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Highly Enantioselective Aldol Reaction: Development of a New Chiral Auxiliary from *cis*-1-Amino-2-hydroxyindan

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Abstract

Boron enolates obtained from optically active oxazolidinone derivative of *cis*-1-amino-2-hydroxyindan are reacted with various aldehydes to provide highly enantioselective aldol products in good yields.

Reaction of chiral enolates derived from a chiral auxiliary with aldehydes has emerged as an extremely useful method for enantiocontrolled generation of aldol products with high optical purity.¹ In this context, a large number of suitable chiral auxiliaries have been developed and utilized efficiently in the enantioselective synthesis of various natural products and biologically active molecules.² Nonetheless, readily accessible and versatile chiral auxiliaries are still in demand. Although optically active cyclic *cis*-1,2-aminoalcohols were employed as amino acid surrogates for HIV-1 protease inhibitors,³ their utility as chiral auxiliaries in the aldol reaction has not been reported. The synthesis⁴ and resolution of *cis*-1-amino-2-hydroxyindan has been described previously by our laboratories^{3a} and its use in amide enolate alkylation has been recently reported.⁵ Here, we describe our results on enantioselective aldol reactions with a new chiral auxiliary which contains a conformationally rigid oxazolidinone derivative of the aminoalcohol **1**.

Both enantiomers of *cis*-1-amino-2-hydroxyindan were obtained in multigram quantities as described previously. Chiral oxazolidinone **2**, m.p. 205 °C, [α]_D –79.4 (*c* 1.4, CHCl₃) was readily prepared by reaction of aminoalcohol **1** with disuccinimidyl carbonate (1.5 equiv.) in acetonitrile in the presence of triethylamine (3 equiv.) at 23 °C for 12 h (88% yield).[†] Compound **2** was then lithiated with BuⁿLi (1.0 equiv.) in dry tetrahydrofuran (THF) and reacted with propionyl chloride (1.1 equiv., –78 °C) to furnish the acylated oxazolidinone **3** (85% yield), m.p. 130 °C, [α]_D +268 (*c* 2.4, CHCl₃).

Reaction of **3** with di-*n*-butylboryl trifluoromethanesulfonate (1.1 equiv.) and triethylamine (1.2 equiv.) at –78 °C for 30 min and then at –78 to 0 °C for 1 h afforded the boron enolate.⁶ Condensation of this resulting enolate with various aldehydes at –78 to 0 °C for several hours as monitored by TLC (2–5 h), resulted in only the diastereoisomer **4** after workup. No other diastereoisomers were detected by 400 MHz ¹H NMR spectroscopy or by HPLC

[†]Reaction of aminoalcohol **1** with di(2-pyridyl) carbonate (1.5 equiv.) and triethylamine (3 equiv.) in CH₂Cl₂ also provided a good yield (81%) of oxazolidinone **2**.

analysis. The absolute configurations of the aldol products were firmly established by comparison of the optical rotation of the corresponding methyl ester with the literature values.^{2a} *E.g.*, exposure of the aldol product **4** ($R^1 = \text{Ph}$) with sodium methoxide (2 equiv.) in methanol at 0 °C for 1 h resulted in the corresponding methyl ester **5** ($[\alpha]_D -23.2$ *c* 2.5; CHCl_3) in 89% isolated yield. The results of the aldol reaction of the oxazolidinone **3** with four different aldehydes are summarized in Table 1. As evidenced, the corresponding aldol products were obtained in good yields. Furthermore, owing to the configurational rigidity of the tricyclic ring system of chiral auxiliary **2**, almost complete diastereofacial selectivity (>99% d.e.) was observed in the aldol condensation with various aldehydes.

The removal of the chiral auxiliary was effectively carried out under exceptionally mild hydrolysis conditions. Thus, treatment of the aldol adduct **4** ($R^1 = \text{Ph}$) with 1 mol dm^{-3} lithium hydroxide solution in THF at 0 °C for 2 h afforded the acid **6** (89% yield) and good recovery (77–85%) of the chiral auxiliary **2**. To further demonstrate the applicability of this new chiral auxiliary, the synthesis of the C_{11} – C_{15} segment of the macrolide antibiotic tylosin⁷ was undertaken. Deprotonation of the oxazolidinone **2** with Bu^nLi followed by acylation with the mixed anhydride resulting from the reaction of crotonic acid and pivaloyl chloride in the presence of triethylamine provided *N*-crotonylimide **7** in 82% yield after silica gel chromatography.

Formation of boron enolate with boron trifluoromethanesulfonate and subsequent condensation with propionaldehyde afforded only isomer **8** in 51% isolated yield. Aldol adduct **8** was then reduced smoothly with lithium aluminium hydride (LAH) in THF at 0 °C to furnish the alcohol **9** (81% yield)[‡] which was previously converted to C_{11} – C_{15} tylosin segment.^{1d}

In conclusion, this new chiral auxiliary complements the monocyclic chiral oxazolidinones derived from amino acids.² Further application of this methodology in the synthesis of biologically important molecules is in progress.

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[‡]All new compounds gave satisfactory spectroscopic and analytical results.

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Scheme 1. Reagents and conditions:

i, Disuccinimidyl carbonate, Et₃N, MeCN, 23 °C; ii, BuⁿLi, THF, 0 °C then MeCH₂COCl, THF, −78 °C; iii, Buⁿ₂BOTf, Et₃N, CH₂Cl₂, −78 to 0 °C then R¹CHO, −78 to 0 °C; iv, NaOMe, MeOH, 0 °C; v, LiOH, THF-H₂O (1:1), 0 °C; (Tf = trifluoromethylsulfonyl)

Scheme 2. Reagents and conditions:

i, BuⁿLi, THF, 0 °C then crotonic acid, Bu^tCOCl, Et₃N, –78 °C; ii, Buⁿ₂BOTf, Et₃N, CH₂Cl₂, –78 to 0 °C then EtCHO, –78 to 0 °C; iii, LAH, THF, 0 °C

Table 1Aldol reaction of **3** with aldehydes

Entry	Aldehyde	Yields (%) ^a	[α] _D (4)	(%) d.e. (4) ^b
1	PhCHO	64	+ 166	>99
2	PhCH=CHCHO	62	+ 181	>99
3	MeCHO	71	+ 191	>99
4	Me ₂ CHCHO	73	+ 184	>99

^aYield of pure products after silica gel chromatography.^bDetermined by HPLC and 400 MHz ¹H NMR spectroscopy.