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Cp*Ir Complex-Catalyzed *N*-Heterocyclization of Primary Amines with Diols: A New Catalytic System for Environmentally Benign Synthesis of Cyclic Amines

Ken-ichi Fujita,* Takeshi Fujii, and Ryohei Yamaguchi*

Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan

fujitak@kagaku.mbox.media.kyoto-u.ac.jp

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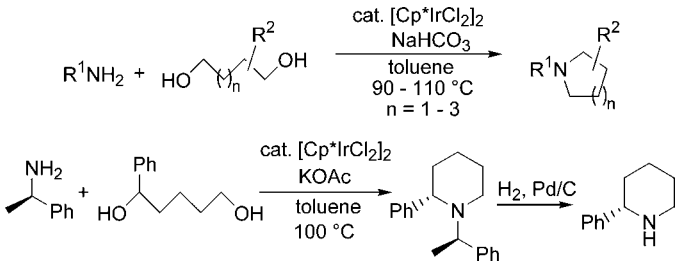
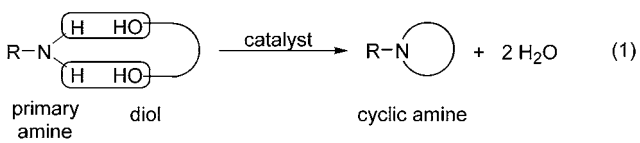
ABSTRACT



A new efficient method for the *N*-heterocyclization of primary amines with diols catalyzed by a Cp*Ir complex was developed. A variety of five-, six-, and seven-membered cyclic amines were synthesized in good to excellent yields with the formation of only water as a byproduct. A two-step asymmetric synthesis of (*S*)-2-phenylpiperidine was also achieved using (*R*)-1-phenylethylamine as a starting primary amine.

N-Heterocyclic compounds have attracted considerable attention owing to their functionality in pharmaceutical chemistry, material chemistry, and synthetic organic chemistry.[1] In particular, pyrrolidine, piperidine, and morpholine derivatives are present in a large class of biologically active natural products.[2] For the past several decades, much effort has been devoted to develop an efficient method for the synthesis of 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 rapidly disclosed and reviewed.[4] From an environmental point of view, *N*-heterocyclization of primary amines with diols should be another attractive method because an *N*-heterocyclic product can be obtained from easily available starting materials in one step without generation of harmful byproducts (generating only H_2O as a byproduct) (eq 1). Although some ruthenium-catalyzed systems for *N*-heterocyclization of primary amines with diols have been reported,[5] most of these systems require high reaction temperature (>150 °C), and applicable substrates are rather restricted. Moreover, asym-



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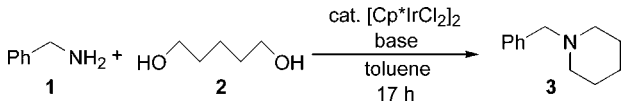
metric synthesis by these catalytic systems has never been studied.

We are currently studying the catalytic activity of iridium complexes bearing pentamethylcyclopentadienyl (Cp*) ligands toward hydrogen-transfer reactions[6,7] and have reported intra- and intermolecular *N*-alkylation of amines with alcohols.[6b,c] In this paper, we wish to report a new efficient system for the synthesis of a variety of *N*-heterocyclic compounds from primary amines and diols catalyzed by a Cp*Ir complex under relatively mild conditions (at 90−110 °C) and its application to the asymmetric synthesis of (*S*)-2-phenylpiperidine.

First, we investigated Cp*Ir-catalyzed *N*-heterocyclization of benzylamine (**1**) with 1,5-pentanediol (**2**) under various conditions. The reactions were performed in the presence of $[Cp^*IrCl_2]_2$ as catalyst and several bases in toluene solvent. The results are summarized in Table 1. When a solution of

Table 1. Synthesis of *N*-Benzylpiperidine (**3**) by the Reaction of Benzylamine (**1**) and 1,5-Pentanediol (**2**) under Various Conditions[a]



1 2 3

entry	**1**/**2**	base	*T* (°C)	yield[b] (%)
1	1.5:1.0	none	110	28
2	1.5:1.0	$NaHCO_3$	110	98
3[c]	1.5:1.0	Na_2CO_3	110	93
4	1.5:1.0	NaOAc	110	96
5	1.5:1.0	$KHCO_3$	110	96
6	1.5:1.0	K_2CO_3	110	80
7	1.5:1.0	Li_2CO_3	110	62
8	1.5:1.0	$NaHCO_3$	90	99
9	1.0:1.0	$NaHCO_3$	90	84

[a] The reaction was carried out at 90 or 110 °C with **1** (2.0 or 3.0 mmol), **2** (2.0 mmol), $[Cp^*IrCl_2]_2$ (0.010 mmol, 1.0% Ir), and base (0.020 mmol, 1.0%) in toluene (1 mL). [b] Determined by GC. [c] $[Cp^*IrCl_2]_2$ (0.0050 mmol, 0.50% Ir) and Na_2CO_3 (0.010 mmol, 0.50%) were used as catalysts.

1 (3.0 mmol), **2** (2.0 mmol), and $[Cp^*IrCl_2]_2$ (0.010 mmol, 1.0% Ir based on diol **2**) in toluene (1.0 mL) was stirred at 110 °C for 17 h, *N*-benzylpiperidine (**3**) was formed in 28% yield (entry 1). The reaction was considerably accelerated by the addition of base (entries 2−7). When the reaction was performed in the presence of $NaHCO_3$ (0.020 mmol, 1.0% based on diol **2**), **3** was formed 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 not as effective (entries 6 and 7). The yield of **3** was excellent even in the reaction at 90 °C (entry 8). Employment of a slight excess of **1** (1.5 equiv) was essential to obtain an excellent result; reaction of **1** and **2** in a 1:1 ratio gave **3** in 84% yield (entry 9).

On the basis of these results, we examined the *N*-heterocyclization of benzylamine with a variety of diols under the optimized conditions. The results are summarized in Table 2. The reactions of benzylamine with 1,4-butanediol, 1,5-pentanediol, and 1,6-hexanediol gave five-, six-, and seven-membered cyclic amines in good to excellent yields, respectively (entries 1−3). Diols with substituents on the methylene chain could be also used as substrates to give substituted cyclic amines (entries 4−7). In the reaction of benzylamine with 2,5-hexanediol, *N*-benzyl-2,5-dimethylpyrrolidine was isolated in 94% yield with a cis/trans ratio of 73:27 (entry 4). The reactions with benzo-fused diols, 1,2-benzenedimethanol and 2-(2-hydroxyethyl)benzyl alcohol, gave *N*-benzylisoindoline and *N*-benzyl-1,2,3,4-tetrahydroisoquinoline, respectively (entries 8 and 9). In the reaction of 1,2-benzenedimethanol, addition of base ($NaHCO_3$) was not effective (entry 8). The morpholine skeleton could be synthesized in good yield (76%) by use of diethylene glycol as a substrate (entry 10). Although aniline could be used as the starting primary amine, higher catalyst loading (5.0% Ir) and a higher reaction temperature were required to obtain a good yield. The reaction of aniline with 1,4-butanediol gave *N*-phenylpyrrolidine in 70% yield (entry 11). Introduction of electron-donating substituents at the phenyl ring of aniline considerably improved the yield (entry 12). Other primary amines, such as phenethylamine and octylamine, could be also used as starting primary amines (entries 13 and 14).

The asymmetric synthesis of piperidines has attracted considerable attention owing to their importance as natural and synthetic biologically active compounds. In many cases, asymmetric synthesis of 2-substituted piperidines can be achieved by noncatalytic multistep reactions.[8,9] In this context, we next examined the asymmetric synthesis of 2-substituted piperidine by the present catalytic system. When the reaction of (*R*)-1-phenylethylamine (99% ee) and 1-phen-

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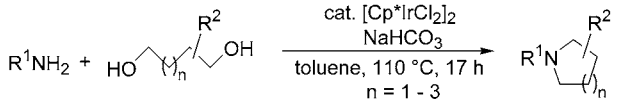
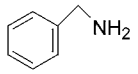
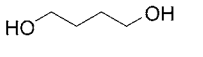
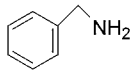
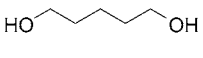
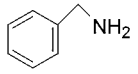
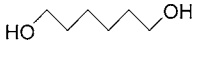
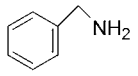
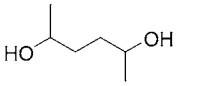
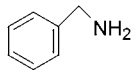
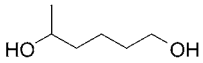
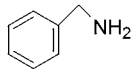
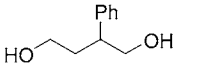
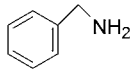
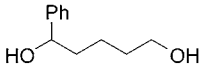
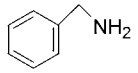
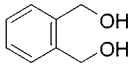
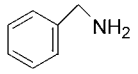
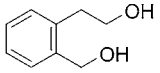
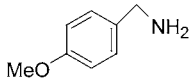
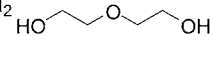
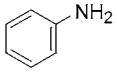
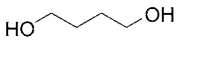
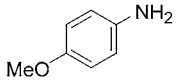
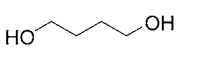
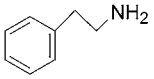
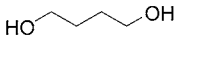
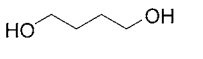
Table 2. Cp*Ir Complex-Catalyzed *N*-Heterocyclization of Primary Amines with a Variety of Diols[a]

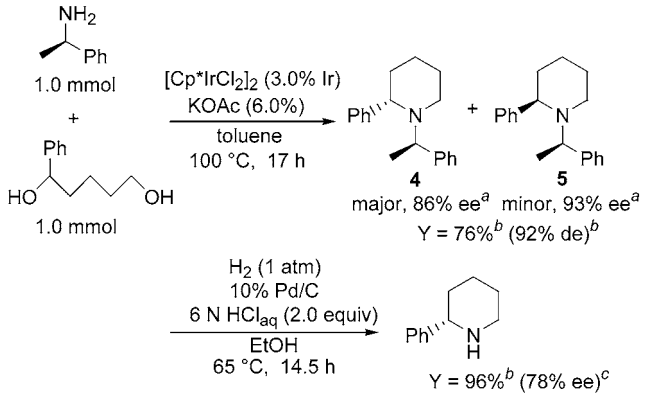


entry	amine	diol	cat. (%Ir)	yield[b](%)
1			1.0	72
2[c]			1.0	91
3[d]			2.0	73
4[e]			1.0	94[f]
5			1.0	79
6			2.0	90
7			4.0	78[g]
8[h,i]			2.0	63
9			2.0	76
10			2.0	76
11[j,k]			5.0	70
12[j]			5.0	90
13			4.0	73
14	n-$C_8H_{17}NH_2$		4.0	81[g]

[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 number of equivalents as the iridium catalyst) in toluene (1 mL). [b] Isolated yield. [c] Reaction temperature was 90 °C. [d] Toluene (3 mL) was used. [e] Na_2CO_3 was used as base. [f] Cis/trans = 73:27 (determined by ^1H NMR analysis). [g] GC yield. [h] Amine (2.0 mmol) was used. [i] Base was not added. [j] Reaction temperature was 130 °C. [k] Reaction time was 40 h.

yl-1,5-pentanediol was carried out in the presence of a catalytic amount of $[Cp^*IrCl_2]_2$ (3.0% Ir) and KOAc (6.0%) in toluene at 100 °C for 17 h, a diastereoisomeric mixture of *N*-(1-phenylethyl)-2-phenylpiperidines **4** and **5** was formed

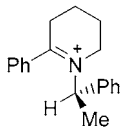
Scheme 1. Asymmetric Synthesis of (*S*)-2-Phenylpiperidine



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

in 76% yield with 92% de (Scheme 1).[10] The enantiomeric excesses of **4** and **5** were 86% ee and 93% ee, respectively.[11] Hydrogenation of this mixture with Pd/C catalyst gave (*S*)-2-phenylpiperidine[12] of 78% ee in a yield of 96%.

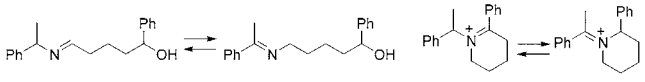
In previous papers, we have presented a mechanism for intermolecular *N*-alkylation of primary amines with primary and secondary alcohols[6c] and intramolecular *N*-alkylation of amino alcohols[6b] catalyzed by a Cp*Ir complex. On the basis of those, a possible mechanism for *N*-heterocyclization of primary amines with diols is described in Scheme 2. *N*-Alkylation of primary amine **1** with one of the alcohol moiety of diol **2** would proceed to afford amino alcohol **6** as an intermediate by the catalytic cycle A. Successively, **6** would be cyclized intramolecularly to give the product **3** via an iminium intermediate in cycle B in a similar manner. The base ($NaHCO_3$) would stimulate the formation of iridium alkoxide species by trapping hydrogen chloride generated at the first step of the reaction.[6a−c] In the case of the reaction of (*R*)-1-phenylethylamine with 1-phenyl-1,5-pentanediol, the iminium intermediate would be **7**. Addition of iridium hydride to the C═N bond in **7** would proceed diastereoselectively to give the product.



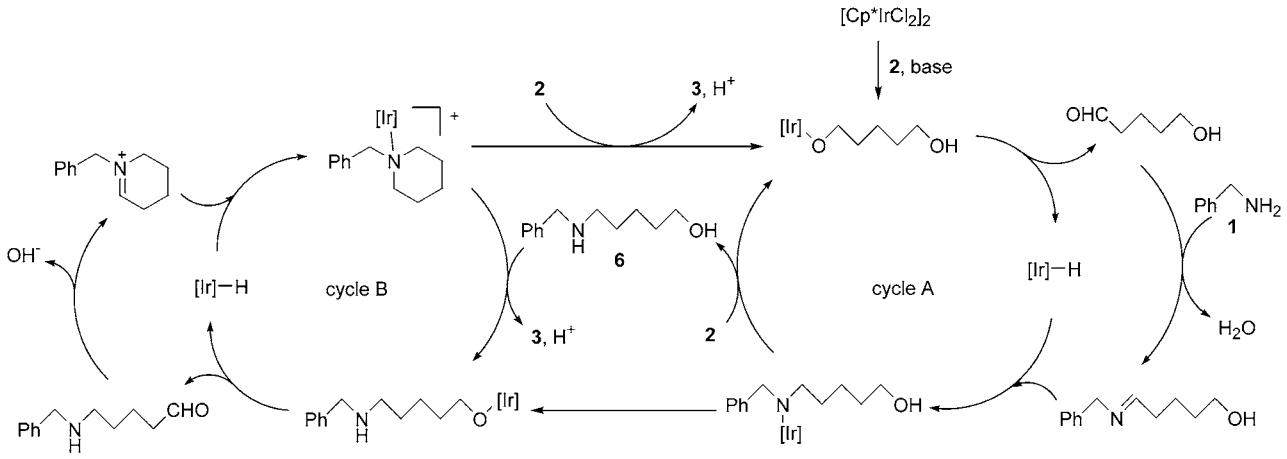
7

(10) 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.

(11) A small extent of racemization of auxiliary 1-phenylethyl group also occurred. This racemization would be probably due to isomerization of imine or iminium intermediate.



Scheme 2. Possible Mechanism



In summary, we have shown a new efficient method for the *N*-heterocyclization of primary amines with diols catalyzed by a Cp*Ir complex. The two-step asymmetric synthesis of (*S*)-2-phenylpiperidine was also achieved by use of (*R*)-1-phenylethylamine as a starting primary amine.

(12) The absolute configuration of the product was determined by comparison of the optical rotation with the literature data. See the Supporting Information.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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