80 °C in a sealed tube for 17 h. Evaporation of the methyl iodide left 100 mg of a yellow solid which was recrystallized from acetonitrile–ethyl acetate to give 92 mg (0.23 mmol, 87%) of methiodide **22**: mp 258–260 °C; NMR, Table I.

A 60-mg (0.15 mmol) sample of methiodide **22** was reduced with 20 mg (2.8 mmol) of lithium in liquid ammonia as before to give 30 mg of crude product which was filtered through silica gel in hexane–5% ether to yield 27 mg of a pale yellow oil. Chromatography on alumina eluting with hexane–10% benzene afforded 22 mg (0.099 mmol, 66%) of (±)-7-epi-α-eudesmol (**21**) as a colorless oil which showed a single peak on GC (150 °C) but would not crystallize: IR 3600, 3465, 2910, 1460, 1435, 1375, 1125, 1100, 940 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.17), 204 (17), 189 (15), 161 (100), 149 (15), 133 (13), 122 (80), 107 (52), 93 (22), 79 (56), 59 (44); molecular ion at 222.1981, calcd for $C_{16}H_{26}O$ 222.1983.

To a 3.5-mm ID glass tube containing 150 μL of technical sulfolane were added 50 mg of K_2CO_3 and a solution of 61 mg (0.23 mmol) of oxazine **20** in 300 μL of methyl iodide. The tube was degassed, sealed, and heated at 80–85 °C for 3 days. The lithium/liquid ammonia reduction and isolation procedure as for **17** gave 3 mg of amine fraction and 30 mg of neutral fraction. Chromatography of the latter on silica gel–25% $AgNO_3$ gave 4 mg (0.018 mmol, 8%) of 7-epi-α-eudesmol (**21**), and 15 mg (0.068 mmol, 30%) of 7-epi-β-eudesmol (**23**) as a waxy solid: mp 62–64 °C; IR 3625, 3525, 2920, 1640, 1465, 1450, 1390, 1380, 1260, 890 cm^{-1}; NMR Table II, in agreement with lit.[4c,6b] values; MS, *m/e* (relative intensity) 222 (0.18), 204 (36), 189 (42), 176 (16), 161 (68), 149 (30), 133 (56), 122 (26), 107 (48), 91 (80), 79 (72), 59 (100); molecular ion at 222.1988, calcd for $C_{15}H_{26}O$ 222.1983.

Alkylation–Deamination of Oxazines 24 and 27. (±)-5-Epi-7-epi-α-eudesmol (26) and (±)-5-Epi-α-eudesmol (28). A solution of 709 mg (2.70 mmol) of oxazine **24** in 25 mL of methyl iodide was left at 25 °C for 2 days. Evaporation of the methyl iodide and recrystallization of the residue from acetonitrile–ethyl acetate gave 945 mg (2.33 mmol, 86%) of methiodide **25**: mp (sealed tube) 248–250 °C dec; NMR, Table I. A sample of 700 mg (1.73 mmol) of **25** was reduced with 120 mg (17.3 mmol) of lithium wire in 100 mL of liquid ammonia for 3 h. Isolation as before afforded 387 mg (1.47 mmol, 85%) of oxazine **24** and 68 mg of a neutral fraction. Chromatography of the latter on alumina eluting with hexane–10% benzene gave 43 mg (0.19 mmol, 11%) of (±)-5-epi-7-epi-α-eudesmol (**26**) as an oil which crystallized from pentane at −20 °C: mp 45–47 °C; IR 3620, 3450, 2910, 1455, 1440, 1370, 1260, 1100 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.9), 204 (21), 189 (18), 161 (16), 149 (35), 135 (11), 121 (10), 109 (55), 93 (26), 81 (21), 59 (100); molecular ion at 222.1983, calcd for $C_{15}H_{26}O$ 222.1983.

A solution of 100 mg (0.38 mmol) of oxazine **27** in 2 mL of methyl iodide was heated at 70 °C in a sealed tube for 4 days. The solvent was evaporated and the residue was recrystallized from acetonitrile–ethyl acetate to give 144 mg (0.36 mmol, 95%) of **27**·MeI: mp (sealed tube) 239–245 °C dec; NMR, Table I. A sample of 104 mg (0.257 mmol) of this methiodide was reduced with 20 mg (2.9 mmol) of lithium in liquid ammonia as above to give 49 mg of crude product which did not contain any oxazine **27** (TLC). Chromatography of the oil on alumina eluting with hexane–10% benzene afforded 36 mg (0.16 mmol, 62%) of (±)-5-epi-α-eudesmol (**28**) which crystallized from pentane at −20 °C: mp 68–69 °C; IR 3600, 3450, 2920, 1450, 1370, 900 cm^{-1}; NMR, Table II; MS, *m/e* (relative intensity) 222 (0.1), 204 (18), 161 (64), 149 (19), 122 (32), 109 (32), 93 (22), 81 (17), 59 (100); molecular ion at 222.1981, calcd for $C_{15}H_{26}O$ 222.1983.

Registry No. (±)-**1**, 69686-15-3; (±)-**2**, 3287-59-0; **5**, 10485-70-8; (±)-**6a**, 95421-18-4; (±)-**6b**, 95421-19-5; (±)-**7a**, 95421-20-8; (±)-**7b**, 95421-21-9; **8**, 70038-03-8; **9**, 38142-31-3; **9** (bromohydrin), 95421-27-5; **10**, 38142-32-4; (±)-**11a**, 95421-16-2; (±)-**11b**, 95421-17-3; (±)-**12**, 95530-47-5; (±)-**13**, 95421-22-0; (±)-**13**·CH_3I, 95529-61-6; (±)-**14**, 95529-59-2; (±)-**14**·CH_3I, 95529-62-7; (±)-**15**, 95529-60-5; (±)-**15**·CH_3I, 95529-63-8; (±)-**16**, 95421-23-1; (±)-**17**, 95421-24-2; (±)-**18**, 95421-25-3; (±)-**20**, 95529-64-9; (±)-**21**, 95529-68-3; (±)-**22**, 95421-26-4; (±)-**23**, 95529-67-2; (±)-**24**, 95529-65-0; (±)-**25**, 95585-28-7; (±)-**26**, 69686-18-6; (±)-**27**, 95529-66-1; (±)-**27**·CH_3I, 95529-69-4; (±)-**28**, 69686-16-4; CH_3N-HOH·HCl, 4229-44-1.

Ruthenium Complex Catalyzed N-Heterocyclization. Syntheses of N-Substituted Piperidines, Morpholines, and Piperazines from Amines and 1,5-Diols

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1,5-Pentanediol reacts with aliphatic and aromatic primary amines in the presence of a ruthenium catalyst modified with phosphine ligands to give N-substituted piperidines in fair to goods yields. The reactions were carried out at 150–180 °C for 5 h in dioxane. The nature of the phosphorus ligands has a remarkable effect on the catalytic activity. For the reaction of aromatic amines, triphenylphosphine is effective, while for aliphatic amines more basic tributyl- or triethylphosphine is preferable. Amines also react with diethylene glycol and N-substituted diethanolamines in the presence of the ruthenium catalyst to give N-substituted morpholines and piperazines in good yields, respectively.

A large variety of methods are known for building up piperidine,[1] morpholine,[2] and piperazine[3] rings. In these methods, substrates such as 1,5-dihalogenopentanes, 1,5-halogenoamines, diethanolamines, *N*-(2-hydroxyethyl)-ethylenediamine, and diethylenetriamines are used as the starting materials, and the hetero rings are usually closed intramolecularly at the nitrogen or oxygen atom.

We have reported the syntheses of N-substituted piperidines from glutaraldehyde and primary amines with $KHFe(CO)_4$ as a reductant.[4] This reaction, however, required a stoichiometric amount of $KHFe(CO)_4$. We have recently developed organic syntheses involving dehydrogenation of an alcohol by a ruthenium catalyst as a key step.[5-7] One possible feature of homogeneous ruthenium

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Table I. Effect of Reaction Conditions on the Synthesis of 1-Phenylpiperidine from 1,5-Pentanediol and Aniline[a]

run	catalyst,[b] mol%	molar ratio[c]	temp, °C	product yield,[d] %
1	1.0	1.5	180	89 (87)[e]
2	1.0	2.0	180	87
3	1.0	4.0	180	79
4	1.0	1.5	150	89
5	1.0	1.5	120	5
6	0.5	1.5	180	66

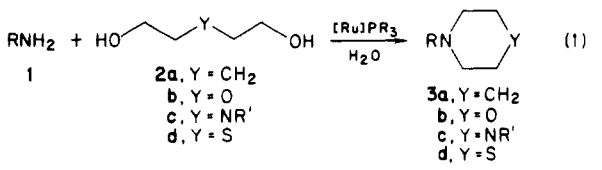
[a] Aniline (1.8 mL, 20 mmol), 1,5-pentanediol, catalyst $RuCl_2(PPh_3)_3$, dioxane (5 mL), reaction time 5 h. [b] Based on an amount of aniline used. [c] [1,5-Pentanediol]/[aniline]. [d] Determined by GLC based on an amount of aniline used. [e] Isolated yield.

catalysis could be high catalytic activity for the hydrogen transfer from alcohols or amines.[8-26] However, this has not been fully utilized in organic syntheses.

This paper deals with the catalytic syntheses of N-substituted piperidine, morpholine, and piperazine derivatives from primary amines and 1,5-diols such as 1,5-pentanediol, diethylene glycol, and ethanolamines. The homogeneous ruthenium catalyst shows high catalytic activity for these reaction. These 1,5-diols are commercially available and the reaction is controlled by phosphine ligands coordinated to the ruthenium catalyst.

Results and Discussion

Piperidines from 1,5-Pentanediol and Amine. An amine (1) reacted with 1,5-pentanediol (**2a**) in the presence of a catalytic amount of a ruthenium complex gives an N-substituted piperidine (**3a**) in good yield (eq 1). The



reaction was investigated by employing aniline as the amine (Table I). $RuCl_2(PPh_3)_3$ was an excellent catalyst to give 1-phenylpiperidine in high yield (run 1). A large excess of 1,5-pentanediol reduced the yield of the product (runs 2 and 3), although the selectivity to the product was still high. The same catalytic activity was maintained at 150 °C (run 4). At 120 °C, however, the conversion of aniline and yield of 1-phenylpiperidine were reduced considerably (run 5).

In this reaction, the catalyst precursor has a critical effect (Table II). For aromatic amines such as aniline, $RuCl_2(PPh_3)_3$ showed the highest activity (run 1). $RuHCl(CO)(PPh_3)_3$ had some activity. However, other ruthenium(II) compounds such as $RuHCl(PPh_3)_3$ and $RuH_2(PPh_3)_4$ showed almost no catalytic activity. Ruthenium(0) complexes such as $Ru(CO)_3(PPh_3)_2$ and (η^6-1,3,5-cyclooctatriene)(η^4-1,5-cyclooctadiene)ruthernium (Ru(cod)(cot)) were not active. With $RuCl_3 \cdot nH_2O$ (run 13) all the substrates were recovered quantitatively.

On the other hand, in the reaction of aliphatic amines such as octylamine, a drastic change in the catalytic activity was observed (Table III). In this case, $RuCl_3 \cdot nH_2O$ combined with PBu_3 showed the highest catalytic activity (run 16). It is well-known that phosphorus(III) ligands modify or improve activities of transition metal catalysts.[27] Employment of PPh_3 as the ligand led to a low yield of 1-octylpiperidine (runs 19–21). Furthermore, surprisingly, by use of a $RuCl_3 \cdot nH_2O$–PBu_3 system, aniline did not react

Table II. Effect of Catalyst Precursor on the Synthesis of 1-Phenylpiperidine from 1,5-Pentanediol and Aniline[a]

run	catalyst	product yield,[b] %
1	$RuCl_2(PPh_3)_3$	89 (87)[c]
7	$RuCl_3 \cdot nH_2O$ + $3PPh_3$[d]	88
8	$RuHCl(CO)(PPh_3)_3$	57
9	$RuHCl(PPh_3)_3$	1
10	$RuH_2(PPh_3)_4$	tr
11	$Ru(CO)_3(PPh_3)_2$	tr
12	Ru(cod)(cot)	0
13	$RuCl_3 \cdot nH_2O$	0
14[e]		0
15	$RuCl_3 \cdot nH_2O$ + $3PBu_3$[f]	0

[a] Aniline (1.8 mL, 20 mmol), 1,5-pentanediol (3.1 mL, 30 mmol), catalyst (0.20 mmol), dioxanne (5 mL), at 180 °C, for 5 h. [b] Determined by GLC based on an amount of aniline used. [c] Isolated yield. [d] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and PPh_3 (0.60 mmol). [e] Without catalyst. [f] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and PBu_3 (0.60 mmol).

Table III. Synthesis of 1-Octylpiperidine from 1,5-Pentanediol and Octylamine.[a] Effect of Catalyst System

run	catalyst system	yield, %[b]
16	$RuCl_3 \cdot nH_2O$ + 3 PBu_3[c]	57 (50)[d]
17	$RuCl_3 \cdot nH_2O$ + 3 PEt_3[c]	58
18	$RuCl_3 \cdot nH_2O$ + 3 PCy_3[c]	tr
19	$RuCl_3 \cdot nH_2O$ + 3 PPh_3[c]	14
20	$RuCl_2(PPh_3)_3$	16
21[e]	$RuCl_2(PPh_3)_3$	18
22	$RuH_2(PPh_3)_4$	6
23	$RuCl_3 \cdot nH_2O$ + 3 P(o-Tol)$_3$[c]	0
24	$RuCl_3 \cdot nH_2O$ + $Ph_2P(CH_2)_2PPh_2$[f]	0
25	$RuCl_3 \cdot nH_2O$ + $Ph_2P(CH_2)_3PPh_2$[f]	18
26	$RuCl_3 \cdot nH_2O$ + $3P(OPh)_3$[c]	0
27	$RuCl_3 \cdot nH_2O$	0

[a] Octylamine (3.3 mL, 20 mmol), 1,5-pentanediol (3.1 mL, 30 mmol), catalyst (0.20 mmol), dioxane (5 mL), at 150 °C for 5 h. [b] Determined by GLC based on an amount of octylamine used. [c] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and phosphorus ligand (0.60 mmol). [d] Isolated yield. [e] At 180 °C. [f] $RuCl_3 \cdot nH_2O$ (0.20 mmol) and diphosphine (0.20 mmol).

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Table IV. Synthesis of N-Substituted Piperidines from 1,5-Pentanediol and Amines[a]

run	amine	catalyst[b]	product	yield, %[c]
28	*p*-toluidine	A	1-(4-methylphenyl)piperidine	61 (72)
29	*m*-toluidine	A	1-(3-methylphenyl)piperidine	82 (93)
30	*o*-toluidine	A	1-(2-methylphenyl)piperidine	80
31	*p*-anisidine	A	1-(4-methoxyphenyl)piperidine	76
32	*o*-anisidine	A	1-(2-methoxyphenyl)piperidine	84
33	*p*-chloroaniline	A	1-(4-chlorophenyl)piperidine	61 (89)
34	*o*-chloroaniline	A	1-(2-chlorophenyl)piperidine	78
35	phenethylamine	B	1-(2-phenylethyl)piperidine	tr
36[d]	phenethylamine	B-1	1-(2-phenylethyl)piperidine	(44)
37[d]	phenethylamine	B	1-(2-phenylethyl)piperidine	60 (62)
38[d]	phenethylamine	C	1-(2-phenylethyl)piperidine	(61)
39[d]	cyclohexylamine	B	1-cyclohexylpiperidine	59
40[d]	benzylamine	B	1-benzylpiperidine	48 (54)
41[d]	laurylamine	B	1-laurylpiperidine	76

[a] Amine (20 mmol), 1,5-pentanediol (3.1 mL, 30 mmol), dioxane (5 mL) at 150 °C, for 5 h. [b] Catalyst A, $RuCl_2(PPh_3)_3$ (0.20 mmol); catalyst B, $RuCl_3 \cdot nH_2O$ (0.20 mmol) and PBu_3 (0.60 mmol); catalyst B-1, $RuCl_3 \cdot nH_2O$ (0.20 mmol) and PBu_3 (0.20 mmol); catalyst C, $RuCl_3 \cdot nH_2O$ (0.20 mmol) and PEt_3 (0.60 mmol). [c] Isolated yield. Figures in parentheses show GLC yields. [d] Reaction at 180 °C.

Table V. Ruthenium-Catalyzed Synthesis of N-Substituted Morpholine from Diethylene Glycol and Amines[a]

run	amine	catalyst[b] (mmol)	product	yield, %[c]
42	aniline	A (0.20)	4-phenylmorpholine	(58)
43	aniline	A (0.40)	4-phenylmorpholine	(63)
44	aniline	A (0.60)	4-phenylmorpholine	73 (78)
45	aniline	A (1.00)	4-phenylmorpholine	(70)
46	aniline	D (0.20)	4-phenylmorpholine	(29)
47	aniline	E (0.20)	4-phenylmorpholine	(0)
48	*o*-chloroaniline	A (0.60)	4-(2-chlorophenyl)morpholine	59
49	*p*-chloroaniline	A (0.60)	4-(4-chlorophenyl)morpholine	61
50	*o*-anisidine	A (0.60)	4-(2-methoxyphenyl)morpholine	73
51	*p*-anisidine	A (0.60)	4-(4-methoxyphenyl)morpholine	67
52	*o*-toluidine	A (0.60)	4-(2-methylphenyl)morpholine	71
53	*p*-toluidine	A (0.60)	4-(4-methylphenyl)morpholine	74
54	octylamine	B-3	4-octylmorpholine	38
55	octylamine	A (0.60)	4-octylmorpholine	(6)
56	laurylamine	B-3	4-laurylmorpholine	45

[a] Amine (20 mmol), diethylene glycol (2.8 mL, 30 mmol), dioxane (10 mL), at 180 °C, for 5 h. [b] Catalyst A, $RuCl_2(PPh_3)_3$; catalyst B-3, $RuCl_3 \cdot nH_2O$ (0.60 mmol) and PBu_3 (1.8 mmol); catalyst D, $RuHCl(PPh_3)_3$; catalyst E, $RuH_2(PPh_3)_4$. [c] Isolated yield. Figures in parentheses show GLC yields.

with 1,5-pentanediol at all (run 15, in Table II). These striking differences may be attributed to the difference in the basicity of these amines. More basic aliphatic amines may require more basic phosphines[28] as the ligands. PEt_3 had the same effectiveness as PBu_3, since they have almost the same basicity.[28] However, addition of tricyclohexylphosphine (PCy_3), having a large cone angle,[30] did not generate catalytic activity (run 18). The steric effect[30] of phosphine ligands would be also important in this reaction as well as basicity.[28] $RuH_2(PPh_3)_4$ had only low catalytic activity (run 22).[32] Other phosphorus ligands, such as bulky tri-*o*-tolylphosphine ($P(o\text{-}Tol)_3$),[30] less basic triphenyl phosphite ($P(OPh)_3$), and chelating diphosphorus(III) ligands failed to enhance the catalytic activity (runs 23–26), $RuCl_3 \cdot nH_2O$ without phosphorus ligand also did not show catalytic activity in this case (run 27). The yield of 1-octylpiperidine was influenced by the molar ratio of PBu_3 to $RuCl_3 \cdot nH_2O$. The highest yield was realized at the molar ratio of 2.0–3.0; the yield of 1-octylpiperidine was 49% at the ratio of 1.0 under the similar reaction conditions of run 16, 57% at 2.0 and 3.0. The higher molar ratio reduced the yield of the product, 53% at the ratio of 4.0, and 28% at 8.0. However, at the ratio less than 0.5, the reaction did not proceed.

The piperidine synthesis utilizing 1,5-pentanediol was carried out with various amines (Table IV). $RuCl_2(PPh_3)_3$ was used as the effective catalyst for the aromatic amines (runs 28–34), while $RuCl_3 \cdot nH_2O$ combined with PBu_3 or PEt_3 is effective as the catalyst for aliphatic amines (runs 35–41). Methyl, methoxyl, and chloro substituents introduced at the phenyl ring did not affect the reaction and the corresponding piperidines were obtained in good yields, even if the substituents were located at the ortho position. Thus, both aromatic and aliphatic amines can be converted into the piperidines by the present procedure, employing the ruthenium catalyst with the suitable phosphine ligand.

Morpholines from Diethylene Glycol and Amines. Amines (1) reacted with diethylene glycol (**2b**) in the presence of a catalytic amount of a ruthenium complex to give N-substituted morpholines (**3b**) in good yields (eq 1). The results are listed in Table V. Aniline reacted with diethylene glycol in the presence of $RuCl_2(PPh_3)_3$ at 180 °C to give 4-phenylmorpholine in 58% yield (run 42). The yield of the product increased to 78% with increasing amounts of catalyst (runs 42–44). However, a larger amount of $RuCl_2(PPh_3)_3$ reduced the yield (run 45). Employment of $RuHCl(PPh_3)_3$ as catalyst was not successful and $RuH_2(PPh_3)_4$ did not show catalytic activity (runs 46–47). From other substitued aminoarenes, the corresponding N-substituted morpholines were obtained in high yields (runs 48–53). Aliphatic amines also reacted with diethylene glycol in the presence of $RuCl_3 \cdot nH_2O$ combined

(28) Basicities of the ligands are as follows:[29] PPh_3, pKa 2.73; PBu_3, pKa 8.43; PEt_3, pKa 8.69; PCy_3, pKa 9.70.
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(30) Larger cone angle shows larger steric size of the phosphorus ligands. The cone angle of the ligands are as follows:[31] $P(o\text{-}Tol)_3$, 194°; PCy_3, 179°; PPh_3, 143°; PBu_3, 132°; PEt_3, 132°; $P(OPh)_3$, 121°.
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Table VI. Ruthenium-Catalyzed Synthesis of N-Disubstituted Piperazine from N-Substituted Diethanolamines and Amines[a]

run	amine	N-substituted diethanolamine	catalyst[b]	product	yield, %[c]
57[d]	aniline	*N*-methyldiethanolamine	A-3	*N*-methyl-*N'*-phenylpiperazine	0
58	aniline	*N*-methyldiethanolamine	A-3	*N*-methyl-*N'*-phenylpiperazine	32
59	aniline	*N*-ethyldiethanolamine	A-3	*N*-ethyl-*N'*-phenylpiperazine	25
60	aniline	*N*-phenyldiethanolamine	A-3	*N,N'*-diphenylpiperazine	44
61	octylamine	*N*-methyldiethanolamine	B-3	*N*-methyl-*N'*-octylpiperazine	19

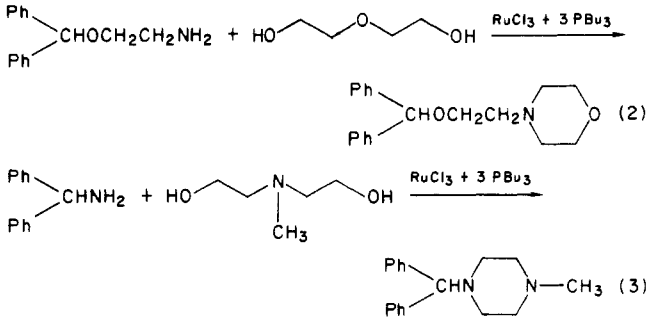
[a] Amine (30 mmol), N-substituted diethanolamine (20 mmol), dioxane (10 mL), at 180 °C, for 5 h. [b] Catalyst A-3, $RuCl_2(PPh_3)_3$ (0.60 mmol); catalyst B-3, $RuCl_3 \cdot nH_2O$ (0.60 mmol) and PBu_3 (1.8 mmol). [c] Isolated yield. Based on an amount of N-substituted diethanolamine used. [d] Aniline (20 mmol), *N*-methyldiethanolamine (30 mmol).

with PBu_3 (runs 54 and 56). In these cases, similarly to the piperidine synthesis, PPh_3 was not a suitable ligand (run 55).

Piperazines from Diethanolamines and Amines. N-Substituted diethanolamines (**2c**) could be used as the source of 1,5-diols for the synthesis of N,N'-disubstituted piperazines (**3c**) (eq 1). The results are shown in Table VI. In constrast to the reaction of 1,5-pentanediol, the piperazines were not obtained when the diethanolamines were used in excess (run 57). Use of excess amine successfully gave the product. *N*-Methyldiethanolamine reacted with aniline to give *N*-methyl-*N'*-phenylpiperazine in moderate yield when the ratio of aniline to the 1,5-diol was 1.5 (run 58). A larger excess of aniline did not increase the yield of the product. *N*-Ethyl- and *N*-phenyldiethanolamine also reacted with aniline to give *N*-ethyl-*N'*-phenyl- and *N,N'*-diphenylpiperazine, respectively (runs 59 and 60). From octylamine and *N*-methyldiethanolamine, *N*-methyl-*N'*-octylpiperazine was obtained only in low yield in the presence of $RuCl_3 \cdot nH_2O$–PBu_3 catalyst (run 61). However, use of diethanolamine without a substituent at the nitrogen only gave intractable mixtures of unidentified organic products.

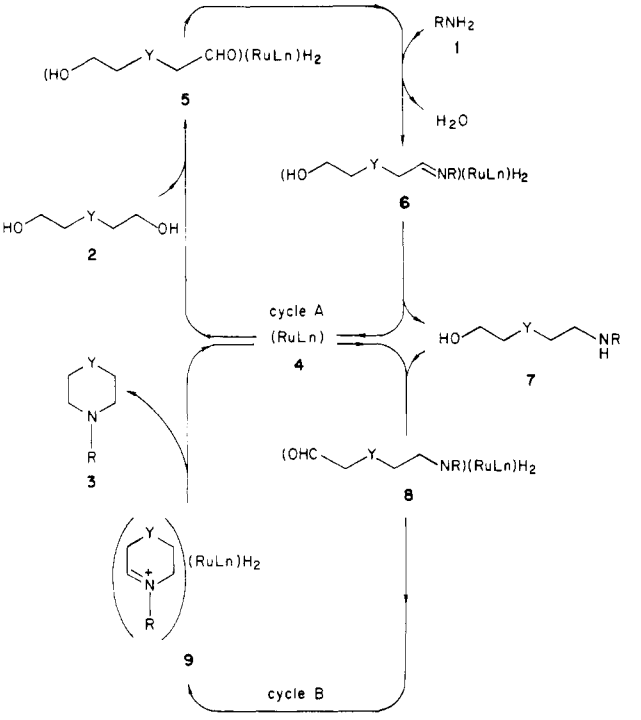
An attempted synthesis of N-substituted thiomorpholines from thiodiethanol (**2d**) and amines (1) was unsuccessful (eq 1). Sulfide group may deactivate the catalyst.

The present reaction was applied for syntheses of two biologically active substances. 4-[2-(Benzhydryloxy)ethyl]morpholine,[33] an antihistamic reagent, was obtained from 2-aminoethyl benzhydryl ether and diethylene glycol in 47% yield as isolated and purified material (eq 2). *N*-Methyl-*N'*-benzhydrylpiperazine (Valoid, Cyclizine),[34-35] a drug for alleviating travel sickness, was synthesized from benzhydrylamine and *N*-methyldiethanolamine in 19% yield in a pure form (eq 3).



Possible Reaction Pathway. In a previous paper,[7] we investigated the reaction of aromatic amines with simple primary alcohols, such as ethanol, 1-butanol, and benzyl alcohol. From the kinetic features of the reaction, the possible catalytic cycle which includes the nucleophilic attack of the aromatic amine on an aldehyde intermediate was proposed.[7] In the present reaction, a similar catalytic cycle is postulated and described in Scheme I. One of the hydroxy group of the 1,5-diol **2** oxidatively coordinates to the active catalyst center (**4**). Such an oxidation pathway via an alkoxohydrido complex has been proposed by several authors.[36-42] The nucleophilic attack of the amine (1) to the resulting aldehyde intermediate (**5**) yields the Schiff base complex (**6**). The hydrogenation of the Schiff base intermediate gives amino alcohol derivative **7**. Successively, **7** is cyclized intramolecularly to give the product **3** via imminium intermediate (**9**) in cycle B in a similar manner. When the reaction is interrupted at shorter reaction time, intermediates (**7**) were isolated in some cases as exemplified by eq 4 (see Experimental Section), and this 5-(phenylamino)pentanol is converted to 1-phenylpiperidine quantitatively.

Scheme I



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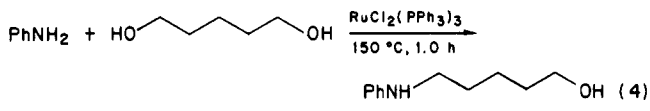

Experimental Section

The amines, 1,5-pentanediol, diethylene glycol, N-substituted diethanolamines, and the solvent were commercial materials and were purified by distillation or recrystallization before use. $RuCl_3 \cdot nH_2O$ (mainly, $n = 3$) was purchased from Engelhard Chemicals and used without further purification. $RuCl_2(PPh_3)_3$,[43] $RuH_2(PPh_3)_4$,[44] $RuHCl(PPh_3)_3$,[45] $RuHCl(CO)(PPh_3)_3$,[46] $Ru(CO)_3(PPh_3)_2$,[47] and Ru(cod)(cot)[48] were prepared according to the methods in the literatures.

General Reaction Procedure. A typical reaction of aniline with 1,5-pentanediol will be described here to exemplify the general reaction procedure. A stainless steel reactor (50 mL, Taiatsu Glass Industry, TVS-1 type) containing a glass liner was used in the reaction. Under argon stream, dioxane (5 mL), aniline (1.8 mL, 20 mmol), 1,5-pentanediol (3.1 mL, 30 mmol), and $RuCl_2(PPh_3)_3$ (192 mg, 0.2 mmol, 1.0 mol% based on aniline) were added with a magnetic stirring bar into the glass linear set in the reactor. After the reactor was sealed, an air purge was confirmed by pressurization (10 atm)–depressurization sequences with argon. The reactor was heated to 150 °C in 30 min in a mantle heater and thermostated at this temperature with stirring for 5 h. The reaction was terminated by rapid cooling and the reactor was discharged. At the bottom of the resulting clear brown solution, unreacted 1,5-pentanediol was separated out as a lower layer and it was discarded. A flash column chromatography (hexane–aluminium oxide 90, Merck, No. 1076) of the evaporated reaction mixture gave 1-phenylpiperidine in 87% yield. Some products were isolated by a vacuum distillation.

Analytical Procedure. All boiling points were uncorrected. The identification of products was made by ^1H, ^{13}C NMR, IR spectra, and elemental analysis. The ^1H and ^{13}C NMR spectra were recorded at 100 and 25.05 MHz, respectively, with a JEOL JNM FX-100 spectrometer. Samples were dissolved in $CDCl_3$, and the chemical shifts were expressed relative to Me_4Si as an internal standard. The IR spectra were measured on a Nicolet Model 5MX Fourier transform infrared spectrometer. Elemental analyses were performed at Microanalytical Center of Kyoto University. The GLC analysis was made by Shimadzu GC-4CM with a column (3 mm × 3 m) packed with Apiezon Greese L (10%) on Neopack 1A, 60–80 mesh. In some cases, the yield was determined by the internal standard method according to the caliblation curve obtained for each product in a separate experiment.

1-Phenylpiperidine: colorless oil; bp 81 °C (0.90 mmHg); ^1H NMR (100 MHz)($CDCl_3$) 1.51 (m, 2 H, CH_2), 1.65 (m, 4 H, CH_2), 3.08 (t, 4 H, N-CH_2), 6.74–7.22 (m, 5 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 24.3 (t, CH_2), 25.8 (t, 2CH_2), 50.5 (t, 2 N-CH_2), 116.4 (d), 119.0 (d), 128.8 (d), 152.1 (s). Anal. Found: C, 82.04; H, 9.53; N, 8.69. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69.

1-Laurylpiperidine: colorless oil; Kugelrohr pot temperature 62 °C (0.10 mmHg); ^1H NMR (100 MHz) ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.26 (m, 18 H, CH_2), 1.50 (m, 8 H, CH_2), 2.32 (m, 6 H, CH_2); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 14.1 (q, CH_3), 22.7 (t, CH_2), 24.6 (t, CH_2), 26.0 (t, 2CH_2), 27.0 (t, CH_2), 27.9 (t, CH_2), 29.4 (t, CH_2), 29.7 (t, 5CH_2), 32.0 (t, CH_2), 54.7 (t, 2 N-CH_2), 59.7 (t, N-CH_2). Anal. Found: C, 80.27; H, 14.02; N, 5.32. Calcd for $C_{17}H_{35}N$: C, 80.56; H, 13.98; N, 5.52.

4-(2-Chlorophenyl)morpholine: colorless oil; bp 82 °C (0.15 mmHg); ^1H NMR (100 MHz) ($CDCl_3$) 3.03 (t, 4 H, N-CH_2), 3.86 (t, 4 H, O-CH_2), 6.88–7.40 (m, 4 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 51.6 (t, 2 N-CH_2), 67.0 (t, 2 O-CH_2), 120.1 (d), 123.7 (d), 127.5 (d), 128.6 (s), 130.5 (d), 148.9 (s). Anal. Found: C, 60.73; H, 6.18; N, 7.26; O, 8.04; Cl, 17.87. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09; O, 8.09; Cl, 17.94. IR (neat) 1118 cm^{-1} (ν_{C-O-C}).

4-Octylmorpholine: colorless oil; bp 78 °C (0.60 mmHg); ^1H NMR (100 MHz) ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.28 (m, 12 H, CH_2), 2.42 (t, 6 H, N-CH_2), 3.71 (t, 4 H, O-CH_2); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 14.1 (q, CH_3), 22.6 (t, CH_2), 26.4 (t, CH_2), 27.6 (t, CH_2), 29.3 (t, CH_2), 29.6 (t, CH_2), 31.9 (t, CH_2), 53.8 (t, 2 N-CH_2), 59.2 (t, N-CH_2), 66.8 (t, 2 O-CH_2). Anal. Found: C, 72.61; H, 12.93; N, 7.03; O, 7.85. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03; O, 8.03. IR (neat) 1121 cm^{-1} (ν_{C-O-C}).

***N*-Ethyl-*N'*-phenylpiperazine**: colorless oil; bp 72 °C (0.20 mmHg); ^1H NMR (100 MHz) ($CDCl_3$) 1.11 (t, 3 H, CH_2CH_3), 2.45 (q, 2 H, N-CH_2CH_3), 2.58 (t, 4 H, N-CH_2), 3.21 (t, 4 H, N-CH_2), 6.57–7.36 (m, 5 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 12.0 (q, CH_2CH_3), 49.0 (t, 2 N-CH_2), 52.2 (t, N-CH_2CH_3), 52.8 (t, 2 N-CH_2), 115.8 (d), 119.4 (d), 128.9 (d), 151.2 (s). Anal. Found: C, 75.45; H, 9.83; N, 14.66. Calcd for $C_{12}H_{18}N_2$: C, 75.75; H, 9.53; N, 14.72.

***N*-Methyl-*N'*-octylpiperazine**: colorless oil; bp 86 °C (0.45 mmHg); ^1H NMR (100 MHz) ($CDCl_3$) 0.88 (t, 3 H, CH_3), 1.27 (m, 12 H, CH_2), 2.20 (t, 2 H, N-CH_2), 2.28 (s, 3 H, N-CH_3), 2.46 (m, 8 H, N-CH_2); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 14.1 (q, CH_3), 22.7 (t, CH_2), 27.0 (t, CH_2), 27.7 (t, CH_2), 29.3 (t, CH_2), 29.6 (t, CH_2), 31.9 (t, CH_2), 46.0 (q, N-CH_3), 53.3 (t, 2 N-CH_2), 55.2 (t, 2 N-CH_2), 58.8 (t, N-CH_2). Anal. Found: C, 74.06; H, 13.47; N, 12.36. Calcd for $C_{13}H_{28}N_2$: C, 73.52; H, 13.29; N, 13.19.

4-[2-(Benzhydryloxy)ethyl]morpholine. 2-Aminobenzhydryl ether[49] was prepared from 2-(hydroxyethyl)phthalimide[50] and benzhydryl bromide according to the methods in the literature. 2-(Aminoethyl)benzhydryl ether (4.55 g, 20 mmol), diethylene glycol (2.8 mL, 30 mmol), $RuCl_3 \cdot nH_2O$ (0.147 g, 0.60 mmol), PBu_3 (0.45 mL, 1.8 mmol), and dioxane (10 mL) were charged into the reactor and stirred magnetically at 180 °C for 5 h under an argon atmosphere. The column chromatography of the reaction mixture on silica gel (Merck, No. 9385) with a hexane/ethyl acetate mixture as eluent (gradient from 98:2 to 2:1 in volume) gave the crude product, which was further purified by Kugelrohr distillation (Shibata, GTO-250RS); pot temperature 210 °C (0.45 mmHg). Thus, 2.82 g of 4-[2-(benzhydryloxy)-ethyl]morpholine was obtained in 47% yield based on 2-aminobenzhydryl ether used: yellow oil; ^1H NMR (100 MHz) ($CDCl_3$) 2.50 (t, 2 H, N-CH_2), 2.65 (t, 4 H, N-CH_2), 3.60 (t, 2 H, O-CH_2), 3.69 (t, 4 H, O-CH_2), 5.36 (s, H, O-CH), 7.25–7.36 (m, 10 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 54.0 (t, 2 N-CH_2), 58.3 (t, N-CH_2), 66.8 (t, O-CH_2), 67.0 (t, 2 O-CH_2), 84.0 (d, O-CH), 126.9 (d), 127.4 (d), 128.3 (d), 142.1 (s). Anal. Found: C, 76.57; H, 7.88; N, 4.92; O, 10.97. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71; O, 10.76. IR (neat) 1121 cm^{-1} (ν_{C-O-C}).

***N*-Benzhydryl-*N'*-methylpiperazine.** A mixture of benzhydrylamine (5.2 mL, 30 mmol), *N*-methyldiethanolamine (2.4 mL, 20 mmol), $RuCl_3 \cdot nH_2O$ (0.147 g, 0.60 mmol), PBu_3 (0.45 mL 1.8 mmol), and dioxane (10 mL) was placed in the reactor and stirred magnetically at 180 °C for 5 h under an argon atmosphere. The column chromatography of the evaporated reaction mixture on silica gel (Merck, No. 15111) with a hexane/ethyl acetate mixture as eluent (gradient from 98:2 to 2:1 in volume) gave *N*-benzhydryl-*N'*-methylpiperazine. The pure product (1.01 g, 3.8 mmol, 19% yield based on *N*-methyldiethanolamine used) was obtained by further Kugelrohr distillation: pot temperature 150 °C (0.09 mmHg); white crystal; mp 106 °C; ^1H NMR (100 MHz) ($CDCl_3$) 2.25 (s, 3 H, N-CH_3), 2.42 (s, 8 H, N-CH_2), 4.20 (s, H, N-CH), 7.11–7.46 (m, 10 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 45.9 (q, N-CH_3), 51.8 (t, 2 N-CH_2), 55.3 (t, 2 N-CH_2), 76.1 (d, N-CH), 126.7 (d), 127.7 (d), 128.3 (d), 142.6 (s). Anal. Found: C, 81.04; H, 8.47; N, 10.44. Calcd for $C_{18}H_{22}N_2$: C, 81.16; H, 8.32; N, 10.52.

5-(Phenylamino)pentanol. The reaction time of run 4 in Table I was shortened to 1 h (eq 4). 5-(Phenylamino)pentanol (1.1 g, 6.2 mmol) was isolated in 31% yield based on aniline used by column chromatography (silica gel, Merck, No. 7734, hexane/ethyl acetate gradient from 98:2 to 2:1 in volume); colorless oil; Kugelrohr pot temperature 120 °C (0.10 mmHg); ^1H NMR

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(100 MHz) ($CDCl_3$) 1.34–1.68 (m, 6 H, CH_2), 3.02 (t, 2 H, N-CH_2), 3.35 (s, 2 H, NH and OH), 3.52 (t, 2 H, CH_2OH), 6.51–7.21 (m, 5 H, Ph); ^{13}C NMR (25.05 MHz) ($CDCl_3$) 23.3 (t, CH_2), 29.1 (t, CH_2), 32.3 (t, CH_2), 43.8 (t, N-CH_2), 62.2 (t, O-CH_2), 112.8 (d), 117.1 (d), 129.1 (d), 148.3 (s). Anal. Found: C, 73.92; H, 9.80; N, 7.57; O, 9.09. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81; O, 8.93.

Supplementary Material Available: NMR data and analyses of 1-(4-methylphenyl)piperidine, 1-(3-methylphenyl)-piperidine, 1-(2-methylphenyl)piperidine, 1-(4-methoxyphenyl)-piperidine, 1-(2-methoxyphenyl)piperidine, 1-(4-chlorophenyl)-piperidine, 1-(2-chlorophenyl)piperidine, 1-octylpiperidine, 1-(phenylethyl)piperidine, 1-cyclohexylpiperidine, 1-benzyl-piperidine, 4-phenylmorpholine, 4-(4-chlorophenyl)morpholine, 4-(2-methoxyphenyl)morpholine, 4-(4-methoxyphenyl)morpholine, 4-(2-methylphenyl)morpholine, 4-(4-methylphenyl)morpholine, 4-laurylmorpholine, *N*-methyl-*N'*-phenylpiperazine, *N,N'*-diphenylpiperazine (6 pages). Ordering information is given on any current masthead page.

Photocycloaddition Reactions of 1,4-Benzoxazin-2-ones and Electron-Poor Olefins

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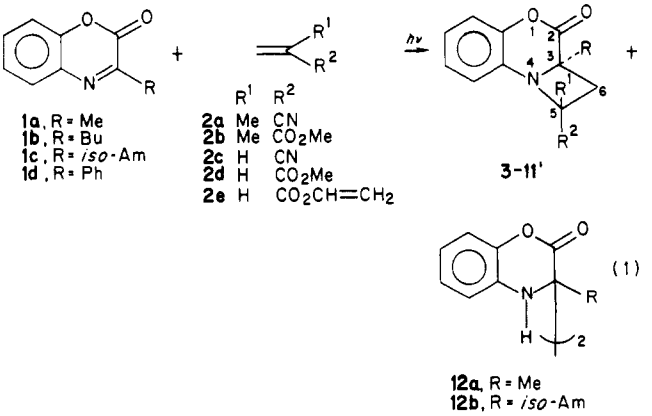
The photochemical reactivity of 1,4-benzoxazin-2-ones 1 with electron-poor olefins 2 such as cyanoolefins and vinyl carboxylates is described. Irradiation of 1,4-benzoxazin-2-ones **1a–c** in the presence of electron-poor olefins **2a–e** afforded azetidine derivatives **3–11'** via (2 + 2) photocycloaddition of the carbon–nitrogen double bond of 1 to olefin. The photoreaction of the 1,4-benzoxazin-2-one **1a** with olefin **2a** occurs from a triplet state.

Although (2 + 2) photocycloadditions of olefins to carbon-carbon[1,2] and carbon–oxygen double bonds[2,3] are common, synthetically useful reactions, similar photocycloadditions to the carbon–nitrogen double bond are rare and are known only for cyclic imines, which are conjugated with imino[4] and carbonyl groups[5–7] on both nitrogen and carbon atoms, and a heteroatom such as nitrogen[4,6] and oxygen[8] on the nitrogen atom. Recently, an additional case has been shown by Ohta et al.[9] that 6-cyanophenanthridine underwent photocycloaddition with electron-rich olefins to give the expected four-membered ring compounds. In view of the limited occurrence of photocycloaddition to the C=N double bond linkage, we have investigated the generality of this process in quinoxalinones.[7] We report here the photocycloaddition of the 1,4-benzoxazin-2-ones 1 to electron-poor olefins 2.

Irradiation of a mixture of 3-methyl-1,4-benzoxazin-2-one (**1a**) and an excess of methacrylonitrile (**2a**) in benzene with a high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere at room temperature for 15 h gave two stereoisomeric azetidine derivatives (**3** and **3'**) in 11% and 74% isolated yields, respectively. The structures for these photoproducts were supported by elemental analyses as well as their spectroscopic properties. Characteristically, these photocycloadducts and others to be described show a carbonyl stretch at around 1760 cm^{-1} and no carbon–nitrogen double bond in the infrared spectrum.

The regiochemistry of cycloaddition was suggested by the chemical shifts of the azetidine ring methylene protons of the (2 + 2) photocycloadducts.[10] Thus the azetidine **3** showed methylene protons at δ 2.94 (d, 1 H, J = 12.2 Hz) and 3.15 (d, 1 H, J = 12.2 Hz) and **3'** showed methylene protons at δ 2.59 (d, 1 H, J = 12.2 Hz) and 3.29 (d, 1 H, J = 12.2 Hz).[10] The stereochemistry of the photocycloadducts **3** and **3'** was assigned as shown in eq 1 on the basis



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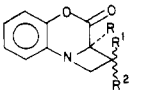

3''

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