Asymmetric Diels−Alder Reactions of Chiral 1-Amino-3-siloxy-1,3-butadiene: Application to the Enantioselective Synthesis of (−)-α-Elemene

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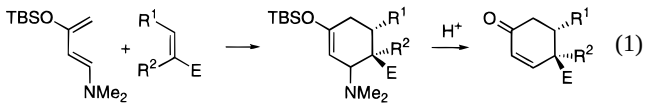
The development of efficient methods for the preparation of structurally complex molecules in enantiomerically pure form is a fundamental challenge of modern organic synthesis. Among various processes capable of controlling the absolute stereochemistry of the final product, the asymmetric Diels−Alder reaction is perhaps the most powerful. The vast majority of investigations on this topic have taken advantage of chirally-modified dienophiles[1] to induce asymmetry in the cycloaddition reaction, although the use of chiral Lewis acid catalysts has also received considerable attention of late.[2] By contrast, there are very few examples of the use of chiral dienes for the Diels−Alder reaction.[3−5] We recently developed an efficient method for the preparation of 1-amino-3-siloxybutadienes and demonstrated their usefulness in various [4 + 2] cycloadditions (eq 1).[6] In a significant advance in this methodology, we report

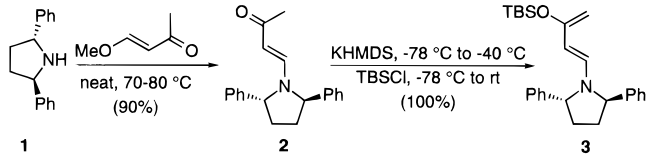


(1)

that chirally-modified versions of the amino siloxy dienes undergo Diels−Alder cycloadditions with high to excellent facial selectivity and provide a simple, reliable route to substituted cyclohexenones having high enantiomeric excesses (ee).

An important advantage of the amino siloxy diene, aside from its high reactivity,[6] is that the amino substituent opens up the possibility of using a chiral amine. Resonance interactions were expected to cause the substituents on the amine to be held in the same plane as the alkene, such that the chiral portion would block one quadrant around the diene. We elected to examine a C_2-symmetric amine, in the hope of circumventing a potential rotomer issue, thereby reducing the number of possible diastereomeric transition states and making the asymmetry-inducing step more predictable.

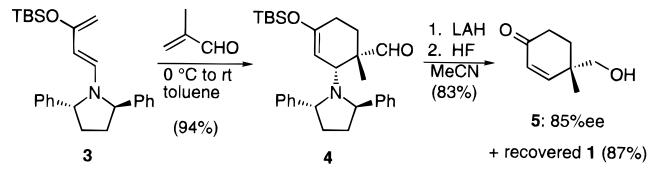
The required chiral diene **3** was prepared by the two-step sequence shown (eq 2). Condensation of the C_2-symmetric (+)-



(2)

trans-diphenylpyrrolidine (**5**), available in >98% ee by Chong's protocol,[7] with methoxybutenone afforded vinylogous amide **2** in 90% yield.[8] Compound **2** was converted to the potassium enolate and silylated using *tert*-butyldimethylsilyl chloride (TBS-Cl) to afford the desired chiral amino siloxy diene **3** in essentially quantitative yield after removal of the solvent and volatile reagents.

We first examined the thermal Diels−Alder reaction of diene **3** with methacrolein, which proceeded from 0 °C to rt and gave in 94% yield a single cycloadduct (**4**), assigned to be the *endo* diastereomer. Reduction of the carbonyl group followed by hydrolysis gave rise to the corresponding cyclohexenone **5** in 85% ee, as determined by GLC analysis of the corresponding trimethylsilyl (TMS) ether using a chiral B-DM column (eq 3). Diphenylpyrrolidine (**1**) was fully recovered, with its enantiomeric purity unchanged.



(3)

The absolute stereochemistry of the newly created quaternary chiral center was established through a concise synthesis of α-elemene, a naturally-derived terpene (Scheme 1).[9] Thus, Wittig methylenation of the Diels−Alder adduct **4** followed by hydrolysis afforded vinylcyclohexenone **7** in high yield. The reaction of the enone with *i*-PrLi in the presence of $CeCl_3$[10] gave the 1,2-addition product, which was oxidized to enone **8** using pyridinium chlorochromate (PCC).[11] A second $CeCl_3$-promoted addition of *i*-PrLi followed by acid-catalyzed dehydration afforded α-elemene (**9**) that was spectroscopically identical to the reported compound. The optical rotation of the synthetic material ($[\alpha]^{20}_D = -99.0°$, $CHCl_3$, $c = 1.1$, 88% ee) confirmed it to possess the opposite absolute stereochemistry to that of the naturally-derived material (lit.[9b] $[\alpha]^{25}_D = +112°$).

(1) For reviews, see: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876−889. (b) Taschner, M. J. *Asymmetric Diels-Alder Reactions*; Taschner, M. J., Ed.; Jai Press, Inc.: Greenwich, 1989; Vol. 1, pp 1−101.

(2) For reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007−1019. (b) Narasaka, K. *Synthesis* **1991**, 1−11.

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(9) (a) Paknikar, S. K.; Bhattacharyya, S. C. *Tetrahedron* **1962**, *18*, 1509−1517. (b) Mehta, G.; Acharyulu, P. V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2759−2760.

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(12) *Typical procedure for the Diels−Alder reaction, followed by reduction and hydrolysis.* (i) A solution of diene **3** (1 mmol) in toluene (2 mL) was treated with the dienophile (1.5−3 mmol) and stirred at 20 °C for 1−3 days. Concentration of the solution in vacuo, followed by flash chromatography on silica gel (with 2−5% triethylamine in the eluent), afforded the corresponding cycloadducts. (ii) The cycloadducts were reduced with lithium aluminum hydride (3−6 mmol) in ether (2−6 mL, 78 °C to rt). The excess hydride was quenched with a minimum amount of water and anhydrous Na_2SO_4 to afford the expected alcohol, which was sufficiently pure for the hydrolysis step. (iii) A solution of the crude alcohol in acetonitrile (3 mL) was treated with 10% aqueous HF in acetonitrile (0.55 mL, 2.0 mmol). After stirring the mixture for 1 h at room temperature, solid K_2CO_3 was added and stirring was continued for 30 min. The solids were removed, and the residue was concentrated and purified directly by flash chromatography to give the desired cyclohexenones shown (Table 1).

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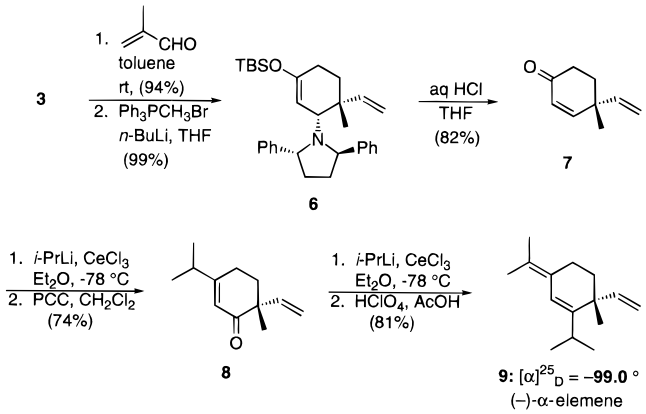
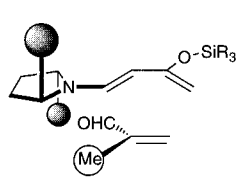
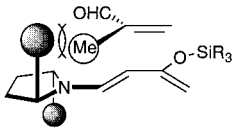
Scheme 1



The asymmetric induction observed for the cycloaddition with methacrolein can be rationalized by considering the two *endo* transition states (**A** and **B**). The major adduct arises via transition state A, in which the larger group on the dienophile is placed in the open pocket of the chiral pyrrolidine.

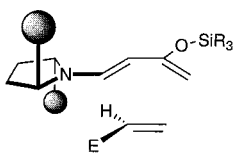


A: favored *endo* TS

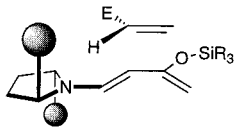


B: disfavored *endo* TS

We have examined the reaction of diene **3** with several different dienophiles, and the results are summarized in Table 1. The reactions of **3** with α-unsubstituted dienophiles are particularly interesting (entries 2−7). For example, the reaction of diene **3** with methyl acrylate proceeded at room temperature to yield a mixture of three diastereomers in ca. 20:2:1 ratio. However, upon reduction of the ester group and acid hydrolysis of the resulting product, the cyclohexenone species was obtained as a 96.5:3.5 ratio of enantiomers by chiral GC (93% ee), much higher than might have been anticipated from the mixture of diastereomers of cycloaddition products. This result emphasizes the advantage of using a C_2-symmetric auxiliary: *diastereofacial selection by the diene induces the same absolute stereochemistry at the carbon* α *to the withdrawing group, for both the endo and exo cycloadducts.* Also noteworthy is the absolute stereochemistry of the electron-withdrawing group, which is opposite to that found for meth- and ethacrolein, seemingly inconsistent with the proposed model. In fact, the result is fully consistent with a steric-effect model. Of the four possible transition states, the two favored should be **C** and **D**, in which the larger group on the dienophile is away from the phenyl group. A sterically

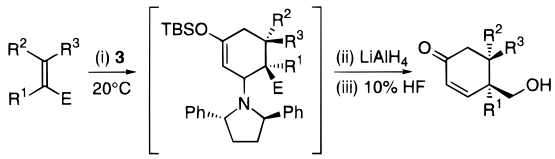


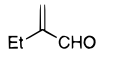
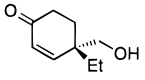
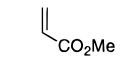
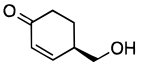
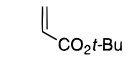
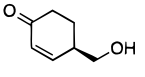
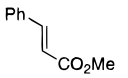
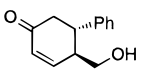
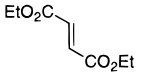
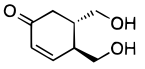
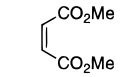
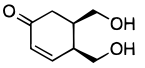
C: favored *exo* TS



D: favored *endo* TS

Table 1. The Diels−Alder Reaction of Diene **7** with Various Dienophiles



Entry[a]	Dienophile	Product	Overall yield (%)	ee(%)
1			75	86[b]
2			68	93[c]
3			71	>98[c]
4[e]			66	96[d]
5			82	92[b]
6			64	98[b]

[a] See ref 12 for a general procedure. [b] ee determined by ^{1}H NMR analysis of the corresponding Mosher ester. [c] ee of the corresponding acetate determined by capillary GLC analysis using a chiral B-DM column (Advanced Separation Technologies, Inc.). [d] ee of the corresponding TMS ether determined by HPLC analysis using chiral Whelk-O 1 column (Regis Technologies, Inc.). [e] Initial cycloaddition carried out at 85 °C.

more demanding withdrawing group would be expected to result in even better facial selectivity. Indeed, the cycloaddition using *tert*-butyl acrylate afforded the cyclohexenone product with greater than 98% ee. As can be seen from the table, other α-unsubstituted acrylates undergo cycloaddition with excellent facial selectivity and provide access to differently functionalized cyclohexenones. Facial discrimination was high even for cycloadditions carried out at rather high temperatures (entry 4, 85 °C).

Our results show that chiral 1-amino-3-siloxy-1,3-butadiene (**3**) represents an important advance to the available methods for asymmetric synthesis. Diene **3** is prepared efficiently and reacts readily with a variety of dienophiles. The cycloadditions proceed with high to excellent facial selectivity, which is particularly remarkable for reactions carried out at room temperature or higher, and allow a simple preparation of substituted cyclohexenones with high ee.

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Supporting Information Available: Experimental procedures and spectral data of all new compounds employed in this study (37 pages). See any current masthead page for ordering and Internet access instructions.

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