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ASYMMETRIC REACTIONS OF CHIRAL IMIDE ENOLATES WITH α-KETO ESTERS

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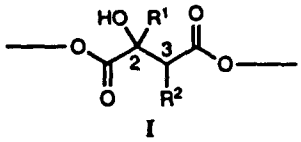
Abstract: A method for the synthesis of a variety of 2-hydroxy-2,3-trisubstituted succinates (I) is presented. The synthesis is achieved by the asymmetric reactions of lithium, boron or titanium enolates of Evans' chiral imides with α-keto esters.

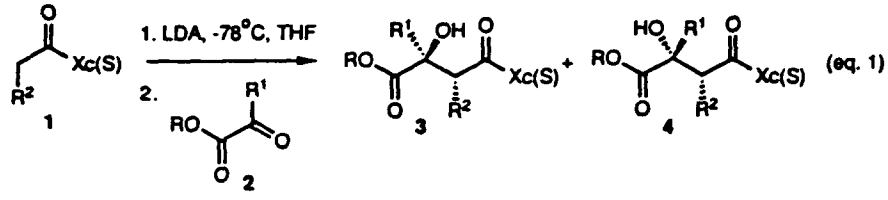
The succinate moiety has been shown to be an effective surrogate for natural amino acid substrates in a variety of inhibitors of Zn-dependent endopeptidases.[1] Of particular interest to us, were compounds incorporating different substituents in R^2 of the 2-hydroxy-2,3-trisubstituted succinate unit (I).



I

Diastereoselective formation of I (R^1=CH_3, C_6H_5; R^2=CH_3) was achieved in good yields by Ojima and co-workers in the $TiCl_4$ mediated asymmetric addition of silyl enol ethers and ketene silyl acetal to α-keto esters.[2] The asymmetric induction reported was in the range of 18-68%. Fang and co-workers have also shown that reactions of 8-phenylmenthyl pyruvate with silyl enol ethers and ketene silyl acetals proceed to form I (R^1=CH_3, R^2=CH_3, C_2H_5, C_6H_5) in good yield and diastereoselectivity.[3]

In the course of our work, we required a method for the synthesis of I that allowed for variation of the R^1-and R^2-substituents, as well as controlled variation of the stereochemistry at C^3. Preparation of I was proposed by the diastereoselective aldol reaction of chiral N-acyloxazolidinones 1 with α- keto esters 2[4]. Lithium enolates of 1, prepared from the *S*-imide and LDA in THF according to the conventional procedure[4], were allowed to react with α-keto esters 2. This reaction proceeds at -78°C in THF in 2-3 h to give good yields of the corresponding aldol-type adducts (Table1).



Xc = *S*-(-)-4-benzyl-2-oxazolidinone

Table 1. Aldol Reactions of Lithium Enolates (1) with Pyruvates (2)

Entry	R	R^1	R^2	3:4[a]	Yield (%)[b]
a	CH_3	CH_3	$CH_2CH(CH_3)_2$	73:27	80
b	C_2H_5	$(CH_2)_2Ph$	$(CH_2)_3Ph$	66:34	76
c	CH_3	CH_3	CH_2Ph	64:36	84
d	CH_3	CH_3	$(CH_2)_2Ph$	64:36	81
e	CH_2Ph	CH_3	$(CH_2)_2Ph$	63:37[c]	70
f	CH_3	CH_3	$(CH_2)_3Ph$	71:29	91
g	CH_3	CH_3	CH_3	83:17	77

a. Isolated yield of each diastereomer after chromatography; b. Isolated yield of isomeric mixture; c. Determined by ^1H NMR spectroscopy.

As shown by Evans, the Z-enolate of 1 reacts preferentially from the *Si* face allowing for the control of the configuration at the C^3-carbon.[5] The control of stereoselectivity at the tertiary carbon ($C^{2)}$ was found to be non-specific. The stereochemistry of C^2 of the major isomer (3g) was determined by X-Ray crystallography (Fig. 1).[6] The readily separated "*anti*" (3) and "*syn*" (4) isomers could be distinguished by their ^1H NMR spectra .[7]

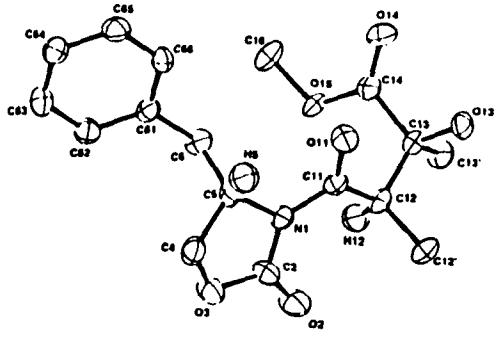


Fig.1. ORTEP drawing of 3 g (Table 1)

To examine the effect exerted by the counter ion on the diastereoselectivity and yield, we also studied the Lewis acid-mediated aldol reactions of boron and titanium enolates of **5** (eq. 2). Heathcock *et. al.* have suggested a dependence of the ratio of the "*syn*" and "*anti*" aldol adducts on the steric bulk of the Lewis acid.[8] Reactions of **5** with methyl pyruvate were elected as a model system and the results are presented in Table 2. Boron enolates of **5**, in the presence of $TiCl_4$ showed moderate selectivity toward "*anti*" adduct **6**, while two other Lewis acids showed no significant enhancement of formation of **6**. Reactions of Ti-enolates of **5** (method B)[9], exhibited modest selectivity toward formation of **6** (entry 4, Table 2).

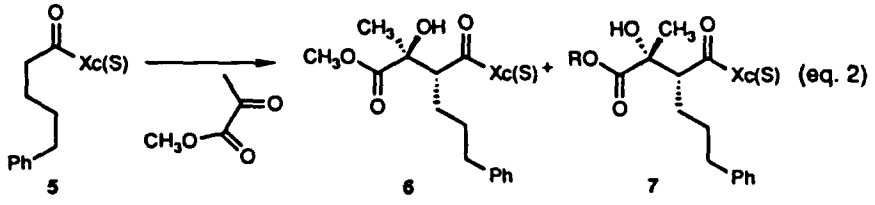
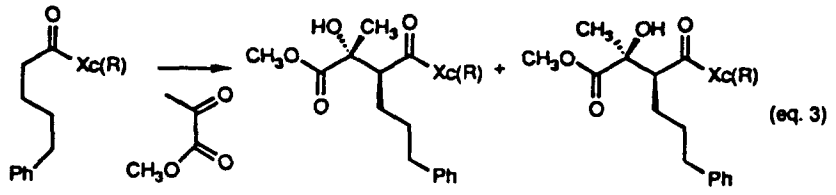


Table 2. Aldol Reactions of Boron,Titanium and Lithium Enolates of (5)

Entry	Method	Conditions	6:7[a]	Yield (%)[b]
1	A	Bu_2BOTf, $TiCl_4$ (2.0eq.)	80:20	65
2	A	Bu_2BOTf, $SnCl_4$ (0.5eq.)	73:27	49
3	A	Bu_2BOTf, Et_2AlCl (1.0eq.)	52:48	56
4	B	$TiCl_4$ (1.0eq.)	78:22	46
5	C	LDA	71:29	91

a. Isolated yield of each diastereomer after chromatography. b. Isolated yield of diastereomeric mixture. Method A. Enolization: 1.2 mmol of Bu_2BOTf, 1.2 mmol i-Pr_2NEt, 1 mmol of **5**, 45 min at 0°C, CH_2Cl_2. Aldol reaction: enolate added to a mixture of 1.5 mmol of methyl pyruvate and Lewis acid, 3h at -78°C, except for entry 3, which required 3h at 0°C. Method B.Enolization: 1 mmol of **5**, 1 mmol of $TiCl_4$, 1 mmol of i-Pr_2NEt, 1h at 0°C in CH_2Cl_2. Aldol reaction: 1.5 mmol of methyl pyruvate, 3h at -78°C. Method C. Enolization: 1.2 mmol of LDA, 1 mmol of **5**, 40 min at -78°C, THF. Aldol reaction: 2mmol of methyl pyruvate, 3h at -78°C to -10°C.

Lewis acid mediated aldol reactions of boron enolates of *R*-imides (**8**) proceeded in yields and diastereoselectivities comparable to *S*-imides (Table 3).



8 9 10

Table 3. Lewis Acid Mediated Reactions of *R*-Imide Boron Enolates (8)

Entry	Method[a]	Lewis Acid (eq.)	9:10[b]	Yield (%)[c]
1	A	$TiCl_4$ (2.0)	79:21	72
2	A	$SnCl_4$ (0.5)	74:26	42
3	A	Et_2AlCl (1.0)	53:47	58

a. See method A, Table 2. b. Determined by 1H NMR spectroscopy
c. Isolated yields of diastereomeric mixture.

Our results represent a route to the synthesis of all possible diastereomers of 1-hydroxy-2,3-disubstituted succinates (I). These succinates can be prepared in multigram quantities and are easily purified by flash chromatography. Excellent control at C^3 is observed and *syn* Me at C^2 is favored. The best selectivity was achieved in the $TiCl_4$ mediated reaction of boron enolates **5**. Efforts are in progress to further study the scope and limitations of this reaction, and will be reported in due course.

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6. Crystal structure will be published in due course.
7. (a) ^1H NMR ($CDCl_3$) of 3 (entry 3,Table 1): δ 1.48(s, 3H), 2.49(dd, J=10.3Hz, 1H), 3.03(d, J=8.8Hz, 2H), 3.06(d, J=3.3Hz, 1H), 3.11(d, J=3.3Hz, 1H), 3.34(t, J=8.1Hz, 1H), 3.69(s, 3H), 3.79(dd, J=1.5Hz, 1H), 4.06(m, 1H), 4.38(s, 1H), 4.69(t, J=8.8Hz, 1H), 7.09-7.27(m, 10H).
(b) ^1H NMR($CDCl_3$) of 4 (entry 3, table 1):δ 1.51(s, 3H), 2.55(dd, J=10.3Hz, 1H), 2.89(dd, J=5.13Hz, 1H), 3.07(t, J=11.35Hz, 1H), 3.19(dd, J=0.25Hz, 1H), 3.39(t, J=7.69, 1H), 3.78(s, 3H), 3.82(m, 2H), 4.14(m, 1H), 4.77(dd, J=5.13Hz, 1H), 7.069-7.270(m, 10H).
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