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Selective Synthesis of Secondary and Tertiary Amines by Cp*Iridium-Catalyzed Multialkylation of Ammonium Salts with Alcohols

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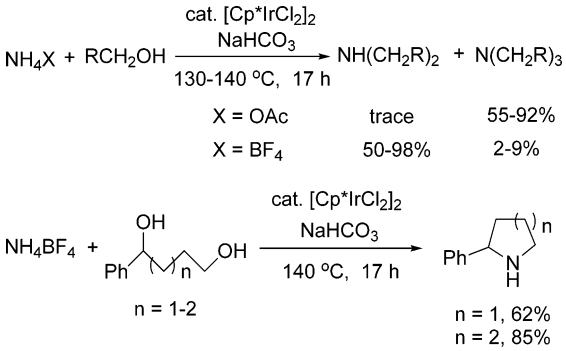
ABSTRACT



The efficient selective synthesis of secondary and tertiary amines has been achieved by means of Cp*Ir-catalyzed multialkylation of ammonium salts with alcohols without solvent: the reactions of ammonium acetate with alcohols gave tertiary amines exclusively, while those of ammonium tetrafluoroborate afforded secondary amines selectively. Using this method, secondary 5- and 6-membered cyclic amines were synthesized from ammonium tetrafluoroborate and diols in one pot.

Acyclic and cyclic amines have been of great importance in many fields of organic chemistry, including biological, medicinal, agrochemical, dyes, and material chemistry. Thus, the development of versatile and efficient methods for the synthesis of amines has attracted much attention and is still occupying an active area of research.[1]

Ammonia or simple salts are attractive nitrogen sources for the synthesis of amines. Recently, there have been some reports on homogeneous catalytic systems using it as the substrate:[2] palladium-catalyzed telomerization of butadiene and ammonia giving primary alkylamines,[3] rhodium- and iridium-catalyzed reductive aminations of carbonyl compounds with ammonium formate and ammonia affording primary alkylamines,[4] and copper- and palladium-catalyzed coupling reactions of ammonia with aryl hailides producing arylamines.[5] While most of them described the synthesis of primary alkyl- and arylamines, Buchwald et al. reported very recently selective palladium-catalyzed arylation of ammonia affording di- and triarylamines.[5c] However, to the best of

(1) For example: (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785. (b) Chiappe, C.; Pieraccini, D. *Green Chem.* **2003**, *5*, 193.

(2) Earlier review concerning the use of ammonia in catalytic reactions: Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1.

(3) Prinz, T.; Driessen-Hölscher, B. *Chem. Eur. J.* **1999**, *5*, 2069.

(4) (a) Kitamura, M.; Lee, D.; Hayashi, S.; Tanaka, S.; Yoshimura, M. *J. Org. Chem.* **2002**, *67*, 8685. (b) Gross, T.; Seayad, A. M.; Ahmad, M.; Beller, M. *Org. Lett.* **2002**, *4*, 2055. (c) Ogo, S.; Makihara, N.; Kaneko, Y.; Watanabe, Y. *Organometallics* **2001**, *20*, 4903.

(5) (a) Lang, F.; Zewge, D.; Houpis, I. N.; Volante, R. P. *Tetrahedron Lett.* **2001**, *42*, 3251. (b) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028. (c) Surry, D. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 10354 and references cited therein.

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our knowledge, there has been no report on selective synthesis of di- and trialkylamines from ammonia or its simple salts.

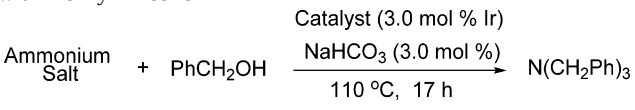
We have reported an atom-economical catalytic system for the synthesis of secondary and tertiary amines by the N-alkylation of primary and secondary amines with alcohols catalyzed by a Cp*Ir complex,[6] in which the high catalytic performance of Cp*Ir complexes for hydrogen transfer reactions is essential.[7] Since the utilization of ammonia or its simple salts as nitrogen sources has been one of the important objectives in catalytic organic chemistry as mentioned above, we report here an efficient selective synthesis of secondary and tertiary alkylamines by the Cp*Ir complex-catalyzed multialkylation of ammonium salts with primary and secondary alcohols without solvent.

We started to investigate the N-alkylation of a variety of ammonium salts with alcohols because ammonium salts are more easily and safely handled than ammonia itself (Table 1). When the reaction of ammonium chloride with benzyl alcohol (3 equiv) in the presence of $[Cp^*IrCl_2]_2$ (3.0 mol % Ir) was carried out at 110 °C for 17 h without solvent, tribenzylamine was obtained in 13% yield (entry 1, Table 1). However, we have found that use of ammonium acetate greatly improved the yield to 72% (entry 2). The results of the reactions of other ammonium salts are summarized in Table 1. As is seen, ammonium salts of weak acids gave better results (entries 7 and 8). It is noted that ammonia itself gave rather poor yields (entries 13 and 14)[8] and that the reaction using an Ir(I) complex such as $[IrCl(cod)]_2$ resulted in no reaction (entry 4). The reactions using Ru catalysts[9] required a higher temperature (140 °C) but gave lower yields of the product (entries 5 and 6). The yields were improved when a slight excess (3.6 equiv) of benzyl alcohol and a higher temperature (130 °C) were employed (entry 15).

The results of the present catalytic trialkylation reactions of ammonium acetate with a variety of primary alcohols are shown in Table 2. In the case of benzylic alcohols, the yields were good to high, and several kinds of functional groups were unaffected (entries 1−9). In the case of aliphatic alcohols, 5 equiv of alcohols and a reaction temperature of 140 °C were needed to obtain good yields of the products (entries 10−13).

The present catalytic reactions would proceed through triple N-alkylations in which three elementary steps (dehydrogenation, imine or iminium ion formation, and hydrogenation) are involved. Based on the proposed mechanism for

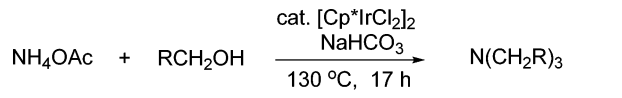
Table 1. Cp*Ir-Catalyzed Trialkylation of Ammonium Salts with Benzyl Alcohol[a]

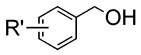
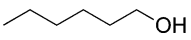
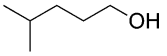
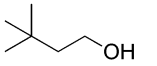
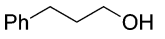


entry	catalyst	ammonium salt	yield[b] (%)
1	$[Cp^*IrCl_2]_2$	NH_4Cl	13
2	$[Cp^*IrCl_2]_2$	NH_4OAc	72
3	none	NH_4OAc	0
4	$[Ir(cod)Cl]_2$	NH_4OAc	0
5	$RuCl_2(PPh_3)_3$	NH_4OAc	0 (45)[c]
6	$RuH_2(PPh_3)_4$	NH_4OAc	0 (16)[c]
7	$[Cp^*IrCl_2]_2$	NH_4HCO_3	43
8	$[Cp^*IrCl_2]_2$	$(NH_4)_2CO_3$	66
9	$[Cp^*IrCl_2]_2$	NH_4NO_3	31
10	$[Cp^*IrCl_2]_2$	$(NH_4)_2SO_4$	3
11	$[Cp^*IrCl_2]_2$	$(NH_4)H_2PO_4$	4
12	$[Cp^*IrCl_2]_2$	$(NH_4)_2HPO_4$	20
13	$[Cp^*IrCl_2]_2$	NH_3 (aq)	10
14	$[Cp^*IrCl_2]_2$	NH_3 (dioxane)	0
15[d]	$[Cp^*IrCl_2]_2$	NH_4OAc	87

[a] The reactions were carried out with ammonium salt (1.0 mmol) and benzyl alcohol (3.0 mmol). [b] GC yield. [c] The yield of the reaction conducted at 140 °C is in parentheses. [d] The reaction was carried out with NH_4OAc (1.0 mmol), $PhCH_2OH$ (3.6 mmol), $[Cp^*IrCl_2]_2$ (0.5 mol % Ir), and $NaHCO_3$ (1.0 mol %) at 130 °C for 17 h.

Table 2. Cp*Ir-Catalyzed Trialkylation of NH_4OAc with Various Primary Alcohols Affording Trialkylamines[a]



entry	alcohol	$[Cp^*IrCl_2]_2$ (mol % Ir)	$NaHCO_3$ (mol %)	yield[b] (%)
				
1	R' = 4-Me	3.0	6.0	92
2	R' = 4-OMe	1.0	2.0	85
3	R' = 4-Cl	3.0	6.0	86
4[c]	R' = 4-Br	3.0	6.0	77
5	R' = 3-Br	3.0	6.0	89
6	R' = 2-Br	5.0	10	71
7	R' = 4-CF_3	3.0	6.0	84
8	R' = 4-CO_2Me	3.0	6.0	70
9[c]	R' = 4-Ph	3.0	6.0	83
10[d]		3.0	30	65[e]
11[d]		5.0	30	55
12[d]		5.0	30	66
13[d]		5.0	30	73

[a] The reactions were carried out with ammonium salt (1.0 mmol) and alcohol (3.6 mmol). [b] Isolated yield. [c] Toluene (1.0 mL) was added as solvent. [d] The reactions were conducted with 5.0 mmol of alcohols at higher temperature (140 °C). [e] GC yield.

(6) Fujita, K.; Li, Z.; Ozeki, N.; Yamaguchi, R. *Tetrahedron Lett.* **2003**, *44*, 2687.

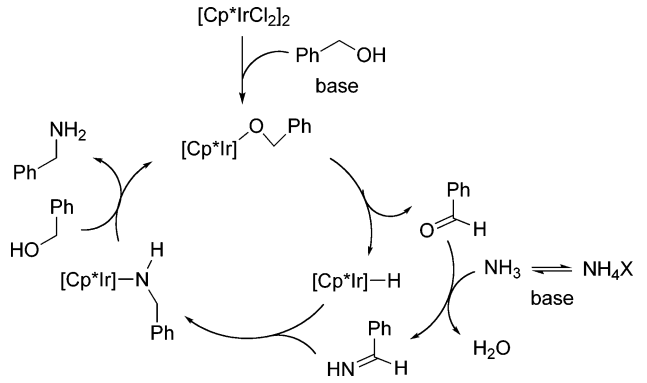
(7) Fujita, K.; Yamaguchi, R. *Synlett* **2005**, 560.

(8) The poor results might be attributed to the diluted conditions.

(9) (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.

Cp*Ir-catalyzed N-alkylation of amines,[6,7] a possible mechanism for the first monoalkylation cycle is depicted in Scheme 1.[10−12] Thus, it is apparent that each of the

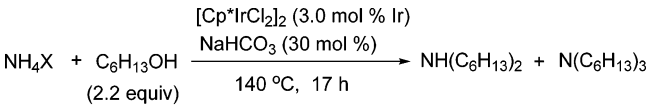
Scheme 1



N-alkylation reactions must take place very smoothly to obtain the good to high yields of products.

As is shown above, ammonium acetate is a good ammonia source for the triple N-alkylations affording tertiary amines. However, it is very difficult to obtain a secondary amine even using 2 equiv of alcohol: the reaction of ammonium acetate with 1-hexanol (2.2 equiv) gave trihexylamine in 35% yield along with a trace amount of dihexylamine (Scheme 2). On the other hand, we have found that the reaction of

Scheme 2

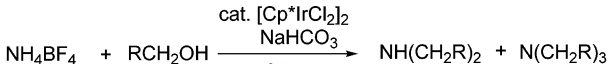


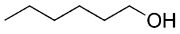
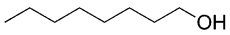
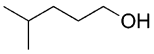
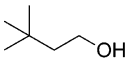
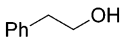
X = OAc	Y = trace	Y = 35%
X = OCOPh	Y = 42%	Y = 12%
X = $OCOCF_3$	Y = 21%	Y = 2%
X = BF_4	Y = 75%	Y = 9%

ammonium benzoate with 1-hexanol (2.2 equiv) gave dihexylamine (42%) as a major product and a small amount of trihexylamine (12%). Thus, after several experiments using other ammonium salts,[13] it is remarkable that the reaction of ammonium tetrafluoroborate resulted in such high selectivity and yield as shown in Scheme 2.

The reactions of ammonium tetrafluoroborate with other primary alcohols also gave secondary amines very selectively. The results are summarized in Table 3.

Table 3. Cp*Ir-Catalyzed Dialkylation of NH_4BF_4 with Various Primary Alcohols Affording Dialkylamines[a]

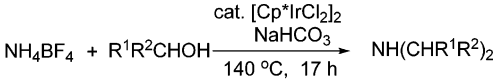


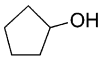
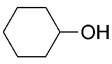
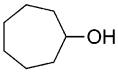
entry	alcohol	$[Cp^*IrCl_2]_2$ (mol % Ir)	$NH(CH_2R)_2$ yield (%)[b]	$N(CH_2R)_3$ yield (%)[b]
1		2.0	75	7
2		3.0	66	8
3		3.0	98	2
4		2.0	78	2
5		3.0	50	9

[a] The reactions were carried out with NH_4BF_4 (1.0 mmol), alcohol (2.2 mmol), and $NaHCO_3$ (30 mol %). [b] GC yield.

In the reactions with secondary alcohols, complete selectivity for the formation of secondary amines was observed probably due to steric hindrance. The results are summarized in Table 4.

Table 4. Cp*Ir-Catalyzed Dialkylation of NH_4BF_4 with Various Secondary Alcohols Affording Dialkylamines[a]



entry	alcohol	yield (%)[b]
1		74
2		86(97)
3		78
4	$C_6H_{13}CH(OH)CH_3$	54[c]
5	$PhCH(OH)CH_3$	77[d,e]

[a] The reaction was carried out with NH_4BF_4 (1.0 mmol), alcohol (3.0 mmol), $[Cp^*IrCl_2]_2$ (3.0 mol % Ir), and $NaHCO_3$ (30 mol %). [b] Isolated yield (GC yield in parentheses). [c] A mixture of diastereomers. [d] NH_4OAc was used instead of NH_4BF_4. [e] Meso/*dl* = 62:38 by ^1H NMR.

Furthermore, this catalytic system for facile formation of secondary amines can be extended to the one-pot synthesis

(10) In the present reaction, catalytic intermediates would be Ir(III) species. There are many examples of Cp*Ir-catalyzed hydrogen transfer reactions in which catalytic intermediates are trivalent iridium species. (a) Suzuki, T.; Yamada, T.; Watanabe, K.; Katoh, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2583. (b) Hanasaka, F.; Fujita, K.; Yamaguchi, R. *Organometallics* **2005**, *24*, 3422. (c) Ogo, S.; Makihara, N.; Watanabe, Y. *Organometallics* **1999**, *18*, 5470. (d) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1201.

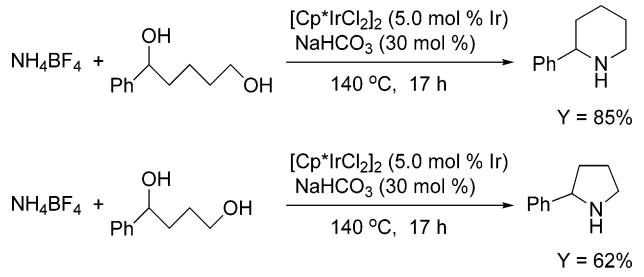
(11) According to a suggestion of one of the referees, we carried out the reactions using cationic Ir(III) complexes, such as $[Cp^*Ir(MeCN)_3](BF_4)_2$ and $[Cp^*Ir(MeCN)_3](PF_6)_2$, to give tribenzylamine in 57% and 21% yields, respectively. These results also support that Ir(III) complexes could be catalytically active species.

(12) We conducted the similar reaction of ammonium acetate with benzaldehyde (3 equiv) using 2-propanol (5 equiv) as hydrogen donor in the presence of $[Cp^*IrCl_2]_2$ (5 mol %) and $NaHCO_3$ (30 mol %) at 110 °C for 17 h to give tribenzylamine (21%) and dibenzylamine (15%), supporting the possible mechanism.

(13) The reactions of other ammonium salts such as NH_4PF_6 and $NH_4SO_3CF_3$ gave trace amount of the product.

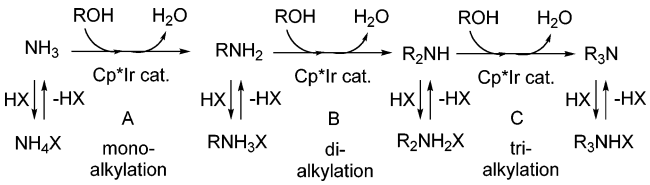
of cyclic amines from an ammonium salt and diols.[14] Thus, the reactions of ammonium tetrafluoroborate with 1-phenyl-1,5-pentanediol and 1-phenyl-1,4-butanediol afford 2-phenylpiperidine and 2-phenylpyrrolidine in 85% and 62% yields, respectively (Scheme 3).

Scheme 3



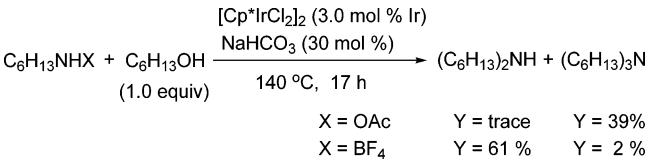
While the precise reason for the present selectivity has not been clear yet, we have assumed the following equilibriums between produced amines and their salts and that the N-alkylation could occur toward free amines (Scheme 4).

Scheme 4



According to the assumption, we have carried out the reactions of hexylammonium salts with 1-hexanol (1 equiv) under the similar conditions as above (Scheme 5). There-action of hexylammonium acetate with

Scheme 5



1-hexanol gave trihexylamine predominantly, indicating that the reaction did not stop at the dialkyaltion step B, probably due to relatively weak acidity of acetic acid. On the other hand, the same reaction of hexylammonium tetrafluorobofrate afforded dihexylamine selectively, demonstrating that the reaction did stop at step B, probably due to stronger acidity of tetrafluoroboric acid. Thus, acidity of a counter acid of an ammonium salt might be one of the factors responsible for the present selectivity.[15]

In summary, we have developed a new atom-economical catalytic system for the selective synthesis of secondary and tertiary amines by means of Cp*Ir-catalyzed multi-alkylation of ammonium salts with alcohols without solvent. Furthermore, this catalytic system can be extended to the efficient one-pot synthesis of cyclic amines from ammonium tetrafluoroborate and diols.

Acknowledgment. This work was supported by KAKENHI (No. 19550106).

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

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(14) We have reported the Cp*Ir-catalyzed synthesis of cyclic tertiary amines by the reaction of primary amines with diols. See: (a) Fujita, K.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525. (b) Fujita, K.; Enoki, Y.; Yamaguchi, R. *Org. Synth.* **2006**, *83*, 217.

(15) We have not succeeded in selective synthesis of primary amines yet.