# Diels-Alder Reactions of a Surfactant 1,3-Diene

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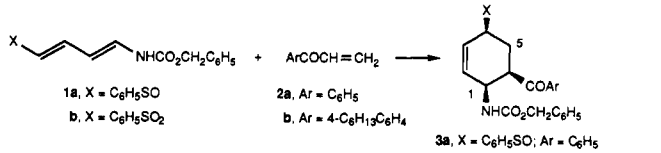
The ability of aqueous micelles and reversed micelles to control the regiochemistry of Diels-Alder reactions of (*E,E*)-6-[[[[4-[(4-hexylphenyl)sulfonyl]-1,3-butadienyl]amino]carbonyl]oxy]-*N,N,N*-trimethyl-1-hexanaminium bromide (**4**) and 1-(4-hexylphenyl)-2-propen-1-one (**2b**) was evaluated. If **2b** and **4** were to react within the micelles in their preferred orientations, cycloadduct **10** would result, as opposed to 6-[[[[*cis*-6-(4-hexylbenzoyl)-*cis*-4-[(4-hexylphenyl)sulfonyl]-2-cyclohexen-1-yl]amino]carbonyl]oxy]-*N,N,N*-trimethyl-1-hexanaminium bromide (**7b**) and its exo isomer **8b**, the theoretically predicted products actually obtained. The orientational effects in the aggregates were not strong enough to overcome the reaction's intrinsically preferred regiochemistry.

## Introduction

The Diels-Alder reaction[2] is one of the most important reactions in organic synthesis. Recently, there have been several reports of Diels-Alder chemistry performed in water[3] and in aqueous surfactant-based media.[4] Dramatic rate and stereoselectivity enhancements have been observed in aqueous media relative to those obtained in conventional organic solvents.[3,4] The subject of the present study is the ability of surfactant-based media to control the regioselectivity of Diels-Alder reactions.

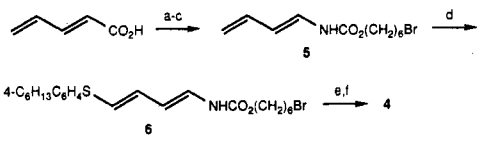
The reactions chosen for study are based on those reported by Overman and co-workers of 1,3-dienes containing both carbamate and sulfur substituents.[5] The reaction of 1,3-diene **1a** with dienophile **2a** at 25 °C gave endo cycloadduct **3a** (85%) as a 1:1 mixture of sulfoxide diastereomers,[5] and **1b** would be expected to react analogously with **2a** to give **3b** (vide infra), based on the parallel nature of the reactions of **1a** and **1b** with acrolein.[5] Products **3a** and **3b** are the theoretically predicted regioisomers.[6]



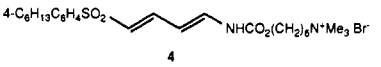

**3a**, X = $C_6H_5SO$; Ar = $C_6H_5$
**b**, X = $C_6H_5SO_2$; Ar = $C_6H_5$
**c**, X = $C_6H_5SO_2$; Ar = 4-$C_6H_{13}C_6H_4$
**d**, X = $C_6H_5S$; Ar = H

Herein we report several Diels-Alder reactions of surfactant **4**, which contains a 1,3-diene component with arylsulfonyl and carbamate substituents. A sulfone group was chosen as in **1b**, instead of a sulfoxide group as in **1a**, in order to simplify product analysis. The *n*-hexyl substituent should not significantly affect the intrinsic reactivity of the diene unit of **4**, compared to that of **1b**, but it imparts substantial hydrophobic character to **4**. The change in the alkoxy group of the carbamate substitutent going from **1b** to **4** should have only a modest effect on the intrinsic cycloaddition reactivity.[7] However, the quaternary ammonium unit of the alkoxy group represents the major portion of the hydrophilic character of surfactant **4**. Ketones **2a** and **2b**, which differ only by an *n*-hexyl group, were used as dienophiles.

**Scheme I**[a]




[a] (*i*-Pr)$_2$NEt, $ClCO_2Et$, $Me_2CO$; (b) $NaN_3$, $H_2O$; (c) $Br(CH_2)_6OH$, 4-*tert*-butylcatechol, $C_6H_5Me$; (d) (*i*-Pr)$_2$NEt, 4-$C_6H_{13}C_6H_4SCl$, THF; (e) *m*-$ClC_6H_4CO_3H$, $CH_2Cl_2$; (f) $Me_3N$, MeOH.




## Results and Discussion

The synthesis of surfactant diene **4** is summarized in Scheme I. (*E*)-2,4-Pentadienoic acid was converted into a mixture of *E,E* carbamate **6** and its *E,Z* isomer through **5** by procedures analogous to those used by Overman and co-workers in the syntheses of **1**.[5] The isomers were separated by flash chromatography on silica gel, and **6** was converted to **4** as illustrated. The critical micelle concentration (cmc) of **4** in $H_2O$ at 25 °C is $(7 \pm 1) \times 10^{-4}$ M. At 50 °C, the temperature of the Diels-Alder reactions, the cmc of **4** should be somewhat but not significantly higher.[8] Ketone **2b** was prepared from 4-$EtCOC_6H_4C_6H_{13}$ by known procedures (see Experimental Section).

Reactions of **1b** with **2a** and **2b** were performed to establish the regio- and stereoselectivities that would likely result from analogous reactions of **4** with these dienophiles in the absence of possible orientational effects within surfactant aggregates. The reactions of **1b** with **2a** in $H_2O$-1,4-dioxane and in $CHCl_3$ gave a single Diels-Alder adduct, **3b**, consistent with the formation of only **3a** from **1a** and **2a**.[5]

The structure of **3b** derived from a single-crystal X-ray diffraction study. The $^1H$ NMR spectrum and homonuclear decoupling experiments indicated that in solution **3b** assumes the half-chair conformation of Figure 1, as in the solid state. The assignment for $H_{4a}$ followed from its pseudoaxial-axial coupling with $H_{5a}$ ($J_{4a,5a}$ = 10.3 Hz). The

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(2) For reviews, see: (a) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10.
(3) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (c) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137. (d) Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001. (e) Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983**, *24*, 1897. (f) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (g) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (h) Colonna, S.; Manfredi, A.; Annunziata, R. *Tetrahedron Lett.* **1988**, *29*, 3347. (i) Griesbeck, A. G. *Tetrahedron Lett.* **1988**, *29*, 3477. (j) Schneider, H.-J.; Sangwan, N. K. *J. Chem. Soc., Chem. Commun.* **1986**, 1787 and references therein.
(4) For example, see: (a) Braun, R.; Schuster, F.; Sauer, J. *Tetrahedron Lett.* **1986**, *27*, 1285. (b) Singh, V. K.; Raju, B. N. S.; Deota, P. T. *Synth. Commun.* **1988**, *18*, 567.
(5) Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335.
(6) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.
(7) Overman, L. E.; Taylor, G. F.; Houk, K. N.; Domelsmith, L. N. *J. Am. Chem. Soc.* **1978**, *100*, 3182.
(8) For comparisons of cmc's of quaternary ammonium surfactants at different temperatures, see: Jaeger, D. A.; Mohebalian, J.; Rose, P. L. *Langmuir* **1990**, *6*, 547.

0022-3263/91/1956-2482$02.50/0 

**Table I. Diels–Alder Reactions of Surfactant 4 with Ketones 2a and 2b at 50 °C**

| entry | 4 concn, M | ketone nature | ketone concn, M[a] | medium | reactn time, h | % yield 7 + 8[b] | 7:8 ratio[b] |
|---|---|---|---|---|---|---|---|
| 1 | 0.25 | **2a** | 1.0 | $H_2O$ | 1 | 50 | 84:16 |
| | | | | | 5 | 91 | 81:19 |
| | | | | | 10 | 98 | 80:20 |
| 2 | 0.10 | **2a** | 0.40 | $H_2O$ | 1 | 51 | 85:15 |
| | | | | | 5 | 91 | 80:20 |
| | | | | | 10 | 99 | 80:20 |
| 3[c] | 0.10 | **2a** | 0.40 | $H_2O$ | 1 | 39 | 91:9 |
| | | | | | 5 | 85 | 90:10 |
| | | | | | 10 | 96 | 87:13 |
| 4 | 0.025 | **2a** | 0.10 | $H_2O$ | 1 | 43 | 91:9 |
| | | | | | 5 | 91 | 90:10 |
| | | | | | 10 | 98 | 89:11 |
| 5 | 0.25 | **2b** | 1.0 | $H_2O$ | 25 | 27 | 94:6 |
| 6 | 0.10 | **2b** | 0.40 | $H_2O$ | 25 | 27 | 86:14 |
| 7[c] | 0.10 | **2b** | 0.40 | $H_2O$ | 25 | 22 | 90:10 |
| 8 | 0.025 | **2b** | 0.10 | $H_2O$ | 25 | 24 | 90:10 |
| 9 | 0.25 | **2a** | 1.0 | $CHCl_3$ | 5 | 12 | 87:13 |
| | | | | | 25 | 43 | 81:19 |
| 10 | 0.10 | **2a** | 0.40 | $CHCl_3$ | 5 | 3 | 85:15 |
| | | | | | 25 | 16 | 84:16 |
| 11[c] | 0.10 | **2a** | 0.40 | $CHCl_3$ | 5 | 3 | 85:15 |
| | | | | | 25 | 15 | 85:15 |
| 12 | 0.25 | **2b** | 1.0 | $CHCl_3$ | 25 | 17 | 84:16 |
| 13 | 0.10 | **2b** | 0.40 | $CHCl_3$ | 25 | 7 | 86:14 |
| 14[c] | 0.10 | **2b** | 0.40 | $CHCl_3$ | 25 | 7 | 84:16 |

[a] All of the reaction mixtures in $H_2O$ were initially heterogeneous; some of them became homogeneous during the reaction period (see the Experimental Section). [b] The values, obtained by HPLC analysis, are averages for at least two runs; the estimated limits of error are ±10%. [c] The reaction mixture also contained 0.10 M HTABr.

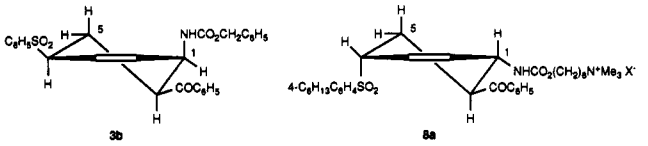
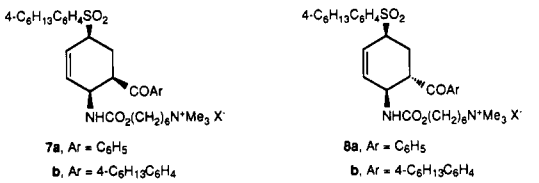



**Figure 1.** Half-chair conformations of **3b** and **8a**.

assignments for $H_{6a}$ and $H_{1e}$ resulted from the former's axial–axial coupling with $H_{5a}$ ($J_{6a,5a}$ = 11.8 Hz) and axial–pseudoequatorial coupling with $H_{1e}$ ($J_{6a,1e}$ = ~4 Hz), respectively. Thus within **3b** the phenylsulfonyl group is pseudoequatorial, the carbamate group pseudoaxial, and the benzoyl group equatorial on a half-chair conformation of the cyclohexene ring. This conformation is analogous to that of **3d**.[9] In the X-ray study the N–$C_1$–$C_6$–$H_{6a}$ torsional angle of 164.3° necessitates the pseudoaxial–equatorial relationship between the carbamate and benzoyl groups.

The reactions of **1b** with **2b** in $H_2O$–1,4-dioxane and in $CHCl_3$ gave only adduct **3c**, which has a half-chair conformation analogous to that of **3b** (see Experimental Section). It is noteworthy that the Diels–Alder reactions of **1b** were successful in $H_2O$–1,4-dioxane at 50 °C. Thus it was correctly anticipated the 1,3-diene unit of **1b** (and **4**) would be stable to aqueous reaction conditions.

Diels–Alder reactions of surfactant **4** with **2a** and **2b** were performed at 50 °C in $H_2O$ and in $CHCl_3$, with and without added hexadecyltrimethylammonium bromide (HTABr). In each case the molar ratio of **2** to **4** was 4:1, and the reaction mixture was analyzed by calibrated reversed-phase HPLC.[10] In both solvents, the major products from the reaction of **4** with **2a** were **7a** and **8a**, and from that of **4** with **2b**, **7b** and **8b**. The results are summarized in Table I. Products **7** and **8** with X = $ClO_4^-$ were characterized after their isolation by preparative HPLC.

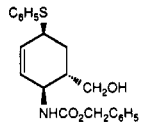



The regiochemistry, stereochemistry, and half-chair conformation of **7a**, analogous to those of **3b** and **3c**, derived from its $^1H$ NMR spectrum and homonuclear decoupling experiments. Irradiation of the signal for $H_{5a}$ had no effect on that for $H_{1e}$ but caused each of those for $H_{4a}$ and $H_{6a}$ to collapse to a broad singlet. Thus **7a** has the indicated regiochemistry. The assignment for $H_{4a}$ resulted from its pseudoaxial–axial coupling with $H_{5a}$ ($J_{4a,5a}$ = ~13 Hz). The assignments for $H_{6a}$ and $H_{1e}$ followed from the former's axial–axial coupling with $H_{5a}$ ($J_{6a,5a}$ = 12.7 Hz) and axial–pseudoequatorial coupling with $H_{1e}$ ($J_{6a,1e}$ = ~4 Hz), respectively. Therefore, **7a** has the indicated endo stereochemistry and a half-chair conformation of the cyclohexene ring with the arylsulfonyl group pseudoequatorial, the carbamate group pseudoaxial, and the benzoyl group equatorial. The structural characteristics of **7b** followed from a comparison of the $^1H$ and $^{13}C$ NMR spectra of **7a** and **7b** (see Experimental Section). The signals for $H_{1e}$, $H_2$, $H_3$, $H_{4a}$, $H_{5a}$, $H_{5e}$, $H_{6a}$, and NH were essentially identical in chemical shift and appearance in the two $^1H$ NMR spectra.

The regiochemistry, stereochemistry, and half-chair conformation of **8a** as illustrated in Figure 1 derived from its $^1H$ NMR spectrum and homonuclear decoupling experiments. Irradiation of the signal for $H_{6a}$ caused that for $H_{1a}$ to sharpen to a broad singlet. Also, irradiation of the signals for $H_{5a}$ and $H_{5e}$ had no effect on that for $H_{1a}$. Thus **8a** has the indicated regiochemistry. The assignment for $H_{4e}$ followed from the absence of its pseudoaxial–axial

(9) Petty, C. B. Ph.D. Dissertation, University of California, Irvine, 1980.
(10) Abidi, S. L. *J. Chromatogr.* **1985**, *324*, 209.

coupling with $H_{5a}$. The assignments for $H_{6a}$ and $H_{1a}$ derived from the former's axial–axial coupling with $H_{5a}$ ($J_{6a,5a}$ = 10.1 Hz) and axial–pseudoaxial coupling with $H_{1a}$ ($J_{6a,1a}$ = ~9 Hz), respectively. Therefore, **8a** has the indicated exo stereochemistry and half-chair conformation of the cyclohexene ring with the arylsulfonyl group pseudoaxial, the carbamate group pseudoequatorial, and the benzoyl group equatorial. This conformation is analogous to that of **9**.[9] The structural characteristics of **8b** derived from a comparison of the $^1H$ NMR spectra of **8a** and **8b** (see Experimental Section).

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Entries 1–8 of Table I were performed in $H_2O$. All of the reaction mixtures were initially heterogeneous. However, some of them became homogeneous during the reaction period, but at different times (see Experimental Section). In entries 1, 2, and 4, the **7a**:**8a** (endo/exo) ratio varied little with changes in the concentrations of **4** and **2a** (from 80:20 to 91:9). Interestingly, the rate for this presumed second-order Diels–Alder reaction,[11] as reflected by the yields of **7a** + **8a** at various times, was also essentially constant. This invariance is consistent with saturation of the micellar pseudophase of **4** with **2a** and reaction exclusively therein in each entry. Even at 0.025 M **4** in entry 4, based on its cmc, ca. 96% of **4** is in micellar form. The reaction mixture of entry 3 contained 0.10 M HTABr, which has a cmc of $1.32 \times 10^{-3}$ *m* in $H_2O$ at 55 °C.[12] In the resultant mixed micellar system, relative to entry 2, the **7a**:**8a** ratios were slightly higher and the reaction somewhat slower.

Entries 5–8 correspond to entries 1–4 with the substitution of **2b** for **2a**. The **7b**:**8b** ratios were comparable to the **7a**:**8a** ratios. The reaction rates in entries 5–8 were about the same and substantially less than those in entries 1–4. Rate comparisons for entries in $H_2O$ are complicated by the fact that all of the reaction mixtures were initially heterogeneous as noted above. Thus it is likely that the lesser reactivity of **2b** compared to **2a** reflects its lower solubility and perhaps other effects of the hexyl group.

Entries 9–14 of Table I were performed in $CHCl_3$. Note that entries 11 and 14 also contained 0.10 M HTABr, which forms reversed micelles in $CHCl_3$.[13] It is probable that **4** also forms reversed micelles since **4** and HTABr have comparable hydrophilic/hydrophobic characters, as indicated by their similar cmc's in $H_2O$ ($7.4 \times 10^{-4}$ M and $9.2 \times 10^{-4}$ *m*,[12] respectively, at 25 °C). In entries 9 and 10, the **7a**:**8a** ratios were similar, but the rate was less in the latter. A neutral compound such as **2a**(**2b**) will partition between the micelles and the bulk $CHCl_3$ phase. Consequently, [**2a**] within a reversed micelle will decrease going from entry 9 to 10, with a resultant lesser rate. In the mixed micellar system of entry 11, the **7a**:**8a** ratio and reaction rate were comparable to those of entry 10.

Entries 12–14 correspond to entries 9–11 with the substitution of **2b** for **2a**. The **7b**:**8b** ratios were comparable to the **7a**:**8a** ratios. The reaction rates of entries 12–14 were less than those of 9–11. Rate comparisons for entries in $CHCl_3$ are more straightforward than those above because all of the reaction mixtures were homogeneous throughout the reaction period. Thus **2b** is indeed less reactive than **2a**, perhaps due to a combination of electronic and steric effects of the hexyl group.

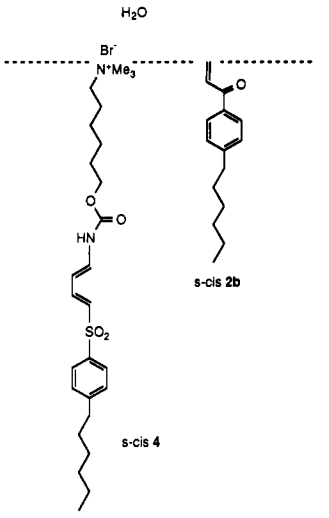



**Figure 2.** Preferred orientations of s-cis **4** and s-cis **2b** at a surfactant aggregate–$H_2O$ interface.

The reaction rates in $H_2O$ were greater than those in $CHCl_3$ even though all of the reaction mixtures in $H_2O$ were at least initially heterogeneous. This result is consistent with similar comparisons for other aqueous Diels–Alder reactions.[3] The endo/exo ratios probably reflect kinetic and not thermodynamic control. In several instances column chromatography of known mixtures of **7** and **8** on neutral alumina resulted in decreased **7**:**8** ratios, consistent with epimerization of the former to the thermodynamically favored latter. Also, the **7**:**8** ratio generally decreased with time in the entries of Table I, perhaps reflecting a small amount of epimerization. Overman and co-workers observed a decrease in endo/exo ratios with time in reactions of acrolein with **1a**, **1b**, and the corresponding sulfenyl diene carbamate.[5] Furthermore, it is interesting to note that the endo stereoselectivity decreased in the reactions of **2a** and **2b** going from **1b** to **4**. Such a dependence of stereoselectivity on remote substituents is unusual.[5]

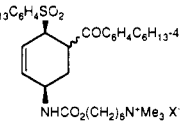
Within an aqueous micelle the quaternary ammonium head group of **4** is located at the aggregate–$H_2O$ interface, and the remainder of **4** is probably directed into the micelle interior. Ketone **2a** should also reside at the interface, but without a single, overwhelmingly preferred orientation. Compounds with as little polarity/surface activity as benzene preferentially reside at the interface of an aqueous micelle, as opposed to within the hydrocarbon interior.[14] Unlike **2a**, **2b** should have a preferred time-averaged orientation with the carbonyl group at/near the interface and the hexyl group extended into the aggregate interior, wherein it can participate in hydrophobic interactions with other alkyl groups. *n*-Hexyl phenyl ether, another compound with both hydrocarbon and polar/surface active portions, is oriented analogously.[15] These orientations for s-cis **4** and s-cis **2b** at an aggregate–$H_2O$ interface are represented in Figure 2. For simplicity, a flat interface is illustrated, whereas that of a micelle is curved, and the alkyl chains are shown in fully extended conformations, although they are most likely folded.[16,17] For **2b** the s-

(11) Isaacs, N. S. *Physical Organic Chemistry*; Longman: Essex, England, 1987; p 658.
(12) Czerniawski, M. *Pol. J. Chem.* **1966**, *40*, 1935.
(13) Seno, M.; Sawada, K.; Araki, K.; Iwamoto, K.; Kise, H. *J. Colloid Interface Sci.* **1980**, *78*, 57.
(14) (a) Mukerjee, P.; Cardinal, J. R. *J. Phys. Chem.* **1978**, *82*, 1620. (b) Mukerjee, P. *Pure Appl. Chem.* **1980**, *52*, 1317.
(15) Suckling, C. J.; Wilson, A. A. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1616.

trans is considerably less stable than the s-cis conformation.[18]

As above, it is assumed that 4 forms reversed micelles in $CHCl_3$. The quaternary ammonium head groups and counterions constitute the micelle core, and the remainder of each 4 is oriented radially outward. Within a reversed micelle, **2a** likely has no preferred orientation, but **2b** should have a time-averaged disposition analogous to that of 4, with the carbonyl group at the micelle core.

Thus within both aqueous micelles and reversed micelles, 4 and **2b** have preferred orientations. If the two were to react in these orientations, cycloadduct **10** would result, which is a regioisomer of **7b** and **8b**, the products actually obtained. Of course, as a prerequisite to reaction, approximation of the diene and dienophile units would require mobility for 4 and/or **2b** along their radial axes. Overall, it is clear that the orientational effects in the aggregates were not strong enough to overcome the reaction's intrinsically preferred regiochemistry.[6,19] Keana and co-workers have reported aqueous Diels–Alder reactions of surfactant 1,3-dienes with symmetrical dienophiles.[20]




**10**

It is important to emphasize that the preferred orientations for **2b** within the aqueous micelles and reversed micelles represent time-averaged arrangements. Within each type of aggregate, a small fraction of **2b** most likely has a disposition opposite to the preferred orientation, and it gives **7b** and **8b** on reaction with 4. Apparently, the differences between the second-order rate constants for the Diels–Alder reactions leading to **7b** and **8b**, and those leading to **10**, are great enough to overcome the lower population of **2b** in the opposite, nonpreferred orientation. Further attempts to use the orientational effects of surfactant aggregates to control the regiochemical course of Diels–Alder reactions will employ a surfactant dienophile and a surfactant 1,3-diene. With this combination the relative amounts of misaligned reactants, which lead to the theoretically predicted products, should be reduced dramatically due to anchoring of the surfactant head groups at the micelle–$H_2O$ interface and within the reversed micelle core. Also, vesicles will be used since they are more ordered than micelles.[21] Indeed the lack of regiochemical control in the reactions of **2b** and 4 in aqueous micelles may simply reflect their disorganized nature.[16]

The involvement in Diels–Alder reactions of the minor s-trans conformation of **2b**, oriented at an interface like the s-cis conformation in Figure 2, cannot be discounted. From it, 7 and 8, the theoretically predicted products, would probably result. However, an inspection of Dreiding molecular models indicates that the extended $\pi$-system (phenyl ring and carbon–oxygen and carbon–carbon double bonds) of s-trans **2b** must deviate from coplanarity much more than does that of s-cis **2a**.

Regiochemical control resulting from orientation of substrates at micelle–water interfaces has been obtained in several photochemical [2 + 2] cycloadditions in aqueous micellar media.[22] However, the anticipated selectivity is not always realized.[23] Whitten and co-workers found regiochemical control in the photodimerization of 4-stilbazolium cations in Aerosol OT reversed micelles.[24] The ability of surfactant aggregates to control the regioselectivity of photochemical, compared to thermal, reactions of oriented molecules apparently benefits from the short lifetime of the reactive excited state. In general, the lifetime is perhaps too short to allow rotation of the excited substrate into an orientation that results in the formation of a different regioisomer.

In summary, **2b** and 4 underwent Diels–Alder reactions within aqueous and reversed micelles, but not in their probable preferred orientations. Therefore, the orientational effects in the aggregates were not strong enough to overcome the reaction's intrinsically preferred regiochemistry.[6]

## Experimental Section

**General Procedures and Materials.** $^1H$ (270 and 400 MHz) and $^{13}C$ (67.8 and 100.4 MHz) NMR spectra were recorded in $CDCl_3$ with $Me_4Si$ and $CDCl_3$ (center line at 77.00 relative to $Me_4Si$) as internal standards, respectively, unless noted otherwise. Only the $^1H$ NMR spectrum of **8b** and the $^{13}C$ NMR spectrum of **7b** were recorded at the higher fields. High resolution mass spectra were obtained as before.[8] Reversed-phase HPLC was performed with UV (254 nm) detection on 8-$\mu$m C18 columns: analytical, 25 cm × 4.6 mm (i.d.) with a 1.5 cm × 4.6 mm (i.d.) guard column (Rainin 83-201-C and 83-201-G, respectively); preparative, 25 cm × 21.4 mm (i.d.) with a 5.0 cm × 21.4 mm (i.d.) guard column (83-221-C and 83-221-G). Eluants were prepared with $NaClO_4$·$H_2O$ and HPLC-grade $H_2O$ and MeCN. Preparative TLC was performed on 1-mm silica gel (Analtech 02013) and 1.5-mm aluminum oxide plates (Merck 5788-7). Silica gel (Merck 9385) and neutral and acidic aluminum oxide (J. T. Baker 0537 and 0538, respectively) were used for column chromatography. HTABr (Aldrich) was purified as before.[25] Tetrahydrofuran (THF) was HPLC-grade, and 1,4-dioxane was distilled from $LiAlH_4$. The cmc measurements were made on a Fisher Model 20 tensiometer with a du Nouy ring. Solutions were dried with $Na_2SO_4$ or $MgSO_4$ and solvents removed by rotary evaporation. Elemental analyses were performed as before.[8]

**1-Phenyl-2-propen-1-one (2a).** With standard procedures[26,27] $C_6H_5COEt$ (Aldrich) was converted into **2a**.[28]

**1-(4-Hexylphenyl)-2-propen-1-one (2b).** By the literature procedure $C_6H_5C_6H_{13}$ (Aldrich) gave 4-$EtCOC_6H_4C_6H_{13}$,[29] which

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(17) The possibility that 4's polar carbamate and sulfone groups reside at the interface along with the head group cannot be discounted. However, if this is the case, a smaller cmc than that obtained would be expected because the 4-hexylphenyl group would be the only part of the chain that could extend directly into the micelle interior. The cmc of sodium 4-*n*-octylbenzenesulfonate at 35 °C is $1.47 \times 10^{-2}$ *m* (Gershman, J. W. *J. Phys. Chem.* **1957**, *61*, 581).

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was converted[26,27] into **2b** as follows. To a solution of 2.19 g (10.0 mmol) of 4-$EtCOC_6H_4C_6H_{13}$ in 80 mL of EtOAc were added 2.11 g (11.0 mmol) of $C_6H_5SeCl$, prepared from $C_6H_5SeSeC_6H_5$ (Aldrich) and $Cl_2$,[27] and 0.10 mL of concentrated hydrochloric acid. The resultant solution was stirred at 25 °C for 24 h, changing from red-orange to pale yellow, and then was washed with saturated aqueous $NaHCO_3$ and dried. The residue was flash chromatographed on a 4 cm × 15 cm column of silica gel with hexane and then 1:9 (v/v) $Et_2O$–hexane as eluants. The former eluted $C_6H_5SeSeC_6H_5$ and the latter, 3.60 g of 4-$MeCH(SeC_6H_5)COC_6H_4C_6H_{13}$ as an oil that contained ca. 5% of 4-$EtCOC_6H_4C_6H_{13}$. This material was used in the next reaction without further purification. Preparative TLC on silica gel with 1:9 $Et_2O$–hexane elution gave a sample of pure 4-$MeCH(SeC_6H_5)COC_6H_4C_6H_{13}$: $^1H$ NMR $\delta$ 7.81 (low field half of AA'XX', $J_{AX} + J_{AX'}$ = 7.7 Hz, 2 H, Ar H), 7.15–7.50 (m, 7 H, Ar H), 4.68 (q, $J$ = 6.8 Hz, 1 H, CH), 2.65 (t, $J$ = 7.7 Hz, 2 H, $CH_2Ar$), 1.50–1.70 (m, 5 H, $CH_3CH$, $CH_2CH_2Ar$), 1.20–1.45 (m, 6 H, $(CH_2)_3$), 0.89 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 196.15, 148.57, 136.50, 133.38, 128.97, 128.81, 128.51, 127.15, 39.76, 35.98, 31.66, 31.03, 28.94, 22.58, 17.36, 14.07.

To a vigorously stirred solution of 3.50 g (10.1 mmol) of 4-$MeCH(SeC_6H_5)COC_6H_4C_6H_{13}$ in 100 mL of MeOH at 25 °C were added 15 mL of $H_2O$, 4.30 g (20.2 mmol) of $NaIO_4$, and 0.848 g (10.1 mmol) of $NaHCO_3$. After 1 h, the reaction mixture was filtered through Celite, concentrated to ca. 50 mL, added to 50 mL of saturated aqueous $NaHCO_3$, and extracted with 1:1 $Et_2O$–hexane. The extracts were dried, and the residue was flash chromatographed on a 4 × 17 cm column of silica gel with hexane and then 1:19 $Et_2O$–hexane as eluants to give 1.68 g (79%) of **2b** as an oil that was further purified by preparative TLC on silica gel with 1:5 $Et_2O$–hexane as eluant. By HPLC analysis (MeCN eluant; flow rate = 1.0 mL/min; retention time = 6.0 min) this material was homogeneous: $^1H$ NMR $\delta$ 7.29 and 7.89 (AA'XX', $J_{AX} + J_{AX'}$ = 8.1 Hz, 4 H, Ar H), 7.18 (dd, $J$ = 17.2, 10.6 Hz, 1 H), 6.44 (dd, $J$ = 17.2, 1.8 Hz, 1 H), 5.90 (dd, $J$ = 10.6, 1.8 Hz, 1 H), 2.67 (t, $J$ = 7.7 Hz, 2 H, $CH_2Ar$), 1.63 (m, 2 H, $CH_2CH_2Ar$), 1.30 (br s, 6 H, $(CH_2)_3$), 0.88 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 190.54, 148.82, 134.96, 132.43, 129.60, 128.87, 128.68, 36.04, 31.66, 31.06, 28.94, 22.58, 14.07; EI HRMS calcd for $C_{15}H_{20}O$ 216.1514, found 216.1513.

**6-Bromohexyl ((*E*)-1,3-Butadienyl)carbamate (5).** A modified literature procedure was used.[30] To a stirred solution of 4.9 g (0.050 mol) of (*E*)-2,4-pentadienoic acid[31] in 30 mL of $Me_2CO$ under $N_2$ at −20 °C was added 8.0 g (0.062 mol) of $(i\text{-}Pr)_2NEt$ (Aldrich). The temperature of the reaction mixture was maintained at 0 to −10 °C until the filtration below. A solution of 5.5 g (0.051 mol) of $ClCO_2Et$ in 15 mL of $Me_2CO$ was added over 30 min, and the reaction mixture was stirred for an additional 30 min, followed by the addition of 6.5 g (0.10 mol) of $NaN_3$ in 25 mL of $H_2O$ (0 °C) during 20 min. The mixture was stirred for 15 min and filtered through Celite, followed by the addition of 50 mL of $H_2O$ (0 °C) and extraction with six 25-mL portions of $C_6H_5Me$. The combined extracts were dried and concentrated to ca. 30 mL at <45 °C. The resultant acyl azide solution was added over 30 min to a stirred solution of 6.0 g (0.033 mol) of $Br(CH_2)_6OH$[32] and 25 mg of 4-*tert*-butylcatechol (Aldrich) in 20 mL of $C_6H_5Me$ at reflux under $N_2$. Then the reaction mixture was refluxed for 15 min and rotary evaporated, and the residue was filtered through a 4 × 12 cm column of neutral aluminum oxide with $Et_2O$ as eluant. The resultant crude product was recrystallized from 2:3 $Et_2O$–hexane (25 °C) to give 5.7 g (67%) of **5** as colorless crystals: mp 72–73 °C; $^1H$ NMR $\delta$ 6.74 (apparent t, $J$ = 12.4 Hz, 1 H, $H_1$), 6.45 (br d, $J$ = 11 Hz, 1 H, NH), 6.28 (dt, $J$ = 17.3, 10.6 Hz, 1 H, $H_3$), 5.69 (apparent t, $J$ = 12.4 Hz, 1 H, $H_2$), 5.04 (d, $J$ = 17.3 Hz, 1 H, $H_{4c}$), 4.91 (d, $J$ = 10.8 Hz, 1 H, $H_{4t}$), 4.13 (t, $J$ = 6.5 Hz, 2 H, $CH_2O$), 3.41 (t, $J$ = 6.7 Hz, 2 H, $CH_2Br$), 1.87 (p, $J$ = 7.0 Hz, 2 H, $CH_2CH_2Br$), 1.58–1.75 (m, 2 H, $CH_2$), 1.30–1.55 (m, 4 H, $(CH_2)_2$); $^{13}C$ NMR $\delta$ 153.60, 134.41, 127.13, 113.07, 111.79, 65.37, 33.51, 32.45, 28.56, 27.61, 24.86. Anal. Calcd for $C_{11}H_{18}BrNO_2$: C, 47.84; H, 6.57. Found: C, 48.01; H, 6.74.

**6-Bromohexyl ((*E*,*E*)-4-((4-Hexylphenyl)thio)-1,3-butadienyl)carbamate (6).** Modified literature procedures were used.[5,33] During 5 min, 5.00 mL of a 1.35 M solution of $Cl_2$ (6.75 mmol) in $CCl_4$ was added dropwise to a stirred solution of 1.16 g (6.00 mmol) of 4-$C_6H_{13}C_6H_4SH$[34] in 10 mL of $CCl_4$ at 0 °C. The reaction mixture was stirred for 20 min at 0 °C and rotary evaporated; the resultant crude red-orange 4-$C_6H_{13}C_6H_4SCl$ was used without purification.

To a stirred solution of 1.24 g (4.50 mmol) of **5** in 40 mL of THF under $N_2$ at −78 °C were added 1.29 g (10.0 mmol) of $(i\text{-}Pr)_2NEt$ and then, over 30 min, the above 4-$C_6H_{13}C_6H_4SCl$ in 20 mL of THF. The reaction mixture was stirred at −78 °C for 30 min and gradually warmed until **5** was almost consumed, as determined by TLC analysis on silica gel with 1:4 $Et_2O$–hexane eluant, and then 0.5 mL of EtOH was added. The reaction mixture was filtered and rotary evaporated, and the resultant crude product was flash chromatographed on a 4.5 × 30 cm column of silica gel with 1:9 and then 1:4 $Et_2O$–hexane as eluants. The former solvent eluted 1.09 g of the *E*,*Z* isomer as an oil, which was unstable at 25 °C, and the latter, *E*,*E* isomer **6** as a crystalline solid. Recrystallization of this solid from 1:4 $Et_2O$–hexane (25 °C) gave 0.91 g (43%) of **6** as colorless crystals: mp 58–60 °C; $^1H$ NMR $\delta$ 7.18 (center) (AA'BB', 4 H, Ar H), 6.69 (apparent t, $J$ = 12.4 Hz, 1 H, $H_1$), 6.49 (d, $J$ = 11.1 Hz, 1 H, NH), 6.31 (dd, $J$ = 14.5, 10.3 Hz, 1 H, $H_3$), 6.14 (d, $J$ = 14.5 Hz, 1 H, $H_4$), 5.73 (dd, $J$ = 14.0, 10.3 Hz, 1 H, $H_2$), 4.12 (t, $J$ = 6.4 Hz, 2 H, $CH_2O$), 3.41 (t, $J$ = 6.7 Hz, 2 H, $CH_2Br$), 2.57 (t, $J$ = 7.7 Hz, 2 H, $CH_2Ar$), 1.20–1.95 (m, 16 H, $(CH_2)_4$), 0.88 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 153.36, 141.78, 132.18, 130.66, 129.63, 129.14, 126.39, 121.69, 110.19, 65.66, 35.49, 33.62, 32.56, 31.66, 31.33, 28.91, 28.67, 27.74, 25.03, 22.58, 14.07; FAB HRMS calcd for $C_{23}H_{34}{}^{79}BrNO_2SLi$ (M + $Li^+$) 474.1654, found 474.1649. Anal. Calcd for $C_{23}H_{34}BrNO_2$: C, 58.97; H, 7.31. Found: C, 59.04; H, 7.33.

**6-Bromohexyl ((*E*,*E*)-4-[(4-Hexylphenyl)sulfonyl]-1,3-butadienyl)carbamate.** To a stirred solution of 0.91 g (1.9 mmol) of **6** in 40 mL of $CH_2Cl_2$ under $N_2$ at −15 °C was added dropwise 0.88 g (4.3 mmol) of 85% *m*-$ClC_6H_4CO_3H$ in 25 mL of $CH_2Cl_2$. The reaction mixture was gradually warmed to 25 °C and stirred until all of the intermediate sulfoxide was consumed, as determined by TLC on aluminum oxide with EtOAc elution, and then it was filtered and rotary evaporated at <30 °C. The resultant crude product was chromatographed on a 4 × 10 cm column of neutral aluminum oxide with EtOAc elution to give 0.795 g (82%) of the title compound as a viscous oil that is unstable at 25 °C: $^1H$ NMR $\delta$ 7.31 and 7.76 (AA'XX', $J_{AX} + J_{AX'}$ = 8.2 Hz, 4 H, Ar H), 7.24 (dd, $J$ = 14.7, 11.8 Hz, 1 H, $H_3$), 7.15 (apparent t, $J$ = 12.3 Hz, 1 H, $H_1$), 6.91 (d, $J$ = 12.3 Hz, 1 H, NH), 6.16 (d, $J$ = 14.7 Hz, 1 H, $H_4$), 5.71 (apparent t, $J$ = 12.3 Hz, 1 H, $H_2$), 4.17 (t, $J$ = 6.6 Hz, 2 H, $CH_2O$), 3.41 (t, $J$ = 6.5 Hz, 2 H, $CH_2Br$), 2.66 (t, $J$ = 7.3 Hz, 2 H, $CH_2Ar$), 1.20–1.95 (m, 16 H, $(CH_2)_4$), 0.88 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 152.81, 148.85, 141.13, 138.65, 136.23, 129.17, 127.37, 125.39, 106.11, 66.34, 35.90, 33.59, 32.53, 31.61, 31.03, 28.86, 28.56, 27.72, 25.00, 22.52, 14.04; FAB HRMS calcd for $C_{23}H_{35}{}^{79}BrNO_4S$ (M + $H^+$) 500.1470, found 500.1456; calcd for $C_{23}H_{34}{}^{79}BrNO_4SLi$ (M + $Li^+$) 506.1554, found 506.1539.

**(*E*,*E*)-6-[[[[4-[(4-Hexylphenyl)sulfonyl]-1,3-butadienyl]amino]carbonyl]oxy]-*N*,*N*,*N*-trimethyl-1-hexanaminium Bromide (4).** A solution of 0.426 g (0.925 mmol) of the above sulfone in 10 mL of 25% (w/v) $Me_3N$–MeOH (Kodak) was allowed to stand for 3 days at 4 °C. The resultant precipitate was collected by filtration and dried (40 °C; 0.1 mmHg) to give 0.357 g (69%) of **4**. After a week at 4 °C the filtrate yielded an additional 60 mg of precipitate. The combined material was recrystallized from MeOH (4 °C) to give **4** as a colorless powder: mp 78–79 °C dec; $^1H$ NMR $\delta$ 9.48 (br s, 1 H, NH), 7.31 and 7.72 (AA'XX', $J_{AX} + J_{AX'}$ = 8.4 Hz, 4 H, Ar H), 7.11–7.26 (m, 2 H, $H_1$, $H_3$), 6.18 (apparent t, $J$ = 12.1 Hz, 1 H, $H_2$), 6.11 (d, $J$ = 14.7 Hz, 1 H, $H_4$),

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4.14 (t, $J$ = 5.4 Hz, 2 H, $CH_2O$), 3.73 (m, 2 H, $CH_2N$), 3.37 (s, 9 H, $(CH_3)_3N$), 2.66 (t, $J$ = 7.8 Hz, 2 H, $CH_2Ar$), 1.15–1.90 (m, 16 H, $(CH_2)_4$), 0.87 (t, 3 H, $CH_3$); $^1H$ NMR (DMSO-$d_6$) $\delta$ 7.42 and 7.71 (AA'XX', $J_{AX} + J_{AX'}$ = 8.1 Hz, 4 H, Ar H), 7.28 (d, $J$ = 13.6 Hz, 1 H, $H_1$), 7.27 (dd, $J$ = 14.3, 11.4 Hz, 1 H, $H_3$), 6.53 (d, $J$ = 14.7 Hz, 1 H, $H_4$), 5.86 (dd, $J$ = 13.6, 11.7 Hz, 1 H, $H_2$), 4.09 (t, $J$ = 6.4 Hz, 2 H, $CH_2O$), 3.20–3.45 (overlap of $CH_2N$ and $H_2O$), 3.06 (s, 9 H, $(CH_3)_3N$), 2.65 (t, $J$ = 7.5 Hz, 2 H, $CH_2Ar$), 1.15–1.75 (m, 16 H, $(CH_2)_4$), 0.85 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 153.71, 148.76, 142.62, 138.73, 137.92, 129.17, 127.07, 123.65, 106.25, 66.40, 65.58, 53.40, 35.82, 31.52, 30.98, 28.80, 27.93, 25.30, 25.24, 22.55, 22.47, 13.99; FAB HRMS calcd for $C_{26}H_{43}N_2SO_4$ (cation) 479.2943, found 479.2955. The cmc of **4** in $H_2O$ at 25 °C is (7 ± 1) × $10^{-4}$ M.

**Diels–Alder Reactions: Product Isolation and Characterization. (a) 1b and 2a.** A mixture of 34 mg (0.10 mmol) of **1b**,[5] 43 mg (0.40 mmol) of **2a** containing 1% (w/w) 4-*tert*-butylcatechol, 0.30 mL of 1,4-dioxane, and 0.10 mL of $H_2O$ was sealed in a 1.2 × 10 cm test tube containing a micro stirring bar. The reaction mixture was stirred at 50 °C for 25 h and then diluted with 1 mL of MeCN. HPLC analysis (eluant = 60:40 MeCN–$H_2O$ and flow rate = 1 mL/min) indicated only one product with retention time = 11.9 min. Preparative TLC on silica gel with 4:1 $Et_2O$–hexane eluant gave 40 mg (88%) of product that was recrystallized from 10:1 $Et_2O$–EtOH (25 °C) to give benzyl (*cis*-6-benzoyl-*cis*-4-(phenylsulfonyl)-2-cyclohexen-1-yl)carbamate (**3b**): mp 72–74 °C; $^1H$ NMR $\delta$ 7.15–8.00 (m, 15 H, Ar H), 6.17 (br s, 2 H, $H_2$, $H_3$), 4.88 (s, 2 H, $CH_2C_6H_5$), 4.69 (m, 1 H, $H_{1e}$), 4.52 (d, $J$ = 9.4 Hz, 1 H, NH), 3.90 (dd, $J$ = 10.3, 6.8 Hz, 1 H, $H_{4a}$), 3.67 (dt, $J$ = 11.8, 4.3 Hz, 1 H, $H_{6a}$), 1.95–2.20 (m, 2 H, $H_{5a}$, $H_{5e}$); $^{13}C$ NMR $\delta$ 198.62, 155.07, 136.34, 136.20, 136.02, 134.17, 133.60, 133.38, 132.86, 129.25, 128.70, 128.38, 128.00, 127.83, 122.29, 66.75, 62.02, 45.90, 43.86, 20.16; FAB HRMS calcd for $C_{27}H_{25}NO_5SLi$ (M + $Li^+$) 482.1612, found 482.1622.

The results of homonuclear decoupling for the $^1H$ NMR spectrum are as follows. Irradiation of the signal for $H_{1e}$ caused that for $H_{6a}$ to collapse to a dd with $J_{6a,5a}$ = 11.8 and $J_{6a,5e}$ = 4.3 Hz; there was no effect on the signals for $H_{4a}$, $H_{5a}$, and $H_{5e}$. Irradiation of the overlapping signals for $H_{5a}$ and $H_{5e}$ caused each of the signals for $H_{4a}$ and $H_{6a}$ to collapse to a br s; there was no effect on the signal for $H_{1e}$.

The reaction of **1b** and **2a** in $CHCl_3$ followed the same procedure. TLC analysis of the reaction mixture indicated that **3b** was formed to the exclusion of the exo stereoisomer.

**(b) 1b and 2b.** A mixture of 17 mg (0.050 mmol) of **1b**, 43 mg (0.20 mmol) of **2b** containing 1% 4-*tert*-butylcatechol, 0.35 mL of 1,4-dioxane, and 0.050 mL of $H_2O$ was sealed in a test tube as above. The heterogeneous reaction mixture was stirred at 50 °C for 25 h and then diluted with 1 mL of MeCN; HPLC analysis with eluant = 90:10 MeCN–$H_2O$ and flow rate = 1 mL/min indicated only one product with retention time = 7.1 min. Preparative TLC on silica gel with 2:3 $Et_2O$–hexane eluant gave 19 mg (68%) of benzyl (*cis*-6-(4-hexylbenzoyl)-*cis*-4-(phenylsulfonyl)-2-cyclohexen-1-yl)carbamate (**3c**) as a viscous oil: $^1H$ NMR $\delta$ 7.10–7.95 (m, 14 H, Ar H), 6.18 (br s, 2 H, $H_2$, $H_3$), 4.90 (s, 2 H, $CH_2C_6H_5$), 4.67 (m, 1 H, $H_{1e}$), 4.51 (d, $J$ = 9.3 Hz, 1 H, NH), 3.90 (apparent t, $J$ = 9.7 Hz, 1 H, $H_{4a}$), 3.67 (dt, $J$ = 12.1, 4.1 Hz, 1 H, $H_{6a}$), 2.63 (t, $J$ = 7.6 Hz, 2 H, $CH_2Ar$), 1.95–2.20 (m, 2 H, $H_{5a}$, $H_{5e}$), 1.60 (m, 2 H, $CH_2CH_2Ar$), 1.30 (br s, 6 H, $(CH_2)_3$), 0.89 (t, 3 H, $CH_3$); $^{13}C$ NMR $\delta$ 198.27, 155.13, 149.25, 136.29, 134.17, 133.68, 133.00, 129.27, 128.92, 128.81, 128.40, 128.16, 128.02, 127.86, 122.18, 66.73, 62.08, 46.00, 43.56, 36.04, 31.63, 30.90, 28.97, 22.55, 20.27, 14.04; FAB HRMS calcd for $C_{33}H_{37}NO_5SLi$ (M + $Li^+$) 566.2553, found 566.2568.

The results of homonuclear decoupling for the $^1H$ NMR spectrum are as follows. Irradiation of the br s for $H_2$ and $H_3$ caused the signal for $H_{1e}$ to become less broad and that for $H_{4a}$ to collapse to a dd with $J_{4a,5a}$ = 9.9 and $J_{4a,5e}$ = 7.3 Hz; there was no effect on the signals for NH, $H_{6a}$, $H_{5a}$, and $H_{5e}$. Irradiation of the signal for $H_{1e}$ caused the br s for $H_2$ and $H_3$ to sharpen, the signal for NH to collapse to an s, that for $H_{4a}$ to sharpen slightly, and that for $H_{6a}$ to collapse to a dd with $J_{6a,5a}$ = 12.0 and $J_{6a,5e}$ = 3.4 Hz; there was no effect on the signals for $H_{5a}$ and $H_{5e}$. Irradiation of the signal for $H_{4a}$ caused the br s for $H_2$ and $H_3$ to sharpen, the signal for $H_{1e}$ to sharpen slightly, and the overlapping signals for $H_{5a}$ and $H_{5e}$ to collapse partially in an ill-defined manner; there was no effect on the signals for NH and $H_{6a}$. Irradiation of the signal for $H_{6a}$ caused the signal for $H_{1e}$ to become less broad and that for $H_{5a}$ and $H_{5e}$ to collapse partially in an ill-defined manner; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{4a}$. Irradiation of the overlapping signals for $H_{5a}$ and $H_{5e}$ caused the signals for $H_{4a}$ and $H_{6a}$ to collapse to an s and a br s, respectively; there was no effect on the signals for $H_2$, $H_3$, $H_{1e}$, and NH.

The regiochemistry, stereochemistry, and half-chair conformation of **3c** derived from the above decoupling experiments. Since irradiation of the overlapping signals for $H_{5a}$ and $H_{5e}$ had no effect on that for $H_{1e}$ but caused the signal for $H_{4a}$ to collapse to a singlet ($J_{4a,3}$ = ~0 Hz), **3c** has the indicated regiochemistry. The assignment for $H_{4a}$ followed from its pseudoaxial–axial coupling with $H_{5a}$ ($J_{4a,5a}$ = 9.9 Hz). The assignments for $H_{6a}$ and $H_{1e}$ followed from the former's axial–axial coupling with $H_{5a}$ ($J_{6a,5a}$ = 12.0 Hz) and axial–pseudoequatorial coupling with $H_{1e}$ ($J_{6a,1e}$ = ~4 Hz), respectively. Thus **3c** has the indicated endo stereochemistry and half-chair conformation for the substituted cyclohexene ring with the phenylsulfonyl group pseudoequatorial, the carbamate group pseudoaxial, and the aroyl group equatorial.

The reaction of **1b** and **2b** in $CHCl_3$ followed the same procedure. TLC analysis of the reaction mixture indicated that **3c** was formed to the exclusion of the exo stereoisomer.

**(c) 2a and 4.** A mixture of 28 mg (0.050 mmol) of **4**, 27 mg (0.20 mmol) of **2a** containing 1% 4-*tert*-butylcatechol, and 0.20 mL of $H_2O$, sealed in a test tube as above, was stirred at 50 °C for 25 h and then diluted with 1 mL of MeCN. By HPLC analysis with eluant = 1:2 0.60 M aqueous $NaClO_4$–MeCN and flow rate = 1 mL/min, the reaction mixture contained 6-[[[[*cis*-6-benzoyl-*cis*-4-[(4-hexylphenyl)sulfonyl]-2-cyclohexen-1-yl]-amino]carbonyl]oxy]-*N*,*N*,*N*-trimethyl-1-hexanaminium bromide (**7a**) and 6-[[[[*trans*-6-benzoyl-*cis*-4-[(4-hexylphenyl)sulfonyl]-2-cyclohexen-1-yl]amino]carbonyl]oxy]-*N*,*N*,*N*-trimethyl-1-hexanaminium bromide (**8a**) with retention times = 11.2 and 14.4 min, respectively. Chromatography on a 1.8 × 5 cm column of neutral aluminum oxide with 50 mL of MeCN and 20 mL of 1:1 MeOH–MeCN as eluants gave 33 mg (93%) of a mixture of **7a** and **8a**, which was separated by preparative HPLC with the above eluant and flow rate = 16.8 mL/min with retention times = 19.0 and 25.6 min, respectively. The eluant collected for each isomer was concentrated to ca. 25% of its original volume, lyophilized, and extracted with $CHCl_3$. To the oily residue was added 1 mL of MeCN and then 3 mL of $H_2O$, and the resultant solution was lyophilized to give a colorless solid. For **7a**: mp 90 → 110 °C dec; $^1H$ NMR $\delta$ 7.30–7.85 (m, 9 H, Ar H), 6.18 (m, 1 H, $H_2$), 6.02 (br d, $J$ = 9.6 Hz, 1 H, $H_3$), 4.74 (d, $J$ = 9.2 Hz, 1 H, NH), 4.67 (br m, 1 H, $H_{1e}$), 3.78–4.00 (m, 3 H, $CH_2O$, $H_{4a}$), 3.73 (dt, $J$ = 13.1, 3.7 Hz, 1 H, $H_{6a}$), 3.32 (m, 2 H, $CH_2N$), 3.18 (s, 9 H, $(CH_3)_3N$), 2.64 (t, $J$ = 7.6 Hz, 2 H, $CH_2Ar$), 2.20 (apparent q, $J$ = 12.8 Hz, 1 H, $H_{5a}$), 1.98 (m, 1 H, $H_{5e}$), 1.15–1.80 (m, 16 H, $(CH_2)_4$), 0.85 (t, 3 H, $CH_3$); $^{13}C$ NMR (1:9 $CD_3CN$–$CDCl_3$) $\delta$ 198.70, 154.96, 149.93, 135.85, 133.54, 132.94, 132.35, 128.97, 128.57, 128.32, 127.62, 121.77, 66.45, 64.17, 61.21, 52.89, 45.58, 43.48, 35.44, 31.11, 30.46, 28.42, 27.91, 25.08, 24.64, 22.28, 22.06, 19.18, 13.53; FAB HRMS calcd for $C_{35}H_{51}N_2O_5S$ (cation) 611.3519, found 611.3521. For **8a**: mp 80 → 190 °C dec; $^1H$ NMR (1:9 $CD_3CN$–$CDCl_3$) $\delta$ 7.25–8.15 (m, 9 H, Ar H), 6.11 (br d, $J$ = 10.8 Hz, 1 H, $H_2$), 5.80 (br d, $J$ = 10.8 Hz, 1 H, $H_3$), 5.18 (d, $J$ = 8.6 Hz, 1 H, NH), 4.65 (br s, 1 H, $H_{1e}$), 4.21 (br s, 1 H, $H_{6a}$), 3.85–4.05 (m, 3 H, $CH_2O$, $H_{4e}$), 3.30 (m, 2 H, $CH_2N$), 3.17 (s, 9 H, $(CH_3)_3N$), 2.69 (t, $J$ = 8.6 Hz, 2 H, $CH_2Ar$), 2.37 (br d, $J$ = 15.0 Hz, 1 H, $H_{5e}$), 2.05 (m, 1 H, $H_{5a}$), 1.10–2.00 (m, 16 H, $(CH_2)_4$), 0.88 (t, 3 H, $CH_3$); $^{13}C$ NMR (1:9 $CD_3CN$–$CDCl_3$) $\delta$ 200.03, 155.61, 149.91, 135.74, 135.39, 134.36, 133.38, 129.11, 128.54, 128.35, 128.30, 119.65, 66.53, 64.22, 58.95, 53.00, 47.70, 42.56, 35.52, 31.20, 30.57, 28.48, 28.07, 25.11, 24.73, 23.71, 22.39, 22.14, 13.64; FAB HRMS calcd for $C_{35}H_{51}N_2O_5S$ (cation) 611.3519, found 611.3526.

The results of homonuclear decoupling for the $^1H$ NMR spectrum of **7a** are as follows. Irradiation of the signal for $H_2$ caused that for $H_{1e}$ to sharpen and that for $H_{4a}$ to sharpen slightly; there was no effect on the signals for NH and $H_{6a}$. Irradiation of the signal for $H_3$ caused that for $H_2$ to collapse to a br s and those for $H_{1e}$ and $H_{4a}$ to sharpen slightly; there was no effect on the signals for NH and $H_{6a}$. Irradiation of the signal for $H_{1e}$ caused that for $H_2$ to collapse to a dd with $J_{2,3}$ = 10.1 and $J_{2,4a}$ = 1.7 Hz and that for $H_{6a}$ to collapse to a dd with $J_{6a,5a}$ = 12.7 and $J_{6a,5e}$

= 3.4 Hz; there was no effect on the signals for $H_3$, $H_{4a}$, and $H_{5a}$. Irradiation of the signal for $H_{4a}$ caused that for $H_2$ to collapse to a dd with $J_{2,3}$ = 10.1 and $J_{2,1e}$ = 5.1 Hz, that for $H_3$ to sharpen slightly, and that for $H_{5a}$ to collapse to an apparent t with $J$ = 12.7 Hz; there was no effect on the signals for NH, $H_{1e}$, and $H_{6e}$. Irradiation of the signal for $H_{6a}$ caused the signal for $H_{1e}$ to sharpen and that for $H_{5a}$ to collapse to an apparent t with $J$ = 12.7 Hz; there was no effect on the signals for $H_2$, $H_3$, and NH. Irradiation of the signal for $H_{5a}$ caused each of those for $H_{4a}$ and $H_{6a}$ to collapse to a br s; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{1e}$.

The results of homonuclear decoupling for the $^1H$ NMR spectrum of **8a** are as follows. Irradiation of the signal for NH caused that for $H_{1a}$ to become less broad; there was no effect on the signals for $H_2$, $H_3$, $H_{6a}$, and $H_{4e}$. Irradiation of the signal for $H_{1a}$ caused the br d for $H_2$ to sharpen with $J_{2,3}$ = 10.1 Hz, the signal for $H_3$ to collapse to a dd with $J_{3,2}$ = 10.1 and $J_{3,4e}$ = 4.2 Hz, that for NH to collapse to a br s, and that for $H_{6a}$ to collapse to a dd with $J_{6a,5a}$ = 10.1 and $J_{6a,5e}$ = 3.4 Hz; there was no effect on the signal for $H_{4e}$. Irradiation of the signal for $H_{6a}$ caused that for $H_{1a}$ to sharpen to a br s and that for $H_{5e}$ to sharpen to an apparent d with $J$ = 17 Hz; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{4e}$. Irradiation of the signal for $H_{4e}$ caused that for $H_2$ to collapse to a dd with $J_{2,3}$ = 10.1 and $J_{2,1a}$ = 3.2 Hz, the br d for $H_3$ to sharpen with $J_{3,2}$ = 10.1 Hz, and the signal for $H_{5e}$ to sharpen to an apparent d with $J$ = 17 Hz; there was no effect on the signals for NH, $H_{1a}$, and $H_{6a}$. Irradiation of the signal for $H_{5e}$ caused that for $H_{6a}$ to collapse to an apparent t with $J$ = 8.8 Hz and that for $H_{4e}$ to sharpen; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{1a}$. Irradiation of the signal for $H_{5a}$ caused the signal for $H_{6a}$ to collapse to a br d with $J$ = 8.6 Hz and that for $H_{4e}$ to sharpen; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{1a}$.

**(d) 2b and 4.** A heterogeneous mixture of 56 mg (0.10 mmol) of **4**, 56 mg (0.40 mmol) of **2b** containing 1% 4-*tert*-butylcatechol, and 1.00 mL of $H_2O$ was stirred at 50 °C for 50 h with a micro stirring bar in a 1.2 × 10 cm test tube capped with a rubber septum, and then it was diluted with 3 mL of MeCN. By HPLC analysis with eluant = 1:4 0.60 M aqueous $NaClO_4$–MeCN and flow rate = 1.5 mL/min, the reaction mixture contained 6-[[[[*cis*-6-(4-hexylbenzoyl)-*cis*-4-[(4-hexylphenyl)sulfonyl]-2-cyclohexen-1-yl]amino]carbonyl]oxy]-*N,N,N*-trimethyl-1-hexanaminium bromide (**7b**), 6-[[[[*trans*-6-(4-hexylbenzoyl)-*cis*-4-[(4-hexylphenyl)sulfonyl]-2-cyclohexen-1-yl]amino]carbonyl]oxy]-*N,N,N*-trimethyl-1-hexanaminium bromide (**8b**), and **4** in a 62:5:33 ratio (**7b**:**8b** = 93:7) with retention times = 16.7, 20.9, and 3.5 min, respectively, in addition to **2b**. It was chromatographed on a 1.7 × 5 cm column of acidic aluminum oxide with 40 mL of THF, 10 mL of MeCN, and 20 mL of 1:1 MeOH–MeCN as eluants. The chromatography was repeated on a fresh column in order to completely remove unreacted **2b**; 54 mg of a mixture of **7b**, **8b**, and **4** resulted. By HPLC analysis, **7b**:**8b** = 89:11, and **7b** and **8b** (51% total) were isolated by preparative HPLC with eluant = 1:9 aqueous 0.60 M $NaClO_4$–MeCN and flow rate = 16.8 mL/min with retention times = 10.3 and 13.2 min, respectively. The eluant collected for each isomer was concentrated to ca. 25% of its original volume, lyophilized, and extracted with $CHCl_3$. To the oily residue were added 1 mL of MeCN and then 3 mL of $H_2O$, and the resultant solution was lyophilized to give a colorless solid for **7b** and a colorless oil for **8b**. For **7b**: mp 110–115 °C; $^1H$ NMR $\delta$ 7.20–7.87 (m, 8 H, Ar H), 6.25 (m, 1 H, $H_2$), 6.04 (br d, $J$ = 9.6 Hz, 1 H, $H_3$), 4.60–4.75 (m, 2 H, NH, $H_{1e}$), 3.73–4.00 (m, 3 H, $CH_2O$, $H_{4e}$), 3.66 (br d, $J$ = 11.6 Hz, 1 H, $H_{6e}$), 3.41 (m, 2 H, $CH_2N$), 3.21 (s, 9 H, $(CH_3)_3N$), 2.65 (m, 4 H, $CH_2Ar$), 2.28 (apparent q, $J$ = 12.9 Hz, 1 H, $H_{5a}$), 1.10–2.05 (m, 25 H, $H_{5e}$, $(CH_2)_4$), 0.88 (t, 6 H, $CH_3$); $^{13}C$ NMR $\delta$ 198.68, 155.42, 150.38, 149.29, 133.83, 133.16, 129.43, 129.04, 128.84, 128.14, 121.97, 67.04, 64.69, 61.71, 53.38, 45.99, 43.67, 36.01, 35.96, 31.63, 31.57, 30.94, 29.68, 28.96, 28.90, 28.29, 25.55, 25.26, 22.88, 22.55, 22.52, 19.63, 14.05; FAB HRMS calcd for $C_{41}H_{63}N_2O_5S$ (cation) 695.4458, found 695.4453. For **8b**: $^1H$ NMR $\delta$ 7.30–8.06 (m, 8 H, Ar H), 6.11 (br d, $J$ = 9.7 Hz, 1 H, $H_2$), 5.78 (br d, $J$ = 9.7 Hz, 1 H, $H_3$), 4.96 (d, $J$ = 9.2 Hz, 1 H, NH), 4.68 (br s, 1 H, $H_{1e}$), 4.18 (br s, 1 H, $H_{6e}$), 3.93–4.08 (m, 3 H, $CH_2O$, $H_{4e}$), 3.42 (m, 2 H, $CH_2N$), 3.21 (s, 9 H, $(CH_3)_3N$), 2.66 (m, 4 H, $CH_2Ar$), 2.41 (m, 1 H, $H_{5e}$), 2.10 (m, 1 H, $H_{5a}$), 1.18–1.87 (m, 24 H, $(CH_2)_4$), 0.88 (m, 6 H, $CH_3$); FAB HRMS calcd for $C_{41}H_{63}N_2O_5S$ (cation) 695.4458, found 695.4465.

The results of homonuclear decoupling for the $^1H$ NMR spectrum of **7b** are as follows. Irradiation of the signal for $H_{5a}$ caused the m for the overlapping signals for $H_{4a}$ and $CH_2O$ to sharpen and the signal for $H_{6a}$ to collapse to a br s; there was no effect on the signals for $H_2$, $H_3$, NH, and $H_{1e}$. The structure of **7b** was assigned on the basis of these decoupling results and comparisons of the $^1H$ and $^{13}C$ NMR spectra of **7a** and **7b**. The structure **8b** derived from a comparison of the $^1H$ NMR spectra of **8a** and **8b**.

In the HPLC analyses of the reactions of **2b** and **4** in both $H_2O$ and $CHCl_3$, a peak was obtained beyond that for **8b** whose area was usually slightly less than that for **8b**. It was collected by preparative HPLC and by $^1H$ NMR analysis corresponded to a mixture of a least two compounds. The FAB mass spectrum of the mixture contained a prominent ion at 695.4496, consistent with the presence of **10** (695.4458 for $C_{41}H_{63}N_2O_5S$ (cation)).

**Diels–Alder Reactions: Determination of 7:8 (Endo/Exo) Ratios.** The reaction mixtures, diluted with MeCN, were analyzed by analytical HPLC after column chromatography on acidic aluminum oxide as described below. For reaction mixtures from **2a** and **4**, eluant = 1:2 aqueous 0.60 M $NaClO_4$–MeCN, flow rate = 1.5 mL/min, retention times = 6.3, 8.4, and 10.0 min for **4**, **7a**, and **8a**, respectively. For those from **2b** and **4**, eluant = 1:14 aqueous 0.60 M $NaClO_4$–MeCN, flow rate = 1.0 mL/min, retention times = 3.6, 7.0, and 8.4 min for **4**, **7b**, and **8b**, respectively. The relative response ratio for **4**, **7a**, and **8a** at 254 nm (1:1.89:1.89) was determined by HPLC analysis of a known mixture of **4**, **7a**, and **8a** and that for **4**, **7b**, and **8b** at 254 nm (1:2.69:2.69) was determined analogously.

For each system below, the reaction mixture was chromatographed as follows. A 0.8 × 6 cm column of acidic aluminum oxide was packed dry, and 1 mL of THF was passed through it. Then the reaction mixture was added to the column and eluted with 4 mL of THF, to remove **2**, 1.5 mL of MeCN, and 3 mL of 1:1 MeOH–MeCN, to give the solution for HPLC analysis.

**(a) 0.25 M 4 and 1.0 M 2.** A mixture of 28 mg (0.050 mmol) of **4**, 27 mg (0.20 mmol) of **2a** (43 mg (0.20 mmol) of **2b**), and 0.20 mL of $H_2O$ ($CHCl_3$) was divided into 30–50-$\mu$L portions, which were sealed in 0.2 × 9 mm capillary tubes. The tubes were held at 50 °C, and, at the appropriate time, the contents of a tube at 25 °C were diluted with 1 mL of MeCN and analyzed as above. Throughout the reaction period at 50 °C the mixtures in $H_2O$ were cloudy/milky and those in $CHCl_3$, homogeneous.

**(b) 0.10 M 4 and 0.40 M 2.** The procedure for (a) was used with 14 mg (0.025 mmol) of **4**, 13 mg (0.10 mmol) of **2a** (22 mg (0.10 mmol) of **2b**), and 0.25 mL of $H_2O$ ($CHCl_3$). Some of the reaction mixtures contained 9.1 mg (0.025 mmol) of HTABr. At 50 °C, the reaction mixture in $H_2O$ with **2a** and without HTABr was cloudy/milky at first and then became homogeneous after ca. 10 h. The same reaction mixture with HTABr became homogeneous after ca. 3 h. The reaction mixtures with **2b** in $H_2O$, with and without HTABr, were cloudy/milky throughout the reaction period, although less so with HTABr. At 50 °C, all reaction mixtures in $CHCl_3$ were homogeneous throughout the reaction period.

**(c) 0.025 M 4 and 0.10 M 2.** The procedure for (a) was used with 14 mg (0.025 mmol) of **4**, 13 mg (0.10 mmol) of **2a** (22 mg (0.10 mmol) of **2b**), and 1.0 mL of $H_2O$. At 50 °C, the reaction mixture with **2a** was cloudy/milky at first and then became homogeneous after ca. 3 h. The reaction mixture with **2b** was cloudy/milky throughout the reaction period.

**X-ray Structure Determination of 3b.** The structure of **3b** was determined at −100 °C on a Nicolet R3m/V diffractometer equipped with a molybdenum tube [$\lambda(K\alpha_1)$ = 0.70926 Å; $\lambda(K\alpha_2)$ = 0.71354 Å] and a graphite monochromator. The compound crystallizes in the centrosymmetric monoclinic space group $P2_1/c$ with four molecules in a cell of dimensions $a$ = 14.299 (4) Å, $b$ = 8.931 (2) Å, $c$ = 18.129 (5) Å, $\beta$ = 98.77 (2)°, and $V$ = 2288.2 (9) Å$^3$. A total of 3001 data were gathered ($R_{int}$ = 0.0318), the octants collected being $+h, +k, \pm l$. The structure has been refined to conventional $R$ factor values of $R$ = 0.0667 and $R_w$ = 0.0708 on the basis of 1060 independent reflections with $I > 3\sigma(I)$ in the $2\theta$ range 4–45°. Absorption corrections have not been applied ($\mu$ = 0.173 mm$^{-1}$). The structure was solved by direct methods and refined by least-squares techniques; the programs used were

from the SHELXTL system.[35] Phenyl rings were treated as rigid groups (C–C = 1.395 Å, bond angles = 120°), and phenyl hydrogens were placed in fixed calculated positions (C–H = 0.96 Å), while all other non-hydrogen atoms were refined anisotropically.

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(35) Sheldrick, G. M. *SHELXTL-PLUS Crystallographic System*, Version 2; Nicolet XRD Corp.: Madison, WI, 1987.

**Registry No.** **1b**, 86802-64-4; **2a**, 768-03-6; **2b**, 131906-57-5; **3b**, 131906-67-7; **3c**, 131906-68-8; **4**, 131906-60-0; **5**, 131906-61-1; **6**, 131906-62-2; **7a**, 131906-70-2; **7b**, 131932-54-2; **8a**, 131906-64-4; **8b**, 131906-59-7; **10**, 131906-66-6; 4-$EtCOC_6H_4C_6H_{13}$, 79219-16-2; $C_6H_5SeCl$, 5707-04-0; 4-$MeCH(SeC_6H_5)COC_6H_4C_6H_{13}$, 131906-71-3; (*E*)-$HO_2CCH{=}CHCH{=}CH_2$, 21651-12-7; $Br(CH_2)_6OH$, 4286-55-9; 4-$C_6H_{13}C_6H_4SH$, 4619-85-6; 4-$C_6H_{13}C_6H_4SO_2CH{=}CHCH{=}CH{=}NHCO_2(CH_2)_6Br$, 131932-55-3.

**Supplementary Material Available:** IR data; X-ray structure of **3b**; tables of atomic coordinates, bond lengths, bond angles, hydrogen atom coordinates, and thermal displacement parameters; and $^1H$ and $^{13}C$ NMR spectra of **2b**, 6-bromohexyl ((*E,E*)-4-[(4-hexylphenyl)sulfonyl]-1,3-butadienyl)carbamate, **4**, **3b**, **3c**, **7a**, **8a**, **7b**, and **8b** (30 pages); observed and calculated structure amplitudes for **3b** (11 pages). Ordering information is given on any current masthead page.

# Asymmetric Aldol Reactions. Use of the Titanium Enolate of a Chiral *N*-Acyloxazolidinone To Reverse Diastereofacial Selectivities

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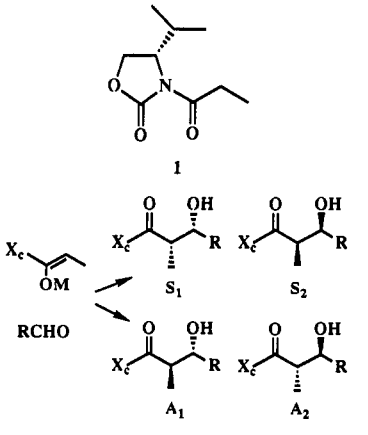
Aldol reactions of the titanium enolate of (*S*)-*N*-propionyl-4-isopropyl-2-oxazolidinone (readily derived from L-valine) with representative aldehydes give high diastereofacial selectivities for the syn aldol adducts expected from chelation control. This represents a remarkable reversal in selectivity compared with the corresponding boron enolate, thus permitting either enantiomeric form of β-hydroxy-α-methyl carboxylic acids to be made from a single, readily available oxazolidinone simply by changing the metal. A lithium interference effect is shown to be easily prevented by use of excess titanium. Use of diethyl ether as solvent rather than THF significantly enhances the stereoselectivity. Mechanistically, the observed stereochemical reversal constitutes very strong evidence that chelation is operative with titanium, presumably through a chelated chairlike transition structure. In this transition structure, the conformation would be rigidly locked by chelation and the titanium would be at least hexacoordinate, resulting in a "superaxial" ligand, thus nicely explaining the high stereocontrol.

The pericyclic transition structures usually associated with the aldol reaction can provide strong acyclic stereocontrol.[1-3] Advances in understanding and application of highly stereocontrolled aldol processes would propel the synthesis of chiral aldol intermediates, which play important roles in syntheses of many important classes of compounds, including macrolide, ionophore, and β-lactam antibiotics.[4]

The very high selectivity in aldol reactions of titanium(IV) enolates recently observed in this laboratory[5,6] led us to consider that titanium enolates should provide highly selective aldol reactions under *chelation control*. The design concept is that titanium(IV), being a transition metal, *combines* two desirable properties: (1) presence of ligands attached to the metal, and (2) a vacant d orbital shell capable of chelation. Boron has given high levels of stereocontrol in aldol reactions, where the presence of bonded ligands is believed to be the controlling factor. However, boron is incapable of chelation because, as a second-row element, it cannot complex with additional groups beyond the aldehyde component of the aldol reaction. On the other hand, chelation control has been postulated for other metals such as lithium, zinc, and Sn(IV), though levels are rarely high. These facts led us to propose that titanium could provide both high selectivity *and* chelation control.

In this paper we describe a remarkable reversal of diastereofacial selectivity in titanium-mediated aldol reactions of **1** to give the product expected from chelation control, $S_2$,[7,8] whereas the opposite diastereofacial selection ($S_1$) is observed with the corresponding boron enolate.[9,10]

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