ORGANIC LETTERS

2006
Vol. 8, No. 23
5303−5305

Room Temperature Hydroamination of *N*-Alkenyl Ureas Catalyzed by a Gold(I) *N*-Heterocyclic Carbene Complex

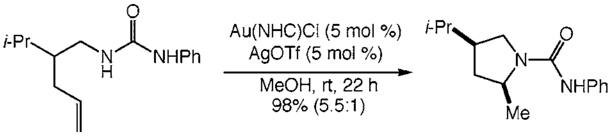
Christopher F. Bender and Ross A. Widenhoefer*

P. M. Gross Chemical Laboratory, Duke University,
Durham, North Carolina 27708-0346

rwidenho@chem.duke.edu

Received August 26, 2006

ABSTRACT



Treatment of an *N*-4-pentenyl or *N*-5-hexenyl urea with a catalytic 1:1 mixture of a gold(I) *N*,*N*-diaryl imidazol-2-ylidine complex and AgOTf at or near room temperature leads to intramolecular *exo*-hydroamination to form the corresponding nitrogen heterocycle in excellent yield.

Saturated nitrogen heterocycles constitute an important class of naturally occurring and biogically active molecules.[1] The addition of the N−H bond of an amine or amide derivative across the C═C bond of a pendent alkene (hydroamination) has received considerable attention as an atom-economical and potentially expedient route to the synthesis of nitrogen heterocycles.[2] However, despite significant effort in this area, the intramolecular hydroamination of unactivated alkenes remains problematic.[2] Although rare earth,[3] alkali,[4] and group 4[5] metal complexes catalyze the intramolecular hydroamination of unactivated alkenes, the synthetic utility of these transformations is compromised by the excessive oxophilicity of the catalysts. Conversely, intramolecular hydroamination of unactivated alkenes catalyzed by late transition metal complexes typically requires either forcing conditions,[6] a sulfonamide nucleophile,[7] or a conjugated alkenyl moiety.[8,9]

In response to the limitations associated with the intramolecular hydroamination of unactivated alkenes, we recently reported the intramolecular hydroamination of *N*-alkenyl carbamates catalyzed by a mixture of the gold(I) phosphine complex Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (**1**) and AgOTf.[10,11] As an example, reaction of **2a** with a catalytic 1:1 mixture of **1** and AgOTf (5 mol %) in dioxane at 60 °C

---

(1) (a) Liddell, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520. (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862.

(2) (a) Beller, M.; Tillack, A.; Seayad, J. In *Transition Metals for Organic Synthesis*, 2nd ed.; Wiley-VCH: Weinheim, 2004; pp 403−414. (b) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (d) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, 2001; pp 91−142. (e) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104.

(3) (a) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (b) Riegert, D.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Org. Chem.* **2006**, *71*, 2514. (c) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 4391. (d) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (e) Gribkov, D. V.; Hultzsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

(4) Crimmin, M. R.; Casely, I. J.; Hill, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2042.

(5) (a) Müller, C.; Loos, C.; Schulenberg, N.; Doye, S. *Eur. J. Org. Chem.* **2006**, 2499. (b) Kim H.; Lee, P. H.; Livinghouse, T. *Chem. Commun.* **2005**, 5205. (c) Thompson, R. K.; Bexrud, J. A.; Schafer, L. L. *Organometallics* **2006**, *25*, 4069.

(6) Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.

(7) (a) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (b) Liu, X.-Y.; Li, C.-H.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (c) Komeyama, K.; Morimoto, T.; Takaki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2938.

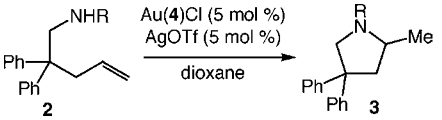
(8) (a) Tiamia, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042. (b) Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134.

(9) For recent examples of the zinc-catalyzed intramolecular hydroamination of unactivated alkenes, see: (a) Zulys, A.; Dochnahl, M.; Hollmann, D.; Löhnwitz, K.; Herrmann, J.-S.; Roesky, P. W.; Blechert, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7794. (b) Dochnahl, M.; Pissarek, J.-W.; Blechert, S.; Löhnwitz, K.; Roesky, P. W. *Chem. Commun.* **2006**, 3405. (c) Meyer, N.; Löhnwitz, K.; Zulys, A.; Roesky, P. W.; Dochnahl, M.; Blechert, S. *Organometallics* **2006**, *25*, 3730.

(10) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747.

10.1021/ol062107i CCC: $33.50 © 2006 American Chemical Society
Published on Web 10/14/2006

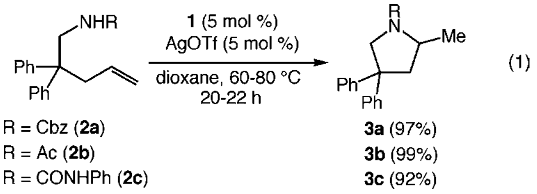
Table 1. Hydroamination of **2a**−**2c** Catalyzed by a 1:1 Mixture of Au(**4**)Cl and AgOTf



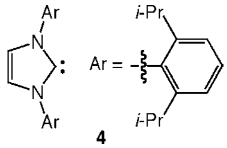
entry	R	temp	time(h)	convn (%)[a]	yield (%)[b]
1	Cbz (**a**)	45 °C	15	100	96
2	Ac (**b**)	45 °C	15	100	99
3	CONHPh (**c**)	45 °C	15	100	93
4	Cbz (**a**)	rt[c]	18	20	
5	Ac (**b**)	rt[c]	18	83	83
6	CONHPh (**c**)	rt[c]	18	100	96

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated material of >95% purity. [c] 22−24 °C.

for 22 h led to isolation of pyrrolidine **3a** in 97% yield (eq 1). *N*-Alkenyl carboxamides and ureas such as **2b** and **2c** also underwent efficient hydroamination in the presence of **1**/AgOTf, although somewhat higher reaction temperature (80 °C) was required (eq 1).[12] Lower reaction temperature in each case led to incomplete conversion.



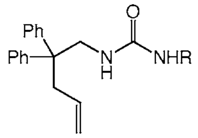
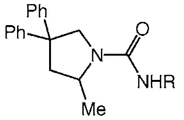
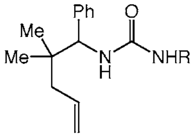
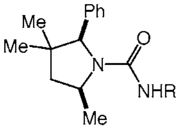
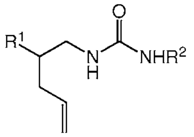
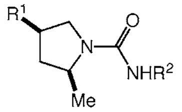
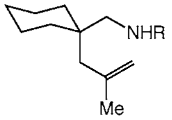
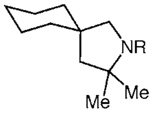
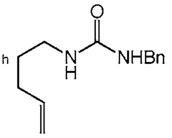
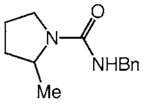
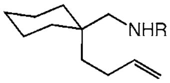
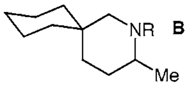
For some time we have sought to identify more active and more general catalyst systems for the intramolecular hydroamination of unactivated alkenes. We noted that sterically hindered, electron-rich phosphines such as P(*t*-Bu)$_2$(*o*-biphenyl) were particularly effective supporting ligands for gold-catalyzed hydroamination.[10] As is the case with electron-rich phosphines, *N*-heterocyclic carbenes are strong σ-donors that form stable compounds with a diverse range of transition metals[13] including gold(I).[14] Furthermore, a number of these ligands, in particular the commercially available 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (**4**), are highly sterically hindered.[15] These characterisitics suggested that **4** might also function as an effective supporting ligand for gold-catalyzed hydroamination.[16] Indeed, here we report that Au(**4**)Cl is an exceptionally active precatalyst for the intramolecular hydroamination of *N*-alkenyl ureas.



4

Initial hydroamination experiments employing Au(**4**)Cl as a precatalyst were encouraging. Treatment of *N*-4-pentenyl derivatives **2a**−**2c** with a 1:1 mixture of Au(**4**)Cl and AgOTf at 45 °C for 15 h in each case led to complete consumption of **2** and isolation of the corresponding pyrrolidine **3** in ≥93%

Table 2. Hydroamination of *N*-Alkenyl Ureas Catalyzed by a 1:1 Mixture of Au(**4**)Cl and AgOTf (5 mol %) at Room Temperature[17] for 15−24 h

entry	substrate	heterocycle[a]	solvent[b]	yield (%)[c]
				
1	R = 4-BrC$_6$H$_4$		**A**	99
2	R = 4-OMeC$_6$H$_4$		**A**	100
3	R = 4-AcC$_6$H$_4$		**A**	100
4	R = Et		**A**	91
5			**B**	97[d]
6			**C**	95
7			**B**	96[e]
				
8	R = Et		**B**	99 (3.9:1)
9	R = Ph		**B**	92 (3.6:1)
				
10[f]	R^1 = R^2 = Ph		**B**	99 (2.9:1)
11[g]	R^1 = Ph, R^2 = Et		**B**	84 (3.3:1)
12	R^1 = *i*-Pr, R^2 = Ph		**B**	98 (5.5:1)
13	 R = CONHPh		**A**	92
14[h]			**B**	98
15	 R = CONHPh		**B**	98

[a] Major diastereomer is shown. [b] Solvent: **A** = dioxane, **B** = MeOH, **C** = MeOH/H$_2$O (95/5). [c] Isolated product of ≥95% purity. [d] Reaction run with 1 mol % catalyst loading. [e] Reaction run exposed to atmosphere. [f] Reaction run at 45 °C with 10 mol % catalyst loading. [g] Reaction run at 45 °C. [h] Reaction run at 45 °C with 10 mol % catalyst loading for 43 h.

---

(11) For the Pd(II)-catalyzed intramolecular hydroamination of *N*-alkenyl carbamates, see: Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.

(12) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143.

(13) (a) Hermann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247.

(14) de Frémont, P.; Scott, N. M.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2005**, *24*, 2411.

(15) Dorta, R.; Stevens, E. D.; Scott, N. M.; Costablile, C.; Cavallo, L.; Hoff, C. D.; Nolan, S. P. *J. Am. Chem. Soc.* **2005**, *127*, 2485.

yield (Table 1, entries 1−3). However, the corresponding room temperature hydroamination of carbamate **2a** or carboxamide **2b** failed to reach completion after 18 h (Table 1, entries 4 and 5).[17] Conversely, reaction of urea **2c** with a 1:1 mixture of Au(**4**)Cl and AgOTf at room temperature for 18 h led to complete consumption of **2c** and isolation of **3c** in 96% yield (Table 1, entry 6).[18] Subsequent experimentation revealed that employment of methanol as solvent in place of dioxane led to a ∼2-fold increase in the rate of hydroamination.

Both *N*′-aryl and *N*′-alkyl *N*-4-pentenyl ureas underwent intramolecular hydroamination at room temperature in high yield in the presence of a catalytic amount of Au(**4**)Cl/AgOTf (Table 2, entries 1−4). The Au(**4**)Cl/AgOTf catalyst system was sufficiently active such that efficient hydroamination was realized with 1 mol % of the catalyst mixture (Table 2, entry 5). Furthermore, neither the rate nor the yield of hydroamination was affected by the presence of a large excess of water or air in the reaction mixture (Table 2, entries 6 and 7). Gold-catalyzed hydroamination of 4-pentenyl ureas monosubstituted at the C(1) or C(2) position formed substituted pyrrolidines that possessed a *cis*-2,5 or *cis*-2,4 substitution pattern, respectively, with up to 5.5:1 diastereoselectivity (Table 2, entries 8−12). Noteworthy was that the diastereoselectivity of these transformations was improved relative to the hydroamination of the corresponding *N*-4-pentenyl carboxamides catalyzed by **1**/AgOTf (≤1.8:1).[12] Gold-catalyzed hydroamination of alkenyl ureas also tolerated substitution at the internal olefinic carbon atom and was effective for the cyclization of an unsubstituted *N*-4-pentenyl urea, although more forcing conditions were required (Table 2, entries 13 and 14). A 5-hexenyl urea also underwent room temperature hydroamination in the presence of Au(**4**)Cl/AgOTf to form the corresponding piperidine derivative in excellent yield (Table 2, entry 15).

In summary, we have reported the first application of a gold(I) carbene complex as a catalyst for the hydroamination of unactivated alkenes. The resulting catalyst system is highly active for the *exo*-hydroamination of *N*-4-pentenyl and *N*-5-hexenyl ureas to form the corresponding nitrogen heterocycles in excellent yield with good regioselectivity and up to 5.5:1 diasteroselectivity.

Acknowledgment. The authors acknowledge the NSF (CHE-0304994 and CHE-0555425), the Petroleum Research Fund (43636-AC1), adminstered by the American Chemical Society, and Johnson & Johnson for support of this research. C.F.B. thanks Duke University for a Charles R. Hauser Fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062107I

---

(16) For recent examples of the application of gold *N*-heterocyclic carbene complexes as catalysts for organic transformations, see: (a) Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, 2048. (b) Fructos, M. R.; Belderrain, T. R.; de Frémont, P.; Scott, N. M.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 5284. (c) Fructos, M. R.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2006**, *25*, 2237. (d) Schneider, S. K.; Herrmann, W. A.; Herdtweck, E. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2363.

(17) Room temperature ranged from 22 to 24 °C.

(18) Treatment of **2c** with HOTf (15 mol %), Au(**4**)Cl (15 mol %), or AgOTf (15 mol %) in methanol at room temperature for 15 h led to no detectable consumption of **2c** by ^{1}H NMR analysis. For an analysis of the role of HOTf in the intramolecular hydroamination of unactivated alkenes with sulfonamides, see: Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.