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Asymmetric reduction of racemic 2-isoxazolines

Masashi Tokizane, Kaori Sato, Tetsuo Ohta *, Yoshihiko Ito

Department of Biomedical Information, Faculty of Life and Medical Sciences, Doshisha University, 1-3 Tatara-Miyakodani, Kyotanabe 610-0394, Japan

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This paper is dedicated to the heartfelt memory of the late Professor Yoshihiko Ito of Doshisha University

ABSTRACT

The kinetic resolution of racemic 2-isoxazolines was carried out by asymmetric reduction using borane with 1,2-amino alcohols as a chiral source. Using excess BH_3–THF in the presence of (−)-norephedrine, optically active 1,3-amino alcohol derivatives were obtained with good ee but in lower yield, while the optically active substrates 2-isoxazolines were recovered with modest ee. The asymmetric reduction using 2.0 equiv of BH_3–SMe_2 was investigated as an alternative strategy for the synthesis of optically active products. After reduction, treatment of the resulting mixture with Et_3N was successful in providing optically active isoxazolidine derivatives in good yields and with good ee. The choice of chiral source was also shown to have a significant effect. In particular, the use of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol reversed the enantioselectivity of the recovered substrates.

1. Introduction

2-Isoxazolines and isoxazolidines are easily transformed to 1,3-amino alcohols, which are often used as intermediates for the preparation of biologically active alkaloids and β-lactams,[1] and have thus received much attention as optically active compounds. They are prepared by asymmetric 1,3-dipolar cycloadditions of nitrile oxides or nitrones to olefins using chiral starting materials, asymmetric catalysis, and a chiral auxiliary,[2] followed by heterogeneous reduction to give chiral 1,3-amino alcohols.[3] Our attempts to obtain optically active isoxazolidines by metal-catalyzed asymmetric 1,3-dipolar cycloaddition of nitrones with olefins have been applied to a limited number of substrates, which contain substituents coordinated to metals.[4] However, a reaction using substrates with no functional groups coordinated to a metal in a bidentate fashion did not show good enantioselectivity. On the other hand, we attempted a palladium-catalyzed decomposition reaction of isoxazolidines with kinetic resolution as a new pathway to obtain optically active isoxazolidines.[4e] In this case, the bidentate coordination of the substrate to the palladium center was also important. Herein, we report the kinetic resolution, which comprised asymmetric reduction of racemic 2-isoxazolines bearing no functional groups coordinated to metals, to 1,3-amino alcohols directly and to isoxazolidines. Our aim is to achieve kinetic resolution by the asymmetric reduction of the C=N double bond using chiral oxazaborolidine generated from 1,2-amino alcohols and borane. This is based on the fact that a chiral oxazaborolidine-mediated reduction of oxime ethers, which are similar in structure to 2-isoxazolines, afforded optically active amines with high enantioselectivity.[5]

2. Results and discussion

2.1. Preparation of 1,3-amino alcohols by asymmetric reduction of racemic 2-isoxazoline 1a via kinetic resolution

Racemic 3,5-diphenyl-2-isoxazoline **1a** was allowed to react with borane in the presence of the chiral source, (−)-norephedrine **4a** (Scheme 1). As the resulting alcohol **2a** was difficult to isolate by column chromatography, **2a** was converted to its *N*-tosyl derivative **3a** in order to determine the yield and enantiomeric excess of the product. The reactions under various conditions are shown in Table 1. When BH_3–THF was used as a reducing agent, the reduction of racemic **1** proceeded at room temperature for 24 h in the absence of **4a**, followed by N-tosylation to give *N*-tosylamino alcohol **3a** in 37% yield in a *syn*/*anti* ratio of 65:35 (entry 1). Under these conditions, substrate **1a** was recovered in 26% yield. Next, in an asymmetric version of the reaction with 1.0 equiv of **4a**, the reaction gave *syn*-**3a** and *anti*-**3a** in low yields with moderate enantiomeric excesses (50% and 67% ee, respectively) (entry 2). In addition, the recovered substrate **1a** showed only 18% ee. When the reduction was carried out with chiral source **4b**, the ee of the product and the recovered starting material were better than those obtained from the reaction using **4a** (entry 3). In this case, however, the material balance was unsuitable. Elongation of the reaction time when using **4a** led to complete consumption of substrate **1a** (entry 4). At 0 °C, the conversion was very low (entry 5).

We then changed the borane source from the BH_3–THF complex to a BH_3–SMe_2 complex. By-products were obtained in large

* Corresponding author. Tel.: +81 774 65 6548; fax: +81 774 65 6789.
E-mail addresses: tota@mail.doshisha.ac.jp, mtkzn-bn8sygt1@nifty.com (T. Ohta).

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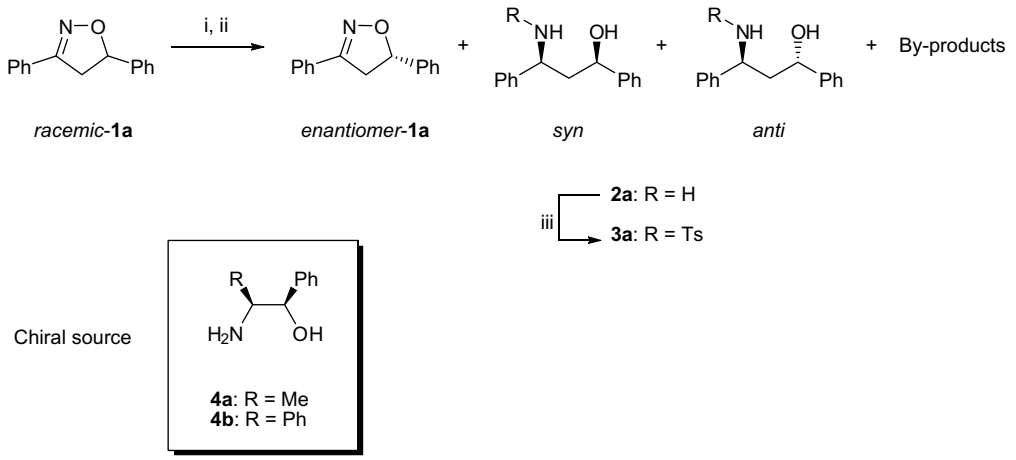


Scheme 1. Reagents and conditions: (i) BH_3–THF, chiral source, solvent; (ii) 10% HCl and then 1 M NaOH; (iii) TsCl, Et_3N.

Table 1
Kinetic resolution of 2-isoxazoline **1a** by asymmetric reduction with 1,2-amino alcohol **4a** or **4b** and BH_3–THF[a]

Entry	Chiral source	Temp. (°C), time (h)	Yield[b] (%)		ee[d] (%) **1a**[e]/*syn*-**3a**[f]/*anti*-**3a**[g]
			1a	**3a** (*syn*/*anti* ratio)[c]	
1[h]	None	rt, 24	26	37 (65:35)	—
2	**4a**	rt, 24	19	28 (75:25)	18/50/67
3	**4b**	rt, 24	12	15 (73:27)	26/56/76
4	**4a**	rt, 72	0	44 (80:20)	—/44/81
5	**4a**	0, 72	62	7 (68:32)	2/N.d.[i]/N.d.[i]

[a] Reaction conditions: (i) A mixture of **1a** (0.6 mmol), the chiral source (0.6 mmol), and 1 M BH_3–THF (2.4 mmol) in CH_2Cl_2 (1.5 mL) was stirred; (ii) 10% HCl (2 mL) was added, followed by 1 M NaOH (10 mL); (iii) a solution of the resulting organic materials, *p*-toluenesulfonyl chloride (1.8 mmol) and triethylamine (2.0 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h.
[b] Determined by ^1H NMR spectroscopy of the isolated compound with anthracene as an internal standard after silica gel column chromatography.
[c] Determined by each yields.
[d] Determined by chiral HPLC (Daicel Chiralpak AS or Chiralcel OD-H).
[e] Configuration was (*S*).
[f] Configuration was (1*R*,3*S*).
[g] Configuration was (1*S*,3*S*).
[h] 1 M BH_3–THF (1.8 mmol) was used.
[i] Not determined.

amounts under these conditions (Scheme 2). By treating these with triethylamine in EtOH, followed by protection of the amino group of the reduced residue, we confirmed that the major component was isoxazolidine.

2.2. Kinetic resolution of racemic 2-isoxazoline by asymmetric reduction to optically active isoxazolidine

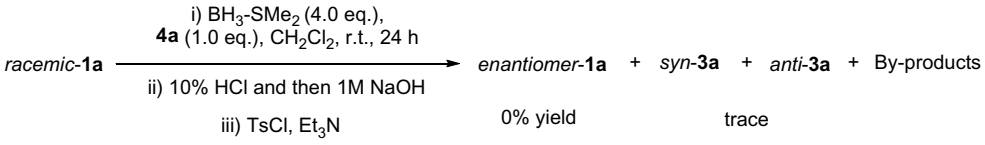
Next, we investigated the formation of isoxazolidine in preference to 1,3-amino alcohol (Scheme 3). In order to achieve a kinetic resolution of **1a**, we examined the reaction with reduced borane and in the absence of a chiral source (Table 2). The reaction using 1.0 equiv of BH_3–SMe_2 with respect to **1a** did not proceed at all (entry 1). Without a chiral source, the use of 1.5 equiv of borane gave **1a**, **2a**, and **6a** in 41%, 30%, and 18% yields, respectively (entry 2). The use of either BH_3–THF or BH_3–SMe_2 resulted in an almost identical *syn*/*anti* ratio. This shows that the selectivity is essentially the same for both species.

2.2.1. Reaction conditions

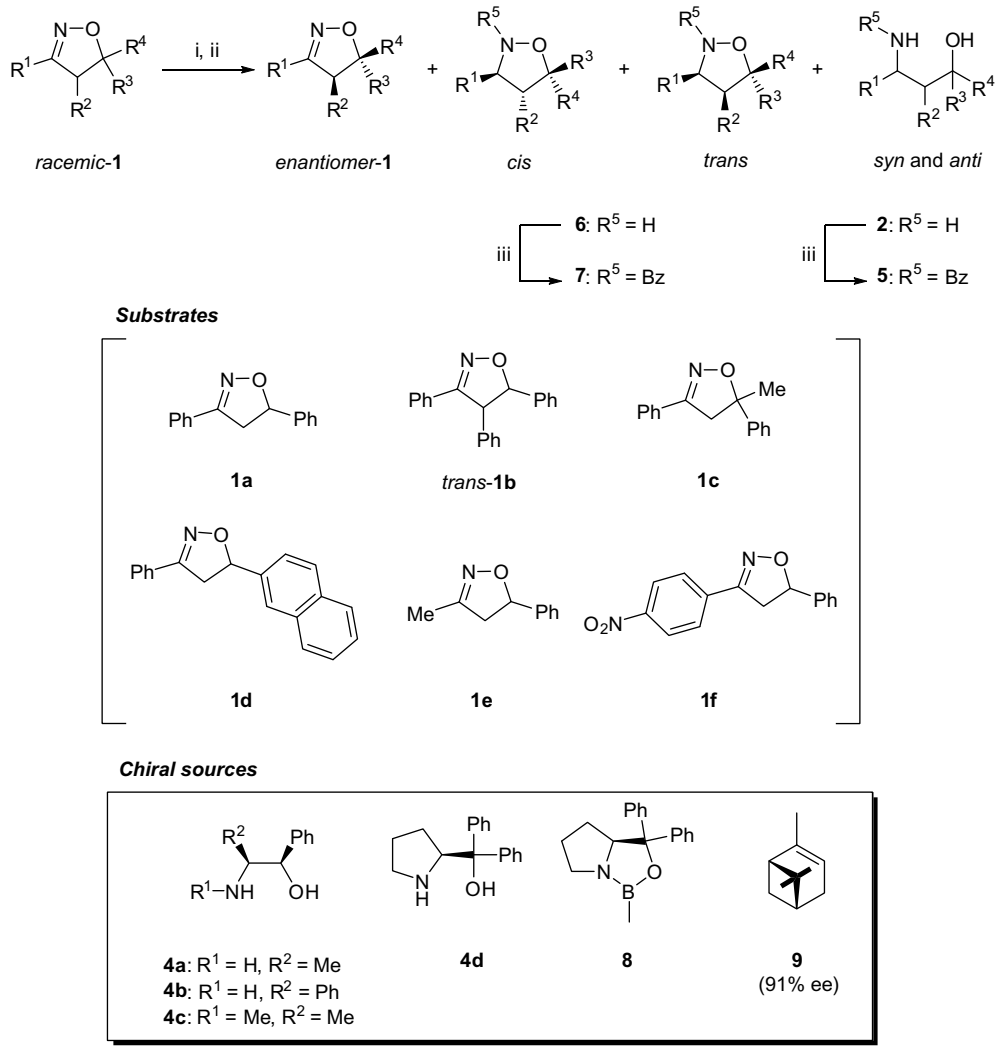
Next, we investigated the preparation of isoxazolidine by the asymmetric reduction of racemic 2-isoxazoline **1a** via kinetic resolution (Table 3). Using chiral source **4a** (**1a**:**4a** = 1:1), the reaction proceeded for 24 h to give **1a** in 62% yield and **7a** in 31% yield (entry 1). No **5a** was observed in the reaction mixture. The ratio of *cis*-**7a** and *trans*-**7a** was 65:35, and the enantiomeric excesses were 77% ee and 78% ee, respectively. The recovered substrate **1a** showed an ee of only 8%. A longer reaction time brought about an increase in the ee of **1a**, with a decrease in yield (entry 2). A reduction in the amount of **4a** used led to a higher conversion (entry 3). Although the use of a larger proportion of BH_3–SMe_2 to **4a** resulted in a greater conversion of **1a**, *cis*- and *trans*-**7a** were formed with comparable ee to the above results (entries 4–6 vs entries 1–3). No reaction occurred at 0 °C over a longer reaction time (entry 7).

2.2.2. Effects of chiral sources

Several chiral sources were examined with the aim of enhancing the ee values (Table 4). The reaction using the bulkier **4b** as a chiral source proceeded with unremarkable ee (entry 2). When (−)-ephedrine **4c** was used, almost no reaction occurred (entry 3). The use of large amounts of **5c** and BH_3–SMe_2 produced a catalytic effect, although racemic products were obtained (entry 4). Chiral source **4d**, derived from proline, made the reaction fast, and the opposite enantiomers of **1a** and *syn*-**5a** were obtained with higher enantiomeric excess (entry 5). Reduction with preformed *B*-Me CBS oxazaborolidine **8** was slow (entry 6) compared to that with amino alcohol **4d**. Olefin **9** was used in the reaction with the aim of generating diisopinocampheylborane, but the enantioselectivity of amino alcohol **5a** was very low (entry 9).



Scheme 2.



Scheme 3. Reagents and conditions: (i) BH_3–SMe_2, chiral source, solvent; (ii) Et_3N, EtOH, reflux; (iii) BzCl, Et_3N, rt.

Table 2
Reduction of 2-isoxazoline **1a** with BH_3–SMe_2[a]

Entry	BH_3 (equiv)	Time (h)	Yield (%)				
			1a[b]	**6a**[b]	**2a**[b]	**7a**[c]	**5a**[c]
						(*cis*/*trans* or *syn*/*anti* ratio)[d]	
1	1.0	48	Quant.	Trace	0	—	—
2	1.5	46	41	18	30	14 (43:57)	30 (72:28)

[a] Reaction conditions: (i) A mixture of **1a** (0.6 mmol) and 2 M BH_3–SMe_2 in toluene (0.6–0.9 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature; (ii) MeOH was added, and the mixture was condensed. Next, triethylamine (0.75 mmol) and EtOH (3 mL) were added, and the resulting mixture was refluxed for 2 h; (iii) a solution of the resulting organic materials, benzoyl chloride (1.2 mmol) and triethylamine (1.5 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h.
[b] Determined by ^{1}H NMR spectroscopy of the reaction mixture with anthracene as an internal standard after the reaction step (ii).
[c] Determined by ^{1}H NMR spectroscopy of the isolated compound with anthracene as an internal standard after silica gel column chromatography.
[d] Determined by each yields.

2.2.3. Effects of substituents of 2-isoxazoline

We examined the kinetic resolution of several racemic 2-isoxazolines **1a**–**1f** using 1.0 equiv of **4a** or **4d** and 2.0 equiv of BH_3–SMe_2 (Table 5). Next, *trans*-**1b**, which has a 4-phenyl substituent, was reduced to give **7** in 57% yield with a *cis*/*trans* ratio of 53:47 and with 76% and 71% ee, respectively. Substrate **1b** was recovered in 41% yield with low ee (entry 2). Compound **1c**, which contains a

Table 3
Kinetic resolution of 2-isoxazoline **1a** by asymmetric reduction with (−)-norephedrine (**4a**) and BH_3–SMe_2[a]

Entry	**4a** (equiv)	BH_3 (equiv)	Temp., time (°C, h)	Yield[b] (%)		ee[d] (%) **1a**[e]/ *cis*-**7a**[f]/*trans*-**7a**[g]
				1a	**7a** (*cis*/*trans* ratio)[c]	
1	1.0	2.0	rt, 24	62	31 (65:35)	8/77/78
2[h]	1.0	2.0	rt, 48	29	67 (64:36)	21/65/74
3[h,i]	0.5	1.5	rt, 48	19	73 (64:36)	29/69/75
4	0.5	2.0	rt, 72	0	80 (59:41)	—/60/78
5[j]	1.0	2.5	rt, 46	0	84 (60:40)	—/58/84
6	1.25	2.5	rt, 21	18	53 (63:37)	28/65/78
7	1.0	2.5	0, 72	Quant.	N.r.	—

[a] Reaction conditions: (i) A mixture of **1a** (0.4 mmol), **4a** and 2 M BH_3–SMe_2 in toluene in CH_2Cl_2 (2 mL) was stirred; (ii) MeOH was added, and the mixture was condensed. Next, triethylamine (0.5 mmol) and EtOH (3 mL) were added, and the resulting mixture was refluxed for 2 h; (iii) a solution of the resulting organic materials, benzoyl chloride (1.2 mmol) and triethylamine (1.5 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h.
[b] Determined by ^{1}H NMR spectroscopy of the isolated compound with anthracene as an internal standard after silica gel column chromatography.
[c] Determined by each yields.
[d] Determined by chiral HPLC (Daicel Chiralpak AS-H or Chiralcel OD-H).
[e] Configuration was (*S*).
[f] Configuration was (3*S*,5*R*).
[g] Configuration was (3*S*,5*S*).
[h] 1.0 mmol scale. Isolated yields.
[i] 1,3-Amino alcohol **5a** was obtained in 4% yield.
[j] 0.6 mmol scale.

Table 4
Kinetic resolution of 2-isoxazoline **1a** by asymmetric reduction using various chiral sources and BH_3–SMe_2[a]

Entry	Chiral source	BH_3 (equiv)	Time (h)	Yield[b] (%)		ee[d] (%) **1a**[e]/*cis*-**7a**[f]/*trans*-**7a**[g]
				1a	**7a** (*cis*/*trans* ratio)[c]	
1[h]	**4a**	2.0	48	29	67 (64:36)	21/65/74
2	**4b**	2.0	30	27	55 (63:37)	20/57/68
3	**4c**	2.0	48	Quant.	Trace	—
4	**4c** (1.5 equiv)	3.0	23	12	45 (60:40) [*syn*-**5a**/*anti*-**5a**: 10/5][i]	0/0/0 [*syn*-**5a**[j]/*anti*-**5a**[k] 0/N.d.[l]]
5[m]	**4d**	2.0	16	23	51 (87:13) [*syn*-**5a**/*anti*-**5a**: 17/trace][i]	−51[n]/26/−5[o] [*syn*-**5a**: −90[p]]
6[m]	**8**	1.0	48	57	14 (82:18)[*syn*-**5a**/*anti*-**5a**: 20/trace][i]	−29[n]/−31[q]/−88[o] [*syn*-**5a**: −88[p]]
7[r]	**9** (1.6 equiv)	2.0	120	Quant.	Trace	—
8[s]	**9** (1.6 equiv)	0.75	48(85 °C)	Quant.	Trace	—
9[s]	**9** (6.3 equiv)	3.0	48(85 °C)	0	N.d.[l] [*syn*-**5a**/*anti*-**5a**: N.d.[l]/N.d.[l]][i]	N.d.[l] [*syn*-**5a**[j]/*anti*-**5a**[k]: 2/9]

[a] Reaction conditions: (i) A mixture of **1a** (0.4 mmol), the chiral source, and 2 M BH_3–SMe_2 in toluene in CH_2Cl_2 (2 mL) was stirred; (ii) MeOH was added, and the mixture was condensed. Next, triethylamine (0.5 mmol) and EtOH (3 mL) were added, and the resulting mixture was refluxed for 2 h; (iii) a solution of the resulting organic materials, benzoyl chloride (1.2 mmol) and triethylamine (1.5 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h.
[b] Determined by ^1H NMR spectroscopy of the isolated compound with anthracene as an internal standard after silica gel column chromatography.
[c] Determined by each yields.
[d] Determined by chiral HPLC (Daicel Chiralpak AS-H or Chiralcel OD-H).
[e] Configuration was (*S*).
[f] Configuration was (3*S*,5*R*).
[g] Configuration was (3*S*,5*S*).
[h] 1.0 mmol scale. Isolated yields.
[i] Yields.
[j] Configuration was (1*R*,3*S*).
[k] Configuration was (1*S*,3*S*).
[l] Not determined.
[m] 0.8 mmol scale.
[n] Configuration was (*R*).
[o] Configuration was (3*R*,5*R*).
[p] Configuration was (1*S*,3*R*).
[q] Configuration was (3*R*,5*S*).
[r] In CH_2Cl_2 (1 mL) and THF (1 mL).
[s] In toluene (2 mL).

quaternary carbon at the 4-position, was reduced in 44% yield with the same regioselectivity but with lower enantiomeric excess in the products; however, the recovered **1c** showed moderate selectivity for conversion (entry 3). The reduction of naphthyl-substituted **1d** was sluggish, and *cis*-**7d** was obtained in 66% ee, accompanied by a 42% yield of **1d** with 15% ee, using **4a** as a chiral source, while the opposite stereoisomer of **1d** was recovered in the reaction using **4d** as a chiral source (entries 4 and 5). 3-Methyl-2-isoxazoline **1e** showed low reactivity (entry 6). Compound **1f**, a 4-nitrophenyl derivative of **1a**, showed almost the same reactivity and selectivity as the reaction of **1a** (entry 7).

Table 5
Kinetic resolution of various 2-isoxazolines **1a**–**1f** by asymmetric reduction with 1,2-amino alcohol **4a** or **4d** and BH_3–SMe_2[a]

Entry	Substrate	Chiral source	Time (h)	Yield[b] (%)		ee[d] (%)**1**[e]/*cis*-**7**[f]/*trans*-**7**[g]
				1	**7** (*cis*/*trans* ratio)[c]	
1[h]	**1a**	**4a**	48	29	67 (64:36)	21/65/74
2	*trans*-**1b**	**4a**	30	41	57 (53:47)	7/76/71
3	**1c**	**4a**	30	53	44 (68:32)	17/58/60
4	**1d**	**4a**	45	42	35 (67:33)	15/66/N.d.[l]
5[i]	**1d**	**4d**	30	15[j]	35[j] (91:9)	−63[k]/43/N.d.[l]
6[i]	**1e**	**4a**	30	Quant.	N.r.	—
7	**1f**	**4a**	45	34	56 (63:37)	13/70/71

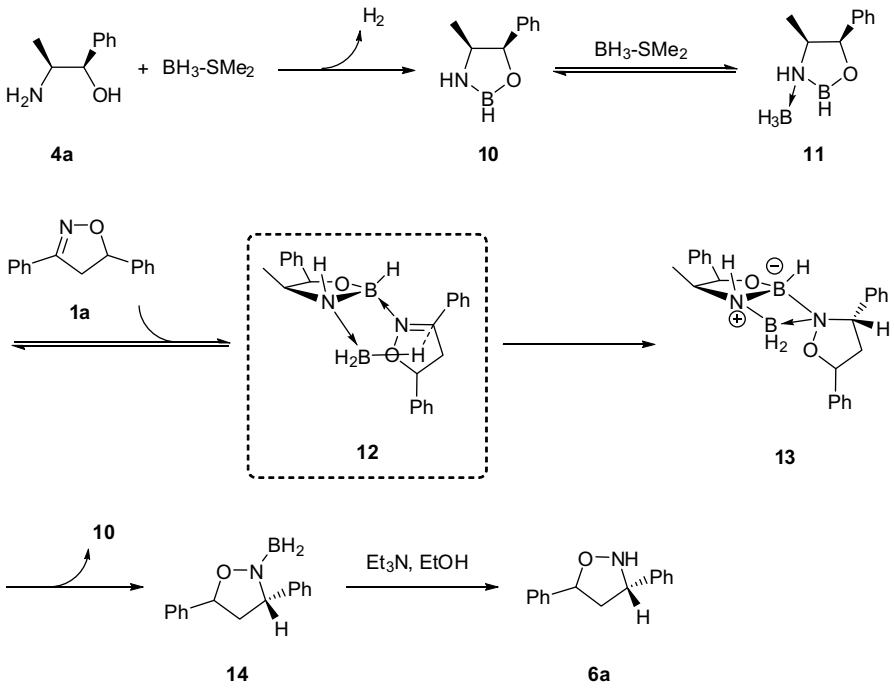
[a] Reaction conditions: (i) A mixture of **1** (0.8 mmol), the chiral source (0.8 mmol) and 2 M BH_3–SMe_2 in toluene (1.6 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature; (ii) MeOH was added, and the mixture was condensed. Next, triethylamine (1.0 mmol) and EtOH (6 mL) were added, and the resulting mixture was refluxed for 2 h; (iii) a solution of the resulting organic materials, benzoyl chloride (1.6 mmol) and triethylamine (2.0 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 2 h.
[b] Isolated yield.
[c] Determined by each yields.
[d] Determined by chiral HPLC (Daicel Chiralpak AS-H, Chiralcel OD-H, Chiralcel OJ-H or Chiralcel OJ-R).
[e] Configuration was (5*S*).
[f] Configuration was (3*S*,5*R*).
[g] Configuration was (3*S*,5*S*).
[h] 1.0 mmol scale.
[i] 0.4 mmol scale.
[j] Determined by ^1H NMR spectroscopy of the isolated compound with anthracene as an internal standard after silica gel column chromatography.
[k] Configuration was (*R*).
[l] Not determined.

2.3. Reaction mechanism

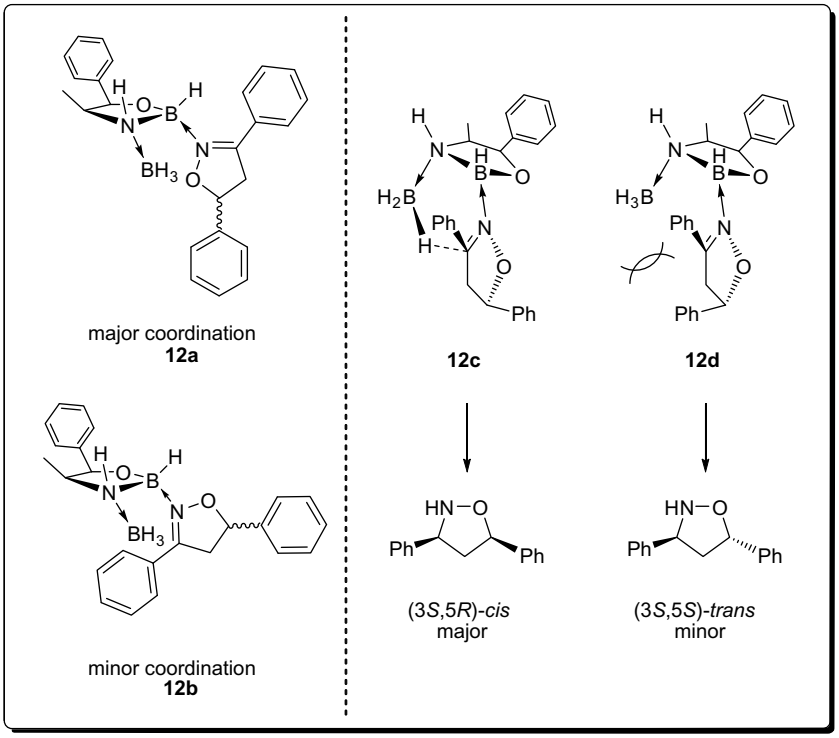
The mechanism for stereoselectivity in the reduction of racemic 2-isoxazolines based on Corey's asymmetric reduction of unsymmetric ketones by optically active oxazaborolidines will be discussed.[6]

As shown in Scheme 4, 1 equiv of BH_3–SMe_2 reacts with 1,2-amino alcohol **4a** to give oxazaborolidine **10**. Another equivalent of BH_3–SMe_2 then reacts with this species to afford the reactive intermediate **11**. Adduct **12** is formed by the reaction of 2-isoxazoline with **11**, followed by the formation of **13** by the addition of the hydride to the C=N double bond in the six-membered transition state. Dissociation of the reduced product **14** from **13** occurs in the final stage. After the reaction, treatment with triethylamine affords the reduction product **6**. In this mechanism, the stereochemistry-determining step is considered to be the pathway from **12** to **13**. Thus, the origin of stereoselectivity is suggested to be as shown in Scheme 5.

The nitrogen atom of oxazaborolidine **10** coordinates to BH_3 to give **11**, so that BH_3 occupies the opposite site to the substituents at the 4- and 5-position of the oxazaborolidine ring. The 2-isoxazoline then coordinates to the Lewis-acidic boron center of intermediate **11**, minimizing steric hindrance (**12a** > **12b**, **12c** > **12d**). Based



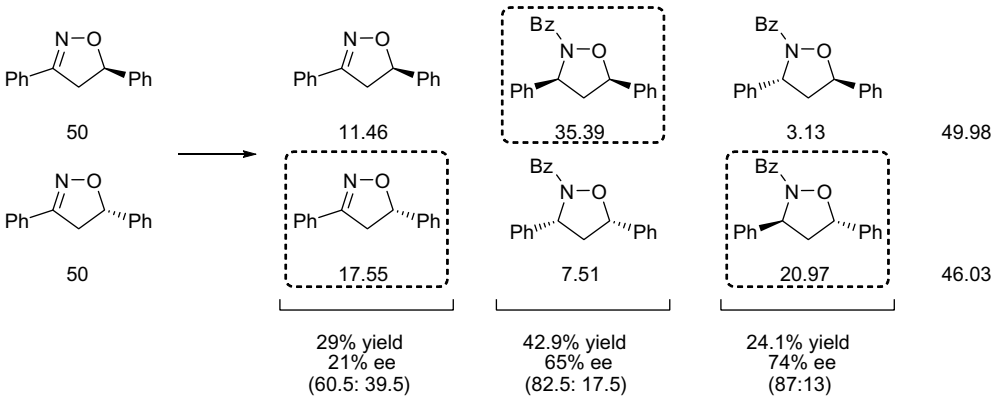
Scheme 4.



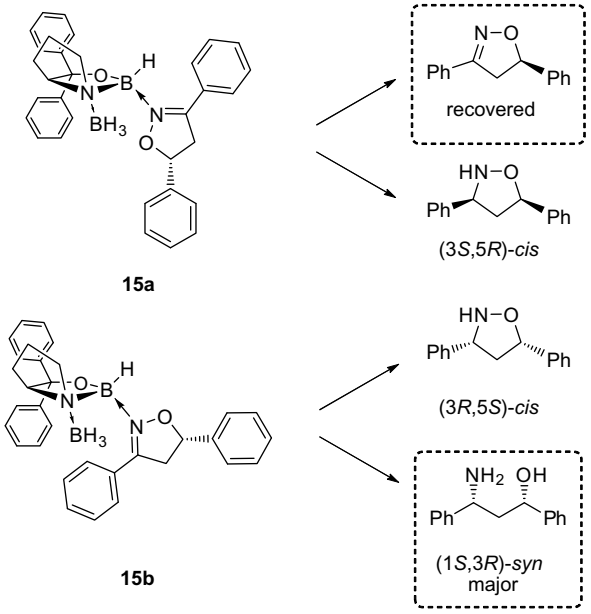
Scheme 5.

on this hypothesis, the *cis*-isomer should be produced in larger amounts than the *trans*-isomer. Scheme 6 shows the results of the reaction of **1a** in terms of the ratios of the key intermediates and products (Table 3, entry 2). The deductions made here are very close to the experimental results.

In contrast, when **4d** was used, the opposite enantiomers were recovered (Table 4, entry 5). Based on these results, intermediate **12b**, which seems to be less favored when **4a** is used, was concluded to be the main intermediate when **4d** is used (Scheme 7, **15b** > **15a**). Although **15b** seems to be subjected to greater steric hindrance than **15a**, the electronic effect and the stacking effect of the phenyl rings increase the stability of the intermediate. In this case, we assume that the kinetic resolution of *cis*-**6a** resulted in the production of *syn*-**2a** with higher enantioselectivity.



Scheme 6.



Scheme 7.

In the case of using excess BH_3–THF, 1,3-amino alcohols were obtained (Table 1). Although boron species derived from 1,3-amino alcohols seem to catalyze the asymmetric reduction, we considered that these species have little effect in the presence of an excess amount of chiral 1,2-amino alcohol. Under these conditions, lower selectivities were due to excess BH_3–THF rather than various boron species.

3. Conclusion

In conclusion, we have reported a new synthetic approach to optically active 2-isoxazolines, isoxazolidines, and 1,3-amino alcohols involving kinetic resolution of racemic 2-isoxazolines with borane in the presence of chiral 1,2-amino alcohols.

Using excess BH_3–THF with (−)-norephedrine **4a**, 1,3-amino alcohols were obtained with moderate enantiomeric excess. Furthermore, isoxazolidines were obtained as the main products with moderate to good ee, when 2.0 equiv of BH_3–SMe_2 was employed for asymmetric reduction. In both cases, the recovered 2-isoxazolines were obtained with modest ee. Using a prolinol derivative as a chiral source, however, the opposite enantiomers were recovered.

We propose that this kinetic resolution by asymmetric reduction is a useful method for the synthesis of optically active 2-isoxazolines and isoxazolidines, bearing no functional groups interacting with metal catalysts, which are difficult to obtain using previously reported reactions such as asymmetric 1,3-dipolar cycloaddition reactions and kinetic decomposition reactions using a palladium catalyst.

4. Experimental

4.1. General

Nuclear magnetic resonance spectra were measured using a JEOL JNM A-400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) and/or Varian Mercury Plus 300-4N spectrometers with tetramethylsilane as an internal standard for ^{1}H NMR and $CDCl_3$ at 77 ppm for ^{13}C NMR. IR spectra were measured on a Shimadzu FTIR-8400 spectrometer. Mass spectral (GC–MS) data were recorded on a Shimadzu QP5000 instrument. High resolution mass spectra (FAB) were measured using a JEOL JMS-700 with *meta*-nitrobenzyl alcohol as the matrix and PEG-200 as the calibration standard. The enantiomeric excesses were determined by HPLC analysis using a HITACHI series L-7100 HPLC using a Daicel Chiralcel OD-H, OJ-H, or Chiralpak AS, AS-H column or Shimadzu LC-10A using a Daicel Chiralcel OJ-R column. Optical rotations were measured using a Horiba SEPA-200 spectrometer.

All reactions were performed under an argon atmosphere using standard Schlenk techniques. All solvents were dried by standard methods and were distilled under argon.[7] Commercially available compounds were used without further purification.

4.2. Preparation of 2-isoxazolines[8]

This is a typical procedure for the preparation of 2-isoxazoline derivatives. In a 300-mL three-necked flask, to a homogeneous solution of benzaldehyde oxime (1.21 g, 10 mmol) and styrene (5.21 g, 50 mmol) in dichloromethane (30 mL) were added acetone (60 mL), distilled water (45 mL), sodium hydrogen carbonate (10 g), and benzyltriethylammonium chloride (0.46 g, 2.0 mmol). This mixture was stirred at room temperature, and to this was added potassium peroxymonosulfate powder (Oxone®) (9.22 g, 15 mmol) over 30 min. After stirring for 22 h, 1 M NaOH aq was added, and the organic materials were extracted with diethyl ether and dichloromethane. The organic layer was dried over sodium sulfate and then concentrated. The resulting materials were isolated by silica gel column chromatography (hexane/ethyl acetate = 7:1) and were purified by recrystallization from hexane and ethyl acetate to give 3,5-diphenyl-2-isoxazoline **1a**.

4.2.1. 3,5-Diphenyl-2-isoxazoline 1a[9]

1.19 g, 53% yield, colorless crystal, mp 74–75 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.35 (dd, J = 8.1, 16.5 Hz, 1H, 4-*H*H), 3.79 (dd, J = 10.8, 16.5 Hz, 1H, 4-H*H*), 5.74 (dd, J = 8.1, 10.8 Hz, 1 H, 5-H), 7.29–7.43 (m, 8H, Ar-H), 7.66–7.71 (m, 2H, Ar-H).

4.2.2. 3,*r*-4,*t*-5-Triphenyl-2-isoxazoline *trans*-1b[10]

trans-Stilbene (7.21 g, 40 mmol) was used, and recrystallization was performed by use of hexane and acetone. 1.74 g, 58% yield, colorless crystals, mp 140–143 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 4.68 (d, J = 5.4 Hz, 1H, 4-H), 5.52 (d, J = 5.4 Hz, 1H, 5-H), 7.26–7.38 (m, 13H, Ar-H), 7.57–7.60 (m, 2H, Ar-H).

4.2.3. 3,5-Diphenyl-5-methyl-2-isoxazoline 1c[9]

α-Methylstylene (4.73 g, 40 mmol) was used, and recrystallization was carried out from hexane and ethyl acetate. 1.03 g, 43% yield, white solid, mp 72–76 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.81 (s, 3H, 5-Me), 3.45 (d, J = 16.5 Hz, 1H, 4-*H*H), 3.53 (d, J = 16.5 Hz, 1H, 4-H*H*), 7.26–7.40 (m, 6H, Ar-H), 7.46–7.50 (m, 2H, Ar-H), 7.63–7.66 (m, 2H, Ar-H).

4.2.4. 5-(2-Naphthyl)-3-phenyl-2-isoxazoline 1d

2-Vinylnaphthalene (1.05 g, 6.8 mmol) was used, and recrystallization was done from dichloromethane and ethanol. 666 mg, 74% yield, colorless crystals, mp 130–133 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.40 (dd, J = 8.1, 16.8 Hz, 1H, 4-*H*H), 3.82 (dd, J = 10.8, 16.8 Hz, 1H, 4-H*H*), 5.89 (dd, J = 8.1, 10.8 Hz, 1H, 5-H), 7.39–7.48 (m, 6H, Ar-H), 7.68–7.71 (m, 2H, Ar-H), 7.81–7.86 (m, 4H, Ar-H). ^{13}C NMR: δ (ppm) 43.6, 83.0, 123.7, 125.2, 126.5, 126.6, 127.0, 127.9, 128.2, 129.0, 129.1, 129.7, 130.4, 133.4, 138.3, 156.3. IR (KBr): 3026, 2866, 1601, 1506, 1447, 1358, 968, 926, 893, 864, 827, 758, 748, 689 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{19}H_{16}NO$ [M+H]$^+$ 274.1232, found 274.1215.

4.2.5. 3-Methyl-5-phenyl-2-isoxazoline 1e[11]

Acetaldehyde oxime (0.20 g, 3.3 mmol) was used. 186 mg, 35% yield, light yellow oily materials. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.01 (s, 3H, 3-Me), 2.89 (dd, J = 8.1, 16.8 Hz, 1H, 4-*H*H), 3.34 (dd, J = 10.8, 16.8 Hz, 1H, 4-H*H*), 5.53 (dd, J = 8.1, 10.8 Hz, 1H, 5-H), 7.25–7.37 (m, 5H, Ar-H).

4.2.6. 3-(4-Nitrophenyl)-5-phenyl-2-isoxazoline 1f[12]

p-Nitrobenzaldehyde oxime (0.55 g, 3.3 mmol) was used, and recrystallization was done from hexane and ethyl acetate. 247 mg, 28% yield, light yellow crystals, mp 126–129 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.37 (dd, J = 8.4, 16.8 Hz, 1H, 4-*H*H), 3.81 (dd, J = 11.1, 16.8 Hz, 1H, 4-H*H*), 5.83 (dd, J = 8.4, 11.1 Hz, 1H, 5-H), 7.32–7.40 (m, 5H, Ar-H), 7.83–7.87 (m, 2H, Ar-H), 8.24–8.29 (m, 2H, Ar-H).

4.3. Asymmetric reduction of racemic 3,5-diphenyl-2-isoxazoline (1a): preparation of 1,3-amino alcohol derivatives 3

4.3.1. 1,3-Diphenyl-3-tosylamino-1-propanols *syn*-3a and *anti*-3a

Under an argon atmosphere in a 80-mL Schlenk tube, 1 M BH_3–THF in THF (0.6 mL, 0.6 mmol) was added by syringe to a solution of (−)-norephedrine **4a** (90.7 mg, 0.6 mmol) in dichloromethane (1.5 mL) at 0 °C, and the resulting mixture was stirred for 30 min at the same temperature. 2-Isoxazoline **1a** (134 mg, 0.6 mmol) was then introduced, and BH_3–THF (1.8 mL, 1.8 mmol) was added dropwise via syringe over 3 min. After stirring for 24 h at room temperature, 10% HCl aq was added, and the mixture was stirred for 30 min. 1 M NaOH aq was used to basify, and the organic materials were extracted with dichloromethane. The organic layer was dried over sodium sulfate and was concentrated in a 100-mL round-bottomed flask. The obtained materials were allowed to react with *p*-toluenesulfonyl chloride (343 mg, 1.8 mmol) in dichloromethane (4 mL) in the presence of triethylamine (202 mg, 2.0 mmol) in an ice bath. After the reaction, 1 M NaOH aq and dichloromethane were added to the mixture, and the organic layer was separated, dried over sodium sulfate, concentrated, and then purified by column chromatography. The yields were determined by ^{1}H NMR analysis of a mixture of the isolated product and anthracene (10.7 mg, 0.06 mmol) (Table 1, entry 2).

(1*R*,3*S*)-*syn*-**3a**: 21% yield, colorless crystals (from hexane/dichloromethane), mp 108–110 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.90 (ddd, J = 3.3, 5.4, 14.4 Hz, 1H, –CH–C*H*H–CH–), 2.22 (dt, J = 9.0, 14.4 Hz, 1H, –CH–CH*H*–CH–), 2.34 (s, 3H, –Ph–CH_3), 2.62 (br s, 1H, –O*H*), 4.51 (dt, J = 5.4, 9.0 Hz, 1H, –C*H*–NH–), 4.58 (br d, J = 7.5 Hz, 1H, –C*H*–OH), 6.18 (d, J = 5.4 Hz, 1H, –N*H*–), 7.04–7.28 (m, 12H, Ar-H), 7.49 (d, J = 8.4 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 21.9, 46.7, 57.9, 73.3, 125.9, 126.9, 127.4, 127.6, 128.1, 128.6, 128.8, 129.4, 137.5, 141.0, 143.1, 144.1. IR (KBr): 3479, 3271, 3061, 3030, 2920, 1599, 1495, 1456, 1429, 1323, 1157, 1092, 1065, 916, 814, 758, 700, 667, 546 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{24}NO_3S$ [M+H]$^+$ 382.1477, found 382.1473. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol/ethanol = 90:9:1, UV 254 nm, 0.7 mL/min): t_R = 29.4 min (minor), t_R = 54.3 min (major); 50% ee.

(1*S*,3*S*)-*anti*-**3a**: 7% yield, colorless crystals (from hexane/dichloromethane), mp 127–130 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.01 (t, J = 6.6, 2H, –CH–CH_2–CH–), 2.35 (s, 3H, –Ph–CH_3), 2.77 (d, J = 3.9, 1H, –O*H*), 4.59 (dt, J = 6.6, 8.4 Hz, 1H, –C*H*–NH–), 4.83 (dt, J = 3.9, 6.6 Hz, 1H, –C*H*–OH), 6.04 (d, J = 8.4 Hz, 1H, –N*H*–), 7.00–7.29 (m, 12H, Ar-H), 7.58 (d, J = 8.4 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 21.9, 46.2, 55.7, 71.0, 125.9, 126.5, 127.4, 127.5, 127.8, 128.7, 129.6, 137.6, 140.7, 143.3, 143.9. IR (KBr): 3483, 3275, 3063, 3028, 2920, 1601, 1493, 1454, 1420, 1319, 1157, 1092, 1061, 972, 814, 752, 702, 667, 567, 548 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{14}H_{14}NO_2S$ [M+H−$C_8H_{10}O$]$^+$ 260.0745, found 260.0727. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol/ethanol = 90:9:1, UV 254 nm, 0.5 mL/min): t_R = 32.8 min (minor), t_R = 42.4 min (major); 67% ee.

4.4. Asymmetric reduction of racemic 2-isoxazolines 1: preparation of isoxazolidine derivatives 7

4.4.1. *N*-Benzoyl-3,5-diphenylisoxazolidines *cis*-7a and *trans*-7a

This is a typical procedure for the preparation of isoxazolidine derivatives **7**. Under an argon atmosphere, (−)-norephedrine (**4a**, 151.2 mg, 1.0 mmol) and dichloromethane (2.5 mL) were added to an 80-mL Schlenk tube. The mixture was cooled in an ice bath, and BH_3–SMe_2 (2 M in toluene, 0.5 mL, 1.0 mmol) was added dropwise. After stirring for 30 min at room temperature, BH_3–SMe_2 (0.5 mL, 1.0 mmol) was added via syringe to the mixture in an ice bath, and then 2-isoxazoline **1a** (223.3 mg, 1.0 mmol) and dichloromethane (2.5 mL) were added. The mixture was allowed to react at room temperature for 48 h. Methanol (20 mL) was then added to stop the reaction. The solution was concentrated by an evaporator. Methanol was then added to the concentrate, and the mixture was concentrated again. To the residue were added triethylamine (124 mg, 1.2 mmol) and ethanol (6 mL), and the mixture was refluxed for 2 h. The mixture was concentrated, triethylamine (253 mg, 2.5 mmol), dichloromethane (4 mL), and benzoyl chloride (281 mg, 2.0 mmol) were added, and the mixture was allowed to react at room temperature for 2 h. After the reaction, 1 M NaOH aq and dichloromethane were added, and the organic materials were extracted. The organic layer was dried over sodium sulfate, concentrated, and then separated by silica gel column chromatography (hexane/ethyl acetate = 10:1) to give the products.

(3*S*,5*R*)-*cis*-**7a**: yield 43%, colorless viscous oil. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.37–2.47 (m, 1H, 4-*H*H), 3.15–3.24 (m, 1H, 4-H*H*), 4.96

(dd, J = 6.0, 10.5 Hz, 1H, 5-H), 5.78 (t, J = 7.8 Hz, 1H, 3-H), 7.25–7.49 (m, 13H, Ar-H), 7.88 (d, J = 7.5 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 46.2, 62.0, 84.5, 126.3, 127.1, 127.7, 128.1, 128.9, 129.0, 129.1, 129.8, 131.7, 133.2, 136.4, 142.1, 171.1. IR (neat): 3063, 3032, 1647, 1578, 1493, 1450, 1350, 1180, 1111, 1072, 1026, 907, 791, 752, 698, 667 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{20}NO_2$ [M+H]$^+$ 330.1494, found 330.1504. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.5 mL/min): t_R = 27.4 min (major), t_R = 32.1 min (minor); 65% ee. $[\alpha]_D^{20} = -4.5$ (c 7.08, $CHCl_3$).

(3*S*,5*S*)-*trans*-**7a**: yield 24%, colorless viscous oil. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.71 (ddd, J = 4.5, 6.3, 12.0 Hz, 1H, 4-*H*H), 2.93 (ddd, J = 6.3, 7.8, 12.0 Hz, 1H, 4-H*H*), 5.39 (t, J = 6.3 Hz, 1H, 5-H), 5.75 (dd, J = 4.5, 7.8 Hz, 1H, 3-H), 7.16–7.47 (m, 13H, Ar-H), 7.70 (d, J = 7.2 Hz, 2H, Ar-H) ppm. ^{13}C NMR: δ (ppm) 44.0, 61.2, 82.1, 126.2, 126.7, 127.9, 128.0, 128.7, 128.8, 129.1, 129.3, 131.3, 133.9, 137.9, 140.9, 169.5. IR (neat): 3059, 3032, 1647, 1578, 1493, 1450, 1354, 1076, 1026, 988, 910, 787, 752, 698, 664 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{20}NO_2$ [M+H]$^+$ 330.1494, found 330.1485. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.5 mL/min): t_R = 31.7 min (major), t_R = 36.9 min (minor); 74% ee. $[\alpha]_D^{20} = -80.25$ (c 3.95, $CHCl_3$).

(*S*)-**1a**: recovered 29%, HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 80:20, UV 254 nm, 0.5 mL/min): t_R = 23.8 min (minor), t_R = 33.8 min (major); 21% ee. $[\alpha]_D^{20} = +52.1$ (c 3.245, $CHCl_3$).

4.4.2. *N*-Benzoyl-*r*-3,*t*-4,*c*-5-triphenylisoxazolidine *cis*-7b, *N*-benzoyl-*r*-3,*c*-4,*t*-5-triphenylisoxazolidine *trans*-7b

The reaction was performed with the same procedure for **1a** using 2-isoxazoline *trans*-**1b** (239.5 mg, 0.8 mmol), (−)-norephedrine (**4a**, 121.0 mg, 0.8 mmol), BH_3–SMe_2 (2 M in toluene, 0.8 mL, 1.6 mmol), and dichloromethane (4.0 mL) at room temperature for 30 h. Products were isolated by silica gel column chromatography (hexane/ethyl acetate = 7:1).

(3*S*,4*R*,5*R*)-*cis*-**7b**: yield 30%; colorless crystals (from hexane/ethyl acetate); mp 133–136 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 3.71 (dd, J = 7.2, 9.9 Hz, 1H, 4-H), 5.03 (d, J = 9.9 Hz, 1H, 5-H), 5.84 (d, J = 7.2 Hz, 1H, 3-H), 7.13–7.49 (m, 18H, Ar-H), 7.95 (d, J = 7.2 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 66.8, 70.2, 91.2, 126.0, 126.9, 127.8, 128.1, 128.2, 128.3, 128.7, 129.0, 129.1, 129.3, 129.8, 131.9, 133.0, 135.2, 136.5, 141.2, 171.0. IR (KBr): 3059, 3032, 1643, 1578, 1493, 1450, 1385, 1346, 1180, 1076, 1026, 988, 918, 752, 698, 667 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{28}H_{24}NO_2$ [M+H]$^+$ 406.1807, found 406.1794. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 99:1, UV 220 nm, 0.5 mL/min): t_R = 36.2 min (major), t_R = 41.8 min (minor); 76% ee. $[\alpha]_D^{20} = -5.3$ (c 4.535, $CHCl_3$).

(3*S*,4*S*,5*S*)-*trans*-**7b**: yield 27%; colorless viscous oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 4.03 (dd, J = 7.2, 9.9 Hz, 1H, 4-H), 5.60 (d, J = 9.9 Hz, 1H, 5-H), 5.88 (br d, J = 7.2 Hz, 1H, 3-H), 6.74–6.76 (m, 2H, Ar-H), 7.04–7.25 (m, 13H, Ar-H), 7.36–7.49 (m, 3H, Ar-H), 7.85 (d, J = 6.9 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 60.5, 67.1, 85.1, 126.6, 127.5, 127.8, 127.9, 128.2, 128.3, 128.4, 128.69, 128.74, 129.3, 129.5, 131.6, 133.6, 133.9, 136.5, 137.2, 168.8. IR (neat): 3063, 3032, 1634, 1576, 1495, 1454, 1337, 1258, 1180, 1076, 1001, 910, 694, 664 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{28}H_{24}NO_2$ [M+H]$^+$ 406.1807, found 406.1778. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.5 mL/min): t_R = 16.4 min (minor), t_R = 25.9 min (major); 71% ee. $[\alpha]_D^{20} = +86.9$ (c 3.705, $CHCl_3$).

(4*S*,5*S*)-*trans*-**1b**: recovered yield 41%, HPLC (Daicel Chiralcel OJ-H, hexane/2-propanol = 90:10, UV 220 nm, 0.7 mL/min): t_R = 17.6 min (minor), t_R = 29.0 min (major); 7% ee. $[\alpha]_D^{20} = +34.8$ (c 4.855, $CHCl_3$).

4.4.3. *N*-Benzoyl-3,5-diphenyl-5-methylisoxazolidines *cis*-7c and *trans*-7c

The reaction was performed via the same method for **1a** using 2-isoxazoline **1c** (189.8 mg, 0.8 mmol), (−)-norephedrine (**4a**, 121.0 mg, 0.8 mmol), BH_3–SMe_2 (2 M in toluene, 0.8 mL, 1.6 mmol), dichloromethane (4.0 mL) at room temperature for 30 h. Reaction products were isolated by silica gel column chromatography (hexane/ethyl acetate = 7:1).

(3*S*,5*R*)-*cis*-**7c**: yield 30%, colorless viscous oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.42 (s, 3H, 5-Me), 2.58 (dd, J = 8.1, 12.0 Hz, 1H, 4-*H*H), 3.03 (dd, J = 8.7, 12.0 Hz, 1H, 4-H*H*), 5.82 (dd, J = 8.1, 8.7 Hz, 1H, 3-H), 7.21–7.48 (m, 13H, Ar-H), 7.94 (d, J = 7.5 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 25.5, 50.3, 61.6, 88.3, 125.1, 126.4, 127.7, 127.98, 128.02, 128.7, 129.0, 129.8, 131.4, 133.7, 141.6, 142.6, 171.0. IR (neat): 3061, 3030, 2972, 1645, 1601, 1578, 1495, 1447, 1360, 1317, 1157, 1101, 1072, 1030, 914, 762, 696, 667 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{23}H_{22}NO_2$ [M+H]$^+$ 344.1651, found 344.1637. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 95:5, UV 220 nm, 0.5 mL/min): t_R = 23.4 min (major), t_R = 26.9 min (minor); 58% ee. $[\alpha]_D^{20} = -5.3$ (c 4.375, $CHCl_3$).

(3*S*,5*S*)-*trans*-**7c**: yield 14%, colorless viscous oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.60 (s, 3H, 5-Me), 2.48 (dd, J = 9.3, 12.6 Hz, 1H, 4-*H*H), 3.40 (dd, J = 7.8, 12.6 Hz, 1H, 4-H*H*), 5.28 (m, 1H, 3-H), 7.07–7.45 (m, 13H, Ar-H), 7.70 (br s, 2H, Ar-H). ^{13}C NMR: δ (ppm) 27.9, 49.0, 61.7, 88.8, 125.5, 126.4, 127.7, 127.9, 128.0, 128.7, 128.9, 129.5, 131.2, 134.2, 141.3, 142.0, 169.6. IR (neat): 3061, 3030, 2980, 1643, 1603, 1578, 1495, 1448, 1379, 1354, 1275, 1178, 1096, 1070, 1028, 910, 764, 735, 700, 667 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{23}H_{22}NO_2$ [M+H]$^+$ 344.1651, found 344.1637. HPLC (Daicel Chiralcel OD-H, hexane:2-propanol = 95:5, UV 220 nm, 0.5 mL/min): t_R = 27.4 min (major), t_R = 43.3 min (minor); 60% ee. $[\alpha]_D^{20} = -75.0$ (c 1.92, $CHCl_3$).

(*S*)-**1c**: recovered yield 53%, HPLC (Daicel Chiralpak AS-H, hexane/2-propanol = 95:5, UV 254 nm, 0.3 mL/min): t_R = 27.9 min (minor), t_R = 33.7 min (major); 17% ee. $[\alpha]_D^{20} = +10.0$ (c 5.51, $CHCl_3$).

4.4.4. *N*-Benzoyl-5-(2-naphthyl)-3-phenylisoxazolidines *cis*-7d and *trans*-7d

The reaction was performed via the same procedure for **1a** using 2-isoxazoline **1d** (218.7 mg, 0.8 mmol), (−)-norephedrine **4a** (121.0 mg, 0.8 mmol), BH_3–SMe_2 (2 M in toluene, 0.8 mL, 1.6 mmol), dichloromethane (4.0 mL) at room temperature for 45 h. Products were isolated by silica gel column chromatography (hexane/ethyl acetate = 7:1).

(3*S*,5*R*)-*cis*-**7d**: yield 23%, colorless viscous oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.53 (ddd, J = 7.2, 10.5, 12.6 Hz, 1H, 4-*H*H), 3.26 (ddd, J = 6.0, 8.7, 12.6 Hz, 1H, 4-H*H*), 5.13 (dd, J = 6.0, 10.5 Hz, 1H, 5-H), 5.84 (dd, J = 7.2, 8.7 Hz, 1H, 3-H), 7.27–7.53 (m, 11H, Ar-H), 7.75–7.81 (m, 4H, Ar-H), 7.91 (d, J = 7.5 Hz, 2H, Ar-H). ^{13}C NMR: δ (ppm) 46.2, 62.1, 84.6, 124.3, 126.4, 126.68, 126.71, 126.8, 127.8, 128.0, 128.1, 128.2, 128.8, 129.1, 129.8, 131.7, 133.15, 133.19, 133.6, 133.7, 142.0, 171.1. IR (KBr): 3028, 1645, 1601, 1576, 1495, 1448, 1333, 1178, 1018, 910, 858, 820, 789, 698, 667 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{26}H_{22}NO_2$ [M+H]$^+$ 380.1651, found 380.1631. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 95:5, UV 220 nm, 0.5 mL/min): t_R = 43.7 min (major), t_R = 55.7 min (minor); 66% ee. $[\alpha]_D^{20} = +21.4$ (c 3.555, $CHCl_3$).

(3*S*,5*S*)-*trans*-**7d**: yield 12%, colorless crystals (from hexane/dichloromethane), mp 101–104 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.80 (ddd, J = 4.8, 6.3, 12.6 Hz, 1H, 4-*H*H), 3.04 (ddd, J = 6.3, 8.1, 12.6 Hz, 1H, 4-H*H*), 5.56 (t, J = 6.3 Hz, 1H, 5-H), 5.79 (dd, J = 4.8, 8.1 Hz, 1H, 3-H), 7.22–7.78 (m, 17H, Ar-H). ^{13}C NMR: δ (ppm) 44.0, 61.1, 82.3, 124.2, 125.7, 126.3, 126.6, 127.8, 127.9, 128.0, 128.3, 128.8, 129.1, 129.3, 131.4, 133.1, 133.3, 133.9, 135.3, 140.9, 169.8. IR (KBr): 3036, 1634, 1599, 1578, 1495, 1450, 1352, 1244, 1090, 1024, 905, 847, 797, 748, 700, 669 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{26}H_{22}NO_2$ [M+H]$^+$ 380.1651, found 380.1643. $[\alpha]_D^{20} = -89.5$ (c 1.755, $CHCl_3$).

(*S*)-**1d**: recovered yield 42%, HPLC (Daicel Chiralcel OJ-R, methanol/acetonitrile = 90:10, UV 254 nm, 0.1 mL/min): t_R = 64.4 min

(minor), t_R = 76.8 min (major); 15% ee. $[\alpha]_D^{20} = +40.3$ (*c* 4.07, $CHCl_3$).

4.4.5. *N*-Benzoyl-3-(4-nitrophenyl)-5-phenylisoxazolidines *cis*-7f and *trans*-7f

The reaction was performed via the same method for **1a** using 2-isoxazoline **1f** (214.6 mg, 0.8 mmol), (−)-norephedrine (**4a**, 121.0 mg, 0.8 mmol), BH_3-SMe_2 (2 M in toluene, 0.8 mL, 1.6 mmol), and dichloromethane (4.0 mL) at room temperature for 45 h. Products were isolated by silica gel column chromatography (hexane/ethyl acetate = 7:1).

(3*S*,5*R*)-*cis*-**7f**: yield 35%, light yellow crystals (from hexane/dichloromethane), mp 110–113 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.39 (ddd, *J* = 7.5, 10.5, 12.3 Hz, 1H, 4-*H*H), 3.29 (ddd, *J* = 6.0, 9.0, 12.3 Hz, 1H, 4-H*H*), 5.01 (dd, *J* = 6.0, 10.5 Hz, 1H, 5-H), 5.92 (dd, *J* = 7.5, 9.0 Hz, 1H, 3-H), 7.28–7.52 (m, 8H, Ar-H), 7.63–7.66 (m, 2H, Ar-H), 7.90–7.93 (m, 2H, Ar-H), 8.23–8.25 (m, 2H, Ar-H). ^{13}C NMR: δ (ppm) 45.8, 61.3, 84.5, 124.4, 126.9, 127.2, 128.2, 129.0, 129.3, 129.9, 132.1, 132.4, 135.8, 147.5, 149.2, 171.4. IR (KBr): 3034, 1647, 1601, 1520, 1493, 1448, 1346, 1109, 1013, 905, 854, 750, 696 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{19}N_2O_4$ [M+H]$^+$ 375.1345, found 375.1321. HPLC (Daicel Chiralcel OJ-R, methanol, UV 254 nm, 0.25 mL/min): t_R = 20.0 min (major), t_R = 39.1 min (minor); 70% ee. $[\alpha]_D^{20} = +5.8$ (*c* 4.83, $CHCl_3$).

(3*S*,5*S*)-*trans*-**7f**: yield 21%, light yellow solid (from hexane/dichloromethane), mp 158–164 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.71 (ddd, *J* = 5.7, 6.9, 12.6 Hz, 1H, 4-*H*H), 3.09 (ddd, *J* = 5.1, 8.4, 12.6 Hz, 1H, 4-H*H*), 5.43 (dd, *J* = 5.1, 6.9 Hz, 1H, 5-H), 5.82 (dd, *J* = 5.7, 8.4 Hz, 1H, 3-H), 7.12–7.47 (m, 8H, Ar-H), 7.64 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.70–7.73 (m, 2H, Ar-H), 8.22–8.27 (m, 2H, Ar-H). ^{13}C NMR: δ (ppm) 43.2, 60.4, 82.4, 124.4, 126.6, 127.3, 128.0, 128.90, 128.92, 129.4, 131.7, 133.1, 137.1, 147.6, 148.4, 170.3. IR (KBr): 3061, 1639, 1601, 1516, 1493, 1448, 1348, 1109, 1016, 881, 854, 745, 692 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{19}N_2O_4$ [M+H]$^+$ 375.1345, found 375.1326. HPLC (Daicel Chiralcel OJ-R, methanol, UV 254 nm, 0.2 mL/min): t_R = 26.1 min (major), t_R = 33.8 min (minor); 71% ee. $[\alpha]_D^{20} = -60.2$ (*c* 1.795, $CHCl_3$).

(*S*)-**1f**: recovered yield 34%, HPLC (Daicel Chiralcel OJ-R, methanol, UV 254 nm, 0.5 mL/min): t_R = 16.5 min (minor), t_R = 27.2 min (major); 13% ee. $[\alpha]_D^{20} = +36.1$ (*c* 2.935, $CHCl_3$).

4.5. Determination of absolute configuration of 1a by conversion to (*S*)-3-hydroxy-1,3-diphenyl-1-propanone[13]

Raney-Ni for hydrogenation was prepared as follows. To a test tube were added 50% Ni–Al alloy (0.18 g), NaOH (0.23 g), and distilled water (5 mL), and the mixture was stirred at 60 °C for 1 h. After removal of the supernatant, the residue was washed three times with distilled water (4 mL) and three times with ethanol (4 mL). Ethanol (1 mL) was then added to the residue, and the mixture was used as a catalyst.

To a 30-mL three-neckeded reaction vessel were added the recovered 2-isoxazoline **1a** (112 mg, 0.5 mmol, 20% ee) and a mixture of methanol and distilled water (14:1, 7.5 mL). To this mixture were added Raney-Ni, prepared as above, and aluminum trichloride (265 mg, 2.0 mmol). The solution was purged using hydrogen gas bubbled from a balloon ten times, and then stirred for 17 h. Solid materials were removed through a Celite pad, and 1 M NaOH aq and diethyl ether were added to the filtrate. The organic layer was separated, dried over sodium sulfate, and was concentrated. The product was isolated by column chromatography (hexane/ethyl acetate = 3:2).

(*S*)-3-Hydroxy-1,3-diphenyl-1-propanone: 18 mg, yield 16%, ^{1}H NMR ($CDCl_3$): δ (ppm) 3.37 (d, *J* = 6.3 Hz, 2H, –CH_2–), 3.58 (br s, 1H, –OH), 5.34 (t, *J* = 6.3 Hz, 1H, –C*H*–OH), 7.29–7.60 (m, 8H, Ar-H), 7.93–7.96 (m, 2H, Ar-H). HPLC (Daicel Chiralpak AS, hexane/ethanol = 94:6, UV 210 nm, 1.0 mL/min): t_R = 9.7 min (major), t_R = 11.1 min (minor); 18% ee.

The absolute configuration of 3-hydroxy-1,3-diphenyl-1-propanone was determined as (*S*) by comparison with the literature.[14] This indicates that the absolute configuration of 2-isoxazoline **1a** should be (*S*). Based on this result, the absolute configurations of **1b**–**1d** and **1f** were concluded to be (5*S*).

4.6. Determination of the regioselectivities of 1,3-amino alcohols 3a

Under argon, into a 20-mL Schlenk tube were introduced $LiAlH_4$ (21.3 mg, 0.56 mmol) and diethyl ether (3.0 mL). To this mixture was added 2-isoxazoline **1a** (89.3 mg, 0.4 mmol) at −15 °C with stirring, and the mixture was stirred at room temperature for 15 h. Excess $LiAlH_4$ was decomposed by the addition of methanol. After the evolution of gas had ceased, 1 M NaOH aq, followed by dichloromethane, was added to the mixture. The resulting solution was stirred for 2 h. A white solid was removed by a Celite pad, and dichloromethane was added to the filtrate. The organic layer was separated, dried over sodium sulfate, and was concentrated. To the residue were added dichloromethane (3.0 mL), triethylamine (81 mg, 0.8 mmol), and *p*-toluenesulfonyl chloride (76 mg, 0.4 mmol) at 0 °C, and the mixture was stirred for 1.5 h at room temperature. To the reaction mixture were added 1 M NaOH aq. and dichloromethane, and the organic layer was extracted, dried over sodium sulfate, and concentrated. ^{1}H NMR analysis of the mixture indicated that two stereoisomers *syn*-**3a** and *anti*-**3a** were formed in a ratio of 91:9. The major product was concluded to be *syn*-**3a** based on reports in the literature[15] that the main product of the reduction of 2-isoxazoline **1a** with $LiAlH_4$ was *syn*-**2a**.

4.7. Determination of the absolute configurations of 1,3-amino alcohol derivatives 3a and 5a and isoxazolidine derivatives 7

The following procedure provides a method for the preparation of 3-benzoylamino-1,3-diphenyl-1-propanols *syn*-**5a** and *anti*-**5a** using nickel chloride and $NaBH_4$. To a 100-mL round-bottomed flask were added 2-isoxazoline (*S*)-**1a** (22.3 mg, 0.1 mmol, 20% ee), ethanol (2.0 mL), nickel chloride anhydride (19.4 mg, 0.15 mmol), and $NaBH_4$ (34 mg, 0.9 mmol), and the mixture was stirred for 21 h at room temperature. Insoluble materials were separated through a Celite pad. After concentration of the solution, dichloromethane (2.0 mL), triethylamine (30 mg, 0.3 mmol), and benzoyl chloride (21 mg, 0.15 mmol) were added, and the mixture was stirred for 2 h at room temperature. To the resulting mixture were added 1 M NaOH and dichloromethane, and the organic layer was extracted, dried over sodium sulfate, concentrated, and was purified by column chromatography (hexane/ethyl acetate = 3:2). The structures of 3-benzoylamino-1,3-diphenyl-1-propanols *syn*-**5a** and *anti*-**5a** were determined by ^{1}H NMR and HPLC analyses compared with those of *syn*-**3a** and *anti*-**3a**. The absolute configurations of *syn*-**5a** and *anti*-**5a** were determined based on the structure of the starting material.

(1*S*,3*R*)-*syn*-**5a**: white solid (from hexane/ethyl acetate), mp 170–173 °C. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.06 (ddd, *J* = 5.7, 7.8, 13.5 Hz, 1H, –CH–C*H*H–CH–), 2.27 (dt, *J* = 7.8, 13.5 Hz, 1H, –CH–CH*H*–CH–), 4.33–4.39 (m, 1H, –C*H*–OH), 5.06 (dt, *J* = 7.8, 8.1 Hz, 1H, –C*H*–NH–), 5.39 (d, *J* = 4.5 Hz, 1H, –O*H*), 7.19–7.54 (m, 13H, Ar-H), 7.83–7.86 (m, 2H, Ar-H), 8.86 (d, *J* = 8.1 Hz, 1H, –N*H*–). ^{13}C NMR: δ (ppm) 46.7, 51.7, 70.8, 126.4, 127.4, 127.5, 128.0, 128.8, 128.87, 128.90, 131.8, 135.3, 144.3, 146.5, 166.1. IR (KBr): 3337, 3059, 3028, 1636, 1574, 1539, 1493, 1458, 1342, 1300, 1277, 1069, 1018, 702, 621, 571 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{22}NO_2$ [M+H]$^+$ 332.1651, found 332.1644. HPLC (Daicel Chiral-

cel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.7 mL/min): t_R = 26.1 min (major), t_R = 37.8 min (minor); 19% ee.

(1*S*,3*S*)-*anti*-**5a**: colorless solid (from hexane/dichloromethane), mp 159–161 °C. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.10–2.30 (m, 2H, –CH–C*H*$_2$–CH–), 4.06 (br s, 1H, –O*H*), 4.70 (dd, *J* = 2.7, 10.5 Hz, 1H, –C*H*–OH), 5.48 (dt, *J* = 3.3, 8.4 Hz, 1H, –C*H*–NH–), 7.21–7.42 (m, 12H, Ar-H and –N*H*–), 7.47–7.52 (m, 2H, Ar-H), 7.78–7.81 (m, 2H, Ar-H). ^{13}C NMR: δ (ppm) 45.5, 52.0, 71.2, 125.9, 126.7, 127.3, 127.69, 127.74, 128.7, 128.9, 129.0, 132.0, 134.1, 141.3, 144.1, 167.7. IR (KBr): 3337, 3059, 3028, 1643, 1578, 1535, 1489, 1450, 1284, 1061, 1030, 752, 698, 567 cm^{-1}. HRMS (FAB$^+$): calcd for $C_{22}H_{22}NO_2$ [M+H]$^+$ 332.1651, found 332.1649. HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.5 mL/min): t_R = 48.9 min (major), t_R = 55.0 min (minor); 28% ee.

From the reaction of *cis*-**7a** (63% ee) with the above reducing agents—nickel chloride and $NaBH_4$—(1*R*,3*S*)-*syn*-**5a** (74% ee) was obtained, while *trans*-**7a** (81% ee) was converted to (1*S*,3*S*)-*anti*-**5a** (81% ee) by the same reduction. These results indicated that the starting materials were (3*S*,5*R*)-*cis*-**7a** and (3*S*,5*S*)-*trans*-**7a**. The absolute configurations of **7b**–**7d** and **7f** were determined by comparison of their ^{1}H NMR and HPLC data with those of *cis*-**7a** and *trans*-**7a**.

(1*R*,3*S*)-*syn*-**5a**: HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.7 mL/min): t_R = 26.5 min (minor), t_R = 36.4 min (major); 74% ee. $[\alpha]_D^{20} = +21.15$ (*c* 1.655, acetone).

(1*S*,3*S*)-*anti*-**5a**: HPLC (Daicel Chiralcel OD-H, hexane/2-propanol = 90:10, UV 220 nm, 0.5 mL/min): t_R = 44.2 min (major), t_R = 50.6 min (minor); 81% ee. $[\alpha]_D^{20} = -13.0$ (*c* 1.15, acetone).

The absolute configuration of **3a** was determined by HPLC analysis compared with that of **5a**. Instead of N-benzoylation, N-tosylation provided *N*-tosyl-3,5-diphenylisoxazolidine (*cis*/*trans* mixture) after asymmetric reduction of **1a** using **4a** (1.0 equiv) and BH_3–SMe_2 (2.5 equiv). *N*-Tosyl-3,5-diphenylisoxazolidine was then allowed to react with nickel chloride/$NaBH_4$ to afford *syn*-**3a** and *anti*-**3a**.

(1*R*,3*S*)-*syn*-**3a**: HPLC (Daicel Chiralcel OD-H, hexane/2-propanol/ethanol = 90:9:1, UV 220 nm, 0.7 mL/min): t_R = 28.7 min (minor), t_R = 54.1 min (major); 68% ee. $[\alpha]_D^{20} = -13.5$ (*c* 2.445, acetone).

(1*S*,3*S*)-*anti*-**3a**: HPLC (Daicel Chiralcel OD-H, hexane/2-propanol/ethanol = 90:9:1, UV 220 nm, 0.5 mL/min): t_R = 39.8 min (minor), t_R = 51.8 min (major); 78% ee. $[\alpha]_D^{20} = -137.3$ (*c* 0.59, acetone).

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