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# AN EFFICIENT SYNTHESIS OF NITROGEN HETEROCYCLES BY Cp*Ir-CATALYZED *N*-CYCLOALKYLATION OF PRIMARY AMINES WITH DIOLS

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**Abstract** – A new efficient method for the *N*-cycloalkylation of primary amines with diols catalyzed by a Cp*Ir complex have been developed. A variety of five-, six-, and seven-membered cyclic amines are synthesized in good to excellent yields in environmentally benign and atom economical manner with the formation of only water as a coproduct. A large scale synthesis of *N*-benzylpiperidine and a two-step asymmetric synthesis of (*S*)-2-phenylpiperidine using (*R*)-1-phenylethylamine as a starting primary amine have been also achieved.

## INTRODUCTION

Considerable attention has been paid to *N*-heterocyclic compounds owing to their functionality in pharmaceutical chemistry, material chemistry, and synthetic organic chemistry.[1] Particularly, pyrrolidine, piperidine, and morpholine derivatives have been found in a variety of biologically active natural products.[2] Thus, much effort has been devoted to develop an efficient synthetic method for such compounds.[3] Recently, a variety of transition metal-catalyzed reactions for the synthesis of *N*-heterocyclic compounds, including hydroamination and ring-closing metathesis, have been reported.[4] From an environmental point of view, *N*-cycloalkyation of primary amines with diols should be another attractive method because *N*-heterocyclic products can be obtained from halogen-free starting materials in

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This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

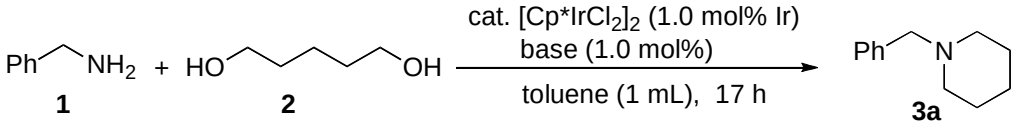
one step without generation of harmful byproducts and only $H_2O$ is a coproduct. Some ruthenium-catalyzed systems for *N*-cycloalkyation of primary amines with diols have been reported so far,[5] most of these systems, however, require high reaction temperature (>150 °C), and applicable substrates are rather restricted. For example, to the best of our knowledge, *N*-cycloalkyation using a diol having a substituent at α-position of the hydroxy moiety has not been reported in the ruthenium-catalyzed systems. Furthermore, asymmetric synthesis by these catalytic systems has never been studied.

We have been studying the catalytic activity of iridium complexes bearing pentamethylcyclopentadienyl (Cp*) ligands toward several hydrogen-transfer reactions[6] and have disclosed intra- and intermolecular *N*-alkylation of amines with alcohols.[7, 8] Here, we wish to report a full account of a new efficient, atom economical system for the synthesis of a variety of *N*-heterocyclic compounds from primary amines and diols catalyzed by a Cp*Ir complex and its application to the asymmetric synthesis of (*S*)-2-phenylpiperidine.[9]

## RESULTS AND DISCUSSION

At first, *N*-cycloalkyation of benzylamine (**1**) with 1,5-pentanediol (**2**) under various conditions has been studied. The reactions were conducted in the presence of $[Cp^*IrCl_2]_2$ as a catalyst in toluene. The results are summarized in Table 1. When a mixture of **1**, **2,** and $[Cp^*IrCl_2]_2$ (1.0 mol% Ir based on diol **2**) in toluene (1.0 mL) was stirred at 110 °C for 17 h, *N*-benzylpiperidine (**3a**) was produced in only 28% yield (entry 1). However, we found that the addition of base (entries 2 - 7) considerably improved the yield. When the reaction was performed in the presence of $NaHCO_3$ (1.0 mol% based on diol **2**), **3a** was obtained in almost quantitative yield (98%) (entry 2). Other bases, such as $Na_2CO_3$, NaOAc, and $KHCO_3$, were also effective (entries 3 - 5), while $K_2CO_3$ and $Li_2CO_3$ were less effective (entries 6 and 7). The excellent yield of **3a** was obtained even in the reaction at 90 °C (entry 8). Use of a slight excess of **1** (1.5 equiv) was essential to obtain an excellent result; the reaction of **1** with **2** in 1:1 ratio gave **3a** in 84% yield (entry 9).

**Table 1.** Cp*Ir Complex-Catalyzed *N*-Cycloalkylation of Benzylamine (**1**) and 1,5-Pentanediol (**2**) Producing *N*-Benzylpiperidine (**3a**) by under Various Conditions




**1** **2** **3a**

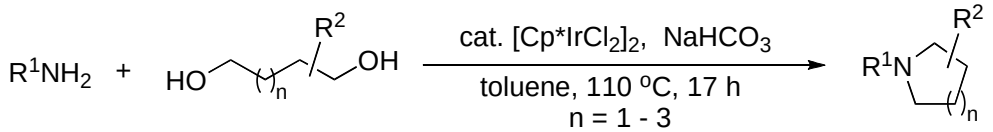
| entry | **1** (mmol) | **2** (mmol) | base | temp. ($^{o}$C) | yield[a](%) |
|---|---|---|---|---|---|
| 1 | 3.0 | 2.0 | none | 110 | 28 |
| 2 | 3.0 | 2.0 | $NaHCO_3$ | 110 | 98 |
| 3[b] | 3.0 | 2.0 | $Na_2CO_3$ | 110 | 93 |
| 4 | 3.0 | 2.0 | NaOAc | 110 | 96 |
| 5 | 3.0 | 2.0 | $KHCO_3$ | 110 | 96 |
| 6 | 3.0 | 2.0 | $K_2CO_3$ | 110 | 80 |
| 7 | 3.0 | 2.0 | $Li_2CO_3$ | 110 | 62 |
| 8 | 3.0 | 2.0 | $NaHCO_3$ | 90 | 99 |
| 9 | 2.0 | 2.0 | $NaHCO_3$ | 90 | 84 |

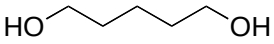
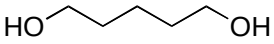
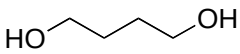
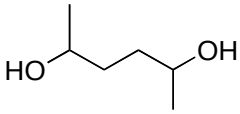
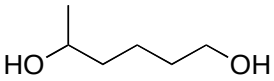
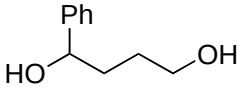
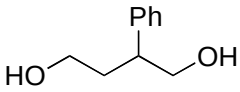
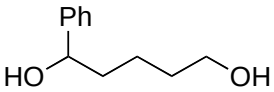
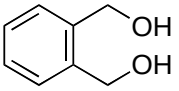
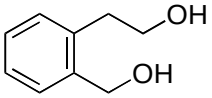
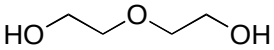
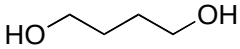
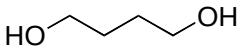
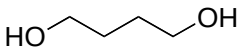
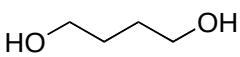
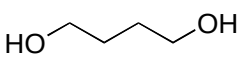
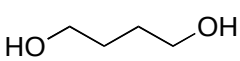
[a]Determined by GC. [b]$[Cp^*IrCl_2]_2$ (0.50 mol% Ir) and $Na_2CO_3$ (0.50 mol%) were used as catalysts.

Since the optimal reaction conditions were in hand, we next examined the *N*-cycloalkyation of benzylamine with a variety of diols. The results are summarized in Table 2. Six-, five-, and seven-membered cyclic amines (**3a-c**) were obtained in the reactions of benzylamine with 1,5-pentanediol, 1,4-butanediol, and 1,6-hexanediol in good to excellent yields, respectively (entries 1 - 4). A large scale synthesis of *N*-benzylpiperidine (**3a**) using 100 mmol of benzylamine and 1,5-pentanediol could be achieved in a high yield with 0.50 mol% Ir of the catalyst (entry 2).[10] The reactions of several subsutituted diols on the methylene chain could also proceed smoothly to give substituted cyclic amines (**3d-h**) (entries 5 - 9). In the reaction of benzylamine with 2,5-hexanediol, a diastereomeric mixtutre of *N*-benzyl-2,5-dimethylpyrrolidine (**3d**) (cis : trans = 73 : 27) was obtained in 94% yield (entry 5). Benzo-fused cyclic amines such as *N*-benzylisoindoline (**3i**) and *N*-benzyl-1,2,3,4-tetrahydroisoquinoline (**3j**) were also synthesized in the reactions of benzylamine with 1,2-benzenedimethanol and 2-(2-hydroxyethyl)benzyl alcohol, respectively (entries 10 and 11). The reaction with 1,2-benzenedimethanol proceeded without base ($NaHCO_3$) (entry 10).

The product **3k** having morpholine skeleton could be synthesized in good yield (76%) by the employment of diethylene glycol as a diol substrate (entry 12). *N*-(3-Pyridylmethyl)pyrrolidine (**3l**), which is known as a nicotinic agonist,[11] could be smoothly synthesized using easily available 3-pyridylmethylamine as a starting material (entry 13). In the reactions of aniline as the starting primary amine, higher catalyst loading (5.0 mol% Ir) and a higher reaction temperature were required to obtain good yields (entries 15 and 16). The reaction of aniline with 1,4-butanediol gave *N*-phenylpyrrolidine (**3n**) in 70% yield (entry 15). Introduction of electron-donating substituents at the phenyl ring of aniline considerably improved the yield (entry 16). The reactions of other primary amines, such as 1-naphthylmethylamine, phenethylamine and octylamine, also afforded the cyclic amines in good yields (entries 14, 17 and 18).

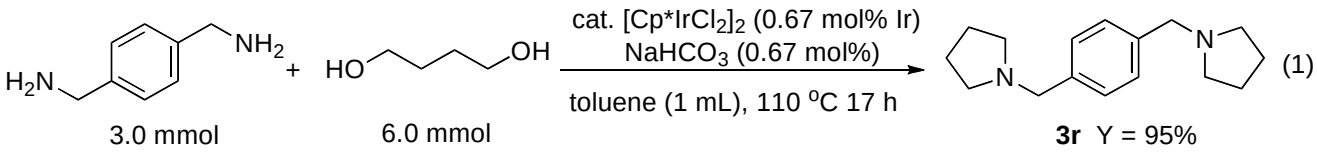
**Table 2.** Cp*Ir Complex-Catalyzed *N*-Cycloalkylation of Primary Amines with a Variety of Diols[a]




| entry | amine | diol | cat. (mol% Ir) | product | yield[b](%) |
|---|---|---|---|---|---|
| 1[c] | $PhCH_2NH_2$ |  | 1.0 | **3a** | 91 |
| 2[d] | $PhCH_2NH_2$ |  | 0.5 | **3a** | 81 |
| 3 | $PhCH_2NH_2$ |  | 1.0 | **3b** | 72 |
| 4[e] | $PhCH_2NH_2$ |  | 2.0 | **3c** | 73 |
| 5[f] | $PhCH_2NH_2$ |  | 1.0 | **3d** | 94[g] |
| 6 | $PhCH_2NH_2$ |  | 1.0 | **3e** | 79 |
| 7 | $PhCH_2NH_2$ |  | 1.0 | **3f** | 98 |
| 8 | $PhCH_2NH_2$ |  | 2.0 | **3g** | 90 |
| 9 | $PhCH_2NH_2$ |  | 4.0 | **3h** | 78[h] |
| 10[i,j] | $PhCH_2NH_2$ |  | 2.0 | **3i** | 63 |
| 11 | $PhCH_2NH_2$ |  | 2.0 | **3j** | 76 |
| 12 | $(4\text{-}MeOC_6H_4)CH_2NH_2$ |  | 2.0 | **3k** | 76 |
| 13 | $(3\text{-}Py)CH_2NH_2$ |  | 1.0 | **3l** | 62 |
| 14 | $(1\text{-}Naph)CH_2NH_2$ |  | 1.0 | **3m** | 91 |
| 15[k,l] | $PhNH_2$ |  | 5.0 | **3n** | 70 |
| 16[k] | $(4\text{-}MeOC_6H_5)NH_2$ |  | 5.0 | **3o** | 90 |
| 17 | $PhCH_2CH_2NH_2$ |  | 4.0 | **3p** | 73 |
| 18 | $n\text{-}C_8H_{17}NH_2$ |  | 4.0 | **3q** | 81[h] |

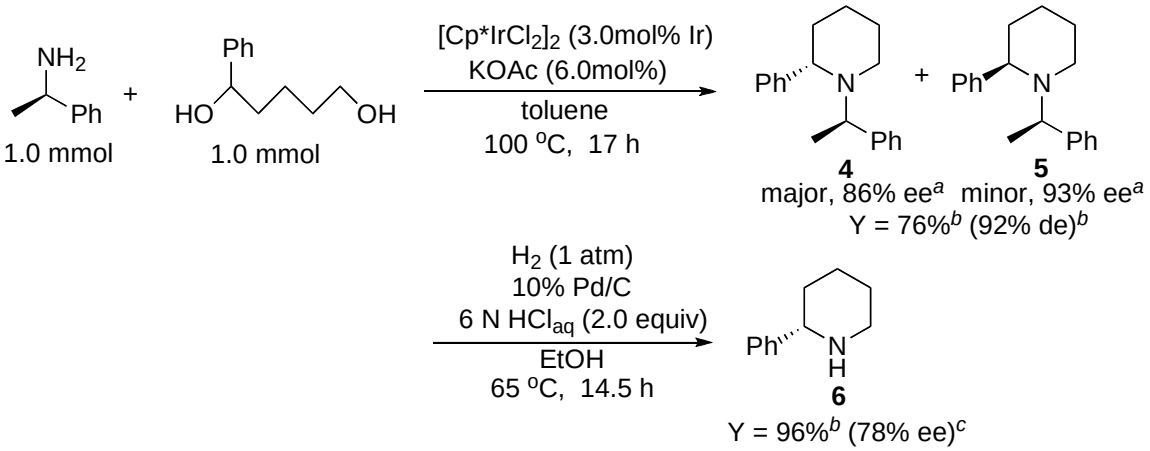
[a]The reaction was carried out at 110 °C for 17 h with amine (3.0 mmol), diol (2.0 mmol), $[Cp^*IrCl_2]_2$ (1.0 - 5.0% Ir), and $NaHCO_3$ (same equivalent to the iridium catalyst) in toluene (1 mL). [b]Isolated yield. [c]Reaction temperature was 90 °C. [d]Reaction was carried out 100 mmol scale using benzylamine (10.7 g, 100 mmol) and 1,5-pentanediol (10.4 g, 100 mmol). [e]Toluene (3 mL) was used. [f]$Na_2CO_3$ was used as base. [g]cis : trans = 73 : 27 (determined by $^1H$ NMR analysis). [h]GC yield. [i]Amine (2.0 mmol) was used. [j]Base was not added. [k]Reaction temperature was 130 °C. [l]Reaction time was 40 h.

Furthermore, we found that the double *N*-cycloalkylation of p-xylylenediamine (3.0 mmol) with 1,4-butanediol (6.0 mmol) under the similar conditions gave 1,4-di(*N*-pyrrolidinylmethyl)benzene (**3r**) in an excellent yield (Eq 1).




The asymmetric synthesis of piperidines has been of importance owing to their various roles as natural and synthetic biologically active compounds. Since many asymmetric synthesis of 2-substituted piperidines reported so far have been achieved by non-catalytic multi-step reactions,[12,13] we were interested in the asymmetric synthesis of 2-substituted piperidine by the present catalytic system and used easily available (*R*)-1-phenylethylamine as a chiral source. When the reaction of (*R*)-1-phenylethylamine (99% ee) and 1-phenyl-1,5-pentanediol was conducted in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$ (3.0 mol% Ir) and KOAc (6.0 mol%) in toluene at 100 °C for 17 h, a diastereoisomeric mixture of *N*-(1-phenylethyl)-2-phenylpiperidines **4** and **5** was formed in 76% yield with 92% de (**4** : **5** = 96 : 4) (Scheme 1).[14] The enantiomeric excesses of **4** and **5** were 86% ee and 93% ee, respectively.[15] Hydrogenation of this mixture with Pd/C catalyst gave (*S*)-2-phenylpiperidine of 78% ee in a yield of 96%. Thus, chiral 2-phenylpiepridiene could be synthesized in two steps.

**Scheme 1**

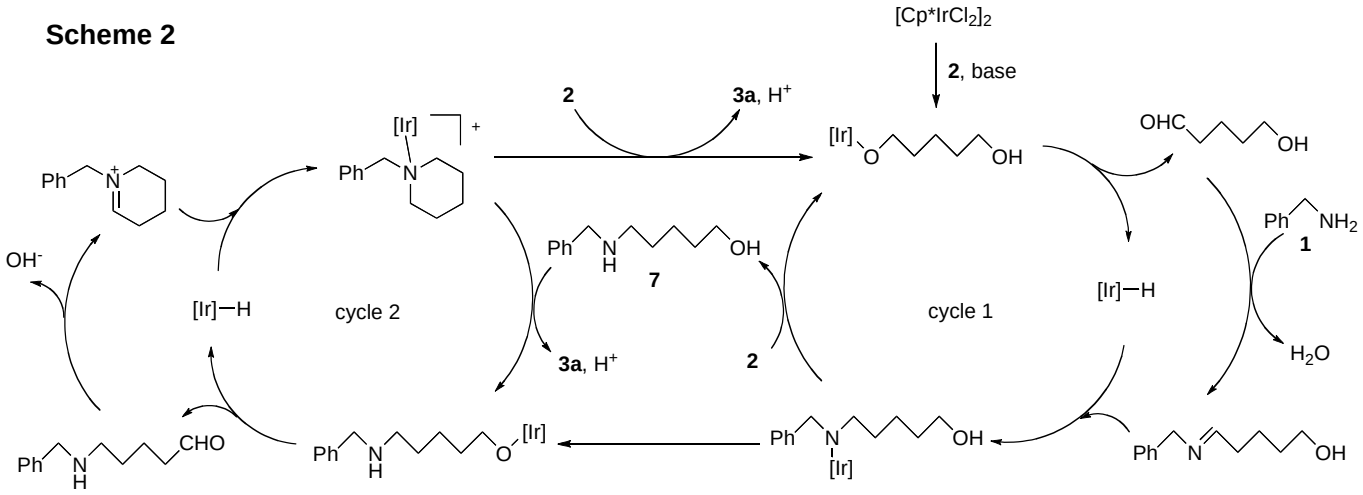



[a]Determined by chiral GC analysis. [b]Determined by GC analysis. [c]Determined by chiral HPLC analysis.

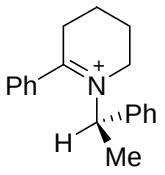
A possible mechanism for the present Cp*Ir complex-catalyzed *N*-cycloalkylation of primary amines with diols is described in Scheme 2, which are based on those for intermolecular *N*-alkylation of primary amines with primary and secondary alcohols[7] and intramolecular *N*-alkylation of amino alcohols.[8] There should be two catalytic cycles 1 and 2. In the former, an intermolecular *N*-Alkylation of primary amine **1**

with one of the alcohol moiety of diol **2** would proceed to afford amino alcohol **7** as an intermediate. Then, in the cycle 2, **7** would be cyclized intramolecularly to give the product **3a** via an iminium intermediate in a similar manner as above. The formation of iridium alkoxide species could be stimulated in the presence of the base ($NaHCO_3$) by trapping hydrogen chloride generated at the first step of the reaction.[6,7,8]

**Scheme 2**




In the reaction of a chiral amine (*R*)-1-phenylethylamine with 1-phenyl-1,5-pentanediol, the cyclic iminium intermediate should be **8**. Therefore, addition of iridium hydride to the C=N bond in **8** would proceed from the opposite side of more bulky phenyl group than methyl group to give the product **4** diastereoselectively.




**8**

In summary, we have shown a new efficient method for the *N*-cycloalkylation of primary amines with diols catalyzed by a Cp*Ir complex. A variety of five-, six-, and seven-membered cyclic amines could be synthesized in good to excellent yields in environmentally benign and atom economical manner with only water as a coproduct. A large scale synthesis of *N*-benzylpiperidine and a two-step asymmetric synthesis of (*S*)-2-phenylpiperidine using (*R*)-1-phenylethylamine as a starting primary amine were also achieved.

## EXPERIMENTAL

**General:** All reactions and manipulations were carried out under an atmosphere of argon by means of

standard Schlenk techniques. $^{1}$H and $^{13}$C NMR spectra were recorded on JEOL A-500 and EX-270 spectrometers. Gas chromatography (GC) analyses were performed on a Shimadzu GC-14A gas chromatograph with a capillary column (Shimadzu CBP1-M25-025 or GL-Science TC-17) and on a GL-Sciences GC353B gas chromatograph with a chiral capillary column (CP-Chirasil-Dex-CB). High-performance liquid chromatography (HPLC) analyses were performed with a TOSOH model CCPS pumping system and a TOSOH UV-8020 ultraviolet detector and a chiral column (Daicel CHIRALCEL OD-H). Optical rotations were measured with a JASCO DIP-1000 polarimeter. Column chromatography was carried out by using Wako-gel C-200. Solvents were dried by using standard procedures and distilled prior to use. The catalyst $[Cp^*IrCl_2]_2$ was prepared according to the literature method.[16] 2-Phenyl-1,4-butanediol, 1-phenyl-1,5-pentanediol, and 2-(2-hydroxyethyl)benzyl alcohol were prepared by reduction of phenylsuccinic acid, 4-benzoylbutyric acid, and homophthalic acid with excess (4 equiv.) lithium aluminum hydride, respectively, according to the literature procedure.[17] All reagents, unless otherwise stated, are commercially available and were used as received.

**General procedure for the synthesis of *N*-benzylpiperidine (3a) under various conditions shown in Table 1:** Under an atmosphere of argon in a heavy-walled glass reactor, benzylamine (2.0 or 3.0 mmol), 1,5-pentanediol (2.0 mmol), $[Cp^*IrCl_2]_2$ (0.010 mmol, 1.0 mol% Ir), base (0.020 mmol, 1.0 mol%), and toluene (1.0 mL) were placed. The reactor was sealed, and the mixture was stirred at 90 or 110 °C for 17 h. The yield of *N*-benzylpiperidine (**3a**) was determined by GC analysis using undecane as an internal standard.

**General procedure for the *N*-heterocyclization of primary amines with a variety of diols shown in Table 2 and Eq 1:** Under an atmosphere of argon in a heavy-walled glass reactor, amine (3.0 mmol), diol (2.0 mmol), $[Cp^*IrCl_2]_2$ (1.0 - 5.0 mol% Ir), base (same equivalent to the iridium catalyst), and toluene (1.0 mL) were placed. The reactor was sealed, and the mixture was stirred at 110 °C for 17 h. After evaporation of the solvent, the products were isolated by column chromatography. The products **3a**,[18] **3b**,[19] **3c**,[20] **3d**,[21] **3e**,[22] **3f**,[23] **3g**,[24] **3h**,[25] **3i**,[26] **3j**,[27] **3k**,[28] **3n**,[29] **3o**,[30] **3p**,[19] **3q**,[31] and **3r**[32] were identified by spectral comparison with literature data.

*N*-(3-pyridylmethyl)pyrrolidine (**3l**): $^{1}$H NMR (270 MHz, $CDCl_3$): δ 1.74 - 1.86 (m, 4H), 2.47 - 2.53 (m, 4H), 3.62 (s, 2H), 7.23 - 7.27 (m, 1H), 7.67 - 7.71 (m, 1H), 8.48 - 8.55 (m, 2H). $^{13}$C NMR (67.8 MHz, $CDCl_3$): δ 23.3 (CH2), 53.9 (CH2), 57.6 (CH2), 123.2 (CH), 134.5 (C), 136.4 (CH), 148.2 (CH), 149.9 (CH). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.76; H, 8.77; N, 17.13.

*N*-(1-naphthylmethyl)pyrrolidine (**3m**): $^{1}$H NMR (270 MHz, $CDCl_3$): δ 1.70 - 1.81 (m, 4H), 2.53 - 2.58 (m, 4H), 4.01 (s, 2H), 7.35 - 7.51 (m, 4H), 7.74 (d, $J$ = 8 Hz, 1H), 7.82 (d, $J$ = 8 Hz, 1H), 8.27 (d, $J$ = 8 Hz, 1H). $^{13}$C NMR (67.8 MHz, $CDCl_3$): δ 23.6 (CH2), 54.4 (CH2), 58.4 (CH2), 124.4 (CH), 125.2 (CH), 125.4 (CH), 125.7 (CH), 126.5 (CH), 127.5 (CH), 128.3 (CH), 132.2 (C), 133.7 (C), 135.5 (C).

**Procedure for the asymmetric synthesis of (*S*)-phenylpiperidine (6) shown in Scheme 1:** Under an atmosphere of argon in a heavy-walled glass reactor, (*R*)-1-phenylethylamine (99%ee) (1.0 mmol), 1-phenyl-1,5-pentanediol (1.0 mmol), $[Cp^*IrCl_2]_2$ (3.0 mol% Ir), KOAc (6.0 mol%), and toluene (0.1 mL) were placed. The reactor was sealed, and the mixture was stirred at 100 °C for 17 h. The yields of *N*-(1-phenylethyl)-2-phenylpiperidines **4** and **5** were determined by GC analysis using undecane as an internal standard. The enantiomeric excesses of **4** and **5** were determined by chiral GC analysis.

[*N*-(*R*)-(1-phenylethyl)-(*S*)-2-phenylpiperidine] (**4**, major isomer): $^1$H NMR (500 MHz, $CDCl_3$): δ 1.18 (d, 3H, *J* = 7 Hz), 1.30 - 1.39 (m, 1H), 1.44 - 1.52 (m, 1H), 1.55 - 1.56 (m, 1H), 1.63 - 1.71 (m, 1H), 1.76 - 1.79 (m, 2H), 2.22 (td, 1H, *J* = 12, 3 Hz), 2.56 (d, 1H, *J* = 12 Hz), 3.50 (dd, 1H, *J* = 11, 3 Hz), 3.83 (q, 1H, *J* = 7 Hz), 7.16 - 7.24 (m, 2H), 7.27 - 7.33 (m, 4H), 7.43 - 7.48 (m, 4H). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 8.1 (CH3), 25.6 (CH2), 26.3 (CH2), 37.2 (CH2), 45.1 (CH2), 54,9 (CH), 65.6 (CH), 126.0 (CH), 126.9 (CH), 127.49 (CH), 127.52 (CH), 127.7 (CH), 128.5 (CH), 144.7 (C), 145.2 (C). Anal. Calcd for $C_{19}H_{23}N$: C, 85.99; H, 8.74; N, 5.28. Found: C, 85.82; H, 8.76; N, 5.23.

[*N*-(*R*)-(1-phenylethyl)-(*R*)-2-phenylpiperidine] (**5**, minor isomer): $^1$H NMR (500 MHz, $CDCl_3$): δ 1.07 - 1.19 (m, 1H), 1.36 (d, 3H, *J* = 7 Hz), 1.45 - 1.65 (m, 5H), 1.74 (td, 1H, *J* = 12, 2 Hz), 3.11 (m, 2H), 3.94 (q, 1H *J* = 7 Hz), 7.01 - 7.03 (m, 2H), 7.21 - 7.31 (m, 4H), 7.36 - 7.43 (m, 4H). $^{13}$C NMR (125.7 MHz, $CDCl_3$): δ 18.5 (CH3), 25.1 (CH2), 26.3 (CH2), 38.2 (CH2), 45.8 (CH2), 56.6 (CH), 65.8 (CH), 126.61 (CH), 126.65 (CH), 127.4 (CH), 127.6 (CH), 128.5 (CH), 128.9 (CH), 138.7 (C), 146.1 (C).

A crude mixture of **4** and **5** (filtered through a pad of silica-gel after the reaction above), Pd on carbon (10%Pd) (270 mg), ethanol (3.5 mL), and 6N HCl aq (0.35 mL) were placed in a flask. The atmosphere was changed to hydrogen, and the mixture was stirred for 14.5 h at 65 °C. After filtration, the yield of 2-phenylpiperidine (**6**) was determined by GC analysis using decane as an internal standard. The enantiomeric excess of 2-phenylpiperidine (**6**) was determined by chiral HPLC analysis. The product 2-phenylpiperidine (**6**) was identified by spectral comparison with literature data.[13]

Optical rotation was measured and determined to be levorotatory {$[\alpha]^{28}_D$ -37.3 (*c* 0.31, $CH_2Cl_2$)}. In the literature, the optical rotation of (*R*)-2-phenylpiperidine has been reported to be dextorotatory {$[\alpha]^{23}_D$ +48.4 (*c* 0.31, $CH_2Cl_2$),[13] $[\alpha]^{20}_D$ +50.0 (*c* 0.31, $CH_2Cl_2$)[33]}. Thus, it is evident that the present *N*-heterocyclization reaction afforded the (*S*)-2-phenylpiperidine.

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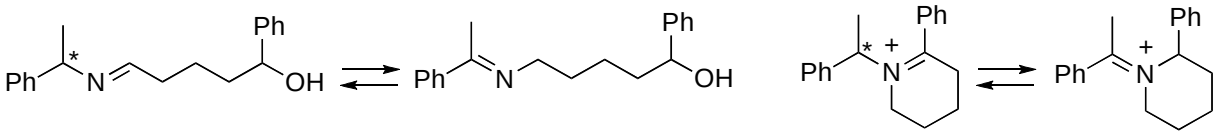
14. A similar result was obtained with use of $NaHCO_3$ as base (Y = 70% with 87% de). However, a slightly better result was obtained with use of KOAc as base.
15. A small extent of racemization of the auxiliary 1-phenylethyl group can account for the reduced enantiomeric excess of the products. This racemization would be probably due to isomerization of

imine and/or iminium intermediate as is shown below.

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