High-Pressure Organic Chemistry. 19. High-Pressure-Promoted, Silica Gel-Catalyzed Reaction of Epoxides with Nitrogen Heterocycles[1,†]

Hiyoshizo Kotsuki,* Katsunori Hayashida, Tomoyasu Shimanouchi, and Hitoshi Nishizawa

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

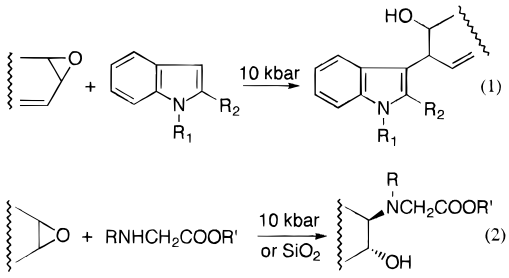
Received June 19, 1995[⊗]

The reaction of epoxides with nitrogen heterocycles such as indoles, pyrroles, imidazoles, and pyrazoles was studied under both high-pressure and silica gel-catalyzed conditions. Whereas it has been reported that the treatment of indole with styrene oxide at 10 kbar and 42 °C for 24 h gave 2-(3-indolyl)-2-phenylethanol in 56% yield, the same compound was obtained in 88% yield when the reaction was conducted on silica gel at rt for 1 week. Similarly, efficient reaction of epoxides with pyrroles, imidazoles, and pyrazoles was achieved. In terms of stereochemical features, the epoxide ring opening reaction of (*R*)-(+)-styrene oxide with indole was found to proceed stereoselectively in an S_N2 fashion at the benzyl carbon, in either case.

Introduction

Epoxides are versatile intermediates in organic synthesis because they are both susceptible to attack by several nucleophiles[2] and readily accessible in optically pure form.[3] The epoxide opening reaction with certain nucleophiles is generally performed with acid or base catalysis, and in the absence of such a catalyst the reaction is moderately slow.[4] These methods have certain disadvantages in that they require large excesses of reagents, long reaction times, and drastic conditions and entail undesirable rearrangement and polymerization side reactions. In our recent papers, we have demonstrated a simple, effective, uncatalyzed way to carry out nucleophilic ring opening reactions of epoxides by applying a high-pressure technique.[5]

For example, indoles reacted with vinyl epoxides at 10 kbar to provide tryptophol derivatives in good yields (eq 1).[6] We also found that aminolysis of epoxides could be achieved efficiently at 10 kbar of pressure (eq 2)[1] and documented the interesting behavior of silica gel as a mild solid catalyst. The synthetic versatility of silica gel for some related epoxide opening reactions was disclosed by others.[7] In addition to these examples, the development of new reactions taking advantage of the catalytic activity of silica gel surfaces is receiving considerable attention from synthetic chemists.[8] Thus, we set out to determine the potential of epoxide opening reactions with indoles or their analogs and to characterize the relationship between high-pressure and silica gel-catalyzed reactions.



Herein, we describe our detailed study of epoxide opening reactions with a variety of nitrogen heteroaromatic nucleophiles: indoles, pyrroles, imidazoles, and pyrazoles.

Results and Discussion

Reaction of Indoles. As reported, indoles have adequate nucleophilicity toward several vinyl epoxides at high pressure even in the absence of any catalyst.[6] We further found that aminolysis is successful under either high-pressure or silica gel-catalyzed conditions.[1] On the basis of these observations, we first examined the nucleophilic epoxide-opening reaction with indoles by adsorption on silica gel.

When a mixture of indole (**2**, 1 mmol) and styrene oxide (**1**, 1 mmol) was adsorbed on silica gel (500 mg) and allowed to react at rt for 1 week, 2-(3-indolyl)-2-phenylethanol (**3**) was obtained in 88% yield (Table 1, run 1b). Compared to the result obtained at high pressure (Table 1, run 1a, 10 kbar, 42 °C, 24 h in acetonitrile; 56% yield),[6] the silica gel-catalyzed method was usually slow but it involves an appealingly simple procedure. Not unexpectedly, conducting the same reaction in dichloromethane solution resulted, for the most part, in a recovery of the starting materials. This means that the supporting environment on a silica gel surface plays an essential role in facilitating the desired epoxide-opening reaction.

* To whom correspondence should be addressed. Tel: +81-888-44-8298. Fax: +81-888-44-8360. E-mail: kotsuki@cc.kochi-u.ac.jp.

† Dedicated to Prof. T. Tokoroyama upon his retirement from Osaka City University.

⊗ Abstract published in *Advance ACS Abstracts,* January 1, 1996.

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(4) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 376.

(5) For a general review of our work in this area, see: Kotsuki, H. *Kagaku to Kogyo (Osaka)* **1994**, *68*, 265.

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(7) Bennett, F.; Patel, N. M.; Girijavallabhan, V. M.; Ganguly, A. K. *Synlett* **1993**, 703. Raubo, P.; Wicha, J. *Synlett* **1993**, 25.

(8) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401, 481. Hojo, M. *Yuki Gosei Kagaku Kyokaishi* **1984**, *42*, 635. Cornelis, A.; Laszlo, P. *Synthesis* **1985**, 909. Isobe, K.; Yagasaki, A. *Acc. Chem. Res.* **1993**, *26*, 524. Corma, A. *Chem. Rev.* **1995**, *95*, 559.

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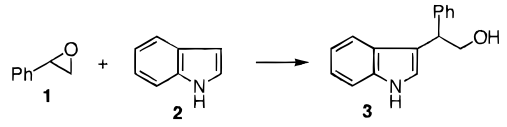
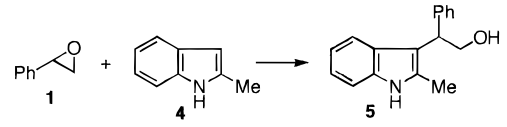
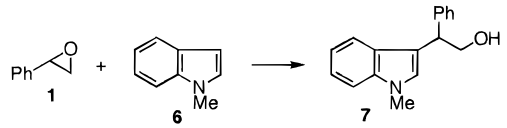
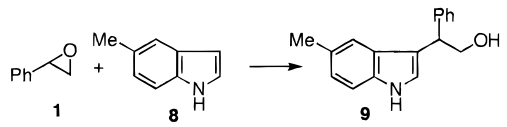
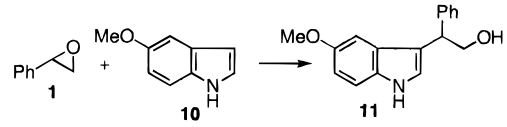
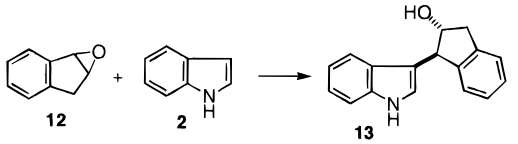
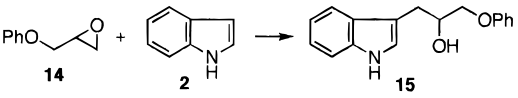
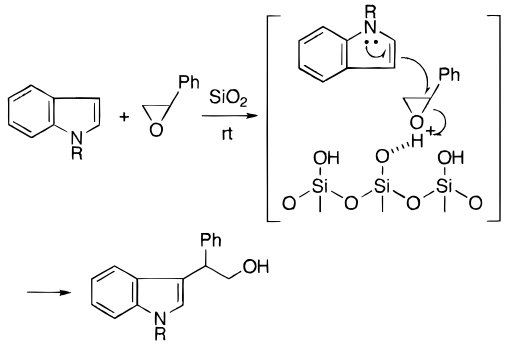
Table 1. Reaction of Indoles with Epoxides[a]

Run	Epoxide	Indole	Reaction Conditions	Product, Yield (%)[b]
				
1a			10 kbar, 42 °C, 24 h	56[c]
b			SiO_2, rt, 7 days	88
				
2a			10 kbar, 42 °C, 24 h	44[c]
b			SiO_2, rt, 7 days	70
				
3a			10 kbar, 42 °C, 24 h	13[c]
b			SiO_2, rt, 7 days	66
				
4a			10 kbar, 42 °C, 3 days	57
b			SiO_2, rt, 7 days	68
				
5a			10 kbar, 42 °C, 3 days	61
b			SiO_2, rt, 7 days	80
				
6a			10 kbar, 42 °C, 24 h	58[c]
b			SiO_2, rt, 7 days	44
				
7a			10 kbar, 65 °C, 3 days	16
b			SiO_2, rt, 10 days	10
c			10 kbar, SiO_2,[d] 65 °C, 3 days	21
d			10 kbar, SiO_2,[e] 65 °C, 3 days	19
e			10 kbar, SiO_2,[f] 65 °C, 3 days	29

[a] All high-pressure reactions with 1 mmol of epoxide and 1 mmol of indole in ca. 1.5 mL of acetonitrile. All silica gel-catalyzed reactions with 1 mmol of epoxide, 1 mmol of indole, and 500 mg of Wakogel-C300. [b] Yields refer to pure isolated compounds. [c] See ref 6. [d] Wakogel C-300 (500 mg / mmol). [e] LC-5H (500 mg / mmol). [f] LC-5H (1000 mg / mmol).

The generality and scope of this method are summarized in Table 1, where the yields obtained at high pressure are also listed for comparison.[9] As can be seen from these data, the high pressure and the silica gel-catalyzed method exhibit comparable efficiency. The substituent effect of an electron-donating group at the 5-position of indole was briefly examined, but no striking effect was observed (Table 1, runs 4 and 5). The only significant difference in reactivity was observed for 1-methylindole (**6**) (Table 1, runs 3a and 3b) for which the silica gel-catalyzed method was superior to the high-pressure reaction. These results can be reasonably explained by the following mechanistic rationale. At high pressure, the driving force for the reaction is a proton transfer from indole to epoxide as pointed out earlier,[6] while on silica gel surfaces protonation of an epoxide ring occurs readily as depicted in Scheme 1.

Scheme 1



In accordance with our previous observations, indoles were only reactive toward vinyl epoxides. However, the extension of the above methodology into aliphatic systems would be valuable. We therefore tried the reaction of phenyl glycidyl ether (**14**) with indole (**2**) and found that the *combination* of the above two methods was most successful. Thus, when the reaction of **14** (1 mmol) and **2** (1 mmol) containing 1000 mg of silica gel (LC-5H) was conducted in 1.5 mL of acetonitrile at 10 kbar, the yield of **15** increased to 29% (Table 1, run 7e). Although the generality of the procedure has yet to be documented, the increased activity of silica gel under high pressure suggests the potential discrimination that might be available with high-pressure techniques.[1,10]

Reaction of Pyrroles. Pyrrole derivatives are important intermediates not only for the synthesis of drugs, pigments, and pharmaceuticals but also for the development of organic functional materials.[11] In general, pyrroles have rather weak nucleophilicity compared with indoles and also show a lability to acidic conditions. Much worse is their enhanced fragility as a result of introduction of alkyl groups on the pyrrole nucleus. It might therefore be necessary to perform the epoxide-based alkylation of pyrroles under carefully controlled conditions.[12] The application of high-pressure or silica gel-catalyzed reaction is certainly feasible here.

After numerous experiments, it was found that synthetically useful amounts of products were obtained when relatively reactive vinyl epoxides were employed as the substrates (Table 2).

Thus, subjecting a 1:1 mixture of pyrrole (**16**) and styrene oxide (**1**) in acetonitrile to 10 kbar of pressure

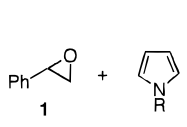
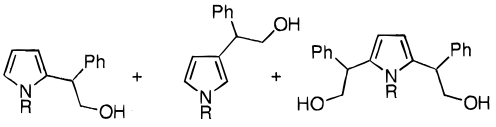
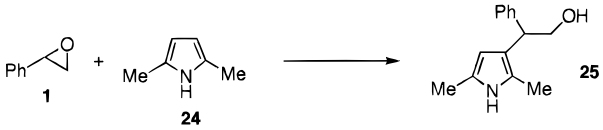
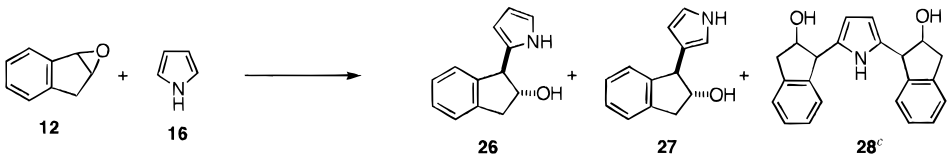
(9) Although the reason is unclear, in a series of indole reactions the use of CH_2Cl_2 as the solvent gave decreased yields.

(10) Dauben, W. G.; Hendricks, R. T. *Tetrahedron Lett.* **1992**, *33*, 603.

(11) Jones, R. A.; Bean, G. P. *The Chemistry of Pyrroles*; Academic Press: London, 1977. Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. For a general review see: Katritzky, A., Rees, C. W., Eds. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, 1984.

(12) For example, see: Tanis, S. P.; Raggon, J. W. *J. Org. Chem.* **1987**, *52*, 819.

Table 2. Reaction of Pyrroles with Vinyl Epoxides[a]

Run	Epoxide	Pyrrole	Reaction Conditions	Products, Yield (%)[b]		
						
	1	**16** R = H **20** R = Me		**17** R = H **21** R = Me	**18** R = H **22** R = Me	**19** R = H[c] **23** R = Me[c]
8a		**16**	10 kbar, 42 °C, 24 h, CH_3CN	22	8	ND[d]
b			10 kbar, 42 °C, 3 days, CH_2Cl_2	11	11	ND[d]
c			SiO_2, rt, 2 days	29	16	7
9a		**20**	10 kbar, 42 °C, 24 h, CH_3CN	12	5	ND[d]
b			10 kbar, 42 °C, 24 h, CH_2Cl_2	16	14	ND[d]
c			SiO_2, rt, 5 days	48	16	17
						
	1	**24**		**25**		
10a			10 kbar, 42 °C, 24 h, CH_3CN	30		
b			10 kbar, 42 °C, 24 h, CH_2Cl_2	41		
c			SiO_2, rt, 2 days	18		
						
	12	**16**		**26**	**27**	**28**[c]
11a			10 kbar, 42 °C, 24 h, CH_3CN	20	10	13
b			10 kbar, 42 °C, 3 days, CH_2Cl_2	15	7	8
c			SiO_2, rt, 7 days	16	23	11

[a] All high-pressure reactions with 1 mmol of epoxide and 1 mmol of pyrrole in 1.5 mL of acetonitrile or dichloromethane. All silica-gel catalyzed reactions with 1 mmol of epoxide, 1 mmol of pyrrole, and 500 mg of Wakogel-C300. [b] Yields refer to pure isolated compounds. [c] Isolated as a diastereomeric mixture. [d] Not detected.

followed by purification by preparative TLC at 0 °C[13] produced the 2-substituted compound **17** and the 3-substituted **18** in 22% and 8% yields, respectively (Table 2, run 8a). Replacing the solvent with dichloromethane caused only a slight difference in product distribution (Table 2, run 8b). The structures of **17** and **18** were readily confirmed by ^1H and ^{13}C NMR spectroscopy. Thus, for compound **17** the protons on the pyrrole ring appear at 6.00 (m), 6.16 (dd, J = 5.3, 2.4 Hz), and 6.69 (dd, J = 3.7, 2.4 Hz) ppm and the carbons at 105.7 (d), 108.1 (d), 117.1 (d), and 131.8 (s) ppm, indicative of a 2-substituted pyrrole derivative. The methylene proton signal at 4.10 ppm and carbon signal at 66.4 ppm is in good agreement with the proposed primary alcohol structure. In compound **18**, except for the pyrrole ring fragment, quite similar data were obtained: 6.13 (dd, J = 4.1, 2.6 Hz), 6.61 (dd, J = 4.1, 2.0 Hz), and 6.74 (dd, J = 4.8, 2.6 Hz) ppm for protons and 108.0 (d), 115.9 (d), 118.3 (d), and 123.6 (s) ppm for carbons. The exclusive formation of these isomers for compounds **17** and **18** clearly shows that the pyrrole attack on styrene oxide (**1**) occurs at the benzyl position with the expected regioselectivity, as is true of indoles.

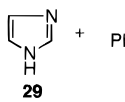
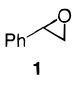
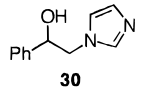
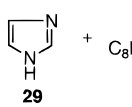
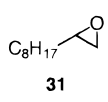
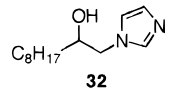
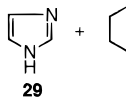
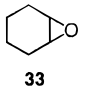
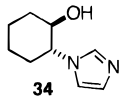
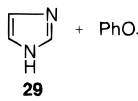
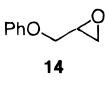
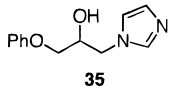
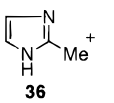
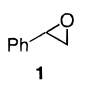
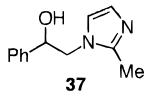
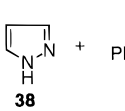
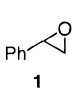
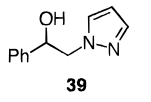
(13) Due to the instability of pyrrole adducts, separation by TLC was best achieved at 0 °C.

On the other hand, the silica gel-catalyzed reaction of **16** with **1** produced **17** (29%) and **18** (16%) along with the 2,5-disubstituted derivative **19** (7%) (Table 2, run 8c). Judging from ^{13}C NMR measurements, this adduct **19** was deemed to be a diastereomeric mixture that was homogeneous on TLC. Interestingly, probably due to some decomposition of impurities on the silica gel, the silica gel-catalyzed method led to much easier purification than the high-pressure method. In any event, these results demonstrate the power of these two techniques. Similar results were obtained for *N*-methylpyrrole (**20**) (Table 2, runs 9a–c) and also for the reaction of indene oxide (**12**) with pyrrole (**16**) (Table 2, runs 11a–c). Under similar conditions, 2,5-dimethylpyrrole (**24**) efficiently reacted with styrene oxide (**1**) to afford the highly labile compound **25** (Table 2, runs 10a–c).

As expected, all of these products were rather unstable even in a refrigerator, and hence, all attempts to increase the product yields were fruitless. For example, prolonged exposure of the substrates to silica gel or longer times at high pressure led only to low yields. In spite of this drawback, the above results offer a valuable tool for preparing pyrrole derivatives, which are not easily accessible by other means.

Reaction of Diazoles. We subsequently investigated

Table 3. Reaction of Epoxides with Imidazoles and Pyrazoles[a]

Run	Substrate	Epoxide	Reaction Conditions	Product, Yield (%)[b]
	 **29**	 **1**		 **30**
12a			10 kbar, 65 °C, 3 days	59
b			SiO_2, rt, 7 days	47
	 **29**	 **31**		 **32**
13a			10 kbar, 65 °C, 3 days	72
b			SiO_2, rt, 10 days	56
	 **29**	 **33**		 **34**
14a			10 kbar, 65 °C, 3 days	65
b			SiO_2, rt, 10 days	39
	 **29**	 **14**		 **35**
15a			10 kbar, 65 °C, 3 days	67
b			SiO_2, rt, 10 days	50
	 **36**	 **1**		 **37**
16a			10 kbar, 65 °C, 3 days	53
b			SiO_2, rt, 8 days	36
	 **38**	 **1**		 **39**
17a			10 kbar, 65 °C, 3 days	61
b			SiO_2, rt, 7 days	53

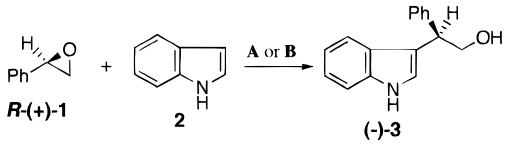
[a] All high-pressure reactions with 1 mmol of epoxide and 1 mmol of azole in 1.5 mL of acetonitrile. All silica-gel catalyzed dry reactions with 1 mmol of epoxide, 1 mmol of azole, and 500 mg of Wakogel-C300. [b] Yields refer to pure isolated compounds.

the epoxide-opening reaction using diazoles as the substrates. The importance of this kind of transformation is well established, particularly in the field of medicinal chemistry.[14] In general, the epoxide-based alkylation of these heterocycles requires rather drastic conditions, i.e., prolonged heating at high temperature with the concomitant use of a strong base. In light of the observations described earlier, we expected that the application of our strategy to these systems would produce the desired adduct.

The results are summarized in Table 3. Imidazole (**29**) was efficiently reacted with styrene oxide (**1**) under high-pressure or silica gel-catalyzed conditions to afford **30** in 59% and 47% yields, respectively, as the sole product (Table 3, runs 12a,b). The structure of **30** was determined on the basis of its ^1H and ^{13}C NMR spectral data. Following are the characteristic signals of the aliphatic portion of this compound: 2.18 (1H, br, O*H*), 4.11 (2H, d, J = 5.7 Hz, CH(OH)CH_2N), and 4.89 (1H, t, J = 5.7 Hz, C*H*(OH)CH_2) ppm for protons and 52.1 (*C*H_2N) and 70.3 (*C*HOH) ppm for carbons, which are in good agreement with those reported for related amino alcohol systems.[1,15] This opening reaction occurs exclusively at the less hindered side of the epoxide ring. This is consistent with an S_N2-type attack of an imidazole nitrogen atom due to its hard nucleophilicity. In accordance with this interpretation, imidazole (**29**) reacted smoothly even with aliphatic epoxides **31**, **33**, and **14** to afford the corresponding adducts **32**, **34**, and **35** (Table 3, runs 13−15).[16] Similar results were obtained for 2-methylimidazole (**36**) and pyrazole (**38**) (Table 3, runs 16 and 17).

Since the presently developed methods can be used under very mild conditions, we believe they provide tremendous utility for preparing a variety of imidazole and pyrazole derivatives, as well as other analogs.[17]

Scheme 2



A: 10 kbar, 42 °C, 24 h 56 (92% ee)
B: SiO_2, rt, 7 days 88 (88% ee)

Stereochemical Feature of Epoxide-Opening Reaction with Indole. We previously suggested that some kind of ionization process might be involved in the reaction of indole (**2**) with styrene oxide (**1**),[6] since it is clear that at high pressure this process is considerably accelerated.[18] However, at high pressure the stereochemical course of our epoxide ring openings was unclear. To clarify this and to determine the mechanistic similarities between the high-pressure and silica gel-catalyzed reactions, we turned to (*R*)-(+)-styrene oxide ((+)-**1**) as a suitable substrate.

The results are summarized in Scheme 2. The enantiomeric purity of the product was determined by HPLC analysis using DAICEL CHIRALECEL OD column (Figure 1). Thus, the high pressure reaction of (+)-**1** with **2** produced (−)-**3** with 92% ee, which was subsequently recrystallized from hexane−dichloromethane to furnish a nearly pure sample (>99% ee by HPLC), mp 82.0−82.5 °C, $[\alpha]^{21}_D$ −0.435 (*c* 0.46, $CHCl_3$). From the silica gel-catalyzed reaction, high enantiomeric excess (88% ee) of the same sign of specific rotation was observed.

The absolute configuration at the newly formed asymmetric center in (−)-**3** was confirmed by independent synthesis from commercially available (*R*)-(−)-styrenediol (**40**) as outlined in Scheme 3. The corresponding TBDMS

(14) For example, see: Hümmer, W.; Gracza, T.; Jäger, V. *Tetrahedron Lett.* **1989**, *30*, 1517. Murabayashi, A.; Makisumi, Y. *Heterocycles* **1990**, *31*, 537. Gala, D.; DiBenedetto, D. J. *Tetrahedron Lett.* **1994**, *35*, 8299. Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000.

(15) Harris, C. E.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746 and references cited therein.

(16) The use of CH_2Cl_2 as the solvent for high-pressure reactions gave generally complex mixtures of products.

(17) The benzene analogs such as benzimidazole were unreactive under these conditions.

(18) le Noble, W. J. *Prog. Phys. Org. Chem.* **1967**, *5*, 207. Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407. le Noble, W. J.; Asano, T.; van Eldik, R. *Ibid.* **1989**, *89*, 549.

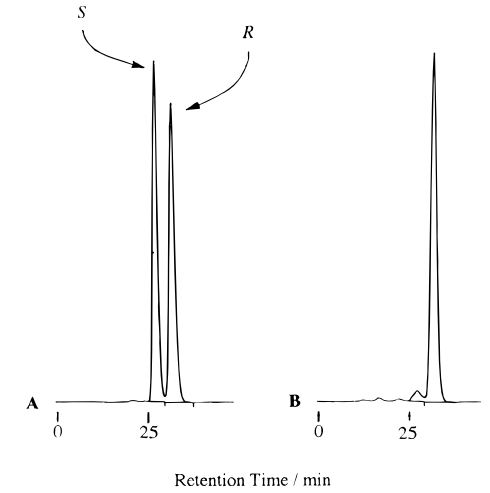
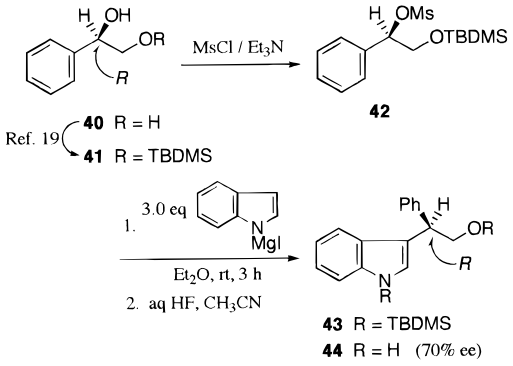


Figure 1. Analytical HPLC data: (A) racemic **3**; (B) (−)-**3** obtained at high pressure. Column: DAICEL CHIRALCEL OD. Eluent: hexane/2-propanol = 80:20. Flow rate: 0.5 mL/min.

Scheme 3



ether **41**[19] was treated with MsCl/Et_3N followed by reaction with indolylmagnesium iodide, prepared *in situ* from indole (**2**) and MeMgI,[20] to afford **43**, which was finally desilylated by careful treatment with aqueous HF to afford **44** with 70% ee. Although the S_N2 inversion at the stage of introduction of an indole function onto **42** was incomplete, the major isomer of **44** was identified as (−)-**3**. Hence, the absolute configuration of (−)-**3** was finally deduced to be the *R* configuration, suggesting that the epoxide ring opening occurred predominantly in an S_N2 inversion manner at the benzyl carbon.[21] This result can be explained by the S_N2 type addition of indole to a protonated epoxide intermeidate via a concerted mechanism (*vide supra*, Scheme 1).

Conclusions

The high-pressure-promoted and silica gel-catalyzed reactions of epoxides with several nitrogen heterocycles have been demonstrated to be effective for the alkylation of these heterocycles. The synthetic superiority of the high-pressure method is apparent from its reliability in conducting the reaction in an almost neutral medium. At the same time, we have explored the novel aspects of silica gel as a mild acid catalyst. The combination of these two techniques provides a new and powerful tool for less reactive substrates. Finally, the stereochemistry in the epoxide-opening step was determined using optically pure styrene oxide, and the reaction occurs highly stereoselectively in an S_N2 inversion manner at the benzyl carbon, by either method. These two methods offer broad utility in organic synthesis, and their application to natural product synthesis and to the design of novel heterocyclic ligands[22] and functionalized materials is now in progress in our laboratory.

Experimental Section

All high-pressure reactions were conducted with a Hikari-Koatsu HR-15-B3 apparatus, and for silica gel-catalyzed reactions Wakogel C-300 was employed unless otherwise noted. HPLC analyses were carried out with a UV (λ = 254 nm) detector and DAICEL CHIRALCEL OD column with hexane/*i*-PrOH as eluent. For general experimental information see our previous paper.[23]

Typical Procedure for the Reaction of Epoxides with Nitrogen Heterocycles. High-Pressure Conditions. A mixture of epoxide (1.5 mmol) and nitrogen heterocycles (1.5 mmol) in acetonitrile (1.5 mL) was placed in a Teflon reaction vessel and allowed to react at 10 kbar under the conditions indicated in Tables 1−3. After evaporation of the solvent, the residue was purified by preparative TLC or by silica gel column chromatography.

Silica Gel-Catalyzed Conditions. To a mixture of epoxide (1.5 mmol) and nitrogen heterocycles (1.5 mmol) in a few milliliters of CH_2Cl_2 was added silica gel (500 mg). After evaporation of most of the organic solvent, the residue was allowed to stand at rt for the period indicated in Tables 1−3. After completion of the reaction, silica gel was removed by filtration and rinsed well with AcOEt. The organic phase was treated as above.

2-(5-Methyl-3-indolyl)-2-phenylethanol (9): R_f (hexane/AcOEt, 1:1) 0.41; mp 137.5−138.0 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3513, 3260, 1485, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.65 (1H br), 2.38 (3H, s), 3.9−4.6 (3H, m), 7.03 (1H, s), 6.9−7.4 (8H, m), 7.94 (1H, br); ^{13}C NMR ($CDCl_3$) δ 21.5, 45.6, 66.4, 110.8, 115.3, 118.8, 122.1, 123.8, 126.5, 127.2, 128.2 (×2), 128.5 (×2), 128.6, 134.7, 141.7. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.34; H, 6.64; N, 5.41.

2-(5-Methoxy-3-indolyl)-2-phenylethanol (11): R_f (hexane/AcOEt, 1:1) 0.34; mp 89.5−90.5 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3409, 1483, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (1H, br), 3.73 (3H, s), 4.0−4.5 (3H, m), 6.85 (1H, s), 6.7−7.4 (8H, m), 7.96 (1H, br); ^{13}C NMR ($CDCl_3$) δ 45.6, 55.8, 66.2, 101.4, 111.8, 112.1, 115.4, 122.7, 126.5, 127.3, 128.2 (×2), 128.4 (×2), 131.6, 141.6, 153.7. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.50; H, 6.42; N, 5.41.

3-(3-Indolyl)-1-phenoxy-2-propanol (15): R_f (hexane/Et_2O, 1:1) 0.11; mp 82.0−83.5 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3418, 1595, 1495, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (1H, br), 3.08 (2H, d, J = 6.4 Hz), 3.92 (1H, dd, J = 13.5, 6.2 Hz), 3.98 (1H, dd, J = 13.5, 4.0 Hz), 4.29 (1H, m), 6.6−7.7 (10H, m), 8.03 (1H, br); ^{13}C NMR ($CDCl_3$) δ 29.5, 70.1, 71.2, 111.2, 111.3, 114.6 (×2), 118.8, 119.5, 121.0, 122.1, 122.9, 127.6, 129.4 (×2), 136.3, 158.6. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.38; H, 6.57; N, 5.29.

2-(2-Pyrrolyl)-2-phenylethanol (17): pale brown oil; R_f (hexane/AcOEt, 1:1) 0.41; FTIR (neat) ν 3385, 1601, 1562, 1493, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (1H, br), 4.10 (3H,

(19) $[\alpha]^{20}_D$ −38.46 (*c* 1.04, $CHCl_3$). Prepared from diol **40** according to the literature procedure: Kim, S.; Chang, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669. Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545. Yamamoto, K.; Takemae, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2111. Leigh, D. A.; Martin, R. P.; Smart, J. P.; Truscello, A. M. *J. Chem. Soc., Chem. Commun.* **1994**, 1373.

(20) Heath-Brown, B.; Philpott, P. G. *J. Chem. Soc.* **1965**, 7165.

(21) For a similar discussion, see: Biggs, J.; Chapman, N. B.; Wray, V. *J. Chem. Soc. B* **1971**, 71. Lin, B.; Whalen, D. L. *J. Org. Chem.* **1994**, *59*, 1638. Boaz, N. W. *Tetrahedron: Asymmetry* **1995**, *6*, 15.

(22) For a successful application to catalytic asymmetric synthesis, see: Kotsuki, H.; Hayakawa, H.; Wakao, M.; Shimanouchi, T.; Ochi, M. *Tetrahedron: Asymmetry* **1995**, *6*, 2665.

(23) Kotsuki, H.; Nishikawa, H.; Mori, Y.; Ochi, M. *J. Org. Chem.* **1992**, *57*, 5036.

m), 6.00 (1H, m), 6.16 (1H, dd, J = 5.3, 2.4 Hz), 6.69 (1H, dd, J = 3.7, 2.4 Hz), 7.26 (5H, m), 8.30 (1H, br); ^{13}C NMR ($CDCl_3$) δ 47.0, 66.4, 105.7, 108.1, 117.1, 127.0, 128.2 (×2), 128.6 (×2), 131.8, 140.4; MS m/z (rel intensity) 187 (M^+, 13), 156 (100), 129 (10), 128 (10), 103 (6), 91 (6), 77 (7), 51 (3), 32 (13); HRMS calcd for $C_{12}H_{13}NO$ 187.0997, found 187.0979.

2-(3-Pyrrolyl)-2-phenylethanol (18): pale brown oil; R_f (hexane/AcOEt, 1:1) 0.33; FTIR (neat) ν 3380, 1492, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (1H, br), 4.04 (3H, m), 6.13 (1H, dd, J = 4.1, 2.6 Hz), 6.61 (1H, dd, J = 4.1, 2.0 Hz), 6.74 (1H, dd, J = 4.8, 2.6Hz), 7.28 (5H, m), 8.10 (1H, br); ^{13}C NMR ($CDCl_3$) δ 47.0, 67.1, 108.0, 115.9, 118.3, 123.6, 126.5, 128.2 (×2), 128.4 (×2), 142.5; MS m/z (rel intensity) 187 (M^+, 12), 156 (100), 129 (14), 128 (13), 77 (4), 51 (2), 32 (17); HRMS calcd for $C_{12}H_{13}NO$ 187.0997, found 187.0978.

2-[5-(2-Hydroxy-1-phenylethyl)-2-pyrrolyl]-2-phenylethanol (19): brown oil; R_f (hexane/AcOEt, 1:1) 0.20; FTIR (KBr) ν 3297, 1489, 1456, 1414 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (2H, br), 3.7−4.3 (6H, m), 5.90 (1H, dd, J = 2.6, 1.5 Hz), 7.23 (10H, m), 8.40 (1H, br); ^{13}C NMR ($CDCl_3$, major diastereomer) δ 47.1 (×2), 66.3 (×2), 105.5 (×2), 126.7 (×2), 128.1 (×4), 128.3 (×4), 131.4 (×2), 140.5, 140.6; MS m/z (rel intensity) 307 (M^+, 15), 276 (100), 258 (9), 245 (39), 156 (8), 107 (5), 91 (5), 77 (3), 40 (2), 32 (28); HRMS calcd for $C_{20}H_{21}NO_2$ 307.1572, found 307.1580.

2-(1-Methyl-2-pyrrolyl)-2-phenylethanol (21): oil; R_f (hexane/AcOEt, 1:1) 0.43; FTIR (neat) ν 3410, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57 (1H, br), 3.33 (3H, s), 3.8−4.3 (3H, m), 6.15 (2H, d, J = 2.4 Hz), 6.58 (1H, t, J = 2.4 Hz), 7.25 (5H, m); ^{13}C NMR ($CDCl_3$) δ 33.8, 46.5, 66.4, 105.6, 106.8, 122.3, 126.9, 128.2 (×2), 128.4, 128.7 (×2), 140.2; MS m/z (rel intensity) 201 (M^+, 12), 183 (2), 170 (100), 149 (6), 128 (8), 115 (3), 105 (5), 91 (4), 77 (4), 57 (5), 42 (7); HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1139.

2-(1-Methyl-3-pyrrolyl)-2-phenylethanol (22): oil; R_f (hexane/AcOEt, 1:1) 0.38; FTIR (neat) ν 3422, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.58 (1H, br), 3.59 (3H, s), 4.03 (3H, m), 6.02 (1H, dd, J = 2.4, 2.0 Hz), 6.42 (1H, dd, J = 2.4, 2.0 Hz), 6.54 (1H, t, J = 2.4 Hz), 7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ 36.1, 47.1, 67.1, 107.7, 119.9, 122.1, 123.7, 126.4, 128.1 (×2), 128.4 (×2), 142.6; MS m/z (rel intensity) 201 (M^+, 24), 183 (2), 170 (100), 154 (7), 149 (2), 128 (16), 115 (4), 102 (2), 77 (4), 65 (2), 42 (12); HRMS calcd for $C_{13}H_{15}NO$ 201.1154, found 201.1160.

2-[1-Methyl-5-(2-hydroxy-1-phenylethyl)-2-pyrrolyl]-2-phenylethanol (23): R_f (hexane/AcOEt, 1:1) 0.36; mp 154.5−156.0 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3301, 1599, 1491, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.80 (1H, br), 2.98 (3H, s), 3.7−4.3 (6H, m), 6.18 (2H, s), 6.9−7.4 (10H, m); ^{13}C NMR ($CDCl_3$, major diastereomer) δ 30.4, 46.9 (×2), 66.3 (×2), 104.5 (×2), 127.0 (×2), 128.2 (×4), 128.7 (×4), 132.1 (×2), 140.2 (×2); MS m/z (rel intensity) 322 (M^+ + 1, 100), 304 (55), 290 (68), 259 (10), 244 (6), 202 (7), 184 (5), 168 (2), 121 (3), 41 (9); HRMS calcd for $C_{21}H_{23}NO_2$ + H 322.1807, found 322.1806.

2-(2,5-Dimethyl-3-pyrrolyl)-2-phenylethanol (25): R_f (CH_2Cl_2/acetone, 4:1) 0.57; mp 70.5−71.5 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3400, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (1H, br), 2.10, 2.19 (each 3H, s), 3.97 (3H, br s), 5.77 (1H, d, J = 2.4 Hz), 7.25 (5H, m), 7.45 (1H, br); ^{13}C NMR ($CDCl_3$) δ 11.2, 13.1, 45.7, 66.8, 104.6, 118.0, 125.6, 126.2, 127.9 (×2), 128.1, 128.4 (×2), 142.8; MS m/z (rel intensity) 216 (M^+ + 1, 48), 215 (52, M^+), 198 (100), 184 (81), 168 (2), 138 (11), 121 (11), 96 (22), 41 (8); HRMS calcd for $C_{14}H_{17}NO$ + H 216.1388, found 216.1396.

***trans*-3-Hydroxy-2-(2-pyrrolyl)benzocyclopentane (26):** oil; R_f (hexane/AcOEt, 1:1) 0.43; FTIR (neat) ν 3380, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (1H, br s), 2.85 (1H, dd, J = 15.8, 6.5 Hz), 3.21 (1H, dd, J = 15.8, 6.8 Hz), 4.18 (1H, d, J = 6.6 Hz), 4.40 (1H, dt, J = 6.8, 6.6 Hz), 5.99 (1H, m), 6.13 (1H, dd, J = 5.5, 2.6 Hz), 6.65 (1H, m), 7.13 (4H, m), 8.08 (1H, br); ^{13}C NMR ($CDCl_3$) δ 39.9, 53.0, 80.9, 106.2, 108.5, 117.2, 124.8, 125.0, 127.0, 127.5, 131.5, 140.1, 141.8; MS m/z (rel intensity) 199 (M^+, 100), 181 (37), 180 (54), 171 (49), 156 (34), 141 (11), 128 (19), 115 (21), 104 (86), 80 (35), 77 (15), 63 (7), 51 (7), 39 (7); HRMS calcd for $C_{13}H_{13}NO$ 199.0997, found 199.1008.

***trans*-3-Hydroxy-2-(3-pyrrolyl)benzocyclopentane (27):** oil; R_f (hexane/AcOEt, 1:1) 0.35; FTIR (neat) ν 3387, 1476 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.34 (1H, br s), 2.88 (1H, dd, J = 15.4, 7.0 Hz), 3.24 (1H, dd, J = 15.4, 6.6 Hz), 4.08 (1H, d, J = 6.6 Hz), 4.43 (1H, q, J = 6.8 Hz), 6.05 (1H, m), 6.59 (1H, m), 6.73 (1H, dd, J = 4.6, 2.4 Hz), 7.13 (4H, m), 8.10 (1H, br); ^{13}C NMR ($CDCl_3$) δ 39.8, 52.6, 81.7, 107.8, 116.0, 118.4, 123.7, 124.5, 124.9, 126.7, 126.8, 139.9, 144.4; MS m/z (rel intensity) 199 (M^+, 100), 181 (47), 180 (48), 171 (84), 156 (43), 141 (17), 128 (25), 115 (26), 104 (93), 80 (40), 77 (20), 63 (8), 51 (8), 39 (7); HRMS calcd for $C_{13}H_{13}NO$ 199.0997, found 199.0986.

3-Hydroxy-2-[5-(3-hydroxy-2-benzocyclopentyl)pyrrolyl]benzocyclopentane (28): R_f (hexane/AcOEt, 1:1) 0.12; mp 73.0−74.5 °C (from CH_2Cl_2/hexane); FTIR (KBr) ν 3312, 1588, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$−acetone-d_6) δ 2.82 (2H, dd, J = 15.6, 6.2 Hz), 2.85 (2H, br s), 3.20 (2H, dd, J = 15.6, 6.6 Hz), 4.16 (2H, br d, J = 6.2 Hz), 4.54 (2H, br dt, J = 6.8, 6.2 Hz), 5.71 (2H, t, J = 2.3 Hz), 7.11 (8H, m); ^{13}C NMR ($CDCl_3$/acetone-d_6) δ 39.4 (×2), 52.4 (×2), 79.1 (×2), 104.4, 104.6, 123.5 (×2), 124.0 (×2), 125.5 (×2), 125.9 (×2), 130.8 (×2), 139.6 (×2), 142.3 (7), 142.4 (3); MS m/z (rel intensity) 332 (M^+ + 1, 100), 331 (M^+, 88), 314 (97), 303 (7), 275 (5), 228 (7), 200 (17), 198 (20), 182 (9), 133 (23), 105 (2), 91 (2), 57 (2), 41 (24); HRMS calcd for $C_{22}H_{21}NO_2$ + H 332.1651, found 332.1638.

2-(1-Imidazolyl)-1-phenylethanol (30): R_f ($CHCl_3$/MeOH, 9:1) 0.38; mp 145.0−145.5 °C (from CH_2Cl_2/hexane) (lit.[24] mp 151−152 °C); FTIR (KBr) ν 3119, 1595, 1512, 1451 cm^{-1}; ^{1}H NMR ($CDCl_3$/CD_3OD) δ 2.18 (1H, br), 4.11 (2H, d, J = 5.7 Hz), 4.89 (1H, t, J = 5.7 Hz), 6.7−7.5 (8H, m); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ 52.1, 70.3, 118.2, 124.1 (×2), 125.4, 125.7, 126.1 (×2), 135.7, 140.5. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 69.96; H, 6.32; N, 14.95.

1-(1-Imidazolyl)-2-decanol (32): R_f ($CHCl_3$/MeOH, 9:1) 0.27; mp 56.0−58.0 °C (from hexane) (lit.[25] mp 59.5−61.0 °C); FTIR (KBr) ν 3229, 1514, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, m), 1.1−1.7 (14H, m), 3.86 (3H, m), 4.56 (1H, br), 6.88 (2H, br s), 7.34 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.5, 25.5, 29.1, 29.4, 29.5, 31.8, 34.6, 53.4, 70.3, 119.7, 127.9, 137.4. Anal. Calcd for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.66; H, 10.91; N, 12.41.

***trans*-2-(1-Imidazolyl)cyclohexanol (34):** R_f ($CHCl_3$/MeOH, 9:1) 0.24; mp 140.0−141.0 °C (from CH_2Cl_2/hexane) (lit.[26] mp 134−135 °C); FTIR (KBr) ν 3108, 1502, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2−2.4 (8H, m), 3.3−3.9 (3H, m), 6.94 (2H, br s), 7.47 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 24.4, 25.2, 32.4, 34.3, 64.0, 73.0, 117.1, 128.3, 136.1. Anal. Calcd for $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 64.68; H, 8.36; N, 16.98.

3-(1-Imidazolyl)-1-phenoxy-2propanol (35): R_f ($CHCl_3$/MeOH, 9:1) 0.38; mp 112.5−114.0 °C (from CH_2Cl_2/hexane) (lit.[27] mp 108 °C); FTIR (KBr) ν 3123, 1597, 1588, 1512, 1495, 1466 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.5−4.5 (5H, m), 6.00 (1H, br s), 6.5−7.5 (8H, m); ^{13}C MMR ($CDCl_3$) δ 50.3, 68.4, 68.6, 114.4 (×2), 120.0, 121.1, 127.9, 129.4 (×2), 137.5, 158.0. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.04; H, 6.59; N, 12.57.

2-(2-Methyl-1-imidazolyl)-1-phenylethanol (37): R_f ($CHCl_3$/MeOH, 9:1) 0.37; mp 117.0−118.0 °C (from Et_2O/hexane) (lit.[24] mp 117−118 °C); FTIR (KBr) ν 3111, 1534, 1503 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (3H, s), 3.98 (2H, d, J = 6.0 Hz), 3.9−4.2 (1H, br), 4.88 (1H, t, J = 6.0 Hz), 6.69 (1H, d, J = 1.3 Hz), 6.79 (1H, d, J = 1.3 Hz), 7.27 (5H, s); ^{13}C NMR ($CDCl_3$) δ 12.6, 53.7, 73.0, 120.0, 125.8 (×2), 126.0, 127.9, 128.5 (×2), 141.5, 144.9. Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.16; H, 6.97; N, 13.75.

2-(1-Pyrazolyl)-1-phenylethanol (39): R_f (hexane/AcOEt, 1:2) 0.43; mp 125.5−127.0 °C (from CH_2Cl_2/Et_2O) (lit.[28] mp 123−127 °C); FTIR (KBr) ν 3210, 1514, 1495, 1453 cm^{-1}; ^{1}H NMR ($CDCl_3$/acetone-d_6) δ 3.36 (1H, br), 4.26 (1H, dd, J = 14.0, 7.0 Hz), 4.33 (1H, dd, J = 14.0, 4.8 Hz), 5.08 (1H, dd, J = 7.0, 4.8 Hz), 6.17 (1H, t, J = 2.0 Hz), 7.1−7.6 (7H, m); ^{13}C NMR

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($CDCl_3$/acetone-d_6) δ 58.1, 71.9, 103.8, 125.0 (×2), 126.5, 127.2 (×2), 129.5, 137.9, 141.0. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.21; H, 6.49; N, 14.87.

(−)-2-(3-Indolyl)-2-phenylethanol [(−)-3]: R_f (hexane/EtO, 1:1) 0.15; mp for a recrystallized pure sample 82.0−82.5 °C (from CH_2Cl_2/hexane, >99% ee); $[\alpha]^{21}_D$ −0.435 (*c* 0.46, $CHCl_3$).

Preparation of 44. To a solution of **41** (140 mg, 0.5 mmol), prepared from **40** according to the literature procedure,[19] and Et_3N (0.21 mL, 1.5 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added methanesulfonyl chloride (114 mg, 1.0 mmol), and the mixture was stirred for 0.5 h. Conventional workup producted the crude mesylate **42**. This sample was dissolved in dry Et_2O (3 mL) and transferred via cannula into a cooled (0 °C) Et_2O solution (4 mL) of indolylmagnesium iodide, prepared from iodole (176 mg, 1.5 mmol) and MeMgI (1.58 M in Et_2O; 1 mL, 1.5 mmol),[20] and the mixture was stirred at rt for 3 h under Ar. After the reaction was quenched with water, the aqueous phase was extracted with AcOEt and treated conventionally to afford **43**, which was directly subjected to the next step.

A solution of **43** in acetonitrile (3 mL) was placed in a Teflon reaction vessel and treated dropwise with 35% aqueous HF (3 mL). After being stirred for 3 h at rt, the mixture was quenched with 1 M NaOH until the solution turned basic and then extracted thoroughly with AcOEt. Conventional workup followed by purification by flash column chromatography (elution with hexane/AcOEt = 2:1) afforded 32 mg (27% from **41**) of **44**. This sample was found by HPLC to be 70% ee.

Acknowledgment. This work was partially supported by Scientific Research Grants (Nos. 05453063 and 07304047) from the Ministry of Education, Science and Culture of Japan. We also thank the Asahi Glass Foundation and the Naito Foundation for financial support of this work. We are also grateful to Prof. Y. Fukuyama of Tokushima Bunri University for HRMS/MS measurements.

Supporting Information Available: ^1H and ^{13}C NMR spectra of **9**, **11**, **15**, **17**−**19**, **21**−**23**, **25**−**28**, **30**, **32**, **34**, **35**, **37**, **39**, (−)-**3**, and **41** (42 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO951106T