

Asymmetric Aldol Reactions Employing a Cyclic Sulfamide Chiral Auxiliary

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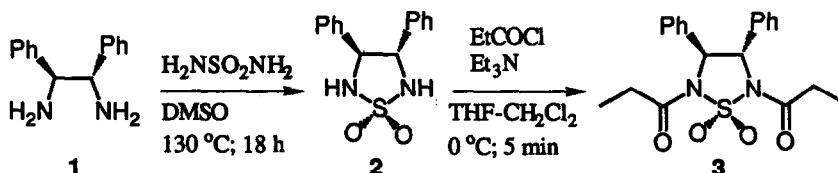
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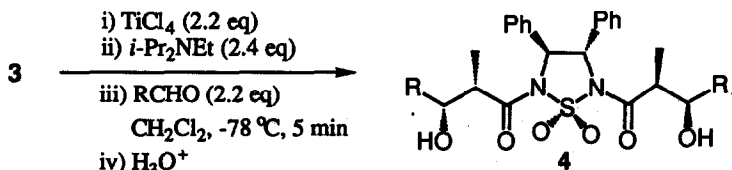
Abstract: A titanium enolate derived from (3*S*,4*S*)-2,5-dipropionyl-3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide (3) reacts with aldehydes to give *syn* aldols with high stereoselection (>95 : 5).

The asymmetric reactions using a chiral cyclic sulfonamide auxiliary such as the Oppolzer's bornanesultam are useful synthetic tools. A variety of asymmetric reactions such as aldol reactions, alkylations, and cycloadditions have been carried out with the bornanesultam auxiliary.¹ There have appeared other types of chiral cyclic sulfonamides recently.² Herein, we wish to report on a new sulfamide chiral auxiliary, 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide (2), which is proven to be efficient for titanium-mediated asymmetric aldol reactions.

Cyclic sulfamide 2³ was synthesized in 60% yield by the reaction of sulfamide itself with (1*R*,2*R*)-diphenyl-1,2-diaminoethane (1) which in turn was obtained from *trans*-stilbene by the known procedure.⁴ Sulfamide 2 has C₂ symmetry and each of the sulfonyl oxygens could exhibit equivalent function, either sterically or stereoelectronically.⁵ *N,N*-dipropionylsulfamide 3⁶ was readily prepared from the sulfamide 2 by the treatment with propionyl chloride in the presence of triethylamine in 95% yield.



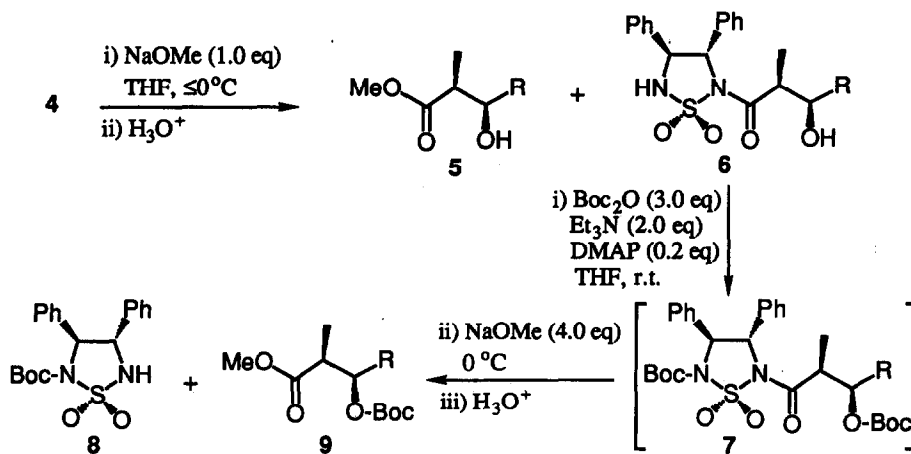
When the titanium enolate of 3, generated by treating 3 with 2.2 molar equivalents of titanium tetrachloride in the presence of 2.4 molar equivalents of diisopropylethylamine in dichloromethane at -78 °C,⁷ was treated with 2.2 molar equivalents of benzaldehyde at -78 °C for less than 5 min, the *syn* aldol product 4 (R=Ph) was given in 91% yield. The *syn*/*anti* selectivity of the reaction was >97 : 3,⁸ and the π -facial selectivity was >99 : 1.⁹ The absolute stereochemistry of the *syn* aldol was identified as (2*S*, 3*S*) by comparing the sign of optical rotation of 5 (R=Ph) with the literature.^{1b,10} The aldol reactions with other aldehydes also exhibited excellent stereoselection and produced dialol 4 with high chemical yields as shown in Table 1.

Table 1. Asymmetric Aldol Reactions of Titanium Enolate of **3**

Entry	R in RCHO	Stereoselection ^a	$[\alpha]_D$ (c) ^b , 4	Yield (%) ^c
1	Ph	>96 : 4	-20.0 (1.3)	91
2	Me	>97 : 3	-53.3 (1.2)	90
3	<i>i</i> -Pr	>97 : 3	-47.4 (1.0)	93
4	(<i>trans</i>)-MeCH=CH	>95 : 5	-58.3 (1.2)	89

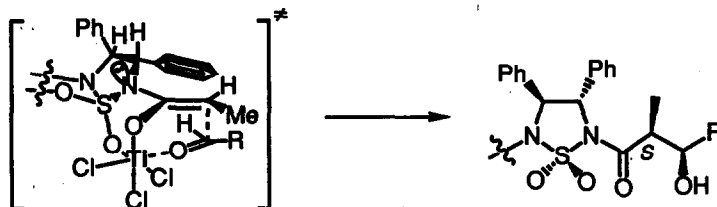
^a The ratio of the major isomer (**4**) vs the sum of all other isomers. ^b Determined in CHCl₃ at 24–28 °C. ^c Yields of **4** after SiO₂ column chromatography.

The conversion of dialdol **4** into **5** and also the recovery of the sulfamide auxiliary **2** can be readily done by the following stepwise sequences: Treatment of **4** with NaOMe rapidly produced only **5** and **6** in quantitative yields respectively. **6** was resisted to undergo the second cleavage reaction. However, when the acidic sulfamide proton in **6** was replaced with Boc group as **7**, the N-acyl bond cleavage selectively occurred on treatment with NaOMe, producing **8** and **9**. Deprotection of the Boc group with CF₃COOH afforded **5** and the chiral auxiliary **2** (overall isolated yields: ≥95% for **2** and ≥80% for **5**).¹¹

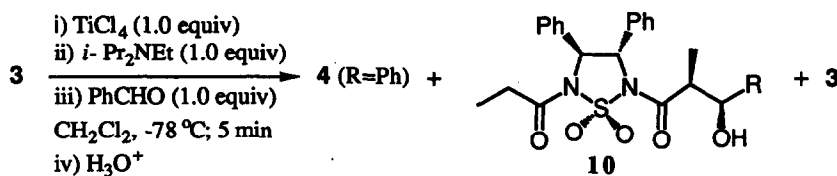


The stereoselectivity for the syn aldol product **4** can be explained by a chelated transition state where titanium coordinates to one sulfonyl oxygen as well as Z-enolate and aldehyde carbonyl oxygens,

as suggested by Oppolzer and co-workers for tin-mediated aldol reactions using a bornanesultam auxiliary.^{1b} Such explanation may be supported further by the recent reports of Thornton and co-workers, which describe chelated transition states for some titanium-mediated asymmetric aldol reactions using N-acyl oxazolidinones.¹²



Because of equivalency of the two sulfonyl oxygens the dialdol reaction of **3** could occur either by a stepwise or by a concomitant manner. Interestingly when we carried out the aldol reaction of **3** with an equimolar amount of reactants at $-78\text{ }^{\circ}\text{C}$, dialdol **4** and monoaldol **10** were formed in a 3:2 ratio with remaining **3**. The preferred formation of dialdol **4** over monoaldol **10** indicates that the titanium-mediated dialdol reaction of **3** occurs through a cooperative manner.¹³ The origin of this synergistic effect is not clear for the moment.



In conclusion, the high stereoselectivity as well as the symmetrical structural feature and effective molecularity of our sulfamide system would provide an efficient tool for other types of asymmetric reactions. Extension to other asymmetric reactions are in progress.

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- Physical data for **2**: mp $184\text{--}185\text{ }^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} -94.5$ (c 1.2, CHCl_3). $^1\text{H NMR}(\text{CDCl}_3, 300\text{MHz})$: δ 7.22–7.35 (m, 10H), 4.79 (s, 2H), 4.78 (s, 2H). Mass (EI): m/e 274 (M^+). Anal. Calcd: C, 61.29;

- H, 5.14; N, 10.21; S, 11.69. Found: C, 61.27; H, 5.06; N, 10.27; S, 12.02.
- Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis*, **1990**, 1023.
 - In the course of our investigations, Davies and co-workers have reported structurally related C₂ symmetric imidazolidin-2-one derivatives and their use in asymmetric reactions including aldol reactions: (a) Davies, S. G.; Mortlock, A. A. *Tetrahedron Lett.* **1992**, *33*, 1117 and references therein. See also, Kanemasa, S.; Onimura, K.; Wada, E.; Tanaka, J. *Tetrahedron: Asymmetry*, **1991**, *2*, 1185.
 - The absolute stereochemistry of **3** (and also **2**) was tentatively assigned as (3*S*,4*S*), assuming that the stereochemistry of **1** was retained under the specified derivatizations.
Physical data for **3**: mp 133-134 °C. $[\alpha]_{\text{D}}^{25}$ -109.1 (*c* 1.1, CH₂Cl₂). ¹H NMR(CDCl₃, 300MHz): δ 7.35-7.47 (m, 10H), 5.42 (s, 2H), 2.70-2.98 (m, 4H), 1.15 (t, 6H, J=7.35 Hz). ¹³C NMR (CDCl₃): δ 170.2, 138.4, 129.4, 128.9, 125.9, 64.0, 28.9, 8.0. IR(CHCl₃, cm⁻¹): 3050-3080(ν_{C-H}), 1717(ν_{C=O}). Mass (EI): *m/e* 386 (M⁺). Anal. Calcd: C, 62.16; H, 5.74; N, 7.25; S, 8.30. Found: C, 62.58; H, 5.85; N, 7.40; S, 8.31.
 - For the generation of titanium enolates, see: (a) Evans, D. A.; Urf, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urf, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047 and references therein.
 - It was determined by ¹H NMR spectrum analysis for a crude mixture containing monoaldol **6** and its diastereomers. The syn stereochemistry of **4** was assigned on the basis of both the characteristic ¹H NMR coupling constant (³J_{H-α,H-β} = 4.2Hz) and the ¹³C chemical shift of α-methyl group (11.61 ppm), see: Heathcock, C. H. *Asymmetric Synthesis*, Academic Press: New York, 1984; Vol 3, 111.
 - It was determined by ¹H NMR spectrum analysis for a crude mixture containing **6** and its diastereomers and/or for the Mosher ester from a crude mixture containing **5** and its enantiomer.
 - Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
 - There was no appreciable epimerization during the cleavage reactions, as judged by the optical purity of **5** (R = Ph: our sample: $[\alpha]_{\text{D}}^{27}$ -22.6° (*c* 1.16, CHCl₃), literature antipode^{1b}: +23.5° (*c* 3.23, CHCl₃)).
 - (a) Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897. (b) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (c) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489.
 - A stepwise reaction was observed for aldol reactions of a structurally related 1,3-dipropionyl-*trans*-4,5-tetramethyleneimidazolidin-2-one. See: Davies, S. T.; Mortlock, A. A. *Tetrahedron Lett.* **1991**, *32*, 4787.

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