ORGANIC LETTERS

2004
Vol. 6, No. 1
23−25

Highly Selective Asymmetric Acetate Aldol Reactions of an *N*-Acetyl Thiazolidinethione Reagent

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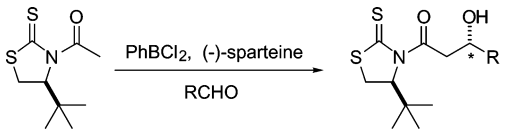
Received October 16, 2003

ABSTRACT



*dr = 9.5:1 to >100:1

A highly diastereoselective acetate aldol reaction that uses a *tert*-leucine-derived thiazolidinethione auxiliary and dichlorophenylborane has been developed. The reaction proceeds in excellent yields and with high diastereoselectivities (drs range from 9.5:1 to >100:1).

In 1981, Evans reported a highly diastereoselective asymmetric aldol reaction using boron enolates of *N*-acyloxazolidinones.[1] Since that time, chiral auxiliary-based aldol bond constructions have been widely used for accessing single isomers of β-hydroxy acid derivatives,[2] and intensive research has given rise to a large number of chiral auxiliaries that can produce *syn*- or *anti*-propionate aldol units in high yields and with excellent diastereoselectivities.[3] However, the development of an auxiliary-based stereoselective acetate aldol reaction has been a more elusive goal. Many of the auxiliaries that work well for propionate aldol reactions give minimal diastereoselection for acetate aldol reactions.[4] Although successful methods in this area using chiral acetate enolates of tin (Nagao−Fujita),[5] lithium (Braun and Yamamoto),[6] boron (Yan),[7] and titanium (Yan, Urpi, and Phillips)[8] are known, these methods have some shortcomings, including the use of expensive reagents and metals, lower levels of diastereoselectivity with aliphatic aldehydes, or the need for extremely low reaction temperatures for satisfactory diastereoselectivities. Furthermore, although the diastereoselectivities for many of these processes are useful, they are

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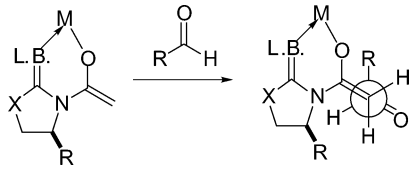
10.1021/ol036020y CCC: $27.50
Published on Web 12/05/2003

moderate when compared with the levels attainable for propionate aldol reactions. These drawbacks have limited the applications of these auxiliaries in the synthesis of complex polyketide-derived natural products.

Aldol reaction diastereoselectivity with a chiral enolate can be considered to be the product of enolate diastereotopic face selectivity coupled with the relative face selectivity between the enolate and aldehyde; to obtain high levels of selectivity in a reaction, both stereocontrol elements must be operative. Evans' oxazolidinone auxiliary fails to give high selectivities in acetate aldol reactions,[1,9] and we speculate that this is due to a loss of the diastereotopic face selectivity of the enolate but that the integrity of the chair transition state (and therefore, the relative face selectivity between the enolate and aldehyde) is maintained. As such, to achieve high selectivities in acetate aldol reactions, we wished to study a system that would provide high diastereoface selectivity in the enolate component. Our strategy is to employ a strongly Lewis acidic metal as the enolate counterion such that it may coordinate to a Lewis basic site on the chiral auxiliary and thereby provide a rigid species with sterically differentiated faces (Scheme 1). Reaction of

Scheme 1



this species with an aldehyde via an open transition state would provide the needed combination of diastereotopic face selectivity and relative face selectivity for high levels of asymmetric induction. In this communication, we describe an acetate aldol protocol utilizing a thiazolidinethione auxiliary that is readily prepared and provides excellent yields and diastereoselectivities in reactions with a variety of aldehydes.

To study the premise that a more Lewis acidic counterion would provide higher levels of diastereoselectivity in acetate aldol reactions, we attempted the preparation of the chlorophenylboryl enolate[10] of the Evans *N*-acetyloxazolidinone reagent (**1**, Figure 1). Unfortunately, treatment of **1** with dichlorophenylborane and a variety of tertiary amine bases in chloroform failed to provide any of the desired enolate.[11] We therefore turned our attention to the more acidic *tert*-leucine-derived *N*-acetyloxazolidinethione reagent **2** (Figure 1) and found that it underwent clean enolization and provided the desired aldol adduct in 65% yield upon treatment with dihydrocinnamaldehyde. We were encouraged to find that

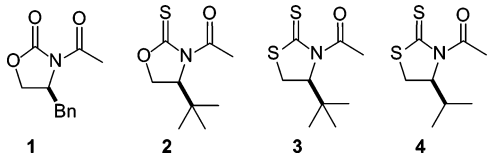
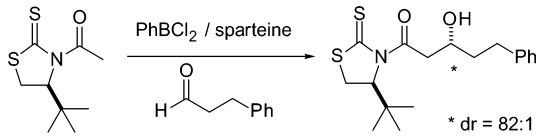


Figure 1. Chiral acetate aldol reagent variants.

this reaction provides a 12:1 ratio of diastereomers. We then synthesized and studied the *tert*-leucine-derived *N*-acetylthiazolidinethione reagent **3** (Figure 1)[12] and were pleased to find that it also underwent clean enolization using 1.0 equiv of dichlorophenylborane and 2.0 equiv of sparteine *and provided an 82:1 ratio of aldol diastereomers upon treatment with dihydrocinnamaldehyde*.[13] The valine-derived thiazolidinethione reagent **4** (Figure 1) provides the product in 78% yield but with significantly reduced diastereoselectivity (6:1), indicating that the bulky *tert*-butyl group is required for high selectivities. Compound **3** was thus chosen for further studies.

After optimization of this reaction, we settled on a procedure in which 1.3 equiv of reagent **3** and dichlorophenylborane, 2.6 equiv of sparteine, and 1.0 equiv of the aldehyde are used (Scheme 2). These conditions are designed

Scheme 2[a]



[a] Conditions: $PhBCl_2$ (1.3 equiv), (−)-sparteine (2.6 equiv), CH_2Cl_2, rt, 30 min; −78 °C, $PhCH_2CH_2CHO$ (1.0 equiv), 5 h; slowly warmed to rt within 2 h; then rt 0.5 h, hexane and H_2O_2, 84% yield.

to provide maximum utilization of the most valuable species in the reaction, which, typically, is the aldehyde. We observed diminished yields when less than 2.6 equiv of sparteine is used due to incomplete enolization[14] and when less than 1.3 equiv of the reagent is used.

Table 1 documents the utility and scope of this process in reactions with representative aldehydes. We find that straight-

(9) Dibutylboryl enolate of Evans' valine-derived oxazolidinone gives a 52:48 ratio of diastereoisomers with isobutyraldehyde and a 72:28 ratio with acetaldehyde (see ref 1).

(10) For aldol reactions using dichlorophenylborane as the Lewis acid, see: (a) Hamana, H.; Sasakura, K.; Sugasawa, T. *Chem. Lett.* **1984**, 1729. (b) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871. (c) Evans, D. A.; Fitch, D. M. *J. Org. Chem.* **1997**, *62*, 454. (d) Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.

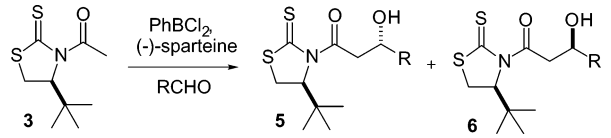
(11) Enolization was followed by ^1H NMR spectroscopy in $CDCl_3$.

(12) Auxiliary **3** has been synthesized from *tert*-leucinol on a 10 g scale by a modification of a general two-step literature procedure for the synthesis of thiazolidinethiones. Slightly harsher conditions are required for the synthesis of **3** than is typically required for other thiazolidinethiones due to the greater steric bulk of the *tert*-butyl group. See Supporting Information for details. (a) McKennon, M. J.; Meyers, A. I. *J. Org. Chem.* **1993**, *58*, 3568. (b) Delaunay, D.; Toupet, L.; Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604.

(13) The corresponding trichlorotitanium enolate (prepared from $TiCl_4$ and sparteine) gave lower diastereoselectivities (drs range from 2:1 to 6:1 for a variety of aldehydes). Enolization with other trialkylamine bases (Hunig's base or triethylamine) provided lower yields.

(14) Enolization was studied by NMR at room temperature in $CDCl_3$. We find that a 2:1 ratio of sparteine to compound **3** provides 92% enolization and that lower ratios of sparteine to **3** provide less enolization (1.5:1, 80% enolization; 1.2:1, 60% enolization).

Table 1. Aldol Reactions of Thiazolidinethione **3** with Representative Aldehydes[a]



entry	aldehyde	dr (**5**:**6**)[b]	yield
1	$PhCH_2CH_2CHO$	82:1	84
2	$(CH_3)_2CHCHO$	43:1	90
3	$CH_3(CH_2)_3CHO$	47:1	84
4	$(CH_3)_2CHCH_2CHO$	>100:1	92
5	$BnOCH_2CHO$	24:1	81
6	$TBSOCH_2CH_2CHO$	45:1	85
7	PhCHO	23:1	78
8	*E*-PhCH=CHCHO	9.5:1	65

[a] For a representative procedure, see Supporting Information. [b] Ratios were determined by 500 MHz ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [c] Yield of the major diastereoisomer after purification.

chain and α- or *β*-branched aliphatic aldehydes react with uniformly high selectivities (drs range from 43:1 to >100:1) and in excellent yields (84−92%, entries 1−4). Sensitive α- or *β*-oxygenated aldehydes such as benzyloxyacetaldehyde and 3-(*tert*-butyldimethylsilyloxy)propanal, are also excellent substrates for the reaction (entries 5 and 6). Aldolization with conjugated aldehydes such as benzaldehyde or *trans*-cinnamaldehyde also gave good yields and selectivities,[15] though the results with cinnamaldehyde are not as good (entries 7 and 8).

The stereochemistry of the products was determined by reductive cleavage of the aldol adducts obtained in entries 1 and 5 of Table 1 to produce the known compounds (*R*)-5-phenylpentane-1,3-diol and (*S*)-1-*O*-benzyl-1,2,4-butanetriol.[16] All other entries in the table were determined by analogy. The sense of asymmetric induction is the same as that observed in propionate aldol reactions using dibutyl boron enolates of Evans' oxazolidinone auxiliaries.[2] Interestingly, it is opposite to that observed by Nagao and Fujita with tin enolates of their thiazolidinethione auxiliary[5] and opposite to that observed by Urpi[8b] and Phillips[8c] with titanium enolates of thiazolidinethione or oxazolidinethione auxiliaries.

This reaction was designed to operate via an open transition state with coordination of the boron to the chiral auxiliary (Figure 2, structure A). However, we cannot rule out reaction via a closed transition state (Figure 2, structure B). The closed transition state minimizes the dipole interactions between the thiocarbonyl group of the auxiliary and the carbonyl group of the aldehyde and the developing carbonyl of the aldolate. Evans has convincingly shown that dipole effects are not important in propionate aldol reactions using his auxiliary; however, thiazolidinethiones likely have a greater dipole moment than oxazolidinones, and dipole minimization considerations could be more important with these reagents.[17]

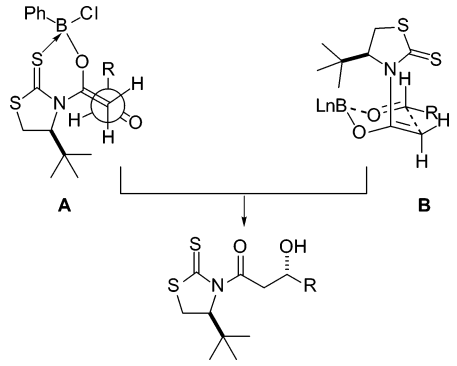


Figure 2. Possible models to account for the observed stereoselectivity.

Thiazolidinethione auxiliaries are known to offer certain advantages over oxazolidinone auxiliaries, including greater ease of cleavage of the auxiliary from the products.[5,18] However, this ease of cleavage can be problematic during the workup of the reaction if it is conducted under overly basic conditions. The procedure described in Supporting Information was optimized to minimize any undesired cleavage of the auxiliary and should be closely followed in order to achieve reproducible results.

In conclusion, we have developed a readily synthesized thiazolidinethione auxiliary that provides high levels of diastereoselection in acetate aldol reactions with a variety of aldehydes in excellent yields. The use of phenyldichloroborane for enolization of the reagent is required in order to achieve high diastereomeric ratios. Further mechanistic studies and applications to the synthesis of natural products are underway and will be reported in due course.

Acknowledgment. This work was supported by the National Institutes of Health (GM48498 to T.S.) and Array Biopharma. We thank Great Lakes Fine Chemicals for a generous gift of *tert*-leucine. NMR instrumentation used in this work was supported in part by the National Science Foundation CRIF program (CHE-0131003).

Supporting Information Available: Experimental procedures for the synthesis of the thiazolidinethione reagent, representative procedure for conducting the aldol reaction, and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Use of neutral silica gel (we used Mallinckrodt Silica Silica Gel 150, 60−200 mesh (75−250 *μ*m), pH of a 5% slurry = 7.0) is crucial to the success of the purification procedure. Other typical "flash" silica gels we used provide cleavage of the auxiliary and lower yields. The addition of triethylamine to the solvent system is not beneficial and leads to cleavage of the auxiliary.

(16) *R*)-5-Phenylpentane-1,3-diol: $[a]_D = +16.9$ (*c* 1.91, EtOH), lit. $[a]_D = +9.6$ (*c* 2.3, EtOH). (*S*)-1-*O*-Benzyl-1,2,4-butanetriol: $[a]_D = -8.32$ (*c* 0.2, MeOH), lit. $[a]_D = -8.4$ (*c* 3.6, MeOH). See: Nelson, S. G.; Spencer, K. L. *J. Org. Chem.* **2000**, *65*, 1227.

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