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ASYMMETRIC ALDOL ADDITION REACTIONS OF A CHIRAL 3-SULFONYL-1,3-OXAZOLIDINE-MASKED LITHIUM 2-FORMYLCYCLOHEXANONE ENOLATE#

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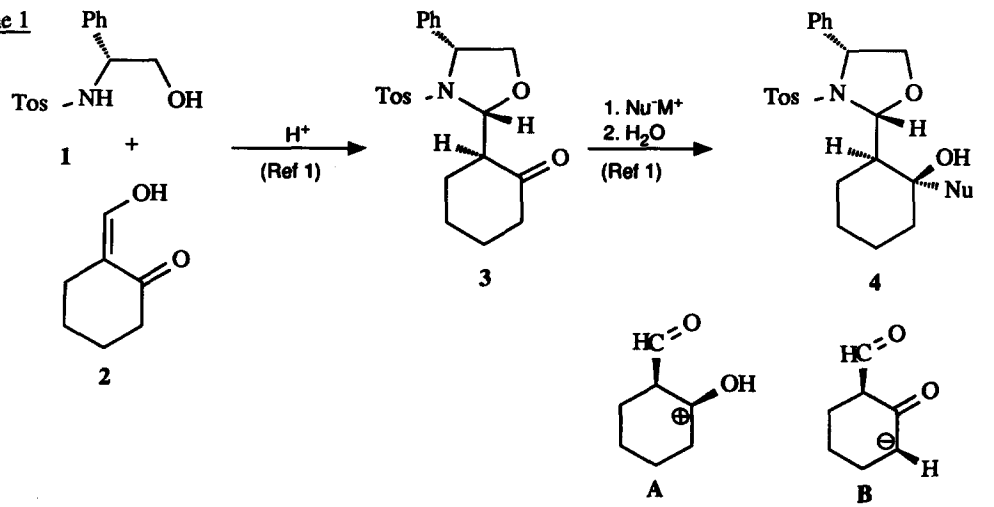
Summary: The title compound, prepared by kinetically controlled deprotonation of a stereohomogeneous 2-(2-oxocyclohexyl)-1,3-oxazolidine, undergoes highly *anti*-stereoselective aldol addition with alkanals.

As it was demonstrated recently by us[1,2] and by Scolastico et al.[3,4] 3-sulfonyl-substituted 1,3-oxazolidines, which are derived from enantiomerically pure ß-hydroxyamines, are powerful tools in asymmetric synthesis. In particular, the *cis*-2-(2-oxocyclohexyl) derivatives[1,2] of type **3** deserve attention because they are formed diastereomerically pure from the tosylamide **1** and 2-(hydroxymethylene)cyclohexanone (**2**) by condensation[1] under kinetic control (Scheme 1). By this, two homogeneous stereocenters are created with one step extending the chiral information from the auxiliary **1** to the cyclohexane ring.

Scheme 1



Carbon nucleophiles, as a consequence, approach virtually exclusively from the less shielded face of the carbonyl group giving rise to diastereomerically and enantiomerically pure derivatives **4** of 2-hydroxycyclohexanecarbaldehyde.[1]

Here, the (*R*)-phenylglycinol-derived ketone **3** serves for an efficient equivalent of synthon **A**. We now report its utilization as excellent precursor for the chiral enolate synthon **B** in asymmetric aldol addition reactions.[5]

Deprotonation[6] of ketone **3** (LDA/TMEDA, THF, -78°C) formed the kinetic enolate[7] **5** with >95% regioselectivity (Scheme 2). It was trapped as trimethylsilylenol ether[8,9] **6** with 88% yield after LC purification on silica gel. The reaction of the lithium enolate **5** with alkanals **7a-c** afforded a single aldol adduct[9,10] **8a-c** in each case (>95% *ds*).[6] In contrast, the alkenal **7d** reacted with lower diastereoselectivity (82:18) to yield the aldol **8d** as the major product.[11]

Scheme 2

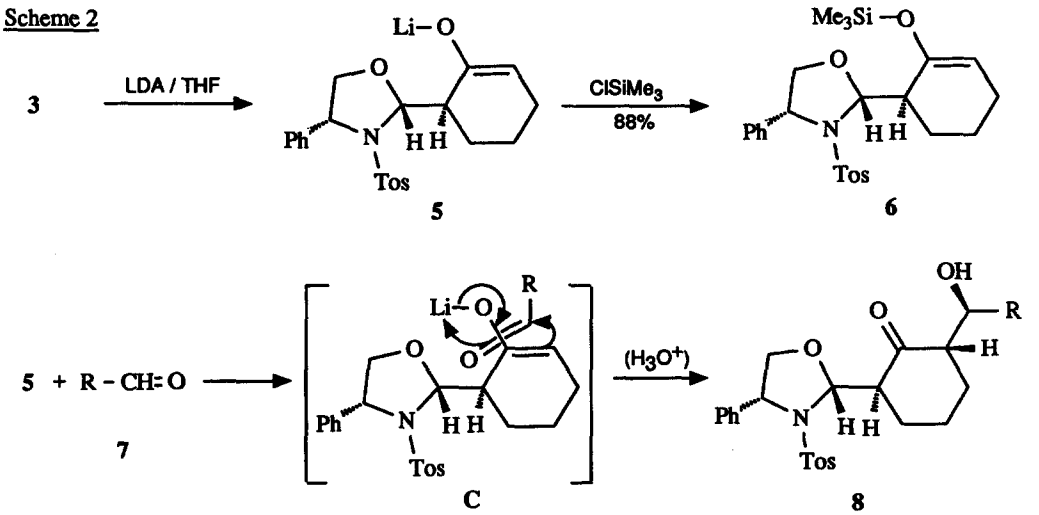
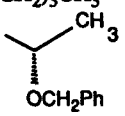
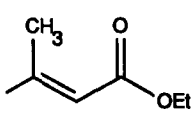


Table 1: Yields of products **8** and diastereoselectivities

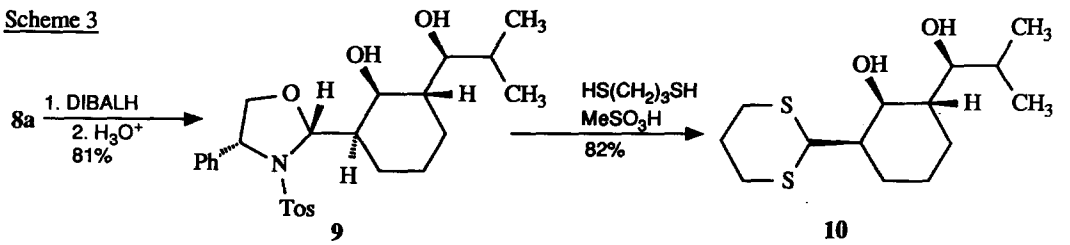
7, 8	R	Yield, (*ds*) [%]
a	$CH(CH_3)_2$	84 (>95)
b	$(CH_2)_3CH_3$	78 (>95)
c		77 (>95)
d		70 (82)

The stereostructure of **8a** was established by an X-ray crystal structure analysis[13] of the diol[9,12] **9**, which was obtained by reduction of **8a** with diisobutylaluminium hydride (DIBALH) in hexane with 81% yield and >95% *ds* (Scheme 3, Figure 1).

The observed *anti*-selectivity of the aldol addition corresponds well to the results obtained by Stiles and Dubois[14] with simpler achiral lithium cyclohexanone enolates. An inspection of the stereostructure of **9**, which also resembles the steric situation in aldol **8a**, reveals that the product ratio is strictly kinetically determined. Any plausible epimerization would lead to a more stable (bis-equatorial) 2,6-*cis*-cyclohexanone. The stereochemical outcome is well explained by the Zimmerman-Traxler model[15], assuming the aldehyde **7** to approach from the less shielded face of enolate **5** via a chair-like[15] or a twist-boat transition state.[16]

The oxazolidine ring in **9** is easily cleaved by 1,3-propanedithiol[1,3,4] (10 mol% CH_3SO_3H, CH_2Cl_2, 24h at 40°C) to afford the dithiane[9,17] **10** with 82% yield (Scheme 3).

Scheme 3



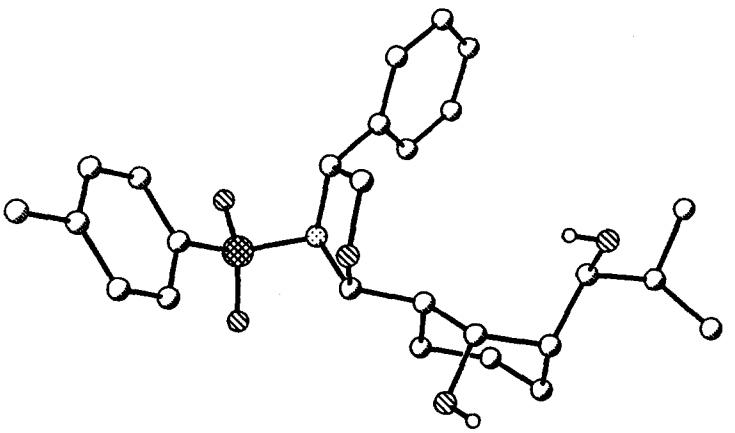


Fig. 1 Structure of **9** in the crystal (O atoms fully shaded, N dotted, S cross-hatched, only hydroxyl H atoms shown

In summary, 2-formylcyclohexanones are converted to enantiomerically pure aldol adducts, derived from the less stabilized enolate, with predictable configuration by two simple synthetic steps. Analogously the enantiomers are accessible by the use of readily available (*S*)-*N*-tosyl-phenyl-glycinol (*ent*-**1a**). The high crystallization tendency of the sulfonamides facilitates any up-grading or structure elucidation, if necessary.

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REFERENCES AND FOOTNOTES

Dedicated to Professor Hans Jürgen Bestmann on the occasion of his 65th birthday.

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6. To a solution of lithium diisopropylamide (LDA; 2 mmol) and *N,N,N',N'*-tetramethylethylene diamine (TMEDA; 2.0 mmol) in THF (7 mL) at -78°C a solution of ketone **3a** (2.0 mmol) in THF (2 mL) is slowly introduced and stirring continued for 1 h. Chlorotrimethylsilane (for **6**; 2.2 mmol) or aldehyde **7** (for **8**; 2.2 mmol) in THF (2 mL) is added. After stirring for 20 h at -78°C and addition of acetic acid (0.25 g) the usual aqueous work-up with dichloromethane as a solvent is accomplished. The products **6** or **8** are purified by flash chromatography on silica gel with diethyl ether/pentane mixtures.

7. Review: D. A. Evans, in ref. 5, p. 1 - 110.

8. **6**: mp 159°C; $[\alpha]_D^{20}$ = -2.7 (c = 1.1, CH_2Cl_2).

9. All new compounds were obtained analytically pure (C,H ± 0.2%).

10. **8**: mp (°C, ether/hexane), **8a**: 55, **8b**: 51, **8c**: 53, **8d**: 63, epi-**8d**: 68. $[\alpha]_D^{20}$ (c = 0.5-1.0, CH_2Cl_2), **8a**: -131.2, **8b**: -125.0, **8c**: -117.4, **8d**: -96.0, *epi*-**8d**: -48.8, **8a**, IR (KBr): 3500 (OH), 1700 (C=O), 1350 and 1165 cm^{-1} (NSO_2)
8a, 300 MHz ^1H NMR ($CDCl_3$, δ): 7.75 (d, J = 8.4 Hz, 3'-Tos-2-and 6-H); 7.33 (d, Tos-3-and 5-H); 7.3 (m, 4'-Ph); 5.85 (d, J = 9.4 Hz, 2'-H); 4.77 (dd, J_{cis} = 7.8, J_{trans} = 7.0 Hz, 4'-H); 4.05 and 3.90 (dd each, J_{gem} = 9.0 Hz, 5'-H_{Si} and-H_{Re}); 3.75 (ddd, J_{cis} = 4.3, J_{trans} = 5.6 Hz, 6-H); 3.47 (ddd, $J_{1",OH}$ = 6.2, $J_{1",2"}$ = 4.6, $J_{1",2}$ = 6.9 Hz, 1"-H); 2.75 (d, OH); 2.63 (ddd, J_{cis} = 5.5, J_{trans} = 11.5, 2-H); 2.43 (s, Tos-CH_3); 2.41 (m, 5-H_{Re}); 2.05 (m, 3-H_{Si}); 2.03(m, 4-H_{Si}); 1.90 (m, 5-H_{Si}); 1.85 (m, 4-H_{Re}); 1.80 (dhept, $J_{2",3"}$ = 6.8 Hz, 2"-H), 1.62 (dddd, $J_{3Re,2}$ = 11.5, J_{gem} = 13.4, $J_{3Re,4Si}$ = 3.9, $J_{3Re,4Re}$= 11.6 Hz); 0.96 and 0.91 (each d, diastereotopic 3"-H_3). - 75 MHz ^{13}C NMR ($CDCl_3$, δ): 213.13 (1-C=O), 144.43, 133.91, 129.84 and 128.03 (Tos), 138.34, 128.58, 127.77 and 126.08 (Ph), 91.16 (C-2'), 76.06 (C-1"),71.74 (C-5'), 62.09 (C-4'), 54.98 (C-6), 52.01 (C-2), 30.89 (C-3), 29.89 (C-2"), 28.69 (C-5), 21.50 (Tos-CH_3), 20.57 (C-4), 19.94 and 15.86 (diastereotopic C-3").

11. The configuration of the minor diastereomer *epi*-**8d** is unknown.

12. The reduction of **8a** was performed with 2.5 equiv. 1 M DIBALH in hexane; **9**: mp = 177°C (ether/hexane); $[\alpha]_D^{20}$ = -82.2 (c = 0.6, CH_2Cl_2).

13. Crystal structure analysis of **9** ($C_{26}H_{35}NO_5S$): space group $P2_12_12_1$, a = 776.5(1), b = 1086.0(1), c = 2927.1(2) pm, V = 2.468 nm^3, Z = 4; crystal dimensions: 0.2 0.3 0.8 mm^3, 4771 measured intensities, $2\Theta_{max}$ = 50° (Mo-Kα), T = 190 K; structure solved by direct methods (SHELXS-86), 3925 symmetry-independent reflexions with $|F| > 3\sigma(F)$ used for anisotropic refinement (309 parameters), H atoms located by difference electron-density determination and refined with a riding model, R = 0.030 [R_w = 0.036, $w^{-1} = \sigma(F)^2 + 2\ 10^{-4}\ F^2$]; tolyl methyl group twofold disordered; crystal packing stabilized by intermolecular hydrogen bonds O-H...O=S; absolute configuration confirmed by η-refinement [η = 0.8(1)]. All relevant crystallographic data have been deposited with the Cambridge Crystallographic Database via the Fachinformationszentrum Karlsruhe, D-7514 Eggenstein-Leopoldshafen 2 (CSD-54790).

14. a) M. Stiles, R. R. Winkler, Y. Chang, L. Traynor *J. Am. Chem. Soc.* **1964**, *86*, 3337; b) J. E. Dubois, M. Dubois *Tetrahedron Lett.* **1967**, 4215; c) see also M. Majewski, D. M. Gleave, *ibid.* **1989**, *30*, 5681.

15. H. E. Zimmerman, M. D. Traxler *J. Am. Chem. Soc.* **1957**, *79*, 1920.

16. For advanced theoretical treatment see: Y. Li, M. N. Paddon-Row, K. N. Houk *J. Org. Chem.* **1990**, *55*, 481; and references.

17. **10**: mp = 41°C (ether/hexane); $[\alpha]_D^{20}$ = +4.7, $[\alpha]_{365}^{20}$ = +21.7 (c = 1.0, CH_2Cl_2).

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