Diastereo- and Enantioselective Synthesis of β-Amino Cyclic Ethers via the Intramolecular Reaction of γ-Alkoxyallylstannane with Imine

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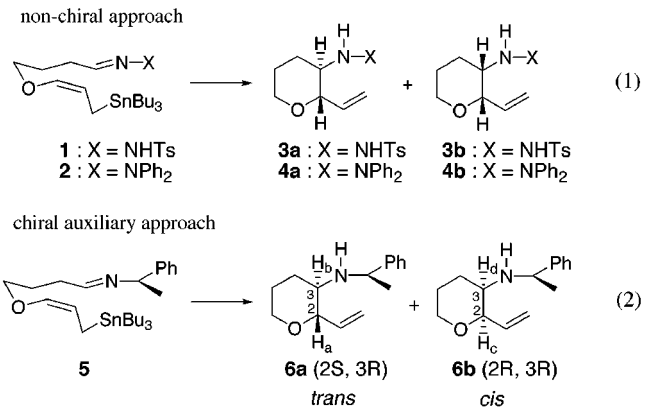
The intramolecular Lewis acid mediated cyclization of γ-alkoxyallylstannanes **1**, **2**, and **14**, bearing a hydrazone group at the terminus of the carbon chain, afforded exclusively the corresponding *trans* β-amino cyclic ethers **3a**, **4a**, and **15**, respectively. The Lewis acid mediated cyclization of γ-alkoxyallylstannane **5**, having (*R*)-(+)-1-phenylethylamine as a chiral auxiliary, afforded exclusively *trans* β-amino cyclic ether **6a** with very high diastereomeric excess (de) in very high chemical yields. The asymmetric cyclization of γ-alkoxyallylstannane with imine **7** in the presence of chiral titanium−BINOL complex **9**, afforded predominantly *cis* β-amino cyclic ether **8b** with high enantiomeric excess (ee). The chiral Lewis acid mediated cyclization of racemic compound **38** containing phenyl as a substituent afforded *cis* isomer **39** with very high enantiomeric excess (ee).

Introduction

In recent years there has been an explosion of interest in the synthesis of cyclic ethers because they are a constitutional unit of marine natural polycyclic ethers.[1] We developed a new strategy for the construction of cyclic ethers via the intramolecular condensation of allylstannane with aldehyde.[2] The usefulness of this methodology was demonstrated by the total synthesis of hemibrevetoxin B[3] and related polycyclic ethers.[1,4] To expand the scope of the heterocycle synthesis via allylic stannanes, we aimed at replacing the oxygen atom of aldehyde by a nitrogen atom, because the allylation of imines has been well studied as well as that of aldehydes,[5] and the replacement of aldehydes (C=O double bond) to C=N double bond would give β-amino cyclic ethers.

We previously reported that the Lewis acid mediated cyclization of γ-oxygen substituted allylic stannanes **1** and **2**, bearing a hydrazone group at the terminus of the carbon chain, afforded the corresponding *trans* β-amino cyclic ethers **3a** and **4a**, respectively, with very high diastereoselectivities in high chemical yields (nonchiral approach) (eq 1).[6] Furthermore, the Lewis acid mediated cyclization of **5**, having a chiral imine group at the terminus of the carbon chain, afforded *trans* β-amino cyclic ether **6a** with very high to good diastereoselectivities in high chemical yields (chiral auxiliary approach) (eq 2).[7]



We now report the detailed investigation of the previous results together with the reagent-controlled asymmetric synthesis of β-amino cyclic ether **8b** from **7** using chiral titanium−BINOL complex **9** (reagent controlled approach) (eq 3).

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(5) For recent reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: New York, 1991; Vol. 2, p 957.

(6) Kadota, I.; Park, J.-Y.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 841.

(7) Park, J.-Y.; Park, C.-H.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 1791.

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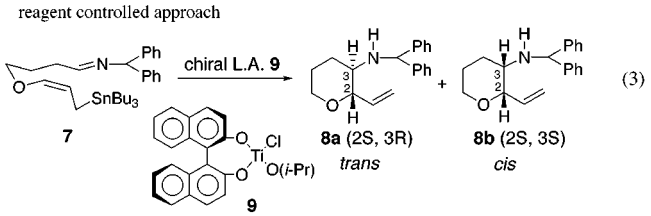


Results and Discussion

Diastereoselective Synthesis of *β*-Aminotetrahydropyran and -furan. The cyclization substrates **1** and **2**, *γ*-alkoxyallylstannanes having a hydrazone group at the terminus of the carbon chain, were easily prepared by the reaction of the corresponding aldehyde with hydrazines and could be easily purified by silica gel column chromatography. The results of the cyclization of **1** and **2** are summarized in Table 1. In all the Lewis acid mediated reactions, *trans* isomers **3a** and **4a** were obtained as the sole product in high to good yields (entries 2, 4−7, and 11−15, Table 1). None of the *cis* isomers **3b** and **4b** could be detected by ^{1}H NMR analysis of the crude product. Although the use of $TiCl_4$ caused decomposition of the substrate (entry 1, Table 1), $TiCl_2(OiPr)_2$ promoted the cyclization of the tosylhydrazone **1** at −78 °C to give **3a** in 94% yield (entry 2, Table 1). No reaction took place with $Ti(OiPr)_4$ even at room temperature, presumably due to its low Lewis acidity (entry 3, Table 1). The use of Lewis acids, such as $ZrCl_4$, $AlCl_3$, $ZnCl_2$, and $BF_3{\cdot}OEt_2$, gave lower yields of the product (entries 4−7, Table 1). Although the reaction proceeded quantitatively in the presence of protic acids such as CF_3SO_3H and CF_3CO_2H, the *trans* selectivity decreased to ca. 7:3 (entries 8 and 9, Table 1). These results suggested that the thermal cyclization of **1** would proceed via cyclic transition state to give *cis* isomer **3b** with high stereoselectivity.[2b] However, unfortunately, only decomposition of **1** took place when it was refluxed in toluene (entry 10, Table 1). Diphenylhydrazone **2** also cyclized in the presence of $TiCl_2(OiPr)_2$ to give the *trans* isomer **4a** quantitatively (entry 11, Table 1). The use of a catalytic amount of $Yb(OTf)_3$ (0.5 equiv) promoted the cyclization to give **4a** with high stereoselectivity in high yield (entry 12, Table 1).[8] The use of smaller amount of the lanthanide catalysts decreased the conversion yield (entries 13−15, Table 1).

The *trans* preference for the cyclization of **1** and **2** is consistent with the proposed acyclic transition state model (Figure 1).[9] The reaction via **10a** is favored in comparison with that via **10b**, because the steric repulsion between the tributylstannylmethyl group and the bulky substituent (NR_2) on the nitrogen atom is alleviated in **10a**. In the presence of protic acids, the formation of the *cis* isomer **3b** increased although it was still a minor product (entries 8 and 9). This may be due to intervention of a cyclic transition state as we previously proposed.[2b,d]

To confirm the stereochemistry of the cyclization product and enhance synthetic utility of this reaction, product **4a** was converted to protected amine **12** by a known procedure (Scheme 1).[10] The treatment of **4a** with BuLi followed by reaction with benzoic anhydride afforded acylated hydrazine **11** in 83% yield. The N−N bond cleavage of **11** was performed using SmI_2 in the presence of HMPA to give the benzoyl amide **12** in 98% yield. The stereochemistry of **12** was unambiguously determined as *trans* by ^{1}H NMR analysis and NOE experiments; H_a and H_b appeared at δ 3.67 and 4.04, respectively, with coupling constant J_{ab} 8.4 Hz. No NOE was observed between H_a and H_b.

We next examined the stereoselective synthesis of *β*-aminotetrahydrofuran derivative (Scheme 2). Aldehyde **13** was treated with 1,1′-diphenylhydrazine hydrochloride and Et_3N to give hydrazone **14** in 87% yield. The cyclization of **14** mediated by $TiCl_2(OiPr)_2$ afforded **15** as a sole product in 82% yield. Cyclic hydrazine **15** was converted to **17** via **16** by a similar procedure as shown in Scheme 2. The structural determination of **17** was

Table 1. Cyclization of 1 and 2[a]

entry	substrate	reagent	equiv	temp (°C)	time (min)	ratio[b] (*trans*:*cis*)	yield (%)[c]
1	**1**	$TiCl_4$	2.0	−78	5	decomposition	
2		$TiCl_2(OiPr)_2$	2.0	−78	5	>95:5	94
3		$Ti(OiPr)_4$	2.0	rt	30	no reaction	
4		$ZrCl_4$	2.0	−78	180	>95:5	81
5		$AlCl_3$	2.0	−78	120	>95:5	68
6		$ZnCl_2$	2.0	−6	180	>95:5	71
7		$BF_3{\cdot}OEt_2$	2.0	−78	5	>95:5	61
8		CF_3SO_3H	2.0	−78	30	71:29	98
9		CF_3CO_2H	2.0	−78	90	70:30	97
10		—[d]		120	60	decomposition	
11	**2**	$TiCl_2(OiPr)_2$	2.0	−78	5	>95:5	97
12		$Yb(OTf)_3$	0.5	rt	1080	>95:5	97
13		$Yb(OTf)_3$	0.2	rt	2880	>95:5	81 (16)
14		$Yb(OTf)_3$	0.2	40	2400	>95:5	75 (24)
15		$La(OTf)_3$	0.2	rt	2880	>95:5	71 (29)

[a] The reactions were carried out with 0.1 mmol/mL substrate in CH_2Cl_2. [b] **3a**:**3b** or **4a**:**4b**. [c] Isolated yield of the cyclization products; values in parentheses are recovery yields. [d] Toluene was used as a solvent.

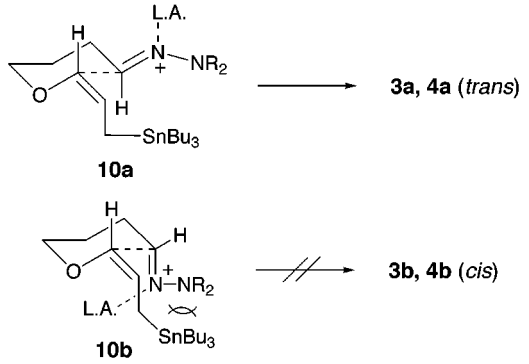
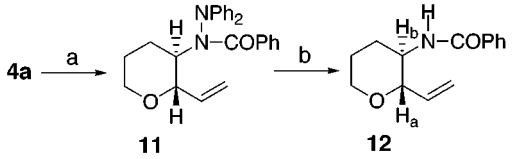


Figure 1. Acyclic transition state model.

Scheme 1[a]



[a] (a) BuLi, THF, -78°C, then $(PhCO)_2O$, -78°C to rt, 83%; (b) SmI_2, HMPA, THF, rt, 98%

(8) Catalytic intermolecular condensation of allylstannane and imine by lanthanide triflates has been reported: Bellucci, C.; Cozzi, P. G.; Umani-Ronchi. *Tetrahedron Lett.* **1995**, *36*, 7289.

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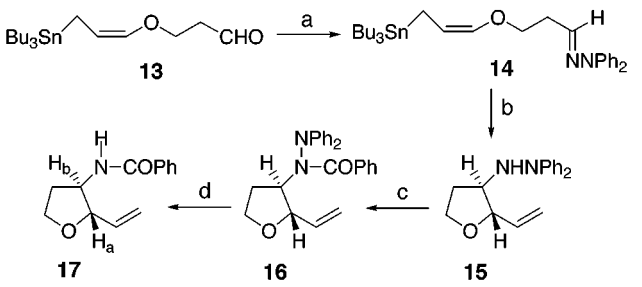
Scheme 2[a]



[a] (a) Ph_2NNH_2·HCl, Et_2N, CH_2Cl_2, rt, 87%; (b) $TiCl_2(OiPr)_2$, CH_2Cl_2, -78°C 82%; (c) BuLi, THF, -78°C, then $(PhCO)_2O$, -78°C to rt, 82%; (d) SmI_2, HMPA, THF, rt, 45%

performed by ^{1}H NMR analysis and NOE experiments; H_a and H_b appeared at δ 4.29 and 4.48, respectively, with coupling constant J_{ab} 4.1 Hz. Irradiation of H_a induced a remarkable enhancement (5.1%) of NH signal.

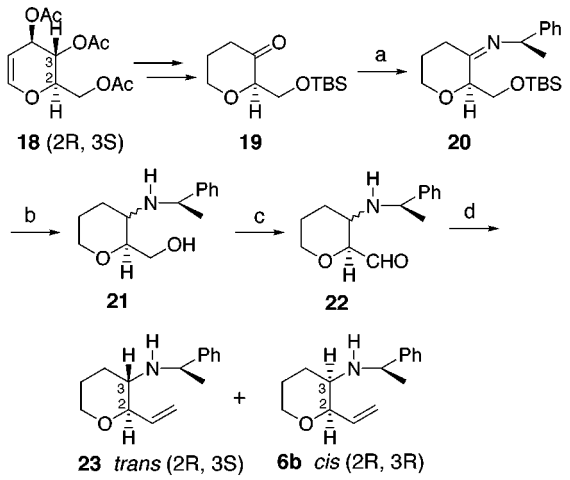
Asymmetric Synthesis of β-Amino Cyclic Ethers *via* the Intramolecular Reaction of γ-Alkoxyallylstannane with Chiral Imine. Encouraged by the successful cyclization of the intramolecular reaction of γ-alkoxyallylstannane with hydrazone, we attempted to extend our methodology to the asymmetric synthesis of β-amino cyclic ethers via the intramolecular reaction of γ-alkoxyallylstannanes with a C=N−R* group, in which R* is a chiral auxiliary (eq 2). Although the asymmetric *intermolecular* allylation of imines with allylstannanes has been investigated during past decade,[11] to the best of our knowledge, the asymmetric *intramolecular* allylation of imines has not been reported so far. γ-Alkoxyallylstannane **5**[12] was easily prepared from the reaction of the corresponding aldehyde precursor, (*Z*)-4-(3-(tributylstannyl)-1-propenoxy)butanal, with (*R*)-(+)-1-phenylethylamine. The results of the cyclization of **5** are summarized in Table 2. The Lewis acid or protic acid mediated reactions gave *trans* isomer **6a** as a major product in high to good yields. The use of $TiCl_2(OiPr)_2$ in CH_2Cl_2 at −78 °C afforded a 77:23 mixture of *trans*-**6a** and *cis*-**6b** in 63% yield (entry 1, Table 2). The stereochemistry of **6a** and **6b** was unambiguously determined to be *trans* and *cis*, respectively, by ^{1}H NMR analysis and NOE experiments; H_a and H_b of **6a** appeared at δ 3.49 and 2.34, respectively, with coupling constant J_{ab} 9.0 Hz. NOEs between H_a and H_b were not observed. On the other hand, H_c and H_d of **6b** appeared at δ 3.97 and 2.63, respectively, and NOEs between H_c and H_d were observed (7%). ^{1}H NMR analysis of the product mixture revealed that the diastereomeric excess (de) of **6a** and **6b** was >95 and 36%, respectively.

Table 2. Asymmetric Synthesis of β-Aminotetrahydropyran Derivative via Cyclization of 5[a]

entry	reagent	temp (°C)	time (min)	**6a** (de):**6b** (de)[b]	yield (%)[c]
1	$TiCl_2(OiPr)_2$	−78	120	77 (>95):23 (36)	63
2	$Yb(OTf)_3$	rt	180	84 (>95):16 (36)	70
3	$ZrCl_4$	−78	180	>98 (91):2	97
4	aq. HCl	0	40	>98 (92):2	98
5	BH_3·OEt_2	−78	60	90 (81):10 (>95)	88
6	CF_3CO_2H	0	10	87 (63):13 (>95)	97
7	$ZnCl_2$	0	120	91 (68):9 (88)	94
8	$AlCl_3$	−78	180	84 (82):16 (70)	87
9	$EtAlCl_2$	0	10	84 (72):16 (47)	89
10	Et_2AlCl	0	90	84 (74):16 (40)	94
11	—[d]	100	2280	decomposition	

[a] The reactions were carried out in CH_2Cl_2. In all cases, 2 equiv of reagents were used. [b] Diastereomic excess (de) was analyzed by ^{1}H NMR analysis. [c] Isolated yield. [d] Toluene was used as a solvent.

Scheme 3[a]



[a] (a) (R)-(+)-1-phenylethylamine, Na_2SO_4, CH_2Cl_2, rt, 98%; (b) DIBAH, Et_2O, 0°C, then washed with 1N HCl/1N NaOH, 69%; (c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78°C, 51%; (d) CH_3Ph_3PBr, NaHMDS, THF, 0°C, 69%

The use of $Yb(OTf)_3$ in CH_2Cl_2 at room temperature afforded an 84:16 mixture of **6a** and **6b** in 70% yield (entry 2, Table 2). The de of **6a** and **6b** was >95 and 36%, respectively. Interestingly, the use of $ZrCl_4$ (entry 3, Table 2) or aqueous HCl solution (36%) (entry 4, Table 2) gave *trans* isomer **6a** as a sole product in 97 or 98% yield, respectively. The de was also high; 91% in entry 3 and 92% in entry 4. The use of Lewis acids, such as $AlCl_3$, $EtAlCl_2$, and Et_2AlCl, gave **6a** and **6b** in the ratio of 84:16 in all cases (entries 8−10, Table 2). Only decomposition of **5** took place when it was refluxed in toluene (entry 11, Table 2).

To determine the absolute configuration of **6a** and **6b**, we decided to synthesize authentic β-amino cyclic ethers (Scheme 3). Tri-*O*-acetyl-D-glucal **18** was converted to **19** according to the reported procedure.[13] Treatment of **19** with (*R*)-(+)-1-phenylethylamine gave **20** in 98% yield. Reduction of **20** with DIBAH afforded a diastereomeric mixture of **21** in 69% yield. Swern oxidation of **21** produced a diastereomeric mixture of the aldehyde **22** in 51% yield. The Wittig reaction of **22** with methylenetriphenylphosphorane gave a 1:3 mixture of *trans*

(11) Diastereoselective addition of allylic metal compounds to chiral imines, prepared by the condensation of aldehyde with optically active amines has been reported, see: (a) Yamamoto, Y.; Shinji, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. (b) Yamamoto, Y.; Ito, W. *Tetrahedron*. **1988**, *44*, 5415. (c) Laschat, S.; Kunz, H. *J. Org. Chem*. **1991**, *56*, 5883. (d) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem*. **1991**, *56*, 1340. (e) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. S.; *Tetrahedron Lett*. **1993**, *34*, 7975. (f) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem*. **1994**, *59*, 7766. (g) Hashimoto, Y.; Takaoki, K.; Sudo, A. Ogasawara, T.; Saigo, K. *Chem. Lett*. **1995**, 235. (h) Gao, Y.; Sato, F. *J. Org. Chem*. **1995**, *60*, 8136. Enantioselective addition of chiral allylboron reagents to achiral imines has been reported, see: (i) Watanabe, K.; Ito, K.; Itsuno, S. *Tetrahedron: Asymmetry*. **1995**, *6*, 1531.

(12) γ-Alkoxyallylstannane **5** was used for further reaction immediately after the reaction of the aldehyde precursor with (*R*)-(+)-1-phenylethylamine, since it decomposed very readily upon treatment with silica gel column.

(13) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc*. **1990**, *112*, 3040.

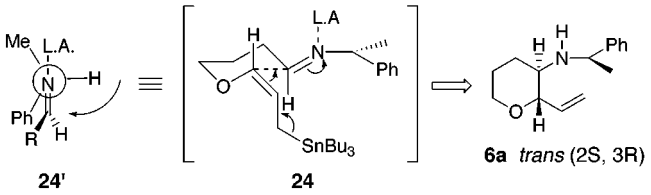
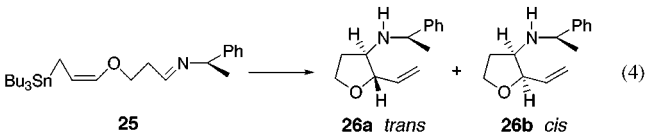


Figure 2. Transition state geometry.

Table 3. Asymmetric Synthesis of *β*-Aminotetrahydrofuran Derivative via Cyclization of 25[a]



(4)

entry	reagent	temp (°C)	time (min)	**26a** (de):**26b** (de)[b]	yield (%)[c]
1	$ZrCl_4$	−78 → 0	120	>98 (11):2	80
2	$ZnCl_2$	0	60	85 (0):15 (45)	72
3	$Yb(OTf)_3$	rt	10	88 (12):12 (>95)	90
4	aq HCl	0	90	80 (12):20 (>95)	89
5	CF_3CO_2H	−78 → 0	120	88 (23):12 (>95)	71

[a] The reactions were carried out in CH_2Cl_2. In all cases, 2 equiv of reagents were used. [b] Diastereomeric excess (de) was analyzed by ^1H NMR analysis. [c] Isolated yield.

isomer **23** and *cis* isomer **6b** in 69% yield. The NMR spectra of the cis (2*R*,3*R*) isomer obtained from **18** was completely identical with those of the cis isomer **6b** obtained in entries 5 and 6 of Table 2. Therefore, the absolute stereochemistry of **6b** was determined unambiguously to be (2*R*,3*R*). The NMR spectra of the *trans*-(2*R*,3*S*)-**23** was completely identical with those of a minor diastereomer of *trans*-**6a**, which was obtained in entries 6−10 of Table 2. Accordingly, the absolute configuration of **6a** was determined unambiguously to be (2*S*,3*R*).

The intramolecular addition of the allylstannane unit to the chiral imine would proceed through the transition state geometry **24** (Figure 2). At the stage for six-membered ring formation in **24**, equatorial−equatorial orientation of C=C and C=N double bond would be more favorable, leading to predominant or exclusive formation of *trans*-**6a**. The asymmetric induction at the imine carbon (C-3 position of **6a**) can be explained by the modified Cram[14,11a] model (**24′**) for imines. The allylic *γ*-carbon would attack the imine carbon from the direction shown by an arrow (**24′**), producing *R* chirality at the C-3 position of **6a**.

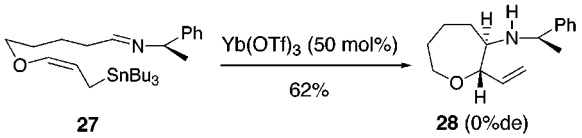
We next examined the asymmetric synthesis of *β*-aminotetrahydrofuran derivatives (eq 4). The results of the cyclization of **25** are summarized in Table 3. The use of $ZrCl_4$ produced *trans* isomer **26a** as a sole product in 80% yield with 11% de (entry 1, Table 3). Although the use of $ZnCl_2$ afforded **26a** as a major product, the de was 0% (entry 2, Table 3). When $Yb(OTf)_3$ was used at room temperature for 10 min, an 88:12 mixture of **26a** and **26b** was obtained in 90% yield (entry 3, Table 3). The use of protic acid, such as HCl (entry 4, Table 3) or TFA (entry 5, Table 3), also afforded **26a** as a major product. The de of **26a** was lower than that of **6a**.

Table 4. Asymmetric Synthesis of *β*-Amino Cyclic Ethers from 7 using Chrial Lewis Acid 9[a]

entry	**9** (equiv)	solvent	time (h)	**8a** (ee):**8b** (ee)[b]	yield (%)[c]
1	2.0	CH_2Cl_2	2	24 (53):76 (82)	80
2	1.0	CH_2Cl_2	2	30 (48):70 (72)	86
3	0.5	CH_2Cl_2	24	31 (41):69 (64)	87
4	0.2	CH_2Cl_2	48	45 (37):55 (56)	69 (8)[d]
5	1.0	toluene	8	27 (62):73 (62)	73
6	1.0	CH_2Cl_2/THF (1:1)	5	13 (22):87 (49)	69
7	1.0	THF	19	11 (15):89 (44)	73
8	1.0	CH_3CN	48	46 (12):54 (36)	70

[a] The reactions were carried out at −78 °C in all cases. [b] Diastereomeric excess was determined by ^1H NMR. %ee was determined by chiral HPLC (Chiralpak AD. hexane−Pr^{i}OH). [c] Isolated yields by column chromatography. [d] The value in parentheses indicated recovery % of substrate **7**.

It is noteworthy that cyclization to a seven-membered ether derivative **27** proceeded very smoothly (eq 5). The use of 50 mol % $Yb(OTf)_3$ in CH_2Cl_2 at room temperature for 24 h afforded a >98:2 mixture of the *trans* and *cis* isomer in 62% yield.[15] ^1H NMR Analysis revealed that the de of the *trans* isomer **28** was regrettably 0%.



(5)

Chiral Lewis Acid Promoted Cyclizations of *γ*-Alkoxyallylstannane with Imine. Asymmetric reactions using chiral Lewis acids are of great current interest as one of the most efficient methods for the preparation of chiral compounds.[16] While rather rapid progress has been made on the enantioselective reactions of carbonyl compounds using chiral Lewis acids (aldol reactions, allylation reactions, Diels−Alder reactions, etc.),[17] very few examples have been reported for their aza analogues.[18] If the asymmetric cyclization of the allylic stannane−imine condensation reaction proceeds by using a chiral Lewis acid catalyst, the synthetic usefulness of the present cyclization methodology would be enhanced. After several fruitless attempts, we found that chiral titanium−BINOL[19] complex **9** is suitable for the asymmetric synthesis of *β*-amino cyclic ethers (eq 3). The cyclization of **7** using chiral Lewis acid **9** (2.0 equiv) in CH_2Cl_2 at −78 °C afforded a 24:76 mixture of *trans*-(2*S*,3*R*)-**8a** and *cis*-(2*S*,3*S*)-**8b** in 80% yield with enantiomeric excess of 82% and 53%, respectively (entry 1, Table 4). The use of 1.0 or 0.5 equiv of chiral Lewis acid **9** increased the yields (86% or 87%, respectively), but the diastereo- and enantioselectivities decreased (entries 2 and 3, Table 4). The reaction proceeded to a certain extent even by the use of 0.2 equiv of **9** (entry 4, Table 4). The use of toluene as a solvent gave a 27:73 mixture of *trans*-(2*S*,3*R*)-**8a** and *cis*-(2*S*,3*S*)-**8b** in 73% yield with 62% and 62% ee, respectively (entry 5, Table 4). When THF was used as a solvent, *β*-amino cyclic ethers **8a** and **8b** were obtained in 73% yield with low enantioselectivities although the diastereoselectivity was high (entry 7, Table

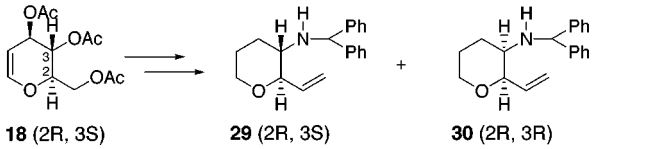
(14) (a) Hoffmann, R. W.; Eichler, G.; Endesfelder, A. *Liebigs Ann. Chem*. **1983**, 2000. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Am. Chem. Soc.* **1984**, *106*, 5031. (c) Wuts, P. G. M.; Jung, Y. W. *Tetrahedron Lett*. **1986**, *27*, 2079.

(15) When $TiCl_2(O\text{-}^iPr)_2$, $ZrCl_4$, or TFA was used as an activator, the substrate was decomposed.

(16) (a) Narasaka, K. *Synthesis* **1991**, 1. (b) Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*; CRC Press: Boca Raton, FL, 1995.

(17) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993.

Scheme 4

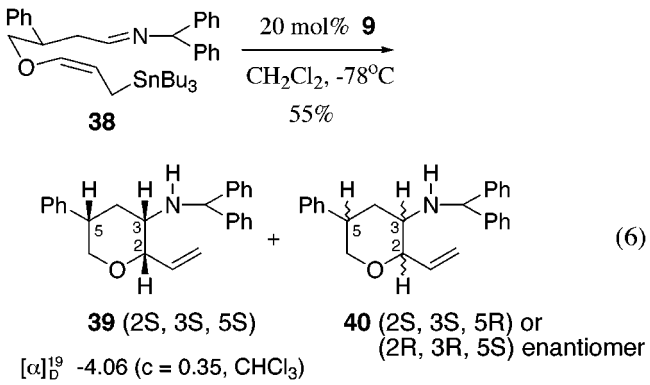


4). The mixed solvent system gave similar result (entry 6, Table 4), and the use of CH_3CN did not give better result (entry 8, Table 4).

The absolute configuration of **8a** and **8b** was determined by synthesizing authentic β-amino cyclic ethers (Scheme 4). Authentic compounds **29** and **30** were prepared by the similar method as shown in Scheme 3. The only difference was that α-aminodiphenylmethane was used instead of (*R*)-(+)-1-phenylethylamine at the procedure (a) in Scheme 4. The $[\alpha]^{23}_D$ of *trans*-**8a** and $[\alpha]^{20}_D$ of *cis*-**8b** were −29.46 and −10.16, respectively, whereas $[\alpha]^{20}_D$ of authentic *trans*-(2*R*,3*S*)-**29** and $[\alpha]^{20}_D$ of *cis*-(2*R*,3*R*)-**30** were +53.38 and +13.45, respectively. Therefore, it was confirmed that the absolute configurations of **8a** and **8b** are unambiguously (2*S*,3*R*) and (2*S*,3*S*), respectively.

We next examined the asymmetric cyclization of several imine-tethered γ-alkoxyallylstannanes. The results are summarized in Table 5. The cyclization of the *trans* allylic stannane **31** using chiral Lewis acid **9** (2.0 equiv) in CH_2Cl_2 at −78 °C afforded an 86:14 mixture of *trans*-(2*R*,3*S*)-**29** and *cis*-(2*S*,3*S*)-**8b** in 66% yield with low enantioselectivities (19% and 28%, respectively) (entry 1). Very interestingly, the *trans* isomer **29** was produced preferentially from the *trans* allylic stannane **31**. This result is in marked contrast to the fact that the *cis* isomer **8b** is afforded predominantly from the *cis* allylic stannane **7**. The cyclization of **32** using 20 mol % of **9** gave a 78:22 mixture of *trans*-(2*R*,3*S*)-**33** and *cis*-(2*R*,3*R*)-**34** in 66% yield. The enantioselectivities of **33** and **34** were 7% and 85%, respectively (entry 2). In the case of substrate **35** having dimethyl substituent at the tether carbon afforded a 45:55 mixture of *trans*-(2*S*,3*R*)-**36** and *cis*-(2*S*,3*S*)-**37** in 80% yield with 93% and 14% enantioselectivities, respectively (entry 3, Table 5).[20] The relative stereochemistry of **33**, **34**, **36**, and **37** were determined by the coupling constants between H−C_2 and H−C_3 and by observing NOEs between those protons (see Experimental Section). The absolute configurations of **33**, **34**, **36**, and **37** were not determined unambiguously, but assumed from their $[\alpha]_D$ values: those (**33** and **36**) exhibiting (+)$[\alpha]_D$ values are assumed to be (2*R*,3*S*) whereas those having (−)$[\alpha]_D$ values are assumed to be (2*S*,3*R*) by comparison with that of **29**. The procedure same as above was used for assignment of the absolute configurations of **34** and **37**.

The cyclization of racemic compound **38**, having a phenyl group at the tether carbon, using 20 mol % of **9** at −78 °C for 24 h afforded an 85:15 mixture of *cis* isomers **39** and **40** in 55% yield with enantiomeric excess of 90% and 36%, respectively (eq 6). The relative stereochemistry of **39** was unambiguously determined by ^{1}H



(6)

NMR analysis and NOE experiments (Figure 3). NOE was observed between H_b and H_a, and H_b and H_c. Long-range coupling was observed between H_a and H_e, and H_d and H_e, respectively. The NOEs and coupling constants of **40** are shown in Figure 3, indicating that the relative stereochemistry of C_2−C_3 was *cis* and that of C_3−C_5 was *trans*. The absolute configuration of **39** was determined by synthesizing authentic β-amino cyclic ethers **45a** and **45b** (Scheme 5). Tri-*O*-acetyl-D-glucal **18** was converted to **41** according to the reported procedure.[13] The Heck-type reaction of **41** with PhI gave **42** as a single stereoisomer in 33% yield. It was not clear whether the stereochemistry of the carbon attached to the phenyl group is up or down, but an important thing is that only a single diastereomer was obtained although the chemical yield was not high. Hydroboration−oxidation of **42** afforded a 2:1 regioisomeric mixture of **43a** and **43b** in 84% yield. Separation of **43a**, followed by protection of the primary OH with acetyl group, gave **44** in 76% yield. The procedure shown in Scheme 3 could convert **44** into a 2:1 mixture of **45a** and **45b**. The ^{1}H NMR spectra of **45a** obtained from tri-*O*-acetyl-D-glucal **18** was completely identical with those of **39**, and $[\alpha]^{19}_D$ of **39** was −4.06 (*c* = 0.35, $CHCl_3$), whereas $[\alpha]^{22}_D$ of **45a** was +4.55 (*c* = 0.40, $CHCl_3$). Therefore, the absolute configuration of **39** was determined unambiguously to be (2*S*,3*S*,5*S*). The relative stereochemistry of **45b** was assigned by the coupling constant (*J* = 8.4 Hz) between H−C_2 and H−C_3. The ^{1}H NMR spectra of **40** was quite different from those of **45a** and **45b**. The absolute stereochemistry of **40** was not determined.

Conclusion

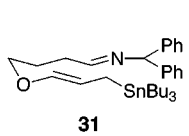
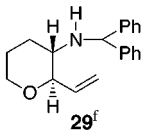
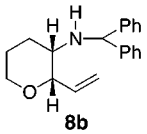
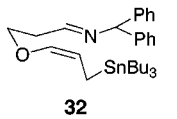
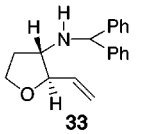
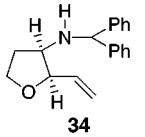
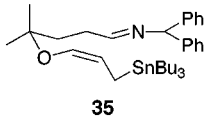
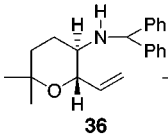
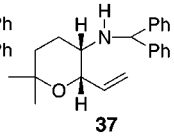
The Lewis acid mediated cyclization of γ-oxygen substituted allylic stannane bearing a hydrazone group at the terminus of the carbon chain afforded the *trans*

(18) (a) Denmark, S. E.; Nakajima, N.; Nicaise, O. J.-C. J. *Am. Chem. Soc.* **1994**, *116*, 8797. (b) Denmark, S. E.; Nicaise, O. J.-C. J. *Chem. Soc., Chem. Commun*. **1996**, 999. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (d) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Chem. Lett.* **1997**, 59. (e) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (f) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (g) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding T.; Lectka, T. *J. Org. Chem*. **1998**, *63*, 6090.

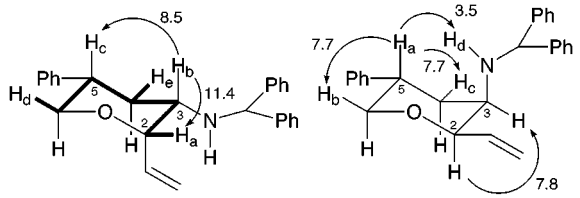
(19) Titanium(IV)−1,1′-bi-2-naphthol complexs were used in some asymmetric reactions: (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, *A. J. Am. Chem. Soc.* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (c) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2571. (d) Ganthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2363. (e) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Lee, S.-S. *Tetrahedron Lett*. **1996**, *37*, 7095.

(20) A referee suggested the interaction between the oxygen atom of substrates and Lewis acids may be responsible for the differences in enantioselectivity observed for **8a** (Table 4, entry4, ee: 37%) and dimethyl derivative **36** (Table 5, entry 3, ee: 93%). This is a plausible explanation for the differences, but the results in the carbon series were not available and therefore we cannot discuss such an interaction at the present time.

Table 5. *β*-Amino Cyclic Ethers from Imine-Tethered *γ*-Alkoxyallylstannanes[a]

entry	Substrate	Product[b]	trans (ee) : cis (ee)[c]	yield (%)[d]
1[e]	 **31**	 **29**[f]  **8b**	86 (19) : 14 (28)	66
2	 **32**	 **33**  **34**	78 (7) : 22 (85)	66
3	 **35**	 **36**  **37**	45 (93) : 55 (14)	80

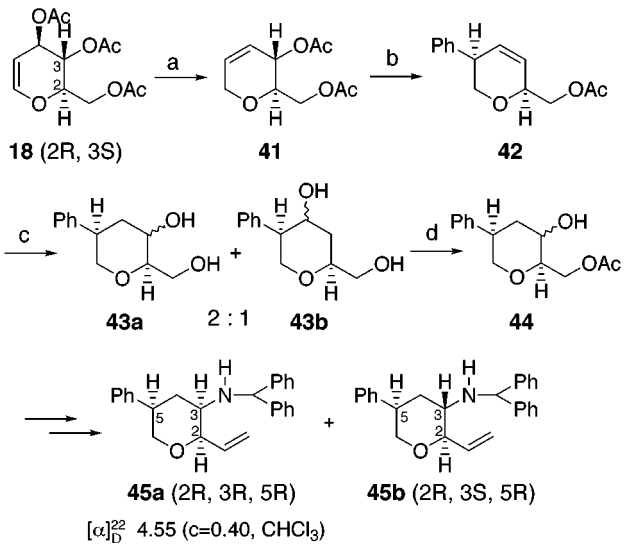
[a] The reactions were carried out at −78 °C with 20 mol % **9** for 24 h. [b] The structural determination of the products was carried out by ^{1}H NMR analysis and NOE experiments. [c] %ee was determined by chiral HPLC (Chrialpak AD. hexane−Pr^{i}OH). [d] Isolated yields by column chromatography. [e] Two equivalents of chiral Lewis acid **9** were used, and the reaction time was 12 h. [f] The optical rotation was $[\alpha]^{20}_D$ 9.48 (c = 0.62, $CHCl_3$).



39 $J_{H2\text{-}H3}$ = 5.8 Hz **40** $J_{H2\text{-}H3}$ = 2.2 Hz

Figure 3. Determination of the stereochemistry.

Scheme 5[a]



18 (2R, 3S) **41** **42** **43a** 2 : 1 **43b** **44** **45a** (2R, 3R, 5R) **45b** (2R, 3S, 5R)

$[\alpha]^{22}_D$ 4.55 (c=0.40, $CHCl_3$)

[a] (a) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C, 97%; (b) 20 mol% $Pd(OAc)_2$, PhI, Et_3N, CH_3CN, 100°C, 33%; (c) $BH_3{\cdot}THF$, H_2O_2, NaOH, rt, 84%; (d) Ac_2O, pyridine, CH_2Cl_2, rt, 76%.

β-amino cyclic ethers with very high diastereoselectivities in high chemical yields (nonchiral approach).

The Lewis acid mediated cyclization of *γ*-oxygen substituted allylic stannane having a chiral imine group at the terminus of the carbon chain afforded the *trans* *β*-amino cyclic ethers predominantly or exclusively in high chemical yields with high diastereomeric excess (chiral auxiliary approach). Furthermore, we have developed the first asymmetric synthesis of *β*-amino cyclic ethers via the chiral Lewis acid-catalyzed intramolecular reaction of *γ*-alkoxyallylstannanes with imine (reagent-controlled approach). These findings provide synthetically useful diastereo- and enantioselective methodologies for preparing oxygen heterocycles having *β*-amino groups.

Experimental Section

General Information. All reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring, unless otherwise indicated. Solvents were purified and dried before use according to the standard procedure. Tributyltin chloride and TMEDA were distilled from CaH_2. All other reagents were purchased at highest commercial quality and used without further purification. MPLC, medium-pressure liquid chromatography, implemented LiChroprep Si 60 (40−63 *μ*m). HPLC, high-performance liquid chromatography, was performed on Shimadzu LC9A and SPD-10A using a Daicel CHIRALPAK AD column (4.6 mm × 250 mm). Chemical shifts are reported in parts per million downfield from internal standard, tetramethylsilane (TMS).

(*Z*)-4-(3-(Tributylstannyl)-1-propenoxy)butyltosylhydrazone (1). To a solution of (*Z*)-4-(3-(tributylstannyl)-1-propenoxy)butanal[2d] (1.57 g, 3.76 mmol) in CH_2Cl_2 (40 mL) at room temperature under an air atmosphere was added *p*-toluenesulfonhydrazide (0.84 g, 4.51 mmol). After 5 h, the reaction mixture was dried over Na_2SO_4, and CH_2Cl_2 solvent was evaporated. Purification by silica gel column chromatography using hexanes−ethyl acetate as an eluent gave **1** (1.81 g, 82%): colorless oil; R_f = 0.20 (hexane/AcOEt, 4:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.81 (d, J = 9.1 Hz, 2H), 7.34 (d, J = 9.1 Hz, 2H), 7.21 (t, J = 5.1 Hz, 1H), 5.65 (dt, J = 6.2, 1.1 Hz, 1H), 4.49 (dt, J = 9.1, 6.2 Hz, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H), 2.32 (dt, J = 5.1, 7.7 Hz, 2H), 1.76 (quint, J = 7.0 Hz, 2H), 1.60 (dd, J = 9.1, 1.1 Hz, 2H), 1.50−0.80 (m, 27H). Anal. Calcd for $C_{26}H_{46}N_2O_3SSn$: C, 53.32; H, 7.92; N, 4.78. Found: C, 53.40; H, 7.89; N, 4.75.

(*Z*)-4-(3-(Tributylstannyl)-1-propenoxy)butyldiphenylhydrazone (2). To a solution of 1,1-diphenylhydrazine hydrochloride (0.63 g, 2.87 mmol) in CH_2Cl_2 (25 mL) at room temperature under an air atmosphere was added triethylamine (0.4 mL, 2.87 mmol), and the resulting mixture was stirred for 10 min. To this solution was added (*Z*)-4-(3-(tributylstannyl)-1-propenoxy)butanal (1.0 g, 2.39 mmol) in CH_2Cl_2 (2 mL). After 5 h, the reaction mixture was diluted with ether, washed with brine, and dried (Na_2SO_4). Concentration and silica gel column chromatography gave **2** (1.32 g,

94%): colorless oil; R_f = 0.80 (hexane/AcOEt, 4:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.40−7.06 (m, 10H), 6.45 (t, J = 5.1 Hz, 1H), 5.77 (dt, J = 6.2, 1.1 Hz, 1H), 4.51 (dt, J = 6.2, 9.1 Hz, 1H), 3.72 (t, J = 6.6 Hz, 2H), 2.37 (dt, J = 5.1, 7.0 Hz, 2H), 1.87 (quint, J = 7.0 Hz, 2H), 1.65 (dt, J = 9.1, 1.1 Hz, 2H), 1.55−0.81 (m, 27H); IR (neat) 3034, 1650, 1091 cm^{-1}; HRMS m/z calcd for $C_{31}H_{48}N_2OSn$ 584.2789, found 584.2751.

***trans*-3-(Tosylhydrazino)-2-vinyltetrahydropyran (3a).** To a solution of **1** (152 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added a solution of $TiCl_2(OiPr)_2$ (1.0 M in CH_2Cl_2, 0.52 mL, 0.52 mmol), and the mixture was stirred for 5 min at the same temperature. The reaction mixture was allowed to warm to room temperature, quenched with satd $NaHCO_3$, extracted with ether. The organic layer was washed with brine, and dried (Na_2SO_4). Concentration and silica gel column chromatography gave **3a** (72 mg, 94%): white solid; R_f = 0.33 (hexane/AcOEt, 2:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 6.05 (s, 1H), 5.76 (ddd, J = 17.4, 10.4, 7.6 Hz, 1H), 5.29 (ddd, J = 17.4, 1.6, 0.9 Hz, 1H), 5.23 (ddd, J = 10.4, 1.6, 0.5 Hz, 1H), 3.88 (ddd, J = 11.3, 4.4, 2.3 Hz, 1H), 3.43 (dd, J = 8.4, 8.2 Hz, 1H), 3.31 (ddd, J = 14.4, 11.3, 3.1 Hz, 1H), 2.56 (ddd, J = 12.0, 8.2, 4.2 Hz, 1H), 2.44 (s, 3H), 2.01 (m, 1H), 1.57 (m, 2H), 1.24 (m, 1H); IR (KBr) 3224, 1597, 1090 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3N_2S$: C, 56.73; H, 6.80; N, 9.45; S, 10.81. Found: C, 56.63; H, 6.84; N, 9.35; S, 10.52.

***cis*-3-(Tosylhydrazino)-2-vinyltetrahydropyran (3b):** colorless oil; R_f = 0.37 (hexane/AcOEt, 2:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 5.99 (s, 1H), 5.84 (ddd, J = 17.4, 10.8, 4.2 Hz, 1H), 5.29 (ddd, J = 17.4, 1.8, 1.8 Hz, 1H), 5.19 (ddd, J = 10.8, 1.8, 1.8 Hz, 1H), 3.97 (m, 1H), 3.95 (dd, J = 4.2, 2.0 Hz, 1H), 3.45 (ddd, J = 14.1, 12.0, 2.5 Hz, 1H), 3.00 (m, 1H), 2.43 (s, 3H), 2.02 (m, 1H), 1.73 (m, 2H), 1.51 (m, 1H), 1.31 (m, 1H); IR (neat) 3244, 1597, 1091 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_3N_2S$: C, 56.73; H, 6.80; N, 9.45; S, 10.81. Found: C, 56.63; H, 6.84; N, 9.35; S, 10.52.

***trans*-3-(Diphenylhydrazino)-2-vinyltetrahydropyran (4a):** white solid; mp 85−87 °C; R_f = 0.65 (hexane/AcOEt, 4:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.29−6.95 (m, 10H), 5.76 (ddd, J = 17.3, 10.5, 8.0 Hz, 1H), 5.38 (ddd, J = 17.4, 1.7, 0.9 Hz, 1H), 5.28 (ddd, J = 10.5, 1.7, 0.5 Hz, 1H), 4.12 (br, 1H), 3.94 (ddd, J = 11.2, 4.1, 1.9 Hz, 1H), 3.68 (dd, J = 8.0, 8.4 Hz, 1H), 3.44 (ddd, J = 14.4, 11.2, 3.1 Hz, 1H), 2.72 (ddd, J = 10.2, 8.4, 4.1 Hz, 1H), 2.20−2.16 (m, 1H), 1.62−1.46 (m, 3H); IR (KBr) 2952, 1588, 1041 cm^{-1}. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 76.59; H, 7.56; N, 9.32.

3-(N^1-Benzoyl-N^2,N^2-diphenylhydrazino)-2-vinyltetrahydropyran (11). To a solution of **4a** (110 mg, 0.373 mmol) in THF (2 mL) at −78 °C was added n-BuLi (0.44 mL of a 1.7 M solution in *n*-hexane, 0.747 mmol), and the resulting mixture was stirred for 20 min. To this yellow solution was added benzoic anhydride (84 μL, 0.447 mmol), and the mixture was allowed to warm to room temperature and stirred for 20 min. The reaction was quenched with saturated sodium hydrogen carbonate, diluted with ether, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the residue by recrystallization (hexane/AcOEt) furnished 124 mg (83%) of **11** as a white solid: mp 167−171 °C; R_f = 0.50 (hexane/AcOEt, 3:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.70−6.80 (m, 15H), 5.91 (ddd, J = 17.4, 10.2, 8.0 Hz, 1H), 5.31 (dd, J = 17.4, 1.4 Hz, 1H), 5.22 (dd, J = 10.2, 1.4 Hz, 1H), 4.40 (m, 1H), 4.06 (dd, J = 8.0, 8.0 Hz, 1H), 3.91 (dd, J = 11.0, 5.0 Hz, 1H), 3.31 (ddd, J = 11.0, 11.0, 2.3 Hz, 1H), 2.26−1.60 (m, 4H); IR (KBr) 2956, 1664, 1490 cm^{-1}. Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.57; N, 7.02. Found: C, 78.30; H, 6.47; N, 7.01.

3-(*N*-Benzoylamino)-2-vinyltetrahydropyran (12). To a solution of **11** (40 mg, 0.10 mmol) in THF (2 mL) at room temperature were slowly added HMPA (0.15 mL, 0.85 mmol) and SmI_2 (4.0 mL of a 0.1 M solution in THF, 0.4 mmol), and the resulting mixture was stirred for 10 min. The reaction was quenched with saturated $NaHCO_3$, diluted with ethyl acetate, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by silica gel column chromatography (CH_2Cl_2/ether, 3:1) gave **12** (23 mg, 98%) as a white solid: mp 140−142 °C; R_f = 0.15 (hexane/AcOEt, 3:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.72−7.40 (m, 5H), 5.93 (ddd, J = 17.3, 10.5, 8.0 Hz, 1H), 5.63 (br, 1H), 5.33 (ddd, J = 17.3, 1.4, 0.9 Hz, 1H), 5.24 (ddd, J = 10.5, 1.4, 0.7 Hz, 1H), 4.04 (m, 2H), 3.67 (dd, J = 8.4, 8.0 Hz, 1H), 3.48 (ddd, J = 11.4, 10.0, 3.3 Hz, 1H), 2.26−2.23 (m, 1H), 1.83−1.70 (m, 2H), 1.56−1.46 (m, 1H); IR (KBr) 2956, 1580, 1091 cm^{-1}. Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; N, 6.05. Found: C, 72.30; H, 7.20; N, 6.02.

3-(*N*-Benzoylamino)-2-vinyltetrahydrofuran (17): white solid; mp 85−87 °C; R_f = 0.20 (hexane/AcOEt, 2:1); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.77−7.39 (m, 5H), 6.25 (br, 1H),5.90 (ddd, J = 17.3, 10.5, 5.3 Hz, 1H), 5.34 (ddd, J = 17.3, 1.7, 1.7 Hz, 1H), 5.19 (ddd, J = 10.5, 1.7, 1.4 Hz, 1H), 4.48 (ddd, J = 11.2, 7.5, 4.1 Hz, 1H), 4.29 (dd, J = 5.3, 4.1 Hz, 1H), 4.05 (ddd, J = 8.5, 8.5, 5.1 Hz, 1H), 4.00 (ddd, J = 8.5, 8.5, 7.4 Hz, 1H), 2.36 (m, 1H), 1.94 (m, 1H); IR (KBr) 3080, 1632 cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.87; H, 6.96; N, 6.44. Found: C, 71.81; H, 7.21; N, 6.64.

(2*S*,3*R*)-3-(2-Phenylethylamino)-2-vinyltetrahydropyran (6a): colorless oil; R_f = 0.42 (hexane/AcOEt, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.03 (m, 5H), 5.95 (ddd, J = 17.4, 10.4, 7.1 Hz, 1H), 5.38 (dd, J = 17.4, 1.5 Hz, 1H), 5.29 (dd, J = 10.4, 1.3 Hz, 1H), 3.90 (m, 1H), 3.84 (quartet, J = 6.6 Hz, 1H), 3.49 (dd, J = 9.0, 7.1 Hz, 1H), 3.35 (m, 1H), 2.34 (ddd, J = 9.0, 8.1, 4.2 Hz, 1H), 1.81 (m, 1H), 1.53 (m, 2H), 1.27 (d, J = 6.6 Hz, 3H), 1.16 (m, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.7, 137.4, 128.3, 126.7, 126.4, 117.9, 84.0, 67.4, 56.3, 56.1, 31.3, 28.1, 26.7, 25.4, 24.2; IR (neat) 3026, 1492 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.85; H, 9.14; N, 6.05. Found: C, 77.63; H, 9.17; N, 6.10. $[\alpha]^{19}_D$ = 2.04 (c = 0.20, $CHCl_3$). The specific rotation of the minor diastereomer of the *trans* product **6a** was $[\alpha]^{18}_D$ = 33.12 (c = 0.20, $CHCl_3$).

(2*R*,3*R*)-3-(2-Phenylethylamino)-2-vinyltetrahydropyran (6b): colorless oil; R_f = 0.75 (hexane/AcOEt, 2:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56−7.03 (m, 5H), 6.00 (ddd, J = 17.5, 10.6, 5.2 Hz, 1H), 5.35 (dd, J = 17.5, 1.6 Hz, 1H), 5.24 (dd, J = 10.6, 1.6 Hz, 1H), 3.97 (m, 2H), 3.82 (quartet, J = 6.6 Hz, 1H), 3.46 (ddd, J = 11.2, 11.2, 2.8 Hz, 1H), 2.63 (m, 1H), 1.86 (m, 1H), 1.66 (br, 1H), 1.61 (m, 1H), 1.46 (m, 1H), 1.32 (m, 1H), 1.25 (d, J = 6.6 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 146.7, 136.6, 128.2, 127.1, 126.7, 115.7, 80.5, 67.5, 57.3, 53.2, 29.1, 24.5, 21.3; IR (neat) 3024, 1450, 1114 cm^{-1}. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.85; H, 9.14; N, 6.05. Found: C, 77.70; H, 9.04; N, 6.20. $[\alpha]^{19}_D$ = 77.05 (c = 0.62, $CHCl_3$).

(2*S*,3*R*)-3-(2-Phenylethylamino)-2-vinyltetrahydrofuran (26a): colorless oil; R_f = 0.18 (hexane/AcOEt, 3:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 5.71 (ddd, J = 17.3, 10.4, 6.8 Hz, 1H), 5.32 (dd, J = 17.3, 1.4 Hz, 1H), 5.13 (dd, J = 10.4, 1.4 Hz, 1H), 3.85 (m, 4H), 2.83 (ddd, J = 7.0, 7.0, 6.1 Hz, 1H), 1.90 (m, 1H), 1.61 (m, 1H), 1.36 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.41; H, 8.79; N, 6.40.

(2*R*,3*R*)-3-(2-Phenylethylamino)-2-vinyltetrahydrofuran (26b): colorless oil; R_f = 0.38 (hexane/AcOEt, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.24 (m, 5H), 5.97 (ddd, J = 17.3, 10.7, 4.1 Hz, 1H), 5.40 (dd, J = 17.3, 1.4 Hz, 1H), 5.31 (dd, J = 10.7, 1.4 Hz, 1H), 4.35 (dd, J = 6.1, 4.1 Hz, 1H), 3.95 (ddd, J = 8.3, 8.3, 4.3 Hz, 1H), 3.79 (quartet, J = 6.6 Hz, 1H), 3.69 (ddd, J = 15.8, 8.0, 7.8 Hz, 1H), 3.23 (ddd, J = 7.0, 7.0, 6.1 Hz, 1H), 1.95 (m, 1H), 1.66 (m, 1H), 1.29 (d, J = 6.6 Hz, 3H). Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.40; H, 8.78; N, 6.42.

(2*S*,3*R*)-3-(2-Phenylethylamino)-2-vinyl-1-oxocycloheptane (28): colorless oil; R_f = 0.38 (hexane/AcOEt, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.22 (m, 5H), 6.04 (ddd, J = 17.2, 10.4, 6.0 Hz, 1H), 5.21 (dd, J = 17.2, 1.3 Hz, 1H), 5.19 (dd, J = 10.4, 1.1 Hz, 1H), 3.91−3.78 (m, 2H), 3.65−3.60 (m, 2H), 2.64 (m, 1H), 1.70−1.23 (m, 6H), 1.28 (d, J = 6.6 Hz, 3H); IR (neat) 3084, 1492, 1109 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO$: C, 78.29; H, 9.44; N, 5.70. Found: C, 77.41; H, 9.54; N, 6.47.

(2*S*,3*R*)-3-(Diphenylmethylamino)-2-vinyltetrahydropyran (8a): white solid; R_f = 0.42 (hexane/AcOEt, 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.17 (m, 10H), 5.90 (ddd, J = 17.5, 10.2, 6.3 Hz, 1H), 5.39 (dd, J = 17.5, 1.1 Hz, 1H), 5.31 (dd, J = 10.2, 1.1 Hz, 1H), 4.99 (s, 1H), 3.91 (m, 1H), 3.59 (dd,

J = 6.3, 6.3 Hz, 1H), 3.40 (ddd, J = 10.2, 10.2, 3.4 Hz, 1H), 2.36 (ddd, J = 10.7, 6.3, 4.1 Hz, 1H), 2.15 (m, 1H), 1.60−1.51 (m, 2H), 1.32−1.23 (m, 1H); HRMS *m/z* calcd for $C_{20}H_{23}NO$ 293.1778, found 293.1764. $[\alpha]^{23}_D = -29.46$ (c = 0.66, $CHCl_3$). The ratio of enantiomers was determined to be 81/19 by HPLC analysis (hexane/i-PrOH = 95/5, flow rate = 0.5 mL/min): t_R = 11.1 min (major enantiomer), t_R = 12.7 min (minor enantiomer); 62% ee.

(2*S*,3*S*)-3-(Diphenylmethylamino)-2-vinyltetrahydropyran (8b): colorless oil; R_f = 0.64 (hexane/AcOEt, 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.15 (m, 10H), 6.05 (ddd, J = 17.3, 10.7, 5.1 Hz, 1H), 5.30 (dd, J = 17.3, 1.7 Hz, 1H), 5.23 (dd, J = 10.7, 1.7 Hz, 1H), 4.93 (s, 1H), 3.96 (m, 2H), 3.48 (ddd, J = 11.7, 11.7, 2.6 Hz, 1H), 2.67 (m, 1H), 2.04−1.86 (m, 2H), 1.49−1.36 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.8, 143.8, 137.0, 128.3, 127.5, 127.3, 126.9, 126.8, 115.6, 81.0, 67.9, 64.3, 52.1, 26.7, 20.8. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.86; H, 7.90; N, 4.77. Found: C, 81.82; H, 7.84; N, 4.72. $[\alpha]^{20}_D = -10.16$ (c = 0.52, $CHCl_3$). The ratio of enantiomers was determined to be 91/9 by HPLC analysis (hexane/i-PrOH = 95/5, flow rate = 0.5 mL/min): t_R = 10.5 min (major enantiomer), t_R = 12.2 min (minor enantiomer); 82% ee.

(2*R*,3*S*)-3-Diphenylmethylamino-2-vinyltetrahydrofuran (33): colorless oil; R_f = 0.64 (hexane/AcOEt, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.18 (m, 10H), 5.78 (ddd, J = 17.0, 10.3, 6.4 Hz, 1H), 5.30 (dd, J = 17.0, 1.6 Hz, 1H), 5.14 (dd, J = 10.3, 1.6 Hz, 1H), 4.92 (s, 1H), 4.11 (m, 1H), 3.90 (m, 2H), 3.03 (ddd, J = 7.2, 5.7, 5.7 Hz, 1H), 2.10 (m, 1H), 1.78 (m, 1H); HRMS *m/z* calcd for $C_{19}H_{21}NO$ 279.1623, found 279.1634. NOE was observed between H−C_2 and H−C_3 (1.8%). $[\alpha]^{20}_D$ = 2.61 (c = 0.31, $CHCl_3$). The ratio of enantiomers was determined to be 53.5/46.5 by HPLC analysis (hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min): t_R = 11.2 min (major enantiomer), t_R = 12.3 min (minor enantiomer); 7% ee.

(2*R*,3*R*)-3-Diphenylmethylamino-2-vinyltetrahydrofuran (34): colorless oil; R_f = 0.74 (hexane/AcOEt, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41−7.18 (m, 10H), 6.03 (ddd, J = 16.8, 10.5, 6.2 Hz, 1H), 5.38 (dd, J = 16.8, 1.4 Hz, 1H), 5.30 (dd, J = 10.5, 1.4 Hz, 1H), 4.88 (s, 1H), 4.31 (dd, J = 6.2, 1.1 Hz, 1H), 4.00 (ddd, J = 8.4, 8.4, 5.2 Hz, 1H), 3.74 (ddd, J = 8.4, 7.4, 7.4 Hz, 1H), 3.31 (ddd, J = 6.2, 6.2, 6.2 Hz, 1H), 2.07 (m, 1H), 1.85 (m, 1H), 1.58 (s, 1H). Anal. Calcd for $C_{19}H_{21}NO$: C, 81.67; H, 7.58; N, 5.01. Found: C, 81.54; H, 7.57; N, 4.96. NOE was observed between H−C_2 and H−C_3 (6.8%). $[\alpha]^{20}_D$ = 0.27 (c = 0.31, $CHCl_3$). The ratio of enantiomers was determined to be 92.5/7.5 by HPLC analysis (hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min): t_R = 10.1 min (major enantiomer), t_R = 13.4 min (minor enantiomer); 85% ee.

(2*S*,3*R*)-6-Dimethyl-3-(diphenylmethylamino)-2-vinyltetrahydropyran (36): white solid; R_f = 0.55 (hexane/AcOEt, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.12 (m, 10H), 5.80 (ddd, J = 17.5, 10.2, 6.3 Hz, 1H), 5.38 (dd, J = 17.5, 1.1 Hz, 1H), 5.29 (dd, J = 10.2, 1.1 Hz, 1H), 4.97 (s, 1H), 3.83 (dd, J = 6.3, 6.3 Hz, 1H), 2.25 (m, 1H), 1.97 (m, 1H), 1.62 (s, 1H), 1.46 (m, 2H), 1.26 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H); IR (neat) 3060, 1492 cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{27}NO$ 321.2093, found 321.2083. No NOE was observed between H−C_2 and H−C_3. $[\alpha]^{20}_D = -2.17$ (c = 0.66, $CHCl_3$) The ratio of enantiomers was determined to be 96.5/3.5 by HPLC analysis (hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min): t_R = 9.5 min (minor enantiomer), t_R = 11.9 min (major enantiomer); 93% ee.

(2*S*,3*S*)-6-Dimethyl-3-(diphenylmethylamino)-2-vinyltetrahydropyran (37): colorless oil; R_f = 0.83 (hexane/AcOEt, 7:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.16 (m, 10H), 6.10 (ddd, J = 17.3, 10.7, 5.1 Hz, 1H), 5.26 (dd, J = 17.3, 1.7 Hz, 1H), 5.19 (dd, J = 10.7, 1.7 Hz, 1H), 4.91 (s, 1H), 4.15 (m, 1H), 2.58 (m, 1H), 1.92 (m, 1H), 1.75 (ddd, J = 8.7, 8.7, 4.2 Hz, 1H), 1.58 (dddd, J = 8.7, 8.7, 4.2, 4.2 Hz, 1H), 1.29 (ddd, J = 8.7, 4.2, 4.2 Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H); IR (neat) 3026, 1490 cm^{-1}. Anal. Calcd for $C_{22}H_{27}NO$: C, 82.18; H, 8.47; N, 4.35. Found: C, 82.07; H, 8.50; N, 4.31. NOE was observed between H−C_2 and H−C_3 (7.0%). $[\alpha]^{20}_D = -4.63$ (c = 0.52, $CHCl_3$). The ratio of enantiomers was determined to be 43/57 by HPLC analysis (hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min): t_R = 11.2 min (minor enantiomer), t_R = 13.8 min (major enantiomer); 14% ee.

(2*S*,3*S*,5*S*)-5-Phenyl-3-(diphenylmethylamino)-2-vinyltetrahydropyran (39): white solid; R_f = 0.64 (hexane/AcOEt, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.16 (m, 15H), 6.33 (ddd, J = 17.3, 10.7, 6.8 Hz, 1H), 5.53 (dd, J = 17.3, 1.7 Hz, 1H), 5.45 (dd, J = 10.7, 1.7 Hz, 1H), 4.95 (s, 1H), 4.44 (dd, J = 6.8, 6.1 Hz, 1H), 3.67 (m, 2H), 2.98 (m, 1H), 2.87 (m, 1H), 2.13 (m, 1H), 1.74 (ddd, J = 12.5, 11.7, 11.4 Hz, 1H), 1.49 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.9, 143.8, 141.6, 132.0, 128.5, 128.4, 127.3, 127.2, 127.0, 126.7, 120.3, 77.3, 77.0, 76.6, 76.5, 66.5, 63.7, 53.1, 42.4, 33.0; IR (KBr) 2922, 1490 cm^{-1}; HRMS *m/z* calcd for $C_{26}H_{27}NO$ 369.2091, found 369.2057. $[\alpha]^{19}_D$ = −4.06 (c = 0.35, $CHCl_3$). The ratio of enantiomers was determined to be 2.4/97.6 by HPLC analysis (hexane/i-PrOH = 99/1, flow rate = 0.5 mL/min): t_R = 12.1 min (minor enantiomer), t_R = 15.9 min (major enantiomer); 90% ee.

(2*S*,3*S*,5*R*) or (2*R*,3*R*,5*S*)-5-Phenyl-3-(diphenylmethylamino)-2-vinyltetrahydropyran (40): white solid; R_f = 0.54 (hexane/AcOEt, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.17 (m, 15H), 6.08 (ddd, J = 17.3, 10.7, 4.8 Hz, 1H), 5.35 (dd, J = 17.3, 1.7 Hz, 1H), 5.29 (dd, J = 10.7, 1.7 Hz, 1H), 4.97 (s, 1H), 4.11−4.02 (m, 2H), 3.45 (dd, J = 11.4, 11.2 Hz, 1H), 1.62 (m, 1H), 2.85 (m, 1H), 2.29 (m, 1H), 1.71 (ddd, J = 13.1, 12.9, 2.9 Hz, 1H), 2.67 (br, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.8, 136.8, 128.5, 127.5, 126.7, 115.7, 80.9, 74.0, 64.6, 52.3, 36.7, 34.0; HRMS *m/z* calcd for $C_{26}H_{27}NO$ 369.2093, found 369.2072.

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Supporting Information Available: Experimental procedures and characterization of **5**, **7**, **13**−**16**, **20**−**23**, **25**, **27**, **31**, **32**, **35**, **38**, and **42**−**44**; copies of ^{1}H NMR and HRMS spectra of all new compounds not accompanied by elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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