Chiral Amino Siloxy Dienes in the Diels−Alder Reaction: Applications to the Asymmetric Synthesis of 4-Substituted and 4,5-Disubstituted Cyclohexenones and the Total Synthesis of (−)-α-Elemene

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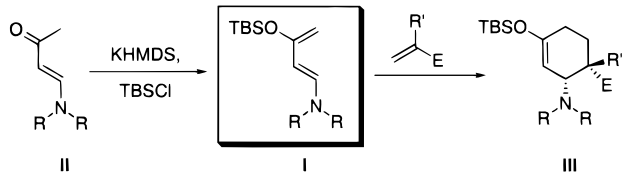
Abstract: Described is a study of the preparation, reactivity, and diastereoselectivity of chiral 1-amino-3-siloxy-1,3-butadienes in the Diels−Alder reaction. These dienes were easily prepared in good yield from the corresponding enantiomerically pure substituted pyrrolidines. All the dienes described underwent cycloadditions readily with several activated dienophiles under mild reaction conditions. An amino siloxy diene containing a C_2-symmetric 2,5-diphenylpyrrolidine auxiliary was found to provide high diastereofacial control, even at or above room temperature. Upon hydrolysis of the cycloadducts, 4-substituted and 4,5-disubstituted cyclohexenones were obtained with ee's ranging from 85% to >98%. A simple model based primarily on steric arguments was developed to rationalize and predict the absolute configurations of final products obtained by this sequence. The synthetic utility of the methodology was illustrated through a concise enantioselective synthesis of (−)-α-elemene. The synthesis also served to establish the absolute stereochemistry of the Diels−Alder product of the chiral amino siloxy diene and methacrolein.

Introduction

An understanding of nonbonding interactions—the steric and electronic factors that determine enantiofacial recognition—that take place in the transition state along the reaction coordinate is of fundamental importance to advances in asymmetric synthesis.[1] Given the weak nature of these interactions, the energy differences between the competing diastereomeric transition states are small and are influenced by subtle factors. An appreciation of these factors not only allows the stereochemical outcome of the reactions to be rationalized but also provides a mechanistic framework for further development of the transformation being studied. An important step in understanding the enantioselection process is the development and testing of simple, reliable models that allow the prediction of the chiral induction.[2] With a good model the reaction can be incorporated with confidence in the asymmetric synthesis of complex targets.[3] We describe here a general method, based on the diastereoselective [4 + 2] cycloadditions of chiral 1-amino-3-siloxy-1,3-dienes (**I***),[4] for the asymmetric syntheses of various 4-substituted and 4,5-disubstituted cyclohexenones with high enantiomeric excesses (ee's). A simple, steric argument model is proposed for predicting the absolute stereochemistry of the products.

We have recently shown that 1-amino-3-siloxy-1,3-dienes (**I**) are prepared efficiently from readily available vinylogous amides (**II**)[5a] and are exceptionally reactive in the Diels−Alder reaction with a wide range of dienophiles.[6] The amino group in the cycloadducts (**III**)[5b] can either be eliminated, to afford substituted cyclohexenones, or used as a handle for the synthesis of nitrogen-containing heterocycles. The latter aspect was recently illustrated through the total synthesis of the *Aspidosperma* alkaloid, tabersonine.[7]



It was evident that amino siloxy dienes possessing a chiral amine would be readily available using the above route and that their cycloadditions with dienophiles could provide simple access to enantiomerically enriched, substituted cyclohexenones (**VI**, Scheme 1). Such compounds are important building blocks for the total synthesis of natural products,[8] and their asymmetric synthesis represents a long-standing problem in organic synthesis.[9] The sequence shown in Scheme 1 provides a simple

(1) (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985. (b) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (c) Cervinka, O. *Enantioselective Reactions in Organic Chemistry*; Ellis Harwood: Chichester, U.K., 1995. (d) Ager, D. J. East, M. B. *Asymmetric Synthetic Methodology*; CRC Press: Boca Raton, FL, 1996.

(2) For recent reviews, see: (a) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1151. (b) Regan, A. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 357.

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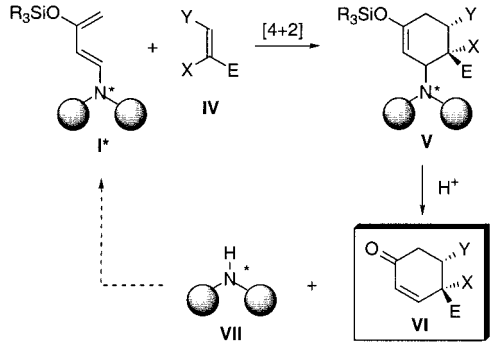
Scheme 1



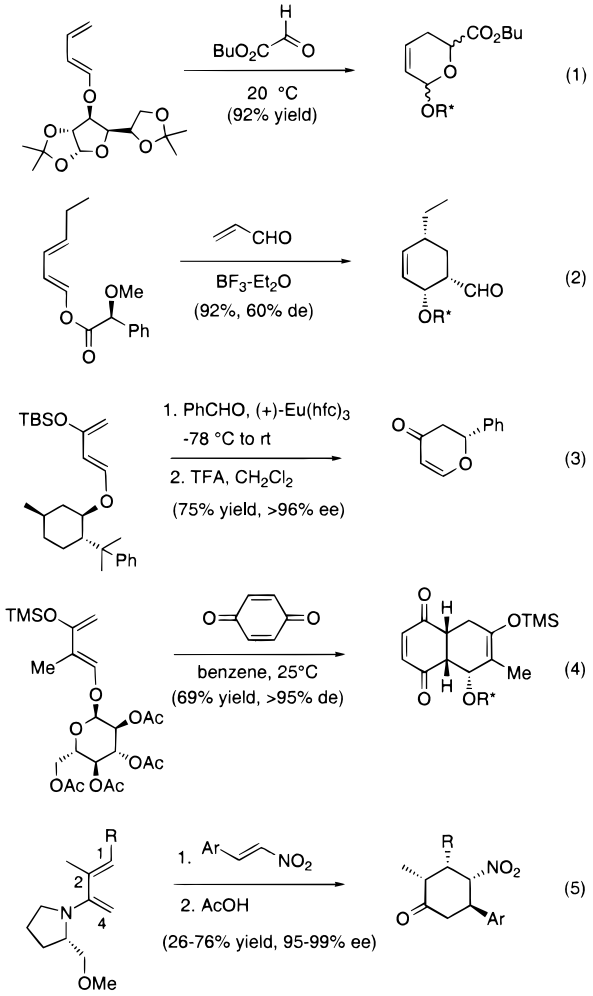
route to enantiomerically enriched 4- and 4,5-disubstituted cyclohexenones, provided that high levels of asymmetric induction are possible for the Diels−Alder reaction. The chiral amine could be reused after hydrolysis of the cycloadduct.

Background

The asymmetric Diels−Alder reaction represents a powerful method for the efficient assembly of various six-membered carbocycles and heterocycles in enantiomerically enriched form.[10] The vast majority of the investigations on this topic have taken advantage of chirally modified dienophiles, mostly acrylate derivatives.[11] The use of chiral Lewis acids has also received considerable attention, particularly of late.[12] By contrast, progress in the area of chiral dienes has been relatively slow over the 20 years since their original conception.[13] Many types of 1,3-dienes are capable of undergoing [4 + 2] cycloadditions, and the introduction of chiral directing groups into them represents an attractive but challenging task. Selected examples of Diels−Alder reactions of chiral nonracemic dienes are discussed below.

Perhaps the first report on the preparation and use of a chiral diene in the Diels−Alder reaction is by David and co-workers, who reported in 1974 a novel approach to disaccharide synthesis based on the cycloaddition of butyl glyoxalate with 1-alkoxy diene, wherein the alkoxy group is a carbohydrate (Scheme 2, eq 1).[14a] Over the next few years, several other carbohydrate-derived dienes were developed by this group.[14] Although only moderate levels of diastereoselection were achieved, these initial reports demonstrated that the two diastereotopic faces of dienes

Scheme 2



can be differentiated by the presence of a chiral auxiliary, thus stimulating further explorations in this important area.

Another noteworthy advance in the chiral diene area was the report by Trost et al. in 1978.[15a] These authors used the Diels−Alder reaction between (S)-*O*-methylmandeloxy substituted diene and acrolein (eq 2) to introduce the necessary chirality of (+)-ibogamine. To explain the observed facial selectivity of the chiral diene, Trost proposed a π-stacking model, in which the phenyl group and the dienyl moiety are aligned in a parallel arrangement.[15a] Three years later Thornton and Siegel proposed a different rationale, which they called a "perpendicular" model, wherein the ester group occupied the *s-trans* conformation.[16] This arrangement, which was suppported on experimental[16a] and theoretical[16c] grounds, leads to a perpendicular orientation of the phenyl group with respect to the diene plane.

In 1983, Danishefsky et al. described the preparation of several enantiomerically pure 1-alkoxy-3-siloxy-1,3-butadienes

(8) Representative examples: (a) Myers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (b) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439. (c) Kobayashi, S.; Eguchi, Y.; Shimada, M.; Ohno, M. *Chem. Pharm. Bull.* **1990**, *38*, 1479. (d) Siegel, C.; Gordon, P. M.; Uliss, D. B.; Handrick, R. G.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865. (e) Smith, A. B., III; Nolen, E. G.; Shirai, R., Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837.

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(12) Reviews: (a) Narasaka, K. *Synthesis* **1991**, 1. (b) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (c) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129. (d) Dias, L. C. *J. Braz. Chem. Soc.* **1997**, *8*, 289. (e) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873.

(13) For an excellent recent review of the subject, see: Barluenga, J.; Suárez-Sobrino, A.; López, L. A. *Aldrichimica Acta* **1999**, *32*, 4.

(14) (a) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2274. (b) David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Chem. Commun.* **1975**, 701. (c) David, S.; Lubineau, A.; Vatele, J.-M. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1831. (d) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299. (e) David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. (f) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1795.

(15) (a) Trost, B. A.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (b) See also: Trost, B. A.; O'Krogly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(16) (a) Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *41*, 5225. (b) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630 and references therein. (c) Tucker, J. A.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1990**, *112*, 5465.

(eq 3).[17] High levels of asymmetric induction were achieved in the hetero Diels−Alder reactions of these dienes with aldehydes in the presence of chiral lanthanide Lewis-acids.[17b] Curiously, the potential application of these chiral dienes in the carbo Diels−Alder reaction was not discussed.

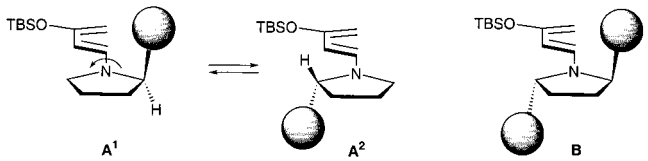
Between 1983 and 1989, Stoodley et al. reported the preparation of several chiral alkoxy dienes based on peracetylated glucopyranosyl auxiliaries (eq 4).[18] Although good diastereoselectivity was observed with highly reactive dienophiles such as maleic anhydride, benzoquinone, etc., the authors have not extended the scope of this method to simple mono-activated dienophiles, which have proven to be unreactive.[18d]

Recently, Enders[19] and Barluenga[20] have independently reported the use of chiral nonracemic 2-amino dienes[21] (eq 5). Various 4-nitro cyclohexanones were prepared in excellent enantiomeric purity (95−99% ee) via reactions of these dienes with nitrostyrenes. Certain unsaturated chromium carbene complexes and *N*-silyl imines were also found to undergo cycloadditions with high asymmetric induction.[20c−d] The reported amino dienes, however, always possess a methyl group on carbon 2, presumably to populate one rotomer of the prolinol-derived auxiliary.

These recent findings, in conjunction with the high Diels−Alder reactivity that we had observed for the 1-amino-3-siloxy-1,3-dienes, motivated us to develop chiral versions of these dienes.[4] We describe here the synthesis of such chiral dienes and their usefulness for the asymmetric synthesis of substituted cyclohexenones. Furthermore, the synthetic utility of the chiral dienes is illustrated through a concise, enantioselective synthesis of (−)-α-elemene, which also served to establish the absolute stereochemistry of the corresponding Diels−Alder adduct.

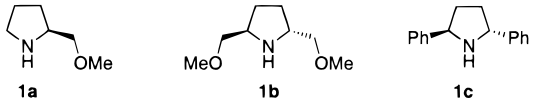
Results and Discussion

Auxiliary Selection. After considering several types of chiral amines, we decided to utilize an auxiliary based on the conformationally rigid five-membered pyrrolidine scaffold, since several substituted pyrrolidines are readily available in enantiomerically pure form[22] and their use in asymmetric synthesis is well precedented.[23] Mono- and disubstituted pyrrolidines were considered. Conformational analysis revealed that for mono-substituted pyrrolidine the corresponding diene could exist in an equilibrium between two conformers **A**$^{\mathbf{1}}$ and **A**$^{\mathbf{2}}$. The resonance interactions between the lone pair on the nitrogen atom and the π-system of the dienyl moiety were expected to hold the pyrrolidine ring in essentially the same plane as the alkene.[6] As a result, the chiral portion of the auxiliary could block either of the two diastereotopic faces of the diene. Although conformer **A**$^{\mathbf{1}}$ would predominate to minimize the allylic A^{1,3} strain, the energy difference between **A**$^{\mathbf{1}}$ and **A**$^{\mathbf{2}}$ was expected to be small. Therefore, a total of 8 diastereomeric transition states would be possible in this case.



The situation is considerably improved in the case of dienes which have a C_2 symmetric 2,5-disubstituted pyrrolidine. Only one rotomer (**B**) is possible in this case. There are still four diastereomeric transition states that must be considered: two endo and two exo.

After this initial analysis several chiral substituted pyrrolidines were considered for incorporation into amino siloxy dienes, and of these three were investigated thoroughly (**1a**−**c**).[24] *(S)*-2-(Methoxymethyl)pyrrolidine (SMP, **1a**) and *(R,R)*-2,5-di-(methoxymethyl) pyrrolidine (RDMP, **1b**) are both commercially available (>99% ee).[25] Particularly attractive was *(R,R)*-2,5-diphenylpyrrolidine (**1c**), since it was expected to be available through catalytic asymmetric reduction of 1,4-diphenylbutane-1,4-dione. Fortunately, just as we initiated the synthesis of **1c**, Chong et al. reported a convenient four-step preparation of this compound in high enantiomeric purity (>98% ee).[26]



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(19) (a) Enders, D.; Meyer, O.; Raabe, G. *Synthesis* **1992**, 1242. (b) Enders, D.; Meyer, O.; Runsink, J. *Synthesis* **1994**, 66.

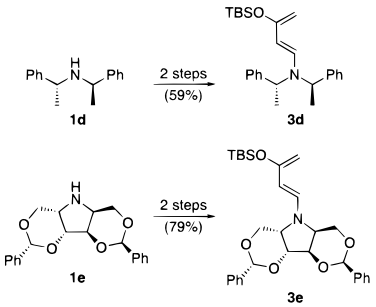
(20) (a) Barluenga, J.; Aznar, F.; Valdes, C.; Martin, A.; Garcia-Granda, S.; Martin, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403. (b) Barluenga, J.; Aznar, F.; Ribas, C.; Valdes, C.; Fernandez, M.; Cabal, M.-P., Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805. (c) Barluenga, J.; Aznar, F.; Martin, A.; Vazquez, J. T. *J. Am. Chem. Soc.* **1995**, *117*, 9419. (d) Barluenga, J.; Canteli, R. M.; Florez, J.; Garcia-Granda, S.; Gutierrez-Rodriguez, A.; Martin, E. *J. Am. Chem. Soc.* **1998**, *120*, 2514.

(21) For reviews, see: (a) Krohn, K *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1582. (b) Enders, D.; Meyer, O. *Liebigs Ann. Chem.* **1996**, 1023.

(22) (a) Pichon, M., Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927. (b) Studer, A. *Synthesis* **1996**, 793.

(23) *Organic Synthesis Highlights*; Waldman, H.. Ed.; VCH: New York, 1995; p 49.

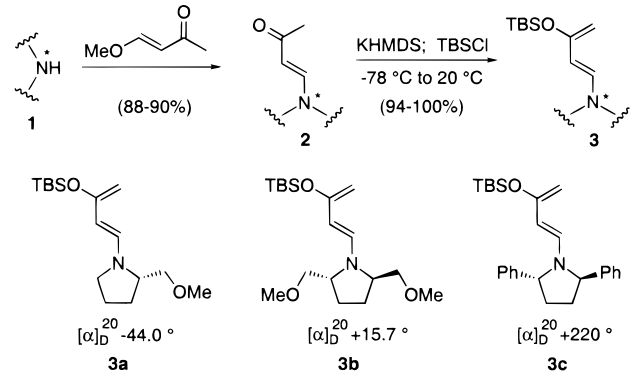
(24) Indeed two other C_2-symmetric amines were expected (**1d** and **1e**). Although both dienes were easily prepared using the general procedure outlined in the text (59% and 79% yields, respectively), they did not give superior results in the cycloaddition reactions compared to those obtained with diene **3c**, and thus they were not investigated as thoroughly. Diene **3d** was prepared from the commercially available secondary amine **1d**. It gave a messy reaction with methacrolein and an unpromising 30:24:29:17 mixture of four diastereomers with methyl acrylate. The mannitol-derived compound **1e**, was also synthesized and examined briefly. However, diene **3e**, derived from this amine, was less reactive than the other dienes, and the yields and ee's were no better than those obtained with diene **3c**. The following results were obtained for the cycloaddition/reduction/hydrolysis sequence using diene **3e**: (a) methacrolein, 33% yield, 67% ee; (b) methyl acrylate, 63% yield, 75% ee; (c) diethyl fumarate, 57% yield, 85% ee.



(25) (a) SMP was purchased from Aldrich Chemical Co. (b) RDMP was purchsed from Acros Organics.

(26) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J.; *Tetrahedron: Asymmetry* **1995**, *6*, 409.

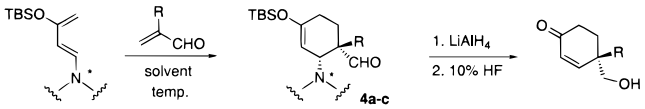
Scheme 3



Synthesis of Chiral Amino Siloxy Dienes. The required chiral dienes (**3a**−**c**) were prepared according to the standard procedure used for the achiral dienes.[5] Chiral amines **1a**−**c** reacted cleanly with 4-methoxy-3-buten-2-one (Scheme 3), affording the corresponding vinylogous amides **2a**−**c** in 88−90% yield. Silylation was accomplished next by treatment of the vinylogous amides with KHMDS followed by the addition of TBSCl. Standard workup procedure, which involved filtration of the reaction mixture followed by removal of all volatile reagents, afforded the desired dienes **3a**−**c** in 94−100% yield. The dienes so prepared were pure by NMR and can be used directly without additional purification. For the studies described, diene **3a** was purified by distillation, whereas dienes **3b** and **3c** were used without purification.

Cycloadditions with Substituted Acroleins. Methacrolein was selected as the initial dienophile to probe the asymmetric induction in the Diels−Alder reactions with chiral dienes **3a**−**c** (Table 1). This selection was based on our previous finding that [4 + 2] cycloaddition of this dienophile with the parent 1-(dimethylamino)-3-siloxy-1,3-diene proceeded under mild conditions and with complete endo selectivity.[5] In the event, the reaction between diene **3a** and methacrolein occurred upon warming the toluene solution from −20 °C to room temperature and afforded the corresponding cycloadduct **4a** in essentially quantitative yield (entry 1). The NMR analysis of the reaction mixture showed that the two possible endo-diastereomers were formed in 85:15 ratio. Reduction of the crude product mixture, followed by HF-mediated elimination gave the expected enone **5** in 79% overall yield and 68% ee, as determined by the NMR analysis of the corresponding (S)-MTPA ester.[27] The RDMP-derived diene **3b** was examined next. We were gratified to observe that the reaction between **3b** and methacrolein proceeded readily at room temperature despite the larger steric bulk of the *trans*-2,5-disubstituted pyrrolidine auxiliary. The NMR analysis of the final reaction mixture revealed that 3 diastereomers were formed in 76:17:7 (endo:endo:exo)[28] ratio (entry 2). The standard reduction-elimination sequence afforded enone **5** in 69% yield and 46% ee. This result was puzzling since the C_2-symmetric auxiliary in **3b** was expected to provide higher diastereoselectivity compared to the SMP-derived diene **3a**. The best results were obtained with diene **3c**, which has a C_2-symmetric pyrrolidine possessing the sterically more demanding phenyl substituents.

Table 1. Asymmetric [4 + 2] Cycloadditions of Chiral Amino Siloxy Dienes with Substituted Acroleins



entry	diene	R	solvent[a]	temp (°C)[a]	cycloadduct (yield, %)[b]	enone (yield, %)[b]	ee (%)[c]
1	**3a**	Me	PhMe	20	**4a** (100)[d]	**5** (79)	68 (*R*)
2	**3b**	Me	PhMe	20	**4b** (100)[e]	**5** (69)	46 (*S*)
3	**3c**	Me	PhMe	20	**4c** (94)[f]	**5** (83)	46 (*S*)[g]
4	**3c**	Me	THF	20	**4c** (85)[f]	**5** (72)	86 (*S*)
5	**3c**	Me	CH_3CN	20	**4c** (52)[f]	**5** (56)	76 (*S*)
6	**3c**	Me	PhMe	−10	**4c** (71)[f]	**5** (79)	88 (*S*)
7	**3c**	Et	PhMe	20	**6** (86)[f]	**7** (87)	88 (*S*)

[a] Solvent used for the cycloaddition step. [b] Isolated yield after silica gel chromatography. [c] Determined by the ^{1}H NMR analysis of the corresponding *S*-MTPA ester. [d] Cycloadduct obtained as a mixture of two diastereomers in 85:15 ratio. [e] Cycloadduct obtained as a mixture of three diastereomers in 76:17:7 ratio. [f] Distereomeric ratio not determined because the NMR signals could not be resolved. [g] Determined by capillary GLC analysis of the corresponding TMS ether using a chiral B-DM column.

Diene **3c** reacted cleanly with methacrolein (20 °C, toluene) to give one major endo-diastereomer (**4c**), as determined from the NMR analysis of the crude reaction mixture. Although the presence of a small amount of minor diastereomer was detected, it was difficult to quantify. Consequently, the product mixture was taken onto the next step. Reduction of the formyl group followed by HF-mediated hydrolysis/elimination afforded enone **5** in 94% yield and 86% ee, as determined by ^{1}H NMR analysis of the corresponding (*S*)-MTPA ester (Table 1, entry 3). Chiral GLC analysis (B-DM column, Advanced Separation Technologies) of the TMS ether obtained from **5** gave a similar value (85% ee), thus confirming the precision of the Mosher ester NMR analysis. It is also noteworthy that the chiral diphenylpyrrolidine auxiliary was recovered in 87% yield after the hydrolysis step.

The effect of solvent and temperature on the asymmetric induction in this reaction was evaluated briefly. When THF was used for the cycloaddition, the Diels−Alder adduct was obtained in slightly lower yield (85% yield, entry 4) but the enantiomeric excess of the final enone (**5**) was essentially the same (86% ee). In acetonitrile, the yield of the cycloadduct and the ee of the final product were lower (entry 5). Temperature appeared to have only a small effect on the asymmetric induction. The reaction conducted in toluene at −10 °C for 24 h resulted in only a slightly higher enantiomeric excess of the final enone (88% ee, entry 6). On the basis of these findings toluene was used as the reaction solvent for the rest of the studies.

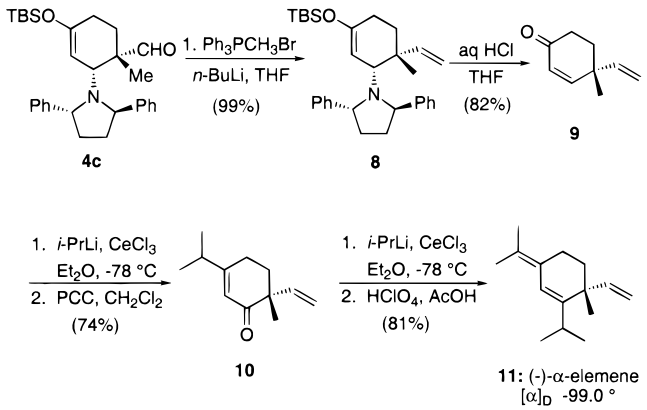
The reaction of diene **3c** with ethylacrolein (entry 7) proceeded in a manner similar to that with methacrolein. The product was primarily the endo-adduct **6** (entry 7), and the cyclohexenone obtained upon reduction and hydrolysis was essentially identical in ee to that obtained with methacrolein. A comparison of the ^{1}H NMR spectra of the (*S*)-MTPA esters of **5** and **7** clearly indicated that both had the same absolute configuration.

Asymmetric Synthesis of (−)-α-Elemene. The absolute configuration of the newly created quaternary chiral center in enone **5** was determined next. Neither enones **5** nor **7**, nor simple derivatives thereof, had previously been reported in enantiomerically enriched form. Thus, to establish the absolute stere-

(27) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S.; *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.

(28) The assignment of the relative stereochemistry was made based on the multiplicity of the silyl enol ether proton. In the case of the endo-isomer this proton is observed as a doublet with a *J* value of 5−6 Hz, due to the coupling to the vicinal proton adjacent to the amino group. The similar resonance corresponding to the exo-diastereomer is usually displayed as a triplet with a very small coupling constant of 1−2 Hz.

Scheme 4

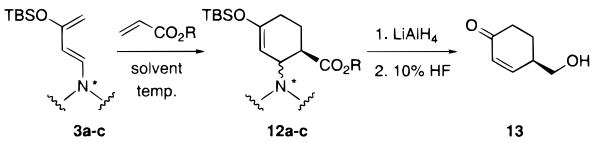


ochemistry of cyclohexenone **5**, we undertook a total synthesisof α-elemene **11**, a naturally derived terpene of known chirality.[29] The synthesis began with the Wittig methylenation of Diels−Alder adduct **4c**, which proceeded in nearly quantitative yield (Scheme 4). The resulting vinyl-substituted compound **8** was treated with a 1.2 M aqueous solution of HCl in THF, which cleanly accomplished both the hydrolysis of the silyl enol ether and the elimination of the diphenylpyrrolidine group to reveal 4-methyl-4-vinyl cyclohexenone (**9**) in 82% yield.

What was required for conversion of enone **9** to α-elemene was the introduction of two isopropyl groups. The reaction of enone **9** with *i*-PrLi in the presence of $CeCl_3$[30] gave the 1,2-addition product, which was oxidized with pyridinium chlorochromate[31] to afford the transposed enone, **10**.[29b] A second $CeCl_3$ promoted addition of *i*-PrLi to **10**, followed by acid-catalyzed dehydration afforded α-elemene (**11**) that was spectroscopically identical to the reported compound.[29] The optical rotation of the synthetic sample ($[\alpha]^{20}_D = -99.0°$, $CHCl_3$, $c = 1.1$) confirmed that its absolute stereochemistry was opposite to that of the naturally derived material (lit.[29a] $[\alpha]^{25}_D = +112°$). The (*S*)-configuration of cyclohexenone **5** was thus firmly established.

Transition-State Model. In developing a model that explains the observed absolute configuration of enones **5** and **7** one needs to first consider the inherent high endo selectivity observed for cycloadditions of α-substituted acroleins with 1-amino-3-siloxy-1,3-dienes.[5] Thus, of the four possible diastereomeric transition states only the two endo ones, $\mathbf{C^1}$ and $\mathbf{C^2}$, are expected to dominate (Scheme 5). The preferred approach of the dienophile is from the α-face of the diene, corresponding to transition structure $\mathbf{C^1}$, such that the larger substituent on the dienophile (alkyl vs CHO) is placed in the "open pocket" of the chiral diphenylpyrrolidine scaffold. This results in the formation of cyclohexenone final products (**5** or **7**) possessing the (*S*)-configuration, in agreement with the experimental results.

Table 2. Asymmetric [4 + 2] Cycloadditions of Chiral Dienes **3a**−**c** with Acrylates



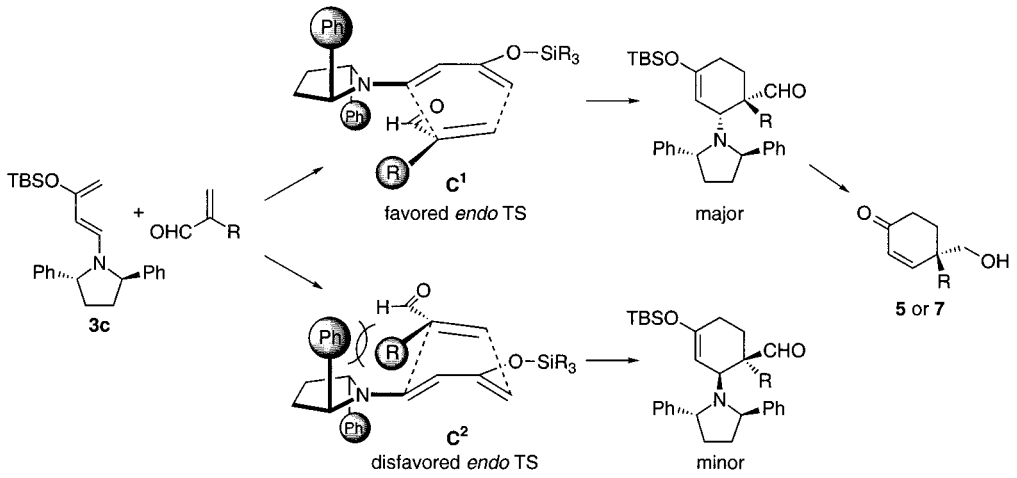
entry	diene	R	cycloadduct (yield, %)[b]	enone **13** (yield, %)[b]	ee (%)[c]
1	**3a**	Me	**12a** (99)[c]	45	26 (*S*)[f]
2	**3b**	Me	**12b** (78)[d]	85	50 (*r*)[f]
3	**3c**	Me	**12c** (81)[e]	72	93 (*R*)[g]
4	**3c**	*t*-Bu	**12c** (82)	86	98 (*R*)[g]

[a] Cycloadditions carried out in toluene at 20 °C. [b] Isolated yield after silica gel chromatography. [c] Determined ratio not determined due to unreselved NMR signals. [d] Cycloadduct obtained as a mixture of four diastereomers in 63:18:15:4 ratio. [e] Cycloadduct obtained as a mixture of three diastereomers in 88:8:4 ratio. [f] Determined by Mosher ester NMR analysis. [g] Determined by capillary GLC analysis of the corresponding acetate using a chiral B-DM column.

Cycloadditions with Acrylates. The cases discussed so far have dealt with cycloadditions that proceeded with endo selectivity. We next examined reactions of the chiral amino siloxy dienes with methyl acrylate (Table 2), a dienophile that had displayed poor endo selectivity in reactions with the parent achiral 1-amino-3-siloxy dienes.[5]

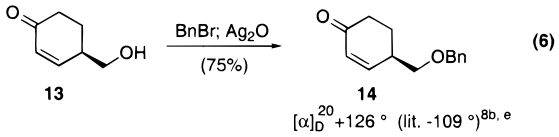
The cycloaddition reaction of diene **3a** with methyl acrylate proceeded under mild conditions as before (20 °C, toluene, entry 1). The product (**12a**) appeared by NMR to be a mixture of all four possible diastereomers. After reduction and hydrolysis of the crude cycloadduct mixture, cyclohexenone **13** was obtained, but with only low enantiomeric enrichment (26% ee). The outcome of the reaction of diene **3b** with the same dienophile was more encouraging (entry 2). Although the initial cycloadduct was again determined to be a mixture of diastereomers, its subjection to the reduction-elimination sequence afforded enone **13** in 85% yield and 50% ee. On the basis of the results with acroleins, the diphenylpyrrolidine derived diene (**3c**) was

Scheme 5



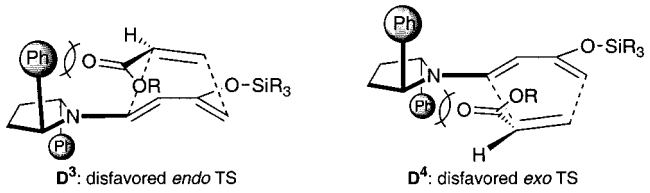
expected to give even higher enantiomeric excess for this reaction. Indeed, cycloadduct **12c** was produced cleanly at room temperature, albeit as a mixture of three diastereomers in 88:8:4 ratio (exo:endo:exo) as judged from the ^{1}H NMR of the crude reaction mixture. Upon reduction of the ester group and acidic hydrolysis, 4-(hydroxymethyl)-cyclohexenone (**13**) was obtained in 72% yield and 93% ee (entry 3). This result corresponds to a remarkable 96.5:3.5 ratio of enantiomers. The measured ee of **13** is in a good agreement with the assumption that the two major diastereomers of cycloadduct **12c** are converted into the same enantiomer of **13**, with the minor diastereomer giving a small amount of the opposite enantiomer. The cycloaddition of diene **3c** with *tert*-butyl acrylate proceeded with even higher facial discrimination and afforded cyclohexenone **13** with >98% ee (entry 4).

The absolute stereochemistry of enone **13** was established by its conversion to the known (−)-4-(benzyloxymethyl)-cyclohexenone **14**.[8b,e] Treatment of enone **13** (98% ee) with an excess of benzyl bromide in the presence of silver oxide afforded benzyloxy enone **14** in 75% yield (eq 6). The positive sign of the optical rotation displayed by this compound confirmed it to possess (*R*)-configuration.



(6)

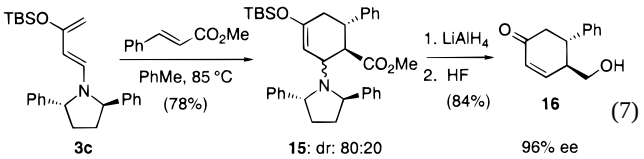
Transition-State Model. A good model for the above reaction must explain not only the absolute stereochemistry of the product—which has the electron-withdrawing group on the opposite face of the cyclohexenone product vis-à-vis the situation with methacrolein—but must also explain the higher selectivity with *tert*-butyl acrylate. All four possible diastereomeric transition states must be considered in order to explain the outcome of the cycloadditions of chiral diene **3c** with acrylate dienophiles. Heeding the requirement that the favored transition states are those with the larger group on the dienophile in the open pocket of the chiral scaffold, the two energetically favored structures are **D^1** and **D^2** (Scheme 6). The two remaining transition states, **D^3** and **D^4**, are expected to be higher in energy, since the withdrawing group and the phenyl group are close to each other, in a sterically unfavorable arrangement. This rationale is consistent with the higher selectivity observed with *tert*-butyl acrylate.



Note that although the two favored transition states, **D^1** and **D^2**, give diastereomeric cycloadducts, the absolute stereochemistry of the carbon α to the electron-withdrawing group is the same for both. After reduction of the ester and hydrolytic elimination of the pyrrolidine, both adducts produce the (*R*)-enantiomer of enone **13**. This result illustrates an important feature of this reaction: *As a consequence of the* C_2 *symmetry in the chiral auxiliary, the diastereofacial selection by the diene induces the same absolute stereochemistry at the carbon* α *to the withdrawing group, for both the endo- and the exo-cycloadducts.*

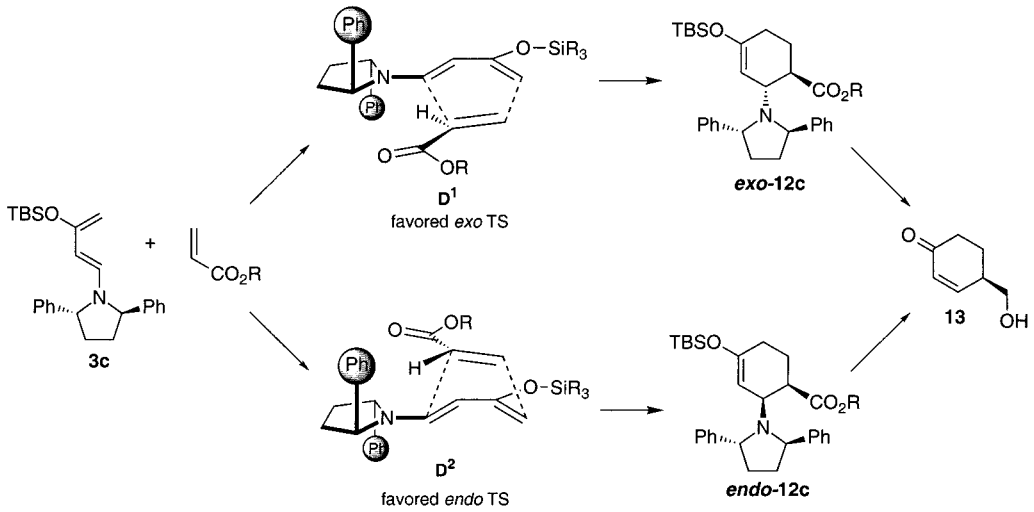
It was evident by this time that chiral diene **3c** was the best candidate for the preparation of various cyclohexenones in high enantiomeric excess. To examine the scope and generality of this method, the reaction of diene **3c** was examined with several other dienophiles.

Cycloaddition with Methyl Cinnamate. The reaction of amino siloxy diene **3c** with methyl cinnamate represents another example in which excellent asymmetric induction is observed despite the formation of several diastereomeric cycloadducts. When a solution containing diene **3c** and methyl cinnamate (3 equiv) was heated to 85 °C for 18 h, the cycloadducts (**15**) were isolated in 78% yield as a mixture of two major diastereomers in 80:20 (exo:endo) ratio (eq 7). A very small amount (2−3%) of a third diastereomer was also detected, but its structure was not assigned. Standard reduction−hydrolysis sequence performed on this product mixture afforded the disubstituted cyclohexenone **16** in 84% yield and 96% ee. The high enantiomeric excess, determined by chiral HPLC analysis of the TMS ether of **16**, is noteworthy given the high temperature of this reaction.



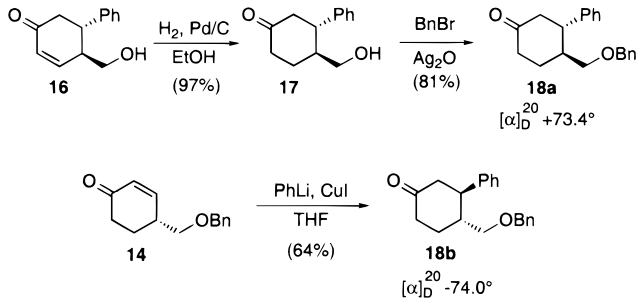
(7)

Scheme 6



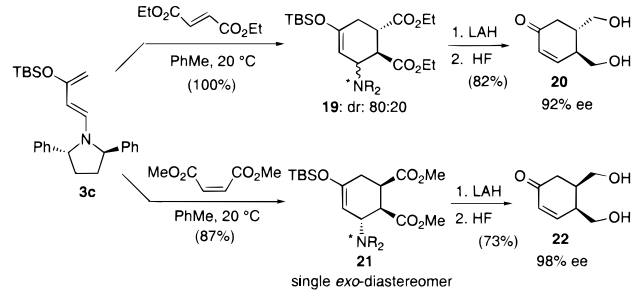
The determination of the absolute stereochemistry of enone **16** proved nontrivial (Scheme 7). Hydrogenation of **16** (H_2, Pd/C, EtOH) followed by benzylation of the alcohol gave saturated ketone **18a** in high yield. The same compound in enantiomeric form was independently prepared from the previously described (*R*)-enone **14** (Eq 6) by the conjugate addition of phenyl cuprate. The (3*R*,4*R*)-ketone **18b** thus obtained was identical in all respects to **18a**, except that its optical rotation had the opposite sign, establishing the absolute configuration of **16** as (4*R*,5*S*).

Scheme 7



Cycloadditions with Doubly-Activated Dienophiles. To further expand the scope of asymmetric [4 + 2] cycloadditions involving chiral amino siloxy diene **3c**, dienophiles containing two electron-withdrawing groups were evaluated next. Diene **3c** reacted smoothly with both diethyl fumarate and dimethyl maleate in toluene at room temperature (Scheme 8). The

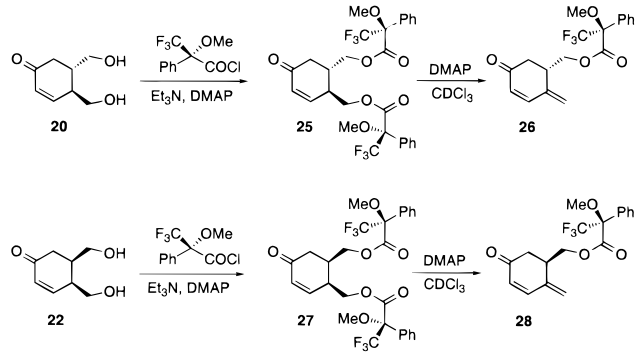
Scheme 8



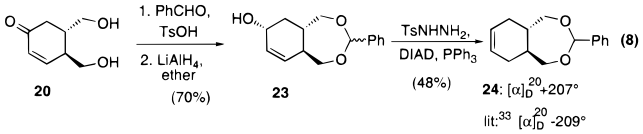
fumarate reaction was complete after 48 h and produced the corresponding cycloadduct **19** in quantitative yield. The product appeared to be a 80:20 mixture of exo- and endo-diastereomers. Reduction of both carboethoxy groups followed by treatment of the resulting diol with HF resulted in the clean formation of enone **20**, isolated in 82% overall yield. The Diels−Alder reaction was noticeably slower for dimethyl maleate and required 4 days to reach completion. The NMR of the crude reaction mixture indicated the formation of a single exo-diastereomer, **21**, which was converted into the cyclohexenone **22**. Enones **20** and **22** were clearly diastereomeric and were formed in high enantiomeric excesses (92% ee and 98% ee, respectively), as determined through their (S)-MTPA diesters (Scheme 9).

The (4*R*,5*S*) configuration of *trans*-disubstituted enone **20** was determined as shown in eq 8. Acetalization of the diolwith benzaldehyde, followed by $LiAlH_4$ reduction of theenone gave benzylidine **23** in good yield. Reductive transposition of the

Scheme 9

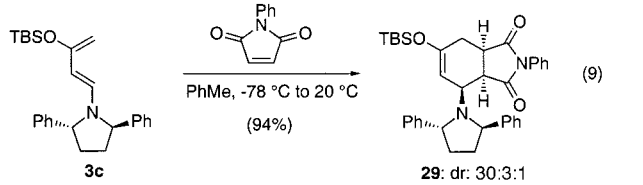


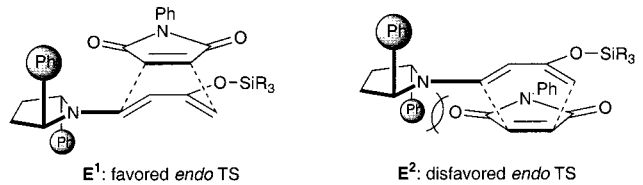
double bond[32] then afforded the desired alkene (**24**) in 48% yield. The optical rotation of the synthetic sample ($[\alpha]^{20}_D$ = +207°) was in good agreement with the literaturevalue obtained for the opposite enantiomer (lit:[33] $[\alpha]^{20}_D$ = −209°).



The MTPA diesters **25** and **27** initially prepared for the purpose of ee determination provided an opportunity for assigning the absolute stereochemistry to the cis substituted cyclohexenone **22** (Scheme 9). It was discovered that in the presence of DMAP diester **25** underwent a slow elimination of one of the acyloxy groups with the formation of dienone **26**. Since esters **26** and **28** were diastereomeric at C(4) based on their analysis by NMR, HPLC, and HRMS, the *(4R,5R)*-configuration was assigned to enone **22**.

The cycloaddition of **3c** with *N*-phenylmaleimide occurred cleanly as the reaction solution was allowed to warm slowly from −78 °C to room temperature (eq 9). Analysis of the final reaction mixture indicated the formation of three diastereomeric cycloadducts in 30:3:1 ratio. The major diastereomer, obtained after chromatographic separation, was assigned to be the endo-adduct **29**. The absolute stereochemistry of **29** has been tentatively assigned based on the expected preferred approach of the dienophile from the top face of the diene (**E**[1]). Approach from the bottom face (**E**[2]) is disfavored because of unfavorable steric and electronic interactions between the phenyl substituent on the diene and the carbonyl group of the dienophile.





A General Stereochemical Model. The usual strategy for achieving high levels of asymmetric induction in the Diels−

(29) (a) Paknikar, S. K.; Bhattacharyya, S. C. *Tetrahedron* **1962**, *18*, 1509. (b) Mehta, G.; Acharyulu, P. V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2759.

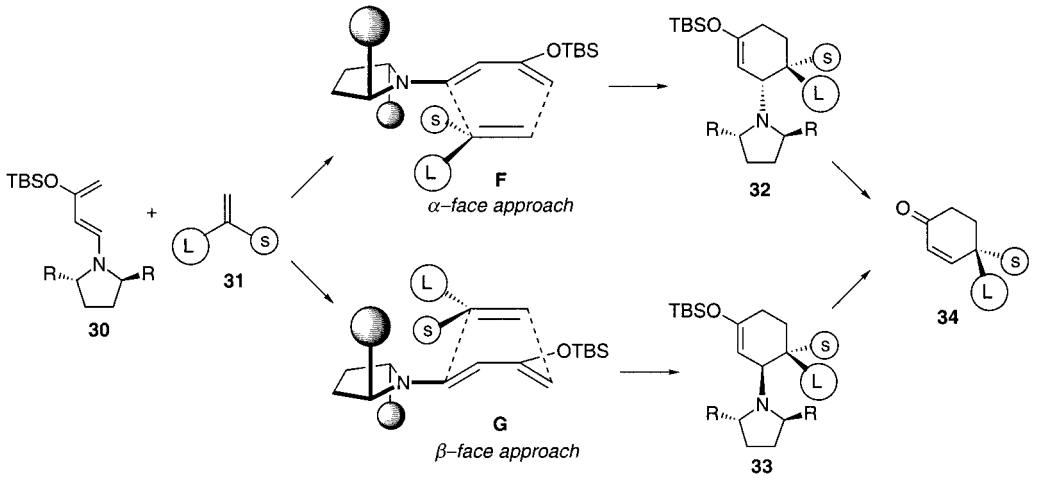
(30) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(31) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(32) (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492. (b) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

(33) Solladie, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555.

Scheme 10



Alder reaction requires both shielding of one of the diastereotopic faces of a chiral diene as well as stereoselective—typically endo-selective—approach of dienophile from the less hindered face. However, only a small number of dienophiles are capable of undergoing [4 + 2] cycloadditions with high endo/exo selectivity, so this approach has limited scope.

By contrast, the chiral amino siloxy diene strategy described above is applicable to a broad range of simple mono- and diactivated dienophiles. Various cyclohexenone derivatives are obtained in high enantiomeric purity, even in cases where the initial cycloadducts are obtained as mixtures of endo- and exo-diastereomers. No separation of the diastereomeric cycloadducts is required prior to removal of the auxiliary (reduction−hydrolysis). This interesting phenomenon can be understood by considering the simple, general model presented in Scheme 10.

The fundamental tenet of this model is the same as in most stereoselective processes: the reaction will proceed by the path with minimum nonbonding interactions. Thus, the two low-energy transition states (**F** and **G**) have the larger group on the dienophile in the open pocket of the diphenylpyrrolidine. This results in formation of two diastereomeric cycloadducts, **32** and **33**, which differ from each other only in the configuration of the amino group. This analysis reveals an important feature of this approach: *Even if the two diastereomeric cycloadducts are formed in equal amounts, the enantiomeric purity of the final product (**34**) can still be high, since upon hydrolysis both adducts are converted into the same enantiomer of the final cyclohexenone product.* This reaction topography differs significantly from the usual methods of controlling absolute stereochemistry in the Diels−Alder reaction. A significant advantage of this method is that it avoids the need for the separation of endo- and exo-diastereomers and opens up the possibility of utilizing a wide variety of dienophiles. Moreover, this simple concept should have implications in other asymmetric processes.

Conclusions

We have demonstrated that chiral amino siloxy dienes can be prepared efficiently from the corresponding nonracemic amines via a two-step sequence. These dienes react with dienophiles under mild conditions and provide convenient access to various substituted cyclohexenones. The amino siloxy diene having the C_2 symmetric *trans*-diphenylpyrrolidine at the 1-position was found to be particularly effective in asymmetric Diels−Alder reactions, affording 4-substituted and 4,5-disubstituted cyclohexenones in 85−98% ee. A simple general model is proposed to rationalize (and predict) the stereochemical course of these reactions. The synthetic utility of this novel chiral diene was demonstrated through the asymmetric synthesis of (−)-α-elemene.

Experimental Section

General Methods. See Supporting Information.

4-[2-(*S*)-Methoxymethyl-pyrrolidin-1-yl]-3-butene-2-one (2a). To a solution of methoxybutenone (0.38 mL, 3.8 mmol) in CH_2Cl_2 (1.5 mL) was slowly added amine **1a** (420 mg, 3.65 mmol). The resulting light yellow solution was stirred for 3 h at 20 °C. Concentration in vacuo, followed by a flash chromatography on silica gel (elution with ether followed by 10% Et_3N in EtOAc) afforded 590 mg (88%) of vinylogous amide **2a** as a clear oil: $[\alpha]^{20}_D = -56.4°$ ($CHCl_3$, c = 1.68); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.0 (m, 4H), 2.11 (s, 3H), 3.25 (m 2H), 3.36 (m, 5H), 3.76 (m, 1H), 5.07 (d, J = 12.9 Hz, 1H), 7.74 (d, J = 12.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 26.8, 27.8, 47.2, 58.9, 61.2, 74.8, 98.4, 148.2, 194.9; IR (neat) 2927, 1652, 1602, 1559, 1358, 1251, 1108, 960 cm^{-1}; HRMS m/z [M$^+$] calcd for $C_{10}H_{17}NO_2$ 183.1259, found 183.1262.

4-[2,5-(*R,R*)-Dimethoxymethyl-pyrrolidin-1-yl]-3-butene-2-one (2b). A solution of methoxybutenone (200 mg, 2.0 mmol) and amine **1b** (236 mg, 1.48 mmol) in toluene (0.4 mL) was heated to 80 °C for 2 h. Concentration of the reaction mixture in vacuo, followed by bulb-to-bulb distillation (225 °C, 0.25 mmHg) afforded the corresponding vinylogous amide **2a** as a clear oil: $[\alpha]^{20}_D = +92.1°$ ($CHCl_3$, c = 0.75); ^{1}H NMR (400 MHz, 55 °C, $CDCl_3$) δ 1.85 (m, 2H), 2.10 (m, 2H), 2.07 (s, 3H), 3.33 (s, 6H), 3.34 (m, 4H), 3.75 (m, 2H), 5.20 (d, J = 13.0 Hz, 1H), 7.69 (d, J = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, 55 °C, $CDCl_3$) δ 26.8, 27.3, 59.0, 60.2, 73.3, 99.6, 146.9, 194.8; IR (neat) 2979, 2884, 1653, 1602, 1558, 1354, 1114, 961 cm^{-1}.

4-[2,5-(*R,R*)-Diphenyl-pyrrolidin-1-yl]-3-butene-2-one (2c). A solution of (+)-*trans*-2,5-diphenylpyrrolidine **1c** (2.78 g, 12.5 mmol) and methoxybutenone (1.63 mL, 16 mmol) in CH_2Cl_2 (3 mL) was heated to 70−80 °C under constant stirring for 2.5 h, allowing the volatiles to evaporate. Upon cooling to room temperature the reaction mixture solidified. Excess methoxybutenone was removed under reduced pressure (50−60 °C, 0.25 mmHg), and the residue was redissolved in a minimum amount of CH_2Cl_2 and purified by flash chromatography on silica gel (elution with 50% EtOAc in hexanes) to afford 3.26 g (90%) of **2c** as a pale yellow solid: mp 147 °C (ether); $[\alpha]^{20}_D = +330°$ ($CHCl_3$, c = 0.985); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (m, 2H), 1.90 (s, 3H), 2.50 (m, 2H), 4,84 (d, J = 13.3 Hz, 1H), 4.93 (m, 1H), 5.09 (m, 1H), 7.18 (d, J = 7.4 Hz, 4H), 7.3 (m, 6H), 7.46 (d, J = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 32.7, 33.2, 63.6, 67.5, 101.8, 125.8, 126.5, 127.4, 127.9, 128.9, 129.1, 140.9, 142.8, 147.4, 195.7; IR ($CHCl_3$) 2982, 1653, 1597, 1550, 1344, 1255, 1216, 700 cm^{-1}; HRMS m/z [M$^+$] calcd for $C_{20}H_{21}NO$ 291.1623, found 291.1612.

General Procedure A. Preparation of 1-Amino-3-siloxy-1,3-butadienes (3). A solution of KHMDS in toluene (0.5 M, 38.4 mL,

19.2 mmol) was diluted with THF (35 mL) and cooled to −78 °C. To the resulting solution was added the vinylogous amide **2** (18.3 mmol) in THF (17 mL) over a period of 20 min. The reaction was warmed to −30 °C over a period of 3 h, cooled to −78 °C and treated with *tert*-butyldimethylchlorosilane (20.1 mmol) dissolved in THF (15 mL). The reaction mixture was allowed to reach room temperature, diluted with ether (350 mL), filtered through dry Celite, and concentrated in vacuo to give essentially pure amino siloxy diene.

4-(2-(*S*)-Methoxymethyl-pyrrolidin-1-yl)-3-(*tert*-butyldimethyl siloxy)-1,3-butadiene (3a). The reaction was performed according to the General Procedure A. The title compound was obtained as a colorless oil in 94% yield after bulb-to-bulb distillation (200 °C, 0.25 mmHg). $[\alpha]^{20}_D = -44.0°$ ($CHCl_3$, $c = 1.39$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.19 (s, 6H), 0.98 (s, 9H), 1.75 (m, 1H), 1.90 (m, 3H), 3.02 (m, 1H), 3.18 (m, 1H), 3.26 (dd, $J = 9.4$, 6.2 Hz, 1H), 3.34 (m, 1H), 3.34 (s, 3H), 3.82 (s, 1H), 3.89 (s, 1H), 4.79 (d, $J = 13.3$ Hz, 1H), 6.93 (d, $J = 13.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.5, 18.3, 23.5, 25.9, 28.5, 48.0, 59.1, 60.2, 75.5, 85.3, 95.7, 136.4, 156.6; IR (neat) 2928, 2857, 1641, 1604, 1362, 1315, 1258, 1022, 828, 779 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{16}H_{31}NO_2Si$ 297.2124, found 297.2120.

4-[2,5-(*R,R*)-Dimethoxymethyl-pyrrolidin-1-yl]-3-(*tert*-butyldimethyl siloxy)-1,3-butadiene (3b). The reaction was performed according to the General Procedure A. The title compound was obtained in 96% yield after the final concentration of the reaction mixture. At this stage the diene was determined to be spectroscopically pure and distillation was not attempted: $[\alpha]^{20}_D = +15.7°$ ($CHCl_3$, $c = 0.86$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.20 (s, 6H), 0.98 (s, 9H), 1.82 (m, 2H), 2.01 (m, 2H), 3.17 (dd, $J = 10.0$, 7.5 Hz, 1H), 3.33 (s, 6H), 3.42 (dd, $J = 10.0$, 4.0 Hz, 1H), 3.64 (m, 2H), 3.83 (s, 1H), 3.89 (s, 1H), 4.85 (d, $J = 13.5$ Hz, 1H), 6.83 (d, $J = 13.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.7, −4.4, 18.3, 25.9, 26.6, 58.9, 59.1, 73.2, 85.3, 96.1, 133.8, 156.6; IR (neat) 2928, 2857, 1641, 1362, 1116, 828 cm^{-1}.

1-[2,5-(*R,R*)-Diphenyl-pyrrolidin-1-yl]-3-(*tert*-butyldimethylsiloxy)-1,3-butadiene (3c). The reaction was performed according to the General Procedure A. The title compound was obtained in 100% yield after concentration of the reaction mixture in vacuo. At this stage the diene was determined to be spectroscopically pure and it was used without further purification. $[\alpha]^{20}_D = +220°$ ($CHCl_3$, $c = 1.24$); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.07 (s, 3H), 0.05 (s, 3H), 0.70 (s, 9H), 1.79 (m, 2H), 2.47 (m, 2H), 3.69 (s, 1H), 3.71 (s, 1H), 4.51 (d, $J = 13.5$ Hz, 1H), 4.87 (m, 1H), 4.89 (m, 1H), 6.61 (d, $J = 13.5$ Hz, 4H), 7.24 (m, 6H), 7.34 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.4, 18.0, 25.6, 33.1, 64.8, 86.2, 97.9, 126.3, 126.8, 128.5, 134.5, 143.8, 156.3; IR (neat) 2929, 1643, 1560, 1333, 1257, 1022,838, 700 cm^{-1}.

General Procedure B. Asymmetric Synthesis of Substituted Cyclohexenones. Preparation of (*4S*)-4-(Hydroxymethyl)-4-methyl-cyclohex-2-ene-1-one (5). (a) Cycloaddition. To a solution of diene **3c** (1.195 g, 2.94 mmol) in toluene (8 mL) at −20 °C was added methacrolein (0.32 mL, 3.8 mmol). The reaction mixture was stirred for 30 min at −20 °C, then allowed to reach room temperature and stirred for 22 h. Concentration in vacuo, followed by flash chromatography on silica gel (elution with 50% ether in hexanes containing 5% Et_3N) afforded 1.31 g (94%) of cycloadduct **4c** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.22 (s, 3H), 0.76 (s, 3H), 0.80 (m, 2H), 0.96 (s, 9H), 1.57 (dd, $J = 17.5$, 6.1 Hz, 1H), 1.69 (m, 1H), 1.77 (m, 1H), 2.55 (m, 2H), 3.46 (d, $J = 5.9$ Hz, 1H), 4.60 (m, 2H), 4.67 (d, $J = 5.9$ Hz, 1H), 7.2−7.3 (m, 10H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.4, −4.0, 18.0, 18.4, 23.2, 25.6, 25.7, 33.1, 48.8, 59.8, 101.8, 126.8, 127.5, 128.3, 152.7, 207.2; IR (neat) 2930, 1721, 1664, 1209, 701 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{30}H_{41}NO_2Si$ 475.2906, found 475.2889.

(b) Reduction. A suspension of lithium aluminum hydride (19 mg, 0.5 mmol) in ether (2 mL) at −78 °C was treated dropwise with a solution of **4c** (129 mg, 0.27 mmol) in ether (2 mL). The reaction mixture was stirred for 3 h at −78 °C, diluted with ether (10 mL), and quenched by addition of a small amount of water (until hydrogen evolution ceased). The resulting mixture was allowed to reach room temperature, and anhydrous Na_2SO_4 was added. The organic layer was carefully decanted from the solid, which was washed twice with ether (15 mL each). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford 118 mg (92%) of the expected alcohol, which was sufficiently pure for the next step.

(c) Hydrolysis. A solution of the crude alcohol described above (110 mg, 0.25 mmol) in acetonitrile (0.5 mL) was treated with a 10% solution of HF in acetonitrile (0.13 mL, 0.5 mL). The reaction mixture was stirred for 5 h at room temperature and purified directly by flash chromatography on silica gel (elution with 50% EtOAc in hexanes−ethyl acetate). This afforded 29 mg (90%) of **5** as a colorless oil: $[\alpha]^{20}_D = -28.0°$ ($CHCl_3$, $c = 1.85$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17 (s, 3H), 1.56 (dd, $J = 6.0$, 5.0 Hz, 1H), 1.78 (dddd, $J = 13.2$, 5.7, 5.7, 1.0 Hz, 1H), 2.10 (ddd, $J = 13.2$, 8.2, 6.8 Hz, 1H), 2.51 (m, 2H), 3.53 (dd, $J = 10.4$, 6.0 Hz, 1H), 3.59 (dd, $J = 10.4$, 5.0 Hz, 1H), 5.99 (d, $J = 10.0$ Hz, 1H), 6.73 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 30.8, 33.9, 38.2, 69.8, 129.1, 155.9, 199.6; IR (neat) 3360, 2924, 1670, 1049, 804 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_8H_{12}O_2$ 140.0837, found 140.0838. The ^{1}H NMR spectrum of this compound was in agreement with that reported in the literature.[34] Enantiomeric excess of **5** was determined to be 85% by capillary GLC analysis of the corresponding TMS ether using a chiral ASTEC B-DM (β-cyclodextrin, dimethyl) column (120 °C; flow rate, 1 mL/min; retention times, 17.96 min (major), 18.73 (minor)).

(*4S*)-4-(Hydroxymethyl)-4-ethyl-cyclohex-2-ene-1-one (7). The title compound was prepared according to General Procedure B in 75% overall yield. The initial Diels−Alder reaction was conducted at 20 °C for 48 h. $[\alpha]^{20}_D = -26.9°$ ($CHCl_3$, $c = 0.658$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.93 (t, $J = 7.5$ Hz, 3H), 1.59 (m, 2H), 1.90 (ddd, $J = 14.0$, 7.7, 5.8 Hz, 1H), 1.95 (ddd, $J = 14.0$, 7.7, 5.8 Hz, 1H), 2.10 (br s, 1H), 2.46 (ddd, $J = 17.5$, 7.7, 5.8 Hz, 1H), 2.52 (ddd, $J = 17.5$, 7.7, 5.8 Hz, 1H), 3.57 (d, $J = 10.8$ Hz, 1H), 3.63 (d, $J = 10.8$ Hz, 1H), 6.03 (d, $J = 10.3$ Hz, 1H), 6.78 (d, $J = 10.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 8.3, 27.8, 33.8, 40.9, 67.1, 129.6, 155.7, 200.0; IR (neat) 3390, 2931, 1669, 1557, 1387, 1044, 799 cm$^{-1;}$ HRMS *m*/*z* [M$^+$] calcd for $C_9H_{14}O_2$ 154.0994, found 154.0995. Enantiomeric excess was determined to be 85% by ^{1}H NMR (400 MHz) analysis of the corresponding Mosher ester. Major diastereomer: δ 4.22 (d, $J = 10.9$ Hz, 1H), 4.29 (d, $J = 10.9$ Hz, 1H); minor diastereomer: δ 4.12 (d, $J = 11.0$ Hz, 1H), 4.40 (d, $J = 11.0$ Hz, 1H).

(*3R,4R*)-3-[2,5-(*R,R*)-Diphenylpyrrolidin-1-yl]-4-methyl-4-vinyl-3-(*tert*-butyldimethylsiloxy)-cyclohex-1-ene (8). To a suspension of methyl triphenylphosphonium bromide (1.07 g, 3.0 mmol) in THF (7 mL) was added dropwise a solution of *n*-butyllithium in hexanes (1.3 mL, 2.5 M, 2.8 mmol). The resulting yellow solution of the ylide was stirred for 30 min, cooled to −78 °C, and treated with aldehyde **4c** (970 mg, 2.04 mmol) dissolved in THF (5 mL). The reaction mixture was allowed to warm to room temperature and stirred for 14 h. Water (10 mL) was added, and the aqueous phase was extracted thrice with ether. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Concentration in vacuo followed by flash chromatography on silica gel (elution with 14% ether in hexanes containing 5% Et_3N) afforded 959 mg (99%) of **8** as an orange oil: $[\alpha]^{20}_D = -46.0°$ ($CHCl_3$, $c = 1.00$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 0.13 (s, 3H), 0.19 (s, 3H), 0.69 (m, 2H),0.72 (s, 3H), 0.95 (s, 9H), 1.38 (dt, $J = 17.2$, 3.8 Hz, 1H), 1.60 (m, 1H), 1.70 (m, 2H), 2.54 (m, 2H), 3.02 (d, $J = 5.8$ Hz, 1H), 4.67 (m, 2H), 4.79 (dd, $J = 17.8$, 1.7 Hz, 1H), 4.85 (d, $J = 5.8$ Hz, 1H), 4.93 (dd, $J = 10.7$, 1.7 Hz, 1H), 6.12 (dd, $J = 17.8$, 10.7 Hz, 1H), 7.2−7.3 (m, 10H); ^{13}C NMR (75 MHz, $CHCl_3$) δ −4.2, −3.9, 18.0, 22.1, 25.7, 26.7, 28.0, 33.2, 40.3, 61.8, 104.3, 110.2, 126.2, 127.5, 127.8, 128.0, 148.1, 151.8; IR (neat) 2958, 2857, 1668, 1205, 836, 70 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{31}H_{43}NOSi$ 473.3113, found 473.3095.

(*4R*)-4-Methyl-4-vinyl-cyclohex-2-ene-1-one (9). To a solution of **8** (960 mg, 2.0 mmol) in THF (12 mL) was added a 1.2 M aqueous solution of HCl (4 mL). The reaction mixture was stirred at room temperature for 21 h, diluted with water, and then extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated. The crude material was dissolved in acetonitrile (3 mL) and treated with a 10% solution of HF in acetonitrile (11 mmol, 3 mL). The resulting mixture was stirred for 2 h at room temperature, concentrated in vacuo, and purified by flash chromatography on silica

(34) Gloor, G.; Schaffner, K. *Helv. Chim. Acta* **1974**, *57*, 1815.

gel (elution with 25% ether in pentane) to afford 223 mg (82%) of **9** as a colorless oil: $[\alpha]^{20}_D = -113°$ ($CHCl_3$, $c = 0.40$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.95 (m, 2H), 2.37 (ddd, $J = 16.6$, 4.8, 4.8 Hz, 1H), 2.46 (ddd, $J = 16.6$, 8.7, 7.6 Hz, 1H), 5.03 (dd, $J = 17.5$, 0.8 Hz, 1H), 5.12 (dd, $J = 10.4$, 0.8 Hz, 1H), 5.80 (dd, $J = 17.5$, 10.4 Hz, 1H), 6.00 (d, $J = 9.6$ Hz, 1H), 6.63 (d, $J = 9.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 34.2, 34.7, 39.3, 114.2, 128.5, 142.5, 155.9, 199.6; IR (neat) 2962, 2869, 1681, 1455, 1201, 922, 801 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_9H_{12}O$ 136.0888, found 136.0897. The ^{1}H NMR spectrum of this compound was in agreement with that reported in the literature.[35]

(*6R*)-3-Isopropyl-6-methyl-6-vinyl-cyclohex-2-ene-1-one (10). To a suspension of anhydrous $CeCl_3$, which was dried immediately prior to use, (369 mg, 1.5 mmol) in THF (5 mL) was added at −78 °C a solution of isopropyllithium in pentane (0.24 M, 6.2 mL, 1.5 mmol). The resulting mixture was stirred for 1 h at −78 °C and treated dropwise with a solution of enone **9** (136 mg, 1.0 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at −78 °C, allowed to reach 0 °C, and quenched by addition of water (1 mL). The resulting mixture was diluted with ether (20 mL), and dried over anhydrous Na_2SO_4. The organic layer was carefully decanted from the solid, which was washed twice with ether (15 mL each). The combined organic layers were additionally dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford 165 mg of the expected 1,2-addition product as a colorless oil. The crude product was dissolved in CH_2Cl_2 (4 mL) and PCC (430 mg, 2 mmol) was added in one portion. The resulting dark red−black mixture was stirred for 2.5 h at room temperature, then diluted with 6 mL of ether. The ethereal solution was decanted from the black resinous residue, which in turn was washed with three 6 mL portions of ether. The combined ethereal phases were washed successively with two 10 mL portions of 5% aqueous NaOH, 10 mL of 5% aqueous HCl, and two 5 mL portions of saturated aqueous $NaHCO_3$ and then dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (elution with 25% ether in pentane) to afford 131 mg (74% for two steps) of **10** as a colorless oil: $[\alpha]^{20}_D = +70.0°$ ($CHCl_3$, $c = 1.10$); ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.09 (d, $J = 6.9$ Hz, 6H), 1.19 (s, 3H), 1.85 (ddd, $J = 13.6$, 9.0, 5.1 Hz, 1H), 1.98 (ddd, $J = 13.6$, 5.1, 5.1 Hz, 1H), 2.35 (m, 3H), 5.00 (dd, $J = 17.6$, 0.8 Hz, 1H), 5.08 (dd, $J = 10.8$, 0.8 Hz, 1H), 5.85 (s, 1H), 5.90 (dd, $J = 17.6$, 10.8 Hz, 1H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 20.6, 20.7, 22.8, 25.0, 34.9, 35.4, 47.4, 114.0, 122.5, 140.8, 170.2, 202.2. ^{1}H NMR and ^{13}C NMR spectra for this sample were in good agreement with those reported for this compound.[29b]

(−)-α-Elemene (11). To a suspension of anhydrous $CeCl_3$, which was dried immediately prior to use, (369 mg, 1.5 mmol) in THF (5 mL) was added at −78 °C a solution of isopropyllithium in pentane (0.30 M, 5.0 mL, 1.5 mmol). The resulting mixture was stirred for 2 h at −78 °C and treated dropwise with a solution of enone **10** (127 mg, 0.71 mmol) in THF (2.5 mL). The reaction mixture was stirred for 2 h at −78 °C, allowed to reach 0 °C, and quenched by addition of water (1 mL). The resulting mixture was diluted with ether (20 mL) and dried with anhydrous Na_2SO_4. The organic layer was carefully decanted from the solid, which was washed twice with ether (15 mL each). The combined organic layers were additionally dried with anhydrous Na_2SO_4 and concentrated in vacuo to afford 149 mg (95%) of the expected 1,2-addition product as a colorless oil.

The crude 1,2-addition product (135 mg, 0.61 mmol) was slowly treated with a solution of $HClO_4$ (70%, 0.07 mL) in acetic acid (2 mL) under constant stirring. The resulting solution was stirred for 2 h and then diluted with water (20 mL) and ether (50 mL). The layers were allowed to separate, and the ethereal phase was washed with three 15 mL portions of saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (elution with pentane) to afford 105 mg (81% for 2 steps) of **11** as a colorless oil: $[\alpha]^{20}_D = -99.0°$ ($CHCl_3$, $c = 1.10$); (lit.[29a] $[\alpha]_D = +112.5°$); **¹**H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, $J = 6.8$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 1.17 (s, 3H), 1.50 (m, 1H), 1.60 (m, 1H), 1.73 (s, 3H), 1.80 (s, 3H), 2.25 (m, 2H), 4.97 (dd, $J = 17.3$, 1.5 Hz, 1H), 5.02 (dd, $J = 10.2$, 1.5 Hz, 1H), 5.77 (dd, $J = 17.6$, 10.8 Hz, 1H), 6.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 20.6, 22.8, 23.6, 24.6, 25.2, 29.3, 37.6, 42.1, 112.3, 119.5, 124.4, 127.8, 146.1, 149.5; IR (neat) 2930, 1635, 1461, 1372, 909 cm^{-1}. ^{1}H The NMR and ^{13}C NMR spectra for this sample were in good agreement with those reported for this compound.[29]

(*4R*)-4-(Hydroxymethyl)-cyclohex-2-ene-1-one (13, 93% ee). The title compound was prepared according to General Procedure B in overall 68% yield. The initial Diels−Alder reaction between diene **3c** and methyl acrylate was conducted at 20 °C for 20 h. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (m, 1H), 1.82 (dddd, $J = 12.6$, 12.6, 9.8, 5.0 Hz, 1H), 2.14 (dddd, $J = 12.6$, 9.7, 5.0, 1.3 Hz, 1H), 2.42 (ddd, $J = 16.8$, 12.6, 5.0, Hz,1H), 2.56 (ddd, $J = 16.8$, 5.0, 5.0 Hz, 1H), 2.65 (m, 1H), 3.71 (m, 2H), 6.08 (dd, $J = 10.0$, 2.2 Hz, 1H), 6.96 (ddd, $J = 10.0$, 2.7, 1.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 36.6, 38.9, 65.1, 130.2, 151.5, 199.9; IR (neat) 3370, 2924, 2871, 1669, 1050, 845 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_7H_{10}O_2$ 126.0681, found 126.0687. Enantiomeric excess was determined to be 93% by capillary GLC analysis of the corresponding acetate using a chiral ASTEC B-DM (β-cyclodextrin, dimethyl) column [160 °C; flow rate, 1 mL/min; retention times: 7.38 min (major), 7.15 (minor)].

(*4R*)-4-(Hydroxymethyl)-cyclohex-2-ene-1-one (13, 98%ee). The title compound was prepared according to General Procedure B in overall 71% yield. The initial Diels−Alder reaction between diene **3c** and *tert*-butyl acrylate was conducted at 20 °C for 20 h. $[\alpha]^{20}_D = +135°$ ($CHCl_3$, $c = 1.21$); ^{1}H and ^{13}C NMR spectra were identical to the compound described above. Enantiomeric excess was determined to be 98% by capillary GLC analysis of the corresponding acetate using a chiral ASTEC B-DM (β-cyclodextrin, dimethyl) column [160 °C; flow rate, 1 mL/min; retention times: 7.38 min (major), 7.15 (minor)].

(*4R*)-4-(Benzyloxymethyl)-2-cyclohexene-1-one (14). To a solution of alcohol **13** (39 mg, 0.31 mmol) in benzyl bromide (2 mL) was added silver oxide (201 mg, 0.87 mmol). The reaction mixture was stirred vigorously for 18 h, diluted with ether (10 mL), and filtered through tightly packed cotton wool. Concentration in vacuo followed by removal of benzyl bromide by bulb-to-bulb distillation (60 °C, 0.5 mmHg) afforded a colorless oil, which was purified by flash chromatography on silica gel (elution with 50% ether in hexane) to afford 41.3 mg (62%) of **14** as a colorless oil: $[\alpha]^{20}_D = +124.4°$ (MeOH, $c = 1.72$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (dddd, $J = 12.6$, 12.6, 9.8, 5.0 Hz, 1H), 2.10 (dddd, $J = 12.6$, 9.7, 5.0, 1.3 Hz, 1H), 2.35 (ddd, $J = 16.8$, 12.6, 5.0, Hz,1H), 2.50 (ddd, $J = 16.8$, 5.0, 5.0 Hz, 1H), 2.72 (m, 1H), 3.43 (dd, $J = 9.2$, 6.5 Hz, 1H), 3.48 (dd, $J = 9.2$, 6.5 Hz, 1H), 4.52 (s, 2H), 6.02 (dd, $J = 10.0$, 2.2 Hz, 1H), 6.92 (ddd, $J = 10.0$, 2.7, 1.3 Hz, 1H), 7.29−7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.9, 36.7, 37.0, 72.4, 73.3, 127.6, 127.8, 128.5, 130.0, 137.9, 151.6, 199.6; IR (neat) 2924, 2856, 1680, 1453, 1112, 739, 698 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1151. The ^{1}H NMR and ^{13}C NMR spectra for this sample were in good agreement with those reported for this compound.[8e]

(*4R,5S*)-4-(Hydroxymethyl)-5-phenyl-cyclohex-2-ene-1-one (16). The title compound was prepared according to General Procedure B in overall 66% yield. The initial Diels−Alder reaction was conducted at 85 °C for 20 h. $[\alpha]^{20}_D = +157°$ ($CHCl_3$, $c = 2.08$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (m, 1H), 2.61 (dd, $J = 16.4$, 4.8 Hz, 1H), 2.70 (dd, $J = 16.4$, 13.6 Hz, 1H), 2.80 (m, 1H), 3.23 (ddd, $J = 13.6$, 10.8, 4.8 Hz, 1H), 3.43 (m, 1H), 3.68 (m, 1H), 6.15 (dd, $J = 10.0$, 2.0 Hz, 1H), 7.12 (dd, $J = 10.0$, 2.1 Hz, 1H), 7.20−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 44.8, 45.1, 62.6, 127.2, 127.3, 128.8, 129.8, 141.6, 152.2, 199.2; IR (neat) 3430, 2884, 1676, 1388, 1253, 1073, 701 cm^{-1}; HRMS *m*/*z* [M$^+$] calcd for $C_{13}H_{14}O_2$ 202.0993, found 202.1006. Enantiomeric excess was determined to be 96% by HPLC analysis of the corresponding TMS ether using a chiral REGIS Whelk-O 1 column [eluent, hexane−2-propanol = 99:1; flow rate, 2 mL/min; retention times: 9.22 min (major), 10.09 min (minor)].

(*3S,4R*)-4-(Hydroxymethyl)-3-phenyl-2-cyclohexene-1-one (17). To a solution of enone **16** (70 mg, 0.35 mmol) in ethanol (5 mL) under nitrogen was added 5% Pd/C (30 mg). The resulting suspension was stirred at 1 atm of hydrogen for 18 h, at which point TLC analysis showed complete disappearance of the starting enone. The reaction mixture was diluted with 10 mL of EtOAc, filtered, concentrated, and purified by flash chromatography on silica gel (elution with 25% EtOAc

(35) Marx, J. N.; Hahn, Y. S. *J. Org. Chem.* **1988**, *53*, 2866.

in hexane) to afford 69 mg (97%) of **17** as a colorless oil: $[\alpha]^{20}_D = +57.4°$ ($CHCl_3$, $c = 1.03$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.65 (br s, 1H), 1.70 (m, 1H), 2.14 (m, 1H), 2.32 (m, 1H), 2.51 (m, 3H), 2.60 (dd, $J = 13.0$, 13.0 Hz, 1H), 2.84 (ddd, $J = 13.0$, 13.0, 4.5 Hz, 1H), 3.27 (dd, $J = 9.0$, 7.5 Hz, 1H), 3.46 (dd, $J = 9.0$, 2.6 Hz, 1H), 7.20 (d, $J = 7.4$ Hz), 7.24 (t, $J = 7.4$ Hz, 1H), 7.32 (t, $J = 7.4$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.8, 40.6, 43.8, 46.6, 48.7, 64.4, 126.9, 127.0, 128.9, 142.5, 210.6; IR (neat) 3400, 2879, 1710, 1419, 1325, 1046, 911, 702; HRMS *m/z* [M^+] calcd for $C_{13}H_{16}O_2$ 294.1170, found 204.1172.

(*3S,4S*)-4-(Benzyloxymethyl)-3-phenyl-2-cyclohexene-1-one (18a). To a solution of the hydroxy ketone **17** (65 mg, 0.32 mmol) in benzyl bromide (2 mL) was added silver oxide (201 mg, 0.87 mmol). The reaction mixture was stirred vigorously for 18 h, diluted with ether (10 mL), and filtered through tightly packed cotton wool. Concentration under reduced pressure followed by removal of benzyl bromide by bulb-to-bulb distillation (60 °C, 0.5 mmHg) afforded colorless oil, which was purified by flash chromatography on silica gel (elution with 17% EtOAc in hexane) to afford 76 mg (81%) of the corresponding benzyl ether **18a** as a colorless oil: $[\alpha]^{20}_D = +73.4°$ ($CHCl_3$, $c = 1.39$). ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (m, 1H), 2.25 (m, 1H), 2.38 (m, 1H), 2.50 (m, 3H), 2.58 (dd, $J = 14.0$, 14.0 Hz, 1H), 2.91 (ddd, $J = 14.0$, 14.0, 5.0 Hz, 1H), 3.10 (dd, $J = 9.0$, 7.0 Hz, 1H), 3.29 (dd, $J = 9.0$, 3.0 Hz, 1H), 4.29 (d, $J = 12.0$ Hz, 1H), 4.35 (d, $J = 12.0$ Hz, 1H), 7.2−7.3 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.5, 40.8, 42.3, 46.6, 48.9, 71.9, 73.0, 126.8, 127.1, 127.4, 127.5, 128.3, 128.7, 138.3, 142.8, 210.5; HRMS *m/z* [M^+] calcd for $C_{20}H_{22}O_2$ 294.1656, found 294.1660.

(*3R,4R*)-4-(Benzyloxymethyl)-3-phenyl-2-cyclohexene-1-one (18b). To a suspension of copper(I) iodide (65 mg, 0.34 mmol) in THF (1.5 mL) was added at −50 °C a 1.8 M solution of phenyllithium in hexanes−ether (0.38 mL, 0.68 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 15 min. To the resulting solution of cuprate was added dropwise enone **14** (37 mg, 0.17 mmol, 98% ee) dissolved in THF (1 mL). The reaction was quenched in 15 min by addition of water and diluted with ether. The separated organic layer was dried over anhydrous Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (elution with 17% EtOAc in hexane) to afford 32 mg (64%) of **18b** as a colorless oil: $[\alpha]^{20}_D = -74.0°$ ($CHCl_3$, $c = 1.01$); ^1H and ^{13}C NMR spectra were identical to those of enantiomeric compound **18b** described above.

(*4R,5S*)-4,5-Bis(hydroxymethyl)-cyclohex-2-ene-1-one (20). The title compound was prepared according to General Procedure B in overall 82% yield. The initial Diels−Alder reaction was conducted at 20 °C for 24 h. $[\alpha]^{20}_D = +130°$ (EtOAc, $c = 0.95$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.25 (m, 1H), 2.37 (dd, $J = 16.5$, 12.0 Hz, 1H), 2.50 (dd, $J = 16.5$, 4.5 Hz, 1H), 2.61 (m, 1H), 3.26 (br s, 1H), 3.65 (dd, $J = 11.0$, 6.5 Hz, 1H), 3.73 (dd, $J = 11.0$, 4.5 Hz, 1H), 3.81 (dd, $J = 11.0$, 6.5 Hz, 1H), 3.86 (dd, $J = 11.0$, 5.0 Hz, 1H), 6.07 (dd, $J = 10.2$, 2.4 Hz, 1H), 6.86 (dd, $J = 10.2$, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 39.8, 40.2, 42.2, 64.3,64.9, 130.1, 151.8, 199.6; IR (neat) 3370, 2884, 1669, 1394, 1075 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_8H_{12}O_3$ 156.0787, found 156.0800. Enantiomeric excess was determined to be 92% by ^1H NMR (400 MHz) analysis of the corresponding Mosher diester. Major diastereomer: δ 4.64 (dd, $J = 11.2$, 4.4 Hz, 1H); minor diastereomer: δ 4.51 (dd, $J = 11.2$, 4.4 Hz, 1H).

(*4R,5R*)-4,5-Bis(hydroxymethyl)-cyclohex-2-ene-1-one (22). The title compound was prepared according to General Procedure B in overall 64% yield. The initial Diels−Alder reaction was conducted at 20 °C for 3 days. $[\alpha]^{20}_D = +196°$ (EtOAc, $c = 1.08$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.40 (m, 1H), 2.55 (m, 2H), 2.87 (m, 1H), 3.21 (br s, 1H), 3.56 (br s, 1H), 3.80 (m, 4H), 6.06 (d, $J = 10.2$ Hz, 1H), 6.89 (dd, $J = 10.2$, 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1, 38.6, 41.03, 60.55, 63.53, 130.3, 149.8, 199.3; IR (neat) 3330, 2886, 1669, 1031 cm^{-1}; HRMS *m/z* [M^+] calcd for $C_8H_{12}O_3$ 156.0787, found 156.0775. Enantiomeric excess was determined to be 98% by ^1H NMR (500 MHz) analysis of the corresponding Mosher diester. Major diastereomer: δ 5.99 (dd, $J = 10.5$, 1.5 Hz, 1H), 6.63 (dd, $J = 10.5$, 5.0 Hz, 1H); minor diastereomer: δ 6.08 (dd, $J = 10.5$, 1.5 Hz, 1H), 6.72 (dd, $J = 10.5$, 5.0 Hz, 1H).

Allylic Alcohol 23. A solution of the diol **20** (11 mg, 0.072 mmol) and benzaldehyde (150 mL) in benzene (0.5 mL) containing a catalytic amount of TsOH was heated to reflux for 5 min. After cooling to room temperature, the reaction mixture was diluted with ether and washed with saturated solution of $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography on silica gel (elution with 33% hexane in ether), affording 12 mg (70%) of the desired acetal as a 1:1 mixture of diastereomers.

To a suspension of lithium aluminum hydride (2 mg, 38 mmol) in ether (0.5 mL) at −78 °C was added the enone (12 mg, 0.05 mmol) obtained in the previous step dissolved in ether (1 mL). The reaction mixture was stirred for 20 min, quenched with water (0.1 mL), diluted with ether, and dried over anhydrous Na_2SO_4. Concentration followed by flash chromatography of the residue on silica gel (elution with 33% hexane in ether) afforded 7 mg (60%) of the allylic alcohol **23** as a mixture of diastereomers.

Benzylidine 24. To a solution of the alcohol **23** (7 mg, 0.028 mmol), *p*-toluenesulfonylhydrazine (13 mg, 0.07 mmol) and triphenylphosphine (27 mg, 0.1 mmol) in benzene (0.3 mL) was added dropwise diisopropylazadicaboxylate (20 mL, 0.1 mmol). The reaction mixture was stirred for 2 h at 20 °C, concentrated, and diluted with methanol (0.5 mL). The resulting solution was stirred for 18 h at 20 °C and purified directly by flash chromatography on silica gel (elution with 20% EtOAc in hexane). The combined fractions containing the product and triphenylphosphine were dissolved in 0.5 mL of iodomethane, concentrated, and repurified by flash chromatography on silica gel (elution with 20% EtOAc in hexane) which afforded 3 mg (48%) of the desired benzylidine **24**: ($[\alpha]^{20}_D = +198°$ ($CHCl_3$, $c = 0.09$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.7 (m, 4H), 2.0 (m, 2H), 3.52 (m, 2H), 3.74 (m, 1H), 3.96 (dd, $J = 15.0$, 3.0 Hz), 5.69 (m, 2H), 5.79 (m, 1H), 7.3−7.4 (m, 3H), 7.50 (d, $J = 8.5$ Hz, 2H); HRMS *m/z* [M^+] calcd for $C_{15}H_{18}O_2$ 230.1306, found 230.1306. The ^1H NMR spectrum and the optical rotation were in good agreement with the reported values.[33]

MTPA Diester 25. To (*R*)-MTPA-Cl (0.24 mmol) was slowly added a solution of the diol **20** (10 mg, 0.06 mmol), triethylamine (100 μL), DMAP (cat.) in EtOAc:$CDCl_3$ = 3:1 (0.9 mL). The reaction mixture was stirred for 30 min at 20 °C, diluted with ether (10 mL), filtered, and concentrated. The resulting crude MTPA diester **25** was used for a next step without any additional purification.

MTPA Ester 26. To a solution of the MTPA diester **25** in $CDCl_3$ (0.5 mL) was added DMAP (0.6 mmol). The resulting solution was stirred for 4 days. At this point the ^1H NMR analysis showed the reaction to have gone to completion. The direct purification of the reaction mixture by flash chromatography on silica gel (elution with 33% EtOAc in hexane) afforded 9 mg of the MTPA ester **26**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (dd, $J = 16.0$, 6.0 Hz, 1H) 2.65 (dd, $J = 16.0$, 6.0 Hz, 1H), 3.20 (q, $J = 6.0$ Hz, 1H), 3.52 (s, 3H), 4.30 (dd, $J = 11.0$, 6.0 Hz, 1H), 4.42 (dd, $J = 11.0$, 6.0 Hz, 1H), 5.36 (s, 1H), 5.41 (s, 1H), 5.96 (d, $J = 10.0$ Hz, 1H), 7.03 (d, $J = 10.0$ Hz, 1H), 7.4−7.5 (m, 5H); HRMS *m/z* [M^+] calcd for $C_{18}H_{17}F_3O_4$ 354.1079, found 354.1081.

MTPA Diester 27. To (*R*)-MTPA-Cl (0.12 mmol) was slowly added a solution of the diol **22** (6 mg, 0.038 mmol), triethylamine (60 mL), DMAP (cat.) in EtOAc:$CDCl_3$ = 5:1 (0.6 mL). The reaction mixture was stirred for 30 min at 20 °C, diluted with ether (10 mL), filtered, and concentrated. The resulting crude MTPA diester **27** was used for for the next step without further purification.

MTPA ester 28. To a solution of the MTPA diester **27** in $CDCl_3$ (0.5 mL) was added DMAP (0.6 mmol). The resulting solution was stirred for 4 days, at which point the ^1H NMR analysis revealed completion of the reaction. The reaction mixture was directly placed on a silica gel column and purified by flash chromatography (elution with 33% EtOAc in hexane), which afforded 6 mg of the MTPA ester **28**. ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (dd, $J = 16.5$, 6.0 Hz, 1H) 2.68 (dd, $J = 16.5$, 6.0 Hz, 1H), 3.19 (q, $J = 6.0$ Hz, 1H), 3.52 (s, 3H), 4.34 (dd, $J = 11.0$, 6.0 Hz, 1H), 4.42 (dd, $J = 11.0$, 6.0 Hz, 1H), 5.31 (s, 1H), 5.40 (s, 1H), 5.93 (d, $J = 10.0$ Hz, 1H), 6.98 (d, $J = 10.0$ Hz, 1H), 7.4−7.5 (m, 5H); HRMS *m/z* [M^+] calcd for $C_{18}H_{17}F_3O_4$ 354.1079, found 354.1082.

Reaction of Diene 3c with *N*-Phenylmaleimide. To a solution of diene **3c** (90 mg, 0.22 mmol) in toluene (2 mL) was added *N*-

phenylmaleimide (35 mg, 0.2 mmol) in toluene (2 mL) at −70 °C. The reaction mixture was stirred for 3 h at −78 °C, slowly allowed to reach room temperature (over 15 h), and concentrated in vacuo. An analysis of the proton NMR spectrum of the crude reaction mixture showed the formation of a 30:3:1 mixture of three diastereomers. The major diastereomer **29** was isolated by flash chromatography on silica gel (elution with 33% ether in hexanes containing 2% Et_3N): $[\alpha]^{20}_D = -49.6°$ ($CHCl_3$, $c = 1.40$); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.19 (s, 3H), −0.11 (s, 3H), 0.92 (s, 9H), 1.90 (m, 2H), 2.41 (dd, $J = 15.5$, 7.5 Hz, 1H), 2.66 (d, $J = 15.5$ Hz, 1H), 2.68 (dd, $J = 9.0$, 6.0 Hz, 1H), 2.89 (m, 2H), 2.96 (dd, $J = 9.0$, 7.5 Hz, 1H), 4.22 (m, 1H), 4.92 (m, 1H), 4.93 (m, 1H), 5.00 (m, 1H), 7.4−7.7 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.4, 17.6, 25.4, 29.7, 33.5, 38.8, 44.3, 56.5, 66.4, 103.5, 126.4, 126.6, 126.8, 128.2, 128.3, 129.0, 132.2, 148.4, 148.9, 177.1, 178.4.

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Supporting Information Available: ^{1}HNMR and ^{13}CNMR of all new compounds in the text (PDF). This material is available free of charge via the Web at http://pubs.acs.org.

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