

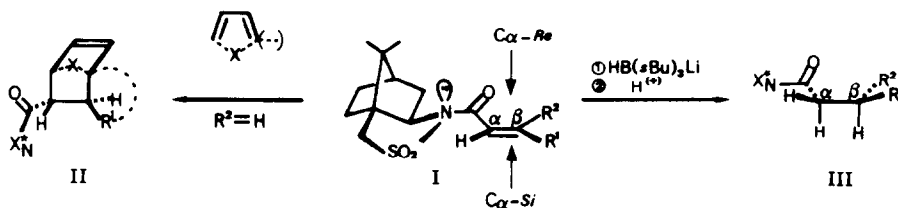
**STABLE AND REACTIVE CONFORMATIONS OF N-ENOYL-BORNANE-10,2-SULTAMS IN THE ABSENCE OF LEWIS ACIDS: ASYMMETRIC 1,4-HYDRIDE ADDITIONS.**

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**Abstract:** Ground-state conformations of non-chelated N-enoylsultams were determined by X-ray (1, 3) and <sup>1</sup>H-NMR-LIS evidence. Conjugate additions of lithium tri-*s*-butylborohydride to 1 and 3 followed by *O*-acylation of the non-isolated "enolates" furnished stereoselectively either (*Z*) or (*E*)-*O*-acyl-*N,O*-ketene acetals (1 → 2, 3 → 4) depending on the *s-cis/s-trans*-conformation of the N-enoylsultams. X-ray diffraction analyses of sultam derivatives 1, 2, 3 and 4 show a pyramidal nitrogen atom. This information provides an insight into the π-face discriminations observed on addition reactions to non-coordinated enoylsultams (e.g. I → II, I → III).

N-Enoylsultams I, R<sup>2</sup> = H undergo remarkably efficient and selective *inter*- and *intra*-molecular Diels-Alder additions of 1,3- dienes (X=CH<sub>2</sub> or H<sub>2</sub>) from the Cα-*Re*-face I → II, when coordinated with EtAlCl<sub>2</sub> or TiCl<sub>4</sub> [1] (Scheme 1).

Scheme 1

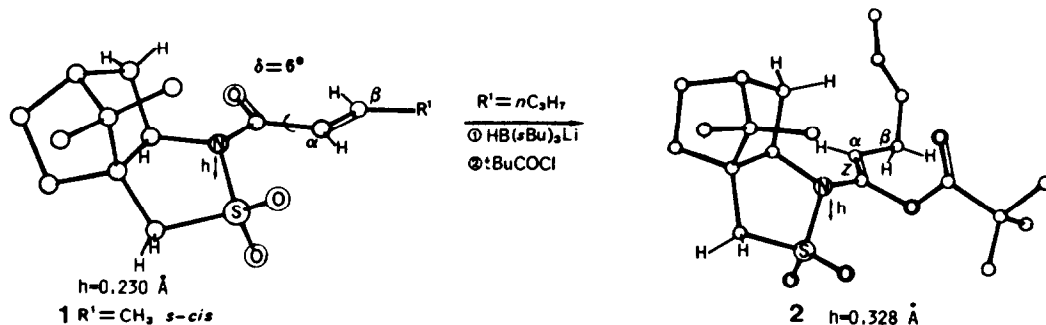


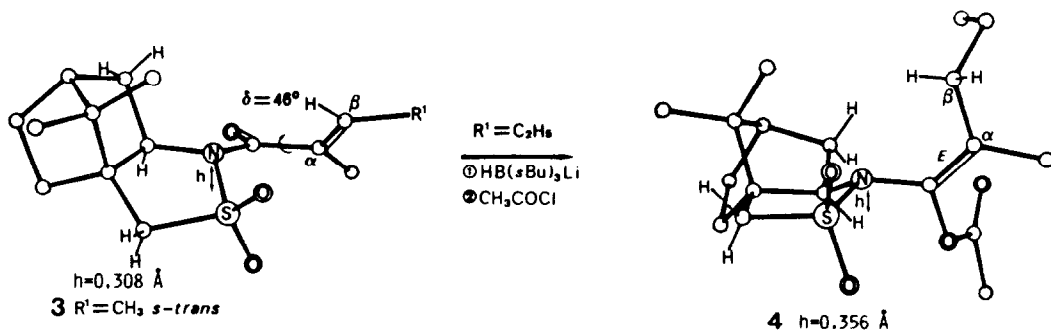
In extension to these results, various other addition reactions of I have been studied and found to proceed with high π-face discrimination [2], even in the absence of a Lewis acid [3].

Thus, osmylations [4] and simple hydrogenations [5] of β,β-disubstituted enoyl sultams I proceeded predominantly from the Cα-*Re*-face. Opposite (Cα-*Si*) face attack on I (90-94% d.e.) was, however, observed with conjugate hydride additions I → III [6].

To predict and understand the topology of these additions an X-ray diffraction study of the non-coordinated (*E*)-crotonoylsultam 1 was carried out [1] (Scheme 2).

Scheme 2





This X-ray analysis shows (in contrast to an acyclic *N*-acylsulfonamide [7]) a pyramidal nitrogen [8] with its three substituents tilted away from the bridgehead C(8)-methyl group. The  $\text{SO}_2$ - and C=O groups are *anti*, the C=O/ $\text{C}\alpha, \text{C}\beta$ - bonds *s-cis* disposed and the O-S-O-angle bisects the plane of the conjugated carbonyl system.  $^1\text{H-NMR}$  measurements in the presence of  $\text{Eu}(\text{fod})_3$  (Figure 1) show also a predominant  $\text{SO}_2/\text{C=O}$ - *anti*- and C=O/ $\text{C}\alpha, \text{C}\beta$ -*s-cis* arrangement in solution (Figure 1) [9].

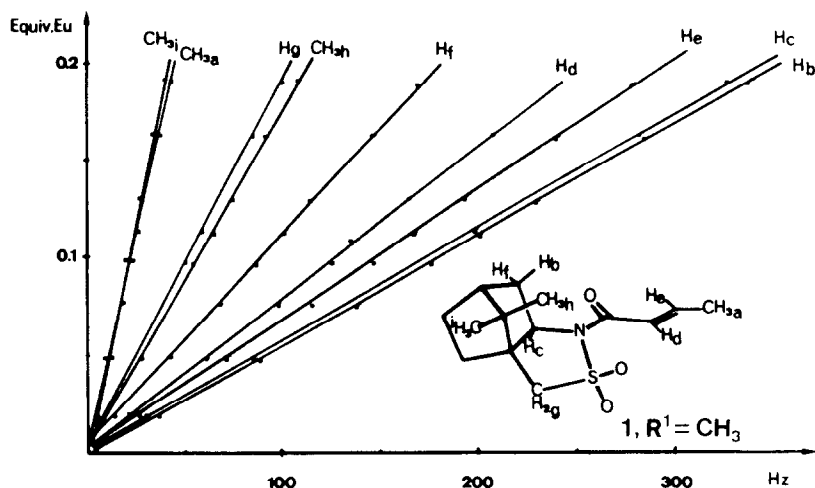
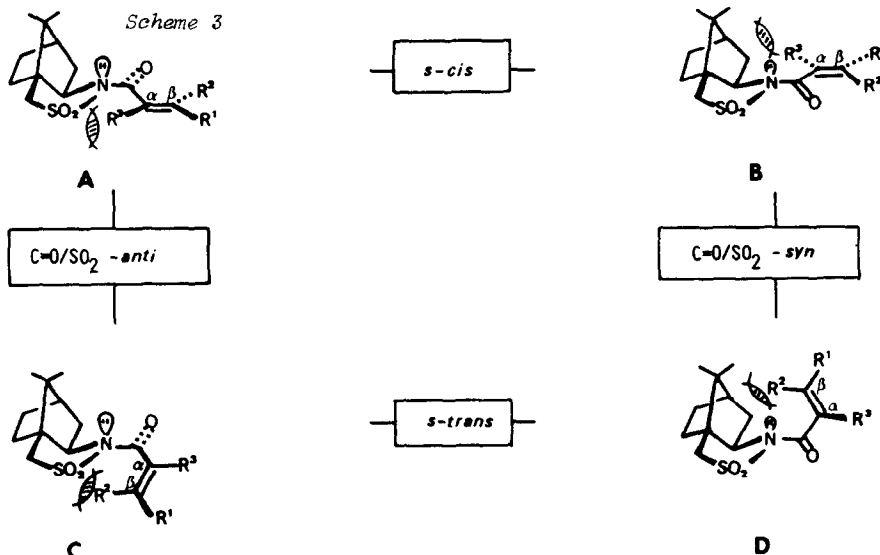


Figure 1:  $\text{Eu}(\text{fod})_3$ -induced downfield-shifts of  $^1\text{H-NMR}$  signals (100 MHz,  $\text{CDCl}_3$ ) of **1**,  $R^1 = \text{CH}_3$ .

We now provide experimental evidence for a reactive conformation of **1** via 1,4 hydride addition and O-acylation of the resulting *O*-lithium-*N,O*-ketene acetal. Thus, successive treatment of (*E*)-2-hexenoylsultam **1**,  $R^1 = n\text{-C}_3\text{H}_7$  (0.64 mmol) with lithium tri-*s*-butylborohydride (0.77 mmol,  $-78^\circ$ , 30 min) and TMEDA (0.9 mmol)/pivaloyl chloride (0.8 mmol) in THF ( $-78^\circ \rightarrow \text{r.t.}$  over 15 h) furnished the *O*-pivaloyl-*N,O*-ketene acetal **2** (67%, Scheme 2). X-ray diffraction analysis of **2** [10] confirms the (*Z*)-configuration of the olefinic bond which carries a pyramidal nitrogen. It thus appears that the *s-cis*-conformation of the enoylsultam **1**,  $R = n\text{-C}_3\text{H}_7$  translates into the (*Z*)-configuration of **2** via the corresponding (*Z*)-*O*-lithium-*N,O*-ketene acetal [11]. In view of previously reported hydride additions to conformationally defined enones [13] (which correlate to the resulting enolate configurations) we expected  $\text{C}\alpha$ -substituted enoylsultams **3** to adopt rather the C=O/ $\text{C}\alpha, \text{C}\beta$ - *s-trans* arrangement. X-ray diffraction measurements [14] of the *N*-tigloylsultam **3**,  $R^1 = \text{CH}_3$  (Scheme 2) displayed as before a pyramidal nitrogen atom flanked by *anti*-disposed  $\text{SO}_2$ - and C=O groups, but a *s-transoid*

conformation ( $46^\circ$  out of plane) [15]. Conjugate hydride addition/enolate O-acetylation of **3**,  $R^1 = C_2H_5$  [16] gave exclusively the (*E*)-O-acetyl-N,O,-ketene acetal **4** as confirmed by X-ray structure elucidation [17].

Based on the above evidence we propose as a general working hypothesis the following topicities for addition reactions to enoylsultams (Scheme 3):



(1) Disposition of the C=O and SO<sub>2</sub> groups *anti* (A, C) in the absence, but *syn* (B, D) in the presence of chelating metals [3].

(2) *s-Cis*-relation of the C=O/C $\alpha$ ,C $\beta$ - bonds when the C $\alpha$ -substituent R<sup>3</sup>=H (A, B) but *s-trans* when R<sup>3</sup>=alkyl and R<sup>2</sup>=H (C, D).

It is therefore plausible to ascribe the C $\alpha$ -Si-face preferred hydride additions **I**  $\rightarrow$  **III** to a reactive conformation A. Consequently, the hydride approaches the  $\pi$ -face of **I** opposite to the lone pair on the N-atom.

We believe that the observed  $\pi$ -face discrimination originates in the chiral information provided by the bornane skeleton which is transmitted, via the pyramidal nitrogen atom, to the remote C $\beta$ -position. Recently, the possible role of pyramidal nitrogen in  $\pi$ -face-selective electrophilic reactions with enamine derivatives has been increasingly considered [12].

It is interesting to note that lithium tri-*s*-butylborohydride adds to **I** from the olefinic C $\alpha$ -Si-face (**I**  $\rightarrow$  **III**) in contrast to cyclopentadiene which undergoes non-catalyzed Diels-Alder additions (**I**  $\rightarrow$  **II**) predominantly (53 - 66% d.e.) from the C $\alpha$ -Re-face. Depending on the reaction type, it seems that additions to non-coordinated **I** can proceed either from the  $\pi$ -face *anti* or *syn* to the lone electron pair on the N-atom. Nitrile oxide additions to **I** as discovered by Curran and coworkers [18] present a striking example of the latter topicity.

There is no doubt that the practical, but theoretically puzzling stereoelectronic bias of N-enoylsultams **I** [18] deserves a more precise understanding. To this end, further work is in progress.

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- [2] Review: W.Oppolzer, *Tetrahedron* 1987, 43, 1969; Erratum: *Tetrahedron* 1987, 43, Issue 18. Discussions of a possible stereoelectronic bias: Ref[3], footnote 8; ref[4], footnote 1.
- [3] Evidence for the conformation of Ti<sup>IV</sup>-chelated enoylsultams will be reported in due course. The  $\pi$ -face discrimination observed on conjugate additions of Grignard reagents to enoylsultams 1 has also been attributed to a chelation of 1 (by Mg): W.Oppolzer, G.Poli *Helv. Chim. Acta* 1987, 70, 2201. To what extent a "chelation" by Os or Pd plays a role in asymmetric osmylations [4] and hydrogenations [5] of 1 remains to be clarified.
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- [5] W.Oppolzer, R.J.Mills, M.Réglier *Tetrahedron Lett.* 1986, 27, 183.
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- [8] The calculated height of the pyramid  $h = 0.230 \text{ \AA}$  indicates a nitrogen-hybridization approximately halfway between  $sp_2$  and  $sp_3$ .
- [9] C.Chapuis, Thesis, Université de Genève 1984, No. 2144, p.56.
- [10] Crystallographic data for compounds 2, 3,  $R^1 = CH_3$ , and 4 have been deposited at the Cambridge Crystallographic Data Center. Observed and calculated structure factors may be obtained from one of the authors (G.B.). The data were collected on a Philips PW1100 diffractometer (MoK $\alpha$ ). The structures were solved by a direct method (Mulan-80) and refined by a full matrix least-squares analysis. The positions of the hydrogen atoms were calculated. The crystals of pivaloate 2 (MeOH), m.p. 94-95° are orthorhombic,  $a=10,388$  (2),  $b=13,271$  (3),  $c=16,391$  (2) Å, space group  $P2_12_12_1$ ,  $z=4$ ,  $d_C = 1.169 \text{ g.cm}^{-3}$ . The final R-factor based on 1601 observed reflections (capillary, argon atmosphere) was 0.084
- [11] It is plausible to assume that the depicted solid state conformation of pivaloate 2 resembles that of the intermediate O-lithium-N,O-ketene acetal. Accordingly, alkylations of the latter (e.g. by MeI) [6] proceed with a  $\pi$ -face discrimination which corresponds to an electrophilic attack at C $\alpha$  from its Re- (bottom) face, opposite to the lone electron pair on the nitrogen atom [12]. This permits the highly selective generation of an additional stereocenter at C $\alpha$ .
- [12] The possibility of a  $\pi$ -face-directing bias of the pyramidal nitrogen atom on the electrophilic attack of enamines and N,O-ketene acetals was first evoked by Eschenmoser and coworkers: L.G.Damm, Thesis, ETH No.6390, 1979; A.Kümin, Thesis, ETH No.6509, 1979; A.Kümin, E.Maverick, P.Seiler, N.Vanier, L.Damm, R.Hobi, J.D.Dunitz, A.Eschenmoser, *Helv. Chim. Acta* 1980, 63, 1158. For related reactions of O-metalated N,O-ketene acetals see: P.Magnus, T.Gallagher, P.Brown, J.C.Huffman, *J. Am. Chem. Soc.* 1984, 106, 2105; A.I.Meyers, B.A.Lefker, K.Th.Wanner, R.A.Aitken, *J. Org. Chem.* 1986, 51, 1936; D.Seebach, E.Juaristi, D.D.Miller, C.Schickli, T.Weber, *Helv. Chim. Acta* 1987, 70, 237; Ref. [2], footnote 8.
- [13] A.R.Chamberlain, S.H.Reich, *J. Am. Chem. Soc.* 1985, 107, 1440.
- [14] The crystals of tigloylsultam 3,  $R^1 = CH_3$  (MeOH/CH<sub>2</sub>Cl<sub>2</sub>), m.p. 181-182°, are orthorhombic,  $a = 6.9758$  (12),  $b = 9.3449$  (12),  $c = 23.230$  (5) Å, space group  $P2_12_12_1$ ,  $z = 4$ ,  $d_C = 1.304 \text{ g.cm}^{-3}$ . The final R-factor based on 1645 observed reflections was 0.047.
- [15] The observed conformation of 3,  $R^1 = CH_3$  provides an explanation why osmylations [4] and hydrogenations [5] of C $\alpha$ -substituted enoyl sultams (e.g. of 3,  $R^1 = CH_3$ ) proceeded with only poor  $\pi$ -face selection in contrast to the corresponding reactions of the C $\alpha$ -unsubstituted enoylsultams 1.
- [16] Dropwise addition of 1M lithium tri-*s*-butylborohydride in THF (0.8 mmol) to enoylsultam 3,  $R^1 = C_2H_5$  (0.643 mmol) in toluene (10 ml) at -80°, stirring at -80° for 5 min then  $\rightarrow$  -30° over 30 min, then at -30° for 30 min, addition of AcCl (1.415 mmol) at -80°, warming to -60° over 1h, quenching with sat. aq. NH<sub>4</sub>Cl, work-up, flash chromatography and crystallization (MeOH) gave 4 (59%).
- [17] The crystals of acetate 4 (MeOH), m.p. 125° are orthorhombic,  $a = 27.272$  (8),  $b = 9.5089$  (13),  $c = 27.272$  (8) Å, space group  $P2_12_12_1$ ,  $z = 4$ ,  $d_C = 1.256 \text{ g.cm}^{-3}$ . The final R-factor based on 1631 observed reflections was 0.057.
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