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

Libo Wang, Shuichi Nakamura and Takeshi Toru*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya, 466-8555, Japan. E-mail: toru@nitech.ac.jp; Fax: +81-52-735-5217; Tel: +81-52-735-5217

Received 7th June 2004, Accepted 24th June 2004
First published as an Advance Article on the web 8th July 2004

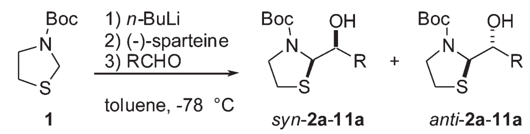
Reaction of lithiated *N*-Boc-thiazolidine 1 with various aldehydes in the presence of (−)-sparteine afforded the products with up to 93% ee. The reaction was confirmed to proceed through a dynamic thermodynamic resolution pathway. Each diastereomeric alcohol could be converted to the corresponding optically 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 dithioacetals[8] and *N*,*O*-acetals[9] have so far been reported. We have previously reported highly enantioselective lithiation-substitution reactions of α-thio carbanions derived from various sulfides[10] 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 ^{1}H 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.

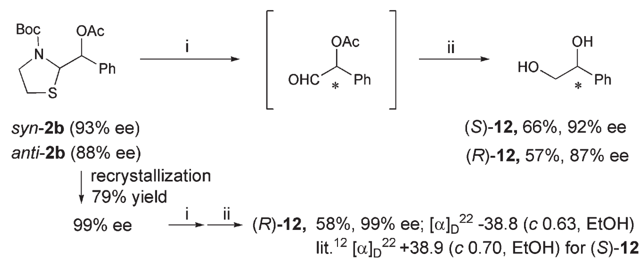
Treatment of *syn*-**2b** with mercury(II) chloride in aqueous CH_3CN at room temperature for 6 h gave 2-acetoxy-2-phenylacetaldehyde which, without isolation, was subjected to reduction with $LiAlH_4$ in THF giving the corresponding (*S*)-1-phenyl-1,2-ethanediol (*S*)-**12** in 92% ee (Scheme 1). No 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.

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



Entry	R	Product	Yield (%)	*syn*/*anti*[a]	*syn* ee (%)[b]	*anti* ee (%)[b]
1	Ph	**2a**	74	42 : 58[c]	93[d]	88[d]
2	*p*-MeC_6H_4	**3a**	65	46 : 54[c]	69[d]	89[d]
3	*p*-$MeOC_6H_4$	**4a**	58	43 : 57[c]	66[d]	90[d]
4	*p*-ClC_6H_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*-Pr	**9a**	54	53 : 47	77	89
9	*c*-Hex	**10a**	69	61 : 39	73	89
10	*tert*-Bu	**11a**	63	51 : 49	72	87

[a] Determined by ^{1}H 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.



Scheme 1 *Reagents and conditions*: (i) $HgCl_2$ (2.5 mole eq.), CH_3CN/H_2O = 8 : 2, rt, 6 h; (ii) $LiAlH_4$ (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 ^{1}H 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.

DOI:10.1039/b408509d

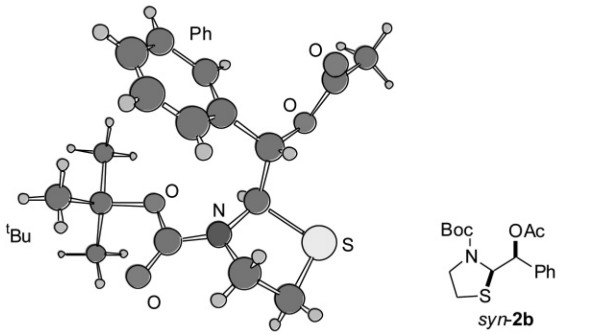
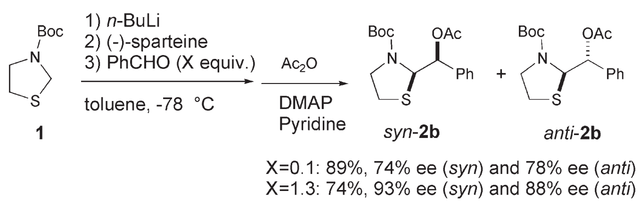


Fig. 1 Chem 3D structure derived from the X-ray crystallography of syn-**2b**.

In order to clarify whether the reaction proceeds through a dynamic thermodynamic resolution[14] 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.



Scheme 2

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.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (no. 11650890) from the Ministry of Education, Science, Sports and Culture of Japan and an NIT research promotion program. We thank Dr Shinya Kusuda, Ono Pharmaceutical Co., Ltd, for the X-ray crystallographic analysis.

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 NH_4Cl was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4 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**: $C_{17}H_{23}NO_4S$, $M = 337.43$, (0.31 × 0.18 × 0.08 mm), orthorhombic, P212121 (#19), $a = 8.23(1)$, $b = 9.09(2)$, $c = 22.54(4)$ Å, $\beta = 90$, $V = 1689(4)$ Å^3, $\mu = 1.871$ mm, $Z = 4$, 31284 reflections measured, 2909 unique (Rint = 0.058). Final R indices [$I > 3\sigma(I)$]: $R = 0.066$, Rw = 0.068. CCDC reference number 241332. See http://www.rsc.org/suppdata/ob/b4/b408509d/ for crystallographic data in .cif or other electronic format.

1 (*a*) D. Hoppe and O. Zschage, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 69–71; (*b*) D. Hoppe, F. Hintze and P. Tebben, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1422–1424; (*c*) D. Hoppe, M. Paetow and F. Hintze, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 394–396. For a review, see: ; (*d*) D. Hoppe and T. Hense, *Angew. Chem., Int. Ed.*, 1997, **36**, 2282–2316.

2 (*a*) For reviews see: P. Beak, A. Basu, D. J. Gallagher, Y. S. Park and S. Thayumanavan, *Acc. Chem. Res.*, 1996, **29**, 552–560; (*b*) P. O'Brien, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1439–1457.

3 (*a*) L. Colombo, C. Gennari, G. Resnati and C. Scolastico, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1284–1286; (*b*) L. Colombo, C. Gennari, C. Scolastico, G. Guanti and E. Narisano, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1278–1283; (*c*) G. Delogu, O. D. Lucchi and P. Maglioli, *J. Org. Chem.*, 1991, **56**, 4467–4473; (*d*) V. K. Aggarwal, R. Franklin, J. Maddock, G. R. Evans, A. Thomas, M. F. Mahon, K. C. Molloy and M. J. Rice, *J. Org. Chem.*, 1995, **60**, 2174–2182.

4 (*a*) J. E. Lynch and E. L. Eliel, *J. Am. Chem. Soc.*, 1984, **106**, 2943–2948; (*b*) J. Kaulen, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 462–463.

5 L. Colombo, M. D. Giacomo, G. Brusotti and G. Delogu, *Tetrahedron Lett.*, 1994, **35**, 2063–2066.

6 L. Colombo, M. D. Giacomo, G. Brusotti and E. Milano, *Tetrahedron Lett.*, 1995, **36**, 2863–2866.

7 (*a*) R. E. Gawley, Q. Zhang and A. T. McPhail, *Tetrahedron: Asymmetry*, 2000, **11**, 2093–2106; (*b*) R. E. Gawley, S. A. Campagna, M. Santiago and T. Ren, *Tetrahedron: Asymmetry*, 2002, **13**, 29–36; (*c*) C. Gaul and D. Seebach, *Org. Lett.*, 2000, **2**, 1501–1504; (*d*) C. Gaul, K. Schärer and D. Seebach, *J. Org. Chem.*, 2001, **66**, 3059–3073; (*e*) C. Gaul, P. I. Arvidsson, W. Bauer, R. E. Gawley and D. Seebach, *Chem. Eur. J.*, 2001, **7**, 4117–4125; (*f*) C. Gaul and D. Seebach, *Helv. Chim. Acta*, 2002, **85**, 772–787.

8 (*a*) J. Kang, J. I. Kim and J. H. Lee, *Bull. Korean Chem. Soc.*, 1994, **15**, 865–868; (*b*) K. Tomioka, M. Sudani, Y. Shinmi and K. Koga, *Chem. Lett.*, 1985, 329–332.

9 N. Kise, T. Urai and J. Yoshida, *Tetrahedron: Asymmetry*, 1998, **9**, 3125–3128.

10 For a review of enantioselective reactions of α-thio carbanions, see: T. Toru and S. Nakamura, In *Organolithiums in Enantioselective Synthesis*; D. M. Hodgson, ed.; Springer: Berlin, 2003; vol. 5, pp. 177–216. See also: (*a*) S. Nakamura, R. Nakagawa, Y. Watanabe and T. Toru, *Angew. Chem., Int. Ed.*, 2000, **39**, 353–355; (*b*) S. Nakamura, R. Nakagawa, Y. Watanabe and T. Toru, *J. Am. Chem. Soc.*, 2000, **122**, 11340–11347; (*c*) S. Nakamura, A. Furutani and T. Toru, *Eur. J. Org. Chem.*, 2002, 1690–1695; (*d*) S. Nakamura, T. Kato, H. Nishimura and T. Toru, *Chirality*, 2004, **16**, 86–89; (*e*) S. Nakamura, T. Ogura, L. Wang and T. Toru, *Tetrahedron Lett.*, 2004, **45**, 2399–2402.

11 S. Nakamura, Y. Ito, L. Wang and T. Toru, *J. Org. Chem.*, 2004, **69**, 1581–1589.

12 (*a*) B. T. Cho and Y. S. Chun, *Tetrahedron: Asymmetry*, 1999, **10**, 1843–1846; (*b*) T. Tsujigami, T. Sugai and H. Ohta, *Tetrahedron: Asymmetry*, 2001, **12**, 2543–2549.

13 For example, the vicinal coupling constants are 4.2 Hz for *syn*-**2b** and 6.6 Hz for *anti*-**2b**.

14 P. Beak, D. R. Anderson, M. D. Curtis, J. M. Laumer, D. J. Pippel and G. A. Weisenburger, *Acc. Chem. Res.*, 2000, **33**, 715–727.

15 (*a*) R. Noyori, M. Tokunaga and M. Kitamura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 36–56; (*b*) R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475–1490; (*c*) S. Caddick and K. Jenkins, *Chem. Soc. Rev.*, 1996, 447–456; (*d*) H. Pellissier, *Tetrahedron*, 2003, **59**, 8291–8327.