

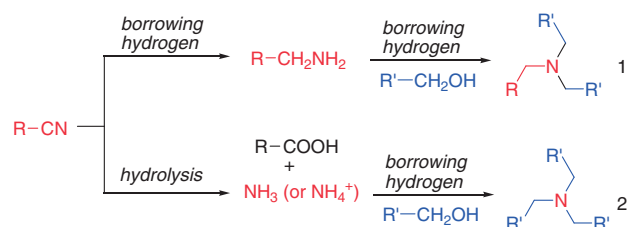
Ruthenium-catalyzed Formation of Tertiary Amines from Nitriles and Alcohols

Saiwen Liu, Ru Chen, and Guo-Jun Deng*

Key Laboratory of Environment-Friendly Chemistry and Applications of Ministry of Education,
College of Chemistry, Xiangtan University, Xiangtan 411105, P. R. China

(Received February 25, 2011; CL-110158; E-mail: gjdeng@xtu.edu.cn)

A ruthenium-catalyzed tertiary-amine formation was developed using the borrowing hydrogen strategy. Various tertiary amines were obtained efficiently from nitriles and primary alcohols. Two possible pathways were found for the tertiary-amine formation under $\text{RuCl}_3/\text{dppf}$ catalytic conditions. The nitriles mainly act as a nitrogen source in this kind of transformation.



Scheme 1. Possible pathways of nitrile reacting with alcohol.

Tertiary and secondary amines are of great importance as building blocks for pharmaceuticals, agrochemicals, dyes, and ligands.¹ A number of catalytic and noncatalytic procedures,² for example, 1) direct amination of amines with alkyl and aryl halides,³ 2) reductive amination of ketones and aldehydes,⁴ 3) hydroamination of unsaturated hydrocarbons with amines,⁵ and 4) direct C–H amination,⁶ have been developed for the synthesis of tertiary and secondary amines in the past decades. In recent years, there has been significant interest in the transition-metal-catalyzed alkylation of amines by alcohols as a more benign alternative to potentially genotoxic alkyl halides. Alcohols are cheap, stable, and commercially available organic compounds.⁷ Most alcohols are poorly electrophilic and not suitable as direct alkylating agents for amines. However, alcohols can be readily activated by oxidizing to aldehydes and used as direct alkylating agents. In a typical amination of alcohol with amine, the alcohol can be activated by the transfer of hydrogen to metal catalyst, generating an aldehyde, followed by in situ imine formation. Reduction of the imine by return of the hydrogen affords the tertiary or secondary amine. The overall process is termed as the “borrowing hydrogen” methodology (Williams et al.) or “hydrogen autotransfer” reaction (Yus et al.) and widely employed for C–C and C–N bond construction.⁸

The first homogeneous alkylation of amines by alcohols under harsh conditions was developed independently by Grigg and Watanabe,⁹ and several ruthenium¹⁰ and iridium¹¹ catalysts have been developed subsequently. Milder conditions have been employed by Yamaguchi and co-workers with $[\text{Cp}^*\text{IrCl}_2]$,¹² and by Beller¹³ and Williams¹⁴ with ruthenium and iridium. In recent years, the borrowing hydrogen methodology has been used in the synthesis of primary amines, secondary amines, tertiary amines, and *N*-alkylated sulfonamides in high yields under mild conditions.¹⁵ Amines, ammonia, ammonium salts, and even urea¹⁶ are used as the nitrogen sources in this kind of transformation.

Recently, we¹⁷ and others¹⁸ developed direct alkylation of nitroarenes with alcohols using the borrowing hydrogen methodology. We are also interested in employing this procedure for other unsaturated nitrogen-containing compounds such as nitriles. Nitriles are useful reagents and can be readily transferred into primary amines by reducing reagents, and can be hydrolyzed to carboxylic acids and ammonia or ammonium salts

in acidic or basic aqueous solutions. The amine formation from ammonium or ammonium salts is well developed recently.^{12b,14a} Therefore, we hypothesized that there are two possible pathways for the formation of tertiary amines when nitriles react with alcohols (Scheme 1): 1) nitrile is reduced to primary amine by hydrogen generated from the alcohol oxidation step, and the primary amine reacts with alcohol to form the “normal” tertiary amine via borrowing hydrogen (pathway 1), 2) nitrile is hydrolyzed to ammonia and reacted with alcohol to generate symmetric tertiary amine (pathway 2). In the second pathway, nitrile only acts as a nitrogen source. *Herein, we report a ruthenium-catalyzed tertiary-amine formation from nitriles and alcohols using borrowing hydrogen methodology.*

We began our investigation by examining the reaction of benzonitrile (**1a**) and 4-methoxybenzyl alcohol (**2a**) under various conditions using toluene as a solvent. As shown in Table 1, the choice of ligand was very important for this kind of reaction using $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ as catalyst, and the reaction, monitored by GC-MS, did not take place in the absence of ligand (Table 1, Entry 1). After screening several phosphine ligands, dppf [1,1'-bis(diphenylphosphino)ferrocene] was found to give the best result (Entry 6). Tris(4-methoxybenzyl)amine (**3a**) was obtained in 90% yield (via pathway 2) together with 7% *N*-benzylbis(4-methoxybenzyl)amine (**4a**) (via pathway 1). Ruthenium complexes such as $[\text{Ru}(\text{CO})\text{HCl}(\text{PPh}_3)_3]$ and $[\text{Ru}(\text{CO})(\text{H})_2(\text{PPh}_3)_3]$ were inefficient catalysts for tertiary-amine formation (Entries 7 and 8). $[\text{Ru}(\text{cod})\text{Cl}_2]/\text{dppf}$ was found to be efficient catalyst for tertiary-amine formation, albeit with lower selectivity (Entry 10). Good combination yield was obtained when the catalyst loading decreased to 2.5 mol% (Entry 11). Decreasing the amount of **2a** decreased the product yield (Entry 12). To our delight, excellent yield was observed when an equivalent of water was added (Entry 13). Under the optimized reaction conditions, the amine formation mainly took pathway 2 and symmetric amine was the major product. If we remove part of the water (mainly generated from the imine formation step) from the reaction system, the reaction might take pathway 1. To prove our deduction, molecular sieves were added to the reaction. Indeed, the yield of **4a** improved to 45% when 100 mg of molecular sieves was added (Entry 14).¹⁹

Table 1. Optimization of the reaction conditions^a

$$\text{Ph-CN} + \text{RCH}_2\text{OH} \longrightarrow \text{N}(\text{CH}_2\text{R})_3 + \text{PhCH}_2\text{N}(\text{CH}_2\text{R})_2$$

1a **2** **3** **4**

R = 4-MeOC₆H₄

Entry	Catalyst	Ligand	Product 3 Yield ^b /%	Product 4 Yield ^b /%
1	RuCl ₃ ·3H ₂ O	none	0	0
2	RuCl ₃ ·3H ₂ O	PPh ₃	9	8
3	RuCl ₃ ·3H ₂ O	dppp	0	0
4	RuCl ₃ ·3H ₂ O	dppe	0	0
5	RuCl ₃ ·3H ₂ O	dppb	0	0
6	RuCl₃·3H₂O	dppf	90	7
7	[Ru(CO)HCl(PPh ₃) ₃]		5	8
8	[Ru(CO)(H) ₂ (PPh ₃) ₃]		3	14
9	[Ru(acac) ₃]	dppf	15	8
10	[Ru(cod)Cl ₂]	dppf	57	38
11 ^c	RuCl ₃ ·3H ₂ O	dppf	65	16
12 ^d	RuCl ₃ ·3H ₂ O	dppf	50	14
13 ^e	RuCl ₃ ·3H ₂ O	dppf	89	6
14 ^f	RuCl ₃ ·3H ₂ O	dppf	20	45

^aConditions: **1a** (0.2 mmol), **2** (1.9 mmol), catalyst (5 mol %), ligand (10 mol %), toluene (0.1 mL), 150 °C, 16 h under argon unless otherwise noted. ^bGC-MS yield based on nitrile. ^cThe catalyst loading is 2.5 mol %. ^d0.8 mmol of **2** was used. ^e0.2 mmol water was added. ^f100 mg 4A molecular sieves was used.

Table 2. Various nitriles used as nitrogen source for tribenzylamine (**3b**) formation^a

$$\text{R-C}_6\text{H}_4\text{-CN} + \text{PhCH}_2\text{OH} \xrightarrow[\text{150 }^\circ\text{C, 16 h}]{\text{RuCl}_3\cdot 3\text{H}_2\text{O (5 mol \%), dppf (10 mol \%), toluene (0.1 mL)}} \text{PhCH}_2\text{N}(\text{CH}_2\text{Ph})_2$$

1 **2b** **3b**

Entry	Nitrile 1	Product 3b Yield ^b /%
1	1a (R = H)	87
2	1b (R = 4-methyl)	79
3	1c (R = 4-methoxy)	60
4	1d (R = 4-chloro)	85
5	1e (R = 4-acetyl)	78
6	1f (R = 2-methyl)	18
7	1g (R = 2-chloro)	81
8	1h (R = 3-nitro)	20

^aConditions: **1** (0.2 mmol), **2b** (1.9 mmol), under argon. ^bIsolated yield based on **1**. Only trace amount of **4** was observed in all cases.

Nitriles mainly act as a nitrogen source in the absence of molecular sieves. To find out the most effective nitrile as the nitrogen source for this kind of transformation, various nitriles were employed under the standard conditions with benzyl alcohol (Table 2). The use of benzonitrile (**1a**) proved to be the most effective, resulting in the formation of tribenzylamine (**3b**) in 87% yield (Entry 1).

The tertiary-amine forming reactions of benzonitrile with various primary alcohols were conducted under the optimized

Table 3. Reaction of benzonitrile with alcohols^a

Entry	Alcohol	Product	Yield ^b /%
1	MeO-C ₆ H ₄ -CH ₂ OH	2a (MeO-C ₆ H ₄ -CH ₂) ₃ N	3a 84
2	Ph-CH ₂ OH	2b (PhCH ₂) ₃ N	3b 87
3	-C ₆ H ₄ -CH ₂ OH	2c (-C ₆ H ₄ -CH ₂) ₃ N	3c 87
4	F-C ₆ H ₄ -CH ₂ OH	2d (F-C ₆ H ₄ -CH ₂) ₃ N	3d 90
5	Cl-C ₆ H ₄ -CH ₂ OH	2e (p-Cl-Ph-CH ₂) ₃ N + (p-Cl-Ph-CH ₂) ₂ N-Ph	3e 86 4e (3e:4e = 3:1)
6	Br-C ₆ H ₄ -CH ₂ OH	2f (Br-C ₆ H ₄ -CH ₂) ₃ N	3f 30
7	m-CH ₃ -C ₆ H ₄ -CH ₂ OH	2g (m-CH ₃ -C ₆ H ₄ -CH ₂) ₃ N	3g 42
8	Cl-C ₆ H ₄ -CH ₂ OH	2h (Cl-C ₆ H ₄ -CH ₂) ₃ N	3h trace
9	m-CH ₃ -C ₆ H ₄ -CH ₂ OH	2i (m-CH ₃ -C ₆ H ₄ -CH ₂) ₃ N	3i 46
10	Ph-CH ₂ CH ₂ OH	2j (Ph-CH ₂ -CH ₂) ₃ N + (Ph-CH ₂ -CH ₂) ₂ N-Ph	3j 78 4j (3j:4j = 3:1)
11	1-butanol	2k Ph-CH ₂ -N(C ₄ H ₉) ₂	4k 68
12	1-hexanol	2l Ph-CH ₂ -N(C ₆ H ₁₃) ₂	4l 60
13	1-octanol	2l Ph-CH ₂ -N(C ₈ H ₁₇) ₂	4m 78

^aConditions: **1a** (0.2 mmol), **2** (1.9 mmol), RuCl₃·3H₂O (5 mol %), dppf (10 mol %), toluene (0.1 mmol), 150 °C, 16 h under argon. ^bIsolated yields based on **1a**.

reaction conditions and the results are summarized in Table 3. The reactions with benzylic alcohols bearing electron-donating (methoxy and methyl groups) and electron-withdrawing substituents (fluoro and chloro) on the aromatic ring proceeded to give the desired products in good to excellent yields (Entries 1–5). The reaction yield decreased dramatically when 4-bromobenzyl alcohol was used as substrate (Entry 6). The position of substituent significantly affected the reaction yield. Moderated yield was achieved when 2-methylbenzyl alcohol was used (Entry 7). Only trace desired product was observed when 2-chlorobenzyl alcohol was used (Entry 8). To our delight, this reaction is not only suitable for benzyl alcohol and its derivatives. Phenethyl alcohol reacted with benzonitrile and gave the corresponding product in 78% total yield (Entry 10). Fatty alcohols such as 1-butanol, 1-hexanol, and 1-octanol were

capable of reacting with benzonitrile and gave tertiary amines (via pathway 1) as the major products in 68%, 60%, and 78% yields, respectively (Entries 11–13).²⁰

In summary, we have developed a ruthenium-catalyzed tertiary-amine forming reaction using nitriles and primary alcohols as starting materials. Nitriles mainly act as a nitrogen source. The reaction mechanism and synthetic application via pathway 1 are currently under investigation.

This work was supported by the National Natural Science Foundation of China (No. 20902076) and the “One Hundred Talent Project” of Hunan Province.

References and Notes

- 1 a) *The Chemistry of Amino, Nitroso, Nitro and Related Groups, Supplement F2*, ed. by S. Patai, John Wiley & Sons, Ltd., Chichester, **1996**. b) S. A. Lawrence, *Amines: Synthesis, Properties and Applications*, Cambridge University Press, Cambridge, **2004**.
- 2 a) D. M. Roundhill, *Chem. Rev.* **1992**, *92*, 1. b) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785.
- 3 For reviews, see: a) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, Wiley, New York, **2002**. b) C. Mauger, G. Mignani, *Aldrichimica Acta* **2006**, *39*, 17. c) M. Willis, *Angew. Chem., Int. Ed.* **2007**, *46*, 3402. d) D. Surry, S. Buchwald, *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. e) Y. Aubin, C. Fischmeister, C. Thomas, J. Renaud, *Chem. Soc. Rev.* **2010**, *39*, 4130.
- 4 a) S. Dayagi, in *The Chemistry of the Carbon-Nitrogen Double Bond*, ed. by S. Patai, John Wiley & Sons, Ltd., Chichester, **1970**, Chap. 2, pp. 61–147. For selected examples, see: b) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849. c) T. Mizuta, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2005**, *70*, 2195.
- 5 a) J. Seayad, A. Tillack, C. G. Hartung, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 795. b) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 5608. c) J. Ryu, G. Y. Li, T. J. Marks, *J. Am. Chem. Soc.* **2003**, *125*, 12584. d) J. F. Hartwig, *Pure Appl. Chem.* **2004**, *76*, 507. e) M. Utsunomiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 2702. f) K. C. Hultsch, D. V. Gribkov, F. Hampel, *J. Organomet. Chem.* **2005**, *690*, 4441. g) A. M. Johns, M. Utsunomiya, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 1828. h) A. Leyva, A. Corma, *Adv. Synth. Catal.* **2009**, *351*, 2876. i) P. Roesky, *Angew. Chem., Int. Ed.* **2009**, *48*, 4892. j) K. Hesp, M. Stradiotto, *ChemCatChem* **2010**, *2*, 1192.
- 6 For reviews on C–H amination, see: a) F. Collet, R. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061. b) A. Armstrong, J. Collins, *Angew. Chem., Int. Ed.* **2010**, *49*, 2282. For selected examples on direct aromatic C–H amination, see: c) W. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560. d) J. Jordan-Hore, C. Johansson, M. Gulias, E. Beck, M. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 16184. e) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058. f) T. Mei, X. Wang, J. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806. g) R. Fan, W. Li, D. Pu, L. Zhang, *Org. Lett.* **2009**, *11*, 1425. h) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 3676. i) Q. Shuai, G. Deng, Z. Chua, D. Bohle, C.-J. Li, *Adv. Synth. Catal.* **2010**, *352*, 632. j) H. Zhao, M. Wang, W. Su, M. Hong, *Adv. Synth. Catal.* **2010**, *352*, 1301.
- 7 G. Tojo, M. Fernández, *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*, ed. by G. Tojo, Springer, New York, USA, **2006**.
- 8 For excellent recent reviews on borrowing hydrogen methodology and hydrogen autotransfer reaction, see: a) G. Guillena, D. J. Ramón, M. Yus, *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. b) M. Hamid, P. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555. c) T. D. Nixon, M. K. Whittlesey, J. M. J. Williams, *Dalton Trans.* **2009**, 753. d) G. Guillena, D. J. Ramón, M. Yus, *Chem. Rev.* **2010**, *110*, 1611. e) A. Watson, J. M. J. Williams, *Science* **2010**, *329*, 635.
- 9 a) R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *J. Chem. Soc., Chem. Commun.* **1981**, 611. b) Y. Watanabe, Y. Tsuji, Y. Ohsugi, *Tetrahedron Lett.* **1981**, *22*, 2667.
- 10 a) Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi, T. Ohta, *J. Org. Chem.* **1984**, *49*, 3359. b) K.-T. Huh, Y. Tsuji, M. Kobayashi, F. Okuda, Y. Watanabe, *Chem. Lett.* **1988**, 449. c) S. Ganguly, D. Roundhill, *Polyhedron* **1990**, *9*, 2517. d) Y. Watanabe, Y. Morisaki, T. Kondo, T. Mitsudo, *J. Org. Chem.* **1996**, *61*, 4214. e) S. Naskar, M. Bhattacharjee, *Tetrahedron Lett.* **2007**, *48*, 3367.
- 11 a) G. Cami-Kobeci, J. M. J. Williams, *Chem. Commun.* **2004**, 1072. b) G. Cami-Kobeci, P. Slatford, M. K. Whittlesey, J. M. J. Williams, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 535. c) B. Blank, M. Madalska, R. Kempe, *Adv. Synth. Catal.* **2008**, *350*, 749.
- 12 a) K. Fujita, R. Yamaguchi, *Synlett* **2005**, 560. b) R. Yamaguchi, S. Kawagoe, C. Asai, K. Fujita, *Org. Lett.* **2008**, *10*, 181. c) K. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64*, 1943.
- 13 a) D. Hollmann, A. Tillack, D. Michalik, R. Jackstell, M. Beller, *Chem. Asian J.* **2007**, *2*, 403. b) F. Shi, M. K. Tse, X. Cui, D. Gördes, D. Michalik, K. Thurow, Y. Deng, M. Beller, *Angew. Chem., Int. Ed.* **2009**, *48*, 5912. c) S. Bähn, S. Imm, K. Mevius, L. Neubert, A. Tillack, J. M. J. Williams, M. Beller, *Chem.—Eur. J.* **2010**, *16*, 3590.
- 14 a) M. Hamid, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 8263. b) M. Hamid, J. M. J. Williams, *Chem. Commun.* **2007**, 725. c) M. Hamid, C. L. Allen, G. Lamb, A. Maxwell, H. Maytum, A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766. d) G. Lamb, A. Watson, K. Jolley, A. Maxwell, J. M. J. Williams, *Tetrahedron Lett.* **2009**, *50*, 3374. e) O. Saidi, A. Blacker, M. Farah, S. Marsden, J. M. J. Williams, *Chem. Commun.* **2010**, 46, 1541. f) O. Saidi, A. Blacker, G. Lamb, S. Marsden, J. Taylor, J. M. J. Williams, *Org. Process Res. Dev.* **2010**, *14*, 1046.
- 15 For other selected examples of C–N bond formation using borrowing hydrogen, see: a) C. Gunanathan, D. Milstein, *Angew. Chem., Int. Ed.* **2008**, *47*, 8661. b) K. Shimizu, M. Nishimura, A. Satsuma, *ChemCatChem* **2009**, *1*, 497. c) R. Martínez, D. J. Ramón, M. Yus, *Org. Biomol. Chem.* **2009**, *7*, 2176. d) X. Cui, F. Shi, M. K. Tse, D. Gördes, K. Thurow, M. Beller, Y. Deng, *Adv. Synth. Catal.* **2009**, *351*, 2949. e) B. Blank, S. Michlik, R. Kempe, *Adv. Synth. Catal.* **2009**, *351*, 2903. f) A. Martínez-Asencio, D. J. Ramón, M. Yus, *Tetrahedron Lett.* **2010**, *51*, 325. g) X. Cui, F. Shi, Y. Zhang, Y. Deng, *Tetrahedron Lett.* **2010**, *51*, 2048. h) X. Cui, Y. Zhang, F. Shi, Y. Deng, *Chem.—Eur. J.* **2011**, *17*, 1021. i) D. Pingan, C. Müller, D. Vogt, *Angew. Chem., Int. Ed.* **2010**, *49*, 8130. j) L. He, X. Lou, J. Ni, Y. Liu, Y. Cao, H.-Y. He, K. Fan, *Chem.—Eur. J.* **2010**, *16*, 13965.
- 16 a) J. He, J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem., Int. Ed.* **2009**, *48*, 9888. b) K. Yamaguchi, J. He, T. Oishi, N. Mizuno, *Chem.—Eur. J.* **2010**, *16*, 7199.
- 17 a) C. Feng, Y. Liu, S. Peng, Q. Shuai, G. Deng, C.-J. Li, *Org. Lett.* **2010**, *12*, 4888. b) Y. Liu, W. Chen, C. Feng, G. Deng, *Chem. Asian J.* **2011**, in press. doi:10.1002/asia.201000945
- 18 a) A. Zanardi, J. Mata, E. Peris, *Chem.—Eur. J.* **2010**, *16*, 10502. b) During the preparation of this manuscript, a secondary amine synthesis from nitroarenes and nitriles with alcohols was reported using K₂CO₃ as base, see: X. Cui, Y. Zhang, F. Shi, Y. Deng, *Chem.—Eur. J.* **2011**, *17*, 2587.
- 19 Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.
- 20 From the reaction mixture, about 10–25% corresponding carboxylic acids were observed via hydrolysis, the majors are converted to the corresponding esters.