Gold Catalysis

DOI: 10.1002/anie.201107605

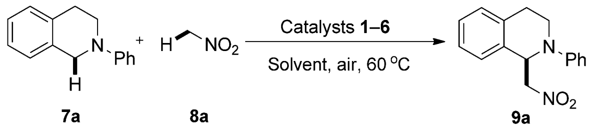
A Highly Efficient Gold-Catalyzed Oxidative C–C Coupling from C–H Bonds Using Air as Oxidant[**]

Jin Xie, Huamin Li, Jiecong Zhou, Yixiang Cheng, and Chengjian Zhu[*]

The construction of C–C bond is a perennial subject of interest for the synthetic chemist. Lately, the homogeneous gold-catalyzed C–C coupling reaction has emerged as a powerful method for the synthesis of intricate scaffolds.[1] In the methods reported, the introduction of a highly functionalized group or a sacrificial external oxidant was usually required, thus diminishing the overall sustainability of the gold-catalyzed process. In recent years, the direct use of two C–H bonds for C–C coupling has become a promising strategy, as C–H bonds are ubiquitous in organic molecules.[2] In 2009 and 2010, the groups of Tse and Nevado reported the gold-catalyzed oxidative homocoupling of simple arenes and oxidative ethynylation of arenes with terminal alkynes using $PhI(OAc)_2$ as an oxidant.[3] However, the gold-catalyzed oxidative C–C coupling of C_{sp^3}–H bonds under aerobic oxidative conditions is still a challenge.[4–5] Directed toward such goals, we became interested in the gold-catalyzed oxidative C–C coupling of amines with various C_{sp^3}–H coupling partners. Although some notable progress has been achieved in this area, a stoichiometric amount of dangerous oxidants or pure oxygen (≥ 1.0 atm), and even specialized reaction conditions are usually necessary.[6,7] These disadvantages have seriously limited the utility of such methods. Therefore, the development of a more environmentally benign and convenient catalytic system for amine functionalization is highly desirable. Following the principle of sustainable chemistry, air is a favorable oxidant, with water as the only waste product, and it has received considerable attention in modern oxidation chemistry.[8] To the best of our knowledge, there is no successful example of a gold-catalyzed α-C–H functionalization of amines using air as the sole oxidant.[5,9] Herein, we wish to report an unprecedented homogeneous gold-catalyzed amine functionalization protocol involving the oxidative C–C coupling of two different C–H bonds with air as a sustainable and efficient oxidant.

In our initial study, the oxidative C–C coupling reaction of *N*-phenyl tetrahydroisoquinoline **7a** with nitromethane **8a** was chosen as a model reaction.[10] The results are summarized in Table 1. To our delight, the aerobic oxidative C–C coupling reaction could occur under the catalysis of **1a** (6 mol%) with methanol as solvent at 60 °C under air, to afford **9a** in 48% yield (Table 1, entry 1). Among the Au^{III} catalysts screened **1b** showed the best catalytic activity (Table 1, entries 1–7). The utilization of Ph_3PAuCl **6** instead of a Au^{III} catalyst resulted in the formation of only a trace amount of product (Table 1, entry 8). Interestingly, a trace amount of the desired product **9a** was obtained in the absence of any catalyst (Table 1, entry 9). When the aerobic oxidative C–C coupling reaction was performed without a solvent at 60 °C under air, it led to a satisfactory yield of 82% (Table 1, entry 10). Notably, the yield could be improved to 86% by adding a small amount of methanol (Table 1, entry 11).

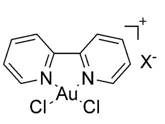
Table 1: Optimization of the aerobic oxidative C–C coupling reaction of amines with nitromethane.[a]



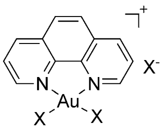
7a **8a** **9a**

Entry	Catalyst (mol%)	Solvent	*t* [h]	Yield [%][b]
1	**1a** (6)	MeOH	6	48
2	**1b** (6)	MeOH	6	71
3	**2a** (6)	MeOH	6	56
4	**2b** (6)	MeOH	6	52
5	**3** (6)	MeOH	6	45
6	**4** (6)	MeOH	6	47
7	$NaAuCl_4$ **5** (6)	MeOH	6	38
8	Ph_3PAuCl **6** (6)	MeOH	6	trace
9	–	MeOH	6	trace
10	**1b** (6)	$MeNO_2$	3	82
11[c]	**1b** (6)	$MeNO_2$	3	86
12[c]	**1b** (3)	$MeNO_2$	3	86
13[c,d]	**1b** (3)	$MeNO_2$	3	12

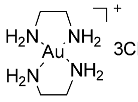
[a] Reaction conditions: **7a** (0.1 mmol, 0.1 M), **8a** (0.20 mL), catalysts **1**–**6** (3–6 mol%), solvent (0.8 mL), air, 60 °C. [b] Yields of the isolated products. [c] 100 μL MeOH was added. [d] The reaction was carried out in Ar (1.0 atm).



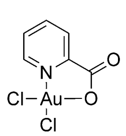
1a: X= Cl
1b: X= $AuCl_4$



2a: X= Cl
2b: X=Br



3



4

---

[*] J. Xie, H. Li, J. Zhou, Prof. Y. Cheng, Prof. C.-J. Zhu
State Key Laboratory of Coordination Chemistry
School of Chemistry and Chemical Engineering
Nanjing University, Nanjing 210093 (P. R. China)
E-mail: cjzhu@nju.edu.cn
Prof. C.-J. Zhu
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Shanghai 200032 (P. R. China)

[**] We gratefully acknowledge the National Natural Science Foundation of China (20832001, 20972065, 21074054, 21172106) and the National Basic Research Program of China (2010CB923303) for their financial support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201107605.

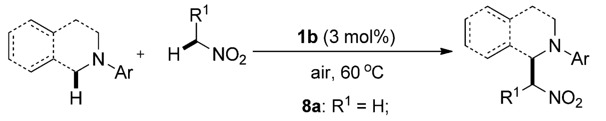
© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Further studies indicated that reducing the catalyst loading of **1b** to 3% barely affected its catalytic efficiency (Table 1, entry 12). A control experiment demonstrated that when the aerobic oxidative C–C coupling reaction was carried out in an Ar atmosphere instead of air, a much lower yield was observed (Table 1, entry 13). Consequently, the optimal reaction conditions include catalysis by 3 mol% of **1b** at 60 °C under air in the presence of a small amount of methanol.

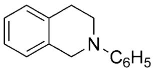
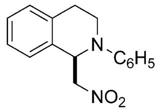
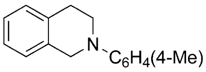
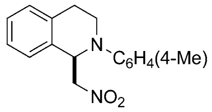
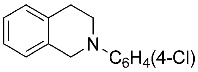
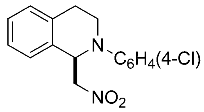
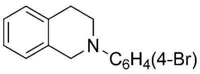
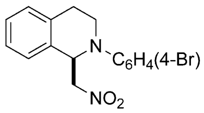
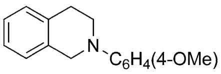
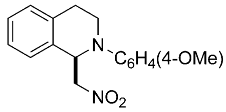
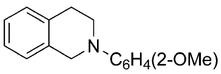
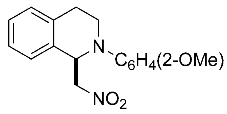
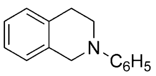
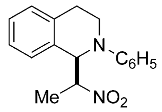
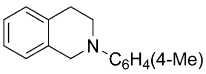
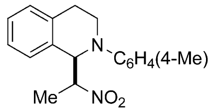
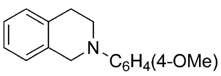
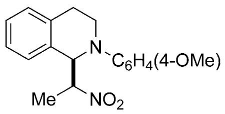
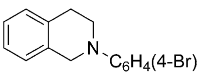
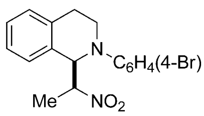
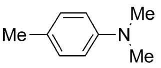
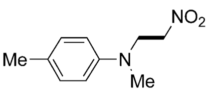
With the optimized reaction conditions established, we investigated the scope of this protocol (Table 2). Initially, different *N*-aryltetrahydroisoquinolines **7a–f** were examined. It was found that electron-donating as well as electron-withdrawing groups on the aromatic rings were compatible under the reaction conditions. They can uniformly furnish the desired products **9a–f** in excellent yield (86–95%; Table 2, entries 1–6). Intriguingly, the less-active nitroethane provided the desired products **9g–j** in 85-91% yield (Table 2, entries 7–10). When a nonbenzylic amine **7g** was employed, a satisfactory yield was also obtained (entry 11).[6c] Furthermore, we increased the scale of the gold-catalyzed reaction to 1.05 g of **7a** to demonstrate the practicability of our protocol, and **9a** was obtained in a good yield of 81%.

To further illustrate the generality of our method, we applied this strategy to the aerobic oxidative C–C coupling reaction of tetrahydroisoquinoline with a series of unmodified ketones (Scheme 1). Although several methods, which include Cu^I/O_2 (1.0 atm), V^{IV}/TBHP, and Ru^{II}/photoredox catalytic systems, have been developed for this transformation either the yield or the scope was unsatisfactory.[10b,d,j] Initially, treatment of **7a** with acetone **10a** in the presence of the catalyst **1b** and without a solvent only afforded the desired product **9l** in 35% yield. Pleasingly, it was found that addition of an acid and molecular sieves (4 Å) were beneficial to the gold-catalyzed coupling reaction. Under the optimized reaction conditions, different *N*-aryltetrahydroisoquinolines **7a–e** with acetone could undergo the coupling reaction smoothly to afford the desired products **9l–p** in good yield (75–86%). The bulky methyl ketones **10b–e** were still effective and gave good results in our catalytic system. Notably, the inert 3,3-dimethylbutan-2-one could also be coupled with **7a** to give **9u** in satisfactory yield with a longer reaction time. Besides the methyl aryl and alkyl ketones, cycloketones could be used to construct C–C bonds, affording **9v,w** in useful synthetic yields.

Table 2: Aerobic oxidative C–C coupling reaction of amines with nitroalkanes.[a]



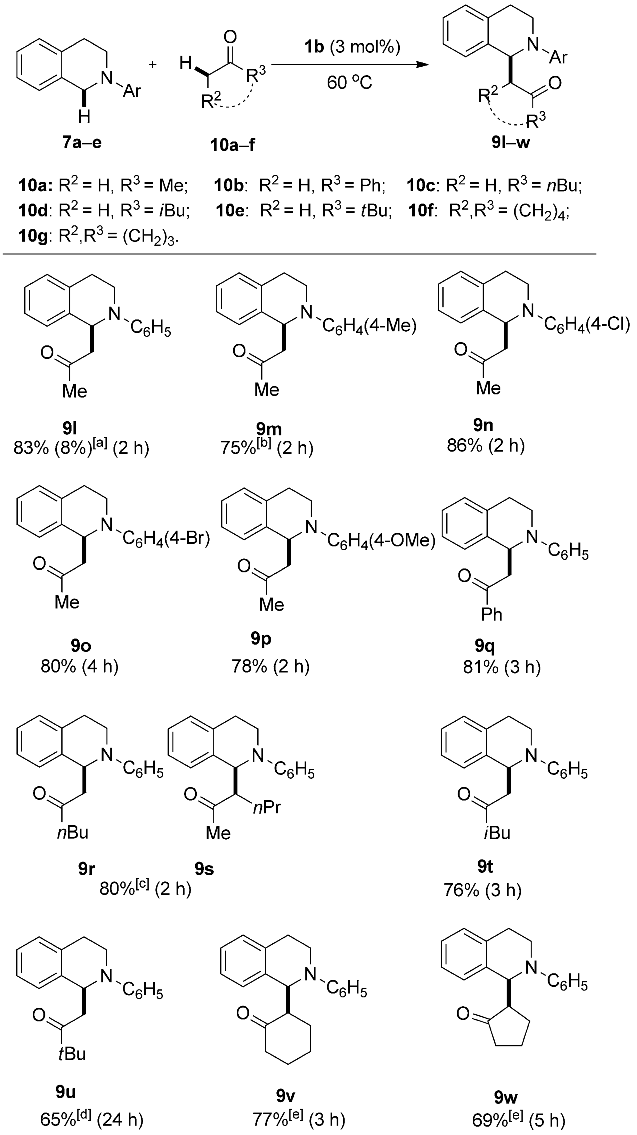
7a–g **8a–b** **9a–k**

Entry	7		t [h]	Product 9		Yield [%][b]
1		**7a**	3		**9a**	86
2		**7b**	1.5		**9b**	90
3		**7c**	3		**9c**	91
4		**7d**	5		**9d**	88
5[c,d]		**7e**	2.5		**9e**	87
6[c]		**7f**	3		**9f**	95
7		**7a**	5		**9g**	90
8		**7b**	3		**9h**	91
9[c,d]		**7e**	1.5		**9i**	85
10		**7d**	2.5		**9j**	90
11		**7g**	30		**9k**	52

[a] Reaction conditions: **7** (0.1 mmol), nitroalkane **8**/MeOH (v/v = 9:1; 1.0 mL), 60 °C, air. [b] Yields of the isolated products. [c] Without methanol. [d] The reaction was performed at 40 °C.

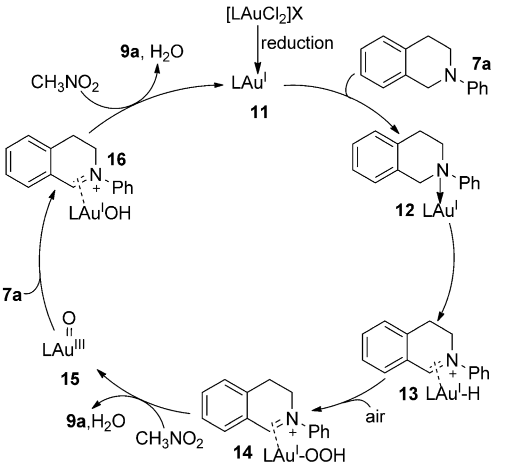
To gain insight into the gold-catalyzed C–C coupling reaction, several control experiments were carried out to elucidate the mechanism. Adding the radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction of **7a** and **8a** dramatically decreased the reaction rate and yield, thus indicating that a radical mechanism could be involved. On the basis of a mass spectrometry study, a cationic iminium species was observed to serve as the key intermediate of the coupling reaction.[11] In the light of the work of Murahashi et al. on the ruthenium-catalyzed oxidative cyanation of amines,[6g] a plausible mechanism is shown in

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Aerobic oxidative C–C coupling reaction of amines with ketones. Reaction conditions: **7** (0.1 mmol), **1b** (3 mol%), ketone **10** (0.1 mL), HOAc (50 μL), M.S. (4 Å; 60 mg), 60 °C. Yields are of the isolated products. [a] The reaction was performed without gold catalyst **1b**. [b] HOAc (30 μL) was used. [c] **9r**/**9s** = 8:1. [d] HOAc (100 μL) was used at 80 °C. [e] MsOH (3 μL) was used. Ms = methanesulfonyl, M.S. = molecular sieves.

Scheme 2. Initially, the Au^{I} species **11** may be generated in situ from the reduction of Au^{III} **1b** by the solvent or substrates.[12] Then, **11** would coordinate to *N*-phenyltetrahydroisoquinoline **7a** to give **12**. An electron transfer followed by a hydrogen transfer from amine **7a** to gold results in the formation of an iminium gold hydride complex **13**.[6a] The AuH species may be different from the CuH and AgH species,[13] and it could form the iminium ion/AuOOH complex **14** in the presence of air (O_2) in a similar way to PdH and RuH.[14] The iminium species **14** can be trapped with nitromethane quickly to afford the desired product **9a**, H_2O and the gold(III) oxo complex **15**. Subsequently, the Au^{III}=O species **15** reacts with another amine **7a** to give iminium intermediate **16** by electron and hydrogen transfer.[15] Finally, **16** could react with nitromethane to yield the product **9a** and complete the catalytic cycle.



Scheme 2. Plausible mechanism (L = 2,2′-bipyridine).

In summary, we have developed a highly efficient homogeneous gold-catalyzed oxidative C–C coupling method for tertiary amines with nitroalkanes and different unmodified ketones by using air as the sole oxidant under mild reaction conditions. The safe, convenient, and environmentally benign process, as well as the broad substrate scope, low catalyst loading, short reaction time, and good yields make this protocol very practical. Further studies on the gold-catalyzed aerobic oxidative C–C coupling mechanisms are under way in our laboratory.

Received: October 28, 2011
Published online: December 15, 2011

Keywords: air · C–C coupling · C–H activation · cross-coupling · gold

---

[1] For recent reviews of gold-catalyzed C-C coupling reactions, see: a) H. A. Wegner, M. Auzias, *Angew. Chem.* **2011**, *123*, 8386; *Angew. Chem. Int. Ed.* **2011**, *50*, 8236; b) M. N. Hopkinson, D. G. Antony, V. Gouverneur, *Chem. Eur. J.* **2011**, *17*, 8248.

[2] For selected reviews of C–C coupling from C–H bonds, see: a) Z. Li, D. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928; b) C.-J. Li, Z. Li, *Pure Appl. Chem.* **2006**, *78*, 935; c) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; d) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281; e) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436; f) S.-L. You, J.-B. Xia, *Top. Curr. Chem.* **2010**, *292*, 165; g) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; h) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780; i) W. Shi, C. Liu, A. Lei, *Chem. Soc. Rev.* **2011**, *40*, 2761.

[3] a) A. Kar, N. Mangu, H. M. Kaiser, M. K. Tse, *J. Organomet. Chem.* **2009**, *694*, 524; b) T. Haro, C. Nevado, *J. Am. Chem. Soc.* **2010**, *132*, 1512.

[4] For reviews on gold-catalyzed C-H reactions, see: a) R. Skouta, C.-J. Li, *Tetrahedron* **2008**, *64*, 4917; b) T.-C. Boorman, I. Larrosa, *Chem. Soc. Rev.* **2011**, *40*, 1910; c) T. Haro, C. Nevado, *Synthesis* **2011**, 2530.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[5] For a review on F^{+} oxidants in Au^{I}/Au^{III} catalysis, see: K.-M. Engle, T. Mei, X. Wang, J.-Q. Yu, *Angew. Chem.* **2011**, *123*, 1514; *Angew. Chem. Int. Ed.* **2011**, *50*, 1478.

[6] For representative examples of α-C-H functionalization of amines, see: a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.* **2003**, *125*, 15312; b) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; c) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3672; d) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2005**, *127*, 6968; e) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931; f) A. J. Catino, J. M. Nichols, B. J. Nettles, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 5648; g) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.* **2008**, *130*, 11005; h) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; i) L. Zhao, O. Basle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4106; j) A. G. Condie, J. Gonzalez-Gomez, C. Stephenson, *J. Am. Chem. Soc.* **2010**, *132*, 1464; k) J. Xie, Z. Huang, *Angew. Chem.* **2010**, *122*, 10379; *Angew. Chem. Int. Ed.* **2010**, *49*, 10181; l) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Fares, M. Klussmann, *J. Am. Chem. Soc.* **2011**, *133*, 8106; m) G. Zhang, Y. Zhang, R. Wang, *Angew. Chem.* **2011**, *123*, 10613; *Angew. Chem. Int. Ed.* **2011**, *50*, 10429.

[7] In 2010, Liang and co-workers reported a Pt^{II}-catalyzed coupling reaction using C–H bonds without oxidants under Ar (1.0 atm) at 85 °C. However, the catalytic efficiency is not satisfactory as this reaction requires a high loading of Pt and long reaction time. See: X.-Z. Shu, Y.-F. Yang, X.-F. Xia, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *Org. Biomol. Chem.* **2010**, *8*, 4077.

[8] For a review on sustainable chemistry: P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301; for selected examples using air as oxidant: a) C. Zhang, N. Jiao, *Angew. Chem.* **2010**, *122*, 6310; *Angew. Chem. Int. Ed.* **2010**, *49*, 6174; b) R.-D. Patila, S. Adimurthya, *Adv. Synth. Catal.* **2011**, *353*, 1695; c) L. Jiang, L. Jin, H. Tian, X. Yuan, X. Yu, Q. Xu, *Chem. Commun.* **2011**, *47*, 10833; d) C.-P. Frazier, J.-R. Engelking, J.-R. Alaniz, *J. Am. Chem. Soc.* **2011**, *133*, 10430; e) M. Nishino, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 6447; f) J.-M. Hoover, S.-S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 16901.

[9] For the first example of gold-catalyzed oxidative α-cyanation of amines, see our work: Y. Zhang, H. Peng, M. Zhang, Y. Cheng, C.-J. Zhu, *Chem. Commun.* **2011**, *47*, 2354.

[10] Tetrahydroisoquinoline derivatives are highly important bioactive compounds and tetrahydroisoquinoline substrates were reported to perform C–H functionalization mainly mediated by Cu^{I}, V^{IV}, Fe^{III}, Fe^{II}, or Ru^{II}, or even metal free. However, a stoichiometric amount of toxic oxidants (such as TBHP, T-HYDRO, TBP, DDQ, BPO), pure oxygen, or harsh reaction conditions are usually necessary. For selected examples: a) O. Baslé, C.-J. Li, *Green Chem.* **2007**, *9*, 1047; b) A. Sud, D. Sureshkumarz, M. Klussmann, *Chem. Commun.* **2009**, 3169; c) O. Baslé, C.-J. Li, *Chem. Commun.* **2009**, 4124; d) Y. Shen, M. Li, S. Wang, T. Zhang, Z. Tan, C.-C. Guo, *Chem. Commun.* **2009**, 953; e) X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2009**, *74*, 7464; f) A. S.-K. Tsang, M. H. Todd, *Tetrahedron Lett.* **2009**, *50*, 1199; g) P. Liu, C.-Y. Zhou, S. Xiang, C.-M. Che, *Chem. Commun.* **2010**, *46*, 2739; h) L. Chua, F.-L. Qing, *Chem. Commun.* **2010**, *46*, 6285; i) G. Kumaraswamy, A. Murthy, A. Pitchaiah, *J. Org. Chem.* **2010**, *75*, 3916; j) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny, D.-C. Fabry, *Chem. Commun.* **2011**, *47*, 2360; k) K. Alagiri, G. Kumara, K.-R. Prabhu, *Chem. Commun.* **2011**, *47*, 11787; see also Ref. [6b–d,j,l].

[11] During the reaction, we can detect the cationic iminium species **13** by mass spectrometry. More interestingly, the cationic iminium species **13** could be observed by mass spectrometry as soon as the gold catalyst **1b** and **7a** were mixed together at room temperature in MeOH/MeCN. For details, see the Supporting Information.

[12] X. Yao, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 6884.

[13] For selected examples of CuH species, see: a) F. Shi, M. Tse, X. Cui, D. Gordes, K. Thurow, Y. Deng, M. Beller, *Angew. Chem.* **2009**, *121*, 6026; *Angew. Chem. Int. Ed.* **2009**, *48*, 5912; AgH species, see: b) K. Shimizu, R. Sato, A. Satsuma, *Angew. Chem.* **2009**, *121*, 4042; *Angew. Chem. Int. Ed.* **2009**, *48*, 3982; AuH species, see: c) A. Escalle, G. Mora, F. Gagosz, N. Mezailles, X. Goff, Y. Jean, P. Floch, *Inorg. Chem.* **2009**, *48*, 8415; d) M. Conte, H. Miyamura, S. Kobayashi, V. Chechik, *J. Am. Chem. Soc.* **2009**, *131*, 7189; e) A. Maldotti, A. Molinari, R. Juarez, H. Garcia, *Chem. Sci.* **2011**, *2*, 1831.

[14] Pd–H and Ru–H species: a) T. Hosokawa, T. Uno, S. Inui, S.-I. Murahashi, *J. Am. Chem. Soc.* **1981**, *103*, 2318; b) T. Hosokawa, S.-I. Murahashi, *Acc. Chem. Res.* **1990**, *23*, 49; c) T. Nishimura, T. Onoue, K. Ohe, S. Uemura, *J. Org. Chem.* **1999**, *64*, 6750; d) K. Yamaguchi, K. Mori, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Am. Chem. Soc.* **2000**, *122*, 7144 and [6a].

[15] M. Cinellu, G. Minghetti, F. Cocco, S. Stoccoro, A. Zucca, M. Manassero, *Angew. Chem.* **2005**, *117*, 7052; *Angew. Chem. Int. Ed.* **2005**, *44*, 6892.

© 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim