl carbamate analog of **12a** with methacrolein. b,c) Favoured and disfavoured transition states for reaction the iminium ion of the carbamate with cyclopentadiene. d,e) Favoured and disfavoured conformations of the iminium ion of pivalamide **12g**. f) Favoured transition state for cycloaddition of the iminium ion of pivalamide **12g** with cyclopentadiene. All energies are relative to starting materials (cyclopentadiene, methacrolein and protonated catalyst).

pseudo-axial in order to relieve A-1,3 strain with the adjacent iminium (Fig 1a). Notably, the (*Z*)-geometry of the iminium places it proximal to the carbamate, consistent with the significant influence of this group. A full conformational search of potential transition states identified the lowest energy pathway proceeding by approach of cyclopentadiene on the more hindered face most stable iminium, proximal to the carboxyl group (Fig 1b). This approach was favoured by 0.5 kcal/mol over attack from the less hindered top face (Fig 1c). The transition states are asynchronous with buildup of positive charge on the diene. The dipole moment for the preferred transition state is significantly lower (6.9 D vs. 9.0 D for Fig 1b vs. 1c) suggesting that there may be an electrostatic stabilization by the carbamate group that favours the more hindered approach.

The pivalamide **12g** displayed opposite facial selectivity to the carbamates. The DFT calculations indicate that in the iminium ion of **12g**, the phenyl group again anchors the ring in an equatorial position. However, a twist about the N-N bond occurs to minimize interaction of the *tert*-butyl group with the diazepane ring (Fig 1d,e). The lowest energy transition state again (Fig 1f) favours approach of cyclopentadiene proximal to the carbonyl group, now on the diastereotopic face of the iminium, resulting in the formation of the opposite enantiomer.[22]

In conclusion, we have shown that diazepane carboxylates are exceedingly reactive catalysts in the Diels-Alder cycloaddition of $\alpha$-substituted enals, with reactions proceeding rapidly using low catalyst loadings for achiral catalyst **1a**. Moreover, incorporation of a stereogenic center in combination with a menthyl carbamate results in a catalyst which retains good reactivity and affords cycloadducts in good to excellent enantioselectivities. DFT calculations suggest that facial selectivity of the reaction arises via an electrostatic stabilization from the carbamate group. Overall, these results suggest that diazepane carboxylates may be a viable platform for a variety of organocatalytic transformations.

## Acknowledgements

The authors thank the Natural Science and Engineering Research Council of Canada for funding of this research.

**Keywords:** organocatalysis, Diels-Alder, hydrazide, electrostatic interactions, A-1,3 strain

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[16] While the reaction of 8a was slow in alcoholic solvents, tiglic aldehyde is sufficiently reactive to permit the use of ethanol as a solvent.

[17] Other solvents such as THF and isopropanol afforded similar ee's.

[18] The absolute stereochemistry of **9e** was established by reduction to the alcohol, and comparison of the corresponding Mosher's ester with literature values. See Supporting Information for details. The absolute configurations of other cycloadducts were assigned by analogy.

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[20] The less reactive diene isoprene afforded lower ee's with a-benzylacrolein and methacrolein (49% and 55% ee, respectively)

[21] The s-trans is preferred over s-cis by 2.8 kcal/mol while the (E)-iminium geometry is disfavoured by 4.5 kcal/mmol. An alternative conformation where a twist along the N-N bond axis places the iminium is below the carbonyl group is 0.9 kcal/mol less stable. See Supporting Information.

[22] Unlike the carbamate where the minor enantiomer arises from attack of cyclopentadiene opposite to the carbonyl, the transition state leading to the minor enantiomer with 12g results from attack of cyclopentadiene on the minor conformer of the iminium ion (Figure 1e), syn to the carbonyl group (see Supporting Information for structure)

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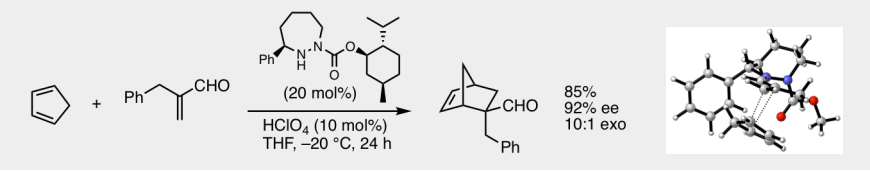


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**Diazepane Carboxylates as Organocatalysts in the Diels-Alder Reaction of α-Substituted Enals**

Diazepane carboxylates efficiently catalyze the Diels-Alder cycloaddition of α-substituted enals with a range of dienes. With chiral diazepane backbones, weak electrostatic interactions favour diene approach from the more hindered face, leading to enantioselectivities of 70-95% with a range of dienophiles.