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Practical and Highly Selective Oxazolidinethione-Based Asymmetric Acetate Aldol Reactions with Aliphatic Aldehydes

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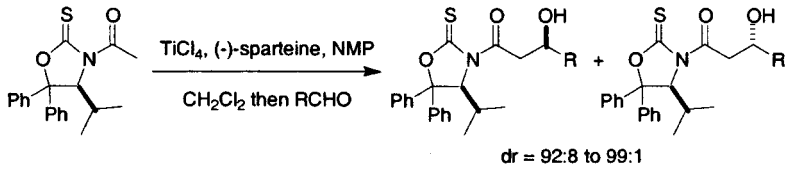
ABSTRACT



The utility of a valine-derived oxazolidinethione for auxiliary-based asymmetric acetate aldol reactions is reported. Titanium(IV) chloride, along with (–)-sparteine and *N*-methylpyrrolidinone, is employed for enolization. Subsequent aldol reaction with aliphatic aldehydes occurs with high diastereoselectivity (from 92:8 to 99:1 dr).

During the past 2 decades the asymmetric aldol reaction has risen to a position of prominence among carbon−carbon bond forming reactions.[1] Although there have been significant advances in catalytic asymmetric variants of the aldol reaction,[2] auxiliary-based aldol reactions remain a valuable and widely employed strategy for the synthesis of the β-hydroxycarbonyl subunit. Pioneering studies by Evans and co-workers in 1981 firmly established *N*-acyloxazolidinones as the method of choice for the synthesis of *syn*-propionate aldol constructs (**1**, Figure 1),[3] while recent work from the Masamune and Abiko laboratories has resulted in an excellent method for the synthesis of *anti*-propionate aldol subunits (**2**, Figure 1) using norephedrine-based auxiliaries.[4]

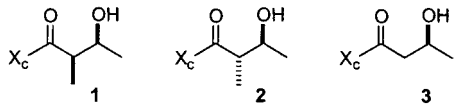


Figure 1. β-Hydroxycarbonyl subunits.

Many of the auxiliaries that work well for propionate aldol reactions give minimal diastereoselection for the synthesis of acetate aldol adducts (**3**).[5] Among successful methods two auxiliary systems currently enjoy widespread recognition as the state of the art for auxiliary-based acetate aldol reactions: Braun's (2-hydroxy-1,2,2-triphenylethyl)acetate (HYTRA) system[6] and the Nagao−Fujita 5-ethyloxazolidinethione and 5-isopropylthiazolidinethione auxiliaries.[7] Despite levels of diastereoselectivity ranging from 76:24 to 98:2, these two methods suffer from several potential drawbacks including extremely low reaction temperatures for satisfactory diastereoselectivity (Braun), an expensive metal source

(1) For selected reviews see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Arya, P.; Qin, H. P. *Tetrahedron* **2000**, *56*, 917. (c) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (d) Carreira, E. M. In *Modern Carbonyl Chemistry*; Otera, J., Ed., Wiley: New York, 2000.

(2) (a) For a review see: Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1353. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (c) Keck, G. E.; Kishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363. (d) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742.

(3) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(4) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586.

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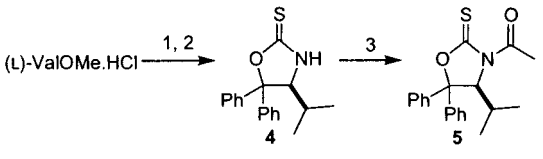
($Sn(OTf)_2$, Nagao−Fujita), and lower levels of diastereoselectivity with aliphatic aldehydes. These drawbacks have limited the applications of these auxiliaries in the synthesis of complex polyketide-derived natural products.

In the case of Evans' oxazolidinones the poor diastereoselection for acetate-type aldol reactions can be attributed in part to the lack of substituents at the α-carbon of the enolate.[8] To compensate for the absence of this control element, we have investigated highly hindered oxazolidinones and oxazolidinethiones[9−11] under reaction conditions that are expected to give highly ordered transition states, and in this Letter we describe the use of valine-derived *N*-acetyl oxazolidinethione **5** to achieve highly selective acetate aldol reactions with aliphatic aldehydes.[12]

Oxazolidinethione **5** was synthesized by a three-step sequence from L-valine methyl ester hydrochloride employing literature methods (Scheme 1).[13] It is noteworthy that this short sequence can be readily achieved on a 0.3 mol scale.

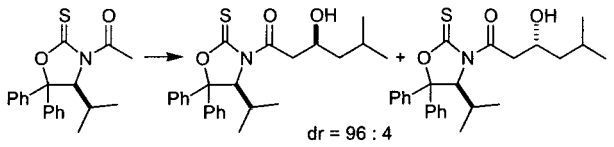
Scheme 1[a]



[a] Conditions: (1) PhMgBr (5 equiv), Et_2O; (2) CS_2, Et_3N, THF, reflux, 42% (over two steps); (3) NaH, THF, AcCl, 96%

Our initial efforts focused on the enolization of **5** under the conditions reported by Crimmins for related propionate aldol reactions.[9b,d] Gratifyingly, treatment of **5** with $TiCl_4$ (1 equiv), followed by (−)-sparteine (1 equiv) and *N*-methylpyrrolidinone (1 equiv) in CH_2Cl_2 at 0 °C, followed by reaction with isovaleraldehyde at −78 °C, provided the desired acetate aldol adduct in excellent yield and with high diastereoselectivity (Scheme 2).[14]

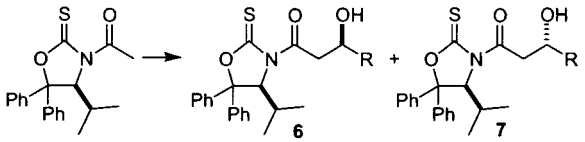
Scheme 2[a]



[a] Conditions: $TiCl_4$ (1 equiv), (−)-sparteine (1 equiv), NMP (1 equiv), CH_2Cl_2, 0 °C, 30 min, then $(CH_3)_2CHCH_2CHO$ (0.77 equiv), −78 °C, 1 h, 82%

Table 1 documents the utility and scope of this system for aldol reactions with aliphatic aldehydes. When 1.3 equiv of the enolate (relative to the aldehyde) are employed, straight-chain and α- or β-branched aliphatic aldehydes react with uniformly high selectivities (dr > 92:8) and in good to excellent yields (entries 1−7). Sensitive aldehydes, such as

Table 1. Aldol Reactions of Oxazolidinethione **5** with Representative Aldehydes[a]



entry	aldehyde	dr (**6**:**7**)[d]	yield (%)[e]
1	$PhCH_2CH_2CHO$	95:5	83
2	*n*-PrCHO	95:5	78
3	EtCHO	93:7	90
4	*n*-BuCHO	95:5	77
5	$(CH_3)_2CHCH_2CHO$	96:4	82
6	*i*-PrCHO	92:8	83
7	$CH_3(CH_2)_4CHO$	95:5	78
8	*trans*-$CH_3CH{=}CHCHO$	99:1	85
9[b]	$PMBOCH_2CHO$	97:3	55
10[c]	$TBDPSOCH_2CH_2CHO$	99:1	56
11	PhCHO	85:15	86

[a] For a representative procedure see Supporting Information. [b] 1.75 equiv of aldehyde used. [c] 1.5 equiv of aldehyde used. [d] Obtained by ^1H NMR spectroscopic analysis of the crude reaction products. [e] Combined yield of both diastereoisomers after purification.

(5) For a review of acetate aldol reactions, see: M. Braun, *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24. For more recent references to other auxiliary-based asymmetric acetate aldol reactions, see: (a) Oppolzer, W.; Starkemann, C. *Tetrahedron Lett.* **1992**, *33*, 2439. (b) Helmchen, G.; Leikauf, U.; Taufer-Knöpfel, I. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 874. (c) Yan, T. H.; Hung, H. C.; Hung, A. W.; Lee, H. C.; Chang, C. S. *J. Org. Chem.* **1994**, *59*, 8187. (d) Bond, S.; Perlmutter, P. *J. Org. Chem.* **1997**, *62*, 6397. (e) Palomo, C.; Gonzalez, A.; Garcia, J. M.; Landa, C.; Oliarbide, M.; Rodríguez, S.; Linden, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 180. (f) Saito, S.; Hatanaka, K.; Kano, T.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 3378. For approaches utilizing metal-based chirality, see: (g) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279. (h) Duthaler, R. O.; Herold, P.; Lottenbach, W.; Oertle, K.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 495. (i) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

(6) (a) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031. (b) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397 and references therein.

(7) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418. For reactions of Sn(II) enolates of 5-substituted thiazolidinethiones with α,β-unsaturated aldehydes, see: Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

(8) The 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 3).

(9) Recent studies from the Yan and Crimmins groups have shown that oxazolidinethiones are valuable auxiliaries for *syn* propionate aldol additions, particularly when employed as their Ti(IV) enolates; see: (a) Yan, T. H.; Tan, C. W.; Lee, H. C.; Lo, H. C.; Huang, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (c) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084. (d) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

(10) Related heterocycles such as (*S*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one ("SuperQuat") have been studied by Davies in the context of conjugate additions and alkylation reactions. For a recent paper, see: Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3475 and references therein.

crotonaldehyde, *p*-methoxybenzyloxyacetaldehyde, and 3-(*tert*-butyldiphenylsilyloxy)propanal are also excellent substrates for the reaction (entries 8−10), although oxygenated aldehydes currently require an excess of aldehyde for reasonable yields. Aldol reaction with benzaldehyde (entry 11) gave lower levels of diastereoselection, and this illustrates a shortcoming of this method.

From a practical viewpoint it is worth noting that the diastereoselectivity of the reaction is remarkably consistent *provided care is taken to ensure that the exact stoichiometry of reagents is employed*.[15] Deviation from the correct stoichiometry of $TiCl_4$ and amine results in inconsistent diastereoselection.

The stereochemical course of the reaction was determined by reductive cleavage of the aldol adducts obtained in entries 1 and 6 to give known compounds (*S*)-5-phenylpentane-1,3-diol and (*R*)-4-methyl-pentane-1,3-diol.[16] The sense of asymmetric induction is opposite to that usually observed when dialkylboryl enolates of oxazolidinones are used.[3] Interestingly it is also the opposite of that observed by Crimmins[9] for titanium enolates of *N*-propionyl oxazolidinethiones, suggesting a mechanistic divergence between the two reactions.

Two models can be considered to account for the observed stereoselectivity. One possibility is a coordinated chair structure (Figure 2, structure A).[17] This structure minimizes the steric interactions between the ligands on titanium and the substituents on the oxazolidinethione ring and is consistent with the following observations: (a) the corresponding oxazolidinone, which is postulated not to be capable of coordination to Ti under these conditions,[18] reacts with much lower dr values of 2.0−3.0:1,[19] and (b) the oxazolidinethione

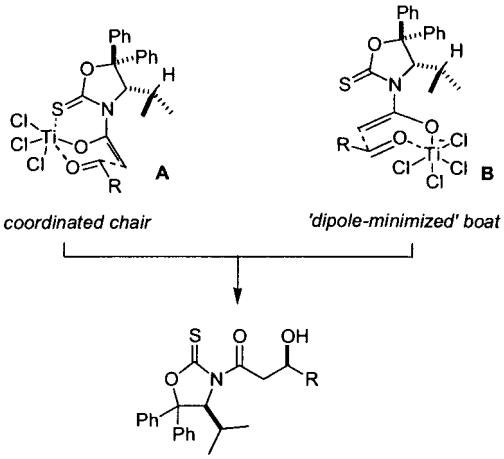


Figure 2. Possible models to account for the observed stereochemistry.

derived from valine without the 5,5-diphenyl substituents reacts with minimal selectivity (dr values of 1.2−2.5:1 vs several aldehydes), which suggests that diastereoselection can be affected by altering the population of rotamers around the auxiliary-enolate by decreasing the interactions between the ligands on titanium and the substituents on the oxazoldinethione.[20]

Alternatively, a dipole-minimized boat structure (Figure 2, structure B) could also give rise to the observed stereochemistry. Boat and twist-boat transition states have been calculated to lie within ±2 kcal/mol of the more commonly proposed chair transition states,[21] and recently Evans has proposed on the basis of calculated transition state energies that *anti*-aldol reactions with thiazolidinethiones proceed via a boat.[22] This model allows for consistency with the facial selectivity observed by Crimmins under the same reaction conditions as we employ and could also rationalize the decreased diastereoselectivity observed with the corresponding oxazolidinone on the basis of differing dipole moments.[23] Further studies will be required to unequivocally discriminate between these two models.

In conclusion, we have described a readily synthesized oxazolidinethione auxiliary that provides high levels of

(11) For two relevant examples of acetate aldol reactions with titanium enolates of thiazolidinethiones, see: (a) González, A.; Aiguadé, J.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949. (b) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.

(12) Seebach has reported the synthesis of the corresponding oxazolidinone. Suprisingly, it exhibited only modest diastereoselectivity for acetate aldol reactions; see: Hintermann, T.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 2093.

(13) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469. (b) Delaunay, D.; Toupet, L. Corre, M. L. *J. Org. Chem.* **1995**, *60*, 6604.

(14) The corresponding Li and B enolates gave poor conversion and diastereoselectivity.

(15) Guz, N. R.; Phillips, A. J. Unpublished results. Repeat reactions with hexanal gave dr values of 95.3:4.7, 95.7:4.3, and 94.6:5.4.

(16) (*S*)-5-Phenylpentane-1,3-diol: $[\alpha]_D = -6.2$ (*c* 0.75, EtOH), lit. −7.2 (*c* 1.52, EtOH). See: Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928. (*R*)-4-Methyl-pentane-1,3-diol: $[\alpha]_D = +16.6$ (*c* 0.25, $CHCl_3$), lit. +12 (*c* 2.43, $CHCl_3$). See: Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A. *J. Org. Chem.* **1992**, *57*, 1412.

(17) Models of this type have previously been proposed for Ti enolates of *N*-acyloxazolidinones generated by transmetalation from lithium enolates (Nerz-Stormes, M.; Thronton, E. R. *J. Org. Chem.* **1991**, *56*, 2489), for oxazolidinethiones generated by enolization with $TiCl_4$ and trialkylamine bases (see ref 9a), and for titanium enolates of thiazolidinethiones generated with trialkylamine bases (Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775). For related aldol reactions with *N*-acyl oxazolidineselones that presumably react via the same transition state, see: (c) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A., III *J. Am. Chem. Soc.* **2000**, *122*, 386.

(18) Crimmins has observed that oxazolidinethiones without substituents at C5 require a second equivalent of titanium to produce "non-Evans" *syn* adducts (ref 9b,d). In contrast, Yan's camphor-based oxazolidinethiones and oxazolidinones react with opposite facial selectivity in the presence of only 1 equiv of titanium (ref 9a).

(19) Guz, N. R.; Phillips, A. J. Unpublished results. The observed facial selectivity is the same as that observed for the oxazolidinethione.

(20) The calculation of transition structures and energies for these reactions is complicated by uncertainty with respect to the ligand sphere around titanium. We have chosen to depict B as the tetrachlorotitanium species on the basis of speculations first advanced by Evans; see (a) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8214. (b) Bilodeau, M. T. Ph.D. Thesis, Harvard University, 1994.

(21) (a) Li, Y.; Paddon Row: M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481. (b) Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron: Asymmetry* **1995**, *6*, 2613.

(22) (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392. (b) Evans, D. A.; Downey, C. W.; Shaw, J. T.; Tedrow, J. S. *Org. Lett.* **2002**, *4*, 1127.

(23) We have calculated the dipole moments (MP2, 6-31G*) for oxazolidinone (5.40 D, lit. 5.07 D Lee, C. M.; Kumler, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 4596) and oxazolidinethione (6.86 D). These values suggest that the rotameric populations around the enolate-auxiliary bond may be different for each system. Calculations were performed using PC Spartan Pro, Wavefunction Inc., Irvine, CA.

diastereoselection for acetate aldol reactions with aliphatic aldehydes. This work also further highlights the practical utility of Crimmins' combination of titanium(IV) chloride and (−)-sparteine for enolization of oxazolidinethiones and subsequent aldol reaction. Mechanistic studies and applications to the synthesis of natural products are underway in these laboratories and will be reported in due course.

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Supporting Information Available: Characterization data and spectra for all new compounds, procedures for the synthesis of **4** and **5**, and a representative procedure for the aldol reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

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