Gold(I)-catalyzed intramolecular hydroamination of unactivated alkenes with carboxamides†

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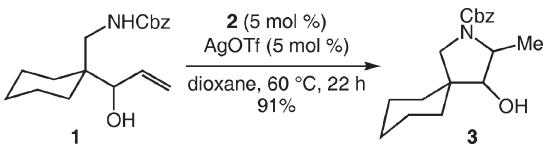
***N*-Alkenyl carboxamides undergo gold-catalyzed intramolecular *exo*-hydroamination to form nitrogen heterocycles in excellent yield.**

The transition metal catalyzed addition of an N–H bond across the C=C bond of a pendent alkene (hydroamination) has received considerable attention as a potentially expedient route to the synthesis of nitrogen heterocycles.[1] A number of amine derivatives have been employed in the catalytic intramolecular hydroamination of alkenes including primary[2] and secondary alkylamines,[3,4] sulfonamides,[5] and, quite recently, labile carbamates.[6,7] Conversely, the transition metal catalyzed intramolecular hydroamination of alkenes with carboxamides has not been demonstrated. Rather, this transformation is typically achieved *via* reaction of the alkene with a stoichiometric amount of a Hg(II) salt or selenium halide, followed by reduction.[8]

As part of a continuing effort directed toward the development of new methods for the hydroamination of unactivated alkenes,[3,6,9] we recently reported the platinum-catalyzed intermolecular hydroamination of ethylene and vinyl arenes with carboxamides.[9] Unfortunately, attempts to extend this protocol to include the intramolecular hydroamination of alkenes with carboxamides were unsuccessful.‡ Partially in response to this shortcoming, we recently developed a gold(I)-catalyzed protocol for the hydroamination of *N*-alkenyl carbamates.[6] As an example, reaction of **1** with a catalytic 1 : 1 mixture of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (**2**) and AgOTf (5 mol%) in dioxane at 60 °C for 22 h formed pyrrolidine **3** in 91% isolated yield (eqn (1)). The high efficiency of this transformation coupled with the mild reaction conditions suggested that mixtures of **2** and AgOTf might also catalyze the intramolecular hydroamination of alkenes with carboxamides. Indeed, here we report the gold(I)-catalyzed intramolecular hydroamination of *N*-alkenyl carboxamides.



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The catalyst system optimized for the intramolecular hydroamination of *N*-alkenyl carbamates proved effective for the intramolecular hydroamination of *N*-4-pentenyl carboxamides, although a somewhat higher reaction temperature was required.§ For example, reaction of a concentrated (1 M) dioxane solution of *N*-(2,2-diphenyl-4-pentenyl)acetamide (**4**) with a catalytic 1 : 1 mixture of **2** and AgOTf (5 mol%) at 80 °C for 21 h led to isolation of pyrrolidine **5** in 99% yield (Table 1, entry 1). Neither the rate nor the yield of the gold-catalyzed hydroamination of **4** was significantly affected by the presence of air or moisture in the reaction vessel (Table 1, entries 2 and 3).¶ Conversely the efficiency of the conversion of **4** to **5** depended strongly on the nature of the exogenous phosphine ligand. In particular, treatment of **4** with a catalytic 1 : 1 mixture of Au(PPh$_3$)Cl and AgOTf (5 mol%) at 85 °C in toluene reportedly led to no significant formation of **5**.[5]

Gold-catalyzed intramolecular hydroamination was effective for primary and secondary alkyl carboxamides, aryl carboxamides, and primary ureas and the protocol tolerated carboxylic esters and unprotected hydroxyl groups (Table 1, entries 4–10). The catalyst system was efficient; 1 mol% of a 1 : 1 mixture of **2** and AgOTf was sufficient to achieve complete conversion of **6** to **7** (Table 1, entry 6). Gold-catalyzed hydroamination of *N*-alkenyl carboxamides tolerated substitution at the C(1), C(2), and C(4) positions of the 4-pentenyl group (Table 1, entries 11–13) and the reaction was effective for the formation of aliphatic heterobicyclic compounds and piperidine derivatives (Table 1, entries 14 and 15). Bicyclic compounds in which a saturated nitrogen-containing ring is fused to an aromatic moiety including the 2-methyl indolines are components of a number of drug targets.[10] We were therefore disappointed that carbamate-protected *o*-allyl aniline derivatives underwent Au-catalyzed intramolecular hydroamination in poor yield.[6] For this reason, it is significant that the Au-catalyzed hydroamination of carboxamide **10** formed 2-methylindoline **11** in 99% yield (Table 1, entry 16).

In summary, we have developed an effective Au(I)-catalyzed protocol for the intramolecular hydroamination of *N*-alkenyl carboxamides to form protected pyrrolidines, piperidines, and heterobicyclic compounds. We continue to work toward optimizing and expanding the scope of the Au(I)-catalyzed hydroamination of C–C multiple bonds.

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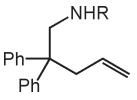
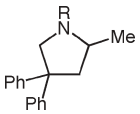
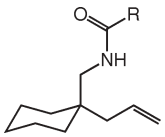
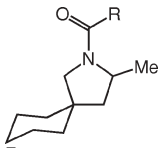
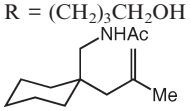
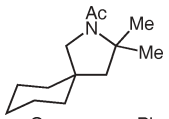
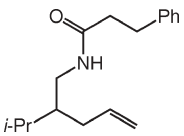
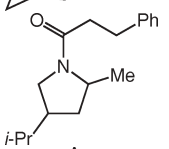
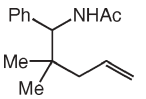
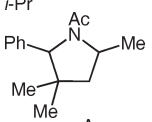
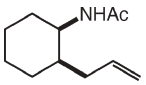
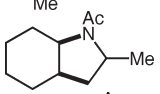
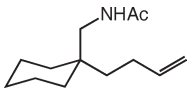
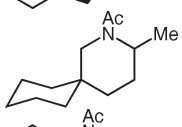
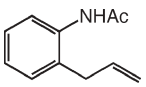
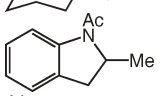
Table 1 Intramolecular hydroamination of *N*-alkenyl carboxamides (1 M) catalyzed by a 1 : 1 mixture of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl (**2**) and AgOTf (5 mol%) in dioxane at 80 °C

Entry	Substrate	Heterocycle	Time/h	Yield (%)[a]
				
1	R = Ac (**4**)	**5**	21	99
2[b]			22	96
3[c]			22	89
4	R = CONHPh		15	92
				
5	R = *n*-Pr (**6**)	**7**	2	91
6[d]			13	86
7	R = Cy (**8**)	**9**	7	97
8	R = Ph		20	95
9	R = $(CH_2)_3CO_2Me$		17	95
10	R = $(CH_2)_3CH_2OH$		18	86
11			15	79
12			22	96 (1.5 : 1)
13			22	92 (1.8 : 1)
14[e]			24	82 (2.5 : 1)
15			15	88
16			22	99
	10	**11**		

[a] Isolated material of ⩾95% purity. [b] Reaction mixture contained water (1 equiv.). [c] Reaction run exposed to air (1 atm). [d] Reaction run with 1 mol% catalyst loading. [e] Reaction run with 10 mol% catalyst loading at 100 °C.

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Notes and references

‡ This catalyst system is effective for the intramolecular hydroamination of unactivated alkenes with secondary amines.[3]

§ PCy_2*o*-biphenyl was an effective supporting ligand and toluene and diglyme were effective solvents for gold-catalyzed hydroamination (see ESI).†

¶ Heating a 1 M dioxane solution of **8** (Table 1, entry 7) that contained either triflic acid (15 mol%) or silver triflate (15 mol%) at 80 °C for 20 h led to no detectable consumption of starting material or formation of **9**.[11]

1 (*a*) M. Beller, A. Tillack and J. Seayad, in *Transition Metals for Organic Synthesis*, ed. M. Beller and C. Bolm, Wiley-VCH, Weinheim, 2nd edn, 2004, pp. 403–414; (*b*) T. E. Muller and M. Beller, *Chem. Rev.*, 1998, **98**, 675; (*c*) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368; (*d*) J. J. Brunet and D. Neibecker, in *Catalytic Heterofunctionalization*, ed. A. Togni and H. Grützmacher, Wiley-VCH, Weinheim, 2001, pp. 91–142; (*e*) S. Hong and T. J. Marks, *Acc. Chem. Res.*, 2004, **37**, 673.

2 (*a*) D. Riegert, J. Collin, A. Meddour, E. Schulz and A. Trifonov, *J. Org. Chem.*, 2006, **71**, 2514; (*b*) D. V. Gribkov, K. C. Hultzsch and F. Hampel, *J. Am. Chem. Soc.*, 2006, **128**, 3748; (*c*) J. Y. Kim and T. Livinghouse, *Org. Lett.*, 2005, **7**, 4391; (*d*) J. A. Bexrud, J. D. Beard, D. C. Leitch and L. L. Schafer, *Org. Lett.*, 2005, **7**, 1959; (*e*) J. Y. Kim and T. Livinghouse, *Org. Lett.*, 2005, **7**, 1737; (*f*) M. R. Crimmin, I. J. Casely and M. S. Hill, *J. Am. Chem. Soc.*, 2005, **127**, 2042; (*g*) A. Zulys, M. Dochnahl, D. Hollmann, K. Löhnwitz, J.-S. Herrmann, P. W. Roesky and S. Blechert, *Angew. Chem., Int. Ed.*, 2005, **44**, 7794.

3 C. F. Bender and R. A. Widenhoefer, *J. Am. Chem. Soc.*, 2005, **127**, 1070.

4 A. Tiamia and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 6042.

5 (*a*) J. Zhang, C.-G. Yang and C. He, *J. Am. Chem. Soc.*, 2006, **128**, 1798; (*b*) D. Karshtedt, A. T. Bell and T. D. Tilley, *J. Am. Chem. Soc.*, 2005, **127**, 12640.

6 X. Han and R. A. Widenhoefer, *Angew. Chem., Int. Ed.*, 2006, **45**, 1747.

7 F. E. Michael and B. M. Cochran, *J. Am. Chem. Soc.*, 2006, **128**, 4246.

8 S. Robin and G. Rousseau, *Tetrahedron*, 1998, **54**, 13681.

9 (*a*) X. Wang and R. A. Widenhoefer, *Organometallics*, 2004, **23**, 1649; (*b*) H. Qian and R. A. Widenhoefer, *Org. Lett.*, 2005, **7**, 2635.

10 (*a*) J. Bermudez, S. Dabbs, K. A. Joiner and F. D. King, *J. Med. Chem.*, 1990, **33**, 1929; (*b*) S. Adachi, K. Koike and I. Takayangi, *Pharmacology*, 1996, **53**, 250; (*c*) S. J. Yoon, Y. Chung, M. S. Lee, D. R. Choi, J. A. Lee, D. K. Yun, E. Y. Moon, H. S. Hwang, C. H. Choi and S. H. Jung, *Patent WO*, 9807719, 1998 (Chem. Abs., 1998, **128**, 204885).

11 For references regarding the acid-catalyzed hydroamination of olefins see: (*a*) B. Schlummer and J. F. Hartwig, *Org. Lett.*, 2002, **4**, 1471; (*b*) L. L. Anderson, J. Arnold and R. G. Bergman, *J. Am. Chem. Soc.*, 2005, **127**, 14542; (*c*) T. C. Wabnitz, J.-Q. Yu and J. B. Spencer, *Chem.–Eur. J.*, 2004, **10**, 484.

