Gold-complexes catalyzed oxidative α-cyanation of tertiary amines†

Yan Zhang,[a] Hao Peng,[a] Ming Zhang,[a] Yixiang Cheng[a] and Chengjian Zhu*[ab]

Received 14th September 2010, Accepted 17th November 2010
DOI: 10.1039/c0cc03844j

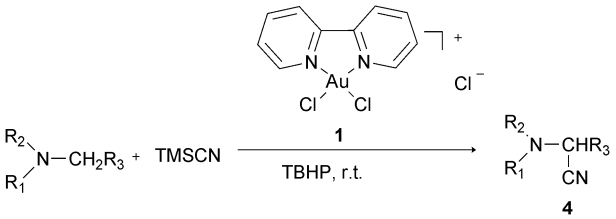
Oxidative α-cyanation of tertiary amines is catalyzed by gold complexes with trimethylsilyl cyanide to afford the corresponding α-aminonitriles in the presence of *tert*-butyl hydroperoxide in good to excellent yields under acid-free conditions at room temperature.

Transition metal catalyzed activation of C–H bonds, especially sp^3 C–H bonds, and subsequent carbon–carbon bond formation which avoids the use of prefunctionalized starting material is therefore a valuable and straightforward synthetic strategy.[1] Although many excellent results have been achieved, catalytic functionalization of sp^3 C–H bonds is still a challenge.[2] Direct cyanation of tertiary amines has attracted much interest since α-aminonitriles are extremely useful synthetic intermediates, which have widely been used in the construction of a variety of synthetically, as well as biologically important compounds such as alkaloids.[3] In order to activate sp^3 C–H bonds at the α-position of tertiary amines, two strategies can be used: (i) treatment with oxometal (M=O) species such as cytochrome P-450 enzyme[4] and (ii) using low-valence metal catalysts such as Ru,[5] V,[6]and Fe.[7]

Organic transformations catalyzed by both gold(I) and gold(III) complexes have been a focus of attention in recent years.[8] New transformations, such as direct arene functionalizations[9] and carbene insertions to benzene, O–H, and N–H bonds,[10] have been developed. Gold species also showed unique activities in mediating reactions involving alkynes and alkenes.[11] In contrast, the gold-catalyzed oxidation chemistry has been less developed,[12] which should have potential applications in synthetic oxidation chemistry.

Herein we report an activation of sp^3 C–H bonds at the α-position (with respect to the nitrogen atom) of tertiary amines catalyzed by gold–bipy complexes with *tert*-butyl hydroperoxide (TBHP) under mild and acid-free conditions which gives the corresponding α-aminonitriles with high efficiency (Scheme 1). To the best of our knowledge, this is the first example of direct oxidative cyanation of tertiary amines catalyzed by gold catalyst.

Initially, the oxidative cyanation of *N*,*N*-dimethylaniline using TBHP as the oxidant was selected as the model reaction for the optimization of reaction conditions. We studied the catalytic efficiency of various gold catalysts (Fig. 1), different cyanide source and solvents. The results are listed in Table 1. Among the gold catalysts tested, **1** was found to be the most effective catalyst for the reaction. No reaction was observed without using any catalyst. $AuClPPh_3$ showed no catalytic activity to the reaction. Although other gold-complexes show moderate catalytic activity, the reactions need a relatively longer time to reach reasonable yields (entries 1–6). TMSCN was the best cyanide source compared to $K_3[Fe(CN)_6]$ and Bu_4NCN (entries 7–10). The reaction also provided an excellent yield when the amount of **1** was reduced to 3 mol% (entries 11 and 12). Methanol is the most effective solvent, although ethanol, ethyl acetate, and acetonitrile can also be used (entries 13–15). Other oxidants, such as H_2O_2, O_2, were also examined. However, no product was detected. After the optimization process, the following oxidative cyanation was performed under the standard conditions: 10 mol% of **1** as the catalyst, 1.2 equiv. of TBHP as the oxidant relative to amines, 2 equiv. of TMSCN as the cyanide source and methanol as the solvent. The reaction temperature was maintained at room temperature without exclusion of air.



Scheme 1

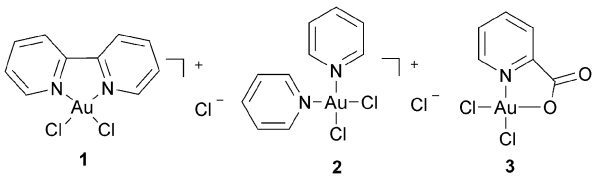


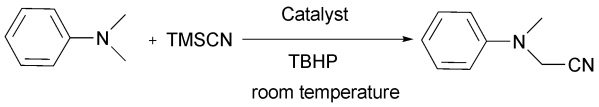
Fig. 1 Gold complexes **1**, **2** and **3**.

In order to explore the scope of substrates of the oxidative cyanations in the **1**/TMSCN/TBHP system, a series of tertiary anilines were investigated in methanol at room temperature. As shown in Table 2, all the substrates were selectively and efficiently converted to the corresponding α-aminonitriles in high to excellent yields. Substituted *N*,*N*-dimethylanilines bearing both electron-donating and electron-withdrawing substituents gave the corresponding cyanated products (entries 1–3). The reaction can also be applied efficiently to cyclic amines: piperidine, pyrrolidine, and tetrahydroisoquinoline derivatives can be converted into the corresponding α-cyanoamines (entries 6, 7, and 9). Thus the protocol developed represents

[a] *State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China. E-mail: cjzhu@nju.edu.cn; Fax: +86 25-83317761; Tel: +86 25-83594886*
[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*

† Electronic supplementary information (ESI) available: Synthetic procedures and characterizations of products and catalysts. See DOI: 10.1039/c0cc03844j

Table 1 Optimization of reaction conditions[a]



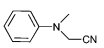
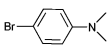
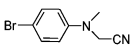
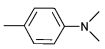
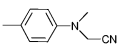
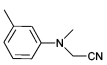
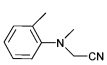
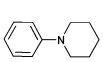
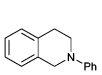
Entry	Catalyst (mol%)	Cyanide source (equiv.)	Equiv. TBHP	*t*/h	Yield[c] (%)
1	None	TMSCN (1.2)	2.0	5	0
2	$AuClPPh_3$ (10)	TMSCN (1.2)	2.0	5	0
3	Bu_4NAuCl_4 (10)	TMSCN (1.2)	2.0	5	80
4	**1**[b] (10)	TMSCN (1.2)	2.0	5	90
5	**2**[b] (10)	TMSCN (1.2)	2.0	5	70
6	**3**[b] (10)	TMSCN (1.2)	2.0	5	62
7	**1** (10)	$K_3[Fe(CN)_6]$ (1.2)	2.0	5	20
8	**1** (10)	Bu_4NCN (1.2)	2.0	5	10
9	**1** (10)	TMSCN (2.0)	1.5	5	93
10	**1 (10)**	**TMSCN (2.0)**	**1.2**	**5**	**98**
11	**1** (8)	TMSCN (2.0)	1.2	5	92
12	**1** (3)	TMSCN (2.0)	1.2	5	83
13[d]	**1** (10)	TMSCN (2.0)	1.2	5	85
14[e]	**1** (10)	TMSCN (2.0)	1.2	5	74
15[f]	**1** (10)	TMSCN (2.0)	1.2	5	76

[a] *Reaction conditions:* 0.5 mmol *N*,*N*-dimethylaniline, ^{t}BuOOH (5–6 M in decane), 1 ml MeOH, rt. [b] Gold complexes: Fig. 1. [c] Yield of the isolated product after column chromatography on silica gel. [d] Ethanol as solvent. [e] Ethyl acetate as solvent. [f] Acetonitrile as solvent.

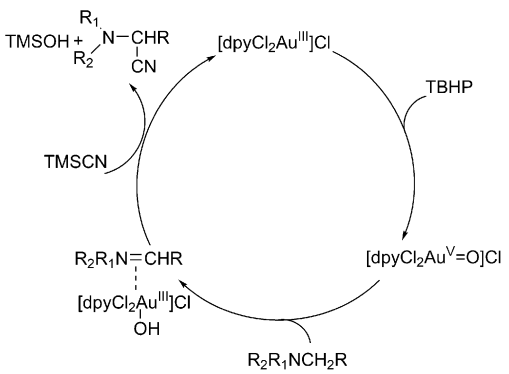
an efficient methodology for the oxidative cyanation of tertiary amines, which are extremely useful synthetic intermediates, and have widely been used in the construction of a variety of synthetically, as well as biologically important compounds.

The exact mechanism for the product formation is not clear at the present stage. Plausible reaction mechanism is showed in Scheme 2. The gold complex $[dpyCl_2Au^{III}]Cl$ undergoes reaction with TBHP to give the oxo-gold[13] species $[dpyCl_2Au^{V}{=}O]Cl$ which produces an iminium ion intermediate by electron transfer and subsequent hydrogen transfer. Nucleophilic attack by TMSCN on the iminium ion intermediate provides the corresponding α-cyanated products, TMSOH and $[dpyCl_2Au^{III}]Cl$ to complete the catalytic cycle.

Table 2 Gold-catalyzed oxidative cyanations of tertiary amines[a]

Entry	Substrate	*t*/h	Product	Yield[b] (%)
1		5		98
2		5		95
3		5		96
4		5		98
5		5		95
6		5		93
7		5		95
8		5		92
9		5		98

[a] *Reaction conditions:* 0.5 mmol amine, 1.0 mmol TMSCN, 0.1 ml of ^{t}BuOOH (5–6 M in decane), 10 mol% gold complex **1**, 1 ml MeOH, rt. [b] Yield of the isolated product after column chromatography on silica gel.



Scheme 2 The proposed reaction mechanism for the gold-catalyzed oxidative cyanation of tertiary amines with TBHP.

In conclusion, we have demonstrated the novel gold-catalyzed activation of sp^3 C–H bonds of tertiary amines in the presence of *tert*-butyl hydroperoxide in good to excellent yields under acid-free conditions at room temperature. The reaction proceeds with high efficiency to give the corresponding α-cyanated amines which are extremely useful synthetic intermediates in the construction of biologically important compounds. Research is currently underway to elucidate the mechanism and to apply the principle to other catalytic systems.

We gratefully acknowledge the National Natural Science Foundation of China (20832001, 20972065, 21074054) and the National Basic Research Program of China ((2007CB925103, 2010CB92330) for their financial support. The Major Scientific and Technological Special Project (2009ZX09103-081) is also acknowledged.

Notes and references

1 (*a*) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (*b*) J. J. Li, T. S. Mei and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 6452; (*c*) D. H. Wang, M. Was, R. Giri and J. Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 7190; (*d*) O. Basle and C.-J. Li, *Org. Lett.*, 2008, **10**, 3661.

2 (*a*) S.-I. Murahashi and D. Zhang, *Chem. Soc. Rev.*, 2008, **37**, 1490; (*b*) C. M. Rao Volla and P. Vogel, *Org. Lett.*, 2009, **11**, 1701; (*c*) M. Wasa, K. M. Engle and J. Q. Yu, *J. Am. Chem. Soc.*, 2009, **131**, 9886; (*d*) Y. H. Zhang, B. F. Shi and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 6097.

3 (*a*) R. H. Crabtree, *J. Organomet. Chem.*, 2004, **689**, 4083; (*b*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*c*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633; (*d*) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698.

4 (*a*) S.-I. Murahashi, *Pure Appl. Chem.*, 1992, **64**, 403; (*b*) S.-I. Murahashi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2443; (*c*) S.-I. Murahashi and N. Komiya, in *Ruthenium in Organic Synthesis*, ed. S.-I.Murahashi, Wiley-VCH, Weinheim, Germany, 2004, pp. 53–93.

5 (*a*) S.-I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (*b*) S.-I. Murahashi, N. Komiya and H. Terai, *Angew. Chem., Int. Ed.*, 2005, **44**, 6931.

6 S. Singhal, S. L. Jain and B. Sain, *Chem. Commun.*, 2009, 2371.

7 (*a*) W. Han and A. R. Ofial, *Chem. Commun.*, 2009, 5024; (*b*) S. Singhal, S. L. Jain and B. Sain, *Adv. Synth. Catal.*, 2010, **352**, 1338.

8 (*a*) M. Buaki, C. Aprile, A. Dhakshinamoorthy, M. Alvaro and H. Garcia, *Chem.–Eur. J.*, 2009, **15**, 13082; (*b*) L. He, J. Ni, L.-C. Wang, F.-J. Yu, Y. Cao, H.-Y. He and K.-N. Fan, *Chem.–Eur. J.*, 2009, **15**, 11833; (*c*) C. M. Chao, D. Beltrami, P. Y. Toullec and V. Michelet, *Chem. Commun.*, 2009, 6988; (*d*) A. Saito, T. Konishi and Y. Hanzawa, *Org. Lett.*, 2010, **12**, 372.

9 (*a*) X. W. Du, X. Xie and Y. H. Liu, *J. Org. Chem.*, 2010, **75**, 510; (*b*) K. Wilckens, M. Uhlemann and C. Czekelius, *Chem.–Eur. J.*, 2009, **15**, 13323; (*c*) Y. Matsumoto, K. B. Selim, H. Nakanishi, K. Yamada, Y. Yamamoto and K. Tomioka, *Tetrahedron Lett.*, 2010, **51**, 404; (*d*) A. Burini, R. Galassi, S. Ricci, F. Bachechi, A. A. Mohamed and J. P. Fackler, *Inorg. Chem.*, 2010, **49**, 513.

10 M. R. Fructos, T. R. Belderrain, P. de Fremont, N. M. Scott, S. P. Nolan and M. M. DiazRequejo, *Angew. Chem., Int. Ed.*, 2005, **44**, 5284.

11 (*a*) T. M. Teng, A. Das, D. B. Huple and R. S. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 12565; (*b*) F. Miege, C. Meyer and J. Cossy, *Org. Lett.*, 2010, **12**, 4144; (*c*) Y. K. Liu, J. Q. Qian, S. J. Lou and Z. Y. Xu, *J. Org. Chem.*, 2010, **75**, 6300; (*d*) E. Brenzovich Jr, E. William, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard and F. D. Toste, *Angew. Chem., Int. Ed.*, 2010, **49**, 5519.

12 (*a*) H. R. Li, B. T. Guan, W. J. Wang, D. Xing, Z. Fang, X. B. Wan, L. P. Yang and Z. J. Shi, *Tetrahedron*, 2007, **63**, 8430; (*b*) H. R. Li, Z. P. Li and Z. J. Shi, *Tetrahedron*, 2009, **65**, 1856.

13 M. A. Cinellu, G. Minghetti, F. Cocco, S. Stoccoro, A. Zucca and M. Manassero, *Angew. Chem., Int. Ed.*, 2005, **44**, 6892.

