ORGANIC LETTERS

2000
Vol. 2, No. 19
3035−3037

Anti-Selective Glycolate Aldol Additions with an Oxapyrone Boron Enolate

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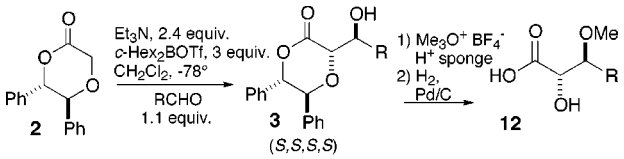
Received August 3, 2000

ABSTRACT



The boron enolate of pyrone 2 undergoes asymmetric aldol reactions with aldehydes to give protected *anti* 1,2-diols 3. The pyrone is readily available from *trans* stilbene using asymmetric dihydroxylation. Yields for the aldol reaction range from 62 to 92% and the selectivities from 6:1 to >20:1 for the *anti* isomers. Protection and hydrogenolysis of the products can be used to remove the pyrone, giving differentially protected diol intermediates 12 that are amenable to multistep synthesis.

Aldol reactions are often key steps in the synthesis of complex polyketide, isoprenoid, and carbohydrate natural products. Of the variations, a general approach to the *anti*-selective oxaacetate or glycolate aldol reaction, a useful process for the generation of contiguous differentially protected diols, is lacking. A new approach to this problem is the aldol reaction of the homochiral diphenyloxapyrone now disclosed. Problems arise with known auxiliaries in that the *E*-enolate geometry, needed in the closed transition state to give the *anti*-product, is not favored.[1] Others are limited in use to only α-alkoxyaldehydes.[1g] In open arrangements as with silyl enolates, the *syn*-product is produced by either the *E*- or *Z*-enolate geometry.[2] Recent methods,[3] especially the norephedrine boron enolate of Masamune,[3a] provide high *anti*-selectivity in propionate versions, yet their application to the *anti* glycolate reaction have not been established.[4] Chiral boron ketone enolates are particularly useful to access either *syn* or *anti* products.[5] Known asymmetric Mukaiyama *anti*-glycolate reactions are limited by the amount of ligand needed and type of aldehyde used.[6] Thioglycolate boron enolates, requiring 2 equiv of a menthone-derived ligand, also react with high selectivity.[7] Recently an erythrulose enolate of limited applicability was shown to give *anti* products.[8] Alternative approaches include osmium-catalyzed asymmetric dihydroxylation (AD) which works very well

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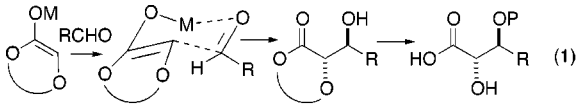
10.1021/ol0002166 CCC: $19.00
Published on Web 08/22/2000

for *syn* diols from *E* olefins but is not useful for applications with *Z*-alkenes leading to *anti* diols.[9] Allylmetals are generally limited to *Z*-γ-alkoxy reagents that give *syn* products.[10] A notable exception, which requires stoichiometric BINAL reduction, is the very useful indium-mediated allyltin additions of Marshall.[11]

While cyclic enolates[12] have the distinct advantage of being constrained to the *E*-conformation, only a few have been used in glycolate aldol reactions.[12a,b] None have been used to give differentially protected products due to deprotection problems. With cyclic glycolates, the *E*-geometry in the chair Zimmerman−Traxler transition arrangement provides the *anti* adduct (eq 1). We now report a general *anti*-



(1)

selective glycolate aldol reaction using enantiopure 5,6-diphenyl-4-oxa-2-pyrone, which is readily available using the Sharpless AD reaction, reacts with a broad range of aldehydes, and allows for the convenient attachment of protecting groups and further elaborations.

S,S-Diol **1** from *trans*-stilbene was obtained using catalytic asymmetric dihydroxylation using AD-mix-α in 85% yield, 98% ee.[13] Reaction with di-*n*-butyltin oxide in refluxing benzene, followed by treatment with *tert*-butyl bromoacetate and trifluoroacetic acid, gave **2** (Scheme 1).[14] Either enantiomeric form of **2** is available in two steps from stilbene by using AD-mix-α or AD-mix-β. Thus, either the *S,S* or the *R,R* enantiomeric *anti* aldol product can be readily accessed. Boron reagents and bases were screened to arrive at the optimal conditions of dicyclohexylboron triflate[15] and triethylamine at −78 °C in methylene chloride with **2**, followed by addition of isobutyraldehyde (1.2 equiv, Table 1).[16] After holding the reaction at that temperature for 2 h and quenching with buffer, methanol, and peroxide followed by standard aqueous workup and chromatography, the desired product **3** was obtained in pure form in 86% yield. The stereochemistry of **3** was confirmed by X-ray crystallography to be the *S,S,S,S* isomer as shown.[17] The minor isomer **4** was shown to be the *S,S,R,R anti* diastereomer.[18] Di-*n*-butylboron triflate gave lower yields and selectivity. The lithium enolate from LDA and the titanium enolates were also found to be less effective.

Scheme 1

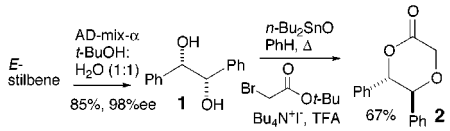
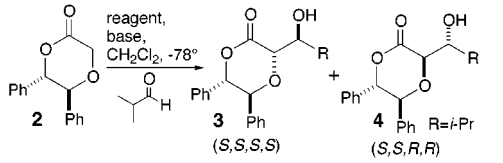


Table 1



reagent	base	yield[a]	dr[b]
n-Bu_2BOTf, 2 equiv.	Et_3N, 1.5 equiv.	37%	4:1
n-Bu_2BOTf, 2 equiv.	Et_3N, 3 equiv.	45%	4:1
n-Bu_2BOTf, 3 equiv.	*i*-Pr_2NEt, 2.5 equiv.	71%	4:1
$TiCl_4$, 2 equiv.	Et_3N, 2 equiv.	40%	3:1
c-Hex_2BOTf, 3 equiv.	Et_3N, 2.5 equiv.	86%	11:1

[a]Yields reported are for chromatographed materials. [b]Diastereomeric ratios were determined by ^1H NMR.

Various aldehydes were reacted in high yields, 70−90% in high to good selectivity, >20:1 to 6:1, using the optimal conditions (Table 2). Straight chain and branched aldehydes gave the best results, providing *anti* products in high yield and selectivity. Propionaldehyde reacted in 92% yield with essentially complete selectivity. Branching at the β-position lead to lower 8:1 selectivity with isovaleraldehyde. Aromatic and unsaturated substrates gave products in lower yields and selectivities. With isovaleraldehyde and benzaldehyde, small amounts of *syn* products (<1−2%) were also detected. 1-Naphthaldehyde gave 4:1 *anti* selectivity together with a significant amount of *syn* products. Reaction of D-glyceral-

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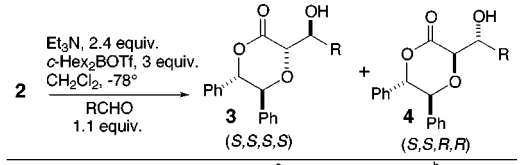
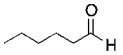
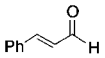
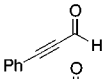
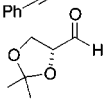
(17) X-ray data: for **3** (R = *i*-Pr): monoclinic space group $P2_1$, a = 12.167(3), b = 5.8264(13), and c = 13.674(4) Å, β = 112.742(14)°, V = 893.9, Z = 2, independent data 1726 (R_{int} = 0.0388) R_1 = 0.0500 [$I > 2\sigma(I)$]. For **3** (R = Ph), monoclinic space group $P2_1$, a = 9.7140(1a), b = 9.316(2), and c = 10.9660(10) Å, β = 106.193(8)°, V = 953.0, Z = 2, independent data 2297 (R_{int} = 0.0146) R_1 = 0.0424 [$I > 2\sigma(I)$] (see Supporting Information).

(18) ^1H NMR coupling constants: *anti* $J_{\alpha,\beta}$ = 4−6 Hz, $J_{\alpha,OH}$ = 3−6 Hz; *syn* $J_{\alpha,\beta}$ = 2 Hz, $J_{\alpha,OH}$ = 6−9 Hz.

Table 2



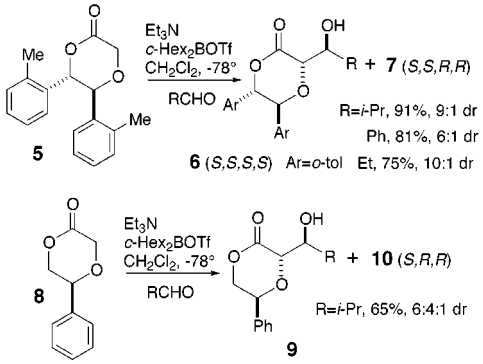
RCHO	yield[a]	dr[b]
	92%	>20:1
	92%	10:1
	91%	8:1[c]
	81%	6:1[c]
1-nap-CHO	71%	4:1[d]
	77%	6:1
	79%	7:1
	62% 70%	16:1[e] 6:1[f]

[a]Yields reported are for chromatographed, pure materials.
[b]Diastereomeric ratios were determined by ^{1}H NMR.
[c]Minor amounts of *syn* diastereomers (<1-2%) were formed.
[d]20% of *syn* isomers (4:1) also formed. [e]*R,R*-**2** was used.
[f]30% of *syn* isomers were formed (10:1).

dehyde acetonide with *S,S*-**2** gave only 6:1 selectivity together with 30% *syn* products. In contrast, *R,R*-**2** prepared using AD-mix-β, gave very high 16:1 selectivity for the *anti* products with no *syn* isomer observed with -glyceraldehyde acetonide. In all other cases only the two *anti* isomers were found.

The transition state appears to be the Zimmerman−Traxler arrangement[19] with boron acting as a Lewis acid for the aldehyde and the enolate locked in the *E*-configuration (eq 1). An open arrangement cannot be ruled out at this time in that excess boron triflate may directly active the aldehyde.[20] Yet, 1 equiv of boron triflate gives a slow reaction with low yields with good *anti* selectivity. In addition, excess triethylamine serves to complex the boron triflate, lowering its ability to directly coordinate the aldehyde, unlike diisopropylethylamine. Thus, a closed arrangement is most likely with the aldehyde reacting away from the C5-phenyl to give the observed *S,S,S,S* stereochemistry. Approach of the aldehyde to the same face bearing the C5-phenyl gives the minor *S,S,R,R anti* isomer. As the size of the aldehyde increases, more *syn* products arise presumably through a twist boat arrangement. With larger aryl groups, as with di-*o*-tolyl **5**[21] made in an analogous fashion to that of **2**, the selectivity for the reaction is not significantly changed (Scheme 2).

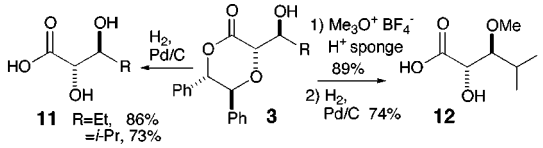
Scheme 2



Interestingly, if the C6-phenyl is removed as in **8**,[22] the selectivity drops to 3:2 for the *anti* isomers together with 10% *syn* isomers reacted with isobutyraldehyde. With pyrone **2**, the selectivity with this aldehyde was much higher at 11:1, giving only *anti* products.

The aldol products can be conveniently elaborated into differentially protected 1,2-diol substrates suitable for multistep applications by first protecting the secondary alcohol in **3** as a silyl ether or as a methyl ether (Scheme 3). The

Scheme 3



benzyl ester−ether pyrone is removed by hydrogenolysis with 10% Pd/C in ethyl acetate to give the protected hydroxy acid **12** and diphenylethane which is easily removed. Alternatively, **3** can be deprotected directly to the pure diol acid **11** in one step. Multistep applications to access differentially protected *anti* diol products and further refinements to the pyrone substrate will be disclosed shortly.

Acknowledgment. We wish to thank the National Institutes of Health (GM57275) and the Brigham Young University Cancer Center for funding and Dr. Bruce Jackson for mass spectrometry.

Supporting Information Available: Experimental details, analytical, NMR, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) (5*S*)-5-Phenyl[1, 4]dioxan-2-one **8** was prepared in five steps and 33% overall yield from (*S*)-mandelic acid as follows: LAH reduction of (*S*)-mandelic acid (Mosher, H. S.; Dale, J. A. *J. Org. Chem.* **1970**, *35*, 4002) gave (*S*)-phenylethylene glycol. Selective protection of the 1° alcohol as the TBDPS ether was followed by alkylation of the 2° alcohol by treatment with NaH and *tert*-butyl bromoacetate. Deprotection using TBAF and treatment with catalytic TFA provided **8**.