ORGANIC
LETTERS

2009
Vol. 11, No. 15
3166−3169

Gold-Catalyzed Intermolecular Markovnikov Hydroamination of Allenes with Secondary Amines

Xiaoming Zeng,[†] Michele Soleilhavoup, and Guy Bertrand*

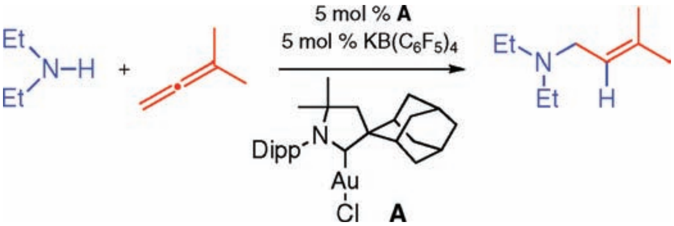
UCR-CNRS Joint Research Chemistry Laboratory (UMI 2957), Department of Chemistry, University of California, Riverside, California 92521-0403

guy.bertrand@ucr.edu

Received March 9, 2009

Downloaded by UNIV MAASTRICHT on August 15, 2009
Published on July 13, 2009 on http://pubs.acs.org | doi: 10.1021/ol901418c

ABSTRACT



A cationic (CAAC)gold(I) complex promotes the addition of all types of nontertiary amines to a variety of allenes, affording allylic amines in good to excellent yields; the amino fragment always adds to the less substituted terminus of the CCC skeleton.

The most widely used chemical reaction for the functionalization of alkenes, alkynes, and allenes is the addition of an A−B bond across a carbon−carbon π-bond.[1] Since nitrogen−carbon bonds are ubiquitous in molecules and of significant importance in human life, as well as for the chemical industry,[2] the so-called hydroamination reaction has attracted considerable interest.[3] However, a close look at the literature reveals that although the intramolecular hydroamination of allenes[4] has been widely studied,[5] the intermolecular version has received limited attention. Depending on the regiochemistry, this reaction can lead to imines, enamines, or allylamines. The allylamines (Markovnikov adducts) are especially interesting since they are among the most versatile intermediates in synthesis, components of many naturally occurring and biologically active molecules, and of industrial importance.[6] In 1992, Bergman reported that zirconium bis(amides) were efficient catalysts to promote the addition of primary arylamines to 1,2-propadiene giving the corre-

---

[†] Present address: Key Laboratory of Green Chemistry & Technology of Ministry of Education at Sichuan University, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China.

(1) For recent general reviews, see: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3159. (c) Chianese, A. R.; Lee, S. J; Gagne, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042–4059.

(2) (a) Maxwell, G. R. In *Synthetic Nitrogen Products*; Kluwer Academic, Plenum Publishers, New York, 2004. (b) Lawrence, S. A. In *Amines: Synthesis, Properties, and Applications*; Cambridge University Press: New York, 2004.

(3) For recent reviews on hydroamination reactions, see: (a) Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795–3892. (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (c) Matsunaga, S. *J. Synth. Org. Chem. Japan* **2006**, *64*, 778–779. (d) Roesky, P. W. *Z. Anorg. Allg. Chem.* **2006**, *632*, 1918–1926. (e) Odom, A. L. *Dalton Trans.* **2005**, 225–233. (f) Hazari, N.; Mountford, P. *Acc. Chem. Res.* **2005**, *38*, 839–849. (g) Hartwig, J. F. *Pure Appl. Chem.* **2004**, *76*, 507–516. (h) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673–686.

(4) *Modern Allene Chemistry*; Krause, N., Hashmi A. S. K., Eds.; Wiley-VCH: Weinheim, 2004.

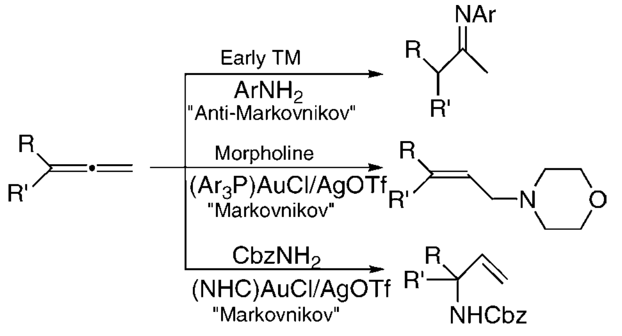
(5) For recent examples of intramolecular hydroamination of allenes, see: (a) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157–3159. (b) Nishima, N.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 4908–4911. (c) Hannedouche, J.; Aillaud, I.; Collin, J.; Schulz, E.; Trifonov, A. *Chem. Commun.* **2008**, 3552–3554. (d) Zi, G. G.; Xiang, L.; Song, H. B. *Organometallics* **2008**, *27*, 1242–1246. (e) Zhang, Z. B.; Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148–14149. (f) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452–2453. (g) Zhang, Z. B.; Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2007**, *9*, 2887–2889. (h) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519–1521. (i) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634–4641.

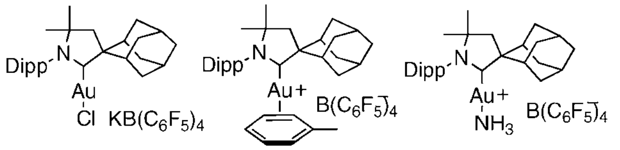
(6) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689–1708.

10.1021/ol901418c CCC: $40.75 © 2009 American Chemical Society
Published on Web 07/13/2009

sponding imines,[7] and more recent papers confirm that early-transition-metal catalysts lead to the anti-Markovnikov adducts (Scheme 1, top).[8] The Markovnikov addition has first been achieved in the presence of equimolar amounts of mercury(II), palladium(II), and platinum(II) salts[9] and then used a palladium(0) catalyst in the presence of triethylammonium iodide[10] or acetic acid[11] as cocatalysts. Gold catalysts[12] have more recently been developed.[13] Yamamoto et al. first demonstrated that 10 mol % of $AuBr_3$ allowed the room-temperature addition of primary arylamines to allene to afford allylic amines[14a] and then described the addition of morpholine to mono- and disubstituted allenes at 80 °C, using 10 mol % of a 1/1 mixture of $(Ar_3P)AuCl$ and AgOTf (Scheme 1, middle).[14b] In 2008, Widenhoefer reported the Markovnikov hydroamination with N-unsubstituted carbamates using catalytic amounts of an equimolar mixture of LAuCl and AgOTf (L = NHC, phosphine) (Scheme 1, bottom).[15] Interestingly, an opposite regioselectivity was observed when compared with Yamamoto's results.[14b] Recently, we have shown that cationic gold(I) complexes (**Cat**) (Figure 1),[16] featuring a bulky cyclic (alkyl)(amino)carbene (CAAC)[17] as ancillary ligand, efficiently promoted the addition of NH_3 to nonactivated alkynes and allenes.[18] These first examples of hydroamination reaction with ammonia prompted us to investigate the scope of application of our catalytic system. Here, we show that **Cat1** [a 1/1 mixture of (CAAC)AuCl and $KB(C_6F_5)_4$] efficiently promotes the intermolecular Markovnikov hydroamination of allenes **A**−**C** (scheme 2) with a variety of primary and, more importantly, secondary amines.

Scheme 1. Previous Results for the Hydroamination of Allenes

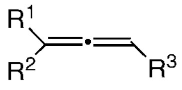




Cat1 **Cat2** **Cat3**

Figure 1. Cationic gold(I) complexes promoting the addition of NH_3 to nonactivated alkynes and allenes.

Scheme 2. Allenes **A**−**C** Used in This Study



A: $R^1 = R^2 = Me, R^3 = H$
B: $R^1 = R^2 = R^3 = H$
C: $R^1 = Ph, R^2 = R^3 = H$

Since, as mentioned above, several catalytic systems are known to promote the hydroamination of allenes with primary amines, we briefly investigated if **Cat1** was efficient as well (Table 1, entries 1−3). In the presence of 5 mol % of **Cat1**, we were pleased to observe that after 12 h at 70 °C, aniline reacted with 1,1-dimethylallene **A** to afford a 60/40 mixture of *N*-allyl- and *N*,*N*′-diallylaniline in 95% yield (entry 1). Clearly, the *N*,*N*′-diallylaniline results from the addition of the primarily formed *N*-allylaniline on allene **A**, which gives a clear indication that secondary arylamines are suitable substrates for our catalytic system. Mesitylamine and even the strongly basic and bulky *tert*-butylamine react with **A**, although under more drastic conditions, giving the secondary allylamines in 74 and 54% yield, respectively (entries 2 and 3).

We then turned our attention to secondary (aryl)(alkyl)-amines using again 5 mol % of **Cat1** (Table 1, entries 4−9).

Downloaded by UNIV MAASTRICHT on August 15, 2009
Published on July 13, 2009 on http://pubs.acs.org | doi: 10.1021/ol901418c

---

(7) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708–1719.

(8) (a) Johnson, J. S.; Bergman, R. G. *J. Am. Chem. Soc.* **2001**, *123*, 2923–2924. (b) Ayinla, R. O.; Schafer, L. L. *Inorg. Chim. Acta* **2006**, *359*, 3097–3102.

(9) (a) Derenzi, A.; Ganis, P.; Panunzi, A.; Vitagliano, A.; Valle, G. *J. Am. Chem. Soc.* **1980**, *102*, 1722–1723. (b) Hodjatkachani, H.; Perie, J. J.; Lattes, A. *Chem. Lett.* **1976**, 405–408.

(10) Besson, L.; Gore, J.; Cazes, B. *Tetrahedron Lett.* **1995**, *36*, 3857–3860.

(11) Al-Masum, M.; Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* **1997**, *38*, 6071–6074.

(12) For recent reviews on gold chemistry: (a) Li, Z.; Brouwer, C.; He, C *Chem. Rev.* **2008**, *108*, 3239–3265. (b) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266–3325. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326–3350. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351–3378. (e) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442. (f) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885–3903. (g) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382–5391. (h) Krause, N.; Belting, V.; Deutsch, C.; Erdsack, J.; Fan, H. T.; Gockel, B.; Hoffmann-Roder, A.; Morita, N.; Volz, F. *Pure Appl. Chem.* **2008**, *80*, 1063–1069. (i) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (j) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449. (k) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

(13) For a recent review on gold-catalyzed hydroamination of allenes, see: Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555–4563.

(14) (a) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314–3317. (b) Nishina, N.; Yamamoto, Y. *Synlett* **2007**, 1767–1770.

(15) Kinder, R. E.; Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 3157–3159.

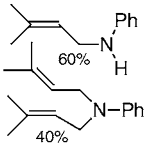
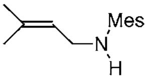
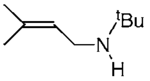
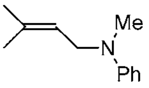
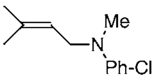
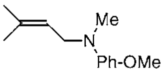
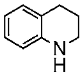
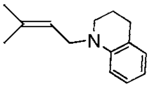
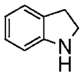
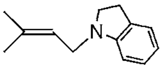
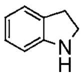
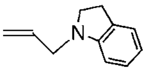
(16) (a) Lavallo, V.; Frey, G. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13569–13573. (b) Frey, G. D.; Dewhurst, R. D.; Kousar, S.; Donnadieu, B.; Bertrand, G. *J. Organomet. Chem.* **2008**, *693*, 1674–1682.

(17) (a) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 5705–5709. (b) Lavallo, V.; Canac, Y.; DeHope, A.; Donnadieu, B.; Bertrand, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7236–7239. (c) Jazzar, R.; Dewhurst, R. D.; Bourg, J.-B.; Donnadieu, B.; Canac, Y.; Bertrand, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2899–2902. (d) Jazzar, R.; Bourg, J.-B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492–3499.

(18) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5224–5228.

Downloaded by UNIV MAASTRICHT on August 15, 2009
Published on July 13, 2009 on http://pubs.acs.org | doi: 10.1021/ol901418c

Table 1. Hydroamination of Allenes with Primary Amines and Secondary (Alkyl)(aryl)amines[a]

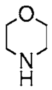
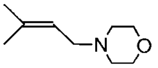
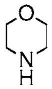
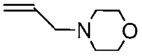
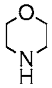
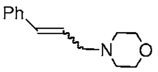
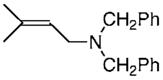
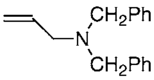
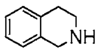
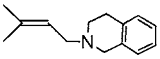
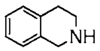
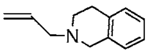
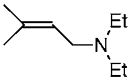
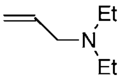
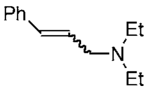
entry	amine	allene	*t* (°C)	time (h)	product	yield[b]
1	$PhNH_2$	**A**	70	12		95[c]
2	$MesNH_2$	**A**	100	5		74
3	${}^tBuNH_2$	**A**	150	30		54
4	PhMeNH	**A**	70	12		98
5	p-Cl-C_6H_4MeNH	**A**	70	12		97
6	p-MeO-C_6H_4MeNH	**A**	70	12		97
7		**A**	70	9		99
8		**A**	70	3		99
9		**B**	70	3		87[d]

[a] **Cat1** (5 mol %), amine (0.5 mmol), allene (0.5 mmol), and C_6D_6 (0.4 mL). [b] Yields are determined by ^1H NMR using benzylmethyl ether as an internal standard. [c] Yield based on allene. [d] Excess allene was used.

In an initial experiment, 1,1-dimethylallene **A** was treated with *N*-methylaniline, and after 12 h at only 70 °C, the desired hydroamination product was obtained in 98% yield (entry 4). Para substitution of the aniline by a chlorine or methoxy group is well tolerated, the corresponding adducts being formed in 97% yields (entries 5 and 6). 1,2,3,4-Tetrahydroquinoline and indoline have been recognized as important synthetic intermediates[19] and exhibit extensive biological activities and potential pharmaceutical applications. Using allene **A**, their allylic amine derivatives have been prepared using our catalytic procedure with up to 99% yield (entries 7 and 8). The hydroamination reaction with secondary (aryl)(alkyl)amines is not limited to 1,1-disubstituted allenes. The parent allene **B** can also be used as shown in entry 9.

Based on these positive results, we investigated the catalytic activity of **Cat1** for the hydroamination of allenes with more basic secondary amines (Table 2). By analogy with the work of Yamamoto, we first reacted morpholine with allenes **A**−**C**, and in all cases, the Markovnikov adduct was obtained in good to excellent yields (entries 1−3). Benzylic and benzocyclic amines also smoothly react with allenes **A** and **B** at temperatures between 70 and 90 °C affording the hydroamination products in 93 to 99% yields after only 8−12 h (entries 4−7). Lastly, we used diethy-

Table 2. Hydroamination of Allenes with Secondary Alkylamines[a]

entry	amine	allene	*t* (°C)	time (h)	product	yield[b]
1		**A**	100	12		92
2		**B**	100	12		89[c]
3		**C**	130	24		66[d,e]
4	$(PhCH_2)_2NH$	**A**	80	12		99
5	$(PhCH_2)_2NH$	**B**	70	12		94[c]
6		**A**	90	12		98
7		**B**	90	8		93[c]
8	Et_2NH	**A**	130	36		98
9	Et_2NH	**B**	150	24		82[c]
10	Et_2NH	**C**	165	24		61[e,f]

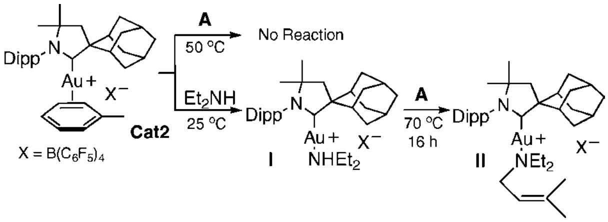
[a] **Cat1** (5 mol %), amine (0.5 mmol), allene (0.5 mmol), and C_6D_6 (0.4 mL). [b] Yields are determined by ^1H NMR using benzylmethyl ether as an internal standard. [c] Excess allene was used; yield based on amine. [d] *E*/*Z* = 2.2. [e] Two equivalents of allene was used; yield based on amine. [f] *E*/*Z* = 3.4.

---

(19) (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446. (b) Higashio, Y.; Shoji, T. *Appl. Cat. A: Gen.* **2004**, *260*, 251–259.

lamine as the prototypical secondary alkylamine. Although drastic conditions are required (130−165 °C, 24−36 h), the addition occurred to yield the Markovnikov adduct in 61 to 98% yields (entries 8−10). These results emphasize the robustness of the catalyst.

Scheme 3. Experiments To Approach the Reaction Mechanism



To gain insight into the mechanism of the gold(I)-catalyzed hydroamination of allenes, the following experiments were performed (Scheme 3). Addition of excess allene **A** to complex **Cat2** did not give the desired allene gold complex at room temperature or even upon heating at 50 °C. This is in marked contrast with the case of alkynes, for which an η^2-alkyne complex was readily formed and isolated.[18,20] On the other hand, upon exposure at room temperature of a solution of **Cat2** in deuterated benzene to 1 equiv of diethylamine, the amine complex **I** was spontaneously and quantitatively obtained. Then, addition of excess allene **A** to a C_6D_6 solution of **I** gave after 16 h at 70 °C complex **II**, which was isolated in 95% yield. These observations call into question an outer-sphere mechanism involving the attack of the amine to an initially formed gold π-allene complex[15] and rather suggest an inner sphere mechanism with transient formation of a tricoordinated gold complex, as proposed by Yamamoto[14] and Tanaka[21] for gold-catalyzed hydroamination of allenes and alkynes, respectively, with arylamines. Moreover, it seems quite likely that the amine complex **I** is the resting state of the catalyst, just as **Cat3** is in the case of the hydroamination with ammonia.[18]

Since we have already shown that **Cat1** promotes the addition of ammonia to allenes,[18] it appears that the catalytic system described here has a broad scope of application; many types of nontertiary amines can be used, as well as a variety allenes. Importantly, the regioselectivity observed (Markovnikov addition) is opposite to that obtained with early transition metal catalysts (anti-Markovnikov addition).[7,8] The regioselectivity is also different from that reported by Windehoefer;[15] using unsubstituted carbamates and a cationic gold(I) complex bearing an NHC or a phosphine ligand, the Markovnikov adduct was formed but at the more substituted terminus of the allene (Scheme 1). This striking difference has not yet been rationalized, and mechanistic studies are under active investigation. Moreover, the hydroamination of 1,3-disubstituted allenes allows for the formation of a chiral center, and we are investigating the possibility of using gold(I) complexes bearing an optically active CAAC ligand for the preparation of enantiomerically enriched allylic amines.[22]

Acknowledgment. Financial support from the NIH (R01 GM 68825) is gratefully acknowledged. Thanks are also due to the China Scholarship Council for a Graduate Fellowship (X.Z.).

Supporting Information Available: General catalytic procedure, experimental details, and characterization of complexes **I** and **II**, as well as ^1H, ^{13}C, and MS spectra for new catalytic products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901418C

---

(20) Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2779–2782.

(21) Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* **2003**, *5*, 3349–3352.

(22) A few examples of intramolecular asymmetric hydroamination of allenes have been reported. See refs 5f,,5g and 12g and: (a) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105–5118. (b) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496–499. (c) Hoover, J. M.; Petersen, J. R.; Pikul, J. H.; Johnson, A. R. *Organometallics* **2004**, *23*, 4614–4620. (d) Roesky, P. W.; Muller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708–2710.

Downloaded by UNIV MAASTRICHT on August 15, 2009
Published on July 13, 2009 on http://pubs.acs.org | doi: 10.1021/ol901418c