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



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 allenes⁴ has been widely studied,⁵ the intermolecular version has received limited attention. Depending on the regiochemistry, this reaction can lead to imines, enamines, or ally-lamines. 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-

ORGANIC LETTERS

2009 Vol. 11, No. 15

3166-3169

[†] 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.

sponding imines,⁷ and more recent papers confirm that earlytransition-metal catalysts lead to the anti-Markovnikov adducts (Scheme 1, top).⁸ The Markovnikov addition has

Scheme 1. Previous Results for the Hydroamination of Allenes



first been achieved in the presence of equimolar amounts of mercury(II), palladium(II), and platinum(II) salts⁹ and then used a palladium(0) catalyst in the presence of triethylammonium iodide¹⁰ or acetic acid¹¹ as cocatalysts. Gold catalysts¹² have more recently been developed.¹³ Yamamoto et al. first demonstrated that 10 mol % of AuBr₃ 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 (Ar₃P)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)

(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.

(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



Figure 1. Cationic gold(I) complexes promoting the addition of NH₃ to nonactivated alkynes and allenes.

(alkyl)(amino)carbene (CAAC)¹⁷ as ancillary ligand, efficiently promoted the addition of NH₃ 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(C₆F₅)₄] efficiently promotes the intermolecular Markovnikov hydroamination of allenes **A**–**C** (scheme 2) with a variety of primary and, more importantly, secondary amines.

Scheme 2. Allenes A-C Used in This Study R^1 R^2 R^3 R^3 $R^1 = R^2 = Me, R^3 = H$ $B: R^1 = R^2 = R^3 = H$ $C: R^1 = Ph, R^2 = R^3 = H$

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).

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

^{(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,

Table 1. Hydroamination of Allenes with Primary Amines and Secondary (Alkyl)(aryl)amines a											
entry	amine	allene	t (°C)	time	product	yield ⁶					

entry	annie	anche	(°C)	(h)	product	yiciu
1	PhNH ₂	Α	70	12	Ph 60% H 40% N-Ph	95 [°]
2	MesNH ₂	A	100	5	Mes N H	74
3	^t BuNH ₂	A	150	30	≻−−N, H	54
4	PhMeNH	A	70	12	Me N Ph	98
5	p-Cl- C ₆ H₄MeNH	Α	70	12	Me N. Ph-Cl	97
6	p-MeO- C ₆ H ₄ MeNH	Α	70	12	Me N Ph-OMe	97
7		Α	70	9	× N	99
8		A	70	3	$\rightarrow N$	99
9		В	70	3		87 ^d

^{*a*} **Cat1** (5 mol %), amine (0.5 mmol), allene (0.5 mmol), and C₆D₆ (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 intermediates¹⁹ 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





^{*a*} Cat1 (5 mol %), amine (0.5 mmol), allene (0.5 mmol), and C₆D₆ (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.

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-

^{(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.

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 C₆D₆ 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 complex¹⁵ and rather suggest an inner sphere mechanism with transient formation of a tricoordinated gold complex, as proposed by Yamamoto¹⁴ and Tanaka²¹ for gold-catalyzed hydroamina-

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

tion 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, ¹³C, and MS spectra for new catalytic products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901418C

⁽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.