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Asymmetric Diels-Alder Cycloaddition with Chiral 2-Alkylsulfinyl-1-nitroalkenes

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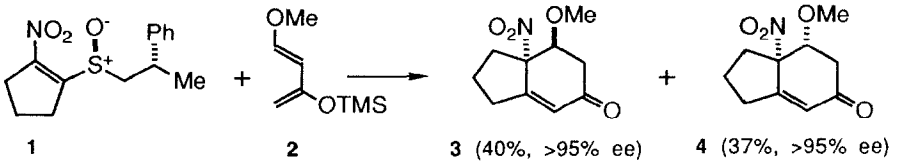
Abstract: The Diels-Alder reaction of chiral 2-alkylsulfinyl-1-nitroalkene **1** and Danishefsky's diene (**2**) afforded adducts **3** and **4** in good chemical yield with a high enantiomeric excess,while diastereomeric nitroalkene **7** gave **8** and **9,** enantiomeric to **3** and **4**, respectively.

The asymmetric Diels-Alder reaction effects one of the most efficient organic transformations in which it can create up to four chiral centers in one step. Recently, optically active tricoordinate sulfur compounds were widely used for asymmetric synthesis including the addition of a carbanion α to the sulfinyl group, the [2,3] sigmatropic rearrangement, the conjugate addition as well as the cycloaddition reaction.[2,3] Pioneering works of Koizumi *et al*[4] and Maignan *et al*[5] have opened a new avenue to the usage of chiral sulfoxides in asymmetric Diels-Alder reactions,[6] by which notable success in the synthesis of natural products has been achieved.[7] Since a chiral auxiliary is located in close proximity to the reaction center in the vinyl sulfoxide system as a dienophile, more efficient chiral induction could be anticipated with this system than with a conventional chiral acrylate. It is well documented that α,β-unsaturated sulfoxides are unexpectedly inert toward dienes,[2a,5b] except for parent vinyl derivative. Therefore an additional activating group is necessary to effect the cycloaddition. The nitro group has been used for this purpose, frequently.[8]

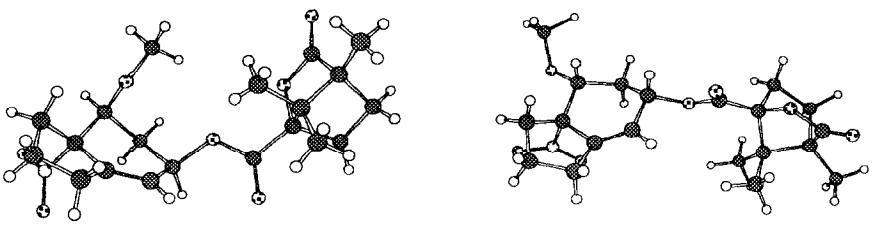
Recently, we reported a chiral induction based on the addition-elimination process with an optically active 2-alkylsulfinyl-1-nitro alkene.[9] A methodology utilizing a chiral auxiliary as a leaving group is attractive because of the direct formation of one enantiomer in excess. We describe here the asymmetric Diels-Alder cycloaddition concomitant with an elimination of the chiral auxiliary using optically active 2-alkylsulfinyl-1-nitroalkenes.

Scheme 1.



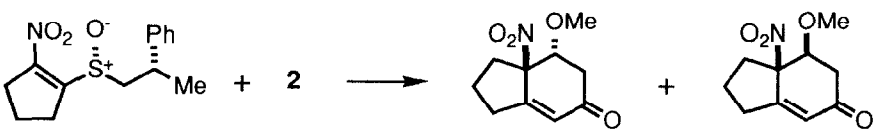
1 2 3 (40%, >95% ee) 4 (37%, >95% ee)

Figure 1. Absolute stereochemistries of **5** (left) and **6** (right) as determined by single X-ray analysis



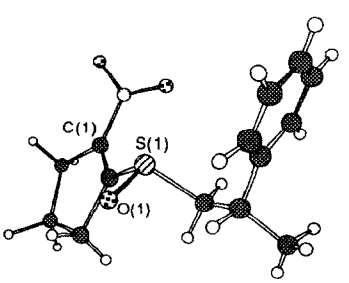
The cycloaddition of a chiral 2-sulfinyl-1-nitroalkene **1**[10] with the Danishefsky's diene (**2**) proceeded smoothly to afford enones **3** and **4** after an acidic work-up, where elimination of the chiral auxiliary occurred expectedly. High enantioselectivities were observed for the both *exo*- and *endo*-adducts **3** and **4**, though the *endo*/*exo* selectivity was poor. They were transformed into (*S*)-camphanates **5** and **6**, respectively, by successive treatment with $NaBH_4$ and (1*S*)-camphanic chloride. The absolute structures of **5**[12] and **6**[12] were unambiguously determined by X-ray analyses, whose perspective views are shown in Figure 1.

Scheme 2.



7 8 (25%, 88% ee) 9 (22%, 91% ee)

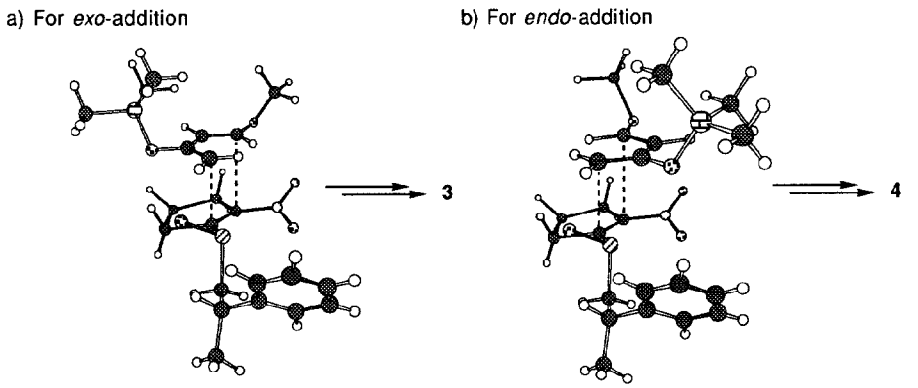
Figure 2. The three-dimensional structure of **1** determined by an X-ray analysis. Note the nearly anti orientation of the oxygen on S(1) against the double bond in the cyclopentene ring.



The reaction of diastereomeric chiral sulfoxide **7** with **2** furnished **8** and **9**, enantiomers of **3** and **4**, respectively, again with a high enantioselectivity. These results, together with the results from the reaction of **1** with the Danishefsky diene (**2**), indicated that the enantioselectivity in the product was not determined by the chiral center on the alkyl chain but the one on the sulfinyl group. The Diels-Alder stereochemistry is primarily influenced by steric factors in the ground state conformation.[13] The more energetically favored conformation dictates the diastereofacial differentiation. The enantioselectivity can be determined by the difference in steric bulk between the alkyl group and the lone pair electrons on the sulfur. As shown in Figure 2, an X-ray analysis of starting sulfoxide **1** indicated an *s-trans* conformation of the S(1)-O(1) bond to the olefinic bond because of electronic and steric repulsions between the nitro group and the sulfinyl oxygen. Assuming that the same conformation is preserved in solution, the *si*-face of C(1) in **1** is totally hindered by the alkyl side chain attached to the sulfur. Thus, the preferred mode of addition of **2** involves a *re*-attack to C(1) in both the *exo*- and *endo*-addition giving **3** and **4** (Figure 3). The absolute configurations observed in the products are consistent with this transition model. This also explains that the absolute configuration of the products did not determined by the chiral center on the side chain of nitroolefins **1** and **7**.

In conclusion, the present study demonstrates the efficient asymmetric construction of the highly functionalized cyclohexane, which is a versatile intermediate for the syntheses of biologically interesting compounds.

Figure 3. Possible approach of the Danishefsky's diene (**2**) to the nitroolefin **1**.[14]



References and Notes

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10) Preparation of **1** was undertaken according to a similar procedure to as previously reported.[11]

11) Node, M.; Kawabata, T.; Fujimoto, M.; Fuji, K. *Synthesis*, **1984**, 234.

12) Crystal data. **1**: $C_{14}H_{17}NO_3S$, space group $P2_12_12_1$ with a = 13.468 (3), b = 15.063 (2), c = 6.920 (1) Å and Dc = 1.322 g cm^{-3} for Z = 4. **5**: $C_{20}H_{27}NO_7$, space group C_2 with a = 22.897 (5), b = 10.133 (2), c = 8.970 (1) Å and Dc = 1.307 g cm^{-3} for Z = 4. **6**: $C_{20}H_{27}NO_7$, space group $P2_12_12_1$ with a = 21.718 (2), b = 12.216 (1), c = 7.619 (1) Å and Dc = 1.293 g cm^{-3} for Z = 4.

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14) This diagram was generated through *Chem3D*.