ORGANIC LETTERS

2008
Vol. 10, No. 4
617−620

Indene-Based Thiazolidinethione Chiral Auxiliary for Propionate and Acetate Aldol Additions

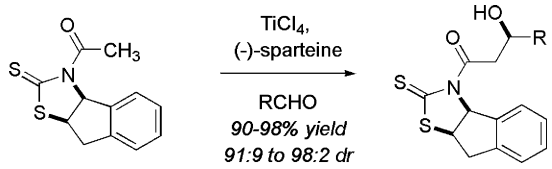
Antonio Osorio-Lozada and Horacio F. Olivo*

Division of Medicinal and Natural Products Chemistry, The University of Iowa, Iowa City, Iowa 52242

horacio-olivo@uiowa.edu

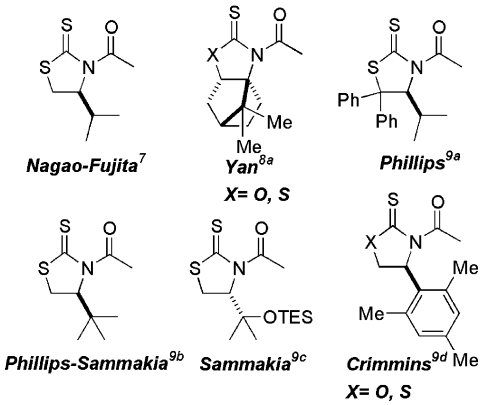
Received December 11, 2007

ABSTRACT



An indene-based thiazolidinethione chiral auxiliary was prepared in two steps from *trans*-1-amino-2-indanol. Chlorotitanium enolates of this chiral auxiliary delivered excellent diastereoselectivities in propionate and acetate aldol additions. The chiral auxiliary was easily removed to deliver several valuable functionalities.

The asymmetric aldol addition mediated by a chiral auxiliary is one of the most commonly used reactions to form a carbon−carbon bond and two chiral carbons adjacent to a carbonyl group stereoselectively.[1] Several methodologies and chiral auxiliaries have been developed for this endeavor; in particular, dibutylboron enolates of *N*-acyloxazolidinones have been valuable to prepare the "Evans" *syn*-propionate aldol products.[2] Utilizing the same chiral auxiliary, titanium-(IV) enolates of *N*-acyloxazolidinones were shown to provide the "non-Evans" *syn*-propionate aldol products.[3] Recent reports by Crimmins showed that by using chlorotitanium-(IV) enolates of *N*-propionate thiazolidinethiones we can access the "Evans" *syn*-aldol product when adding 1 equiv of sparteine and the "non-Evans" *syn*-aldol product when adding 2 equiv of the same base.[4] This change in facial selectivity is the result of switching of mechanistic pathways between chelated and nonchelated transition states. Evans reported the *anti*-aldol reaction promoted by catalytic amounts of magnesium halide in the presence of triethylamine and chlorotrimethylsilane.[5] These conditions deliver the "Evans" *anti*-aldol product when using an oxazolidinone and the opposite aldol product when using a thiazolidinethione.



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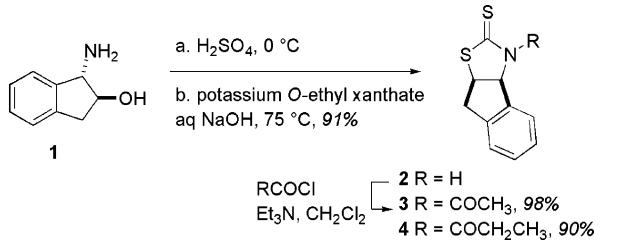
10.1021/ol702980p CCC: $40.75
Published on Web 01/19/2008

Chiral auxiliary driven acetate-type aldol reactions have proven more difficult than their propionate counterpart. *N*-Acetate oxazolidinones and other chiral auxiliaries did not provide the diastereoselectivities achieved with the corresponding *N*-propionates.[6] Several methods and strategies have been realized to solve this problem. Among them, Nagao's acetate aldol reaction with tin enolate of *N*-acetyl thiazolidinethione delivered high diastereoselectivities.[7] However, the high price and irreproducibility of the tin triflate prompted others to investigate other Lewis acids for this aldol reaction. The more economic titanium(IV) enolate was found to be highly efficient.[8] More sterically encumbered thiazolidinethiones and oxazolidinethiones have also been prepared to deliver higher diastereoselectivities, albeit at a higher price for starting materials and or longer reaction sequences.[9] In this paper, we report a new thiazolidinethione analogue of indene-based Ghosh's oxazolidinone,[10] which was easily prepared from commercially available *trans*-1-amino-2-indanol.[11] The rigidity and nature of this chiral auxiliary promised to deliver high diastereoselectivities in aldol reactions and crystalline products.

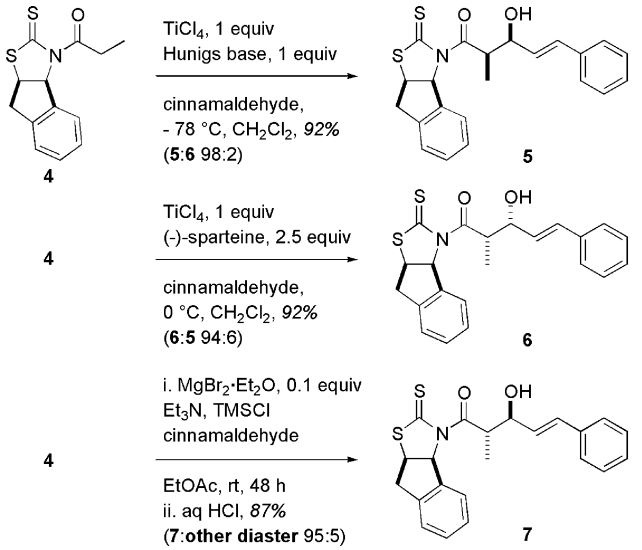
A general procedure for the synthesis of chiral oxazolidinethiones and thiazolidinethiones is to treat 1,2-aminols derived from α-amino acids with carbon disulfide and base.[12] Oxazolidinethiones are obtained preferentially when a mild base is employed, and thiazolidinethiones can be prepared in excellent yields when a stronger base is used instead. However, when this latter method was applied to *trans*-amino-2-indanol **1**,[13] thiazolidinethione **2** was obtained in poor yield. Instead, we found that the thiazolidinethione **2** was obtained in very good yield when the *trans*-aminoindanol **1** was first treated with sulfuric acid, and then the crude sulfated indanol was treated with potassium ethyl xanthate and aqueous sodium hydroxide and the mixture heated to 75 °C for 16 h, Scheme 1.[14] Using this protocol, only one purification by column chromatography was required to obtain clean thiazolidinethione **2**.

Scheme 1



Acylation of the chiral auxiliary was accomplished in very good yields by treating the thiazolidinethione with the corresponding acyl chloride or by coupling with the carboxylic acid.[15] The titanium enolate derived from *N*-propionate derivative **4** was added to cinnamaldehyde to test its diastereoselectivity using the conditions reported by Crimmins, Scheme 2.[4a] Indeed, when 1 equiv of titanium tetrachloride and 1 equiv of Hunig's base were employed, a closed transition state where both the aldehyde and the auxiliary are coordinated to the titanium enolate delivered the "non-Evans" *syn*-aldol product **5** in 92% yield (98:2 dr). When 2.5 equiv of (−)-sparteine and 1 equiv of titanium tetrachloride were employed, an open transition state where the chiral auxiliary is not coordinated to the titanium enolate

Scheme 2



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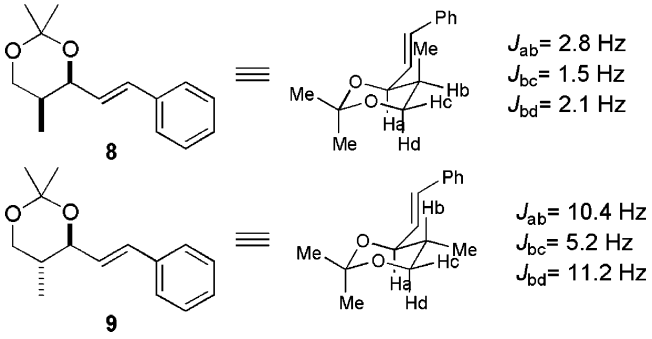
delivered the "Evans" *syn*-aldol product **6** in 92% yield (94:6 dr). Employing 1.2 equiv of sparteine and 1.2 equiv of *N*-methylpyrrolidinone, we also obtained aldol product **6** (92% yield), as reported by Crimmins.[4b] Using the conditions reported by Evans for *anti*-aldol reaction,[5] catalytic amounts of magnesium bromide, trimethylsilyl chloride, and triethylamine, the *anti*-aldol product **7** was isolated in 87% yield.

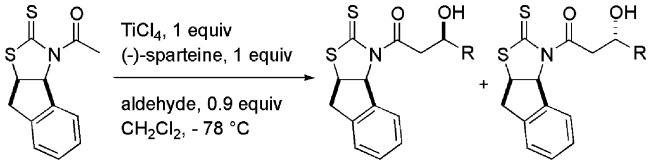
To confirm the relative stereochemistry of the aldol products, compounds **5**−**7** were reduced with sodium borohydride to the corresponding diols and treated with 2,2-dimethoxypropane to obtain acetonides **8** and **9**. Analysis of the ^{1}H NMR coupling constants of acetonides **8** and **9** was valuable to establish their stereochemistry, Scheme 3.

Scheme 3



The acetate aldol reaction employing *N*-acetylthiazolidinethione **3** was investigated with different types of aldehydes, Table 1. Following the optimized procedure reported by Crimmins,[9d] 1 equiv of *N*-acetyl thiazolidinethione **3** was treated with 1 equiv of titanium(IV) chloride and 1 equiv of (−)-sparteine, and 0.9 equiv of aldehyde was added to the reaction mixture at −78 °C. These reaction conditions worked very well with aliphatic, α,β-unsaturated, and aromatic aldehydes. Yields of aldol products ranged between 90 and 98% and diastereoselectivities from 91:9 to 98:2. The stereochemistry of the aldol products was confirmed by X-ray crystallographic analyses of products **10b** and **10i**. In addition, aldol product **10c** was reduced to (+)-(*R*)-4-methylpentane-1,3-diol, confirming the stereochemistry of the product.

Table 1. Acetate Aldol Additions of Thiazolidinethione **3**

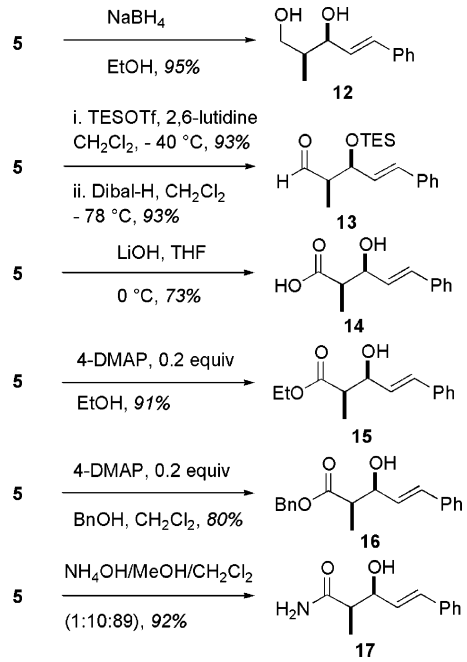


entry	aldehyde	yield[a] (%)	dr[b] (**10**/**11**)
1	propionaldehyde	98	93:7
2	butyraldehyde	94	93:7
3	isobutyraldehyde	92	94:6
4	isovaleraldehyde	97	93:7
5	acrolein	93	98:2
6	2-methyl-2-pentenal	91	91:9
7	cinnamaldehyde	90	98:2
8	benzaldehyde	91	93:7
9	3-furaldehyde	93	98:2

[a] Combined yield of diastereomers after purification. [b] Obtained by ^{1}H NMR spectroscopy of crude reaction mixtures.

The versatility of the new chiral auxiliary was investigated by the conversion of the aldol products into other functional groups, Scheme 4. As mentioned previously, aldol product **5** was reduced with sodium borohydride to diol **12**. Reduction of the TES-protected aldol product **5** with Dibal-H delivered aldehyde **13**. Hydrolysis of the aldol product **5** with lithium hydroxide gave carboxylic acid **14**. Displacement of the thiazolidinethione auxiliary with ethanol and benzyl alcohol mediated by DMAP was carried out smoothly under mild conditions.[16] Ammonolysis of the chiral auxiliary provided amide **17**.[17] As shown with other thiazolidinethiones, the indene-based thiazolidinethione can be easily removed to furnish different functionalities.

Scheme 4



In summary, we have prepared a valuable indene-based thiazolidinethione chiral auxiliary from *trans*-1-amino-2-indanol. Propionate and acetate aldol reactions with different types of aldehydes delivered products with high diastereoselectivity. The chiral auxiliary of the aldol products was removed under mild conditions to provide other function-

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alities in high yields. This new chiral auxiliary is more economic than other sterically encumbered ones and should find use in the syntheses of natural products.

Acknowledgment. This research was supported with funds provided by the Center for Environmentally Beneficial Catalysis under the National Science Foundation Engineering Research Grant (EEC-0310689) and the ACS-GCI-PRF. We thank Dr. Dale Swenson (University of Iowa) for obtaining the X-ray crystal analysis of aldol products **10b** and **10i**. We also thank Drs. Nataraj Kalyanaraman and Raju Subramanian (Amgen, Thousand Oaks, CA) for obtaining the HRMS spectra.

Supporting Information Available: Spectroscopic data for all new compounds (**2**−**17**) and copies of ^{1}H and ^{13}C NMR spectra. Crystallographic information (CIF) for compounds **10b** and **10i**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702980P