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N-Thioacyl 1,3-Amino Alcohols: Synthesis via Ring-Opening of Oxiranes with Thioamide Dianions and Applications as Key Intermediates Leading to Stereochemically Defined 5,6-Dihydro-4*H*-1,3-oxazines and 1,3-Amino Alcohols

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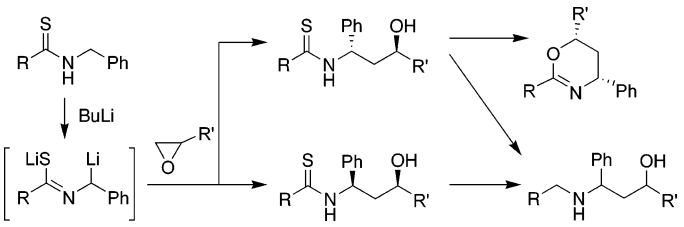
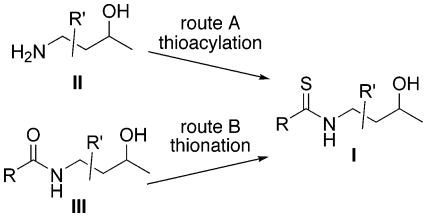


N-Thioacyl 1,3-amino alcohols were synthesized via the ring-opening of oxiranes with thioamide dianions generated from *N*-benzyl thioamides and BuLi in a highly regio- and stereoselective manner. The diastereomers of *N*-thioacyl 1,3-amino alcohols were readily separated by column chromatography to give stereochemically defined *N*-thioacyl 1,3-amino alcohols. They underwent intramolecular cyclization with Bu_4NF and EtI to give 5,6-dihydro-4*H*-1,3-oxazines. The reaction was specific with *anti*-*N*-thioacyl 1,3-amino alcohols, and *cis*-5,6-dihydro-4*H*-1,3-oxazines were obtained with high efficiency, whereas the reaction of a *syn*-alcohol gave a thioimidate as a major product. The reduction of *N*-thioacyl 1,3-amino alcohols with $LiAlH_4$ gave *N*-alkyl 1,3-amino alcohols in high yields. The use of optically active propylene oxide as a starting material gave the corresponding oxazine and alcohols in optically pure forms.

Introduction

Although little information is available regarding *N*-thioacyl 1,3-amino alcohols **I**, they are an interesting class of compounds as key precursors leading to nitrogen atom-containing heterocycles[1] as well as skeletons in biologically related molecules.[2] Two representative procedures for their synthesis have been reported to date: i.e., thioacylation of amines with dithioic acid esters or dithioic acid salts (route A)[1a,b,3] and thionation of *N*-acyl 1,3-amino alcohols (route B)[1d,4] (Scheme 1).

SCHEME 1



In these reactions, the carbon skeletons of **I** were preformed as in 1,3-amino alcohols **II** and *N*-acyl 1,3-amino alcohols **III**, and the sulfur atom of **I** was introduced to **II** and **III** in the final step to prepare **I**. Recently, carbon−carbon bond-forming reactions using carbanions

(1) (a) Lawson, A.; Searle, C. E. *J. Chem. Soc.* **1957**, 1556. (b) Laduron, F.; Nyns, C.; Janousek, Z.; Viehe, H. G. *J. Prakt. Chem.* **1997**, *339*, 697. (c) Wipf, P.; Hayes, G. B. *Tetrahedron* **1998**, *54*, 6987. (d) Leflemme, N.; Dallemagne, P.; Rault, S. *Tetrahedron Lett.* **2004**, *45*, 1503.

(2) (a) Brossmer, R.; Isecke, R.; Herrler, G. *FEBS Lett.* **1993**, *323*, 96. (b) Brossmer, R.; Gross, H. J. *Methods Enzymol.* **1994**, *247*, 153. (c) Terada, T.; Kitajima, K.; Inoue, S.; Koppert, K.; Brossmer, R.; Inoue, Y. *Eur. J. Biochem.* **1996**, *236*, 852. (d) Brossmer, R.; Klenk, H.-D.; Herrler, G. *Virology* **1996**, *218*, 127. (e) Guzaev, A. P.; Manoharan, M. *J. Am. Chem. Soc.* **2001**, *123*, 783. (f) Hwang, O.; Kim, G.; Jang, Y. J.; Kim, S. W.; Choi, G.; Choi, H. J.; Jeon, S. Y.; Lee, D. G.; Lee, J. D. *Mol. Pharm.* **2001**, *59*, 1249.

(3) (a) Sicher, J.; Pankova, M.; Jonas, J. Svoboda, M. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2727. (b) Drefahl, G.; Horhold, H. H. *Chem. Ber.* **1961**, *94*, 1641. (c) Legrand, L.; Lozac'h, N. *Phosphorus Sulfur Relat. Elem.* **1986**, *26*, 111. (c) Isecke, R.; Brossmer, R. *Tetrahedron* **1994**, *50*, 7445. (d) Katritzky, A. R.; Moutou, J.-L. Yang, Z. *Synthesis* **1995**, 1497.

(4) Haske, B. J.; Matthews, M. E.; Conkling, J. A.; Perzanowski, H. P. *J. Org. Chem.* **1967**, *32*, 1579.

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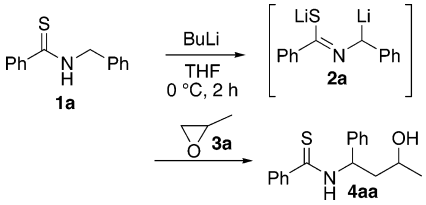
SCHEME 2. Ring-Opening of Propylene Oxide 3a with a Thioamide Dianion 2a



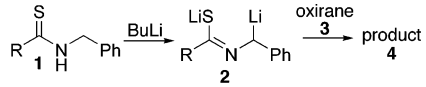
derived from a wide range of thioamides have been extensively studied.[5] Among them, we noted that thioamide dianion **2a** generated from thioamide **1a** and BuLi underwent ring-opening of propylene oxide (**3a**) to give *N*-thioacyl 1-phenyl-1,3-amino alcohol **4aa**[6a] during our studies on the reactivity of reactive species derived from thioamides[6] (Scheme 2).

Characteristically, the carbanion adjacent to the nitrogen atom is selectively generated, and the oxirane is electrophilically introduced to the carbon atom α to the nitrogen atom. Since various types of oxiranes are readily available,[7] the protocol in Scheme 2 may provide a new synthetic route to *N*-thioacyl 1,3-amino alcohols. We report here details of the synthesis of *N*-thioacyl 1,3-amino alcohols via the ring-opening of oxiranes with thioamide dianions. Synthetic reactions with *N*-thioacyl 1,3-amino alcohols leading to 5,6-dihydro-*4H*-1,3-oxazines and 1,3-amino alcohols are also reported.

Results and Discussion

Ring-Opening of Oxiranes with Thioamide Dianions. The wide applicability of the ring-opening of oxiranes with thioamide dianions **2** is illustrated in Table 1. The thioamide dianions **2b** and **2c** were efficiently generated from thioamides **1b** and **1c** with 2 equiv of BuLi at 0 °C, and **3a** was then added to the reaction mixture at the same temperature. The ring-opening of **3a** with **2b** and **2c** proceeded smoothly with high regioselectivity to give *N*-thioacyl 1,3-amino alcohol **4ab** and **4ac** in respective yields of 90 and 80% (entries 1 and 2). The reaction of thioamide dianion **2a** with monosubstituted oxirane **3b** took place under reaction conditions identical to those for **3a** (entry 3), whereas the reaction with oxiranes **3c** and **3d** was carried out below −45 °C (entries 4 and 5). As a result, functional groups such as methoxy and hydroxy groups and chlorine atom remained intact and did not affect the regioselectivity, although the stereoselectivity was slightly dependent on these substituents. The use of the oxirane bearing a *tert*-butyl group **3e** enhanced the stereoselectivity probably because of the steric reason (entry 6). Notably, although products **4a**−**e** were obtained as stereoisomeric mixtures, they could be separated as single isomers by ordinary column

TABLE 1. Ring-Opening of Oxiranes with Thioamide Dianions 2 Derived from Thioamides 1 and BuLi[a]



1a R = Ph, **1b** R = *t*-Bu, **1c** R = 4-FC_6H_4

entry	1	oxirane 3	product 4 yield[b]
1	**1b**	**3a** R' = Me	**4ab** 90% *anti* : *syn* = 44 : 56
2	**1c**	**3a** R' = Me	**4ac** 80% *anti* : *syn* = 48 : 52
3	**1a**	**3b** R' = CH_2OMe	**4b** 79% *anti* : *syn* = 53 : 47
4[c]	**1a**	**3c** R' = CH_2Cl	**4c** 94% *anti* : *syn* = 57 : 43
5[d]	**1a**	**3d** R' = CH_2OH	**4d** 48% *anti* : *syn* = 19 :81
6		**3e** R' = *t*-Bu	**4e** 83% *anti* : *syn* = 14 : 86
7	**1a**	**3f**	**4f** 7%; **4f'** 92%
8	**1c**	**3g**	**4g** 46%; **4g'** 27%
9	**1a**	**3h**	**4h** 42%; **4h'** 39%
10	**1a**	**3i**	**4i** 41%; **4i'** 49%
11	**1a**	**3j**	**4j** 29%; **4j'** 64%
12	**1a**	**3k**	**4k** 65%

[a] The reaction was carried out as follows, unless otherwise noted. Thioamide dianions **2** were treated with oxiranes **3** (1 equiv) in THF at 0 °C for 1 h. [b] Isolated yield. [c] At −45 °C. [d] BuLi (3.5 equiv) and **3d** (1.6 equiv) were used at −78 °C.

(5) For reviews, see: (a) Metzner, P. In *Topics in Current Chemistry*; Page, P. C. B., Ed.; Springer-Verlag: Berlin, 1999; Vol. 204, p 127. (b) Murai, T. In *Topics in Current Chemistry*; Kato, S., Ed.; Springer-Verlag: Berlin, 2005; Vol. 251, p 247.

(6) (a) Murai, T.; Aso, H.; Tatematsu, Y.; Itoh, Y.; Niwa, H. *J. Org. Chem.* **2003**, *68*, 8514. (b) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968. (c) Murai, T.; Ohta, Y.; Mutoh, Y. *Tetrahedron Lett.* **2005**, *46*, 3637.

(7) For recent reviews of the synthesis of oxiranes, see: (a) Lane, B. S.; Burgess, K.; *Chem. Rev.* **2003**, *103*, 2457. (b) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (c) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (d) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611.

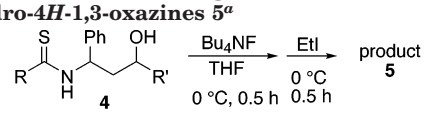
chromatography on silica gel.[8] In contrast to the reaction with **3a**−**e**, ring-opening of styrene oxide (**3f**) with thioamide dianion **2a** proceeded exclusively at the carbon atom bearing a phenyl group to give **4f′** as a major product (entry 7).[9] In this reaction, the stereochemistry of two successive carbon atoms was also controlled. The trans-opening of oxiranes with thioamide dianions **2** was proven by the reaction with cyclohexene oxide (**3g**) and oxirane bearing an acetal group **3h** to give two diastereomers **4g**, **4g′** and **4h**, **4h′** out of four possible isomers (entries 8 and 9). The high stereoselectivity of the ring-opening of oxiranes was further illustrated by the reaction with *cis*- (**3i**) and *trans*-2-butene oxide (**3j**) (entries 10 and 11). In the reaction with **3i**, two diastereomers **4i** and **4i′** were formed in a nearly equal ratio, whereas the reaction with **3j** gave the other two isomers **4j** and **4j′**.

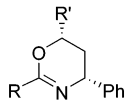
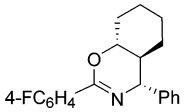
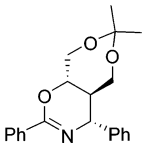
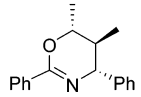
The ring-opening of 1,1,2-trisubstituted oxirane **3k** with **2a** exhibited high regio- and stereoselectivity to give *N*-thioacyl 1,3-amino alcohol **4k** in good yield (entry 12). The stereochemistry of *syn*-**4d**, **4f′**, **4j′**, and **4k** was unequivocally determined by X-ray molecular analyses.[11] On the basis of the NMR spectra of these products, the stereochemistry of other products **4** was determined.

Synthesis of 5,6-Dihydro-4*H*-1,3-oxazines via Intramolecular Cyclization of *N*-Thioacyl 1,3-Amino Alcohols. Due to the broad utility of 5,6-dihydro-4*H*-1,3-oxazines as key intermediates in organic syntheses, several synthetic methods have been developed.[12] In particular, [1,4]-cycloaddition reactions of *N*-acyl imines or iminiums with alkenes have been investigated to achieve their stereoselective synthesis.[13] Thus, the intramolecular cyclization of *N*-thioacyl 1,3-amino alcohols obtained was examined to obtain stereochemically defined oxazines. The conversion of *N*-thioacyl 1,3-amino alcohols to thiazines has been developed,[1c,d,14] whereas to the best of our knowledge their conversion to oxazines has not been reported.

After several disappointing results, we found that treatment of *anti*-*N*-thioacyl 1,3-amino alcohols **4** with 2 equiv of Bu_4NF, followed by the reaction with 2 equiv of EtI, gave 4,6-*cis*-oxazines **5** in good yields (Table 2). Functional groups such as methoxy group and fluorine and chlorine atoms did not affect the reaction course, and the corresponding products were obtained in yields of 54−77% (entries 3−6). The intramolecular cyclization of alcohols **4g**−**i** proceeded with better efficiency than that of other alcohols to give 4,5,6-trisubstituted oxazines **5g**−**i** in higher yields (entries 7−9). Notably, the intramolecular cyclization of alcohols **4** was specific with *anti*-alcohols **4**. The reaction of *syn*-**4** did not give the desired oxazines at all. For example, the reaction of *syn*-**4e** with Bu_4NF and EtI under conditions identical to those in Table 2 gave the thioimidate **6e** as a stereoisomeric mixture in 78% yield (Scheme 3). No ethylation took place at the oxygen atom of **6e** at this temperature.

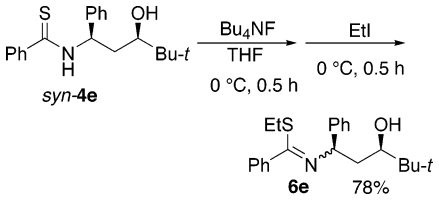
TABLE 2. Intramolecular Cyclization of *N*-Thioacyl 1,3-Amino Alcohols 4 Leading to 5,6-Dihydro-4*H*-1,3-oxazines 5[a]



entry	4	product 5		yield[b]
				
1	*anti*-**4aa**	**5aa**	R = Ph, R' = Me	57%
2	*anti*-**4ab**	**5ab**	R = *t*-Bu, R' = Me	49%
3	*anti*-**4ac**	**5ac**	R = 4-FC_6H_4, R' = Me	77%
4	*anti*-**4b**	**5b**	R = Ph, R' = CH_2OMe	75%
5[c]	*anti*-**4c**	**5c**	R = Ph, R' = CH_2Cl	54%
6	*anti*-**4e**	**5e**	R = Ph, R' = *t*-Bu	66%
7	**4g**	**5g**		71%
8[c]	**4h**	**5h**		90%
9	**4i**	**5i**		76%

[a] The reaction was carried out as follows, unless otherwise noted. *N*-Thioacyl 1,3-amino alcohols **4** were treated with Bu_4NF (2 equiv) and EtI (2 equiv) in THF at 0 °C for 1 h. [b] Isolated yield. [c] Bu_4NF (3 equiv) and EtI (4 equiv) were used.

SCHEME 3



(8) The two diastereomers of *N*-thioacyl 1,3-amino alcohols **4** were easily distinguished on the basis of their light yellow color during the column purification.

(9) The ring-opening of styrene oxide (**3f**) with organolithium reagents has often been carried out in the presence of Lewis acids to obtain high regioselectivity and to avoid the rearrangement of **3f**.[10] In contrast, regioselective ring-opening of **3f** with thioamide dianion **2a** was achieved even in the absence of Lewis acids.

(10) (a) Imogai, H.; Larcheveque, M. *Tetrahedron: Asymmetry* **1997**, *8*, 965. (b) Botuha, C.; Haddad, M.; Larcheveque, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1929.

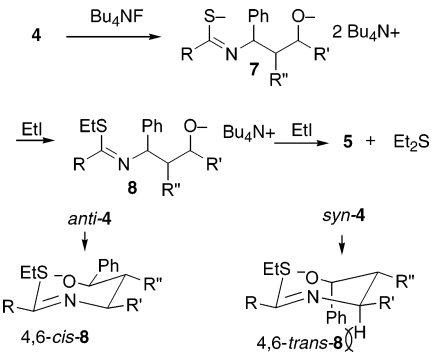
(11) For details, see the Supporting Information.

(12) For recent examples, see: (a) Liu, S.; Müller, J. F. K.; Neuburger, M.; Schaffner, S.; Zehnder, M. *Helv. Chim. Acta* **2000**, *83*, 1256. (b) Kuznetsov, V. V.; Brusilovskii, Y. E. *Chem. Heterocycl. Commun.* **2001**, *37*, 574. (c) Nakajima, N.; Saito, M.; Kudo, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3579. (d) Gaulon, C.; Gizecki, P.; Dhal, R.; Dujardin, G. *Synlett* **2002**, 952. (e) Nakajima, N.; Isobe, T.; Irisa, S.; Ubukata, M. *Heterocycles* **2003**, *59*, 107. (f) Palko, M.; Hetenyi, A.; Fueloep, F. *J. Heterocycl. Chem.* **2004**, *41*, 69. (g) Tse, M. K.; Doebler, C.; Bhor, S.; Klawonn, M.; Maegerlein, H. H. Beller, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5255.

(13) (a) Gizecki, P.; Dhal, R.; Toupet, L.; Dujardin, G. *Org. Lett.* **2000**, *2*, 585. (b) Katritzky, A. R.; Ghiviriga, I.; Chen, K.; Tymoshenko, D. O.; Abdel-Fattah, A. A. A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 530. (c) Gizecki, P.; Dhal, R.; Poulard, C.; Gosselin, P.; Dujardin, G. *J. Org. Chem.* **2003**, *68*, 4338.

(14) Nishio, T.; Konno, Y.; Ori, M.; Sakamoto, M. *Eur. J. Org. Chem.* **2001**, 3553.

SCHEME 4

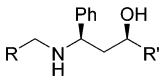
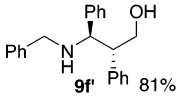
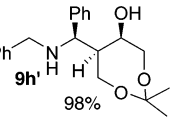
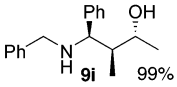
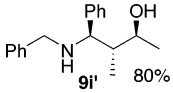
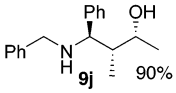
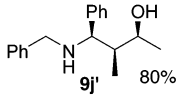
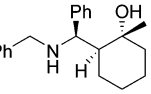


A plausible reaction pathway for the present reaction is shown in Scheme 4.

The deprotonation from alcohols **4** with Bu_4NF takes place at both their nitrogen and oxygen atoms to form dianions **7**. Ethylation then proceeds selectively at the sulfur atom to give thioimidates **8**, probably because of the greater nucleophilicity of thiolates compared to alcoholates in **7**. The thioimidates **8** undergo cyclization through the attack of alcoholates to the carbon atom of **8** followed by the elimination of ethanethiolate, which may be further trapped with excess EtI, to give oxazines **5** along with Et_2S. For the reaction of *anti*-**4**, intramolecular cyclization may proceed via a six-membered cyclic transition state, where two substituents (Ph and R′) are oriented at the equatorial positions as in 4,6-*cis*-**8**. On the other hand, the reaction of *syn*-**4** may involve unfavorable 4,6-*trans*-**8** where 1,3-diaxial interaction may be present. Consequently, no cyclization occurs with *syn*-**4**.

Reduction of *N*-Thioacyl 1,3-Amino Alcohols. The importance of stereochemically defined 1,3-amino alcohols has been well documented, and methods for their synthesis have been extensively developed.[15] For example, construction of their stereocenters has involved the reduction of 1,3-amino ketones,[15g,i] 1,3-imino alcohols,[15h,m] and isoxazolines.[15a,n] The reduction of stereochemically defined isoxazolidines[15l,o] also provides 1,3-amino alcohols. Nevertheless, it is still not easy to obtain stereochemically pure 1,3-amino alcohols with high efficiency. Therefore, the reduction of *N*-thioacyl 1,3-amino alcohols **4** was tested since a variety of reducing agents have been used for the reduction of thioamides. Among these, $LiAlH_4$ was used to efficiently reduce **4**.[16] The results are shown in Table 3. In all cases, thiocarbonyl groups in **4** were selectively converted to methylene groups to give the corresponding 1,3-amino alcohols **9** in high yields. While both Et_2O and THF were effective as solvents,[17] the reaction in Et_2O required a longer reaction time.

TABLE 3. Reduction of *N*-Thioacyl 1,3-Amino Alcohols 4 with $LiAlH_4$[a]

entry	4		product 9	yield[b]
				
1	*syn*-**4ab**	**9a**	R = *t*-Bu, R′ = Me	93%
2	*syn*-**4b**	**9b**	R = Ph, R′ = CH_2OMe	97%
3[c]	*syn*-**4c**	**9c**	R = Ph, R′ = CH_2Cl	80%
4	**4f′**		 **9f′**	81%
5	**4h′**		 **9h′**	98%
6	**4i**		 **9i**	99%
7	**4i′**		 **9i′**	80%
8	**4j**		 **9j**	90%
9	**4j′**		 **9j′**	80%
10[d]	**4k**		 **9k**	84%

[a] The reaction was carried out as follows, unless otherwise noted. *N*-Thioacyl 1,3-amino alcohols **4** were treated with $LiAlH_4$ (4 equiv) under reflux in THF for 15 min. [b] Isolated yield. [c] Under reflux in Et_2O for 2 h. [d] For 3 h.

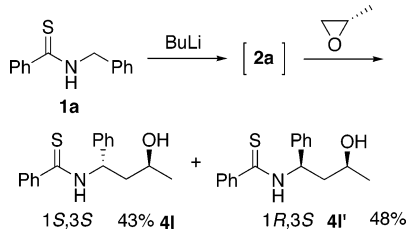
Reaction with Enantiopure Propylene Oxide. Finally, optically active propylene oxide was used as a starting material in the present two-step synthesis of 5,6-dihydro-4*H*-oxazines and 1,3-amino alcohols. The (*S*)-propylene oxide was cleaved with thioamide dianion **2a**

(15) For recent examples of the stereoselective syntheses of 1-aryl-1,3-amino alcohols, see: (a) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773. (b) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855. (c) Kuethe, J. T.; Comins, D. L. *Tetrahedron Lett.* **2003**, *44*, 4179. (d) Rezaei, M.; Harris, T. M.; Rizzo, C. J. *Tetrahedron Lett.* **2003**, *44*, 7513. (e) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018. (f) Minter, A.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (g) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208. (h) Kochi, T.; Tang, T. P. Ellman, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 11276. (i) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178. (j) Bernardi, L.; Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Folegatti, M.; Grilli, S.; Mazzanti, A.; Ricci, A. *Tetrahedron: Asymmetry* **2004**, *15* 245. (k) Rodriquez, A. C.; Ramos, A. P.; Hawkes, G. E.; Berti, F.; Resmini, M. *Tetrahedron: Asymmetry* **2004**, *15*, 1847. (l) Revuelta, J.; Cicchi, S.; Brandi, A. *Tetrahedron* **2004**, *45*, 8375. (m) Matsubara, R.; Vital, P.; Nakamura, Y.; Kiyohara, H.; Kobayashi, S. *Tetrahedron* **2004**, *60*, 9769. (n) Kennedy, A.; Nelson, A.; Perry, A. *Synlett*, **2004**, 967. (o) Chandrasekhar, S.; Babu, B. N.; Ahmed, M.; Reddy, M. V.; Jagadeesh, S. B. *Synlett* **2004**, 1303. (p) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *Synlett* **2004**, 1409. (q) Cordova, A. *Chem. Eur. J.* **2004**, *10*, 1987.

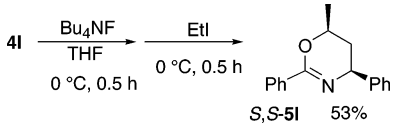
(16) (a) Seebach, D.; Lubosch, W.; Enders, D. *Chem. Ber.* **1976**, *109*, 1309. (b) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. (c) Goasdoue, C.; Gaudemar, M.; Mladenova, M. *J. Organomet. Chem.* **1981**, *208*, 279. (d) Goasdoue, C.; Goasdoue, N.; Gaudemar, M. *J. Organomet. Chem.* **1984**, *263*, 273.

(17) In the reduction of **4c** in THF, the chlorine atom was also substituted with the hydrogen atom, but the reduction in Et_2O gave the desired product **9c**.

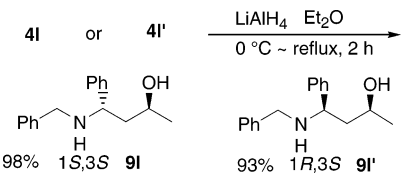
SCHEME 5



SCHEME 6



SCHEME 7



derived from thioamide **1a** and BuLi to form two diastereomers **4l** and **4l′** in a combined yield of 91% (Scheme 5).

The two diastereomers **4l** and **4l′** were successfully separated as a diastereomerically pure form. Compound **4l** was subjected to intramolecular cyclization to form enantiomerically pure oxazine **5l** in good yield (Scheme 6).

Furthermore, the reduction of **4l** and **4l′** with $LiAlH_4$ produced 1,3-amino alcohols **9l** and **9l′** as an enantiomerically pure form (Scheme 7).

In summary, we have demonstrated the regio- and stereoselective ring-opening of oxiranes with thioamide dianions, followed by chromatographic separation, to give stereochemically defined *N*-thioacyl 1,3-amino alcohols. Intramolecular cyclization of *N*-thioacyl 1,3-amino alcohols with Bu_4NF and EtI provided an efficient route to stereochemically defined 5,6-dihydro-4*H*-1,3-oxazines with high efficiency. This reaction was specific with *anti*-alcohols. Highly efficient reduction of *N*-thioacyl 1,3-amino alcohols was achieved with $LiAlH_4$ to produce 1,3-amino alcohols, where the relative stereochemistry of two or three carbon centers is defined. The ready availability of various types of optically active oxiranes has enhanced the wide applicability of the present reaction, as exemplified by the reaction of (*S*)-propylene oxide. Further studies on the thioamide dianions and products obtained here are in progress.

Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere.

General Procedure for the Synthesis of *N*-Thioacyl 1,3-Amino Alcohols. A Representative Procedure for the Synthesis of *N*-3-Hydroxy-1-phenylbutyl 1,1-Dimethylpropanethioamide (4ab). To a solution of *N*-phenylmethyl 2,2-dimethylpropane thioamide (**1b**) (1.036 g, 5 mmol) in THF (15 mL) was added butyllithium (1.6 M solution in hexane, 6.50 mL, 10 mmol) at 0 °C under Ar atmosphere. The mixture was stirred at that temperature for 0.5 h. After the addition of propylene oxide (**3a**) (0.35 mL, 5.0 mmol), the mixture was stirred at that temperature for 1 h. The reaction mixture was poured onto water and extracted with Et_2O (70 mL). The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (hexane/AcOEt = 1:1) to give *anti-N*-(3-hydroxy-1-phenylbutyl) 2,2-dimethylpropanethioamide (0.541 g, 2.03 mmol, 41%, R_f = 0.25) and *syn-N*-(3-hydroxy-1-phenylbutyl) 2,2-dimethylpropanethioamide (0.645 g, 2.43 mmol, 49%, R_f = 0.39) as a pale yellow solid. *Anti*: mp 46−48 °C; IR (KBr) 3350, 3029, 2965, 2927, 1515, 1455, 1382, 1351, 1131, 757, 698 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.34 (s, 9H), 1.93−1.96 (m, 1H), 1.97−1.98 (m, 1H), 2.60 (br, 1H), 3.87 (dqd, J = 9.3, 6.3, 2.9 Hz, 1H), 5.62 (td, J = 14.6, 6.3 Hz, 1H), 7.23−7.35 (m, 5H), 8.32 (br, 1H); ^{13}C NMR($CDCl_3$) δ 24.6, 30.0, 44.5, 44.7, 58.5, 66.6, 126.5, 127.5, 128.8, 141.2, 212.3; MS (EI) *m/z* 265 (M^+); HRMS calcd for $C_{15}H_{23}NOS$ 265.1500, found 265.1476. *Syn*: mp 65−67 °C; IR (KBr) 3237, 3027, 2969, 1524, 1386, 1359, 1120, 1070, 970, 758, 700 cm^{-1}; ^1H NMR($CDCl_3$) δ 1.21 (d, J = 6.3 Hz, 3H), 1.38 (s, 9H), 1.92−2.01 (m, 2H), 2.50 (br, 1H), 3.87 (dqd, J = 2.4, 3.4, 6.3 Hz, 1H), 5.97 (td, J = 7.8, 2.4 Hz, 1H), 7.22−7.36 (m, 5H), 8.87 (br, 1H); ^{13}C NMR($CDCl_3$) δ 23.9, 30.2, 43.2, 44.7, 57.1, 64.7, 126.3, 127.4, 128.8, 139.9, 212.3; MS (EI) *m/z* 265 (M^+); HRMS calcd for $C_{15}H_{23}NOS$ 265.1500, found 265.1509.

General Procedure for the Intramolecular Cyclization of *N*-Thioacyl 1,3-Amino Alcohols. A Representative Procedure for the Synthesis of (4α,6α)-5,6-Dihydro-2-(4-fluorophenyl)-6-methyl-4-phenyl-(4*H*)-1,3-oxazine (5ac). To a solution of *N*-(1*R**,3*R**)-3-hydroxy-1-phenylbutyl-4-fluorobenzenecarbothioamide (0.469 g, 1.55 mmol) in THF (16 mL) was added tetrabuthylammonium fluoride (1.0 M solution in THF, 3.30 mL, 3.30 mmol) at 0 °C under Ar atmosphere. The mixture was stirred at that temperature for 0.5 h. After the addition of ethyl iodide (0.27 mL, 3.4 mmol), the mixture was stirred at that temperature for 0.5 h. The reaction mixture was poured onto Et_2O (40 mL), and the organic layer was washed with 3 × 10 mL of water. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel (hexane/Et_2O = 1:1) to give (4α,6α)-5,6-dihydro-2-(4-fluorophenyl)-6-methyl-4-phenyl-(4*H*)-1,3-oxazine (0.321 g, 1.19 mmol, 77%, R_f = 0.71) as a white solid: mp 95−97 °C dec; IR (KBr) 3027, 2975, 1652, 1603, 1507, 1283, 1152, 1138, 846, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (d, J = 6.4 Hz, 3H), 2.29 (ddd, J = 13.7, 4.9, 2.4 Hz, 2H), 4.50 (dqd, J = 11.7, 6.4, 2.4 Hz, 1H), 4.71 (dd, J = 11.7, 4.9 Hz, 1H), 7.02−8.07 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 21.4, 38.7, 56.6, 71.7, 114.9 (d, J_{C-F} = 21.5 Hz), 126.4, 127.8, 128.6, 129.5 (d, J_{C-F} = 8.8 Hz), 130.2 (d, J_{C-F} = 2.4 Hz), 144.6, 155.1, 164.4 (d, J_{C-F} = 249.6 Hz); MS (EI) *m/z* 269 (M^+). Anal. Calcd for $C_{17}H_{16}FNO$: C, 75.82; H, 5.99. Found: C, 76.11; H, 6.04.

General Procedure for the Reduction of *N*-Thioacyl 1,3-Amino Alcohols. A Representative Procedure for the Synthesis of *syn-N*-2,2-Dimethylpropyl 3-Hydroxy-1-phenylbutylamine (9a). To a solution of lithium aluminum hydride (0.0790 g, 2.08 mmol) in THF (2 mL) was added *syn-N*- (3-hydroxy-1-phenylbutyl) 2,2-dimethylpropanethioamide (0.1330 g, 0.501 mmol) at 0 °C, and the mixture was heated at reflux for 15 min with stirring. Then, to the reaction mixture were added water (0.079 mL), 15% NaOH aq (0.079 mL), and water (0.237 mL) at 0 °C. The resulting oil was filtered and concentrated in vacuo to give *syn-N*-2,2-dimethylpropyl 3-hydroxyphenylbutylamine (0.1097 g, 0.466 mmol, 93%) as a pale yellow oil: IR (KBr) 3348, 2954, 2865, 1466, 1454, 1364, 1121, 909, 755, 733, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (s, 9H, CH_3), 1.18 (d, J = 5.9 Hz, 3H, CH_3), 1.75-1.86 (m, 2H, CH_2), 2.26 (d, J = 11.2 Hz, 1H, CH_2NH), 2.32 (d, J = 11.2 Hz, 1H, CH_2NH),

3.90−3.99 (m, 2H, CHPh, C*H*OH), 7.24-7.37 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 23.0, 27.7 (CH_3), 31.2 (C), 43.1, 60.0 (CH_2), 65.3, 61.7 (CH), 126.5, 127.1, 128.5, 143.0 (Ar); MS (EI) *m/z* 235 (M^+); HRMS calcd for $C_{15}H_{25}NO$ 235.1936, found 235.1931.

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Supporting Information Available: Spectroscopic data for **4**, **5**, **6e**, and **9** and tables of crystallographic data for *syn*-**4d**, **4f′**, **4j′**, and **4k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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