$C_{11}H_{11}NO_2S$: C, 64.36; H, 5.40; N, 6.82; S, 15.61. Found: C, 64.09; H, 5.88; N, 7.21; S, 15.21.

Further elution gave also 490 mg (23%) of the more polar 2-hydroxythiochromone (**4a**): mp 206–208 °C; MS, *m/e* 178 (M^+, 61%); ^1H NMR 6.18 (s, 1 H, CH), 7.40 (m, 3 H, H_6, H_7, H_8), 8.17 (m, 1 H, H_5). Anal. Calcd for $C_9H_6O_2S$: C, 60.65; H, 3.39; S, 17.99. Found: C, 60.81; H, 3.61; S, 18.20.

The 3-hydroxybenzothiophene-2-carboxamides (**3b–d**) and the 2-hydroxythiochromone **4b** listed in Table II were prepared according to this procedure.

For **3b** (33% yield): mp 146–149 °C; ^1H NMR ($CDCl_3$, δ) 3.28 (s, 6 H, CH_3), 3.90 (s, 3 H, CH_3), 7.03 (dd, *J* = 2 Hz, 9 Hz, 1 H, H_5), 7.13 (d, *J* = 2 Hz, H_7), 7.90 (d, *J* = 9 Hz, 1 H, H_4), 13.45 (s, 1 H, OH). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 61.25; H, 5.56; N, 5.95; S, 13.62. Found: C, 59.33; H, 5.76; N, 5.94; S, 14.33.

For **3c** (7% yield): mp, 141–143 °C; ^1H NMR ($CDCl_3$, δ) 3.27 (s, 6 H, CH_3), 6.77 (d, *J* = 9 Hz, 1 H, H_5), 7.17 (d, *J* = 2 Hz, H_7), 7.33 (t, *J* = 9 Hz, 1 H, H_6), 7.90 (s, 1 H, OH). Anal. Calcd for $C_{11}H_{11}NO_3S$: C, 59.70; H, 5.01; N, 6.33; S, 14.49. Found: C, 59.77; H, 5.18; N, 6.05; S, 14.75.

2-Hydroxy-5-methoxythiochromone (4d). A mixture of *S*-(2-acetyl-3-methoxyphenyl) dimethylthiocarbamate (0.253 g, 1.0 mmol) and sodium hydride (57.6 mg, 1.2 mmol, 50% dispersion in mineral oil) in DMF (10 mL) was stirred for 18 h at room temperature under an atmosphere of nitrogen. Dilute HCl (1 N) was added and the mixture was extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed by using 50% ethyl acetate in hexane as eluent to yield 150 mg (72%) of 2-hydroxy-5-methoxythiochromone (**4d**): mp 158–160 °C; ^1H NMR 4.05 (s, 3 H, CH_3), 6.10 (s, 1 H, CH), 6.80–7.50 (m, 3 H, H_6, H_7, H_8), 10.3 (s, 1 H, OH).

The compounds listed in Table III were prepared according to this procedure.

For **4b** (79% yield): mp 146–149 °C; ^1H NMR ($CDCl_3$, δ) 3.28 (s, 6 H, CH_3), 3.90 (s, 3 H, CH_3), 7.03 (dd, *J* = 2 Hz, 9 Hz, 1 H, H_5), 7.13 (d, *J* = 2 Hz, H_7), 7.90 (d, *J* = 9 Hz, 1 H, H_4), 13.45 (s, 1 H, OH). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 61.25; H, 5.56; N, 5.95; S, 13.62. Found: C, 59.33; H, 5.76; N, 5.94; S, 14.33.

2-Hydroxy-4-methoxyacetophenone. A mixture of 2,4-dihydroxyacetophenone (15.2 g, 0.1 mol), potassium carbonate (13.8 g, 0.1 mol), and methyl iodide (14.2 g, 0.1 mol) in acetone (250 mL) was refluxed for 22 h. The mixture was filtered and the filtrate was concentrated in vacuo to a residue that was chromatographed on silica gel, eluting with 15% ethyl acetate in hexane to yield 2-hydroxy-4-methoxyacetophenone (15.3 g, 92%): mp 49–50 °C; ^1H NMR 2.58 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3O), 6.40 (m, 2 H, H_3, H_5), 7.63 (d, *J* = 9 Hz, 1 H, H_6). Anal. Calcd for $C_9H_{10}O_3$: C, 65.04; H, 6.06. Found: C, 64.94; H, 6.22.

2-Hydroxy-6-methoxyacetophenone. A mixture of 2,6-dihydroxyacetophenone (15.2 g, 0.1 mol), potassium carbonate (13.8 g, 0.1 mol), and methyl iodide (14.2 g, 0.1 mol) in acetone (250 mL) was refluxed for 22 h. The mixture was filtered and the filtrate was concentrated in vacuo to a residue that was chromatographed on silica gel, eluting with 15% ethyl acetate in hexane to yield 2-hydroxy-6-methoxyacetophenone (14.0 g, 84%): mp 57–58 °C; ^1H NMR 2.70 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3O), 6.40 (d, *J* = 9 Hz, 1 H, H_3), 6.58 (d, *J* = 9 Hz, 1 H, H_5), 7.38 (t, *J* = 9 Hz, 1 H, H_4). Anal. Calcd for $C_9H_{10}O_3$: C, 65.04; H, 6.06. Found: C, 64.74; H, 6.24.

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Ruthenium Complex Catalyzed N-Heterocyclization. Syntheses of Quinolines and Indole Derivatives from Aminoarenes and 1,3-Propanediol of Glycols

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Aniline reacts with 1,3-propanediol under reflux in diglyme with spontaneous hydrogen evolution in the presence of a catalytic amount of ruthenium trichloride hydrate ($RuCl_3 \cdot nH_2O$)–tributylphosphine (PBu_3) to give quinoline in good yield. The yield of quinoline was markedly affected by the molar ratios of aniline to 1,3-propanediol and PBu_3 to $RuCl_3 \cdot nH_2O$. The best yield (76%) was achieved at the molar ratios of 2.5 of aniline/1,3-propanediol and 2.0 of $PBu_3/RuCl_3 \cdot nH_2O$. Also, N-substituted anilines react with ethylene glycol in the presence of a catalytic amount of dichlorotris(triphenylphosphine)ruthenium ($RuCl_2(PPh_3)_3$) to give N-substituted indole derivatives. The reactions were carried out at 180 °C in dioxane with spontaneous hydrogen evolution. Aminoarenes also react with 2,3-butanediol and 1,2-cyclohexanediol (mixture of cis and trans) in the presence of $RuCl_2(PPh_3)_3$ to give the corresponding 2,3-dimethylindoles and 1,2,3,4-tetrahydrocarbazoles in good to excellent yields. As the key intermediates of the reactions, *N,N'*-diarylpropylenediamine (**5a**) and *N,N'*-diarylethylenediamine (**5b**) and their dehydrogenated imine derivatives are postulated.

The Skraup and related syntheses[1] are well-known as the method for the preparation of quinoline derivatives. This method, however, requires a large amount of sulfuric acid at temperatures above 150 °C, and the reaction is often violent.

Recently, transition-metal-catalyzed synthesis of quinoline derivatives under nonacidic conditions has been developed.[2-5] However, these methods are sucessful only with substituents on the heterocyclic ring.[6]

On the other hand, the Fischer indole synthesis is by far the most widely used route to substituted indoles and has been extensively reviewed.[7] It involves the rearrangement

(1) Manske, R. H. F.; Kulka, M. In *Organic Reaction*; Adams, R., Ed.; Wiley: New York, 1953; Vol. 7, p 59.
(2) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490.
(3) Boyle, W. J.; Mares, F. *Organometallics* **1982**, *1*, 1003.
(4) Watanabe, Y.; Suzuki, N.; Tsuji, Y.; Chim, S. C.; Mitsudo, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 1116.
(5) Watanabe, Y.; Tsuji, Y.; Shida, J. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 435.
(6) Claret, P. A. *Comprehensive Organic Chemistry*; Sammers, P. G., Ed.; Pergamon: Oxford, 1979; Vol. 4, p 160.
(7) (a) Robinson, B. *Chem. Rev.* **1963**, *63*, 273. (b) Idem. Ibid. **1969**, *69*, 227.

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Table I. Effects of Solvents and Temperatures on the Synthesis of Quinoline from Aniline and 1,3-Propanediol[a]

run	solvent	bp, °C	yield,[b] %
1	diglyme	162	76 (59)[c]
2	1,3-dimethyl-2-imidazolidinone	222	45
3	1-methyl-2-pyrrolidinone	202	44
4	DMF	153	44
5	benzonitrile	188	43
6	*p*-xylene	138	39
7	toluene	111	21
8	dioxane	101	4

[a] Aniline (4.6 mL, 50 mmol), 1,3-propanediol (1.4 mL, 20 mmol), catalyst $RuCl_3 \cdot nH_2O$ (157 mg, 0.6 mmol)–PBu_3 (0.30 ml, 1.2 mmol), solvent (10 mL), under reflux for 5 h. [b] Determined by GLC based on the amount of 1,3-propanediol used. [c] Isolated yield.

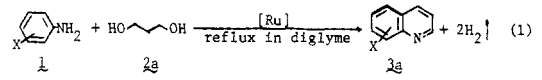
of arylhydrazones by heating or with an acid catalyst. α-Arylamino ketones and aldehydes, which are prepared from α-halocarbonyl compounds and aminoarenes, cyclized to indoles with loss of water on heating with acid catalyst (Bischler synthesis).[8] Treatment of *o*-alkylanilides with strong bases such as sodium amide and potassium *tert*-butoxide at 200–400 °C results in the formation of indoles (Madelung synthesis).[9] However, these precedents are restricted to the particular substrates, which are not easily accessible.

The simplest way to build up an indole skeleton would be an intermolecular reaction between aminoarenes and C_2 fragments. Recently, such synthetic methodologies have been attempted, mostly from an industrial point of view. In these reactions acetaldehyde,[10] ethylene oxide,[11] and ethylene glycol[12] were used as the C_2 fragment with aminoarenes. However, all these reactions were carried out over heterogeneous catalyst under very severe reaction conditions, at 300–700 °C, and in some cases yields were not so satisfactory.

This study deals with the first example of synthesis of quinolines without substituents on the N-hetero ring from aminoarenes and 1,3-propanediol and syntheses of indole derivatives from aminoarenes and glycols[13] using homogeneous transition-metal catalyst. The ruthenium-catalyzed reactions between aminoarenes and 1,3-propanediol or glycols proceed smoothly with spontaneous hydrogen evolution to give the corresponding free quinolines and indole derivatives.

Results

Synthesis of Quinolines. Aminoarenes **1** reacted with 1,3-propanediol (**2a**) in the presence of a catalytic amount of a ruthenium complex to give quinoline derivatives in good to excellent yields (eq 1).



Detailed effects of the reaction conditions, temperatures, and solvents were examined with aniline and 1,3-propanediol as the substrates (Table I). Diglyme was an excellent solvent for the reaction (run 1). Other polar solvents reduced the product yield, although the conversions of the substrates were high (runs 2–5). With solvents having lower boiling points, the conversion and yield were considerably reduced (runs 6–8).

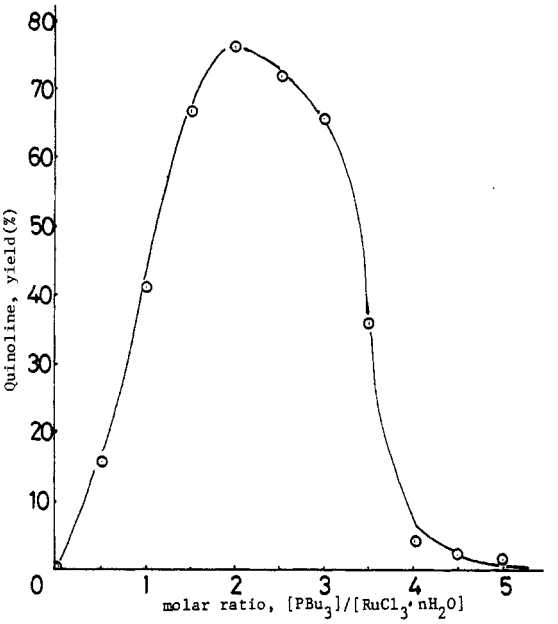


Figure 1. Effect of the molar ratio of PBu_3 to $RuCl \cdot nH_2O$ on the synthesis of quinoline from aniline and 1,3-propanediol. Aniline (4.6 mL, 50 mmol), 1,3-propanediol (1.4 mL, 20 mmol), $RuCl \cdot nH_2O$ (157 mg, 0.6 mmol), and diglyme (10 mL) under reflux for 5 h.

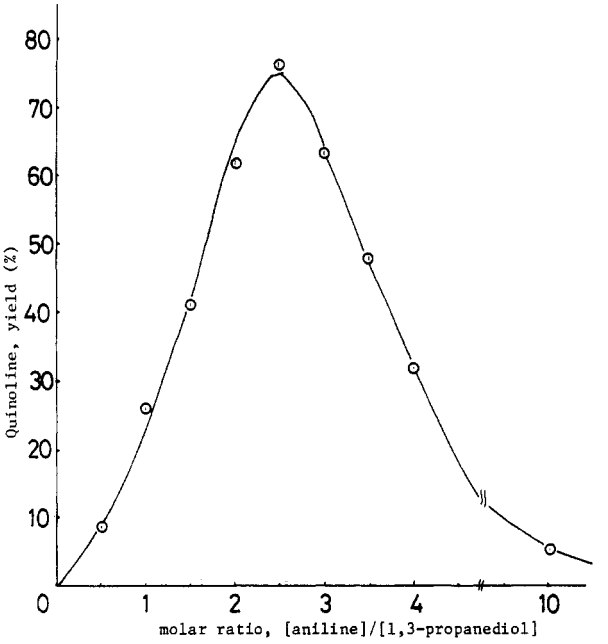


Figure 2. Effect of the molar ratio of aniline to 1,3-propanediol on the synthesis of quinoline using $RuCl \cdot nH_2O$–$2PBu_3$. 1,3-Propanediol (1.4 mL, 20 mmol), $RuCl \cdot nH_2O$ (157 mg, 0.6 mmol), PBu_3 (0.30 mL, 1.2 mmol), and diglyme (10 mL) under reflux for 5 h.

In the reaction, the yields of quinoline were critically influenced by the molar ratio of PBu_3 to $RuCl_3 \cdot nH_2O$ (Figure 1) with the highest yield at a molar ratio of 2.0. The yield of quinoline was also affected by the molar ratio of aniline to 1,3-propanediol (Figure 2) with the highest yield (76%) at the molar ratio of 2.5.

Phosphorus(III) ligands had a noticeable effect on the reaction (Table II). The presence of more basic phos-

(8) Remers, W. A. *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, p 317.
(9) (a) Remers, W. A. *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, p 385. (b) Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S. *J. Org. Chem.* **1973**, *38*, 3004.
(10) Jpn. Kokai 72-33355; *Chem. Abst.* **1972**, *77*, 164472.
(11) Jpn. Kokai 81-61353; *Chem. Abst.* **1981**, *95*, 115293.
(12) (a) U.S. Patent 1984, 4436917, 1984; *Chem. Abst.* **1984**, *101*, 7024. (b) Jpn. Kokai 83-32863; *Chem.* Abst. **1983**, *99*, 55μtc378. (c) Jpn. Kokai 81-63958; *Chem. Abst.* **1984**, *95*, 150441.
(13) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 377.

Table II. Catalyst Precursor for the Synthesis of Quinoline from Aniline and 1,3-Propanediol[a]

run	catalyst	yield,[b] %
1	$RuCl_3 \cdot nH_2O + 2PBu_3$	76 (59)[c]
9	$RuCl_3 \cdot nH_2O + 2PEt_3$	74
10	$RuCl_3 \cdot nH_2O + 2PCy_3$	0
11	$RuCl_3 \cdot nH_2O + 2PEt_2Ph$	65
12	$RuCl_3 \cdot nH_2O + 2PEtPh_2$	56
13	$RuCl_3 \cdot nH_2O + 2PPh_3$	49
14	$RuCl_3 \cdot nH_2O + 2P(OPh)_3$	38
15	$RuCl_3 \cdot nH_2O + 2P(OBu)_3$	22
16	$RuCl_3 \cdot nH_2O + PPh_2CH_2PPh_2$	48
17	$RuCl_3 \cdot nH_2O + PPh_2(CH_2)_2PPh_2$	46
18	$RuCl_3 \cdot nH_2O + PPh_2(CH_2)_3PPh_2$	48
19	$RuCl_3 \cdot nH_2O + PPh_2(CH_2)_4PPh_2$	55

[a] Aniline (4.6 mL, 50 mmol), 1,3-propanediol (1.4 mL, 20 mmol), $RuCl_3 \cdot nH_2O$ (157 mg, 0.6 mmol), diglyme (10 mL) under reflux for 5 h. [b] Determined by GLC based on the amount of 1,3-propanediol used. [c] Isolated yield.

Table III. Syntheses of Quinoline Derivatives from Aminoarenes and 1,3-Propanediol[a]

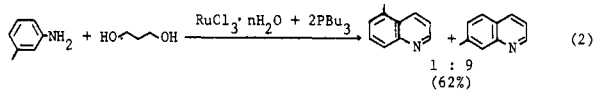
run	aminoarene	product	yield,[b] %
1	aniline	quinoline	76 (59)
20	*o*-toluidine	8-methylquinoline	(59)
21	*p*-toluidine	6-methylquinoline	78 (56)
22	*o*-chloroaniline	8-chloroquinoline	(48)
23	*p*-chloroaniline	6-chloroquinoline	63 (47)
24	*o*-anisidine	8-methoxyquinoline	0
25	*p*-anisidine	6-methoxyquinoline	74 (53)
26	1-aminonaphthalene	7,8-benzoquinoline	50 (37)

[a] Aminoarene (50 mmol), 1,3-propanediol (1.4 mL, 20 mmol), $RuCl_3 \cdot nH_2O$ (157 mg, 0.6 mmol)–PBu_3 (0.30 mL, 1.2 mmol), diglyme (10 mL) under reflux for 5 h. [b] Determined by GLC based on the amount of 1,3-propanediol used. Figures in parentheses show isolated yields.

phorus ligands,[14] such as tributyl- and triethylphosphine, had a favorable effect on the catalytic activity (runs 1 and 9). Triethylphosphine had the same effectiveness as tributylphosphine, since they have almost the same basicity.[14] However, tricyclohexylphosphine (PCy_3), having a large cone angle,[16] had no catalytic activity (run 10). The steric effect of phosphorus ligands must therefore be important in this reaction as well as the basicity. Other phosphorus ligands such as the less basic triphenyl phosphite and tributyl phosphite led to low yields (runs 14 and 15). Chelating diphosphorus(III) ligands were as effective as triphenylphosphine (runs 16–19). Triphenylarsine and triphenylantimony failed to enhance the catalytic activity.

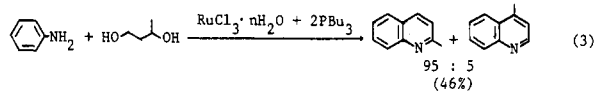
Under similar reaction conditions, rhodium and palladium complexes, such as $RhCl(PPh_3)_3$, $RhH(PPh_3)_3$, $Pd(OAc)_2$, and $PdCl_2$, showed low catalytic activities, giving only traces of quinoline with low conversion of the substrates.

The present method utilizing 1,3-propanediol was applied to a variety of aminoarenes (Table III). Methyl and chloro substituents introduced at the phenyl ring did not inhibit the reaction, and the corresponding quinolines were obtained in good to excellent yields, even if the substituents were located at the ortho position. *o*-Anisidine, however, did not give product, and the starting materials were completely recovered (run 24). It is considered in this case that the two adjacent substituents, methoxy and amino groups, coordinate to the metal center to deactivate the catalyst. From *m*-toluidine and 1,3-propanediol, two isomeric quinolines (molar ratio 1:9) were isolated as a mixture in 62% yield (eq 2).



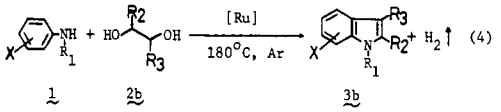
(2)

An unsymmetrical 1,3-diol was employed in the reaction. 1,3-Butanediol and aniline under similar reaction conditions also gave two isomeric quinolines (molar ratio 95:5) which were isolated as a mixture in 46% yield (eq 3). An attempted synthesis of quinoline derivatives from aminoarenes and glycerol was unsuccessful.



(3)

Syntheses of Indoles and 1,2,3,4-Tetrahydrocarbazole. Aminoarenes (1) reacted with glycols (**2b**) in the presence of a catalytic amount of ruthenium complex to give indole derivatives in good to excellent yields (eq 4)



(4)

1 2b 3b

Detailed effects of the reaction conditions were examined with *N*-methylaniline and ethylene glycol as the substrates (Table IV). The yield of the product, 1-methylindole, was considerably affected by the molar ratio of *N*-methylaniline to ethylene glycol (runs 27–32). The highest yield was realized at a molar ratio of 2.5 (run 29). The reaction required a temperature higher than 160 °C. At 120 °C, the conversion of ethylene glycol was low and the yield of 1-methylindole was considerably reduced (run 35).

In this reaction, the catalyst precursor had a critical effect (Table V). Ruthenium(III) chloride hydrate ($RuCl_3 \cdot nH_2O$) without phosphorus ligand was totally inactive (run 36). $RuCl_2(PPh_3)_3$ showed the highest activity (run 29). $RuCl_3 \cdot nH_2O$ combined with triphenylphosphine (PPh_3) showed almost the same activity as $RuCl_2(PPh_3)_3$ (run 37). Diethylphenylphosphine (PEt_2Ph) and ethyldiphenylphosphine ($PEtPh_2$) were also effective as phosphorus ligands (runs 39 and 40). The reactions were carried out in a 50-mL autoclave. After the reaction, hydrogen pressure was built up to ca. 7 kg cm^{-2}. With $RuCl_2(PPh_3)_3$ as the catalyst, there was no difference between the reactions in the autoclave (run 29) and under

Table IV. Effect of Reaction Conditions on the Synthesis of 1-Methylindole from *N*-Methylaniline and Ethylene Glycol[a]

run	[amine]/[EG][b]	temp, °C	product yield,[c] %
27	4.0	180	33
28	3.0	180	43
29	2.5	180	51 (46)[d]
30	2.0	180	42
31	1.5	180	21
32	1.0	180	16
33	2.5	200	50
34	2.5	150	31
35	2.5	120	9

[a] Ethylene glycol (1.1 mL, 20 mmol), *N*-methylaniline, $RuCl_2(PPh_3)_3$ (192 mg, 0.20 mmol), reaction time 5 h. [b] Molar ratio of *N*-methylaniline to ethylene glycol. [c] Determined by GLC based on the amount of ethylene glycol used. [d] Isolated yield.

(14) Basicities of the ligands are as follows:[15] PCy_3, pK_a 9.70; PEt_3, PK_a 8.69; PBu_3, pK_a 8.43; PEt_2Ph, PK_a 6.25; PPh_3, pK_a 2.73.

(15) Streuli, C. A. *Anal. Chem.* **1960**, *32*, 985.

(16) Larger cone angle shows larger steric size of the phosphorus ligands. The cone angle of the ligands are as follows:[17] PCy_3, 170°; PPh_3, 145°; $PEtPh_2$, 140°; PEt_2Ph, 136°; PEt_3, 132°; PBu_3, 132°; $P(OPh)_3$, 128°; $P(OBu)_3$, 109°.

Table V. Effect of Catalyst Precursor on the Synthesis of 1-Methylindole from *N*-Methylaniline and Ethylene Glycol[a]

run	catalyst	product yield,[b] %
29	$RuCl_2(PPh_3)_3$	51 (46)[c]
36	$RuCl_3 \cdot nH_2O$	0
37	$RuCl_3 \cdot nH_2O + 3PPh_3$	49
38[d]	$RuCl_2(PPh_3)_3$	48
39	$RuCl_3 \cdot nH_2O + 3PEt_2Ph$	49
40	$RuCl_3 \cdot nH_2O + 3PEtPh_2$	46
41	$RuCl_3 \cdot nH_2O + 3PBu_3$	trace
42[d]	$RuCl_3 \cdot nH_2O + 3PBu_3$	46
43	$RuCl_3 \cdot nH_2O + 1.5PPh_2(CH_2)_2PPh_2$	0
44	$RuCl_3 \cdot nH_2O + 1.5PPh_2(CH_2)_3PPh_2$	30
45	$RuCl_3 \cdot nH_2O + 1.5PPh_2(CH_2)_4PPh_2$	37
46	$RuCl_3 \cdot nH_2O + 3PCy_3$	0
47	$RuCl_3 \cdot nH_2O + 3P(OPh)_3$	0
48	$RuCl_3 \cdot nH_2O + 3AsPh_3$	trace
49	$RuCl_3 \cdot nH_2O + 3SbPh_3$	trace
50	$RuHCl(PPh_3)_3$	trace
51	$RuH_2(PPh_3)_4$	trace
52	$RuBr_2(PPh_3)_3$	36
53	Ru(cod)(cot)	0
54	$Ru_3(CO)_{12}$	0

[a] *N*-Methylaniline (5.4 mL, 50 mmol), ethylene glycol (1.1 mL, 20 mmol), catalyst (0.20 mmol), dioxane (5 mL), at 180 °C for 5 h. [b] Determined by GLC based on the amount of ethylene glycol used. [c] Isolated yield. [d] Under reflux in diglyme.

reflux in diglyme (run 38). However, $RuCl_3 \cdot nH_2O$ combined with tributylphosphine (PBu_3) was almost inactive in the autoclave (run 41) but active under reflux in diglyme (run 42). This phenomenon indicated that dissociation of hydride on a ruthenium center[18-20] may be affected by hydrogen pressure and the nature of the phosphorus ligands. Bidentate ligands of the type $Ph_2P(CH_2)_nPPh_2$ were effective for $n = 3$ or 4 but deactivated the catalyst for $n = 2$, giving the most stable chelate (runs 43–45). Very bulky tricyclohexylphosphine (PCy_3)[17] and less basic triphenyl phosphite ($P(OPh)_3$) were not beneficial (runs 46 and 47). Other ligands such as triphenylarsine ($AsPh_3$) and triphenylantimony ($SbPh_3$) failed to enhance the catalytic activity (runs 48 and 49). Other ruthenium(II) complexes such as $RuHCl(PPh_3)_3$ and $RuH_2(PPh_3)_4$ showed almost no catalytic activity (runs 50 and 51). Ruthenium(0) complexes such as (η^6-1,3,5-cyclooctadiene) (η^4-1,5-cyclooctatriene)ruthenium (Ru(cod)(cot)) and $Ru_3(CO)_{12}$ were not active (runs 53 and 54). These ruthenium catalysts (runs 43–54) did not improve the activity under reflux in diglyme.

Under similar reaction conditions, rhodium complexes ($RhCl(PPh_3)_3$, $RhH(PPh_3)_3$) showed low catalytic activity to afford 1-methylindole in only 4–5% yields with low conversions of the substrates.

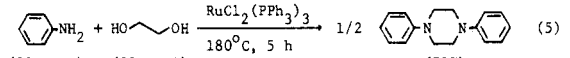
The yield was affected by the solvent employed (Table VI). The highest yield was reaclized in dioxane (run 29). The reaction proceeded similarly in diglyme, 1,3-dimethyl-2-imidazolidinone, 1-methyl-2-pyrrolidinone, and 1-hexene (runs 55–58). 1-Hexene was partly hydrogenated to hexane, which reduced the evolved hydrogen considerably (run 58). The reactions were considerably suppressed in DMF, acetonitrile, and Me_2SO, which seemed to interact strongly with the transition-metal center (runs 59–61).[21]

Table VI. Solvent Effect in the Synthesis of 1-Methylindole from *N*-Methylaniline and Ethylene Glycol[a]

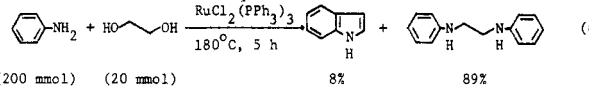
run	solvent	product yield,[b] %
29	dioxane	51 (46)[c]
55	diglyme	47
56	1,3-dimethyl-2-imidazolidinone	45
57	1-methyl-2-pyrrolidinone	34
58	1-hexene	39
59	DMF	19
60	acetonitrile	5
61	Me_2SO	0

[a] *N*-Methylaniline (5.4 mL, 50 mmol), ethylene glycol (1.1 mL, 20 mmol), catalyst $RuCl_2(PPh_3)_3$ (192 mg, 0.2 mmol), solvent (5 mL), at 180 °C for 5 h. [b] Determined by GLC based on the amount of ethylene glycol used. [c] Isolated yield.

Indole itself was obtained in only trace amount from aniline and ethylene glycol. Instead, 1,4-diphenylpiperazine was isolated in 73% yield (eq 5). Employment of aniline in large excess resulted in only a slight increase in indole formation (8% yield) (eq 6).

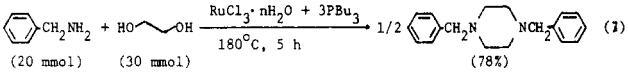


(5)



(6)

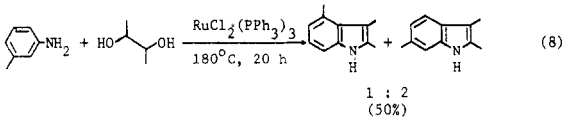
Similar reaction between benzylamine and ethylene glycol also gave 1,4-dibenzylpiperazine in 78% isolated yield (eq 7).



(7)

The present N-heterocyclization was carried out with various substrates (Table VII). N-substituted aromatic amines reacted with ethylene glycol to give the corresponding 1-substituted indoles (runs 62–65). In these reactions, however, indole formation suffered from N-alkyl exchange reaction catalyzed by ruthenium complex,[22,23] which gave the corresponding *N*-*N*′-dialkyl aromatic amine.

2,3-Butanediol could be used as a substituted C_2 fragment to afford 2,3-dimethylindoles in good to excellent yields (runs 66–72). In these reactions, piperazine formation as shown in eq 5 and 7 did not occur appreciably, even if the primary aromatic amines were used as the substrate, and the yields of the indoles were rather high. From *m*-toluidine and 2,3-butanediol, two isomeric indoles (molar ratio 1:2) were isolated as a mixture in 50% yield (eq 8).



(8)

1,2-Cyclohexanediol (mixture of cis and trans) reacted with aminoarenes to give 1,2,3,4-tetrahydrocarbazole derivatives in good yields (runs 73–80). The reactions were rather sluggish and required a longer reaction time.

Unsymmetrical glycols were employed in the reactions. Propylene glycol and *N*-methylaniline under similar re-

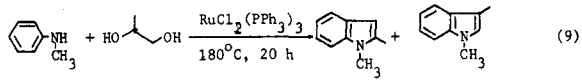
(17) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
(18) Collman, J. P.; Roper, W. R. *Adv. Organomet. Chem.* **1968**, *7*, 53.
(19) Halpern, J. *Acc. Chem. Res.* **1970**, *3*, 386.
(20) Vaska, L. *Inorg. Chim. Acta* **1971**, *5*, 295.
(21) (a) Dunn, T.; Buffagni, S. *Nature (London)* **1960**, *188*, 937. (b) Idem. *J. Chem. Soc.* **1961**, 5105. (c) Rollinson, C. L.; White, R. C. *Inorg. Chem.* **1962**, *1*, 281. (d) Bell, W. E.; Madan, S. K.; Wills, J. E. *Inorg. Chem.* **1963**, *2*, 303.
(22) Khai, B.-T.; Concilo, C.; Porzi, G. *J. Organomet. Chem.* **1981**, *208*, 249.
(23) Jung, C. W.; Fellmann, J. D.; Garrow, P. E. *Organometallics* **1983**, *2*, 1042.

Table VII. Syntheses of Indole Derivatives from Various Aminoarenes and Glycols[a]

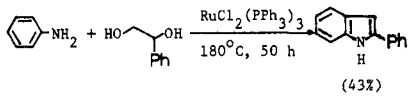
run	aminoarene	glycol	reactn time, h	product	yield,[b] %
62	*N*-ethylaniline	ethylene glycol	5	1-ethylindole	34 (27)
63	*N*-propylaniline	ethylene glycol	5	1-propylindole	(28)
64	*N*-butylaniline	ethylene glycol	5	1-butylindole	(25)
65	*N*-ethyl-4-methylaniline	ethylene glycol	5	1-ethyl-5-methylindole	(34)
66	aniline	2,3-butanediol	20	2,3-dimethylindole	46 (40)
67	*N*-methylaniline	2,3-butanediol	20	1,2,3-trimethylindole	(58)
68	*o*-toluidine	2,3-butanediol	20	2,3,7-trimethylindole	(50)
69	*p*-toluidine	2,3-butanediol	20	2,3,5-trimethylindole	(80)
70	*o*-chloroaniline	2,3-butanediol	20	7-chloro-2,3-dimethylindole	(72)
71	*p*-chloroaniline	2,3-butanediol	20	5-chloro-2,3-dimethylindole	(89)
72	*p*-anisidine	2,3-butanediol	20	5-methoxy-2,3-dimethylindole	(48)
73	aniline	1,2-cyclohexanediol	50	1,2,3,4-tetrahydrocarbazole	(46)
74	*N*-methylaniline	1,2-cyclohexanediol	50	9-methyl-1,2,3,4-tetrahydrocarbazole	(47)
75	*N*-ethylaniline	1,2-cyclohexanediol	50	9-ethyl-1,2,3,4-tetrahydrocarbazole	(30)
76	*o*-toluidine	1,2-cyclohexanediol	50	8-methyl-1,2,3,4-tetrahydrocarbazole	(30)
77	*p*-toluidine	1,2-cyclohexanediol	50	6-methyl-1,2,3,4-tetrahydrocarbazole	(46)
78	*o*-chloroaniline	1,2-cyclohexanediol	50	8-chloro-1,2,3,4-tetrahydrocarbazole	(45)
79	*p*-chloroaniline	1,2-cyclohexanediol	50	6-chloro-1,2,3,4-tetrahydrocarbazole	(65)
80	*p*-anisidine	1,2-cyclohexanediol	50	6-methoxy-1,2,3,4-tetrahydrocarbazole	(39)

[a] Aminoarene (50 mmol), glycol (20 mmol), dioxane (5–10 mL), $RuCl_2(PPh_3)_3$ (192 mg, 0.2 mmol), at 180 °C. [b] Determined by GLC based on the amount of glycol used. Figures in parentheses show isolated yields.

action conditions gave two isomeric indoles, 1,2-dimethyl- and 1,3-dimethylindole, as an equimolar mixture in 50% yield (eq 9). On the other hand, 2-phenylindole was se-



(9)



(10)

lectively obtained in 43% yield by the reaction between styrene glycol and aniline (eq 10).

An attempted synthesis of indole derivatives from aminoarene and other C_2 fragments such as acetol, glyoxal, and diacetyl was unseccessful.

The differences between the catalytic system of quinoline synthesis and that of indoles syntheses may be related the basicity of products. Being more basic products, quinolines may require more basic phosphines as the ligands.

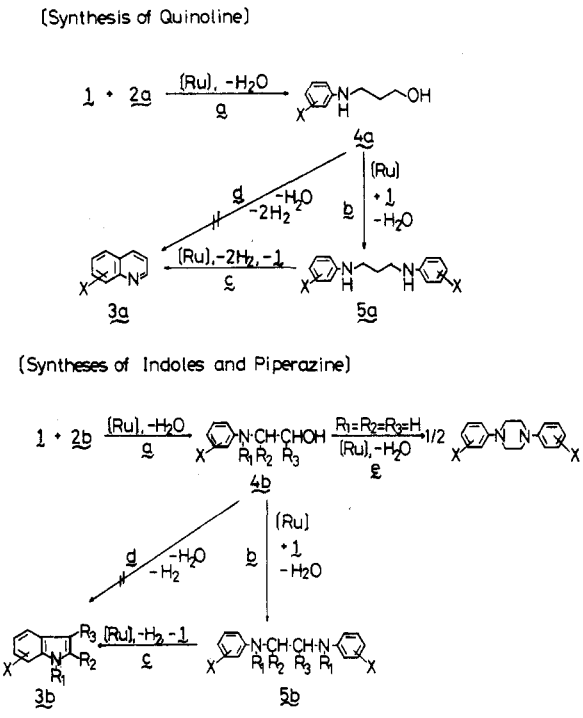
It is noteworthy that the present N-heterocyclization does not require any hydrogen acceptors. The feature simplifies workup; hydrogen was evolved into the gas phase during the reaction.

Discussion

One of the most characteristic features in homogeneous ruthenium catalysis appears to be a high catalytic activity for hydrogen transfer from alcohols or amines.[24-39] We have reported several organic syntheses utilizing this feature of homogeneous ruthenium catlaysts.[40-43]

Possible reaction pathways for the present quinoline and indole syntheses are shown in Scheme I. The first step in the proposed catalytic cycle is the formation of 3-anilino-1-propanol derivatives (**4a**) or 2-anilinoethanol derivatives (**4b**) (path a in Scheme I). In some reactions,

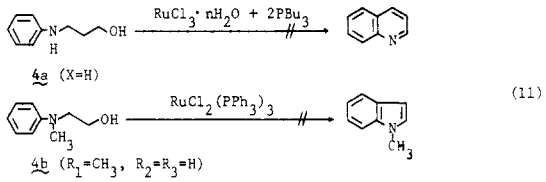
Scheme I. Reaction Pathway



(24) Matsumoto, M.; Kumada, K. *J. Am. Chem. Soc.* **1972**, *104*, 1433.
(25) Tovrog, B. S; Diamond, S. E.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 5067.
(26) Khai, B.-T.; Concilo, C.; Porzi, G. *J. Org. Chem.* **1981**, *46*, 1759.
(27) Sasson, Y.; Blum, J. *J. Org. Chem.* **1975**, *40*, 1887.
(28) Regen, S. L.; Whitesides, G. M. *J. Org. Chem.* **1972**, *37*, 1832.
(29) Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1984**, *263*, 93.
(30) Shvo, Y.; Blum, Y.; Reshey, D. *J. Organomet. Chem.* **1982**, *238*, C79.
(31) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *235*, 93.
(32) Arcelli, A.; Khai, B.-T.; Porzi, G. *J. Organomet. Chem.* **1982**, *231*, C31.
(33) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.
(34) Murahashi, S.-I.; Ito, K.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, *22*, 5327.
(35) Tomioka, H.; Takai, K.; Ohshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.
(36) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *Tetrahedron Lett.* **1981**, *22*, 4107.
(37) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611.
(38) Jung, C. W.; Garrow, P. E. *Organometallics* **1982**, *1*, 658.
(39) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *Chem. Lett.* **1982**, 1179.
(40) Tsuji, Y.; Nishimura, H.; Huh, K.-T.; Watanabe, Y. *J. Organomet. Chem.* **1984**, *286*, C44.
(41) Tsuji, Y.; Ohta, T.; Minbu, H.; Ido, T.; Watanabe, Y. *J. Organomet. Chem.* **1984**, *270*, 333.
(42) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.
(43) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.

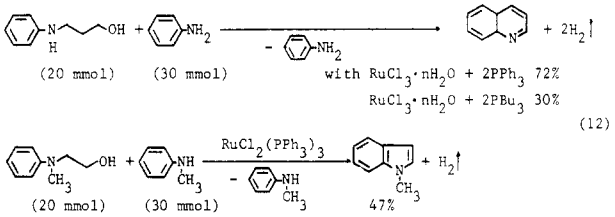
4a was detected by GLC. In most reactions, **4b** was detected by GLC, and from the reaction mixture of run 34, 2-(methylphenylamino)ethanol (**4b**; X = H, R_1 = CH_3, R_2 = R_3 = H) was isolated in 37% yield as well as 1-methylindole. Similar N-alkylation of amine using alcohols has been reported recently.[42,43] The mechanism of the N-alkylation was fully investigated by kinetic measurements.[43] The reaction involves the following steps: (1) oxidative addition of alcohol to the metal center to give an aldehyde intermediate, (2) nucleophilic attack of amine on the aldehyde species to give the imine, and (3) hydrogenation of the imine intermediate to N-alkylated amine.[43] The piperazine derivatives (eq 5 and 7) may be derived by bimolecular cyclization of **4b** (path e in Scheme I) when primary amines react with ethylene glycol.

In order to check the intermediary of **4a** and **4b** in the present quinoline and indole formation, 3-anilino-1-propanol (**4a**; X = H) was treated in diglyme under reflux with a catalytic amount of $RuCl_3 \cdot nH_2O$–$2PBu_3$ and 2-(methylphenylamino)ethanol (**4b**; X = H, R_1 = CH_3, R_2 = R_3 = H) was allowed to react at 180 °C in the presence of $RuCl_2(PPh_3)_3$; quinoline and 1-methylindole were not obtained, indicating that products are not formed directly from **4a** or **4b** through intramolecular cyclization (path d in Scheme I, eq 11).



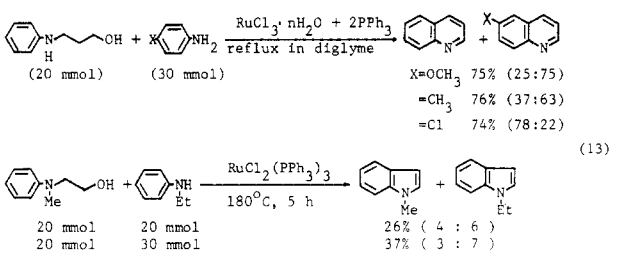
(11)

On the other hand, quinoline was obtained in 73% yield in the presence of $RuCl_3 \cdot nH_2O$–$2PPh_3$ and in 30% yield in the presence of $RuCl_3 \cdot nH_2O$–$2PBu_3$ when 3-anilino-1-propanol was allowed to react with 1.5 equiv of aniline. The reasons for the difference in catalytic activities between the $RuCl_3 \cdot nH_2O$–$2PPh_3$ and $RuCl_3 \cdot nH_2O$–$2PBu_3$ systems are not yet clear. Also, 1-methylindole was obtained in 47% yield when 1.5 equiv of *N*-methylaniline was present in the reaction with **4b** (X = H, R_1 = CH_3, R_2 = R_3 = H) (eq 12).



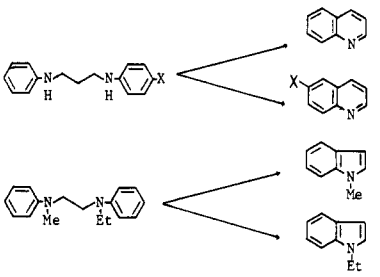
(12)

Furthermore, when a mixture of 3-anilino-1-propanol and para-substituted anilines was allowed to react under similar reaction conditions, two different quinolines, quinoline and 6-substituted quinoline, were obtained. When a mixture of 2-(methylphenylamino)ethanol and *N*-ethylaniline was reacted under similar reaction conditions, two different indoles, 1-methylindole and 1-ethylindole, were obtained (eq 13).



(13)

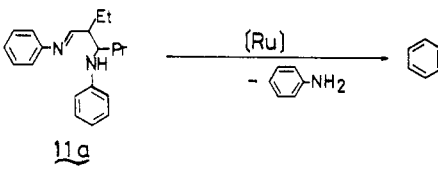
This phenomenon can be interpreted by assuming a propylenediamine type intermediate (**5a**) and an ethylenediamine type intermediate (**5b**). In these reaction, the hydroxy groups of 3-anilino-1-propanol (**4a**) and 2-(methylphenylamino)ethanol (**4b**) are considered to be aminated with para-substituted aniline or *N*-ethylaniline to give *N*-aryl-*N'*-phenylpropylenediamine and *N*-ethyl-*N'*-methyl-*N*,*N'*-diphenylethylenediamine. These intermediated (**5a** and **5b**) gave two quinolines and two indoles according to the direction of the intramolecular cyclization (eq 14).



(14)

The direction of the intramolecular cyclization is considered to be affected by the basicities of the aminoarenes used. More basic para-substituted anilines, such as *p*-toluidine (pK_a, 5.11) and *p*-anisidine (pK_a, 5.34), reacted with 3-anilino-1-propanol to give 6-substituted quinolines predominantly. Less basic *p*-chloroaniline (pK_a, 3.98) gave quinoline as a major product. 1-Methyl-*N*,*N'*-diphenylpropylenediamine (**5a**; X = H, 1-methyl) derived from aniline and 1,3-butanediol gave 2-methylquinoline as a major product (vide supra; eq 3). This phenomenon is related to the differences in basicity of the alternative nitrogens, which are expected to be similar to *N*-ethylaniline ($PhNHCH_2CH_3$; pK_a, 5.11) and *N*-isopropylaniline ($PhNHCH(CH_3)_2$; pK_a, 5.77).

A possible mechanism from **5a** to **3a** is shown in Scheme II. We have reported[44] that the Schiff base dimer (**11a**),[45] prepared from aniline and butanal, readily forms the quinoline skeleton in the presence of ruthenium catlayst (eq 15). In the previous paper,[44] we have propesed that

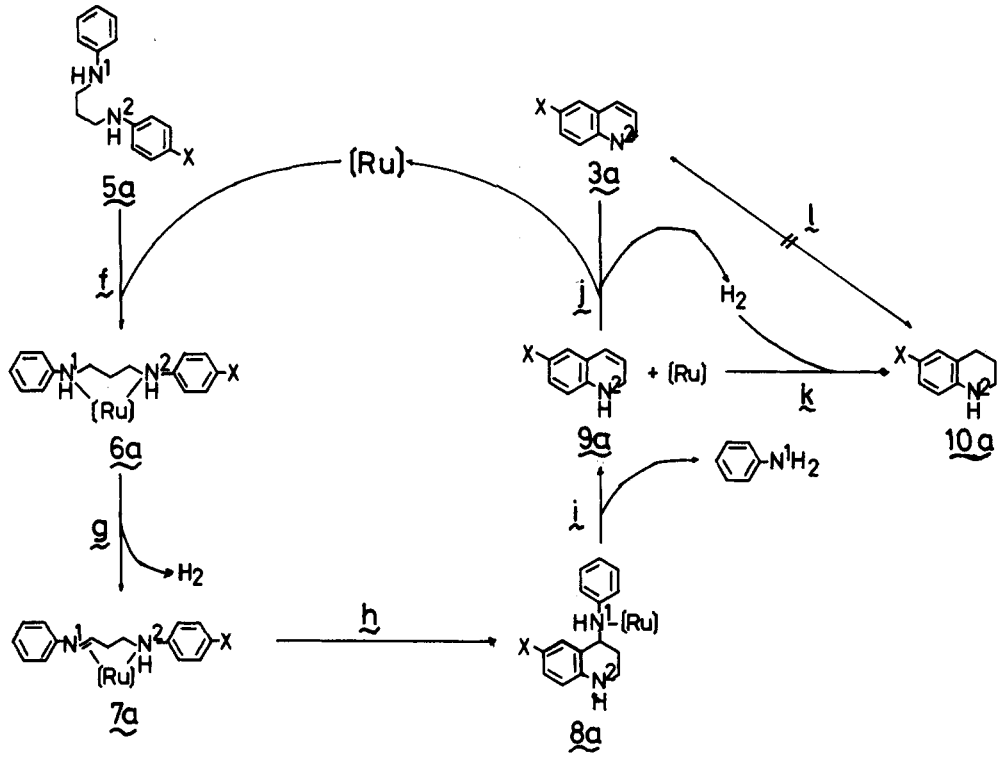


(15)

this ring–closure process occurs through an ortho-metallation.[46] However, in this study, the ring–closure process appears to be related to the difference in basicity of the alternative nitrogens in **5a**. Although the ruthenium metal center is strongly coordinated by a more basic amino group N^2 in **5a**, a chelate intermediate (**6a**) is easily dehydrogenated on a less amino group N^1 in **5a** (path g in Scheme II). Ruthenium catalysts are known to be active for the dehydrogenation of an amine to an imine or to an iminium intermediate.[47,48] The imine intermediate (**7a**), introduced from less basic amine due to dehydrogenation, makes an attack on the ortho position of more basic aromatic amine. The complex (**7a**) may undergo an electrophilic substitu-

(44) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y.; Shida, J. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2452.
(45) Kharash, M. S.; Ruchlin, I.; Mayo, R. *J. Am. Chem. Soc.* **1940**, *62*, 494.
(46) Omae, I. *Chem. Rev.* **1979**, *79*, 28 and references cited therein.
(47) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613.
(48) Murahashi, S.-I.; Yoshimura, N.; *Tsumiyama*, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, *105*, 5002.

Scheme II. Possible Mechanism[a]



[a] Basicity: $N^2 > N^1$, X = CH_3, OCH_3.

tion reaction to give **8a** intramolecularly (path h in Scheme II). Quinoline **3a** is obtained through the 1,2-dihydroquinoline intermediate (**9a**) (path j in Scheme II). Homogeneous ruthenium complexes are well-known as good catalysts for hydrogen-transfer reaction.[49-54] Indeed, indoline was dehydrogenated quantitatively into indole (**3b**) with spontaneous hydrogen evolution under the same conditions, while 1,2,3,4-tetrahydroquinoline (**10a**) and 1,2,3,4-tetrahydrocarbazole were not converted at all under the same conditions (path l in Scheme II).

A possible mechanism for **5b** to **3b** appears to be essentially similar to that from **5a** to **3a**.

Thus, propylenediamine **5a**, ethylenediamine **5b**, and their dehydrated imine intermediates should be key species for the present N-heterocyclization. quinolines and indoles are formed through intramolecular cyclization of **5** (path c in Scheme I). In the present N-heterocyclization, the yields of the products were appreciably affected by the molar ratio of aromatic amine to 1,3-propanediol or glycol (vide supra; Figure 2 and runs 27–32). Products were obtained in the highest yield at the molar ratio of 2.5 in the reactions of aromatic amine with 1,3-propanediol or glycol. Such excess of aminoarene should be favorable for formation of the diamine intermediate (**5a**) from the anilino alcohol species (**4**).

Experimental Section

The amines, 1,3-propanediol, 1,3-butanediol, ethylene glycol, 2,3-butanediol, 1,2-cyclohexanediol (mixture of cis and trans), propylene glycol, styrene glycol, and the solvents were commercial materials and purified by distillation or recrystallization before use. 3-Anilino-1-propanol was synthesized with aniline and trimethylene oxide by the method in the literature.[55] $RuCl_3 \cdot nH_2O$ (mainly $n = 3$) was purchased from Engelbard Chemicals and used without further purification. $RuCl_2(PPh_3)_3$,[56] $RuBr_2(PPh_3)_3$,[57] $RuHCl(PPh_3)_3$,[58] $RuH_2(PPh_3)_4$,[59] Ru(cod)(cot),[60] and $Ru_3(CO)_{12}$[61] were prepared according to the methods in the literature.

General Reaction Procedure. Synthesis of Quinoline. A typical reaction of aniline with 1,3-propanediol is described here to exemplify the general reaction procedure. A 100-mL three-necked Pyrex flask is equipped with a reflux condenser and a gas buret. Under argon stream, diglyme (10 mL), 1,3-propanediol (1.4 mL, 20 mmol), aniline (4.6 mL, 50 mmol), and $RuCl_3 \cdot nH_2O$ (157 mg, 0.6 mmol, 3 mol % based on 1,3-propanediol)–PBu_3 (0.30 mL, 1.2 mmol)) were added with a magnetic stirring bar in the reactor. The mixture was stirred and heated at reflux for 5 h under argon atmosphere. The reaction was terminated by rapid cooling, and the reactor was discharged. Evolved hydrogen was measured by means of a buret, and the identity of the gaseous product was checked by GLC (active carbon). The reaction product was isolated by distillation and flash column chromatography (hexane–aluminum oxide 90, Merch No. 1076). Quinoline was isolated in 59% yield.

Syntheses of Indoles. A typical reaction of *N*-methylaniline with ethylene glycol is 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), *N*-methylaniline (5.4 mL, 50 mmol), ethylene glycol (1.1 mL, 20 mmol), and $RuCl_2(PPh_3)_3$ (192 mg, 0.2 mmol, 1.0 mol % based on ethylene glycol)) were added with a magnetic stirring bar into the glass liner set in the reactor. After the reactor was sealed, an air purge was confirmed by three pressurization (10 atm)–depressurization

(49) Hirai, K.; Suzuki, H.; Moro-oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 3413.
(50) Takahashi, M.; Ishii, N.; Suzuki, H.; More-oka, Y.; Ikawa, T. *Chem. Lett.* **1981**, 1361.
(51) Takahashi, M.; Suzuki, H.; More-oka, Y.; Ikawa, T. *Chem. Lett.* **1981**, 1435.
(52) Scharf, H. D.; Frauenrath, H. *Chem. Ber.* **1980**, *113*, 1472.
(53) Komiya, S; Yamamoto, A. *J. Mol. Catal.* **1979**, *5*, 279.
(54) Sasson, Y.; Rempel, G. L. *Tetrahedron Lett.* **1974**, *15*, 4133.
(55) Searles, S.; Gregory, V. P. *J. Am. Chem. Soc.* **1974**, *76*, 2789.
(56) Hallmann, P. S.; Stephenson, T. A.; Wilkinson, G. *Inorg. Synth.* **1970**, *12*, 237.
(57) Stephenson, T. A.; Wilkinson, G. *J. Inorg. Nucl. Chem.* **1966**, *28*, 945.
(58) Hallmann, P. S.; McGarvey, B. R.; Wilkinson, G. *J. Chem. Soc. A.* **1968**, 3142.
(59) Yong, R.; Wilkinson, G. *Inorg. Synth.* **1977**, *17*, 75.
(60) Itho, K,; Nagashima, H.; Ohshima, T.; Ohshima, N.; Nishiyama, H. *J. Organomet. Chem.* **1984**, *272*, 179.
(61) Mantovani, A.; Cenini, S. *Inorg. Synth.* **1976**, *16*, 47.

sequences with argon. The reactor was heated to 180 °C in 30 min in a mantle heater and thermostated at this temperature for 5 h with stirring. The reaction was terminated by rapid cooling, and the reactor was discharged. Evolved hydrogen was measured by means of a buret, and the identity of the gaseous produce was checked by GLC (active carbon). The reaction mixture was diluted with ether (100 mL), and excess aminoarene was removed by washing the ethereal solution with 100 mL aqueous 5% HCl. The ether layer was separated and dried with anhydrous magnesium sulfate. Distillation of the evaporated solution gave 1-methylindole in 46% yield.

Analytical Procedure. All boiling points and melting points were uncorrected. The identification of products was made by ^{1}H NMR, ^{13}C NMR, and IR spectra and elemental analysis. The ^{1}H 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 $CDCl_3$ or Me_2SO-d_6, and the chemical shifts are expressed relative to Me_4Si as an internal standard. The IR spectra were measured on a Nicolet Model 5MX Fourier transfer infrared spectrometer. Elemental analyses were performed at Microanalytical Center of Kyoto University. The GLC analyses of products were made by Shimadzu GC-8APF with a column (3 mm × 3 m) packed with Poly-I 110 (5%) on Chromosorb W AW DMCS, 60–80 mesh. The GC analysis of gaseous product was made by Shimadzu GC-8AT with a column (3 mm × 3 m) packed with active carbon, 60–80 mesh. In some cases, the yields were determined by the internal standard method according to the calibration curve obtained in separate experiments for each product.

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Supplementary Material Available: Experimental procedure, NMR data, IR data, and analyses of 5-methyl- and 7-methylquinoline (eq 2), 2-methyl- and 4-methylquinoline (eq 3), quinoline, 8-methylquinoline, 6-methylquinoline, 8-chloroquinoline, 6-chloroquinoline, 6-methoxyquinoline, 7,8-benzoquinoline, 1,4-diphenylpiperazine (eq 5), 1,4-dibenzylpiperazine (eq 7), 2,3,4-trimethyl- and 2,3,6-trimethylindole (eq 8), 1,2-dimethyl- and 1,3-dimethylindole (eq 9), 2-phenylindole (eq 10), 1-methylindole, 1-ethylindole, 1-propylindole, 1-butylindole, 1-ethyl-5-methylindole, 2,3-dimethylindole, 1,2,3-trimethylindole, 2,3,7-trimethylindole, 2,3,5-trimethylindole, 7-chloro-2,3-dimethylindole, 5-chloro-2,3-dimethylindole, 5-methoxy, 2,3-dimethylindole, 1,2,3,4-tetrahydrocarbazole, 9-methyl-1,2,3,4-tetrahydrocarbazole, 9-ethyl-1,2,3,4-tetrahydrocarbazole, 8-methyl-1,2,3,4-tetrahydrocarbazole, 6-methyl-1,2,3,4-tetrahydrocarbazole, 8-chloro-1,2,3,4-tetrahydrocarbazole, 6-chloro-1,2,3,4-tetrahydrocarbazole, and 6-methoxy-1,2,3,4-tetrahydrocarbazole (8 pages). Ordering information is given on any current masthead page.

Regiocontrolled Opening of Cyclic Ethers Using Dimethylboron Bromide

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The cleavage of various cyclic ethers (3- to 7-membered rings) was achieved under very mild conditions using dimethylboron bromide to afford the corresponding bromo alcohols. In particular, 2-substituted tetrahydrofurans were regioselectively cleaved by a predominantly S_N2-type mechanism favoring the formation of primary vs. secondary bromides. Dimethylboron bromide also cleaved chemoselectively substituted tetrahydrofurans in the presence of functional groups such as acyclic ethers, silyl ethers, esters, amides, ketones, etc.

We have reported previously on the synthetic utility of organoboron bromide reagents such as dimethylboron bromide (Me_2BBr) in the transformation of functional groups. Examples include the regeneration (i) of parent alcohols from alkyl, benzyl, MEM, MOM, and MTM ethers,[1,2] (ii) of aldehydes and ketones from their corresponding acetals and ketals,[2] (iii) of diols from their acetonides,[2] and (iv) of sulfides from sulfoxides.[3] α-Bromo ethers obtained under aprotic conditions from acetals treated with Me_2BBr have also served as useful intermediates for the synthesis of thioglycosides,[4] cyanomethyl ethers,[4] and hemithioacetals.[4]

We have also recently described the synthesis of optically active 1,3-diols and commented on their usefulness as precursors in the synthesis of natural products.[5] Our approach to the syntheses of these 1,3-diols was based on the stereocontrolled preparation of optically active 4-hydroxytetrahydrofuran derivatives followed by a regiocontrolled opening of the newly formed heterocycle by dimethylboron bromide.

Our interest in Me_2BBr arose from its tendency to cleave a C–O bond in a S_N2 fashion,[1] in contrast to other reagents such as BBr_3. This was illustrated by the treatment of 2-methyltetrahydrofuran with Me_2BBr, which led predominantly to 5-bromo-2-pentanol.[1]

We are reporting, herein, on an expanded study of the opening of cyclic ethers with Me_2BBr. The scope and limitations of this reagent in these reactions are discussed.

Results and Discussion

I. Cleavage of Symmetrical Cyclic Ethers. We have found that dimethylboron bromide reacts with simple cyclic ethers of various ring sizes to give the corresponding bromo alcohols in excellent yield, as summarized in Table I.

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(1) Guindon, Y.; Yoakim, C.; Morton, H. E. *Tetrahedron Lett.* **1983**, *24*, 2969.
(2) (a) Guindon, Y.; Morton, H. E.; Yoakim, C. *Tetrahedron Lett.* **1983**, *24*, 3969. (b) Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.
(3) Guindon, Y.; Atkinson, J. G.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 4538.
(4) Morton, H. E.; Guindon, Y. *J. Org. Chem.* **1985**, *50*, 5379.
(5) (a) Lactone portion of compactin: Guindon, Y.; Yoakim, C.; Bernstein, M. A.; Morton, H. E. *Tetrahedron Lett.* **1985**, *26*, 1185. (b) (1*R*,3*R*,5*S*)-*endo*-1,3-Dimethyl-2,9-dioxabicyclo[3.3.1]nonane: Guindon, Y.; St-Denis, Y.; Daigneault, S.; Morton, H. E. *Tetrahedron Lett.* **1986**, *27*, 1237.

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