Racemic and Asymmetric Diels−Alder Reactions of 1-(2-Oxazolidinon-3-yl)-3-siloxy-1,3-butadienes

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Achiral and chiral 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes were prepared from readily available starting materials. Although more stable than the parent 1-amino-3-siloxy dienes, the 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes are still very reactive in Diels−Alder reactions, somewhat more than 1,3-dialkoxy-1,3-butadienes (e.g., Danishefsky's diene). The cycloadditions of the achiral and chiral dienes with several different dienophiles were examined. The reactions proceeded in good yield, with modest to high endo selectivity. The chiral dienes exhibited excellent facial selectivity in cycloadditions with α-substituted acroleins, maleic anhydride and *N*-phenylmaleimide. Upon reduction and hydrolysis of the cycloadducts, substituted cyclohexenones were obtained with ee's ranging from 22% to >98%.

Introduction

The Diels−Alder reaction continues to play a central role in complex molecule synthesis.[1] The importance of this cycloaddition stems from its remarkable selectivity profile: Many of these reactions proceed with high regio-, endo-, and facial selectivities, so as to produce, in a single step, six-membered ring products with up to four chiral centers. The versatility of the Diels−Alder reaction has increased with the advent of new, heteroatom-substituted dienes, which not only are more reactive but also give highly functionalized, useful products.[2] Finally, asymmetric variants have made the Diels−Alder reaction all the more important, enabling the synthesis of complex products in enantiomerically enriched form.[3−6] We describe here the results of an extensive study on the synthesis and Diels−Alder reactivity of achiral and chiral 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes. Such dienes are easy to prepare, are stable, and readily undergo Diels−Alder reactions to afford, for the chiral versions, products with as high as ≥98% ee.

We recently reported on the preparation and Diels−Alder reactivity of 1-amino-3-siloxy-1,3-butadienes (**2**). These dienes are easily prepared from vinylogous amides (**1**) and exhibit extraordinary reactivity and versatility in [4 + 2] cycloadditions (Scheme 1).[7−9] This methodology was incorporated into a new strategy to *Aspidosperma* alkaloids, culminating in the synthesis of (±)-tabersonine.[10] In an effort to expand the utility of amino siloxy dienes, we explored chirally modified versions of these dienes. Specifically, we found that the cycloaddition of a diene possessing the C_2-symmetric *trans*-2,5-diphenylpyrrolidine unit (**4**) proceeded with remarkably high diastereofacial selectivity with several different dienophiles and yielded, after eliminative workup, a variety of substituted cyclohexenones with 88% to >98% ee.[11,12] The advantage of C_2 symmetry in the amine was that the same steric environment was maintained near the diene, regardless of rotation of the auxiliary about the nitrogen−carbon bond. Although this chemistry represented one of the most direct and general methods for

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(12) Two preparative procedures have been accepted for publication in *Organic Syntheses*, one for the synthesis of amino siloxy diene **2** (R = Me) and the other for the use of this diene in a Diels−Alder reaction: Kozmin, S. A.; He, S.; Rawal, V. H. *Org. Synth.* **2000**, *78*, in press.

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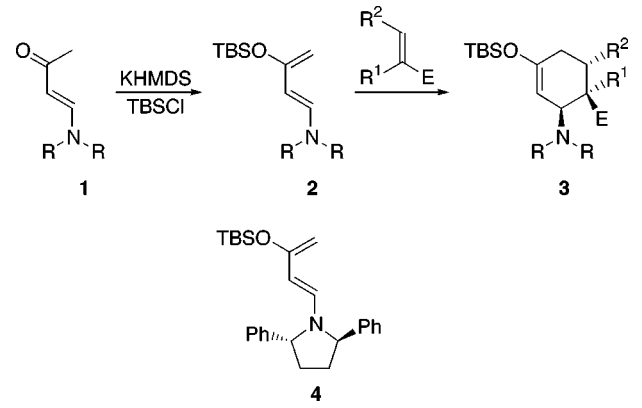
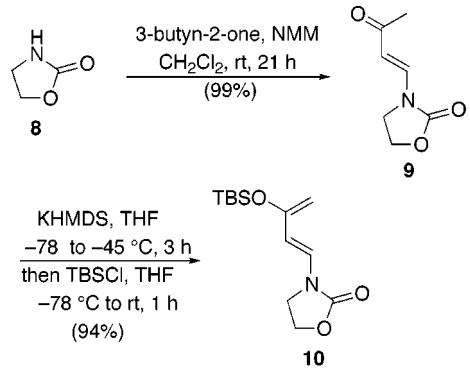
Scheme 1

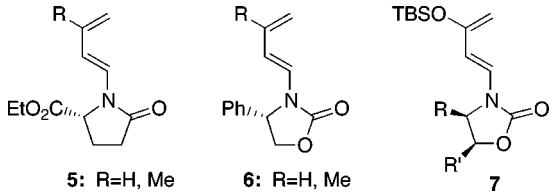


Scheme 2



the preparation of enantiomerically enriched 4- and 4,5-disubstituted cyclohexenones, it suffered from the inconvenience associated with the preparation of the required auxiliary.

Among other readily available auxiliaries for our amino siloxy dienes,[13,14] the amide or carbamate linkage on the diene was attractive since such dienes have been found to afford high endo selectivity with several dienophiles.[14a,f,15,16] The carbonyl group on the amide nitrogen was expected to preferentially adopt the anti conformation, away from the dienyl moiety. The alkyl group on the amide would then occupy the position proximal to the diene, such that a chiral element on the alkyl group would block one face of the diene. This approach was first demonstrated by Smith and co-workers through diene **5**, which showed excellent diastereoselectivity in some Diels−Alder reactions.[14a] Subsequently, Stevenson et al. reported oxazolidinone containing dienes **6**, which underwent cycloadditions with *N*-phenylmaleimide with good to high diastereoselectivities.[14f] In our own work, we have incorporated the advantageous properties of the oxazolidinone auxiliary to amino siloxy dienes, which possess many of the same advantages of 1,3-dialkoxy-1,3-butadienes, such as Danishefsky's diene, including the possibility of generating a cyclohexenone upon hydrolysis.



Results and Discussion

Achiral Dienes. Before exploring the chemistry of chiral 1-oxazolidinone substituted siloxy dienes (e.g., **7**), we first prepared and explored the reactivity of the parent, achiral oxazolidinone substituted diene **10**. Of the routes examined, that shown in Scheme 2 is the most straightforward and highest yielding. The condensation of 2-oxazolidinone (**8**) with 3-butyn-2-one (prepared in situ by Jones oxidation of 3-butyn-2-ol) in the presence of *N*-methylmorpholine (NMM) in CH_2Cl_2 at room temperature afforded the desired vinylogous amide **9** in quantitative yield.[17] Deprotonation of **9** using potassium

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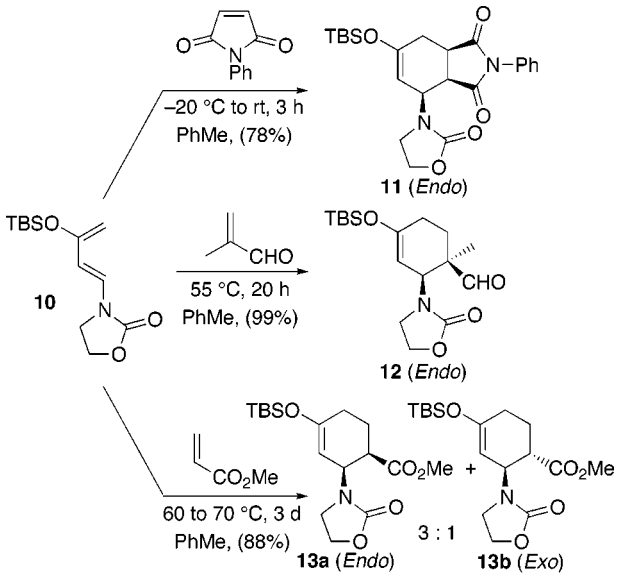
(14) For examples of chiral amino dienes, see: (a) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295−3298. (b) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242−1244. (c) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403−4404. (d) Schlessinger, R. H.; Pettus, T. R. R. *J. Org. Chem.* **1994**, *59*, 3246−3247. (e) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66−72. (f) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.* **1995**, *36*, 9533−9536. (g) Barluenga, J.; Aznar, F.; Martin, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419−9426. (h) Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C.; Fernandez, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805−811. (i) Barluenga, J.; Canteli, R.-M.; Florez, J.; Garcia-Granda, S.; Gutierrez-Rodriguez, A.; Martin, E. *J. Am. Chem. Soc.* **1998**, *120*, 2514−2522.

(15) For examples of the synthesis of 1-*N*-acylamino-1,3-dienes, see: (a) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 587−589. (b) Overman, L. E.; Taylor, G. F.; Jessup, P. J. *Tetrahedron Lett.* **1976**, 3089−3092. (c) Overman, L. E.; Clizbe, L. A. *J. Am. Chem. Soc.*, **1976**, *98*, 2352−2354, 8295. (d) Overman, L. E.; Taylor, G. F.; Petty, C. B.; Jessup, P. J. *J. Org. Chem.* **1978**, *43*, 2164−2167. (e) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 981−984. (f) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, 4537−4540. (g) Overman, L. E.; Clizbe, L. A.; Freerks, R. L.; Marlowe, C. K. *J. Am. Chem. Soc.* **1981**, *103*, 2807−2815. (h) Zezza, C. A.; Smith, M. B. *J. Org. Chem.* **1988**, *53*, 1161−1167. Several of the papers in this group also discuss the Diels−Alder reactivity of the dienes.

(16) For examples of the Diels−Alder reaction of 1-*N*-acylamino-1,3-dienes, see: (a) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836−3837. (b) Oppolzer, W.; Frostl, W. *Helv. Chim. Acta* **1975**, *58*, 590−593. (c) Oppolzer, W.; Frostl, W.; Weber, H. P. *Helv. Chim. Acta* **1975**, *58*, 593−595. (d) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182−3189. (e) Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179−5185. (f) Stork, G.; Morgans, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 7110−7111. (g) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816−2822. (h) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373−5379. (i) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030−3031. (j) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685−2686.

(17) Lee, E.; Kang, T. S.; Joo, B. J.; Tae, J. S.; Li, K. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 417−420.

Scheme 3



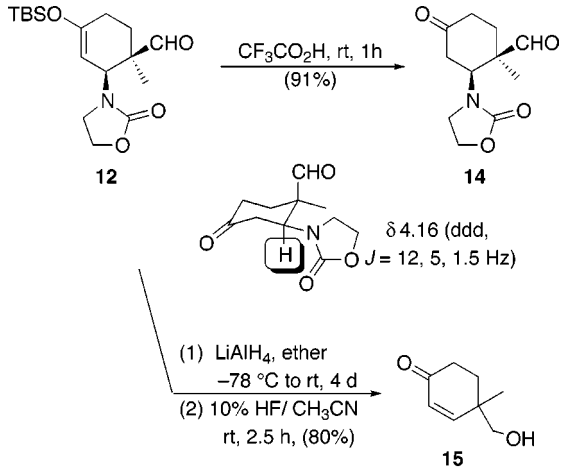
hexamethyldisilazide (KHMDS) in tetrahydrofuran (THF) at −78 °C and trapping of the resulting enolate with *tert*-butyldimethylsilyl chloride (TBSCl) gave the desired diene **10**, a white solid, in 94% yield. Larger scale preparation of **10** was carried out more conveniently using NaHMDS, which is available commercially from Aldrich as a 1 M solution in THF. With either base, the crude product is formed in high purity and can be used without purification.

The Diels−Alder reaction of diene **10** was examined with three different dienophiles (Scheme 3). Diene **10** reacted with *N*-phenylmaleimide at −20 °C to room temperature to produce cycloadduct **11** in 78% yield, with essentially complete endo selectivity, with no detectable signals from the exo isomer in the ^{1}H NMR spectrum of the reaction mixture. The reaction with methacrolein required slightly higher temperature and afforded cycloadduct **12** in 99% yield, again with total endo selectivity. As was the case with the parent amino siloxy dienes,[7] the cycloaddition with methyl acrylate was less diastereoselective. The cycloaddition took place at 60−70 °C and provided in 88% yield a 3:1 mixture of endo/exo diastereomers.

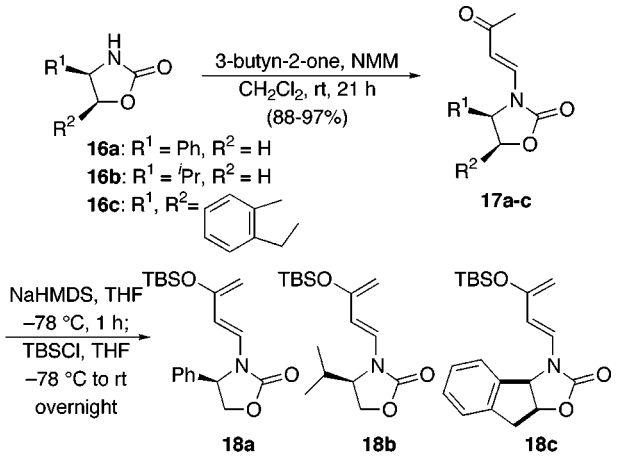
Effective protocols were developed for the selective hydrolysis of the cycloadduct (Scheme 4). Treatment of the methacrolein adduct (**12**) with trifluoroacetic acid at room temperature for 1 h yielded the desilylated cyclohexanone product (**14**) in 91% yield, with the oxazolidinone intact. The different signals in the ^{1}H NMR of cyclohexanone **14** were assigned using ^{1}H COSY experiments, and the C-3 proton was observed at δ 4.16 as a ddd multiplet with coupling constants J = 12 (axial), 5 (equatorial), and 1.5 (long range with CHO) Hz. The coupling constants are consistent with the chair conformation of **14**, in which the oxazolidinone sits in the equatorial position and the aldehyde occupies the axial position. Reduction of **12** with $LiAlH_4$ in ether at room temperature produced the amino alcohol, which was then treated with 49% aqueous HF in acetonitrile to afford the 4,4-disubstituted cyclohexenone product (**15**) in 80% overall yield.

Kinetics. As anticipated, the Diels−Alder reaction conditions required for the oxazolidinone siloxy diene were more vigorous than for its amino siloxy diene

Scheme 4



Scheme 5

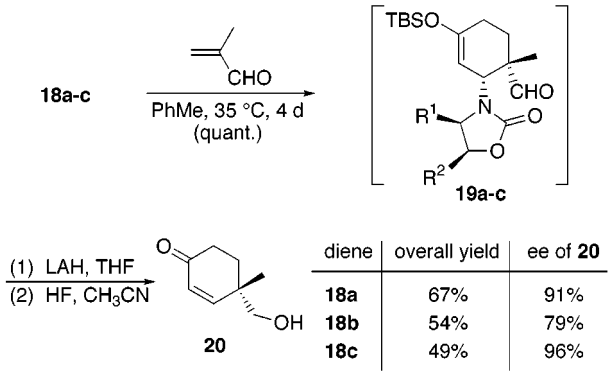


counterpart, diene **2**. The reduced reactivity of diene **10** is a natural consequence of having an electron-withdrawing group on nitrogen. Interestingly, the oxazolidinone diene (**10**) is still very reactive in Diels−Alder chemistry. In a simple competition experiment using methacrolein as the dienophile, the oxazolidinone-siloxy diene was found to be somewhat more reactive than the TBS-derivative of Danishefsky's diene (1-methoxy-3-(*tert*-butyldimethylsiloxy)-1,3-butadiene) in Diels−Alder reactions.[7a,8] To get more precise data on the relative reactivity of the oxazolidinone diene, the second-order rate constant was determined for its reaction with methacrolein in $CDCl_3$ ($K_2 = 1.2 \times 10^{-5}$) and C_6D_6 ($K_2 = 5.4 \times 10^{-6}$, see the Supporting Information). For the purpose of comparison, the kinetics of the TBS derivative of Danishefsky's diene were redetermined ($K_2 = 4.3 \times 10^{-6}$ in $CDCl_3$).[8,18] The data confirm that despite the presence of the electron-withdrawing group on the nitrogen at C_1, diene **10** is still very reactive, about three times more reactive than TBS-Danishefsky's diene.

Chiral Dienes. The success of the achiral diene encouraged us to examine the cycloaddition of chiral oxazolidinone-derived dienes. Three chiral dienes (**18a**−**c**) were synthesized, using procedures that paralleled those used for the preparation of achiral diene **10** (Scheme 5). The phenyl-substituted oxazolidinone (**16a**), required for

(18) The rate constant redetermined for TBS version of Danishefsky's diene was slightly different from that reported earlier (see ref 8).

Scheme 6



diene	overall yield	ee of **20**
18a	67%	91%
18b	54%	79%
18c	49%	96%

diene **18a**, was prepared in 84% overall yield by a modification of the reported procedure.[19] (*R*)-Phenylglycine was reduced using $LiBH_4$/TMSCl in THF, and the resultant (*R*)-phenylglycinol was heated with diethyl carbonate in the presence of a catalytic amount of K_2CO_3 to yield (*R*)-4-phenyl-2-oxazolidinone **16a**. Oxazolidinones **16b** and **16c**, which are commercially available, can be prepared analogously from the corresponding commercially available amino alcohols. As before, treatment of the oxazolidinones with 3-butyn-2-one gave vinylogous amides **17** in 88−97% yield. The chiral oxazolidinone-derived dienes **18a**−**c** were obtained upon treatment of vinylogous amides **17a**−**c** with NaHMDS in THF at −78 °C for 1 h followed by silylation with TBSCl and allowing the reaction mixture to warm to room-temperature overnight. The phenyloxazolidinone substituted diene **18a** was obtained in quantitative yield, and the crude product was clean by NMR. Crystallization of the crude diene from ether and hexanes afforded pure **18a** as pale yellow crystals in 76% yield. Silylation of the enolate of vinylogous amide **17b** proceeded smoothly to afford the isopropyl-substituted derivative **18b** in reasonably pure state. On the other hand, silylation of the 1-amino-2-indanol derivative **17c** with TBSCl did not go to completion, possibly due to the steric hindrance of the indanyl group. The ^{1}H NMR spectrum of the reaction mixture showed a 1:2 mixture of **17c** and **18c** accompanied by minor byproducts. Diene **18c** was also less stable compared with dienes **18a** and **18b** and gradually decomposed during storage in a refrigerator.

To evaluate the reactivity and diastereofacial selection capability of the three chiral auxiliaries, we examined the Diels−Alder reactions of chiral dienes **18a**−**c** with methacrolein (Scheme 6). In general, the chiral dienes (**18**) were comparable in reactivity to their achiral counterpart, diene **10**. The cycloadditions were carried out in toluene at 35 °C (bath temp.), and the cycloadducts **19** were transformed directly into cyclohexenone **20**. The crude cycloadducts, which can be isolated in high purity in quantitative crude yield (>17:1, endo/exo by NMR for **19a**), were treated with $LiAlH_4$ to reduce both the oxazolidinone and aldehyde carbonyls, and the resulting amino diol was hydrolyzed with 49% aqueous HF in acetonitrile to cyclohexenone **20** in 49−67% overall yields. In all three cases cyclohexenone **20** was obtained enriched in the (*S*)-enantiomer,[11] as determined by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester.[20] The best diastereoselectivity was obtained using the aminoindanol-derived diene **18c**, which yielded cyclohexenone **20** in 96% ee. The phenylglycinol containing diene gave lower, but still quite good, diastereoselectivity. The asymmetric induction observed for the cycloadditions with methacrolein can be rationalized by considering the two endo transition states, **A** and **B** (Figure 1, illustrated for diene **18a**). As discussed earlier, the s-trans rotamer of the oxazolidinone is expected to be of lower energy, presumably to avoid steric interaction between the carbonyl oxygen and the hydrogen at C2.[14a,f] Of the two transition states, **A** is expected to be favored for steric reasons, with the dienophile approaching the diene from the face away from the aryl group. The higher diastereoselectivity with diene **18c** is presumably due to more efficient shielding of the diene upper face by the aromatic ring of the indanyl group compared to the phenyl group.

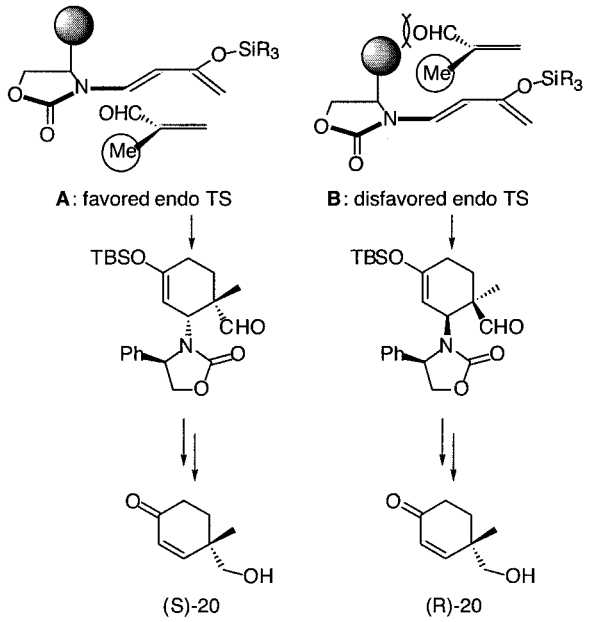


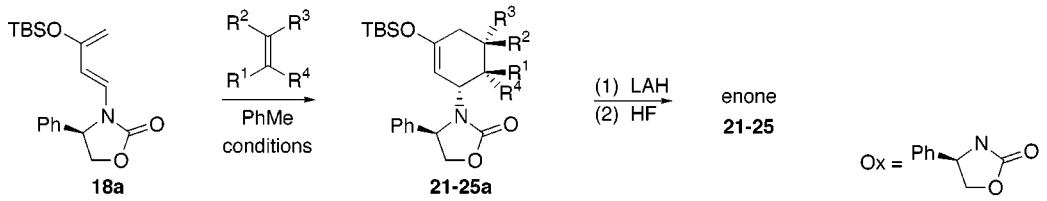
Figure 1. Probable low energy transition states leading to **20**.

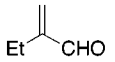
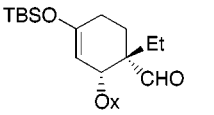
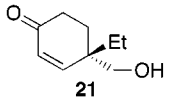
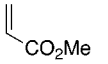
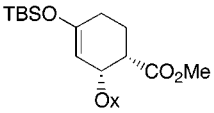
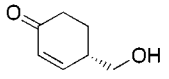
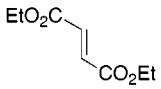
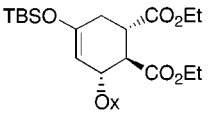
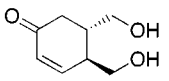
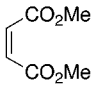
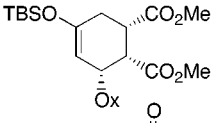
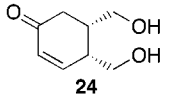
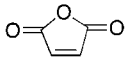
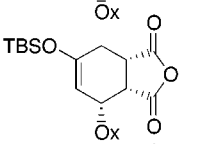
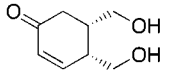
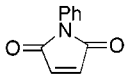
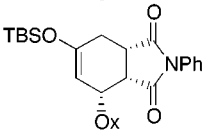
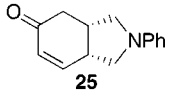
The Diels−Alder reaction of diene **18a** was then examined with several different dienophiles in order to determine the scope of this methodology (Table 1). In all cases the intermediate cycloadducts were not isolated, but were converted directly to cyclohexenone derivatives **21**−**25** by the reduction−hydrolysis protocol. The Diels−Alder reaction of ethacrolein proceeded at 35 °C as before in excellent yield and with high endo and facial selectivities. After LAH reduction and HF hydrolysis, the expected cyclohexenone (**21**) was isolated in 65% overall yield. The ee of this compound, as determined by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester, was 92% (*S*), comparable to that observed for the methacrolein adduct (entry 1).[11,20] The cycloaddition reaction with methyl acrylate proceeded with much lower endo/exo selectivity. The endo/exo mixture was subjected to the reduction−hydrolysis protocol to afford enone **22**, with 55% ee (entry 2). The cycloadditions of both diethyl fumarate and dimethyl maleate were low yielding. The latter, in particular, reacted very sluggishly and even after 4d at 65 °C only a small amount of the cycloadduct was observed. The unreactivity of maleate with these

(19) Nicolas, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766−770.

(20) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165−7166.

Table 1. The Diels–Alder Reaction of Diene 18a with Various Dienophiles



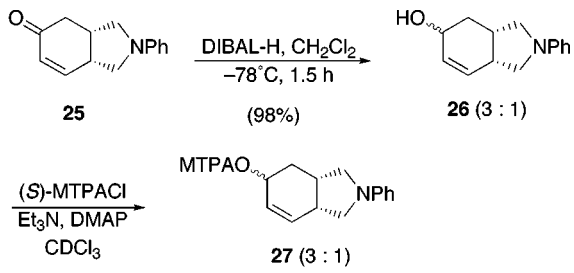
entry	dienophile	conditions[a]	product	(endo):(exo)[b]	yield[c] (%)	product	yield[d] (%)	ee (%)
1		35 °C 4 d	 **21a**	>17:1	quant[f]	 **21**	65	92[g]
2		60 °C 4 d	 **22a**	(1:6.4):(2:2.5)	81	 **22**	63	55[g]
3		50 °C 3 d	 **23a**	1:3.1:6.8:7.9[e]	78	 **23**	24	22[g]
4		65 °C 4 d	 **24a**	–	–	 **24**	<5	–
5		−45 °C to rt 11 h	 **24aa**	>50:1	quant[f]	 **24**	32	>98[g]
6		−45 °C to rt 24 h	 **25a**	>50:1	quant	 **25**	51	>98[h]

[a] Conditions for the Diels-Alder reaction. [b] endo:exo ratio was determined by ^{1}H NMR analysis of the crude reaction mixture, as described previously (ref 7). [c] Isolated yield. [d] Overall isolated yield from diene **18a**, without purification of the Diels-Alder adduct. [e] endo and exo diastereomers could not be assigned with confidence. [f] Crude yield. [g] ee and absolute stereochemistry were determined by ^{1}H NMR analysis of the corresponding Mosher esters, as described previously (ref 11). [h] ee was determined by ^{1}H NMR analysis of the corresponding Mosher esters of the allylic alcohols derived from DIBAL-H reduction of the enones. The assigned absolute stereochemistry is in analogy with that for related compounds.

dienes stands in contrast to our previous experience with the parent amino siloxy diene and its chiral version.[7,8,11]

On the other hand, maleic anhydride reacted cleanly with the diene **18a**. The reaction was started at −45 °C and allowed to warm to room temperature overnight (11 h) to afford the cycloadduct as essentially a single stereoisomer in quantitative crude yield (entry 5). Unfortunately, after the reduction−hydrolysis sequence the final cyclohexenone product (**24**) was isolated in only 32%, due in large measure to the difficulty associated with extracting the amino triol intermediate from the aluminum residues arising from the LAH reduction, as well as to the overall high water solubility of enone-diol **24**. However, the enantiomeric excess of **24** was excellent (>98% ee), as determined by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester.[11,20] The reaction with *N*-phenylmaleimide also proceeded with high endo and facial selectivities[14f] and gave, after reduction−hydrolysis of the cycloadduct, cyclohexenone derivative **25** in 51% yield with >98% ee. The ee of **25** was determined by Mosher ester analysis of allylic alcohols **26** (3:1), obtained by diisobutylaluminum hydride (DIBAL-H) reduction of the enone (Scheme 7). The ^{1}H NMR analysis of Mosher esters **27** revealed the presence of only two diastereomers, in exactly the same ratio as the original alcohols (3:1), indicating >98% ee for enone **25**. Cinnamaldehyde, tiglic aldehyde and citraconic anhydride were unreactive with diene **18a** under the standard Diels−Alder conditions.

Scheme 7



The observed absolute asymmetric induction in the Diels−Alder reactions above can be understood by con-

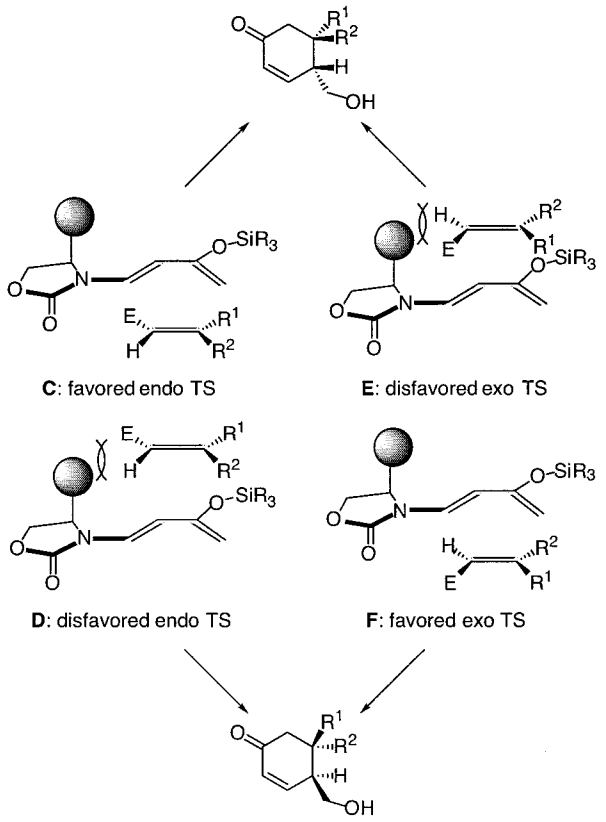


Figure 2. Possible transition states for the diastereoselective Diels−Alder reaction.

sidering a general transition state model, shown in Figures 2. The different examples can be classified into two groups, those that are highly endo selective and those that are not. Based on the proposed transition states in Figure 2, one would expect, a priori, that endo-selective cycloadditions would exhibit higher diastereofacial selectivity than exo-selective cycloadditions. Of the two endo transition states **C** and **D**, the latter is expected to be much higher in energy, as it places the electron-withdrawing group in close proximity to the phenyl group on the oxazolidinone. By comparison, the energy difference between the two exo-transition states (**E** and **F**) is expected to be smaller (except for meth- and ethacrolein, vide infra), since the more congested transition only has a hydrogen close to the oxazolidinone phenyl group. For reactions that give an endo−exo mixture, only a poor ee of the final product can be expected since the two diastereomers are expected to be enriched in the opposite enantiomer of the final enone. The observed results are consistent with this analysis. The high ee's obtained from meth- and ethacroleins, maleic anhydride, and *N*-phenylmaleimide are consistent with the high endo selectivities of their Diels−Alder reactions with an amino siloxy diene. The slightly lower excesses observed for meth- and ethacrolein in this group can be understood by recognizing that, unlike the other dienophiles, even the exo pathway for these dienophiles should exhibit high diastereofacial selectivity (consider **E** and **F**, wherein H is replaced with an R group), resulting in formation of the opposite enantiomer of the final product. The considerably lower ee's of cyclohexenones **22** and **23** can be attributed to the fact that the cycloadditions of methyl acrylate and diethyl fumarate with diene **18a** are not highly endo-selective.

Conclusion

The results described above demonstrate that 1-(2-oxazolidinon-3-yl)-3-siloxy-1,3-butadienes are easily prepared from readily available starting materials and are highly reactive in Diels−Alder reactions. The chiral versions of these dienes (**18**) show considerable promise as an important surrogate to 1,3-dialkoxy-1,3-butadienes (e.g., Danishefsky's diene) for asymmetric synthesis. The diastereoselectivities of the α-substituted dienophiles, maleic anhydride, and *N*-phenylmaleimide were excellent. However, the diastereoselectivities with methyl acrylate and diethyl fumarate were poor. Although not pursued due to its higher cost, the 1-amino-2-indanol-derived diene shows even more promise for asymmetric Diels−Alder reactions.[21]

Experimental Section

General Methods. All reactions were carried out under a nitrogen atmosphere. Common solvents were purified before use. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were purified by distillation from potassium−benzophenone ketyl. Dichloromethane (CH_2Cl_2), benzene, and toluene were distilled from calcium hydride. All reagents were reagent grade and purified further when necessary. KHMDS was used from newly opened 100 mL bottles, purchased from Aldrich, Inc. Reactions were monitored by thin-layer chromatography (TLC) using 250 μm Whatman precoated silica gel plates. Flash column chromatography was performed over EM Science Laboratories silica gel (230−400 mesh) or Davisil Grade 633 Type 60A (200−425 mesh, Fisher Scientific). Melting points (mp) were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Carbon and proton NMR spectra were recorded on a Brüker DRX-500 spectrometer. ^{1}H NMR chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane, and splitting patterns are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{13}C NMR chemical shifts are reported as δ values (ppm) relative to chloroform-*d* (77.0 ppm). Infrared spectra (IR) were recorded with Nicolet 20 SXB FTIR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Mass spectra were obtained on either a Kratos MS-30 or a Kratos VG 70−250S mass spectrometer at The Ohio State University Campus Chemical Instrumentation Center. Optical rotations were measured on Perkin-Elmer 241 polarimeter at the sodium D line (1 mL sample cell).

Preparation of 4-(2-Oxazolidinon-3-yl)-3-butene-2-one (9). A solution of CrO_3 (1.01 g, 10.1 mmol) in H_2SO_4/H_2O (3.6 mL/18 mL) was added slowly over 30 min to a stirring solution of 3-butyn-2-ol (ca. 6−9 mmol) in H_2SO_4/H_2O (5.4 mL/18 mL) at 0 °C. The mixture was stirred at 2−10 °C for 4 h, and then CH_2Cl_2 (25 mL) was added. The reaction mixture was then washed with saturated $NaHCO_3/H_2O$ (7.5 mL/7.5 mL), and the organic layer was dried with $MgSO_4$ and then filtered. The crude butynone product in ca. 25 mL of CH_2Cl_2 was added to a stirring solution of 2-oxazolidinone (267 mg, 3.07 mmol) and *N*-methylmorpholine (0.66 mL, 6.0 mmol) in CH_2Cl_2 (20 mL). After 21 h at room temperature, the solution was concentrated in vacuo and the residue purified by flash chromatography on silica gel (elution with 10% methanol in ethyl acetate) to afford the product **9** as a pale yellow solid (469 mg, 99%). The product of larger scale reactions were purified by crystallization from ethyl acetate and hexanes: mp 88−91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.82 (t, J = 8 Hz, 2H), 4.56 (t, J = 8 Hz, 2H), 5.49 (d, J = 14.5 Hz, 1H), 7.82 (d, J = 14.5 Hz, 1H); ^{13}C

(21) A wide of chiral oxazolidones can be prepared via the Sharpless asymmetric aminohydroxylation methodology. For a leading recent reference, see: Barta, N. S.; Sidler, D. R.; Somerville, K. B.; Weissman, S. A.; Larsen, R. D.; Reider, P. J. *Org. Lett.* **2000**, *2*, 2821−2824.

NMR (125 MHz, $CDCl_3$) δ 26.8, 42.0, 62.6, 110.8, 137.8, 154.6, 196.7; IR ($CHCl_3$) 3018, 1782, 1760, 1690, 1626, 1599, 1480, 1414, 1348, 1215, 1094, 1037, 963, 755, 666 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_7H_9NO_3$ 155.0582, found 155.0594.

Preparation of 3-(*tert*-Butyldimethylsiloxy)-1-(2-oxazolidinon-3-yl)-1,3-butadiene (10). Method A. To a stirred, chilled solution (−78 °C, bath) of KHMDS in toluene (0.5 M, 2.1 mL, 1.05 mmol) and THF (2.1 mL) was added dropwise a solution of vinylogous imide **9** (155 mg, 1.00 mmol) in THF (2.3 mL). The reaction mixture was warmed to −45 °C over 2.5 h, cooled to −78 °C, and treated with a solution of *tert*-butyldimethylsilyl chloride (166 mg, 1.10 mmol) in THF (0.8 mL). The cold bath was removed, and the reaction mixture was allowed to reach room temperature. Dilution with ether (20 mL) followed by filtration through dry Celite and concentration in vacuo gave 253 mg (94%) of diene **10** as a white solid. Although the crude diene obtained through this procedure is of high purity (by NMR) and was used directly for cycloaddition chemistry, if desired it can be further purified via bulb-to-bulb distillation at 200 °C and 0.15 mmHg.

Method B. A stirred solution of NaHMDS in THF (1.0 M, 6.6 mL, 6.6 mmol) and THF (6.6 mL) was cooled to −78 °C (bath) and then treated dropwise over 15 min with a solution of vinylogous imide **9** (931 mg, 6 mmol) in THF (15 mL). After 30 min, a solution of *tert*-butyldimethylsilyl chloride (995 mg, 6.6 mmol) in THF (1.5 mL) was added. The stirred mixture was allowed to gradually warm to room temperature over 6 h and then concentrated in vacuo. The resultant orange solid was dissolved in ether, and the NaCl that precipitated was removed by filtration through Celite. The Celite pad was washed with more ether, and the combined filtrate was concentrated. Hexanes was added, causing the precipitation of the diene along with more NaCl. This solid was filtered through Celite, which was then washed with EtOAc to dissolved the desired diene. The filtrate was evaporated to give 1.54 g (95% yield) of diene **10** as a light orange solid: mp 85−87 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.99 (s, 9H), 3.74 (t, J = 8 Hz, 2H), 4.21 and 4.22 (each s, 1H), 4.46 (t, J = 8 Hz, 2H), 5.34 (d, J = 14.0 Hz, 1H), 7.17 (d, J = 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, 18.2, 25.8, 42.5, 62.0, 93.3, 109.2, 125.0, 153.8, 155.1; IR ($CHCl_3$) 3019, 2959, 2931, 2860, 1789, 1656, 1482, 1414, 1327, 1274, 1218, 942, 842, 753, 668 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{13}H_{23}NO_3Si$ 269.1447, found 269.1437.

Diels−Alder Reaction between Diene 10 and *N*-Phenylmaleimide. A solution of diene **10** (500 mg, 1.86 mmol) in toluene (3 mL) cooled to −20 °C was treated with a solution of *N*-phenylmaleimide (215 mg, 1.24 mmol) in toluene (2 mL). After 1 h, the reaction mixture was warmed to room temperature, diluted with toluene (5 mL), and stirred for another 2 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (2:1 ethyl acetate−hexanes) followed by recrystallization from toluene to give 430 mg (78%) of adduct **11** as a colorless solid. (3a*S**,4*R**,7a*S**)-6-(*tert*-Butyldimethylsilyloxy)-3a,4,7,7a-tetrahydro-4-(2-oxazolidinon-3-yl)-2-phenyl-1*H*-isoindole-1,3-(2*H*)-dione: mp 135−137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 and 0.17 (each s, 3H), 0.92 (s, 9H), 2.49 (dd, J = 16.5, 9 Hz, 1H), 2.80 (dd, J = 16.5, 2.5 Hz, 1H), 3.36 (dt, J = 2.5, 9 Hz, 1H), 3.59−3.69 (m, 3H), 4.30−4.36 (m, 2H), 4.77−4.79 (m, 1H), 4.94−4.95 (m, 1H), 7.24 (d, J = 7.5 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.46 (t J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.4, 17.9, 25.5, 28.5, 38.4, 41.9, 43.5, 49.6, 62.4, 98.4, 126.1, 128.6, 129.2, 131.7, 153.2, 158.0, 175.8, 177.8; IR ($CHCl_3$) 3019, 1745, 1711, 1386, 1216, 842, 755 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{23}H_{30}N_2O_5Si$ 442.1924, found 442.1919.

Diels−Alder Reaction between Diene 10 and Methacrolein. Methacrolein (2.46 mL, 29.6 mmol) was added to a stirred solution of diene **10** (2.00 g, 7.40 mmol) in toluene (7.4 mL) at room temperature. The reaction mixture was heated to 55 °C for 20 h. Concentration in vacuo afforded 2.50 g (99%) of clean cycloadduct **12** as a pale yellow solid. Crystallization from CH_2Cl_2 and hexanes afforded pure (3*R**,*4S**)-1-(*tert*-Butyldimethylsilyloxy)-4-formyl-4-methyl-3-(2-oxazolidinon-3-yl)-cyclohexene: mp 141−142 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.17, 0.17 (each s, 3H), 0.93 (s, 9H), 1.21 (s, 3H), 1.63 (ddd, J = 14, 6, 2 Hz, 1H), 1.88 (ddd, J = 14, 11, 7 Hz, 1H), 2.10 (ddd, J = 18, 11, 6 Hz, 1H), 2.17 (ddd, J = 18, 7, 2 Hz, 1H), 3.38 (dt, J = 5.5, 8.5 Hz, 1H), 4.26 (dt, J = 5.5, 8.5 Hz, 1H), 3.55 (q, J = 8.5 Hz, 1H), 4.21 (q, J = 8.5 Hz, 1H), 4.64 (d, J = 5.7 Hz, 1H), 4.66 (d, J = 5.7 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.3, 17.9, 18.6, 24.5, 25.5, 25.9, 42.4, 48.4, 53.8, 62.1, 98.3, 155.7, 158.6, 203.7; IR ($CHCl_3$) 3020, 2951, 2860, 1748, 1669, 1415, 1224, 840, 750, 668 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{17}H_{29}NO_4Si$ 339.1866, found 339.1855.

Diels−Alder Reaction between Diene 10 and Methyl Acrylate. Methyl acrylate (1.37 mL, 18.6 mmol) was added to a solution of diene **10** (1.00 g, 3.7 mmol) in toluene (3.7 mL) at room temperature. After 20h, the solution was heated to 60 °C (bath) and stirred for 22 h. Removal of the solvent and analysis by ^{1}H NMR showed presence of the diene **10**. The crude product was redissolved in toluene (4 mL), treated with more methyl acrylate (1.37 mL, 18.6 mmol), and heated in an oil bath (72 °C) for 21 h. The volatiles were removed in vacuo and the residue purified by flash chromatography on silica gel (elution with 25% hexanes in ethyl acetate) to afford 1.15 g (88%) of a 3:1 ratio (by NMR) of *endo* (**13a**):*exo* (**13b**) diastereomers. To obtain spectroscopic data, the diastereomers were separated by flash chromatography on silica gel (elution with 25% hexanes in diethyl ether). (3,4-*cis*)-1-(*tert*-Butyldimethylsilyloxy)-4-methyoxycarbonyl-3-(2-oxazolidinon-3-yl)cyclohexene (**13a**): mp 125−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 and 0.16 (each s, H), 0.92 (s, 9H), 1.86−1.96 (m, 2H), 2.10−2.15 (m, 2H), 2.79 (ddd, J = 10.5, 5.5, 5.0 Hz, 1H), 3.56 (q, J = 8 Hz, 1H), 3.62−3.66 (m, 1H), 3.69 (s, 3H), 4.22−4.26 (m, 2H), 4.73 (d, J = 5 Hz, 1H), 4.89 (t, J = 5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.6, −4.3, 18.0, 21.5, 25.5, 28.7, 42.8, 43.5, 49.0, 51.9, 62.1, 100.3, 156.1, 158.0, 173.5; IR ($CHCl_3$) 3019, 2956, 2860, 1733, 1665, 1418, 1255, 1212, 1064, 862, 841, 750, 667 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{17}H_{29}NO_5Si$ 355.1815, found 355.1839. (3,4-*trans*)-1-(*tert*-Butyldimethylsilyloxy)-4-methyoxycarbonyl-3-(2-oxazolidinon-3-yl)cyclohexene (**13b**): mp 116−117 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 and 0.16 (each s, 3H), 0.92 (s, 9H), 1.95−2.08 (m, 3H), 2.13−2.20 (m, 1H), 2.56 (dt, J = 4.5, 10 Hz, 1H), 3.48 (q, J = 8 Hz, 1H), 3.56 (q, J = 8 Hz, 1H), 3.70 (s, 3H), 4.29−4.36 (m, 2H), 4.62 (t, J = 2.2 Hz, 1H), 4.81−4.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.5, −4.5, 17.9, 23.9, 25.5, 28.5, 40.6, 42.7, 52.1, 62.0, 102.9, 154.3, 157.8, 173.4; IR ($CHCl_3$) 3020, 2956, 2860, 1751, 1747, 1733, 1665, 1423, 1258, 1198, 1047, 871, 841, 752, 667 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{17}H_{29}NO_5Si$ 355.1815, found 355.1814.

Hydrolysis of Cycloadduct 12 with Trifluoroacetic Acid: Preparation of (3*R,*4S**)-4-Formyl-4-methyl-3-(2-oxazolidinon-3-yl)cyclohexanone (14).** Neat CF_3CO_2H (0.5 mL) was added to cycloadduct **12** (50 mg, 0.15 mmol) at room temperature. After 1 h, the reaction mixture was directly purified by flash chromatography on silica gel (elution with 1:1 ethyl acetate/hexanes) to afford cyclohexanone **14**, 30 mg (91%), as a pale yellow solid: mp 112−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.76 (ddd, J = 14.5, 12.5, 5 Hz, 1H), 2.24 (ddd, J = 14.5, 6, 4 Hz, 1H), 2.32 (dddd, J = 16, 12.5, 6, 1 Hz, 1H), 2.46 (dddd, J = 16, 5, 4, 2 Hz, 1H), 2.52 (ddd, J = 15, 5, 2 Hz, 1H), 3.14 (ddd, J = 15, 12, 1 Hz, 1H), 3.58−3.66 (m, 2H), 4.16 (ddd, J = 12, 5, 1.5 Hz, 1H), 4.29−4.37 (m, 2H), 9.64 (d, J = 1.5, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.9, 30.1, 37.4, 41.8, 43.1, 49.9, 56.0, 62.2, 158.7, 203.8, 206.5; IR ($CHCl_3$) 3019, 2973, 1747, 1725, 1718, 1420, 1216, 1077, 755, 668 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_{11}H_{15}NO_4$ 225.1001, found 225.1014.

$LiAlH_4$ Reduction−Hydrolysis Sequence of the Cycloadduct 12: Preparation of 4-(Hydroxymethyl)-4-methylcyclohex-2-ene-1-one (15). Cycloadduct **12** (100 mg, 0.29 mmol) was dissolved in ether (10 mL) and added dropwise to lithium aluminum hydride powder (112 mg, 3.0 mmol) at −78 °C. The cold bath was removed, and the reaction was allowed to warm to room temperature (4d), diluted with ether (15 mL), and quenched by addition of a small amount of water until hydrogen evolution ceased. Anhydrous Na_2SO_4 was

added, and the organic layer was carefully decanted. The remaining solid washed with ether (5 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford 86 mg of the expected alcohol, which was sufficiently pure for the next step. A solution of the crude alcohol (86 mg) in acetonitrile (0.5 mL) was treated with a 10% solution of HF in acetonitrile (3.8 M, 0.2 mL, 0.78 mmol, prepared from 49% aqueous HF). The reaction mixture was stirred for 2.5 h at room temperature and purified directly by flash chromatography on silica gel (elution with ethyl acetate) affording 33 mg (80% from cycloadduct **12**) of **15** as a colorless oil. The ^{1}H NMR spectrum of this sample was in agreement with that reported previously by us for this compound.[11]

Preparation of (*R*)-2-Phenylglycinol.[19] The title compound was prepared according to the reported procedure. To a stirring solution of $LiBH_4$ (4.67 g, 214 mmol) in THF (107 mL) was added trimethylsilyl chloride (54.4 mL, 429 mmol) at room temperature. The resultant white suspension was cooled to 0 °C and then treated with (*R*)-phenylglycine (16.2 g, 107 mmol) over 5 min. After the mixture was stirred for 1 h at 0 °C, the cold bath was removed and the mixture allowed to stir at room temperature for 2 d. After being cooled back to 0 °C, the reaction was quenched by dropwise addition of MeOH (80 mL) and then concentrated in vacuo. A solution of 20% aqueous KOH (65 mL) was added the residue at 0 °C, followed by water (40 mL) and CH_2Cl_2 (32 mL). The organic phase was separated and the aqueous phase reextracted with CH_2Cl_2 (5 × 30 mL). The combined organic phase was dried over $MgSO_4$ and concentrated to yield a yellow solid, which was filtered and washed well with hexanes to give the title compound as a pale yellow solid (13.6 g, 93%): mp 76−79 °C (lit.[19] mp 76.5−78.5 °C) for (*S*)-2-phenylglycinol. The product was sufficiently pure by ^{1}H NMR and used for the next reaction without further purification.

Preparation of (*R*)-4-Phenyl-2-oxazolidinone.[19] A modification of the reported procedure was used. A round-bottomed flask fitted with a 10 cm Vigreux column, a stir bar was charged with (*R*)-phenylglycinol (13.60 g, 99 mmol), diethyl carbonate (24 mL, 198 mmol), and K_2CO_3 (2.10 g, 15 mmol), and the resultant mixture heated at 130 °C for 2.5 h. The phenylglycinol dissolved upon heating, and a white precipitate (phenyloxazolidinone) gradually formed. EtOH was distilled off over the course of the heating (2.5 h). After cooling, the residue was dissolved in CH_2Cl_2 (200 mL), and water (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resultant solid was filtered and washed well hexanes containing a small amount of ethyl acetate to afford 14.52 g (90%) of the title compound, which was sufficiently pure by ^{1}H NMR for use in the next reaction: mp 129−131 °C; $[\alpha]^{25}_D = -58.4°$ ($CHCl_3$, $c = 1.00$) (lit.[19] mp 128−130 °C, $[\alpha]^{22}_D = +58.0°$ ($CHCl_3$, $c = 1.00$)) for (*S*)-4-phenyl-2-oxazolidinone.

Preparation of (*R*)-4-(4-Phenyl-2-oxazolidinon-3-yl)-3-butene-2-one (17a). A solution of CrO_3 (29.3 g, 293 mmol) in H_2SO_4/H_2O (104 mL/522 mL) was added slowly over 40 min to a stirring solution of 3-butyn-2-ol (20.9 mL, 267 mmol) in H_2SO_4/H_2O (157 mL/522 mL) at 0 °C. The mixture was stirred at 2−10 °C for 4 h and then diluted with CH_2Cl_2 (725 mL). The CH_2Cl_2 layer was separated, washed with saturated $NaHCO_3$ and water, and dried with $MgSO_4$. The resulting crude butynone was added to a stirring solution of (*R*)-4-phenyl-*2*-oxazolidinone (14.52 g, 89 mmol) and *N*-methylmorpholine (19.1 mL, 174 mmol) in CH_2Cl_2 (580 mL). After 16 h at room temperature, the reaction mixture was concentrated in vacuo, and the residue purified by recrystallization (ethyl acetate and hexanes) to give 18.10 g (88%) of the title compound as orange crystals: mp 161−162 °C; $[\alpha]^{25}_D = -194°$ ($CHCl_3$, $c = 1.00$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.17 (s, 3H), 4.24 (dd, $J = 9$, 5 Hz, 1H), 4.82 (t, $J = 9$ Hz, 1H), 5.08 (dd, $J = 9$, 5 Hz, 1H), 5.29 (d, $J = 14.5$ Hz, 1H), 7.24−7.26 (m, 2H), 7.37−7.44 (m, 3H), 7.81 (d, $J = 14.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.6, 58.1, 71.0, 112.3, 125.7, 129.3, 129.6, 136.5, 137.1, 155.0, 196.8; IR ($CHCl_3$) 3020, 1778, 1770, 1665, 1638, 1602, 1407, 1218, 770, 668 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{13}H_{13}NO_3$ 231.0895, found 231.0895.

Preparation of (*R*)-4-(4-Isopropyl-2-oxazolidinon-3-yl)-3-buten-2-one (17b). The title compound was prepared from 1.00 g of (*R*)-(4-isopropyl-2-oxazolidinone (7.74 mmol) and 1.82 mL of 3-butyn-2-ol (23.2 mmol) in the same manner as described above for vinylogous amide **17a**. Purification by flash chromatography on silica gel (elution with 1:3 ethyl acetate/hexanes) gave 1.628 g of the product. Crystallization from ethyl acetate (5 mL) and hexanes (10 mL) gave pure **17b** in two crops (first crop: 1.128 g, second crop: 0.284 g; total 1.412 g, 92%) as colorless needles: mp 76.5−78 °C; $[\alpha]^{25}_D = -75.0°$ ($CHCl_3$, c=1.00); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 and 0.97 (each d, $J = 7$ Hz, 3H), 2.28 (s, 3H), 2.36−2.43 (m, 1H), 4.08 (dt, $J = 9$, 3 Hz, 1H), 4.33 (dd, $J = 9$, 3 Hz, 1H), 4.37 (t, $J = 9$ Hz, 1H), 5.63 (d, $J = 14.5$ Hz, 1H), 7.75 (d, $J = 14.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 17.8, 26.4, 26.6, 58.3, 63.5, 111.0, 137.4, 154.9, 197.0; IR ($CHCl_3$) 2966, 1769, 1627, 1598, 1413, 1199 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{10}H_{15}NO_3$ 197.1052, found 197.1054.

Preparation of (3a*R-cis*)-3,3a,8,8a-Tetrahydro-3-(3-oxo-1-butenyl)-2*H*-indeno[1,2-*d*]oxazol-2-one (17c). The title compound was prepared from 1.00 g of (3a*R-cis*)-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (5.71 mmol) and 1.34 mL of 3-butyn-2-ol (17.1 mmol) in the same manner as described above for vinylogous amide **17a**. The crude product was recrystallized from CH_2Cl_2 (20 mL)−ethyl acetate (5 mL) to give 1.045 g (first crop: 0.952 g, second crop: 0.093 g) of the pure compound as a colorless needles. The mother liquid was purified by flash chromatography on silica gel (elution with ethyl acetate:CH_2Cl_2, 1:10 to 1:2) to afford additional 0.305 g of the pure product. Total yield was 1.350 g (97%): mp 204.5−206 °C; $[\alpha]^{25}_D = -735°$ ($CHCl_3$ $c = 1.04$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.42 (d, $J = 3.5$ Hz, 2H), 5.38 (dt, $J = 7$, 3.5 Hz, 1H), 5.53 (d, $J = 7$ Hz, 1H), 6.07 (d, $J = 15$ Hz, 1H), 7.24 (t, $J = 7$ Hz, 1H), 7.30 (d, $J = 7$ Hz, 1H), 7.36 (t, $J = 7$ Hz, 1H), 7.48 (d, $J = 7$ Hz, 1H), 7.82 (d, $J = 15$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.7, 37.5, 62.6, 79.6, 111.2, 125.7, 125.9, 128.2, 130.2, 137.7, 138.1, 139.8, 154.1, 197.0; IR ($CHCl_3$) 1763, 1625, 1261, 1196, 1035, 971, 757 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{14}H_{13}NO_3$ 243.0895, found 243.0902.

Preparation of (*R*)-3-(*tert*-Butyldimethylsiloxy)-1-(4-phenyl-2-oxazolidinon-3-yl)-1,3-butadiene (18a). A solution of vinylogous imide **17a** (9.25 g, 40 mmol) in THF (280 mL) was added dropwise over 1 h to a chilled solution (dry ice−acetone bath) of NaHMDS (1.0 M in THF, 44 mL, 44 mmol) in THF (80 mL). After 1 h at −78 °C, a solution of *tert*-butyldimethylsilyl chloride (6.63 g, 44 mmol) in THF (32 mL) was added, and the solution was allowed to warm gradually to room temperature overnight. After removal of the volatiles in vacuo, the resultant orange solid was dissolved in ether (100 mL), and the precipitated NaCl was removed by filtration through Celite and washed with ether. The filtrate was concentrated in vacuo to afford an orange solid that was crystallized from ether (10 mL)−hexanes (40 mL) to give 10.56 g (first crop: 9.33 g, second crop: 1.23 g; total 76%) of the title product as a pale yellow crystals: mp 77−78 °C; $[\alpha]^{25}_D = -128°$ ($CHCl_3$, $c = 1.00$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 and 0.14 (each s, 3H), 0.95 (s, 9H), 3.98 (s, 1H), 4.10 (s, 1H), 4.13 (dd, $J = 9$, 5.5 Hz, 1H), 4.71 (t, $J = 9$ Hz, 1H), 5.02 (dd, $J = 9$, 5.5 Hz, 1H), 5.20 (d, $J = 14$ Hz, 1H), 7.10 (d, $J = 14$ Hz, 1H), 7.26 (d, $J = 7$ Hz, 2H), 7.35 (t, $J = 7$ Hz, 1H), 7.40 (t, $J = 7$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.7, 18.2, 25.7, 58.7, 70.5, 93.5, 111.0, 124.0, 125.8, 128.8, 129.4, 137.9, 153.6, 155.5; IR ($CHCl_3$) 3021, 2959, 2931, 2859, 1766, 1750, 1657, 1405, 1309, 1218, 1037, 833, 762 cm^{-1}; HRMS *m/z* [M$^+$] calcd for $C_{19}H_{27}NO_3Si$ 345.1760, found 345.1749.

Preparation of (*R*)-3-(*tert*-Butyldimethylsiloxy)-1-(4-isopropyl-2-oxazolidinon-3-yl)-1,3-butadiene (18b). A solution of NaHMDS (1 M in THF, 4.4 mL, 4.4 mmol) was diluted with THF (12 mL) was cooled to −78 °C then treated dropwise over 15 min with a solution of vinylogous imide **17b** (789 mg, 4.0 mmol) in THF (10 mL). After 1 h at −78 °C, a solution of

tert-butyldimethylsilyl chloride (663 mg, 4.4 mmol) in THF (3.2 mL) was added, and the solution allowed to gradually warm to room temperature overnight. After evaporation of the volatiles, the resultant dark brown oil was dissolved in ether (50 mL), and the precipitated NaCl was removed by filtration through Celite and washed with ether. Evaporation of the ether yielded an oil which still contained some NaCl. The residue was redissolved in ether and filtered through Celite. This filtration-concentration procedure was repeated two more times and finally yielded 1.448 g of the title compound as a brown oil. Although the product was sufficiently pure by ^{1}H NMR for use in subsequent steps, it still contained a small amount of NaCl precipitate: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.20 and 0.21 (each s, 3H), 0.85 and 0.95 (each d, J = 7 Hz, 3H), 0.99 (s, 9H), 2.38−2.41 (m, 1H), 4.01 (dt, J = 8.5, 3 Hz, 1H), 4.20−4.23 (m, 3H), 4.37 (t, J = 8.5 Hz, 1H), 5.50 (d, J = 15 Hz, 1H), 7.05 (d, J = 15 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.6, 13.8, 17.8, 18.2, 25.8, 26.5, 58.6, 62.9, 93.3, 109.5, 124.1, 153.9, 155.3; IR ($CHCl_3$) 2960, 2930, 2858, 1759, 1659, 1413, 1203, 1026, 840, 781 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{16}H_{29}NO_3Si$ 311.1917, found 311.1909.

Preparation of (3a*R*-*cis*)-3-[3-(*tert*-Butyldimethylsiloxy)-1,3-butadienyl]-3,3a,8,8a-tetrahydro-2*H*-indeno[1,2-*d*]oxazol-2-one (18c). A solution of NaHMDS in THF (1.0 M, 4.4 mL, 4.4 mmol) was diluted with THF (8 mL) and cooled to −78 °C. A solution of vinylogous amide **17c** (973 mg, 4.0 mmol) in THF (100 mL) was then added dropwise over 1.5 h. After 1 h at −78 °C, a solution of *tert*-butyldimethylsilyl chloride (663 mg, 4.4 mmol) in THF (3.2 mL) was added. The reaction mixture was allowed to warm to room-temperature overnight and then concentrated in vacuo. The resultant dark brown oil was dissolved in ether (50 mL), and the precipitated NaCl was removed by filtration through Celite and washed with ether. The filtrate was concentrated in vacuo to give a dark brown oil. ^{1}H NMR showed that the crude product consisted primarily of the starting ketone and the desired diene (ketone:diene=ca. 1:2). Purification by flash chromatography on silica gel (elution with 1:10 ethyl acetate:hexanes containing 4% Et_3N) afforded 873 mg (61%) of impure diene. A second chromatographic purification gave 432 mg (30%) of the diene as an orange oil. Although some impurities were still present, this diene was used for the Diels−Alder reaction: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.00 (s, 9H), 3.40 (d, J = 3.5 Hz, 2H), 4.29 and 4.31 (each s, 1H), 5.31 (dt, J = 7, 3.5 Hz, 1H), 5.48 (d, J = 7 Hz, 1H), 5.93 (d, J = 15 Hz, 1H), 7.16 (d, J = 15 Hz, 1H), 7.24−7.39 (m, 3H), 7.54 (d, J = 7 Hz, 1H); HRMS *m*/*z* [M$^+$] calcd for $C_{20}H_{27}NO_3Si$ 357.1760, found 357.1761.

Typical Procedure for the Asymmetric Diels−Alder Reaction, Followed by Reduction and Hydrolysis: Preparation of (*S*)-4-(Hydroxymethyl)-4-methylcyclohex-2-en-1-one (20). To a solution of diene **18a** (173 mg, 0.5 mmol) in toluene (0.5 mL) was added methacrolein (207 μL, 2.5 mmol), and the resulting solution was heated to 35 °C for 4 d. Excess methacrolein and toluene were removed in vacuo using a Kugelrohr bulb-to-bulb distillation apparatus. The resultant solid was dissolved in THF (2−4 mL) and added to a suspension of lithium aluminum hydride (76 mg, 2.0 mmol) in THF (2 mL, 4 mL in the case of ether) at 0 °C. After 30 min, the cold bath was removed and the solution was allowed to warm to room temperature over 5 h at room temperature. The solution was cooled to 0 °C, diluted with ether (5−10 mL), quenched by addition of a small amount of water until hydrogen evolution ceased, and stirred vigorously for 1 h. Anhydrous Na_2SO_4 was added, and the solids were removed by filtration through Celite, and washed well with ether followed by ethyl acetate or CH_2Cl_2. The filtrate was concentrated in vacuo and the residue dissolved in acetonitrile (2 mL) and treated with 49% aqueous HF (0.26 mL). The reaction mixture was stirred for 3h at room temperature then purified directly by flash chromatography on silica gel (elution with 1:1 ethyl acetate/hexanes) to afford **20** as a colorless oil (47 mg, 67% overall yield from diene **18a**). The ^{1}H NMR spectrum of this sample was in agreement with that reported previously by us.[11] The enantiomeric excess was determined via Mosher ester to be 91%.[20]

The structure of the major Diels−Alder cycloadduct was confirmed by ^{1}H and ^{13}C NMR, IR, and HRMS spectra of the crude reaction product. (3*R*,4*S*)-1-(*tert*-Butyldimethylsilyloxy)-4-formyl-4-methyl-3-[(*R*)-4-phenyl-2-oxazolidinon-3-yl]cyclohexene (**19a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.21 (s, 3H), −0.12 (s, 3H), 0.77 (s, 9H), 1.18 (s, 3H), 1.61−1.62 (m, 1H), 2.03−2.09 (m, 3H), 4.04 (dd, J = 8.5, 3 Hz, 1H), 4.08 (d, J = 5.5 Hz, 1H), 4.48 (t, J = 8.5 Hz, 1H), 4.70 (d, J = 5.5 Hz, 1H), 4.73 (dd, J = 8.5, 3 Hz, 1H), 7.17−7.39 (m, 5H), 9.76 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.1, −4.5, 17.7, 18.8, 25.1, 25.4, 25.6, 49.9, 54.4, 59.2, 70.8, 99.9, 126.2, 128.4, 129.0, 141.4, 153.2, 158.5, 204.8; IR ($CHCl_3$) 3019, 2973, 2932, 1737, 1380, 1214, 1068, 757, 669 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{23}H_{33}NO_4Si$ 415.2179, found 415.2192.

Preparation of (*S*)-4-(Hydroxymethyl)-4-methylcyclohex-2-en-1-one (20). The Diels−Alder reaction was conducted as described in the typical procedure with diene **18b** (181 mg, estimated to be 86% pure, 0.5 mmol) and methacrolein (207 μL, 2.5 mmol) in toluene (0.5 mL) at 35 °C for 4 d. Subsequent reductive hydrolysis afforded the title compound (38 mg, 54% overall yield). The ^{1}H NMR spectrum of the final product was in agreement with that reported previously by us;[11] the enantiomeric excess was determined to be 79% via Mosher ester analysis.[20]

Preparation of (*S*)-4-(Hydroxymethyl)-4-methylcyclohex-2-en-1-one (20). The Diels−Alder reaction was conducted as described in the typical procedure using diene **18c** (89 mg, 0.25 mmol) and methacrolein (104 μL, 1.25 mmol) in toluene (0.25 mL) at 35 °C for 4 d. Subsequent reductive hydrolysis afforded the title compound (17 mg, 49% overall yield). The ^{1}H NMR spectrum of the product was in agreement with that reported previously by us;[11] the enantiomeric excess was determined to be 96% by ^{1}H NMR analysis of the corresponding Mosher ester.[20]

Preparation of (*S*)-4-(Hydroxymethyl)-4-ethylcyclohex-2-en-1-one (21). The Diels−Alder reaction was conducted as described in the typical procedure using the diene **18a** (173 mg, 0.5 mmol) and ethacrolein (245 μL, 2.5 mmol) in toluene (0.5 mL) at 35 °C for 4 d. Subsequent reductive hydrolysis afforded the title product (50 mg, 65% overall yield). The ^{1}H NMR spectrum of the product was in agreement with that reported previously by us,[11] and the enantiomeric excess was determined to be 92%.[20]

Preparation of (*S*)-4-(Hydroxymethyl)cyclohex-2-en-1-one (22). The Diels−Alder reaction was conducted as described in the typical procedure using the diene **18a** (346 mg, 1 mmol) and methyl acrylate (459 μL, 5 mmol) in toluene (1 mL) at 60 °C for 4 d. Subsequent reductive hydrolysis afforded the title product (40 mg, 63% overall yield). The ^{1}H NMR spectrum of the product was in agreement with that reported previously by us,[11] and the enantiomeric excess was determined to be 55%.[20]

Preparation of (*4S*-*trans*)-4,5-Bis(hydroxymethyl)cyclohex-2-en-1-one (23). The Diels−Alder reaction was conducted as described in the typical procedure using the diene **18a** (173 mg, 0.5 mmol) and diethyl fumarate (409 μL, 2.5 mmol) in toluene (0.5 mL) at 50 °C for 3 d. Subsequent reductive hydrolysis followed by purification was performed by flash chromatography on silica gel twice (first elution with ethyl acetate, then 20:1 ether:MeOH) gave the title product (19 mg, 24% overall yield). The ^{1}H NMR spectrum of the product was in agreement with that reported previously by us,[11] and the enantiomeric excess was determined to be 22%.[20]

Preparation of (*4R*-*cis*)-4,5-Bis(hydroxymethyl)cyclohex-2-en-1-one (24). The Diels−Alder reaction was carried out using the typical procedure with the following modifications. To a solution of diene **18a** (173 mg, 0.5 mmol) in toluene (0.5 mL) was added a solution of maleic anhydride (49 mg, 0.5 mmol) in toluene (1.5 mL) at −45 °C (acetonitrile−CO_2). The reaction mixture was stirred for 11 h at −45 °C to room temperature. Subsequent reductive hydrolysis followed by purification was performed by flash chromatography on silica gel twice (first elution with ethyl acetate, then 20:1 ether: MeOH) gave the title product (25 mg, 32% overall yield). The ^{1}H NMR spectrum of the product was in agreement with that

reported previously by us,[11] and the enantiomeric excess was determined to be >98%.[20]

The structure of the major Diels−Alder cycloadduct was confirmed by ^{1}H and ^{13}C NMR, IR, and HRMS spectra of the crude product. (3a*S*,4*R*,7a*S*)-6-(*tert*-Butyldimethylsilyloxy)-3a,4,7,7a-tetrahydro-4-[(*R*)-4-phenyl-2-oxazolidinon-3-yl)-1,3-isobenzofurandinone: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.21 (s, 3H), −0.12 (s, 3H), 0.79 (s, 9H), 2.38 (dd, J = 16, 8 Hz, 1H), 2.68 (dd, J = 16, 3 Hz, 1H), 3.43−3.47 (m, 1H), 3.81−3.85 (m, 1H), 4.10 (dd, J = 8, 4 Hz, 1H), 4.61 (m, 2H), 4.77 (t, J = 8 Hz, 1H), 4.88 (dd, J = 8, 4 Hz, 1H), 7.28 (d, J = 7 Hz, 2H), 7.35 (t, J = 7 Hz, 1H), 7.41 (t, J = 7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2, 17.8, 25.3, 29.0, 39.1, 41.9, 49.5, 59.3, 71.4, 97.9, 125.9, 128.9, 129.6, 140.2, 153.1, 158.4, 171.2, 173.0; IR ($CHCl_3$) 2929, 1772, 1756, 1648, 1416, 1222, 953, 783, 687 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{23}H_{29}NO_6Si$ 443.1764, found 443.1763.

Preparation of (3a*R*-*cis*)-2,3,3a,4,5,7a-Hexahydro-5-oxo-2-phenyl-1*H*-isoindole (25). To a solution of diene **18a** (173 mg, 0.5 mmol) in toluene (0.5 mL) was added a solution of *N*-phenylmaleimide (87 mg, 0.5 mmol) in toluene (0.75 mL) at −45 °C (acetonitrile−CO_2). The reaction mixture was allowed to warm to room temperature over 24 h. Toluene was removed in vacuo, and the resultant light orange oil was dissolved in ether (4 mL) and added to a suspension of lithium aluminum hydride (152 mg, 4.0 mmol) in ether (2 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then warmed to 35−40 °C for 1 d. The reaction mixture was cooled to 0 °C, diluted with ether (ca. 10 mL), quenched by addition of a small amount of water (until hydrogen evolution ceased), and stirred for 1 h. Anhydrous Na_2SO_4 was added. The solids were removed by filtration through a small amount of Celite and washed well with ether followed by ethyl acetate. The filtrate was concentrated in vacuo, and the residual oil was dissolved in acetonitrile (2 mL) and then treated with 49% aqueous HF (0.26 mL). After being stirred for 2 h at room temperature, the solution was neutralized with saturated aqueous $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (elution with 1:9 ethyl acetate/hexanes) to afford the title compound (**25**) as a pale yellow solid (55 mg, 51% overall yield from diene **18a**): mp 161−167 °C; $[\alpha]^{25}_D$ = −160° ($CHCl_3$, c = 1.01); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.57 (dd, J = 17, 5.5 Hz, 1H), 2.67 (dd, J = 17, 5.5 Hz, 1H), 2.96−3.03 (m, 1H), 3.14−3.17 (m, 2H), 3.40 (dd, J = 9.5, 4 Hz, 1H), 3.47 (t, J = 8.5 Hz, 1H), 3.64 (dd, J = 9, 7 Hz, 1H), 6.06 (dd, J = 10, 1.5 Hz, 1H), 6.52 (d, J = 8 Hz, 2H), 6.70 (t, J = 7 Hz, 1H), 6.76 (dd, J = 10, 3 Hz, 1H), 7.23 (t, J = 8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 37.9, 38.4, 51.4, 53.0, 111.5, 116.2, 129.2, 130.0, 147.1, 150.1, 197.5; IR ($CHCl_3$) 3020, 1675, 1599, 1507, 1482, 1367, 1215, 760, 668 cm^{-1}.

The enantiomeric excess was determined as follows: A solution of the enone **25** (8.5 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) at −78 °C was treated with a 1.0 M solution of diisobutylaluminum hydride in CH_2Cl_2 (0.12 mL, 0.12 mmol). After 1.5 h, the reaction was quenched by addition of a small amount of water, and the mixture was allowed to warm to room temperature. The inorganic precipitate was removed by filtration through Celite and washed well with CH_2Cl_2 (ca. 30 mL). The filtrate was concentrated in vacuo to give an allylic alcohol in 8.4 mg (98%) yield as a 3:1 mixture of diastereomers. ^{1}H NMR analysis of the corresponding Mosher ester prepared in situ showed no detectable change in this diasteromeric ratio, which corresponds to >98% ee.[20]

The structure of the major Diels−Alder cycloadduct was confirmed by ^{1}H and ^{13}C NMR, IR and HRMS spectra of the crude product. (3a*S*,4*R*,7a*S*)-6-(*tert*-Butyldimethylsilyloxy)-3a,4,7,7a-tetrahydro-2-phenyl-4-[(*R*)-4-phenyl-2-oxazolidinon-3-yl)]-1*H*-isoindole-1,3-(2*H*)-dione: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.22 (s, 3H), −0.14 (s, 3H), 0.79 (s, 9H), 2.42 (dd, J = 16, 8 Hz, 1H), 2.73 (dd, J = 16, 2 Hz, 1H), 3.27−3.31 (m, 1H), 3.27 (dd, J = 9, 7 Hz, 1H), 4.06 (dd, J = 8, 4 Hz, 1H), 4.63 (m, 1H), 4.66−4.67 (m, 1H), 4.77 (t, J = 8 Hz, 1H), 4.96 (dd, J = 9, 4 Hz, 1H), 7.25−7.27 (m, 2H), 7.30−7.35 (m, 3H), 7.39−7.42 (m, 3H), 7.47−7.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.2, −5.1, 17.8, 25.3, 29.4, 38.4, 41.5, 50.1, 59.5, 71.3, 98.3, 125.9, 126.4, 128.6, 128.7, 129.2, 129.4, 131.8, 140.8, 152.4, 158.4, 176.4, 177.8; IR ($CHCl_3$) 2969, 2798, 1758, 1713, 1468, 1382, 1293, 1204, 1071, 999, 737 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{29}H_{34}N_2O_5Si$ 518.2236, found 518.2264.

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Supporting Information Available: Kinetics data for diene **10** and ^{1}H NMR and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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