Asymmetric Aldol Reactions Employing a Camphor-Derived Chiral Oxazinone Auxiliary

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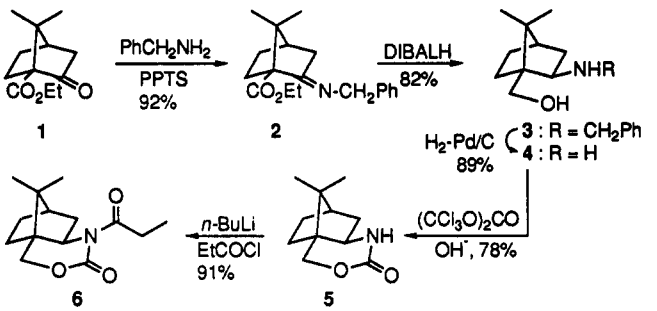
Summary: The aldol reactions of triisopropoxytitanium enolate of camphor-derived *N*-propionyloxazinone **6** with representative aldehydes afforded "chelation-controlled" syn aldols with excellent stereoselection (99:≤1).

The stereoselective aldol reaction employing a chiral auxiliary is an important methodology in organic synthesis. It has been known that stereoselectivity of the aldol reaction is dependent on several factors such as enolate geometry, metal, substrate, and others.[1] The aldol reaction of boron enolates employing amino acid-derived chiral auxiliaries, which was developed by Evans and co-workers, has been widely used. Recently asymmetric aldol reaction of titanium(IV) enolates has attracted significant mechanistic as well as synthetic attention.[2] Titanium can have hexacoordination and the aldol reaction of titanium enolates could have a different transition structure from that of tetracoordinate boron; thus it would give a different stereoisomer from that of boron even with the same chiral auxiliary. Thornton and co-workers have demonstrated[2a,g] that the triisopropoxytitanium enolates of a valine-derived *N*-propionyloxazolidinone react with aldehydes to give "non-Evans" syn aldols.[3] This opposite sense of π-facial selectivity in comparison to the corresponding aldol reactions with *n*-butylboron enolates, prepared with an equimolar amount of dibutylboron triflate (the original Evans aldol protocol), has been explained by means of chelation control: the titanium coordinates to the oxazolidinone carbonyl oxygen as well as *N*-acyl and aldehyde carbonyl oxygens in the transition state.[4]

The "chelation-controlled" syn aldols[3] have also been obtained in titanium-mediated aldol reactions using a camphor-derived chiral oxazolidinone auxiliary by the same authors.[2b] Although the camphor-derived system has apparent advantages of conformational rigidity and steric congestion, the observed π-facial and syn/anti selectivity are only moderate. Furthermore, the other syn isomers are also produced (2–13%), which could be explained by a non-chelated transition structure. We surmised that the insufficient π-facial selectivity (S_1/S_2 selectivity) originated from a diminished steric influence of the *syn*-7-methyl group of the camphor moiety to the *N*-acyl group, because the latter is located away from the methyl group. Therefore, we have designed a new camphor-derived auxiliary **5** such that one enolate face located in the proximity of the camphor moiety and thus experiences an efficient facial bias during an aldol reaction. In this Communication, we wish to report an efficient synthesis of **5**, the first chiral auxiliary having an oxazinone structure, and the realization of nearly complete stereoselection in titanium-mediated aldol reactions employing this auxiliary.

Scheme I



Scheme II

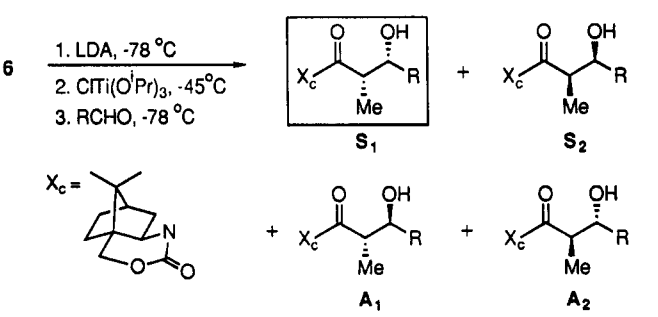


Table I. Diastereoselective Aldol Reaction of Titanium Enolate of 6 with Representative Aldehydes

entry	R in RCHO	stereoselection[a]	$[\alpha]_D$ (c)[b]	mp, °C	% yield[c]
1	Ph	99:<1	−181 (2.1)	135–136	79
2	Pr	99:<1	−204 (1.1)	91–93	63
3	Me	99:<1	−229 (1.5)	96–97	84
4	i-Pr	99:<1	−212 (1.0)	115–117	70
5	t-Bu	99:<1	−211 (1.0)	173–174	75
6	trans-MeCH=CH	99:1	−226 (1.0)	93–94	70

[a] The ratio of S_1 vs the sum of all other isomers. [b] In $CHCl_3$ at 23–25 °C. [c] Yields of S_1 after SiO_2 column chromatography.

The oxazinone auxiliary **5** was synthesized from the ketopinic acid ethyl ester (**1**)[5] as illustrated in Scheme I. The stereoselective introduction of the amino group on C-2 in **1** was achieved by the reduction of the imino-ester **2** with excess DIBALH;[6] the exo amino alcohol **3** was obtained

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. *Top. Stereochem.* **1982**, *13*, 1–115. (b) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 111–212.

(2) (a) Nerz-Stormes, M.; Thornton, E. R. *J. Org. Chem.* **1991**, *56*, 2489. (b) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299. (c) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047. (d) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (e) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (f) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (g) Nerz-Stomes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897. (h) Reetz, M. T.; Jung, A. *Tetrahedron Lett.* **1983**, *105*, 4833.

(3) Heathcock and co-workers have used this terminology to distinguish one syn aldol product separately from the other syn product which is expected to be produced when an equimolar amount of *n*-Bu_2BOTf is used in the original Evans' aldol protocol, see ref 2d. One reviewer commented that this terminology might best be reserved for aldol products which have the Evans chiral auxiliary attached. We used "chelation-controlled syn" instead of "non-Evans syn", conforming to the suggestion.

(4) For a related discussion of chelation-controlled aldol reactions using metal enolates other than Ti-enolate, see: (a) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (b) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767 and references therein.

(5) Bartlett, P. D.; Knox, L. H. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 689.

(6) Hydrogenolysis of the oxime derived from **1** in the presence of a catalyst such as Pd/C or Pt_2O was unsuccessful; reduction with $LiAlH_4$ at 50 °C or hydrogenolysis with Raney Ni at 60 °C produced endo and exo amino alcohols in comparable amounts. For an example of imine reduction with DIBALH, see: Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

0022-3263/92/1957-5065$03.00/0

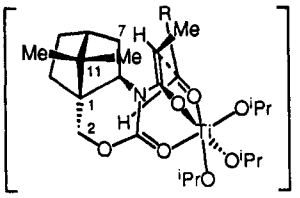


Figure 1.

exclusively. Hydrogenolysis of **3** afforded the known amino alcohol **4**[7] (mp 238–240 °C, $[\alpha]_D$ −67.9° (*c* 1.0 in $CHCl_3$)), and subsequent treatment with triphosgene under basic condition[8] gave the desired oxazinone **5** (mp 240–242 °C; $[\alpha]_D$ −155° (*c* 0.85 in $CHCl_3$) as a crystalline compound.

The titanium-mediated asymmetric aldol reactions employing **6** were carried out according to a literature procedure.[2b] Thus, when the triisopropoxytitanium enolate of **6**, generated by transmetalation of the corresponding lithium enolate with 3 molar equiv of chlorotitanium triisopropoxide in diethyl ether at −40 °C, was treated with 2 molar equiv of benzaldehyde at −78 °C, one syn aldol product[9] was formed exclusively. Both the syn/anti and π-facial selectivity were remarkable in that only S_1 (in a few cases, with ≤1% of other products) was observed in the ^1H NMR spectra of the crude aldol products. The absolute stereochemistry of the syn aldol product was determined by correlating the sign of the specific rotation for the cleaved product, methyl 3-hydroxy-2-methyl-3-phenylpropionate,[10] with those in the literature[11] (Scheme II). The aldol reactions with other representative aldehydes also exhibited nearly complete syn/anti and π-facial selectivity and produced S_1 as listed in Table I. All the aldol products are readily crystallized, which is a characteristic of camphor derivatives.

The production of S_1 with the triisopropoxytitanium enolate of **6** can be explained by a chelated transition structure (Figure 1), as suggested by Thornton and coworkers: the *Z*-enolate oxygen, oxazinone, and aldehyde carbonyl oxygens coordinate to the Ti, and C–C bond formation occurs through a chairlike transition state. The nearly complete S_1/S_2 selectivity excludes the possibility of non-chelation reaction and provides an excellent example of the chelation-control in aldol reactions. The aldol reactions of **6** via boron enolate under the original Evans condition produced different syn aldols,[12] which further supports the chelation control for the titanium-mediated aldol reactions.

The remarkable π-facial selectivity of our oxazinone system is thought to originate from the steric influence of the *syn*-11-methyl group and the C-7 methylene group[13] over one enolate face in the chelated transition structure, as intended in its design. It is particularly notable that our oxazinone system also exhibits excellent syn/anti selectivity, in contrast to the moderate selectivity of the Thornton's system.

These results demonstrate that our chiral oxazinone system constitutes a structurally well organized unit with an extremely well defined facial bias. It is promising for other types of asymmetric reactions that operate under chelation control.

Acknowledgment. We are grateful to the Korea Science and Engineering Foundation (CBM center) and the Ministry of Education (Basic Science Research Institute) for financial support.

Supplementary Material Available: Experimental procedures and physical and spectral data for all compounds (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) In MeOH (*c* 1.1), $[\alpha]_D$ −48.4°. The literature value, $[\alpha]_D$ −48.1° (*c* 2.6 in MeOH); mp 238–242 °C: Ikota, N.; Sakai, H.; Shibata, H.; Koga, K. *Chem. Pharm. Bull.* **1986**, *34*, 1050.

(8) Pridgen, L. N.; Prol, J., Jr.; Alexander, B.; Gillyard. *J. Org. Chem.* **1989**, *54*, 3231.

(9) The syn stereochemistry was assigned on the basis of its ^1H NMR coupling constant ($^3J_{H\text{-}2,H\text{-}3}$ = 2.9 Hz) and the chemical shift of C-2 methyl group (10.8 ppm) on ^{13}C NMR spectrum, see: ref 1b. It was further confirmed by comparison of ^1H NMR spectra with the corresponding anti isomer ($^3J_{H\text{-}2,H\text{-}3}$ = 8.8 Hz) which was obtained by the aldol reaction with lithium enolate: The reaction of lithium enolate of **6** with benzaldehyde gave three aldols (S_1:S_2:A_1 = 44:4:52), which was similar to Thornton's results.[2b] For the diagnostic values [$J_{H\text{-}2,H\text{-}3}$ and δ_C(Me-2)] of each aldol product, see supplementary material.

(10) Treatment of the aldol product with lithium hydroperoxide (Evans, D.A.; Britton, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141) followed by CH_2N_2 produced (2*S*,3*S*)-methyl 3-hydroxy-2-methyl-3-phenylpropionate in 77% isolated yield ($[\alpha]^{24}_D$ −22.9° (*c* 0.35 in $CHCl_3$); lit.[4b] of the antipode, +23.5° (*c* 3.23 in $CHCl_3$)). However, for the other aldol products, there appeared significant amounts of oxazinone ring-cleaved side products under the hydrolytic condition; in these cases, the chiral auxiliary was removed under a reductive condition. A representative procedure for the reductive-cleavage reaction: To the aldol product (2 mmol) in THF (4 mL) at 0 °C was added 2-methoxypropene (6–10 mmol) and PPTS (0.05 mmol). After the reaction was complete by TLC on alumina (ca. 30 min), the reaction temperature was lowered to −78 °C, $LiAlH_4$ (3 mL, 1.0 M in ether) was added dropwise, and the reaction temperature was allowed to rise to 0 °C (ca. 2 h). The excess hydride was carefully decomposed with 20% aqueous Rochelle's salt, and the mixture was stirred vigorously at room temperature. After complete phase separation (ca. 2 h), it was extracted with ether, dried over K_2CO_3–Na_2SO_4 (1:1), and concentrated to give monoprotected 1-R,2-Me-1,3-propanediol. Deprotection with THF–2 N HCl (3:1) and SiO_2 column chromatography afforded the diol (60–70% yields). For the diagnostic $J_{H\text{-}2,H\text{-}3}$ and the optical rotation value of the diol, see supplementary material.

(11) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Reference 4b.

(12) In this case anti isomers were also accompanied; this indicates that the chiral oxazinone auxiliary is not so effective in "non-chelation-controlled" aldol reactions as in the "chelation-controlled" aldol reactions. Details of the results and $TiCl_4$-mediated aldol reactions will be reported in due course.

(13) After completion of this work, asymmetric aldol reactions employing a new camphor-derived oxazolidinone has been reported by Yan and co-workers. They also suggested that a methylene group of the camphor moiety sterically influences on stereoselectivity: Yan, T.-H.; Chu, V.-V.; Lin, T.-C.; Tseng, W.-H.; Cheng, T.-W. *Tetrahedron Lett.* **1991**, *32*, 5563. For the other type of camphor derivative developed as a chiral auxiliary, see: Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. *J. Am Chem. Soc.* **1992**, *114*, 2258.