(s, 3 H), 4.9 (s, 1 H), 6.90 (d, 2 H), 7.30 (d, 2 H), 7.60 (s, 1 H); MS m/z 260 ($M - H^+$), 296 ($M + Cl^-$).

1-*p*-Anisyl-3-isopropylidene-4-acetoxy-2-azetidinone (13). Reaction of β-lactam **12** (1.04 g, 0.004 mol) with lead tetraacetate (2.21 g, 0.005 mol) by following the method described for **10a** gave the title compound in 79% yield: mp 105 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1620 (C=C), 1720 (ester CO), 1750 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.15 (s, 3 H), 2.20 (s, 3 H), 3.80 (s, 3 H), 6.90 (d, 2 H), 7.05 (s, 1 H), 7.40 (d, 2 H); MS m/z 293 ($M + NH_4^+$). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.18; N, 5.09. Found: C, 65.37; H, 6.01; N, 4.98.

3-Isopropylidene-4-acetoxy-2-azetidinone (14). Reaction of **13** (1.1 g, 0.004 mol) with cerric(IV) ammonium nitrate (6.15 g, 0.011 mol) in 25 mL of acetonitrile and 25 mL of water as solvent gave the title compound in 83% yield: mp 92 °C (methylene chloride–hexanes); IR (Nujol) 1620 (double bond), 1745 (ester CO), 1780 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3 H), 2.05 (s, 3 H), 2.15 (s, 3 H), 6.20 (s, 1 H), 6.97 (br s, 1 H); MS m/z 187 ($M + NH_4^+$). Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.38; N, 8.15.

1-*p*-Anisyl-3-ethyl-4-carbomethoxy-2-azetidinone (7a). To a solution of β-lactam **5a** or **6a** (0.15 g, 0.0006 mol) in 25 mL of ethyl acetate was added a catalytic amount of 5% Pt–C. The hydrogenation was carried out under atmospheric pressure. Workup of the reaction mixture yielded the β-lactam in quantitative yield. This compound is identical in all respect with the compound prepared from **5a**.

***cis*-1-*p*-Anisyl-3-acetyl-4-carbomethoxy-2-azetidinone (8a).** To a well-cooled (−75 °C) solution of β-lactam **5c** (0.82 g, 0.003 mol) in 50 mL of methylene chloride was passed ozone until the color of the reaction turned blue. Excess ozone was removed by passing N_2 through the reaction mixture. Finally, 1.5 mL of dimethyl sulfide was added to it. The reaction mixture was stirred at −78 °C for 15 min and at room temperature for $^1/_2$ h, washed with water and brine, and dried over Na_2SO_4. Removal of solvent gave a colorless gummy mass, which was passed through Florisil. Subsequent crystallization from methylene chloride–hexanes gave **8a** as a crystalline solid: mp 103 °C; yield 87%; IR (Nujol) 1650 (ketone CO), 1755 (ester and lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$–DMSO-d_6) δ 2.24 (s, 3 H), 3.8 (s, 3 H), 3.85 (s, 3 H), 4.55 (d, 1 H, J = 5.85 Hz), 4.65 (d, 1 H, J = 5.85 Hz), 6.83 (d, 2 H), 7.2 (d, 2 H); MS m/z 295 ($M + NH_4^+$).

***trans*-1-*p*-Anisyl-3-acetyl-4-carbomethoxy-2-azetidinone (15).** β-Lactam **8a** (0.27 g, 0.001 mol) was dissolved in 25 mL of dry benzene. To it 2 drops of DBN was added, and the reaction mixture was refluxed overnight under nitrogen. After cooling the organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, water, and brine successively. Removal of solvent gave an oil, which was purified through column chromatography to yield 0.22 g (83%) of the title compound: mp 139 °C (methylene chloride–hexanes); IR (Nujol) 1720 (ketone, ester CO), 1760 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 3.9 (s, 3 H), 3.95 (s, 3 H), 4.4 (d, 1 H, J = 2.8 Hz), 4.9 (d, 1 H, J = 2.8 Hz); MS m/z 295 ($M + NH_4^+$).

1-*p*-Anisyl-3-isopropylidene-4-carbethoxy-2-azetidinone (6d). The title β-lactam was obtained in quantitative yield from **5d** (1.44 g, 0.005 mol) according to the method used to prepare **17**: mp 94 °C (methylene chloride–hexanes); IR ($CHCl_3$) 1660 (C=C), 1725 (ester CO), 1745 (β-lactam CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, 3 H), 1.9 (s, 3 H), 2.20 (s, 3 H), 3.80 (s, 3 H), 4.30 (q, 2 H), 4.9 (s, 1 H), 6.92 (d, 2 H), 7.38 (d, 2 H); MS m/z 290 ($M + H^+$).

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Registry No. **4a**, 124156-20-3; **4b**, 124156-21-4; **5a**, 124156-22-5; **5b**, 119873-85-7; **5c**, 124175-15-1; **5d**, 124156-25-8; (*E*)-**6a**, 124156-30-5; (*Z*)-**6a**, 124156-31-6; (*E*)-**6b**, 124156-32-7; (*Z*)-**6b**, 124156-33-8; **6c**, 124156-34-9; **6d**, 124156-35-0; **7a**, 124156-23-6; **7b**, 124156-24-7; **7c**, 124156-26-9; **7d**, 124156-27-0; **8a**, 124156-37-2; **9a**, 124223-53-6; **9b**, 124156-28-1; *cis*-**10a**, 124223-54-7; *trans*-**10a**, 124223-55-8; *cis*-**10b**, 124156-29-2; *trans*-**10b**, 124156-39-4; *cis*-**11a**, 77139-45-8; *trans*-**11a**, 77139-44-7; *cis*-**11b**, 77139-47-0; *trans*-**11b**, 77139-46-9; **12**, 124156-36-1; **13**, 124242-54-2; **14**, 94492-87-2; **15**, 124156-38-3; methyl glyoxalate, 922-68-9; *p*-anisidine, 104-94-9; ethyl glyoxalate, 924-44-7; crotonyl chloride, 10487-71-5; 3,3-dimethylacryloyl chloride, 3350-78-5.

Ruthenium-Catalyzed Dehydrogenative N-Heterocyclization: Indoles from 2-Aminophenethyl Alcohols and 2-Nitrophenethyl Alcohols

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Indole derivatives **3** were readily obtained from 2-aminophenethyl alcohols **1** in the presence of 2 mol % (based on **1**) of $RuCl_2(PPh_3)_3$ under reflux in toluene. Indole (**3a**) was afforded from 2-aminophenethyl alcohol (**1a**) quantitatively. Other indoles (**3**) were also obtained in 73–99% isolated yields from the corresponding **1**, which were easily prepared by condensation between the corresponding 2-nitrotoluenes and aldehydes followed by reduction. During the reaction, a stoichiometric amount of hydrogen was spontaneously evolved into the gas phase. With a heterogeneous and homogeneous binary catalyst system, indoles were afforded in one pot from 2-nitrophenethyl alcohols **2** under a hydrogen atmosphere.

Introduction

The Fischer indole synthesis is most widely used to construct an indole skeleton and has been extensively reviewed.[1] It involves the rearrangement of arylhydrazones on heating and/or with acid catalysts. α-Arylamino ketones and aldehydes are readily prepared from α-halocarbonyl compounds and arylamines, and they cyclize to indoles with acid catalysts (Bischler synthesis).[2] 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).[3] As for

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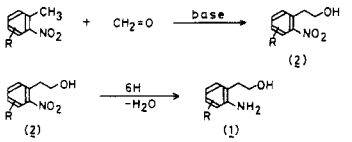
(2) Remers, W. A. *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, p 317.

(3) (a) Reference 2, p 385. (b) Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S.; Koleter, G. *J. Org. Chem.* **1973**, *38*, 3004.

0022-3263/90/1955-0580$02.50/0

Scheme I

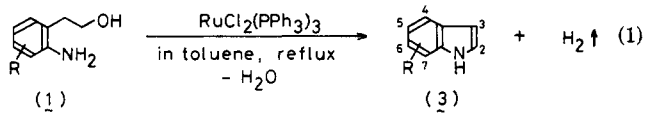


a transition-metal-catalyzed reaction, Hegedus showed that indoles are afforded from 2-allylanilines in the presence of a palladium(II) catalyst and benzoquinone as a reoxidant for palladium.[4] However, these precedent procedures require particular substrates that are not always easily accessible.

In recent years, on the other hand, there has been increasing interest in more straightforward and efficient indole syntheses utilizing various C-2 fragments with aminoarenes.[5] We have recently developed an indole synthesis from ethylene glycol and aminoarenes catalyzed by a homogeneous ruthenium catalyst.[6] Ethylene glycol can be utilized as the C-2 fragment, and the reactions with aminoarenes give indoles in good yields.

2-Aminophenethyl alcohols 1 are another promising substrates for indoles, even from an industrial point of view, since 1 are easily obtained from 2-nitrotoluenes and formaldehyde via condensation followed by reduction (Scheme I; see Experimental Section). In spite of such potential usefulness of 1, the transformation of 1 into indoles has met with only limited success, i.e., severe reaction conditions being necessary (200–340 °C over a copper or a nickel solid catalyst,[7] with 0.6 equiv of concentrated HNO_3 at 220 °C[8]).

We have recently reported the N-alkylation with hydroxy functionalities[9] and also N-heterocyclizations[6,10] involving the N-alkylation as a key step. This paper deals with the indole synthesis from 2-aminophenethyl alcohols 1 in the presence of a homogeneous ruthenium catalyst.[11] The reactions proceed readily without the aid of a hydrogen acceptor, and the corresponding indoles are afforded in good-to-excellent yields with spontaneous hydrogen evolution (eq 1). Indole synthesis from 2-nitrophenethyl alcohols is also described.



Results and Discussion

Indoles from 2-Aminophenethyl Alcohols. Synthesis of indole (**3a**, R = H) from 2-aminophenethyl alcohol (**1a**, R = H) was carried out under various reaction conditions and with various homogeneous transition-metal catalysts (Table I). 2-Aminophenethyl alcohol (**1a**) was cyclized into indole (**3a**) quantitatively when the reaction was carried out in toluene under reflux in the presence of a catalytic amount (2.0 mol % based on **1a**) of $RuCl_2(PPh_3)_3$ (run 1). During the reaction, a stoichiometric amount of hydrogen was spontaneously evolved into the gas phase. This feature is extremely important and favorable as a synthetic method, since the present reaction does not require any hydrogen acceptors, which are often indispensable in many dehydrogenation processes and cause tedious workup procedures. The reflux in *p*-xylene and diglyme gave also indole in excellent yields (runs 2 and 3). However, the reaction at 80 °C in toluene (run 4) or under reflux in dioxane (run 5) reduced the yields considerably. The nature of the catalyst has a critical effect on the present indole synthesis. Ruthenium trichloride without phosphorus ligand showed only low catalytic activity (runs 6 and 7), and most starting materials were recovered intact. Addition of triphenylphosphine(pK_a 2.73,[12] cone angle 143°[13]) to the ruthenium trichloride enhanced the catalytic

Table I. Effect of Catalyst Precursors on Indole Formation from 2-Aminophenethyl Alcohol[a]

run	catalyst	solvent	yield,[b] %
1[c]	$RuCl_2(PPh_3)_3$	toluene	100
2	$RuCl_2(PPh_3)_3$	*p*-xylene	100
3	$RuCl_2(PPh_3)_3$	diglyme	98
4[d]	$RuCl_2(PPh_3)_3$	toluene	30
5	$RuCl_2(PPh_3)_3$	dioxane	17
6	$RuCl_3 \cdot nH_2O$	toluene	2
7	$RuCl_3 \cdot nH_2O$	diglyme	5
8	$RuCl_3 \cdot nH_2O + PPh_3$[e]	toluene	82
9	$RuCl_3 \cdot nH_2O + PBu_3$[e]	toluene	4
10	$RuCl_3 \cdot nH_2O + PBu_3$[e]	diglyme	45
11	$RuH_2(PPh_3)_4$	toluene	19
12	$RuHCl(CO)(PPh_3)_3$	toluene	58
13	$RuHCl(PPh_3)_3$	toluene	18
14	Ru(cod)(cot) + PPh_3[e]	toluene	64
15	Ru(cod)(cot)	toluene	0
16	$RhCl(PPh_3)_3$	toluene	8
17	$PdCl_2(PPh_3)_2$	toluene	tr[f]
18	$Pd(PPh_3)_4$	toluene	0
19	$PtCl_2(PPh_3)_2$	toluene	tr[f]
20	$CoCl_2(PPh_3)_2$	toluene	tr[f]
21	$FeCl_3 \cdot nH_2O + PPh_3$[g]	toluene	tr[f]

[a] 2-Aminophenethyl alcohol (2.0 mmol), catalyst (0.04 mmol), and solvent (5.0 mL), under reflux for 6 h. [b] Yields of indole were determined by GLC. [c] 2-Aminophenethyl alcohol (7.0 mmol), $RuCl_2(PPh_3)_3$ (0.14 mmol), and toluene (10 mL) were charged. [d] At 80 °C. [e] [phosphine]/[Ru] = 3.5. [f] tr = trace. [g] $FeCl_3 \cdot nH_2O$ (0.4 mmol), PPh_3 (2.4 mmol).

Table II. Synthesis of Indoles from 2-Aminophenethyl Alcohols[a]

run	substrate 1[b]	product 3[b]	yield,[c] %	$10^{-3}k_{obs}$,[d] $dm^3\ mol^{-1}\ s^{-1}$
1	**a**, R = H	**a**, R = H	100[e]	2.88
22	**b**, R = 4-Me	**b**, R = 6-Me	80	3.27
23	**c**, R = 5-OMe	**c**, R = 5-OMe	94	4.57
24	**d**, R = 6-Cl	**d**, R = 4-Cl	92	6.50
25	**e**, R = 4-Cl	**e**, R = 6-Cl	82	9.38
26	**f**, R = 6-Br	**f**, R = 4-Br	73	6.88

[a] 2-Aminophenethyl alcohol derivative 1 (7.0 mmol), $RuCl_2(PPh_3)_3$ (0.14 mmol), and toluene (10 mL), under reflux for 6 h. [b] See eq 1. [c] Isolated yields. [d] See eq 3. [e] Determined by GLC.

(4) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
(5) (a) U.S. Patent 4,436,917, 1984; *Chem. Abstr.* **1984**, *101*, 7024. (b) Japanese Kokai, 83-32863; *Chem. Abstr.* **1983**, *99*, 55378. (c) Japanese Kokai, 81-63958; *Chem. Abstr.* **1981**, *95*, 150441. (d) Japanese Kokai, 81-61353; *Chem. Abstr.* **1981**, *95*, 115293.
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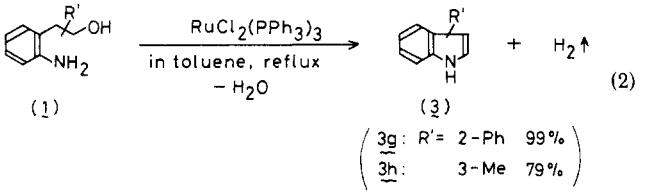
(8) Japanese Kokai, 77-142063; *Chem. Abstr.* **1978**, *88*, 120988.
(9) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
(10) (a) Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365. (b) Tsuji, Y.; Yokoyama, Y.; Huh, K.-T.; Watanabe, Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3456.
(11) Preliminary communication: Tsuji, Y.; Huh, K.-T.; Yokoyama, Y.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1575.
(12) Streuli, C. A. *Anal. Chem.* **1960**, *32*, 985.
(13) A larger cone angle shows a larger steric size of the phosphorus ligands. See: Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.

activity drastically to an extent compared with $RuCl_2(PPh_3)_3$ (run 8). On the other hand, more basic tributylphosphine (pK_a 8.43,[12] cone angle 132°[13]) was less effective (runs 9 and 10). Other di- or zerovalent ruthenium complexes were employed as the catalyst (runs 11–15). $RuHCl(CO)(PPh_3)_3$ (run 12) and (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium (Ru(cod)(cot)) combined with PPh_3 (run 14) showed some catalytic activities. However, all these ruthenium catalyst systems (runs 11–15) were less active than $RuCl_2(PPh_3)_3$. On the other hand, other group 8–10 transition-metal complexes showed almost no catalytic activities (runs 16–21).

Several substituted 2-aminophenethyl alcohols (**1b–f**) were prepared by the method illustrated in Scheme I and were subjected to the present indole synthesis catalyzed by $RuCl_2(PPh_3)_3$. As shown in Table II, the corresponding indoles (**3b–f**) were readily obtained in high isolated yields (runs 22–26). The aromatic C–Br bond was tolerated in this catalytic reaction (run 26). Thus, 4-bromoindole (**3f**), a key intermediate in ergot alkaloid synthesis,[14] was readily obtained from 2-amino-6-bromophenethyl alcohol (**1f**), which was prepared via Sandmeyer bromination of 2-methyl-3-nitroaniline[15] followed by the condensation with formaldehyde and reduction with a $Zn/CaCl_2/H_2O$ system.[16] Indole derivatives having substituents at N-hetero rings are also accessible as exemplified by eq 2. The



(1) (3) (2)

3g: R' = 2-Ph 99%
3h: 3-Me 79%

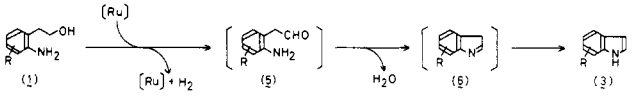
condensation of 2-nitrotoluene with benzaldehyde and the successive hydrogenation over Rh/C afforded **1g** (cf. Scheme I). The reaction between 2-ethylnitrobenzene and formaldehyde also gave **1h**. Under the same reaction conditions as Table II, 2-phenylindole (**3g**) and 3-methylindole (**3h**) were obtained from **1g** and **1h** in 99% and 79% isolated yields, respectively.

Invariably, a stoichiometric amount of hydrogen was evolved spontaneously into the gas phase in these reactions. By measuring the volume of the evolved hydrogen, which corresponds to the amount of indoles formed, kinetic features of the reaction could be investigated. No apparent induction periods were observed. Plots of $-\ln(1 - x/a_0)$ vs time were linear over 70% conversions of 2-aminophenethyl alcohols **1**, where x is the amount of indoles **3** formed and a_0 is the amount of **1** charged. Furthermore, a straight line with a zero intercept was obtained on plotting the observed rate constants against the different initial catalyst concentrations ($[Ru]_0 = 6.10 \times 10^{-3} \sim 2.44 \times 10^{-2}$ mol dm^{-3}; $[Ru]_0 = [RuCl_2(PPh_3)_3]_0$). Thus the rate law for the present indole synthesis is expressed by eq 3. The k_{obs} values determined for each indole derivative are listed in Table II.

$$d[3]/dt = k_{obs}[Ru]_0[1] \quad (3)$$

The present N-heterocyclization to indole seems to proceed via intramolecular N-alkylation which might produce indoline intermediate **4**. Similar $RuCl_2(PPh_3)_3$-catalyzed N-alkylation of amines with an alcohol functionality has been reported recently[9,10] and from the

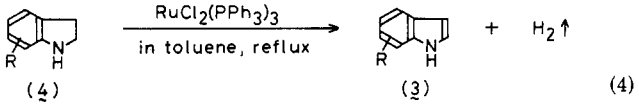
Scheme II



(1) (5) (6) (3)

kinetic features of the reaction, the possible catalytic cycle including nucleophilic attack of the amine on an aldehyde intermediate was proposed.[9] Further, in the N-heterocyclization of aminoarenes with *vic*-diols (affording indoles) and with 1,3-diols (affording quinolines), the first steps were similar N-alkylations with the alcohol functionalities.[6] In these related reactions, the nature of the catalyst precursors had a critical effect and virtually only $RuCl_2(PPh_3)_3$ showed high catalytic activity. In the present indole synthesis, the same tendency has been observed (Table I).

To check the intermediacy of indolines, two indoline derivatives (**4a** and **4e**) were subjected to the catalytic reaction under the same reaction conditions as Table II (eq 4). These two indolines were dehydrogenated quan-



(4) (3) (4)

4a: R = H
4e: 6-Cl

titatively into indoles **3a** and **3e** with spontaneous hydrogen evolution. Dehydrogenation of indoline to indole would proceed via imine intermediate **6** (see Scheme II), and **6** easily converted to indole **3** by bond rearrangement, since **3** is more stable than **6** because of its π-conjugation system with an aromatic ring.[17] The rate of the dehydrogenation of indoline was also expressed by eq 5 over

$$d[3]/dt = k_{obs}[Ru]_0[4] \quad (5)$$

70% conversions. The k_{obs} values were 2.03×10^{-2} (eq 4, **3a**) and 1.59×10^{-2} dm^3 mol^{-1} s^{-1} (eq 4, **3e**), respectively. These rates are 7.0 and 1.7 times faster than those of run 1 and 25 in Table II, the rates for indole formation from 2-aminophenethyl alcohols **1a** and **1e**. If the reaction proceeded via indoline **4**, it might be detected in the reaction mixture. Indeed, according to microcomputer simulations for the consecutive first-order reactions, A → B → C (A = 1, B = **4**, C = **3**, assuming the ratio of the two steps are 7.0 and 1.7), **4a** should be detected in 11% maximum yield at 25% conversion of **1a** and also **4e** in 29% maximum yield at 51% conversion of **1e**. However, even by careful GLC analyses, no or only a trace of indolines, if any, could be found in the present indole synthesis. So we consider that indoline is not involved in the main catalytic cycle.

From these observations, the possible reaction pathway is postulated and illustrated in Scheme II. The hydroxy group of **1** oxidatively coordinates to the active catalyst center[18] to give **5**. Such an oxidative pathway via an alk-

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(17) 1,2,3,4-Tetrahydroquinoline did not convert under the same reaction conditions, since dehydrogenation via the corresponding imine complex could not construct a similar π-conjugation system by bond rearrangement. Indeed, we postulated other reaction mechanisms, including the formation of *N,N'*-diphenylpropylenediamine, in previously reported ruthenium-catalyzed quinoline synthesis from aniline and 1,3-propanediol.[6]

(18) From the results shown in Table I and our previous paper,[9] we presume the active ruthenium species to be divalent, containing PPh_3 as a ligand. Indeed a Ru(0) catalyst system such as Ru(cod)(cot) combined with PPh_3 showed catalytic activity (run 14), but Pertici et al. have reported that Ru(cod)(cot) converted to a Ru(II) species under reflux in toluene.[19] Thus, the present reaction would be rationalyzed by a Ru(II) ⇄ Ru(IV) catalyst system.

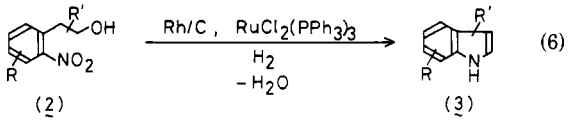
Table III. Synthesis of Indoles from 2-Nitrophenethyl Alcohols

run	substrate 2, mmol	catalyst	solvt, mL	time,[a] h	product 3[b]	yield,[c] %
27	**a**, 5.3	Pd/C (0.1 g)–$RuCl_2(PPh_3)_3$ (0.12 mmol)	20	17	**a**	96[d]
28	**e**, 5.0	Rh/C (0.07 g)–$RuCl_2(PPh_3)_3$ (0.10 mmol)	7	7	**e**	88
29	**g**, 5.0	Rh/C (0.07 g)–$RuCl_2(PPh_3)_3$ (0.10 mmol)	7	7	**g**	96
30	**h**, 7.6	Rh/C (0.1 g)–$RuCl_2(PPh_3)_3$ (0.14 mmol)	10	11	**h**	77

[a] The reaction was performed at room temperature for this period and then under reflux for 6 h. [b] The same notions as in the Table II and eq 3–4. [c] Isolated yields. [d] Determined by GLC.

oxohydrido complex has been proposed for N-alkylation of amines with alcohols by us[9] and for hydrogen transfer from alcohols by other authors.[20-26] The nucleophilic attack of the amine to the aldehyde moiety of **5** yields the Schiff base intermediate **6**. Although hydrogenation of the Schiff base moiety could give indoline derivatives, bond rearrangement of **6** should be very fast and affords indole **3** selectively.

Indoles from 2-Nitrophenethyl Alcohols. 2-Nitrophenethyl alcohols **2** are precursors for 2-aminophenethyl alcohols **1** (Scheme I). So, one-pot indole synthesis from **2** is an intriguing process and attempted in the present study. The $RuCl_2(PPh_3)_3$-catalyzed reactions under hydrogen pressure[27] (30–80 kg cm^{-2}) at 110–130 °C or with $HCOOH/Et_3N$ system as a hydrogen source[28] at 130–150 °C were unsuccessful. After several other trials, we found that heterogeneous and homogeneous binary catalyst systems realized this one-pot indole synthesis (eq 6). Both



(2) (3) (6)

the heterogeneous catalyst (Pd/C or Rh/C) and $RuCl_2(PPh_3)_3$ were added to toluene solution of **2**, and the solution was stirred under hydrogen atmosphere at room temperature. After the hydrogen uptake ceased, the reaction was further carried out under reflux. Among the heterogeneous catalysts, Pd/C showed high catalytic activity for reduction of 2-nitrophenethyl alcohol (**2a**) to 2-aminophenethyl alcohol (**1a**) under hydrogen atmosphere at room temperature and generated **1a** cyclized to indole in 96% yield by $RuCl_2(PPh_3)_3$ under subsequent reflux conditions (run 27 in Table III). Of course Pd/C alone showed extremely low catalytic activity for the present indole synthesis both from 2-nitrophenethyl alcohol and from 2-aminophenethyl alcohol.[29] However, in the catalyst system of Pd/C–$RuCl_2(PPh_3)_3$, halogen-containing 2-nitrophenethyl alcohol **2e** was easily decomposed and gave intractable mixtures even at room temperature. Other heterogeneous catalysts such as Ru/C were less effective in the present reaction. Consequently, we found that Rh/C is the efficient catalyst for selective reduction of nitro group on 2-nitrophenethyl alcohols **2**. As shown in Table III, the corresponding indoles were obtained from various 2-nitrophenethyl alcohols **2** including **2e** in good-to-excellent yields by our binary catalyst system. The homogeneous catalyst did not affect the heterogeneous one and vice versa.

Experimental Section

Materials. 2-Aminophenethyl alcohol (**1a**), 2-nitrophenethyl alcohol (**2a**), indoline (**4a**), PBu_3, and PPh_3 were commercial materials and were purified by distillation or recrystallization before use. Pd on carbon (5% Pd), Rh on carbon (5% Rh), $RuCl_3 \cdot nH_2O$ (mainly $n = 3$), and $FeCl_3 \cdot nH_2O$ (mainly $n = 6$) were purchased and used without further purification. Complexes $RuCl_2(PPh_3)_3$,[30] $RuH_2(PPh_3)_4$,[31] $RuHCl(CO)(PPh_3)_3$,[32] $RuHCl(PPh_3)_3$,[33] Ru(cod)(cot),[34] $RhCl(PPh_3)_3$,[35] $PdCl_2(PPh_3)_2$,[36] $Pd(PPh_3)_4$,[37] $PtCl_2(PPh_3)_2$,[38] and $CoCl_2(PPh_3)_2$[39] were prepared according to literature methods.

2-Aminophenethyl Alcohols 1 (Scheme I). A typical reaction procedure[40] is described for the synthesis of 6-chloro-2-aminophenethyl alcohol (**1d**). 2-Chloro-6-nitrotoluene (25 g, 146 mmol), paraformaldehyde (60 mmol), DMSO (20 mL), and Triton B (benzyltrimethylammonium hydroxide, 40% solution of MeOH, 1.8 mL) were placed in a 100-mL three-necked Pyrex flask equipped with a reflux condenser. The reaction mixture was stirred at 90 °C for 2 h. The product, 2-chloro-6-nitrophenethyl alcohol (**2d**), was isolated from the mixture by distillation (50 °C/0.2 mmHg) in 92% yield based on paraformaldehyde as a lemon yellow solid. The reductions of **2** to **1** were carried out with a $Zn/CaCl_2/H_2O$ system (method A)[16] or under hydrogen (1 atm) over Rh/C or Pd/C (method B).[41] The reduction of **2d** to **1d** was performed by method A. In a 500-mL four-necked round-bottomed flask, zinc powder (42 g), $CaCl_2$ (4.2 g), ethanol (150 mL), and water (50 mL) were placed. Ethanol (10 mL) solution of 2-chloro-6-nitrophenethyl alcohol (**2d**, 10.2 g) was added to the solution under reflux and kept at this temperature for 8 h. After cooling, the whole mixture was filtrated and extracted with ether. Evaporation of ether and recrystallization afforded 6-chloro-2-aminophenethyl alcohol (**1d**) in 45% yield.

Indoles 3 from 2-Aminophenethyl Alcohols 1. A 50-mL two-necked Pyrex flask equipped with a reflux condenser and a gas buret was charged with $RuCl_2(PPh_3)_3$ (0.14 mmol, 2 mol % based on **1**), toluene (10 mL), and 2-aminophenethyl alcohol (**1**, 7.0 mmol) in this order under an argon flow. The reaction mixture became completely homogeneous after 5 min of stirring at room temperature. Then, the flask was immersed into a preheated silicone oil bath (ca. 120 °C), and the reaction was performed under reflux for 6 h.

Indoles 3 from 2-Nitrophenethyl Alcohols 2. A typical procedure is described for **2g**. A mixture of **2g** (5.0 mmol), $RuCl_2(PPh_3)_3$ (0.1 mmol), rhodium on carbon (0.07 g), and toluene

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(7.0 mL) was placed in a two-necked flask under an argon stream. The atmosphere was changed to hydrogen, and the mixture was stirred at room temperature (for 7 h) until hydrogen uptake ceased. Then, the reaction temperature was raised to the refluxing point of solvent, and the reaction was performed for another 6 h. The product **3g** was isolated by Kugelrohr distillation (pot temperature 85 °C/0.07 mmHg) in 96% yield.

Analytical Procedure. The identification of products was made by ^1H and ^{13}C NMR and IR spectral and elemental analysis, which were all consistent with those of authentic samples.

The ^1H NMR spectra were obtained at 270 MHz with a JEOL GSX-270 and the ^{13}C NMR spectra at 25.05 MHz with a JEOL JNM FX-100 spectrometers. Samples were dissolved in $CDCl_3$, and the chemical shifts were expressed relative to tetramethylsilane as an internal standard. Elemental analyses were performed at the Microanalytical Center of Kyoto University. GLC analyses were performed on a Shimadzu GC-8APF chromatograph equipped with a glass column (3 mm × 3 m) packed with Silicone OV-17 (5% on Chromosorb W(AW), 60-80 mesh) or PEG-HT (5% on Uniport HP, 60-80 mesh). The products were isolated by a vacuum distillation with a Kugelrohr apparatus. The yield of indole (**3a**) was determined by GLC with naphthalene as the internal standard.

5-Methoxyindole (3c): white solid; mp 48.5-50.0 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 3.81 (s, 3 H, CH_3O), 6.43 (br, 1 H, indole-3-*H*), 6.84 (dd, 1 H, indole-2-*H*, J = 2.7, 8.1 Hz), 7.02-7.16 (m, 3 H, Ar), 7.98 (br, 1 H, N*H*); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 55.69 (q, CH_3O), 102.03 and 102.13 (d and d, indole-C^3 and Ar), 111.47 and 112.00 (d and d, Ar), 124.60 (d, indole-C^2), 127.95 and 130.67 (s and s, Ar), 153.78 (s, CH_3O-*C*). Anal. Calcd for C_9H_9NO: C, 73.4; H, 6.2; N, 9.5; O, 10.9. Found: C, 73.31; H, 6.20; N, 9.27; O, 11.15.

6-Chloroindole (3e): white solid; mp 88.1-88.8 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 6.52 (br, 1 H, indole-3-*H*), 7.09 (dd, 1 H, indole-2-*H*, J = 1.8, 8.4 Hz), 7.14-7.55 (m, 3 H, Ar), 8.06 (br, 1 H, N*H*); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 102.57 (d, indole-C^3), 110.64 (d, indole-C^7), 120.27 and 121.24 (d and d, Ar), 124.45 (d, indole-C^2), 126.16 and 127.56 (s and s, indole-C^6 and C^3-*C*-C^4), 135.78 (s, N-*C*-C^7). Anal. Calcd for C_8H_6ClN: C, 63.4; H, 4.0; Cl, 23.4; N, 9.2. Found: C, 63.22; H, 3.90; Cl, 23.24; N, 9.28.

3-Methylindole (3h): white solid; mp 98.0-98.5 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 2.30 (s, 3 H, CH_3), 6.82 (br, 1 H, indole-2-*H*), 7.10-7.21 (m, 4 H, Ar), 7.56 (d, 1 H, N*H*, J = 7.3 Hz); ^{13}C NMR (25.05 MHz, $CDCl_3$) δ 9.55 (q, CH_3), 110.74 (d, indole-C^7), 111.09 (s, indole-C^3), 118.48 (d, indole-C^4), 118.77 (d, indole-C^6), 121.46 (d, indole-C^2 and -C^5), 127.85 (s, C^3-*C*-C^4), 135.82 (s, N-*C*-C^7). Anal. Calcd for C_9H_9N: C, 82.4; H, 6.9; N, 10.7. Found: C, 82.36; H, 6.89; N, 10.69.

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Registry No. **1a**, 5339-85-5; **1b**, 109277-81-8; **1c**, 124043-85-2; **1d**, 100376-53-2; **1e**, 124043-86-3; **1f**, 109277-82-9; **2a**, 15121-84-3; **2d**, 102493-68-5; **2e**, 16764-17-3; **2g**, 16764-13-9; **2h**, 64987-77-5; **3a**, 120-72-9; **3b**, 3420-02-8; **3c**, 1006-94-6; **3d**, 25235-85-2; **3e**, 17422-33-2; **3f**, 52488-36-5; **3g**, 948-65-2; **3h**, 83-34-1; **4a**, 496-15-1; **4e**, 52537-00-5; $RuCl_2(PPh_3)_3$, 15529-49-4; $RuCl_3$, 10049-08-8; $RuH_2(PPh_3)_4$, 19529-00-1; $RuHCl(CO)(PPh_3)_3$, 16971-33-8; $RuHCl(PPh_3)_3$, 99944-74-8; Ru(cod)(cot), 91947-90-9; $RhCl(PPh_3)_3$, 74735-07-2; *o*-$NO_2C_6H_4CH_3$, 88-72-2; 1-chloro-2-methyl-3-nitrobenzene, 83-42-1; 1,4-dimethyl-2-nitrobenzene, 89-58-7; 1-methoxy-3-methyl-4-nitrobenzene, 5367-32-8; 4-chloro-1-methyl-2-nitrobenzene, 89-59-8; 1-bromo-2-methyl-3-nitrobenzene, 55289-35-5; 1-ethyl-2-nitrobenzene, 612-22-6.

Homocoupling of Alkyl Halides and Cyclization of α,ω-Dihaloalkanes via Activated Copper

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The homocoupling of alkyl halides utilizing a highly activated form of zerovalent copper has been studied. Allyl and benzyl halides produce high yields of their respective homocoupled dimers 1,5-hexadiene and 1,2-diphenylethane. An 83% yield of tetradecane was produced from *n*-heptyl iodide. The yield drops substantially for the corresponding bromo and chloro compounds. The yield is also strongly solvent and temperature dependent. Secondary and tertiary alkyl iodides and bromides produce moderate to low yields of homocoupling accompanied by substantial amounts of the corresponding alkane and alkenes. The copper-mediated cyclization of α,ω-dihaloalkanes has also been examined. The yield of cycloalkanes is moderate to high for the smaller rings with the yield decreasing substantially as the ring size increases. The compound *meso*-1,2-dibromo-1,2-diphenylethane was found to produce exclusively *trans*-stilbene in high yield. The activated copper was produced by reducing $CuI{\cdot}PR_3$ with a preformed solution of lithium naphthalenide. Complexes using triethylphosphine and tri-*n*-butylphosphine were both studied. The product yields were found to be similar in both cases.

Introduction

Organocopper compounds are increasingly being used in organic synthesis due in large measure to their ability to undergo substitution reactions with alkyl halides and 1,4-addition reactions with α,β-unsaturated carbonyl compounds.[1] Our research endeavors have been aimed at developing a form of copper with sufficient reactivity to allow the direct oxidative addition of the metal to organic halides to produce organocopper compounds without utilizing the traditional lithium and Grignard precursors. This approach would allow the functionalization of organocopper reagents in ways not permitted when the traditional highly reactive precursors are used.

Rieke and Ebert have recently reported the successful development of such a form of activated copper.[2] Rieke and co-workers have further developed stable functionalized primary alkylcopper reagents and have explored the reactions of these compounds with epoxides, acid chlorides, and α,β-unsaturated ketones.[3] In the course of further

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