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Gold-Catalyzed Hydroamination/ Cycloisomerization Reaction of 1,6-Enynes

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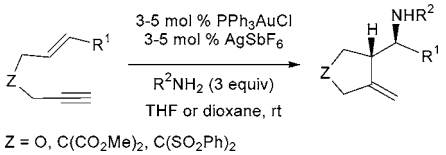
ABSTRACT



An efficient Au(I) catalytic system is described for the hydroamination/cycloisomerization reaction of functionalized 1,6-enynes. The reaction leads to carbo- and heterocyclic amino derivatives in good to excellent yields. The cyclizations were conducted in the presence of PPh_3-AuCl/$AgSbF_6$ catalyst in THF or dioxane at room temperature. The use of allyloxycarbonyl carbamate has allowed the formation of free amino derivatives via sequential Au- and Pd-catalyzed reactions.

Recent years have witnessed a substantial growth in the number of gold-catalyzed reactions for carbon−nitrogen bond formations.[1] In fact, hydroamination is a highly challenging reaction and is especially difficult to manage on unactivated olefins.[2] Some very efficient gold catalysts were able to promote inter- or intramolecular C−N bond creations starting from tosylamine or amine carbamate derivatives and allenes or alkenes.[3] Our research team along with others have found that metal-catalyzed cycloisomerization reactions of enynes in the presence of an external nucleophile such as water or alcohol have led to novel rearrangements (Scheme 1).[4] This type of transformation has long been restricted to oxygen nucleophiles, but recently, electron-rich aromatic systems were found to be suitable

(1) For representative examples and seminal references, see: (a) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2007**, *46*, in press. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (d) Gorin, D. J.; Toste, D. *Nature* **2007**, *446*, 395. (e) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (f) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (g) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (h) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6090. (i) Höffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (j) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (k) Pyykkö, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4412. (l) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (m) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237.

(2) For recent reviews, see: (a) Müller, T. A.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555.

(3) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (b) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (c) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.*, **2006**, *45*, 1744. (d) Morita, N.; Krause, N. *Eur. J. Org. Chem.* **2006**, 4634. (e) Liu, X.-Y.; Che, C.-M. *Org. Lett.* **2006**, *8*, 2707. (f) Shi, M.; Liu, L.-P.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (g) Nishina, N.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314. (h) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (i) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (j) Morita, N.; Krause, N. *Org. Lett.* **2004**, *6*, 4121. (k) For a recent asymmetric addition to allenes, see: LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2452.

(4) Representative references: (a) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-N.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706. (b) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850. (c) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.−Eur. J.* **2003**, *9*, 2627. (d) Méndez, M.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 10511. (e) Nishizawa, M.; Yadav, V. K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2003**, *5*, 1609. (f) Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293. (g) Nieto-Oberhuber, C.; Muñoz, M. P.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (h) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (i) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141. (j) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Synlett* **2007**, 1780.

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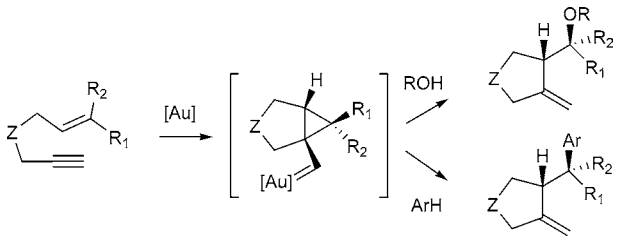
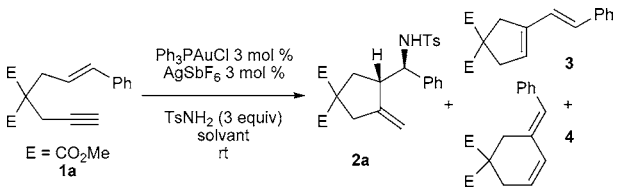
Scheme 1



reaction partners for such a rearrangement (Scheme 1).[5] To the best of our knowledge, Kozmin's group[3a] has described a unique example of intramolecular addition of an amino group to an alkene followed by trapping by an alkyne moiety. In pursuit of the investigation on atom-economical metal-catalyzed cycloisomerization reactions,[6] we have envisaged to develop mild conditions for the Au-catalyzed intermolecular addition of amines to carbon−carbon double bond concomitant with a cyclization process. We wish therefore to present in this paper our preliminary results of the hydroamination/cycloisomerization reactions of 1,6-enynes leading to cyclic functionalized amines.

Initial efforts have focused on the optimization of an efficient system starting from enyne **1a** as a model substrate (Table 1). The use of PPh_3AuCl associated with silver salt

Table 1. PPh_3AuCl-Catalyzed Hydroamination/ Cycloisomerization Reaction of Enynes



			products ratio (%)[a]		
entry	solvent	time (h)	**2a**	**3**	**4**
1	toluene	18	14	/	86
2	CH_2Cl_2	15	25	/	75
3	ether	17	20	36	44
4	MeCN	17	/	/	/
5	THF	16	46	33	20
6	dioxane	17	56	14	30
7[b]	dioxane	15	77	10	13

[a] Determined by ^1H NMR spectroscopy. [b] 5 mol % of catalyst.

$AgSbF_6$ in toluene has allowed the formation of the desired product **2a** as a minor compound (Table 1, entry 1). Competition with the classic cycloisomerization of enyne **1a** leading to the known[4g] dienes **3** and **4** has occurred, and the outcome of the reaction was studied in various solvents. The use of dichloromethane or ether did not give better results (Table 1, entries 2 and 3). A more coordinating solvent such as acetonitrile completely inhibited the reaction, and starting material was recovered unchanged (Table 1, entry 4). THF and dioxane have appeared as more suitable solvents for such a reaction (Table 1, entries 5 and 6). Indeed, the desired tosylamine **2a** was detected as the major product. A positive effect was observed in the presence of 5 mol % of catalyst in dioxane (Table 1, entry 7). Careful chromatography on silica gel has led to the desired amino derivative **2a** in a modest 38% yield.[7] The moderate isolated yield compared to the observed conversion and product ratio was due to the difficulty to eliminate excess tosylamine.

Anticipating that the outcome of the hydroamination/ cycloisomerization reaction may also depend on the external amine, we have decided to screen several amines and to confront them to various 1,6-enynes in the presence of the optimized system (Table 2). We were pleased to find that by switching from tosylamine to ethyl or benzyl carbamates, a clean and smooth reaction still occurred on carbo- and hetero-1,6-enynes and allowed good to excellent yields. The addition of ethylcarbamate to enynes **1a**−**c** afforded the corresponding cyclic derivatives **2b**−**d** in 51−78% isolated yields (Table 2, entries 1−3). Benzylcarbamate derivatives **2e** and **2f** were also synthesized in 64% and 76% yields, respectively (Table 2, entries 4 and 5). It was also highly challenging to try to perform the same reaction in the presence of aromatic amines (Table 2).[8] The *para*-nitroaniline was an excellent candidate for the aminocyclization reaction. The nitro-containing carbo- and heterocycles **2g**−**2i** were isolated in moderate to good yields (Table 2, entries 6−8). The *ortho*-cyanoaniline-substituted alkenes **2j**−**2l** were also obtained in good to excellent yields (Table 2, entries 9−11).

The presence of CF_3 and a halogen group such as chloride was also compatible with the reaction conditions and afforded the corresponding amines **2m** and **2n** in 86% and 77% yields, respectively (Table 1, entries 12 and 13).

The use of allyloxycarbonylcarbamate was found to be highly valuable: the corresponding carbamates **2o** and **2p** were obtained in 82% and 92% isolated yields (Scheme 2). Moreover, a clean deprotection was performed in the presence of the water-soluble system $Pd(OAc)_2$/TPPTS.[9,10] The corresponding free amines **5a** and **5b** were easily separated from the catalyst and isolated in 56% and 71% yields, respectively.

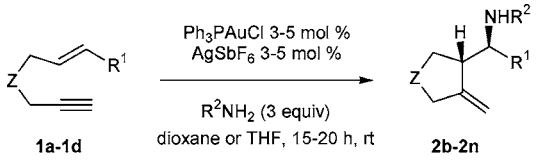
(5) (a) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (b) Toullec, P. Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427. (c) Amijs, C. H. M.; Ferrer, C.; Echavarren, A. M. *Chem. Commun.* **2007**, 698.

(6) (a) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (b) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949. (c) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (d) Genin, E.; Toullec, P. Y.; Marie, P.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. *Arkivoc* **2007**, *v*, 67.

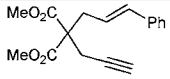
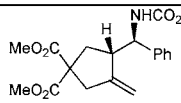
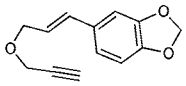
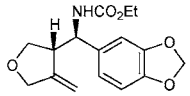
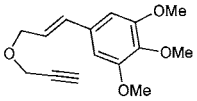
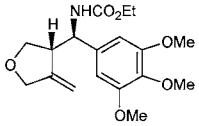
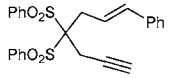
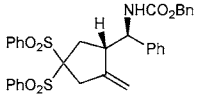
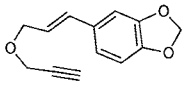
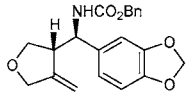
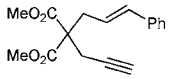
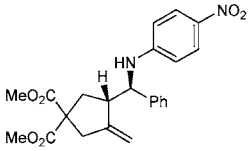
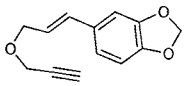
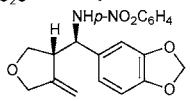
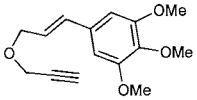
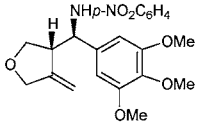
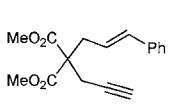
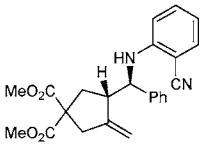
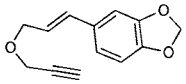
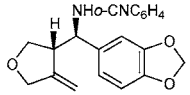
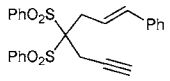
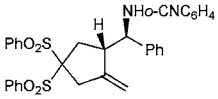
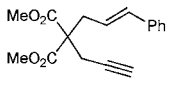
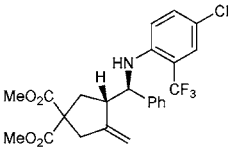
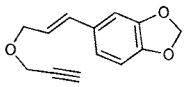
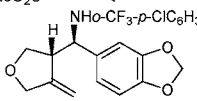
(7) A mixture of PPh_3AuCl (3−5 mol %, M = 494) and $AgSbF_6$ (3−5 mol %, M = 343.6) in distilled THF or dioxane (2.5 M) was stirred under an argon atmosphere at room temperature for 3 min. The aminonucleophile (3 equiv) and then the enyne (1 equiv) were finally added. After completion of the reaction, the mixture was filtered through a short pad of silica gel (EtOAc) and the solvents were evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography.

(8) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828 and references cited therein.

Table 2. PPh_3AuCl-Catalyzed Hydroamination/Cycloisomerization of Enynes



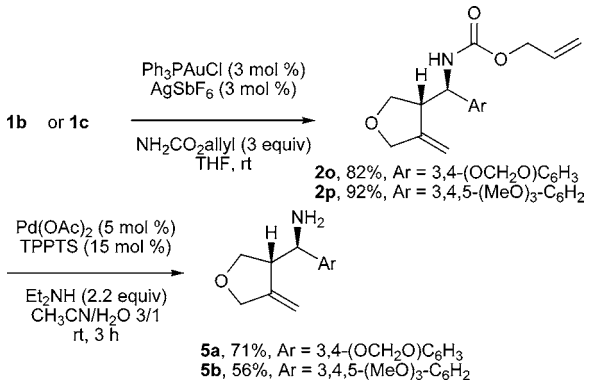
1a-1d **2b-2n**

entry	enynes		amine	alcohol		solvent	yield[a] (%)
1[b]		**1a**	H_2NCO_2Et		**2b**	dioxane	51
2		**1b**	H_2NCO_2Et		**2c**	THF	76
3		**1c**	H_2NCO_2Et		**2d**	THF	78
4		**1d**	H_2NCO_2Bn		**2e**	THF	64
5		**1b**	H_2NCO_2Bn		**2f**	THF	76
6[b]		**1a**	*p*-$NO_2C_6H_4NH_2$		**2g**	dioxane	46
7		**1b**	*p*-$NO_2C_6H_4NH_2$		**2h**	THF	78
8		**1c**	*p*-$NO_2C_6H_4NH_2$		**2i**	THF	71
9[b]		**1a**	*o*-$CNC_6H_4NH_2$		**2j**	dioxane	93
10		**1b**	*o*-$CNC_6H_4NH_2$		**2k**	THF	55
11		**1d**	*o*-$CNC_6H_4NH_2$		**2l**	THF	83
12[b]		**1a**	*o*-CF_3-*p*-$ClC_6H_3NH_2$		**2m**	dioxane	86
13		**1b**	*o*-CF_3-*p*-$ClC_6H_3NH_2$		**2n**	THF	77

[a] Isolated yield. [b] 5 mol % of catalyst.

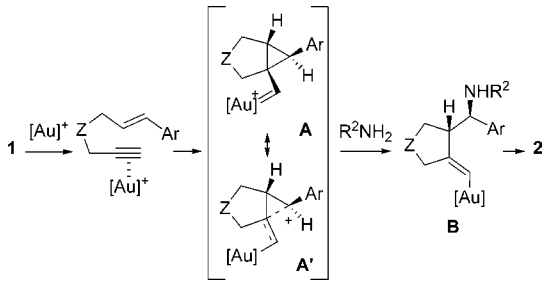
In all enyne/amine combinations tested, a single diastereoisomer of **2** has been formed. The *anti* diastereospecificity of the reaction was unambiguously established by X-ray analysis of derivative **2d** (see Supporting Information for

Scheme 2. Gold-Catalyzed Hydroamination/ Cycloisomerization Reactions of Enynes **1b** and **1c** with Allyloxycarbonylcarbamate



details). On the basis of this observation, we propose a mechanism closely related to the one associated with the alkoxy- and carbocyclization reactions of enynes (Scheme 3).[4] Initial complexation of the carbophilic Lewis acid

Scheme 3. Proposed Mechanism



cationic gold catalyst to the alkyne function allows the formation of a transient unstable cyclopropylcarbene **A**[11] via stereoselective attack of the alkene function on the alkyne. Addition of the external amine nucleophile releases a vinylaurate intermediate **B**. Protodemetalation completes the catalytic cycle. The presence of an aromatic ring on the external position of the alkene moiety being essential to the obtention of **2** in high yield, we postulate that the lifetime of intermediate **A** may be increased due to the stabilization of tautomeric form **A′** where the carbocation is located at the benzylic position. Decomposition pathways leading to known skeletal rearrangement products **3** and **4** are hence disfavored, and selective addition of the external nitrogen nucleophile giving intermediate **B** occurs.[12]

In conclusion, we have found that the combination of Au(I) and silver salts promotes a highly efficient hydroamination/cycloisomerization reaction of enynes under very mild conditions. This diastereoselective process implied the hydroamination reaction of unactivated alkene combined with a cyclization process. The addition of ethyl, benzyl, and allyl carbamate led to the corresponding cyclic protected amines in good to excellent yields. In the case of the allyloxycarbonyl protected derivatives, the smooth Pd-catalyzed deprotections were efficiently performed. The reaction conditions were compatible with electron-poor aromatic amines, including ones bearing chloride atoms. These derivatives are particularly interesting considering the possibility to further functionalize the substituted aniline ring. Further studies will be directed to the application of this methodology to the synthesis of natural and biologically active products.

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Supporting Information Available: Experimental procedure, full analyses of amines **2a**−**2p** and **5a**−**5b**, and X-ray analysis of **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A mechanism relying on a concerted diastereoselective hydroamination/carbocyclization sequence leading directly to vinylaurate intermediate **B** cannot be ruled out.