Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2687–2690

TETRAHEDRON
LETTERS

N-Alkylation of amines with alcohols catalyzed by a Cp*Ir complex

Ken-ichi Fujita,[a,*] Zhenzi Li,[b] Naohiro Ozeki[b] and Ryohei Yamaguchi[b,*]

[a]*Department of Natural Resources, Graduate School of Global Environmental Studies, Kyoto University, Kyoto 606-8501, Japan*
[b]*Graduate School of Human and Environmental Studies, Kyoto University, Kyoto 606-8501, Japan*

Received 16 December 2002; revised 3 February 2003; accepted 6 February 2003

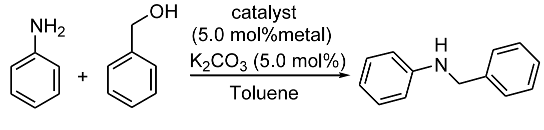
Abstract—A new effective catalytic system consisting of $[Cp^*IrCl_2]_2/K_2CO_3$ (Cp* = pentamethylcyclopentadienyl) for the *N*-alkylation of primary amines with alcohols has been developed. As an example, the reaction of aniline with benzyl alcohol in the presence of $[Cp^*IrCl_2]_2$ (5.0 mol%Ir) and K_2CO_3 (5.0 mol%) in toluene at 110°C for 17 h gave benzylaniline in an isolated yield of 88%.

The alkylation of primary amines to secondary or tertiary amines is one of the most fundamental and important reactions in synthetic organic chemistry. The *N*-alkylation with alkyl halides is a well-known method,[1] but use of alkyl halides is undesirable from an environmental point of view, and it generates wasteful salts as byproducts. The reductive amination of aldehydes and ketones is another well-known method, which has been developed as the most useful tool in the synthesis of various amines.[2] However, this method requires the use of strong reducing reagents or dangerous hydrogen gas and is not always selective for monoalkylation of primary amines.

The *N*-alkylation of amines with alcohols is an attractive method because (1) it does not generate harmful byproducts (only H_2O as byproduct); (2) alcohols are more readily available than corresponding halides or carbonyl compounds in many cases. Although some catalytic systems for *N*-alkylation of amines with alcohols have been studied with ruthenium[3] and rhodium catalysts,[4] most of these systems require high reaction temperature (>150°C), and applicable amines and alcohols are very restricted. During the course of our investigation on the chemistry of pentamethylcyclopentadienyl (Cp*) iridium complexes,[5] we found a catalytic activity of $[Cp^*IrCl_2]_2$ toward hydrogen-transfer reactions between organic molecules,[6] and reported Oppenauer-type oxidation of alcohols[5a] and oxidative *N*-heterocyclization of amino alcohols,[5b] which prompted us to study *N*-alkylation of amines with alcohols. In this paper, we wish to report a Cp*Ir complex-catalyzed *N*-alkylation of primary amines with alcohols.

First, we investigated Cp*Ir-catalyzed *N*-alkylation of aniline with benzyl alcohol under various conditions. The reactions were performed in the presence of several catalysts and base (K_2CO_3) in toluene as a solvent. The results are summarized in Table 1. In each reaction,

Table 1. Catalytic *N*-alkylation of aniline with benzyl alcohol under various conditions[a]



Entry	Catalyst	Temp. (°C)	Time (h)	Yield (%)[b]
1	$[Cp^*IrCl_2]_2$	110	17	100
2[c]	$[Cp^*IrCl_2]_2$	110	17	30
3	$[Cp^*IrCl_2]_2$	90	17	52
4	$[Cp^*IrCl_2]_2$	90	40	81
5	$[Cp^*IrHCl]_2$	110	17	55
6	$[IrCl(cod)]_2$	110	17	3
7	$[Cp^*RhCl_2]_2$	110	17	43

[a] The reaction was carried out with aniline (1.0 mmol), benzyl alcohol (1.0 mmol), catalyst (5.0 mol%metal), and K_2CO_3 (0.050 mmol) in toluene (0.5 mL).
[b] Determined by GC.
[c] The reaction was carried out without K_2CO_3.

Keywords: iridium catalyst; *N*-alkylation; hydrogen transfer; amine; alcohol.

* Corresponding author. Tel.: +81-75-753-6827; fax: +81-75-753-6634; e-mail: fujitak@kagaku.mbox.media.kyoto-u.ac.jp

0040-4039/03/$ - see front matter

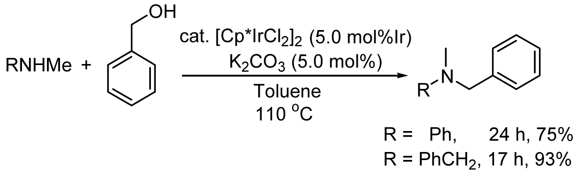
doi:10.1016/S0040-4039(03)00371-X

mono-alkylated benzylaniline was formed as a single product; no formation of di-alkylated dibenzylaniline was observed. Benzylaniline was formed quantitatively when the reaction was performed at 110°C for 17 h in the presence of [Cp*IrCl$_2$]$_2$ (5.0 mol%Ir) and K$_2$CO$_3$ (5.0 mol%) (entry 1). The yield of benzylaniline considerably decreased when the reaction was performed in the absence of K$_2$CO$_3$ (entry 2). The reaction also proceeded at lower temperature (90°C), but longer reaction time was necessary to obtain a satisfactory result (entries 3 and 4). Other iridium catalysts [Cp*IrHCl]$_2$, [IrCl(cod)]$_2$ (cod = 1,5-cyclooctadiene), or rhodium catalyst [Cp*RhCl$_2$]$_2$, showed lower activity than [Cp*IrCl$_2$]$_2$ (entries 5–7).

Results obtained from *N*-alkylation of anilines with various primary and secondary alcohols are summarized in Table 2.[7] The present *N*-alkylation system could be applied to a variety of primary and secondary alcohols. *N*-Alkylation of aniline with benzyl alcohols bearing electron-donating (Me, OMe) and electron-withdrawing (Cl, NO$_2$) substituents at the aromatic ring proceeded to give benzylaniline derivatives in good to excellent yields (entries 2–7). Other primary alcohols, β-phenethyl alcohol or 1-octanol were also applicable to this reaction (entries 8 and 9).[8] When the reaction of aniline with 1-octanol was performed using an excess amount of 1-octanol (2.6 equiv.) for 40 h, the di-alkylated product was obtained in a yield of 36% as well as the mono-alkylated product (63%) (entry 10), indicating that the second alkylation is sufficiently slow. The reaction of aniline with secondary alcohols proceeded in good to excellent yields (entries 11–13). The reaction of substituted anilines with benzyl alcohol also proceeded satisfactorily (entries 14 and 15).

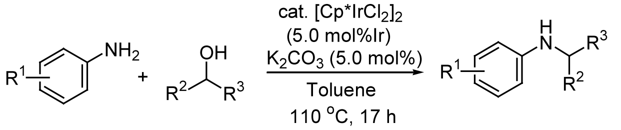
We next examined the *N*-alkylation of other primary amines. The results are summarized in Table 3.[7] *N*-alkylation of benzylamine with several primary and secondary alcohol proceeded in good yields (entries 1–6).[8] When the reaction of benzylamine with 1-octanol was performed using an excess amount of 1-octanol (2.6 equiv.) for 40 h, dioctylbenzylamine was obtained as a major product (80%) (entry 4), indicating that di-alkylation of benzylamine is easier than that of aniline. Other primary amines, such as β-phenethyl- and octylamine were also alkylated by the present catalytic system (entries 7–9).

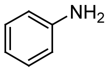
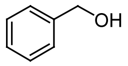
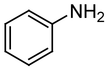
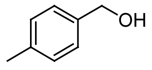
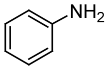
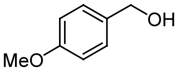
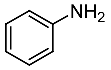
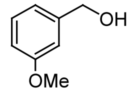
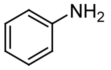
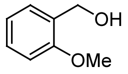
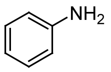
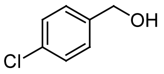
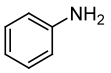
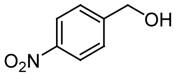
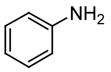
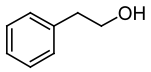
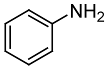
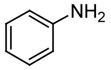
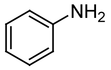
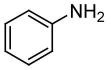
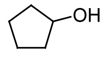
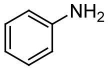
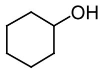
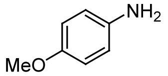
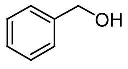
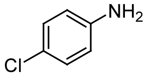
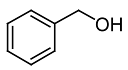
N-Alkylation of secondary amines was also examined. Reactions of *N*-methylaniline and *N*-methylbenzylamine with benzyl alcohol proceeded to give corresponding tertiary amines in good yields (Eq. (1)).



(1)

Table 2. Cp*Ir catalyzed *N*-alkylation of anilines with various primary and secondary alcohols[a]

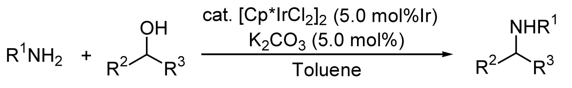


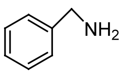
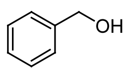
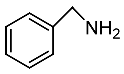
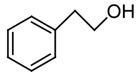
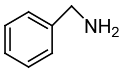
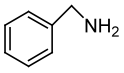
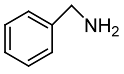
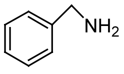
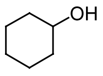
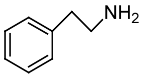
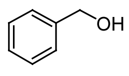
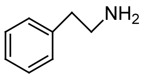
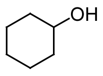
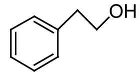
entry	amine	alcohol	yield (%)[b]
1			88(100)
2			92
3			95
4			87
5			95
6			83
7[c]			86
8[d]			90
9		1-octanol	79
10[e]		1-octanol	63+36[f]
11[c]		2-octanol	69
12			85
13			92
14			93
15			95

[a] The reaction was carried out at 110 °C for 17 h with anilines (1.0 mmol), alcohols (1.0 mmol), [Cp*IrCl$_2$]$_2$ (5.0 mol%Ir), and K$_2$CO$_3$ (0.050 mmol) in toluene (0.5 mL). [b] Isolated yield. The values in parentheses are GC yield. [c] Reaction time was 40 h. [d] Reaction time was 24 h. [e] The reaction was carried out at 110 °C for 40 h with aniline (1.0 mmol), 1-octanol (2.6 mmol), [Cp*IrCl$_2$]$_2$ (5.0 mol%Ir), and K$_2$CO$_3$ (0.050 mmol) in toluene (0.5 mL). [f] Octylaniline (63%) and dioctylaniline (36%) were isolated.

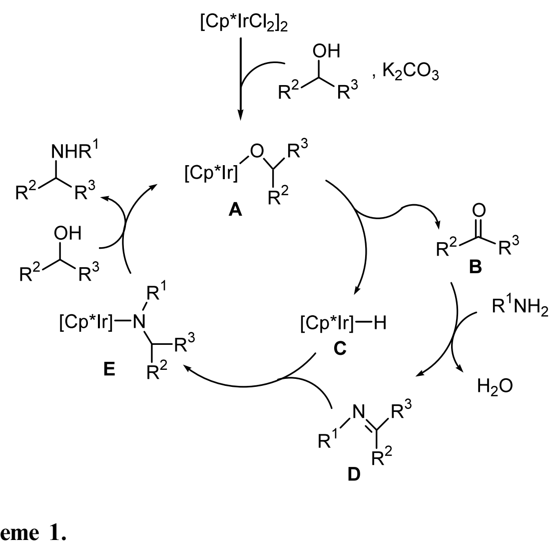
Although the mechanism for the present reaction is not completely clear yet, a possible mechanism is shown in Scheme 1. The first step of the reaction would involve catalytic oxidation of an alcohol to the corresponding

Table 3. Cp*Ir catalyzed *N*-alkylation of primary amines with various alcohols[a]



entry	amine	alcohol	temp. (°C)	time (h)	yield (%)[b]
1			110	17	67
2			90	17	74
3		1-octanol	90	17	88
4[c]		1-octanol	110	40	80[d]
5		2-octanol	110	24	82
6			90	17	83
7			110	17	77
8			110	17	72
9	octylamine		90	48	61

[a]The reaction was carried out with amines (1.0 mmol), alcohols (1.0 mmol), $[Cp^*IrCl_2]_2$ (5.0 mol%Ir), and K_2CO_3 (0.050 mmol) in toluene (0.5 mL). [b]Isolated yield. [c]The reaction was carried out with benzylamine (1.0 mmol), 1-octanol (2.6 mmol), $[Cp^*IrCl_2]_2$ (5.0 mol%Ir), and K_2CO_3 (0.050 mmol) in toluene (0.5 mL). [d]Dioctylbenzylamine (80%) was isolated.



Scheme 1.

carbonyl compound **B**, with the generation of a hydrido iridium species **C**. We have already revealed the catalytic activity of $[Cp^*IrCl_2]_2$ toward oxidation of primary and secondary alcohols to the corresponding carbonyl compounds.[5a] The carbonyl intermediate **B** would readily react with primary amine to afford an imine **D**. Then addition of the hydrido iridium **C** to a C=N bond of **D** would occur to give an amido iridium species **E**. The species **E** would react with an alcohol to give product and regenerate the catalytically active alkoxo iridium complex **A**. The base (K_2CO_3) would stimulate the first oxidation step as we have already reported.[5a]

In summary, we have developed a new effective catalytic system for *N*-alkylation of primary amines with alcohols, which is applicable to a wide variety of amines and alcohols. It should be noted that the present *N*-alkylation proceeds with high selectivity for mono-alkylation under milder condition (90–110°C) compared to the known catalytic systems with ruthenium[3] and rhodium[4] catalysts, which are applicable to a limited kind of amines and alcohols and/or require high reaction temperature (>150°C).

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (No. 14550806). We thank Mr. T. Fujii for his valuable technical assistance.

References

1. Smith, M. B.; March, J. *Advanced Organic Chemistry*; 5th ed.; Wiley: New York, 2001; p. 499.
2. (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*; 5th ed.; Wiley: New York, 2001; p. 1187; (b) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849 and references cited therein.
3. (a) Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667; (b) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229; (c) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359; (d) Bitsi, G.; Schleiffer, E.; Antoni, F.; Jenner, G. *J. Organomet. Chem.* **1989**, *373*, 343; (e) Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, *61*, 4214.
4. Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611.
5. (a) Fujita, K.; Furukawa, S.; Yamaguchi, R. *J. Organomet. Chem.* **2002**, *649*, 289; (b) Fujita, K.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2002**, *4*, 2691.
6. Several groups have reported hydrogen transfer reactions catalyzed by Cp*Ir complexes: (a) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199; (b) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186; (c) Ogo, S.; Makihara, N.; Watanabe, Y. *Organometallics* **1999**, *18*, 5470; (d) Ogo, S.; Makihara, N.; Kaneko, Y.; Watanabe, Y. *Organometallics* **2001**, *20*, 4903; (e) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *Org. Lett.* **2002**, *4*, 2361.

7. Typical procedure: In a heavy-walled glass reactor under an atmosphere of argon were suspended $[Cp^*IrCl_2]_2$ (0.025 mmol) and K_2CO_3 (0.050 mmol) in toluene (0.5 mL). Then amine (1.0 mmol) and alcohol (1.0 mmol) were added, and the mixture was stirred at 110°C for 17 h in the sealed reactor. The products were isolated by silica gel column chromatography. The products were identified by NMR analysis.
8. *N*-Methylation by methanol was unsuccessful. *N*-Methylation by methanol is known to be considerably difficult. Huh, K.-T.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449.