

Highly enantioselective reaction of lithiated *N*-Boc-thiazolidine: a new chiral formyl anion equivalent

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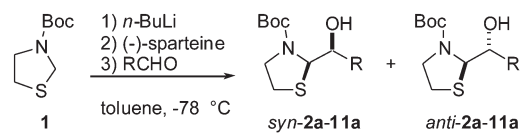
Reaction of lithiated *N*-Boc-thiazolidine **1** with various aldehydes in the presence of (–)-sparteine afforded the products with up to 93% ee. The reaction was confirmed to proceed through a dynamic thermodynamic resolution pathway. Each diastereomeric alcohol could be converted to the corresponding optically active 1,2-ethanediols.

Asymmetric induction using organolithium compounds is a useful method for asymmetric synthesis. Since Hoppe and co-workers showed highly enantioselective lithiation-substitution reactions of dipole stabilized α -oxy carbanions,¹ asymmetric reactions of carbanions α to hetero atoms have been extensively studied.² Diastereoselective reactions of carbanions derived from dithioacetals,³ hemithioacetals,⁴ 1,3-dioxolanes,⁵ 1,3-oxazolidines,⁶ and *N,S*-acetals,⁷ have been reported. However, only a little attention has been paid to the enantioselective reactions of carbanions located between two hetero atoms. Enantioselective reactions of dithioacetals⁸ and *N,O*-acetals⁹ have so far been reported. We have previously reported highly enantioselective lithiation-substitution reactions of α -thio carbanions derived from various sulfides¹⁰ and the enantioselective reaction using unsymmetrical dithioacetals as a chiral formyl anion equivalent.¹¹ In continuation of our study towards developing an efficient chiral formyl anion equivalent, we examined enantioselective reaction of *N,S*-acetals, which has not hitherto been known. We report herein the first highly enantioselective reaction of lithiated *N*-Boc-thiazolidine with various aldehydes.

We examined the reaction of lithiated *N*-Boc-thiazolidine with various aldehydes in the presence of (–)-sparteine in toluene (Table 1).† A toluene solution of *N*-Boc-thiazolidine **1** was treated with *n*-BuLi (1.2 eq.) at –78 °C. After (–)-sparteine was added, the solution was stirred for 30 min at –78 °C, and then the aldehyde was added. When benzaldehyde was allowed to react, the product **2a** was obtained in 74% yield. Since it was difficult to separate the *syn*- and *anti*-isomers formed by column chromatography, the obtained alcohols were converted to the corresponding acetates **2b**, the diastereomers of which could be easily separated by column chromatography. The *syn/anti* ratio of **2b** was determined to be 42:58 by ¹H NMR spectral analysis. The optical purities of the *syn*- and the *anti*-isomers were determined to be 93% ee and 88% ee, respectively, by HPLC analyses using chiral columns (entry 1). The reaction of lithiated *N*-Boc-thiazolidine with other aromatic aldehydes such as *p*-tolualdehyde, *p*-anisaldehyde, *p*-chlorobenzaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde gave the corresponding products **3b–7b** in similar *syn/anti* ratios to that of **2b**. Generally, the *anti*-isomers have higher enantiomeric purity than the *syn*-isomers except **2a** (entries 2–6). The reaction with aliphatic aldehydes such as propionaldehyde, isobutyraldehyde, cyclohexanecarbaldehyde, and pivalaldehyde also afforded the products **8a–11a** in which the *syn*-isomers were preferentially formed (entries 7–10). Both the *syn*- and *anti*-isomers were found to be formed with high enantioselectivity.

Treatment of *syn*-**2b** with mercury(II) chloride in aqueous CH₃CN at room temperature for 6 h gave 2-acetoxy-2-phenylacetaldehyde which, without isolation, was subjected to reduction with LiAlH₄ in THF giving the corresponding (*S*)-1-phenyl-1,2-ethanediol (*S*)-**12**

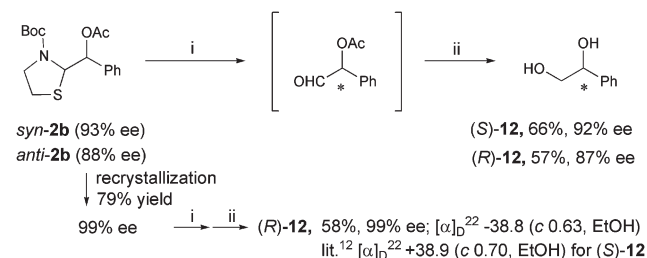
Table 1 Enantioselective reaction of lithiated **1** with various aldehydes



Entry	R	Product	Yield (%)	<i>syn/anti</i> ^a	<i>syn</i> ee (%) ^b	<i>anti</i> ee (%) ^b
1	Ph	2a	74	42:58 ^c	93 ^d	88 ^d
2	<i>p</i> -MeC ₆ H ₄	3a	65	46:54 ^c	69 ^d	89 ^d
3	<i>p</i> -MeOC ₆ H ₄	4a	58	43:57 ^c	66 ^d	90 ^d
4	<i>p</i> -ClC ₆ H ₄	5a	65	42:58 ^c	60 ^d	88 ^d
5	1-naphthyl	6a	55	22:78 ^c	64 ^d	88 ^d
6	2-naphthyl	7a	72	42:58 ^c	65 ^d	90 ^d
7	Et	8a	67	59:41	46	– ^e
8	<i>i</i> -Pr	9a	54	53:47	77	89
9	<i>c</i> -Hex	10a	69	61:39	73	89
10	<i>tert</i> -Bu	11a	63	51:49	72	87

^a Determined by ¹H NMR spectral analysis. ^b Determined by HPLC analysis using Chiralcel OD–H, OJ–H, or Chiralpak AD–H. ^c Determined by the corresponding acetate. ^d Determined by HPLC analysis of the corresponding acetate. ^e The enantiomer was not separable by HPLC analyses using various chiral columns.

in 92% ee (Scheme 1). No substantial racemization was observed during the reaction. In a similar manner, *anti*-**2b** afforded (*R*)-**12** in 87% ee. The product *anti*-**2b** was recrystallized from hexane once to improve the enantiomeric purity to 99% ee, and the same treatment as above afforded (*R*)-**12** in 99% ee. Since the enantiomeric purity of other products could also be improved by recrystallization, the enantioselective reaction of lithiated *N*-Boc-thiazolidine provides an efficient route to the synthesis of optically pure 1,2-ethanediols.



Scheme 1 Reagents and conditions: (i) HgCl₂ (2.5 mole eq.), CH₃CN/H₂O = 8:2, rt, 6 h; (ii) LiAlH₄ (3.0 mole eq.), THF, 0 °C–rt, 3 h.

The absolute stereochemistry of diols **12** derived from *syn*-**2b** and *anti*-**2b** was assigned to be *S* and *R*, respectively, by comparison of the values of the specific rotations with those reported.¹² The relative stereochemistry of *syn*-**2b** was determined to be (1'*S*,2*R*) by X-ray crystallography (Fig. 1).‡ In addition, it was found that the *anti*-isomers always have larger vicinal coupling constants in the ¹H NMR spectra than the *syn*-isomers.¹³ Since the configuration of the thiazolidyl carbon of **2** is supposed to be *R* irrespective of the aldehydes reacted, the configurations of *syn*- and *anti*-**3–11** were assigned to be the same as those of *syn*- and *anti*-**2**, respectively.

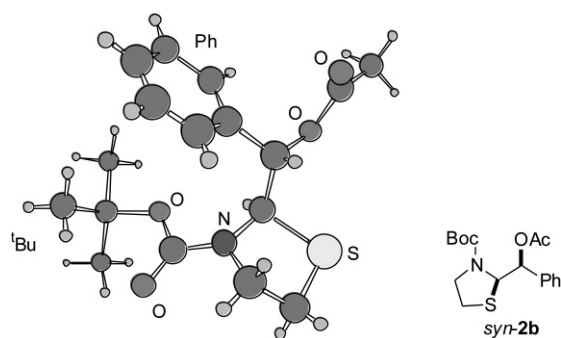
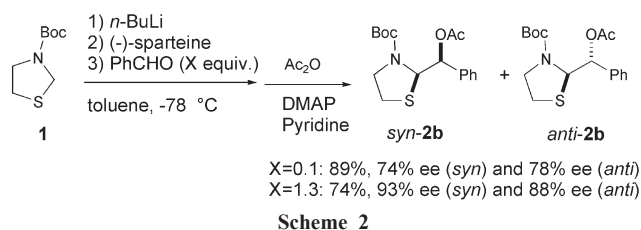


Fig. 1 Chem 3D structure derived from the X-ray crystallography of *syn*-2b.

In order to clarify whether the reaction proceeds through a dynamic thermodynamic resolution¹⁴ or a dynamic kinetic resolution pathway,¹⁵ we examined Beak's test using an insufficient amount of the electrophile.^{2a} The reaction of lithiated **1** with benzaldehyde in the presence of (–)-sparteine afforded *syn*-2b and *anti*-2b with 93 and 88% ee, respectively, after acetylation (Table 1, entry 1). On the other hand, when 0.1 eq. of benzaldehyde was used, *syn*-2b and *anti*-2b were formed in 74 and 78% ee, respectively. These enantioselectivities were lower in comparison with those of the corresponding isomers obtained in the reaction with 1.3 eq. of benzaldehyde (Scheme 2). These results suggest that the reaction proceeds through a dynamic thermodynamic resolution pathway.



In summary, lithiated *N*-Boc-thiazolidine serves as a new chiral formyl anion equivalent affording highly enantiomerically pure products, which could be converted to optically active 1,2-ethanediols.

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Notes and references

† **Typical procedure for the reaction of *N*-Boc-thiazolidine **1** with benzaldehyde:** A 1.46 M solution of *n*-BuLi (0.49 mL, 0.72 mmol) in hexane was added to a solution of **1** (114 mg, 0.60 mmol) in toluene (1.0 mL) at –78 °C. The mixture was stirred for 10 min and then a solution of (–)-sparteine (169 mg, 0.72 mmol) in toluene (0.4 mL) was added. After the reaction mixture was stirred for 1 h, benzaldehyde (83 mg, 0.78 mmol) was added and the reaction mixture was stirred for an additional 30 min. Saturated aqueous NH₄Cl was added and the aqueous layer was extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel, hexane/ethyl acetate 90:10) to give **2a** (131 mg, 74%). To a solution of **2a** (131 mg, 0.44 mmol) in pyridine

(1.0 mL) was added 4-dimethylaminopyridine (5.4 mg, 0.044 mmol) and acetic anhydride (225 mg, 2.2 mmol), and the mixture was stirred for 3 h at room temperature. Usual work up and purification by column chromatography (silica gel, hexane/ethyl acetate 97:3) gave *syn*-2b (64 mg, 93% ee) and *anti*-2b (87 mg, 88% ee).

‡ Crystal data for *syn*-2b: C₁₇H₂₃NO₄S, *M* = 337.43, (0.31 × 0.18 × 0.08 mm), orthorhombic, P2₁2₁2₁ (#19), *a* = 8.23(1), *b* = 9.09(2), *c* = 22.54(4) Å, β = 90, *V* = 1689(4) Å³, μ = 1.871 mm, *Z* = 4, 31284 reflections measured, 2909 unique (*R*_{int} = 0.058). Final *R* indices [*I* > 3σ(*I*)] *R* = 0.066, *R*_w = 0.068. CCDC reference number 241332. See <http://www.rsc.org/suppdata/ob/b4/b408509d/> for crystallographic data in .cif or other electronic format.

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