Catalytic Asymmetric Construction of Morpholines and Piperazines by Palladium-Catalyzed Tandem Allylic Substitution Reactions

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Reaction of 1,4-diacetoxy-*cis*-2-butene (**1a**) with 2-(benzylamino)ethanol (**2a**) was catalyzed by a palladium complex (5 mol %) coordinated with (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl to give optically active (*R*)-4-benzyl-2-vinylmorpholine (**3a**) of up to 65% ee. Optically active 1,4-bis-(*p*-tolylsulfonyl)-2-vinylpiperazine (**7a**) (60% ee) was also obtained from 1,4-dicarbomethoxy-2-butene (**1b**) and 1,2-bis[(*p*-tolylsulfonyl)amino]ethane (**6a**) in a similar manner. This cyclization proceeds through a tandem allylic substitution via π-allylpalladium intermediates. The palladium-catalyzed reaction with 2-amino-1,3-propanediols 17 gave 2-vinyl-5-(hydroxymethyl)morpholines of up to 73% ee.

Introduction

Nitrogen heterocycles have aroused considerable interest due to their presence in a number of therapeutically and biologically active compounds.[1] Compared to the remarkable development of catalysis to provide carbocyclic compounds in an optically active form,[2,3] only a few methods have been reported for catalytic asymmetric synthesis of heterocycles.[4] Recently, it has been reported by Saegusa and co-workers that 2-buten-1,4-ylene diesters react with 2-aminoethanols or 1,2-diaminoethanes in the presence of palladium catalyst bearing triisopropyl phosphite ligand to give morpholine or piperazine skeleton.[5] These results prompted us to examine the extension of this reaction to the catalytic asymmetric cyclization by use of a chiral palladium catalyst. Here we wish to report the catalytic asymmetric construction of six-membered nitrogen heterocycles such as morpholines and piperazines.

Results and Discussion

1. Asymmetric Synthesis of 2-Vinylmorpholines and 2-Vinylpiperazines. Reaction of 1,4-diacetoxy-*cis*-2-butene (**1a**) with 2-(benzylamino)ethanol (**2a**) in THF in the presence of chiral phosphine–palladium catalysts and triethylamine gave 4-benzyl-2-vinylmorpholine (**3a**) as a single regioisomer (Scheme I). The vinylmorpholine

Scheme I

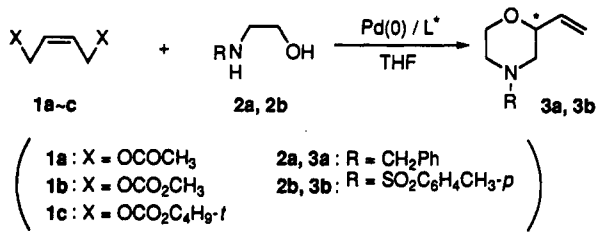

Table I. Palladium-Catalyzed Asymmetric Synthesis of 3a from 1a and 2a[a]

entry	ligand	temp (°C), time (h)	yield (%)[b] of **3a**	ee %[c]
1	(*R*)-MOP[d]	40, 24	31	16 (2*R*)
3	(*S,S*)-chiraphos[e]	40, 24	20	18 (2*R*)
3	(*R*)-(*S*)-BPPFA[f]	40, 2	60	13 (2*S*)
4	(*R*)-(*S*)-FcP*[g]	40, 2	55	18 (2*S*)
5	(*R*)-BINAP[h]	40, 14	72	61 (2*R*)
6[i]	(*R*)-BINAP	40, 72	22	65 (2*R*)
7[j]	(*R*)-BINAP	40, 1	44	64 (2*R*)
8[k]	(*R*)-BINAP	40, 24	73	58 (2*R*)
9[l]	(*R*)-BINAP	80, 22	76	49 (2*R*)

[a] All entries were carried out in THF under N_2 in the presence of palladium catalyst prepared in situ by mixing $Pd_2(dba)_3$·$CHCl_3$ (5 mol % Pd) and ligand ([Pd]/[P] = 1/2) unless otherwise noted. The ratio of **1a**/**2a** = 1/1. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral stationary phase column (DAICEL CHIRACEl-OJ, *n*-hexane/2-propanol = 59/1). Absolute configuration in parentheses. [d] (*R*)-2-(Diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (ref 8). [e] (2*S*,3*S*)-2,4-Bis(diphenylphosphino)butane (ref 9). [f] (*R*)-1-[(*S*)-1',2-Bis(diphenylphosphino)ferrocenyl]ethylamine (ref 10). [g] (*R*)-*N*-Methyl-*N*-bis[(hydroxymthyl)methyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (ref 10b). [h] (*R*)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (ref 6). [i] $[PdCl(\pi\text{-}C_3H_5)]_2$ was used in place of $Pd_2(dba)_3$·$CHCl_3$. [j] Pd[(*R*)-BINAP]$_2$ (5 mol %) (ref 7) was used. [k] Solvent = benzene. [l] Solvent = 1,2-dichloroethane.

3a was isolated by silica gel column chromatography and the enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (CHIRALCEL-OJ, eluent: *n*-hexane/2-propanol = 59/1). The results summarized in Table I reveal that the most stereoselective phosphine ligand is (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl ((*R*)-BINAP).[6] The cyclization with palladium catalyst prepared in situ by mixing tris(dibenzylidene-

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(1) For recent examples: (a) Ortwine, D. F.; Malone, T. C.; Bigge, C. F.; Drummond, J. T.; Humblet, C.; Johnson, G.; Pinter, G. W. *J. Med Chem.* **1992**, *35*, 1345. (b) Demaine, D. A.; Smith, S.; Barraclough, P. *Synthesis* **1992**, 1065. (c) Phillips, G. B.; Morgan, T. K., Jr.; Lumma, W. C., Jr.; Gomez, R. P.; Lind, J. M.; Lis, R.; Argentieri, T.; Sullivan, M. E. *J. Med. Chem.* **1992**, *35*, 743.

(2) Reviews on catalytic asymmetric reactions: (a) Brunner, H. *Synthesis* **1988**, 645. (b) Brunner, H. *Top. Stereochem.* **1988**, *18*, 129. (c) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257. (d) Noyori, R.; Kitamura, M. *Modern Synthetic Methods;* Scheffold, R., Ed.; Springer-Verlag: New York, 1989; Vol. 5, p 115. (e) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901. (f) Noels, A. F.; Graziani, M.; Hubert, A. J., Eds. *Metal Promoted Selectivity in Organic Synthesis*; Kluwer Academic Publishers: Dordrecht, 1991.

(3) For catalytic asymmetric Diels–Alder reactions: (a) Yamamoto, H.; Maruoka, K.; Furuta, K. *Selectivities in Lewis Acid Promoted Reactions;* Schinzer, D. Ed.; Kluwer Academic Publishers: Dordrecht, 1989; p 281. (b) Taschner, M. J. *Organic Synthesis, Theory and Applications;* Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1989.

(4) For recent examples: (a) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 669. (b) Mori, M.; Nukui, S.; Shibasaki, M. *Chem. Lett.* **1991**, 1797. (c) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327.

(5) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388.

(6) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

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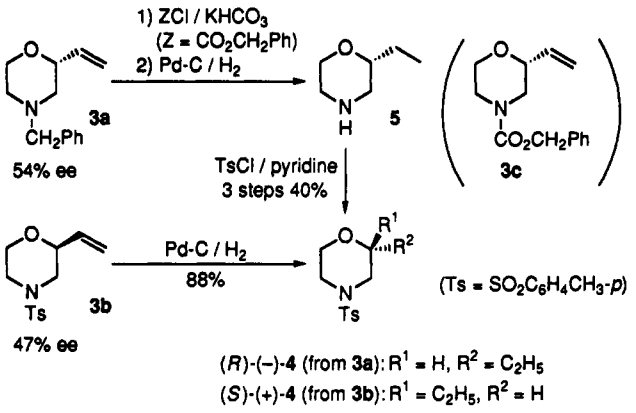
acetone)dipalladium ($Pd_2(dba)_3$·$CHCl_3$) and BINAP gave **3a** of 61% ee in 72% yield (entry 5). The use of bis(BINAP)palladium(0)[7] or palladium catalyst generated from $[PdCl(\pi\text{-}C_3H_5)]_2$ and BINAP increased the enantioselectivity to 65% though the chemical yield was lower (entries 6 and 7). Palladium complexes of other phosphine ligands including (*R*)-(2-diphenylphosphino)-2′-methoxy-1,1′-binaphthyl ((*R*)-MOP),[8] (2*S*,3*S*)-bis(diphenylphosphino)butane ((*S*,*S*)-chiraphos)[9]or optically active ferrocenylphosphine ligands[10] were less catalytically active and/or less stereoselective (entries 1–4).

The catalytic cyclization forming vinylmorpholine was examined with 2-[(*p*-tolylsulfonyl)amino]ethanol (**2b**) (Scheme I). The cyclization did not take place with diacetate **1a** under similar reaction conditions to those for **2a**, 84% of the starting diacetate being recovered after 24 h. Dicarbonate esters, methyl carbonate **1b** and *tert*-butyl carbonate **1c**, were found to undergo the reaction with sulfonamide **2b** to give optically active 2-vinyl-4-(*p*-tolylsulfonyl)morpholine (**3b**) in 32 and 64% yields, respectively. The enantiomeric excess was determined by the HPLC analysis to be 50% ee. It is known that an allylic carbonate reacts with a palladium(0) to give a cationic π-allylpalladium complex along with a carbonate anion which undergoes the decarboxylation to generate an alkoxy anion.[11] Abstraction of the acidic proton on amide nitrogen by the alkoxy anion will increase the nucleophilicity of the amide to react with the π-allylpalladium intermediate.

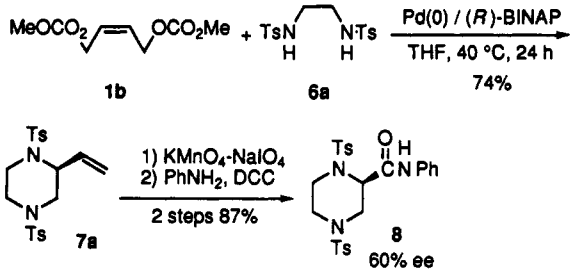
The absolute configuration of vinylmorpholines (+)-**3a** and (+)-**3b** was determined by correlation with the known 2-ethyl-4-(*p*-tolylsulfonyl)morpholine (**4**).[12] Since direct hydrogenolysis of the *N*-benzyl moiety of **3a** was not successful, stepwise transformation of **3a** to 2-ethylmorpholine (**5**) was carried out. Thus, the benzyl group in **3a** was replaced by carbobenzyloxy by treatment with 10 equiv of benzyl chloroformate in the presence of potassium bicarbonate,[13] and removal of carbobenzyloxy and hydrogenation of vinyl in **3c** giving 2-ethylmorpholine (**5**)[12] was achieved simultaneously by palladium-catalyzed hydrogenation (H_2 (1 atm), 10% Pd–C (5 mol %)). Ethylmorpholine **5** was readily converted into sulfonamide **4** (three steps 40% yield from **3a**) which turned out to be the (*R*) isomer by measurement of the optical rotation (**4** (from(+)-**3a**): $[\alpha]^{20}_D$ −18.8° (*c* 2.0, chloroform), lit.[12] for (*S*)-**4**: $[\alpha]^{20}_D$ +37° (chloroform)). On the other hand, hydrogenation of **3b** gave **4** with opposite configuration, (*S*) (**4** (from(+)-**3b**): $[\alpha]^{20}_D$ +14.8° (*c* 1.1, chloroform)) (Scheme II). It follows that vinylmorpholines **3a** and **3b** obtained by the asymmetric cyclization have absolute configuration of (*R*) and (*S*), respectively.

Optically active piperazine **7a** was also synthesized from **1b** and 1,2-bis[(*p*-tolylsulfonylamino]ethane (**6a**) under similar conditions. The reaction in THF in the presence of $Pd_2(dba)_3$·$CHCl_3$ (5 mol %) and (*R*)-BINAP (1 equiv to Pd) at 40 °C for 24 h gave 74% yield of 2-vinylpiperazine **7a**. The enantiomeric excess of **7a** was determined to be 60% ee by HPLC analysis (Sumichiral OA-4500, *n*-hexane/dichloroethane/ethanol = 50/15/1) of anilide **8** which was prepared by the oxidation with potassium permanganate–sodium periodate followed by condensation of the resulting carboxylic acid with aniline by use of dicyclohexylcarbodiimide (Scheme III). Interestingly, 1,4-dibenzylpiperazine **7b** obtained in 71% yield from diacetate **1a** and 1,2-bis(benzylamino)ethane (**6b**) was racemic (*vide infra*).

Scheme II



Scheme III



The absolute configuration of **7a** was determined by correlation with (*R*)-**13** which was prepared from commercially available (*R*)-2-ethyl-2-aminoethanol ((*R*)-**10**) by the following reactions: Bis[(*p*-tolylsulfonyl)amino]ethanol (**9**) reacted with (*R*)-**10** to give hydroxy diamine (*R*)-**11**, the treatment of which with *p*-toluenesulfonyl chloride in the presence of pyridine gave a mixture of tris(*p*-tolylsulfonyl) derivative (*R*)-**12** and piperazine (*R*)-**13**. The crude mixture was exposed to sodium hydride to complete the cyclization giving (*R*)-(−)-**13** ($[\alpha]^{20}_D$ −6.2° (*c* 0.55, chloroform)) as a pure material. Comparison of the optical rotation of **13** which was obtained from **7a** by the palladium-catalyzed hydrogenation with that of authentic (*R*)-**13** revealed the absolute configuration of (+)-**7a** to be (*S*) ((*S*)-(+)-**13** (from **7a**): $[\alpha]^{20}_D$ +5.2° (*c* 1.1, chloroform)) (Scheme IV).

2. Reaction Pathway. In the reaction of **1** with **2**, morpholine **3** bearing a vinyl group at the C-2 position was produced as a single regioisomer. Scheme V illustrates the plausible reaction pathway for the regioselective formation of **3a** in the reaction of **1a** with **2a**. The first nucleophilic allylic substitution on π-allylpalladium intermediate **14** which is generated by the reaction of 1,4-diacetoxy-2-butene with a palladium(0) species (step I) takes place with the amino group in **2a** at the sterically less-hindered π-allyl carbon to give allylic amine **15** (step II). The nucleophilic attack of the amino group rather than the hydroxy group is consistent with the reports that

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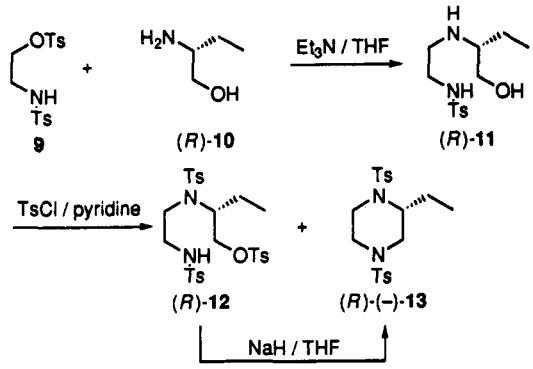
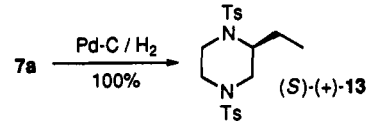
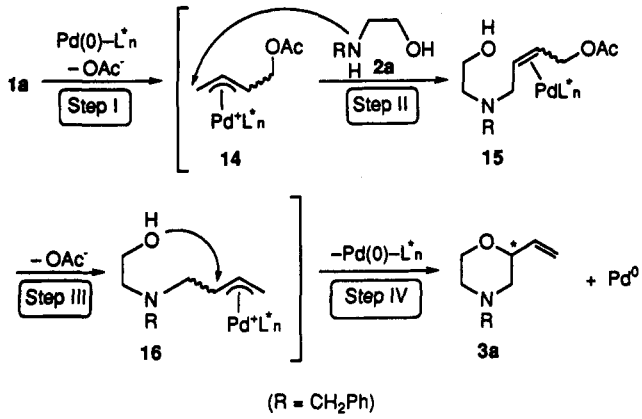
(8) (a) Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887. (b) Uozumi, Y.; Tanahashi, A.; Lee, S-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.
(9) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.
(10) (a) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7. (b) Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191.
(11) (a) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. (b) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.
(12) Bettoni, G.; Franchini, C.; Perrone, R.; Tortorella, V. *Tetrahedron* **1980**, *36*, 409.
(13) Rice, K. C. *J. Org. Chem.* **1975**, *40*, 1850.

Scheme IV





Scheme V



(R = CH_2Ph)

nitrogen nucleophiles are generally more reactive toward π-allylpalladium than oxygen nucleophiles.[14] Formation of π-allylpalladium intermediate **16** followed by intramolecular attack of hydroxy group on the π-allyl[15] produces the morpholine **3a** where the vinyl group is placed on the carbon bonded to the second nucleophile, namely the hydroxy group on **2a**.

This cyclization reaction consists of several steps as shown in Scheme V. In order to specify the enantioselective step, reactions of (*E*) and (*Z*) isomers of **1a** and **1b** were examined under the same reaction conditions (Scheme VI). Table II reveals that the reaction of (*E*)-**1a** with 2-(benzylamino)ethanol (**2a**) gave exactly the same stereochemical outcome as that of (*Z*)-**1a** (entries 1 and 2).

It has been reported that the nucleophilic attack of benzylamine on π-allylpalladium is much faster than the *syn–anti* isomerization of a π-allylpalladium intermediate bearing the alkyl group at 1 position of the π-allyl.[16] Accordingly, the allylic amines **15** (Scheme V) formed at the first nucleophilic substitution of (*E*)-**1a** and (*Z*)-**1a** must have (*E*) and (*Z*) olefinic double bonds, respectively,

(14) Few reports have appeared which demonstrate the intermolecular nucleophilic attack of alkoxy anions to π-allylpalladium complexes. For a recent review: Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1992**, *3*, 1089.

(15) For a recent example for intramolecular attack of hydroxy group: Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747.

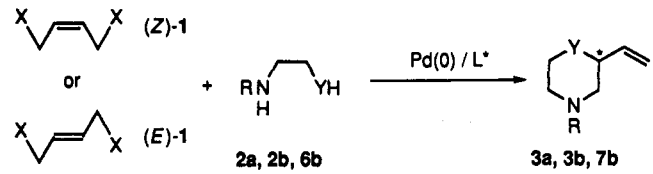
(16) Hayashi, T.; Kishi, K.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 1743.

Table II. Palladium-Catalyzed Asymmetric Cyclization using (*E*)- and (*Z*)-1[a]

entry	substrates	product	yield (%)[b]	% ee[c]
1	(*E*)-**1a**, **2a**	**3a**	72	61 (*R*)
2	(*Z*)-**1a**, **2a**	**3a**	72	61 (*R*)
3[d]	(*E*)-**1b**, **2b**	**3b**	38	47 (*R*)
4[d]	(*Z*)-**1b**, **2b**	**3b**	32	50 (*R*)
5	(*E*)-**1a**, **6b**	**7b**	70	<3
6	(*Z*)-**1a**, **6b**	**7b**	71	<3

[a] All reactions were run in THF at 40 °C in the presence of triethylamine and palladium catalyst prepared in situ by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*)-BINAP. The ratio of 1/2(6)/triethylamine/Pd/BINAP = 1.0/1.0/2.0/0.05/0.05 unless otherwise noted. [b] Isolated yield. [c] Determined by HPLC analysis with a chiral stationary phase column (see text). [d] Triethylamine was not used.

Scheme VI



1a: X = OAc
1b: X = OCOOMe

2a, 3a: R = CH_2Ph, Y = O
2b, 3b: R = $SO_2C_6H_4CH_3$-*p*, Y = O
6b, 7b: R = CH_2Ph, Y = NCH_2Ph

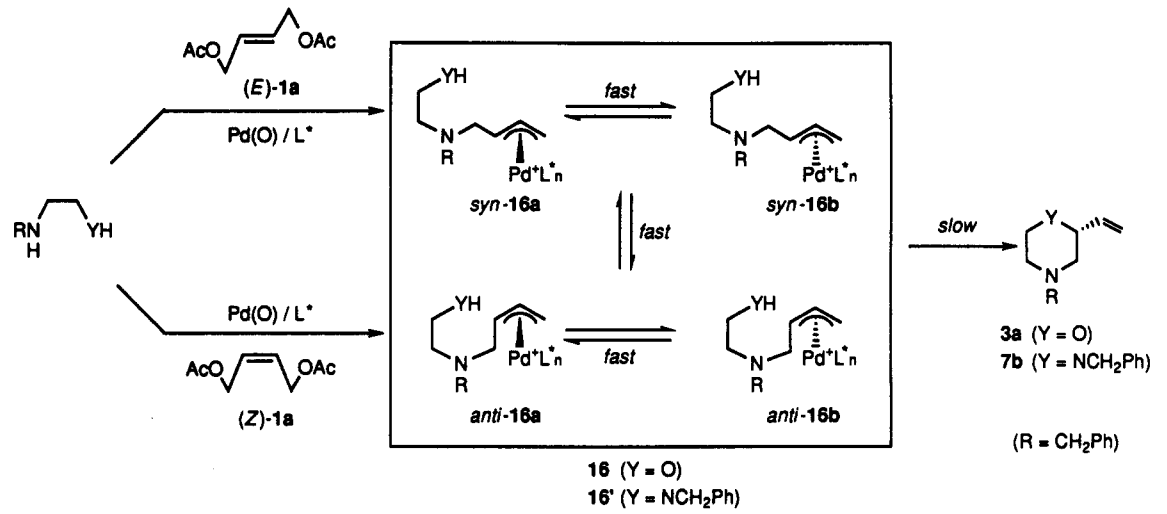
the oxidative addition of which to palladium(0) will give π-allylpalladium intermediate having *syn*-π-allyl (*syn*-**16**) and its *anti*-isomer (*anti*-**16**), respectively (Scheme VII). The same stereochemical results observed in the reaction of (*E*)-**1a** and (*Z*)-**1a** indicates that the second nucleophilic attack takes place after the *syn–anti* isomerization and epimerization of π-allylpalladium intermediates **16** reach the equilibrium, and the enantiomeric purity of the product **3a** is related to thermodynamic stability of the diastereomeric isomers *syn*-**16a**, *anti*-**16a**, *syn*-**16b**, and *anti*-**16b** at equilibration.

The important role of the equilibration of the π-allyl intermediates **16** on the stereoselectivity was also observed in the reaction of **1b** with **2b** where (*E*) and (*Z*) isomers of **1b** gave almost the same results with respect to enantiomeric purity of morpholine **3b** (entries 3 and 4).

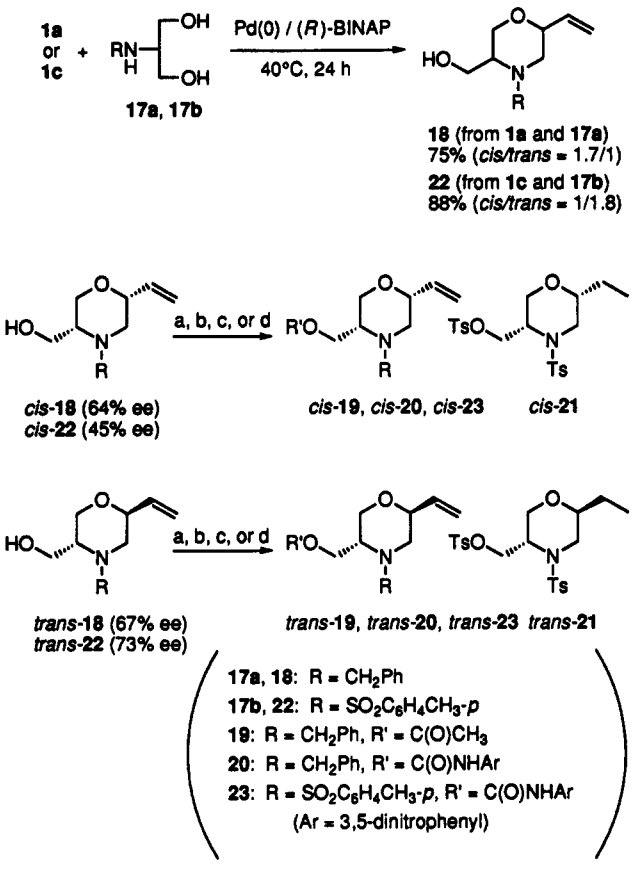
The formation of racemic piperazine **7b** in the reaction of 1,2-bis(benzylamino)ethane (**6b**) is accounted for by the high reactivity of the amino nucleophile toward π-allylpalladium. Thus, the cyclization by the second nucleophilic attack of the benzylamino group takes place before the equilibration of π-allylpalladium intermediates **16′**. The equilibration would bring about one of the diastereomeric isomers **16′** more than others.

3. 2,5-Disubstituted Morpholines. The catalytic asymmetric cyclization was extended to one step synthesis of 2,5-disubstituted morpholines (Scheme VIII). The reaction of *N*-benzylserinol (**17a**) with **1a** in the presence of the palladium–(*R*)-BINAP catalyst under the similar conditions followed by separation by silica gel column chromatography gave 47% yield of *cis*-2-vinyl-5-(hydroxymethyl)morpholine (*cis*-**18**) and 28% yield of its *trans* isomer (*trans*-**18**). The *cis*/*trans* stereochemistry was determined by ^1H NMR studies of the acetates **19**. The HPLC analysis of (3,5-dinitrophenyl)carbamates **20** with a chiral stationary phase column (*cis*-**18**: Sumichiral OA-1100, *n*-hexane/dichloroethane/ethanol = 50/15/1. *trans*-**18**: Sumichiral OA-2500I, *n*-hexane/dichloroethane/ethanol = 50/15/1) revealed that the enantiomeric purities

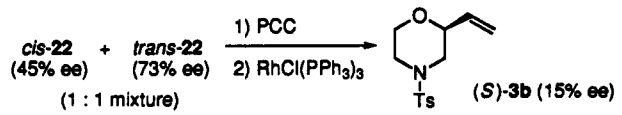
Scheme VII



Scheme VIII[a]



[a] (a) For **19**: Ac_2O/pyridine. (b) For **20**, **23**: 3,5-$(O_2N)_2C_6H_3NCO$/pyridine. (c) For **21** (from **18**): (i) $PhCH_2OCOCl/KHCO_3$, (ii) Pd-C/H_2, (iii) TsCl/pyridine. (d) For **21** (from **22**): (i) Pd-C/H_2, (ii) TsCl/pyridine



of *cis*-**18** and *trans*-**18** are 64% ee and 67% ee, respectively. The reaction of *N*-(*p*-tolylsulfonyl)serinol also gave cyclization product **22** in 88% yield as a mixture of *cis* and *trans* isomers in a ratio of 1:1.8. The reversal of the diastereoselectivity in the reaction of **17a** and **17b** is interesting, though it is difficult to rationalize the selectivity. The *cis* and *trans* isomers of **22** were fully characterized by ^{1}H NMR of 2-ethyl-5-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (**21**) and the enantiomeric excess was determined by the HPLC analysis of carbamates **23** to be 45% ee for *cis*-**22** and 73% ee for *trans*-**22**. The absolute configuration at C-2 position of **22** was determined by the correlation with 2-vinylmorpholine **3b**, which was realized by the oxidation of primary alcohol into aldehyde with pyridinium chlorochromate followed by decarbonylation with Wilkinson's complex.[17] The results and correlation between **18** and **22** via *N*,*O*-bis(*p*-tolylsulfonyl) derivative **21** demonstrated that the *cis* isomers of **18** and **22** have (2*R*,5*R*) configuration and their *trans* isomers have (2*S*,5*R*) configuration.

To summarize, we have established a new method for catalytic asymmetric construction of morpholines and piperazines. This method was realized by use of tandem allylic substitution reactions via π-allylpalladium intermediates having an optically active phosphine ligand. Mechanistic consideration revealed that the asymmetric induction is controlled by the thermodynamic equilibration of the π-allylpalladium intermediates before the second nucleophilic attack giving the heterocycles.

Experimental Section

General. Melting points were measured with a hot stage microscope (YANACO MP-S3) and are uncorrected. ^{1}H NMR spectra were measured on a JEOL JNM-EX90 spectrometer (90 MHz), JEOL JNM-EX270 spectrometer (270 MHz), or JEOL JNM-EX400 spectrometer (400 MHz) in $CDCl_3$. Chemical shifts of protons are reported in δ ppm referred to tetramethylsilane as an internal standard. The detailed ^{1}H NMR assignments for *cis*-**18**, *trans*-**18**, *cis*-**19**, *trans*-**19**, *cis*-**21**, and *trans*-**21** were performed by decoupling experiments. IR spectra were recorded on a Perkin Elmer 1720X FT-IR spectrometer. EI-mass spectra and high-resolution mass spectra were measured on a JEOL JMS-DX-303 spectrometer at an ionization voltage of 70 eV. Silica gel column chromatography was carried out using Merck silica gel 60 (70325 mesh ASTM). Air- and moisture-sensitive reactions were performed under usual inert atmosphere techniques. All dry solvents were distilled under N_2. THF and Et_2O were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from CaH_2. The purity of all compounds was judged to be ≥95% by ^{1}H NMR spectral determination.

(*R*)-4-Benzyl-2-vinylmorpholine (3a)[5] (Table I, entry 6). To a solution of tris(dibenzylideneacetone)dipalladium (6.5 mg, 0.0063 mmol) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaph-

(17) Tsuji, J.; Ohno, K. *Synyhesis* **1969**, 157.

thyl (7.8 mg, 0.013 mmol) in 2.5 mL of THF was added triethylamine (70 μL, 0.5 mmol) at ambient temperature, and the solution was stirred for 90 min. To the solution was added **2a** (38 mg, 0.25 mmol) and (*Z*)-**1a** (43 mg, 0.25 mmol), and the mixture was heated with stirring at 40 °C for 14 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure to give a red-brown residue. The residue was chromatographed on silica gel (elution with *n*-hexane/EtOAc = 1/3) to give **3a** as a pale yellow oil (36 mg, 72%). The enantiomeric excess was determined by HPLC analysis (CHIRALCEL OJ, *n*-hexane/2-propanol = 59/1) to be 61% ee: $[\alpha]_D^{20}$ +4.9° (*c* 0.84, chloroform); ^{1}H NMR ($CDCl_3$) δ 7.33–7.27 (m, 5H), 5.80 (ddd, *J* = 17.5, 10.6, 5.6 Hz, 1H), 5.29 (dt, *J* = 17.5, 1.7 Hz, 1H), 5.14 (dt, *J* = 10.6, 1.7 Hz, 1H), 4.06–4.01 (m, 1H), 3.89 (ddd, *J* = 11.2, 3.3, 1.7 Hz, 1H), 3.71 (dt, *J* = 11.2, 2.3 Hz, 1H), 3.51 (s, 2H), 2.76 (dt, *J* = 11.2, 2.3 Hz, 1H), 2.67 (ddd, *J* = 11.2, 4.2, 2.4 Hz, 1H), 2.18 (dt, *J* = 11.1, 3.3 Hz, 1H), 1.93 (dd, *J* = 11.1, 10.2 Hz, 1H).

(*S*)-4-(*p*-Tolylsulfonyl)-2-vinylmorpholine (3b). A solution of tris(dibenzylideneacetone)dipalladium (6.5 mg, 0.0063 mmol) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (7.8 mg, 0.013 mmol) in 2.5 mL of THF was stirred at ambient temperature for 90 min. To the solution were added **2b** (54 mg, 0.25 mmol) and (*Z*)-**1c** (71 mg, 0.25 mmol), and the mixture was heated with stirring at 40 °C for 24 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure to give red-brown residue. The residue was chromatographed on silica gel (elution with *n*-hexane/EtOAc = 3/1) to give **3b** as a pale yellow solid (43 mg, 64%). The enantiomeric excess was determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/2-propanol = 19/1) to be 50% ee: mp 126–127 °C; $[\alpha]_D^{20}$ +33.7° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 5.72 (ddd, *J* = 17.5, 10.9, 5.6 Hz, 1H), 5.33 (dt, *J* = 17.5, 1.3 Hz, 1H), 5.22 (dt, *J* = 10.9, 1.3 Hz, 1H), 4.08–4.02 (m, 1H), 3.95 (ddd, *J* = 11.6, 3.3, 1.3 Hz, 1H), 3.72 (dt, *J* = 11.2, 2.6 Hz, 1H), 3.61 (dt, *J* = 11.2, 1.3 Hz, 1H), 3.53 (br d, *J* = 11.6 Hz, 1H), 2.44 (s, 3H), 2.41 (dt, *J* = 11.6, 3.6 Hz, 1H), 2.12 (dd, *J* = 11.2, 10.6 Hz, 1H); MS m/z 267 (M^+), 224, 155, 112 (bp); HRMS calcd for $C_{13}H_{17}O_3NS$ 267.0929, found 267.0951. Anal. Calcd for $C_{13}H_{17}O_3NS$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.27; H, 6.52; N, 5.20.

(*R*)-4-(*p*-Tolylsulfonyl)-2-ethylmorpholine (4) (from 3a).[12] To the solution of **3a** (54% ee, 201 mg, 0.99 mmol) in chloroform (25 mL) were added potassium bicarbonate (1.73 g, 17.3 mmol) and benzyl chloroformate (1.4 mL, 9.9 mmol) at ambient temperature. The mixture was refluxed for 24 h. After being cooled, the mixture was washed with H_2O, 1 N HCl, and saturated $NaHCO_3$. The organic phase was concentrated under reduced pressure. The residue was dissolved in 15 mL of MeOH and to the solution were added 1 N KOH (11 mL) and $KHCO_3$ (1.1 g, 11 mmol). The mixture was stirred at ambient temperature for 12 h and followed by acidification (pH ≅ 2) with concd HCl. The mixture was concentrated under reduced pressure to give an aqueous residue. The residue was extracted with Et_2O (30 mL x 2). The extract was washed with H_2O and saturated $NaHCO_3$ and dried over Na_2SO_4. After concentration under reduced pressure, benzyl alcohol was removed by bulb-to-bulb distillation to give a brown oily residue. The residue was chromatographed on silica gel (*n*-hexane/EtOAc = 2/1) to give 4-(carbobenzyloxy)-2-vinylmorpholine as pale yellow oil (237.1 mg, 0.96 mmol, 97%): ^{1}H NMR ($CDCl_3$) δ 7.36–7.31 (m, 5H), 5.79 (ddd, *J* = 17.2, 10.9, 5.5 Hz, 1H), 5.35 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.23 (dt, *J* = 10.9, 1.4 Hz, 1H), 5.15 (s, 2H), 4.15–3.84 (m, 4H), 3.59 (dt, *J* = 11.7, 2.5 Hz, 1H), 3.04 (br t, *J* = 10.8 Hz, 1H), 2.77 (br t, *J* = 10.8 Hz, 1H); MS *m/z* 247 (M^+), 156, 112, 91 (bp); HRMS calcd for $C_{14}H_{17}O_3N$ 247.1209, found 247.1231.

To the solution of 4-(carbobenzyloxy)-2-vinylmorpholine (220 mg, 0.89 mmol) in THF (10 mL) was added 10% palladium on charcoal (95 mg). The mixture was stirred at ambient temperature for 15 h under H_2 atmosphere (1 atm). The mixture was filtered through Celite plug and the filtrate was concentrated under reduced pressure to give crude 2-ethylmorpholine (**5**) which was dissolved in CH_2Cl_2 (2 mL). To the solution was added pyridine (105 μL, 1.3 mmol) and *p*-tolylsulfonyl chloride (191 mg, 1 mmol), and the mixture was stirred at ambient temperature for 4 h. After concentration under reduced pressure, the residue was chromatographed on silica gel to give **4** (98 mg, 0.36 mmol two steps, 40%): $[\alpha]_D^{20}$ −18.8° (*c* 2.0, chloroform) (lit. rotation for (*S*)-**4**;[12] $[\alpha]_D^{20}$ +37° (chloroform)); ^{1}H NMR ($CDCl_3$) δ 7.53 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.79 (dd, *J* = 11.6, 2.0 Hz, 1H), 3.56 (dt, *J* = 11.6, 2.6 Hz, 1H), 3.44 (br t, *J* = 11.6 Hz, 2H), 3.32 (m, 1H), 2.34 (s, 3H), 2.28 (dt, *J* = 11.6, 3.6 Hz, 1H), 1.93 (dd, *J* = 10.9, 10.2 Hz, 1H), 1.35 (dq, *J* = 14.2, 7.3 Hz, 2H), 0.83 (t, *J* = 7.6 Hz, 3H); MS *m/z* 269 (M^+), 240, 155, 114 (bp); HRMS calcd for $C_9H_9O_3NS$ (M^+ − 29 (ethyl)) 240.0695, found 240.0671.

(*R*)-4-(*p*-Tolylsulfonyl)-2-ethylmorpholine (4) (from 3b).[12] To a solution of **3b** (47% ee, 25 mg, 0.095 mmol) in THF (1 mL) was added 10% palladium on charcoal. The mixture was stirred at ambient temperature under an atmospheric pressure of hydrogen for 12 h. After filtration of the mixture, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane/EtOAc = 3/1) to give **4** (22.4 mg, 88%): $[\alpha]_D^{20}$ +14.8° (*c* 2.0, chloroform) (lit. rotation for (*S*)-**4**;[12] $[\alpha]_D^{20}$ +37° (chloroform)).

1,4-Bis(p-tolylsulfonyl)-2-vinylpiperazine (7a).[5] Solution of tris(dibenzylideneacetone)dipalladium (13 mg, 0.013 mmol) and (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (15.6 mg, 0.026 mmol) in 5 mL of THF was stirred at ambient temperature for 90 min. To the solution were added **6a** (184.1 mg, 0.5 mmol) and (*Z*)-**1b** (101.2 mg, 0.5 mmol), and the mixture was heated with stirring at 40 °C for 24 h. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure to give a brown solid. The solid was washed with Et_2O and dissolved in CH_2Cl_2. Insoluble materials were filtered off and the filtrate was concentrated under reduced pressure to give powder. The powder was collected by filtration and washed with Et_2O to give **7a** (155.7 mg, 74%): mp 165–167 °C; $[\alpha]_D^{20}$ +8.8° (*c* 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ 7.60 (d, *J* = 8.3 Hz, 2H), 7.56 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 5.73 (ddd, *J* = 17.5, 10.6, 6.3 Hz, 1H), 5.25 (d, *J* = 17.5 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 4.45 (br s, 1H), 3.66–3.55 (m, 3H), 3.24 (ddd, *J* = 14.0, 11.6, 2.6 Hz), 2.57 (dd, *J* = 11.6, 3.6 Hz, 1H), 2.48–2.41 (m, 1H), 2.45 (s, 3H), 2.41 (s, 3H).

1,4-Bis(*p*-tolylsulfonyl)piperazine-2-carboxamide (8). To the solution of **7a** (50 mg, 0.12 mmol) in *t*-BuOH (2.4 mL) were added the 2.4 mL of aqueous solution of $NaIO_4$ (381 mg, 1.78 mmol) and $KMnO_4$ (48 mg, 0.30 mmol) at ambient temperature. The mixture was made basic (pH ≅ 8) with the addition of 1 N NaOH and stirred overnight. After removal of approximately half of the solvent *in vacuo*, the mixture was acidified (pH 2∼3) by concd HCl. The mixture was extracted by CH_2Cl_2 (20 mL × 2) and evaporated. The residue was dissolved in Et_2O (20 mL) and extracted by 1 N NaOH. The aqueous phase was acidified (pH ≅ 2) and extracted by Et_2O (20 mL × 2). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give crude 1,4-bis(*p*-tolylsulfonyl)piperazine-2-carboxylic acid (48 mg). The crude material was taken on to the next step without purification.

To a solution of the crude material in benzene (3 mL) were added dicyclohexylcarbodiimide (22.7 mg, 0.11 mmol) and aniline (10 μL, 0.11 mmol). The mixture was stirred for 14 h at ambient temperature. After filtration, the filtrate was washed with 10% HCl and saturated $NaHCO_3$ and dried over Na_2SO_4. After removal of the solvent, powdery material was collected by filtration and washed with Et_2O to give **8** (50 mg, 81%). The enantiomeric excess was determined by HPLC analysis with chiral stationary phase column (Sumichiral OA-4500, *n*-hexane/dichloroethane/EtOH = 50/15/1) to be 60% ee: ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.35–7.26 (m, 6H), 7.13 (t, *J* = 7.3 Hz, 1H), 4.60 (br s, 1H), 4.38 (br d, *J* = 12.2 Hz, 1H), 3.95 (br d, *J* = 14.2 Hz, 1H), 3.51 (br d, *J* = 11.9 Hz, 1H), 3.31 (ddd, *J* = 14.9, 11.6, 3.3 Hz, 1H), 2.44 (s, 3H), 2.42 (s, 3H), 2.32–2.25 (m, 2H); MS *m/z* 514 (M^+ + 1), 513 (M^+), 421, 358, 238, 83 (bp); HRMS calcd for $C_{25}H_{27}O_5N_3S_2$ 513.1392, found 513.1390.

The purity of titled compound **8** was judged to be >98% by the HPLC analysis.

(*R*)-1,4-Bis(*p*-tolylsulfonyl)-2-ethylpiperazine ((*R*)-13). A solution of **9** (1.12 g, 3 mmol), (*R*)-**10** (270 mg, 3 mmol), and triethylamine (840 μL, 6 mmol) in 3 mL of CH_2Cl_2 was stirred

at ambient temperature for 7 days. After concentration, the resulting residue was dissolved in benzene (5 mL) and pyridine (5 mL). To the solution was added *p*-toluenesulfonyl chloride (1.43 g, 7.5 mmol) and refluxed for 19 h. The reaction mixture was diluted with benzene, washed with 10% HCl, saturated $NaHCO_3$, and brine, and dried over Na_2SO_4. After removal of solvent, the residue was chromatographed on silica gel (*n*-hexane/EtOAc = 3/1) to give a mixture of (*R*)-**12** and (*R*)-**13** (84 mg). To a suspension of NaH (60% mineral oil dispersion, 11.2 mg, 0.28 mmol) in 10 mL of THF was added a solution of the mixture ((*R*)-**12** and (*R*)-**13**) in THF (7 mL) at 5 °C. The reaction mixture was stirred at 5 °C for 19 h. The mixture was diluted with Et_2O, quenched with a small amount of water, washed with H_2O, and dried over Na_2SO_4. After removal of solvent, the resulting residue was chromatographed on silica gel (*n*-hexane/EtOAc = 3/1) to give (*R*)-**13** (74 mg, 0.18 mmol, 6%): $[\alpha]^{20}_D$ −6.2° (*c* 0.55, chloroform); IR (Nujol) ν 1559, 1342, 1310, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 3.75 (br d, J = 12.2 Hz, 1H), 3.59 (d, J = 11.5 Hz, 2H), 3.20 (ddd, J = 13.6, 12.2, 3.0 Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 2.28 (dd, J = 11.9 and 3.3 Hz, 1H), 2.19 (dd, J = 11.9, 3.0 Hz, 1H), 1.72 (ddq, J = 14.0, 7.6, 6.6 Hz, 1H), 1.49 (ddq, J = 14.0, 7.3, 6.6 Hz, 1H), 0.82 (dd, J = 7.6, 7.3 Hz, 3H); MS *m/z* 422 (M^+), 393, 267 (bp); HRMS calcd for $C_{20}H_{26}O_4N_2S_2$ 422.1335, found 422.1306. Anal. Calcd for $C_{20}H_{26}O_4N_2S_2$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.88; H, 6.44; N, 6.71.

(*S*)-1,4-Bis(*p*-tolylsulfonyl)-2-ethylpiperazine ((*S*)-13). A mixture of **7a** (60% ee, 21 mg, 0.05 mmol) and 10% palladium on charcoal (5.3 mg) in THF (1.5 mL) was stirred under H_2 atmosphere (1 atm). After filtration, removal of the solvent under reduced pressure gave white precipitates, and the precipitates were collected by filtration to give (*S*)-**13** (21 mg, 100%): $[\alpha]^{20}_D$ +5.2° (*c* 1.1, chloroform); ^1H NMR ($CDCl_3$) δ 7.61 (d, J = 8.6 Hz, 2H), 7.55 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 3.75 (br d, J = 12.2 Hz, 1H), 3.59 (d, J = 11.5 Hz, 2H), 3.20 (ddd, J = 13.6, 12.2, 3.0 Hz, 1H), 2.45 (s, 3H), 2.39 (s, 3H), 2.28 (dd, J = 11.9 and 3.3 Hz, 1H), 2.19 (dd, J = 11.9, 3.0 Hz, 1H), 1.72 (ddq, J = 14.0, 7.6, 6.6 Hz, 1H), 1.49 (ddq, J = 14.0, 7.3, 6.6 Hz, 1H), 0.82 (dd, J = 7.6, 7.3 Hz, 3H).

1,4-Dibenzyl-2-vinylpiperazine (7b).[5] According to the general procedure as described for **3a**, (*E*)-**1a** (40 mg, 0.23 mmol) was reacted with **6b** (60 mg, 0.25 mmol) for 24 h. After workup, followed by silica gel column chromatography (*n*-hexane/EtOAc = 2/1) gave **7b** (46 mg, 70%) as a light brown oil: ^1H NMR ($CDCl_3$) δ 7.32–7.24 (m, 10H), 5.86 (ddd, J = 17.5, 8.9, 1.7 Hz, 1H), 5.29 (dd, J = 17.5, 1.7 Hz, 1H), 5.20 (dd, J = 10.2, 1.7 Hz, 1H), 4.07 (d, J = 13.4 Hz, 1H), 3.53 (dd, J = 15.5, 12.5 Hz, 2H), 3.10 (d, J = 13.4 Hz, 1H), 3.03–3.00 (m, 1H), 2.77–2.71 (m, 3H), 2.24–2.05 (m, 3H), 3.04–2.80 (m, 1H); MS *m/z* 292 (M^+), 251, 201, 91 (bp).

***N*-Benzylserinol (17a).** To a solution of (*dl*)-serine (5.25 g, 0.05 mol) in Et_2O (50 mL) and sat $NaHCO_3$ (50 mL) was added benzoyl chloride (5.8 mL, 0.05 mol) dropwise at 0 °C. The reaction mixture was stirred at ambient temperature for 5 days and separated. The aqueous phase was acidified (pH 3) with concd HCl, extracted with EtOAc (50 mL × 3), and dried over Na_2SO_4. After removal of solvent, the resulting precipitates were collected by filtration and washed with Et_2O and CH_2Cl_2 to give 5.21 g of *N*-benzoylserine. To a suspension of $LiAlH_4$ (760 mg, 20 mmol) in THF (20 mL) was added *N*-benzoylserine (2.09 g, 10 mmol) at 0 °C. The mixture was refluxed for 16 h. After being cooled to room temperature, the reaction mixture was diluted with 50 mL of Et_2O and quenched by portionwise addition of $Na_2SO_4 \cdot 10H_2O$ and brine. The mixture was stirred for an additional 1h and then filtered through a Celite plug. The filter cake was washed with Et_2O. The combined filtrates were dried over Na_2SO_4, and concentrated under reduced pressure to give pale yellow precipitates. The precipitates were collected by filtration and washed with Et_2O to give **17a** (2.75 g, 70%): IR (Nujol) ν 3375 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53–7.24 (m, 5H), 3.83 (s, 2H), 3.74 (d, J = 5.6 Hz, 1H), 3.60 (ddd, J = 22.1, 11.2, 5.6 Hz, 4H), 2.75 (ddd, J = 11.2, 5.6, 5.4 Hz, 1H); MS *m/z* 182 (M^+ + 1), 181 (M^+), 105, 91 (bp); HRMS calcd for $C_{10}H_{16}O_2N$ (M^+ + 1) 182.1181, found 182.1172. Anal. Calcd for $C_{10}H_{15}O_2N$: C, 66.26; H, 8.35; N, 7.73. Found: C, 65.98; H, 8.36; N, 7.77.

***N*-(*p*-Tolylsulfonyl)serinol (17b).** To a solution of (*dl*)-serine (10.5 g, 0.1 mol) in Et_2O (100 mL) and saturated $NaHCO_3$ (100 mL) was added *p*-toluenesulfonyl chloride (19 g, 0.1 mol) at 0 °C. The reaction mixture was stirred at ambient temperature for 1 day. The aqueous phase was acidified (pH ≅ 3) with concd HCl to give colorless precipitates. The resulting precipitates were collected by filtration and dried to give 11.47 g of *N*-(*p*-tolylsulfonyl)serine. To a solution of *N*-(*p*-tolylsulfonyl)serine (4.25 g, 16 mmol) in THF (100 mL) was added $LiAlH_4$ (950 mg, 25 mmol) at 0 °C. The mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with 100 mL of Et_2O and quenched by portionwise addition of $Na_2SO_4 \cdot 10H_2O$ and brine and acidified by dropwise addition of concd HCl. The mixture was stirred for an additional 1 h and filtered through a Celite plug. The filter cake was washed with Et_2O. The combined filtrates were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **17b** as colorless powder (1.96 g): mp 108–109 °C; IR (Nujol) ν 3402, 2922, 1320, 1152 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 5.22 (d, J = 7.3 Hz, 1H), 3.72 (ddd, J = 11.2, 5.0, 4.0 Hz, 2H), 3.62 (ddd, J = 11.2, 6.6, 4.3 Hz, 2H), 3.30 (ddd, J = 7.3, 4.3, 4.0 Hz, 2H), 2.43 (s, 3H), 2.04 (dd, J = 6.6, 5.0 Hz, 2H); MS *m/z* 246 (M^+ + 1), 245 (M^+), 214, 155, 91 (bp); HRMS calcd for $C_{10}H_{15}O_4NS$ 245.0722, found 245.0705. Anal. Calcd for $C_{10}H_{15}O_4NS$: C, 48.97; H, 6.16; N, 5.71; S 13.07. Found: C, 49.44; H, 6.22; N, 5.45; S, 13.00.

Cyclization Reaction of 1a with 17a. According to the general procedure as described for **3a**, **17a** (47 mg, 0.25 mmol) was allowed to react with (*Z*)-**1a** (41 mg, 0,25 mmol) for 14 h. After workup, silica gel column chromatography (*n*-hexane/EtOAc = 2/1) gave *cis*-**18** (26 mg, 47%) and *trans*-**18** (15 mg, 28%). *cis*-**18**: IR (neat) ν 3415, 2857, 1116, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.24 (m, 5H), 5.76 (ddd, J = 17.6, 10.7, 5.9 Hz, 1H), 5.27 (dt, J = 17.6, 1.5 Hz, 1H), 5.16 (dt, J = 10.7, 1.5 Hz, 1H), 4.15 (dddd, J = 9.8, 5.9, 2.9, 1.5 Hz, 1H), 3.92 (dd, J = 11.7, 4.9 Hz, 1H), 3.91 (dd, J = 10.7, 6.8 Hz, 1H), 3.89 (s, 2H), 3.84 (dd, J = 11.7, 2.0 Hz, 1H), 3.78 (dd, J = 10.7, 5.9 Hz, 1H), 2.75 (dd, J = 13.2, 9.8 Hz, 1H), 2.71–2.66 (m, 1H), 2.55 (dd, J = 13.2, 2.9 Hz, 1H); MS *m/z* 233 (M^+), 202, 91 (bp); HRMS calcd for $C_{14}H_{19}O_2N$ 233.1416, found 233.1426. *trans*-**18**: IR (neat) ν 3415, 2855, 1115, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.28 (m, 5H), 5.71 (ddd, J = 17.1, 10.7, 5.9 Hz, 1H), 5.26 (d, J = 17.1 Hz, 1H), 5.13 (d, J = 10.7 Hz, 1H), 4.18 (d, J = 13.2 Hz, 1H), 4.01 (dd, J = 11.7, 3.9 Hz, 1H), 3.94 (dd, J = 11.5, 3.9 Hz, 1H), 4.00–3.88 (m, 1H), 3.77 (dd, J = 11.5, 10.8 Hz, 1H), 3.44 (br d, J = 11.7 Hz, 1H), 3.15 (d, J = 13.2 Hz, 1H), 2.76 (dd, J = 11.7, 2.4 Hz, 1H), 2.51 (ddt, J = 10.8, 3.9, 1.5 Hz, 1H), 2.03 (dd, J = 11.7, 10.7 Hz, 1H); MS *m/z* 233 (M^+), 202, 91 (bp); HRMS calcd for $C_{14}H_{19}O_2N$ 233.1416, found 233.1394.

4-Benzyl-2-vinyl-5-(acetoxymethyl)morpholine (19 from 18). A typical procedure is given for **(2*R*,5*S*)-4-benzyl-2-vinyl-5-(acetoxymethyl)morpholine (*cis*-19)**: A mixture of *cis*-**18** (33 mg, 0.14 mmol), acetic anhydride (27 μL, 0.28 mmol), and a small amount of DMAP in triethylamine (1 mL) was stirred at ambient temperature for 15 h. After concentration under reduced pressure, the residue was chromatographed on silica gel (*n*-hexane/EtOAc = 1/1) to give 27 mg of *cis*-**19** as a pale yellow oil (69%): IR (neat) ν 2858, 1741, 1371, 1235, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36~7.24 (m, 5H), 5.77 (ddd, J = 17.1, 10.7, 5.9 Hz, 1H), 5.27 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 4.50 (ddd, J = 10.7, 4.9, 1.0 Hz, 1H), 4.34 (dd, J = 10.7, 7.8 Hz 1H), 4.03 (dddt, J = 8.8, 5.9, 4.4, 1.5 Hz, 1H), 3.96 (dd, J = 11.2, 2.0 Hz, 1H), 3.87 (d, J = 13.7 Hz, 1H), 3.80 (ddd, J = 11.2, 2.9, 1.0 Hz, 1H), 3.71 (d, J = 13.7 Hz, 1H), 2.87 (dddd, J = 7.8, 4.9, 2.9, 2.0 Hz, 1H), 2.53 (dd, J = 12.2, 4.4 Hz, 1H), 2.49 (dd, J = 12.2, 8.8 Hz, 1H), 2.05 (s, 3H); MS *m/z* 275 (M^+), 218, 202, 91 (bp); HRMS calcd for $C_{16}H_{21}O_3N$ 275.1522, found 275.1501. **(2*S*,5*S*)-4-Benzyl-2-vinyl-5-(acetoxymethyl)morpholine (*trans*-19).** 77% yield; IR (neat) ν 2961, 2850, 1742, 1227, 1093 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.24 (m, 5H), 5.71 (ddd, J = 17.1, 10.7, 5.4 Hz, 1H), 5.24 (dt, J = 17.1, 1.5 Hz, 1H), 5.12 (dt, J = 10.7, 1.5 Hz, 1H), 4.27 (dd, J = 11.7, 3.9 Hz 1H), 4.16 (d, J = 13.7 Hz, 1H), 4.12 (dd, J = 11.7, 5.4 Hz, 1H), 4.00 (dd, J = 11.7, 3.4 Hz, 1H), 3.96 (dddt, J = 10.3, 5.4, 2.4, 1.5 Hz, 1H), 3.52 (dd, J = 11.7, 10.3 Hz, 1H), 3.16 (d, J = 13.7 Hz, 1H), 2.70 (dd, J = 11.7, 2.4 Hz, 1H), 2.62 (dddd, J = 10.3, 5.4, 3.9, 3.4 Hz, 1H), 2.08 (s, 3H) 1.94 (dd, J = 11.7, 10.3 Hz,

1H); MS m/z 275 (M^+), 218, 202, 91 (bp); HRMS calcd for $C_{16}H_{21}O_3N$ 275.1522, found 275.1506.

Cyclization Reaction of 1a with 17b. According to the general procedure as described for **7a**, **17b** (61 mg, 0.25 mmol) was reacted with (*Z*)-**1a** (43 mg, 0.25 mmol) for 14 h. After workup, silica gel column chromatography (*n*-hexane/EtOAc = 2/1) gave *cis*-**22** and *trans*-**22** (1:1.8, 65 mg, 88%). *cis*-**22**: IR (neat) ν 3452, 2922, 1598, 1451, 1343, 1163, 1114, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.74 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 5.71 (ddd, J = 17.5, 10.6, 5.3 Hz, 1H), 5.30 (d, J = 17.5 Hz, 1H), 5.22 (d, J = 10.6 Hz, 1H), 3.95 (d, J = 11.9 Hz, 1H), 3.83–3.67 (m, 4H), 3.68 (dd, J = 12.5, 3.0 Hz, 1H), 3.48 (dd, J = 12.2, 3.0 Hz, 1H), 2.98 (dd, J = 14.5, 11.9 Hz, 1H), 2.43 (s, 3H); MS m/z 297 (M^+), 266 (bp), 155, 91; HRMS calcd for $C_{14}H_{19}O_4NS$ 297.1035, found 297.1040. *trans*-**22**: IR (neat) ν 3452, 2922, 1598, 1451, 1343, 1163, 1114, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 5.75 (ddd, J = 17.2, 10.9, 5.3 Hz, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.24 (d, J = 10.9 Hz, 1H), 4.17 (ddd, J = 9.2, 5.3, 2.6 Hz, 1H), 4.22–4.13 (m, 1H), 3.82 (d, J = 5.9 Hz, 2H), 3.77 (dd, J = 11.9, 2.6 Hz, 1H), 3.58 (ddd, J = 12.9, 9.6, and 3.0 Hz, 1H), 2.78–2.72 (m, 2H), 2.53 (dd, J = 11.9, 9.2 Hz, 1H), 2.45 (s, 3H); MS m/z 297 (M^+), 266 (bp), 155, 91; HRMS calcd for $C_{14}H_{19}O_4NS$ 297.1035, found 297.1039. Since complete separation of*cis*-**22** and *trans*-**22** was difficult, each of the diastereomers was isolated and fully characterized in 4-(*p*-tolylsulfonyl)-2-ethyl-5-[[(*p*-tolylsulfonyl)oxy]methyl]morpholines *cis*-**21** and *trans*-**21** (vide infra).

4-(*p*-Tolylsulfonyl)-2-ethyl-5-[[(*p*-Tolylsulfonyl)oxy]methyl]morpholine (21 from 18). The conversion of *cis*-**18** and*trans*-**18** into **21** was carried out according to the procedures for the preparation of **4** from **3a** to give compounds *cis*-**21** and *trans*-**21**, respectively. **(2*R*,5*S*)-4-(*p*-Tolylsulfonyl)-2-ethyl-5-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (*cis*-21)**: 69% yield; $[\alpha]^{20}_D$ −36.5° (*c* 0.43, chloroform (64% ee)); ^1H NMR ($CDCl_3$) δ 7.73 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.3 Hz, 2H), 4.15 (dd, J = 10.8, 10.7 Hz, 1H), 4.02 (dd, J = 10.8, 6.4 Hz, 1H), 4.04–4.00 (m, 1H), 3.85 (d, J = 12.2 Hz, 1H), 3.53 (dd, J = 13.7, 2.9 Hz, 1H), 3.44 (dd, J = 12.2, 2.4 Hz, 1H), 3.14 (ddt, J = 10.7, 5.4, 2.9 Hz, 1H), 2.58 (dd, J = 13.7, 10.7 Hz, 3H), 2.46 (s, 3H), 2.44 (s, 3H), 1.44–1.28 (m, 2H), 0.89 (t, J = 7.3 Hz, 1H); MS m/z 453 (M^+), 298, 268 (bp); HRMS calcd for $C_{21}H_{27}O_6NS_2$ 453.1281, found 453.1278. **(2*S*,5*S*)-4-(*p*-Tolylsulfonyl)-2-ethyl-5-[[(*p*-tolylsulfonyl)oxy]methyl]morpholine (*trans*-21)**: 56% yield; ^1H NMR ($CDCl_3$) δ 7.75 (d, J = 8.3 Hz, 2H), 7.63 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 4.36 (dd, J = 10.3, 4.9 Hz, 1H), 4.15 (dd, J = 9.8, 8.8 Hz, 1H), 3.84 (dd, J = 11.7, 2.9 Hz, 1H), 3.51 (dd, J = 11.7, 4.4 Hz, 1H), 3.57–3.48 (m, 2H), 3.34 (dd, J = 12.7, 3.4 Hz, 1H), 2.87 (dd, J = 12.7, 5.9 Hz, 1H), 2.47 (s, 3H), 2.45 (s, 3H), 0.87 (t, J = 7.3 Hz, 3H); MS m/z 453 (M^+), 298, 268 (bp), 91; HRMS calcd for $C_{21}H_{27}O_6NS_2$ 453.1281, found 453.1297.

4-(*p*-Tolylsulfonyl)-2-ethyl-5-[[(*p*-toluenesulfonyl)oxy]methyl]morpholine (21) (from 22). A typical procedure is given for the preparation of **(2*R*,5*S*)-4-(*p*-tolylsulfonyl)-2-ethyl-5-[[(*p*-toluenesulfony)oxy]methyl]morpholine (*cis*-21)**:To a solution of *cis*-**22** (14 mg, 0.047 mmol) in THF (1 mL) was added 10% palladium on charcoal (5 mg) and the reaction mixture was stirred under H_2 atmosphere (1 atm) at ambient temperature for 15 h. After filtration, the filtrate was concentrated under reduced pressure to give crude 4-(*p*-tolylsulfonyl)-2-ethyl-5-(hydroxymethyl)morpholine. To a solution of the resulting 4-(*p*-tolylsulfonyl)-2-ethyl-5-(hydroxymethyl)morpholine in CH_2Cl_2 (0.5 mL) was added pyridine (54 μL, 0.68 mmol) and *p*-tolylsulfonyl chloride (9 mg, 0.05 mmol). The mixture was stirred at ambient temperature for 3 days. After removal of the solvent, the residue was chromatographed on silica gel to give *cis*-**21** (16 mg, 76%). **(2*S*,5*S*)-4-(*p*-Tolylsulfonyl)-2-ethyl-5-[[(*p*-toluenesulfonyl)oxy]methyl]morpholine (*trans*-21b)**: 75% yield. Products were weighed and identified by comparison of NMR and mass spectra to that of authentic samples mentioned above.

(*S*)-4-(*p*-Tolylsulfonyl)-2-vinylmorpholine (3b) (from 22). To a mixture of pyridinium chlorochromate (71 mg, 0.33 mmol) and powdered molecular sieves 4A (140 mg) was added a solution of a 1:1 mixture of **22a** (73% ee) and **22b** (45% ee) (49 mg, 0.165 mmol) in 3.5 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred at ambient temperature for 2 h and filtered through a Celite plug. The filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (n-hexane/EtOAc = 1/1) to give 4-(*p*-tolylsulfonyl)-2-vinylmorpholine-5-carboxaldehyde as white precipitates. The aldehyde was dissolved in 2 mL of benzene. To the solution was added $RhCl(PPh_3)_3$ (104 mg, 0.11 mmol) and the mixture was stirred under reflux for 4 h. After being cooled to room temperature, the mixture was filtered through Florisil. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/EtOAc = 3/1) to give **3b** (19.4 mg, two steps 43%): $[\alpha]^{20}_D$ +10.4° (c 0.47, chloroform).

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Supplementary Material Available: ^1H NMR spectra for *cis*-**18**,*trans*-**18**,*cis*-**19**,*trans*-**19**,*cis*-**21**,and*trans*-**21** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.