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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*-cycloalkylation of primary amines with diols should be another attractive method because *N*-heterocyclic products can be obtained from halogen-free starting materials in

one step without generation of harmful byproducts and only H₂O is a coproduct. Some ruthenium-catalyzed systems for *N*-cycloalkylation 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*-cycloalkylation 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 reactions⁶ 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*-cycloalkylation of benzylamine (**1**) with 1,5-pentanediol (**2**) under various conditions has been studied. The reactions were conducted in the presence of [Cp*IrCl₂]₂ as a catalyst in toluene. The results are summarized in Table 1. When a mixture of **1**, **2**, and [Cp*IrCl₂]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 NaHCO₃ (1.0 mol% based on diol **2**), **3a** was obtained in almost quantitative yield (98%) (entry 2). Other bases, such as Na₂CO₃, NaOAc, and KHCO₃, were also effective (entries 3 - 5), while K₂CO₃ and Li₂CO₃ 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

$\text{Ph-CH}_2\text{-NH}_2 + \text{HO-CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \xrightarrow[\text{toluene (1 mL), 17 h}]{\text{cat. [Cp}^*\text{IrCl}_2\text{]}_2 \text{ (1.0 mol\% Ir), base (1.0 mol\%)}} \text{Ph-CH}_2\text{-N(CH}_2\text{)}_5$					
1	2				3a
entry	1 (mmol)	2 (mmol)	base	temp. (°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 ₂ CO 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 ₂ CO ₃	110	80
7	3.0	2.0	Li ₂ CO ₃	110	62
8	3.0	2.0	NaHCO ₃	90	99
9	2.0	2.0	NaHCO ₃	90	84

^aDetermined by GC. ^b[Cp*IrCl₂]₂ (0.50 mol% Ir) and Na₂CO₃ (0.50 mol%) were used as catalysts.

Since the optimal reaction conditions were in hand, we next examined the *N*-cycloalkylation 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 substituted 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 mixture 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 (NaHCO₃) (entry 10).

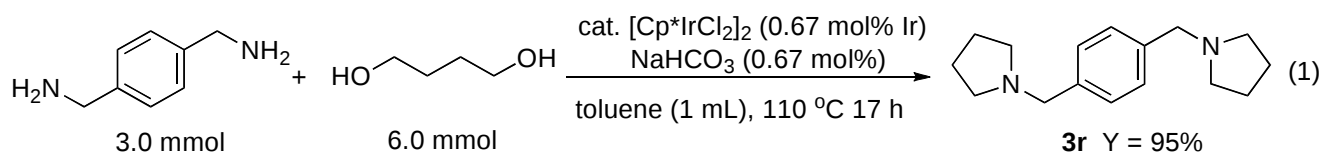
The product **3k** having morpholine skeleton could be synthesized in good yield (76%) by the employment of diethylene glycol as a diol substrate (entry 12). *N*-(3-Pyridylmethyl)pyrrolidine (**3l**), which is known as a nicotinic agonist,¹¹ could be smoothly synthesized using easily available 3-pyridylmethylamine 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 ₂ NH ₂		1.0	3a	91
2 ^d	PhCH ₂ NH ₂		0.5	3a	81
3	PhCH ₂ NH ₂		1.0	3b	72
4 ^e	PhCH ₂ NH ₂		2.0	3c	73
5 ^f	PhCH ₂ NH ₂		1.0	3d	94 ^g
6	PhCH ₂ NH ₂		1.0	3e	79
7	PhCH ₂ NH ₂		1.0	3f	98
8	PhCH ₂ NH ₂		2.0	3g	90
9	PhCH ₂ NH ₂		4.0	3h	78 ^h
10 ^{i,j}	PhCH ₂ NH ₂		2.0	3i	63
11	PhCH ₂ NH ₂		2.0	3j	76
12	(4-MeOC ₆ H ₄)CH ₂ NH ₂		2.0	3k	76
13	(3-Py)CH ₂ NH ₂		1.0	3l	62
14	(1-Naph)CH ₂ NH ₂		1.0	3m	91
15 ^{k,l}	PhNH ₂		5.0	3n	70
16 ^k	(4-MeOC ₆ H ₅)NH ₂		5.0	3o	90
17	PhCH ₂ CH ₂ NH ₂		4.0	3p	73
18	n-C ₈ H ₁₇ NH ₂		4.0	3q	81 ^h

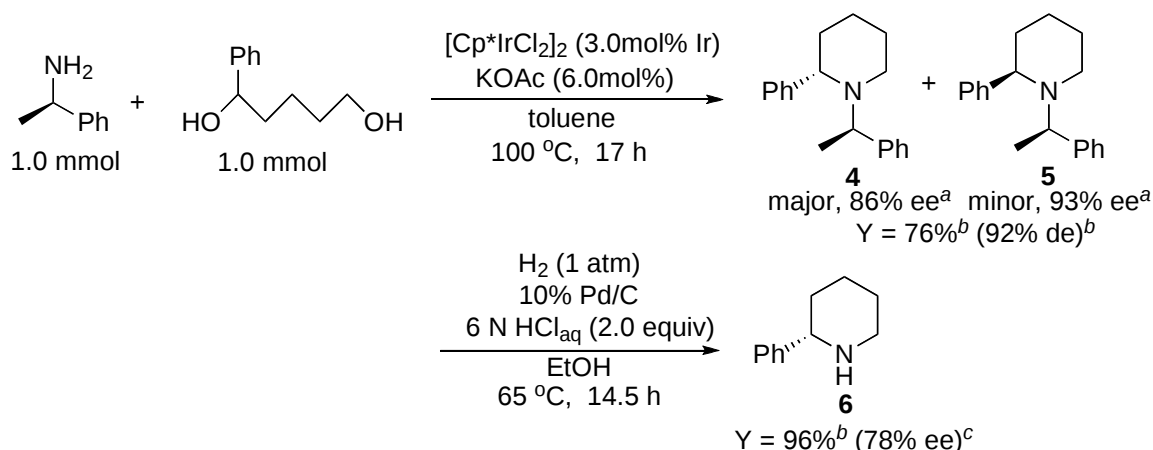
^aThe reaction was carried out at 110 °C for 17 h with amine (3.0 mmol), diol (2.0 mmol), [Cp*IrCl₂]₂ (1.0 - 5.0% Ir), and NaHCO₃ (same equivalent to the iridium catalyst) in toluene (1 mL). ^bIsolated yield. ^cReaction temperature was 90 °C. ^dReaction was carried out 100 mmol scale using benzylamine (10.7 g, 100 mmol) and 1,5-pentanediol (10.4 g, 100 mmol). ^eToluene (3 mL) was used. ^fNa₂CO₃ was used as base. ^gcis : trans = 73 : 27 (determined by ¹H NMR analysis). ^hGC yield. ⁱAmine (2.0 mmol) was used. ^jBase was not added. ^kReaction temperature was 130 °C. ^lReaction 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 $[\text{Cp}^*\text{IrCl}_2]_2$ (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-phenylpiperidine could be synthesized in two steps.

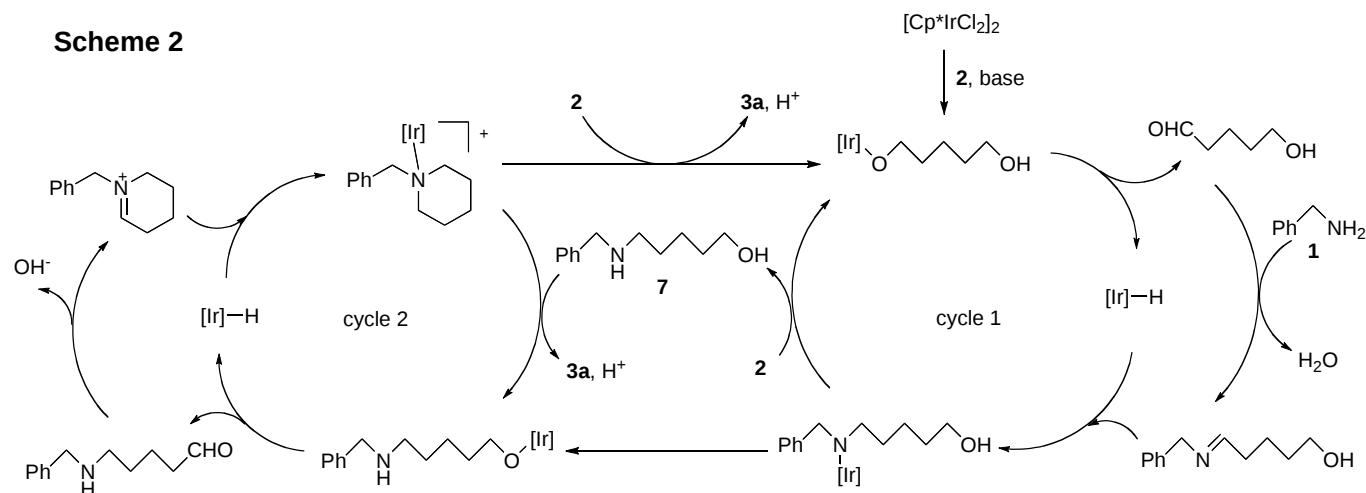
Scheme 1



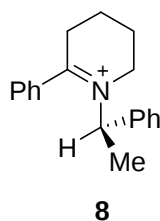
^aDetermined by chiral GC analysis. ^bDetermined by GC analysis. ^cDetermined by chiral HPLC analysis.

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 alcohols⁷ 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}



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.



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. ^1H 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 $[\text{Cp}^*\text{IrCl}_2]_2$ 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), $[\text{Cp}^*\text{IrCl}_2]_2$ (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), $[\text{Cp}^*\text{IrCl}_2]_2$ (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**): ^1H 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 $\text{C}_{10}\text{H}_{14}\text{N}_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 73.76; H, 8.77; N, 17.13.

N-(1-naphthylmethyl)pyrrolidine (**3m**): ^1H 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*IrCl₂]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): ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.7 MHz, CDCl₃): 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 C₁₉H₂₃N: 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): ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125.7 MHz, CDCl₃): 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

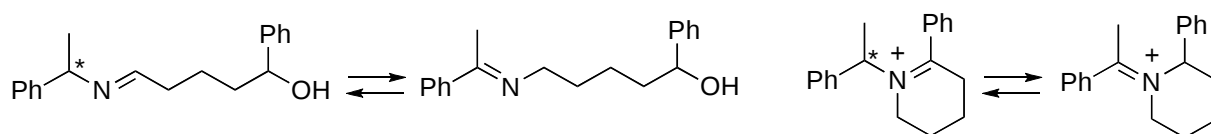
Optical rotation was measured and determined to be levorotatory {[α]_D²⁸ -37.3 (c 0.31, CH₂Cl₂)}. In the literature, the optical rotation of (*R*)-2-phenylpiperidine has been reported to be dextorotatory {[α]_D²³ +48.4 (c 0.31, CH₂Cl₂)},¹³ [α]_D²⁰ +50.0 (c 0.31, CH₂Cl₂)³³. Thus, it is evident that the present *N*-heterocyclization reaction afforded the (*S*)-2-phenylpiperidine.

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 14. A similar result was obtained with use of NaHCO₃ 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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