ORGANIC LETTERS

2009
Vol. 11, No. 12
2671−2674

Gold(I)-Catalyzed Intramolecular Dihydroamination of Allenes with *N,N'*-Disubstituted Ureas To Form Bicyclic Imidazolidin-2-ones

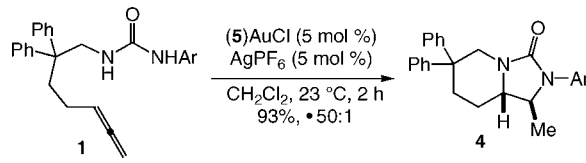
Hao Li and Ross A. Widenhoefer*

Duke University, Department of Chemistry, French Family Science Center, Durham, North Carolina 27708-0346

rwidenho@chem.duke.edu

Received April 6, 2009

ABSTRACT



Reaction of *N*-δ-allenyl urea 1 with a catalytic 1:1 mixture of gold(I) *N*-heterocyclic carbene complex (5)AuCl [5 = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] and $AgPF_6$ at room temperature for 2 h led to isolation of bicyclic imidazolidin-2-one 4 in 93% yield with ≥98% diastereomeric purity. Gold-catalyzed dihydroamination was effective for a number of *N*-δ- and *N*-γ-allenyl ureas to form the corresponding bicyclic imidazolidin-2-ones in good yield with high diastereoselectivity.

Vicinal diamines and related carboxamide derivatives such as imidazolidin-2-ones are components of a number of naturally occurring and biologically active molecules and find application as chiral ligands and auxiliaries.[1,2] The direct diamination of an alkene represents a particularly attractive approach to the synthesis of vicinal diamines.[3,4] Recent efforts in this area have led to the development of effective processes for the uncatalyzed[5,6] or Pd(II)-[7,8] or Ni(II)-catalyzed[9] oxidative diamination of alkenes with HN-R-NH functionality and for the Pd(0)-[10] or Cu(I)-catalyzed[11] diamination of alkenes with di-*tert*-butyldiaziridinone and related reagents. In this context, we considered the catalytic dihydroamination of allenes as a redox-neutral and atom-economic alternative to alkene diamination for the synthesis of vicinial diamine derivatives. Such an approach would obviate the need for a stoichiometric oxidant or specialized diaziridine reagent and would present new opportunities for stereoselective synthesis. Here, we describe the gold(I)-catalyzed, diastereoselective intramolecular dihydroamination of allenes with *N,N'*-disubstituted ureas to form polycyclic imidazolidin-2-ones.

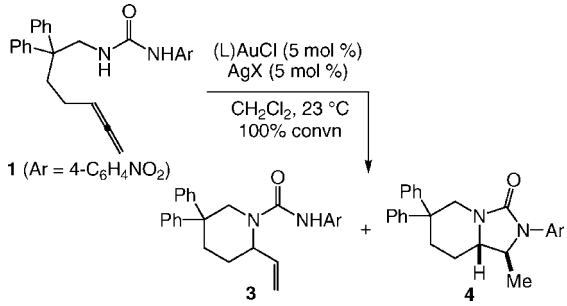
(1) Lucet, D.; Gall, T. L.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580.

(2) For examples of biologically active imidazolidin-2-ones, see: (a) Li, J.; Sutton, J.; Nirschl, A.; Zou, Y.; Wang, H.; Sun, C.; Pi, Z.; Johnson, R.; Krystek, S.; Seethala, R.; Golla, R.; Sleph, P.; Beehler, B.; Grover, G.; Fura, A.; Vyas, V.; Li, C.; Gougoutas, J.; Galella, M.; Zahler, R.; Ostrowski, J.; Hamann, L. *J. Med. Chem.* **2007**, *50*, 3015. (b) Salituro, F. G.; Baker, C. T.; Court, J. J.; Deininger, D. D.; Kim, E. E.; Li, B.; Novak, P. M.; Rao, B. G.; Pazhanisamy, S.; Porter, M. D.; Schairer, W. C.; Tung, R. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3637. (c) Spaltenstein, A.; Almond, M. R.; Bock, W. J.; Cleary, D. G.; Furfine, E. S.; Hazen, R. J.; Kazmierski, W. M.; Salituro, F. G.; Tung, R. D.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1159. (d) Kazmierski, W. M.; Furfine, E.; Gray-Nunez, Y.; Spaltenstein, A.; Wright, L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685. (e) Heidempergher, F.; Pillan, A.; Pinciroli, V.; Vaghi, F.; Arrigoni, C.; Bolis, G.; Caccia, C.; Dho, L.; McArthur, R.; Varasi, M. *J. Med. Chem.* **1997**, *40*, 3369. (f) Reichard, G. A.; Stengone, C.; Paliwal, S.; Mergelsberg, I.; Majmundar, S.; Wang, C.; Tiberi, R.; McPhail, A. T.; Piwinkski, J. J.; Shih, N.-Y. *Org. Lett.* **2003**, *5*, 4249. (g) Shue, H. J.; Chen, X.; Shih, N.-Y.; Blythin, D. J.; Paliwal, S.; Lin, L.; Gu, D.; Schwerdt, J. H.; Shah, S.; Reichard, G. A.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Liu, F.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3896. (h) Shue, H.-J.; Chen, X.; Schwerdt, J. H.; Paliwal, S.; Blythin, D. J.; Lin, L.; Gu, D.; Wang, C.; Reichard, G. A.; Wang, H.; Piwinski, J. J.; Duffy, R. A.; Lachowicz, J. E.; Coffin, V. L.; Nomeir, A. A.; Morgan, C. A.; Varty, G. B.; Shih, N.-Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1065.

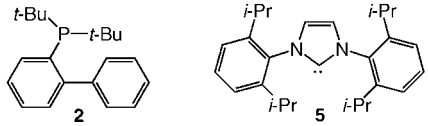
10.1021/ol900730w CCC: $40.75
Published on Web 05/18/2009

We initially targeted *N*-*δ*-allenyl ureas as substrates and cationic gold(I) complexes as catalysis for allene dihydroamination. *δ*-Allenyl ureas were targeted as substrates both to control the regioselectivity of allene hydroamination and to render the challenging alkene hydroamination step intramolecular. Cationic gold(I) complexes were targeted as catalysts owing to the high activity of these complexes toward the hydroamination of both allenes[12] and alkenes[13] with carboxamide derivatives. An initial experiment was encouraging, and treatment of the *N*-2,2-diphenyl-5,6-heptadienyl urea **1** with a catalytic 1:1 mixture of the gold phosphine complex (**2**)AuCl [**2** = P(*t*-Bu)$_2$-*o*-biphenyl] and AgOTf (5 mol %) in CH_2Cl_2 at room temperature for 24 h led to complete consumption of **1** to form an 4:1 mixture of vinyl piperidine derivative **3** and bicyclic imidazolidin-2-one **4** (Table 1, entry 1).

Table 1. Effect of Ligand and Counterion on the Gold(I)-Catalyzed Dihydroamination of **1**



entry	L	X	time (h)	**3**:**4**[a]	dr (**4**)[a]
1	**2**	OTf	24	4:1	—
2	**2**	SbF_6	24	3.8:1	—
3	**5**	SbF_6	24	2.5:1	—
4	**2**	ClO_4	24	4.2:1	—
5	**2**	OAc	24	5:1	—
6	**2**	BF_4	24	4:1	—
7	**5**	BF_4	24	4:1	—
8	**2**	PF_6	2	1:16	11:1
9	**5**	PF_6	2	≤1:50	≥50:1

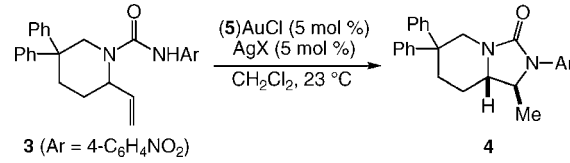


[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

Optimization of the gold(I)-catalyzed dihydroamination of **1** revealed the pronounced effect of the silver salt, in particular $AgPF_6$, on the conversion of **3** to **4** (Table 1).[14] Employment of $AgSbF_6$, $AgClO_4$, AgOAc, or $AgBF_4$ in combination with either phosphine catalyst (**2**)AuCl or the *N*-heterocyclic carbene complex (**5**)AuCl [**5** = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidine] led to predominant formation of **3** after 24 h at room temperature (Table 1, entries 2−7). In sharp contrast, treatment of **1** with a catalytic 1:1 mixture of $AgPF_6$ and (**2**)AuCl led to formation of a 1:16 mixture of **3**:**4** after 2 h, the latter as a 11:1 diastereomeric mixture (Table 1, entry 8). Substitution of (**5**)AuCl for (**2**)AuCl led to further increase in both the selectivity and diastereoselectivity of dihydroamination (Table 1, entry 9).[14]

The effectiveness of $AgPF_6$ relative to closely related silver salts as a cocatalyst for the gold-catalyzed dihydroamination of **1** was mirrored in the gold(I)-catalyzed conversion of **3** to **4** (Table 2). Treatment of **3** with a catalytic 1:1 mixture

Table 2. Effect of Counterion on the Gold(I)-Catalyzed Conversion of **3** to **4**



entry	X	time (h)	convn[a] (%)
1	SbF_6	24	52
2	ClO_4	24	66
3	BF_4	24	48
4	PF_6	2	>98

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture.

of (**5**)AuCl and $AgSbF_6$, $AgClO_4$, or $AgBF_4$ at room temperature for 24 h led to partial (48−66%) conversion (Table 2, entries 1−3). In contrast, conversion of **3** to **4** was complete within 2 h at room temperature in the presence of a catalytic 1:1 mixture of (**5**)AuCl and $AgPF_6$ (Table 2, entry 4).

In a preparative-scale experiment, reaction of **1** with a catalytic 1:1 mixture of (**5**)AuCl and $AgPF_6$ (5 mol %) at room temperature for 2 h led to isolation of **4** in 93% yield with ≥98% diastereomeric purity (Table 3, entry 1). The cis-relationship of the tertiary hydrogen atom and the exocyclic methyl group of **4** was assigned unambiguously by X-ray crystallography (see the Supporting Information). In addition to **1**, *N*-*δ*-allenyl ureas that possessed an *N*′-phenyl (**6**), *N*′′4-methoxyphenyl (**7**), or *N*′-benzyl (**8**) group underwent gold(I)-catalyzed intramolecular dihydroamination to form polycyclic imidazolidin-2-ones **9**−**11** in excellent yield as single diastereomers (Table 3, entries 2−4). The *N*-5,6-heptadienyl urea **12** that lacked substitution at the 2-position of the heptadienyl chain and the heteroatom-substituted *N*-*δ*-allenyl urea derivatives **13** and **14** underwent gold-catalyzed intramolecular dihydroamination to form imidazolidin-2-ones **15**−**17** in good yield as single diastereomers (Table 3, entries 5−7). The *N*-5,6-heptadienyl urea **18** that possessed a single methyl group at the 4-position of the heptadienyl chain underwent gold(I)-catalyzed dihydroamination to form a separable ∼3:1 mixture of diastereomeric bicyclic imidazolidin-2-ones. From this mixture, imidazolidin-2-one **19** was isolated in 70% yield with ≥98%

Table 3. Intramolecular Dihydroamination of *N*-γ- and *N*-δ-Ureas Catalyzed by a Mixture of (**5**)AuCl (5 mol %) and $AgPF_6$ (5 mol %) in CH_2Cl_2 at Room Temperature

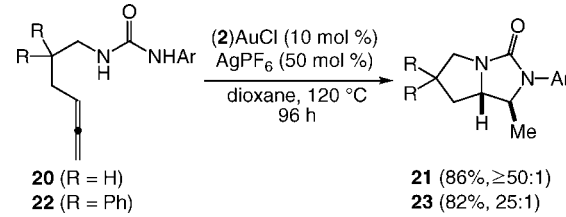
entry	substrate[a]	product	time (h)	yield (%)[b]
1	Ar = $C_6H_4NO_2$ (**1**)	**4**	2	93
2	Ar = Ph (**6**)	**9**	16	94
3	Ar = C_6H_4OMe (**7**)	**10**	16	96
4	**8**	**11**	16	96
5	X = CH_2 (**12**)	**15**	16	83
6	X = O (**13**)	**16**	16	90
7	X = NTs (**14**)	**17**	24	86
8	**18**	**19**	60[c]	70

[a] Ar = 4-$C_6H_4NO_2$ unless noted otherwise. [b] Isolated material of >95% purity with ≥98% diastereomeric purity. [c] Crude reaction mixture consisted of a ~3:1 mixture of diastereomers. The minor diastereomer of **19** (*epi*-**19**) was epimeric at the methyl-bound stereocenter of the piperidine ring (see the Supporting Information).

diasteromeric purity (Table 3, entry 8). The relative configuration of **19** was established by NOESY analysis (see the Supporting Information).

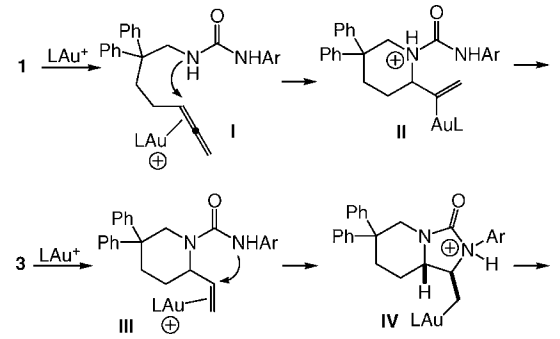
N-γ-Allenyl ureas also underwent gold(I)-catalyzed dihydroamination to form bicyclic imidazolidin-2-ones, although higher catalyst loading and considerably higher reaction temperature was required. Higher reaction temperature, in turn, required employment of the less active but more thermally robust gold phosphine complex (**2**)AuCl in place of (**5**)AuCl. In an optimized procedure (see the Supporting Information), reaction of *N*-γ-allenyl urea **20** with a catalytic mixture of (**2**)AuCl (10 mol %) and $AgPF_6$ (50 mol %) in dioxane at 120 °C for 96 h led to exclusive formation of imidazolidin-2-one **21**, which was isolated in 86% yield with ≥98% diastereomeric purity (Scheme 1).[15] *N*-2,2-Diphenyl-4,5-hexadienyl urea **22** also underwent dihydroamination under these conditions to form **23** in 82% isolated yield with 96% diastereomeric purity (Scheme 1).

Scheme 1



Outer-sphere pathways for the gold(I)-catalyzed hydrofunctionalization of C−C multiple bonds have been proposed on the basis of stereochemical[16] and computational analyses.[17] On the basis of these precedents, we propose that the gold(I)-catalyzed dihydroamination of *N*-allenyl ureas occurs via two successive outer-sphere C−N bond forming processes (Scheme 2). In the specific case of the gold(I)-

Scheme 2



catalyzed conversion of **1** to **4**, outer-sphere attack of the internal nitrogen atom on gold π-allene complex **I** followed

(3) For early approaches to alkene dihydroamination that employ a stoichiometric amount of transition metal or heavy metal salt, see: (a) Backvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163. (b) Aranda, V. G.; Barluenga, J.; Aznar, F. *Synthesis* **1974**, 504. (c) Barluenga, J.; Aznar, F.; de Mattos, M. C. S.; Kover, W. B.; Garcia-Granda, S.; Pérez-Carreño, E. *J. Org. Chem.* **1991**, *56*, 2930. (d) Chong, A. O.; Oshima, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 3420. (e) Becker, P. N.; White, M. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 5676.

(4) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190.

(5) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039.

(6) (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (b) Zawaba, T. P.; Chelmer, S. R. *Org. Lett.* **2007**, *9*, 2035.

(7) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308.

(8) (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586. (b) Muñiz, K.; Hövelmann, C. H.; Campos-Gómez, E.; Barluenga, J.; González, J. M.; Streuff, J.; Nieger, M. *Chem. Asian J.* **2008**, *3*, 776. (c) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763. (d) Muñiz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem. Asian J.* **2008**, *3*, 1248. (e) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542. (f) Hövelmann, C. H.; Streuff, J.; Brelot, L.; Muñiz, K. *Chem. Commun* **2008**, 2334.

(9) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125.

(10) (a) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (b) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 11688. (c) Xu, L.; Du, H.; Shi, Y. *J. Org. Chem.* **2007**, *72*, 7038. (d) Xu, L.; Shi, Y. *J. Org. Chem.* **2008**, *73*, 749.

(11) Zhao, B.; Du, H.; Shi, Y. *Org. Lett.* **2008**, *10*, 1087.

(12) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066.

by proton transfer/protodeauration of the resulting alkenyl gold species **II** would form **3** (Scheme 2). Outer-sphere attack of the second nitrogen atom on the gold π-alkene complex **III** followed by proton transfer/protodeauration of alkyl gold species **IV** would then form **4**. The origin of the high diastereoselectivity of gold(I)-catalyzed dihydroamination remains unclear. Diastereoselectivity may be determined either by the conversion of **III** to **IV** in the event that C−N bond formation is irreversible or by the conversion of **IV** to **4** in the case of reversible C−N bond formation followed by irreversible protodeauration.[17]

In summary, we have developed effective Au(I)-catalyzed protocols for the intramolecular dihydroamination of γ- and δ-allenyl ureas to form bicyclic imidazolidin-2-ones that proceed in good yield with excellent diastereoselectivity. We are currently working toward the development of more effective and more general allene dihydroamination protocols and toward the elucidation of the kinetics and mechanism of gold(I)-catalyzed allene dihydroamination.

Acknowledgment is made to the NIH (GM-080422) and Johnson & Johnson for support of this research and to the NCBC (2008-IDG-1010) for support of the Duke University NMR facility. We thank Marina G. Dickens (Department of Chemistry, Duke University) for determining the X-ray crystal structure of **4**.

Supporting Information Available: Experimental procedures, analytical and spectroscopic data for allenyl ureas and imidazolidin-2-ones, and X-ray crystallographic data for **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL900730W

(13) (a) Han, X.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1747. (b) Bender, C. F.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 5303. (c) Bender, C. F.; Widenhoefer, R. A. *Chem. Commun.* **2006**, 4143.

(14) Treatment of **1** with either $AgPF_6$ or (**5**)AuCl alone or with a mixture of $AgPF_6$ and **5** or HBF_4 and **5** in CH_2Cl_2 led to no detectable formation of either **3** or **4** after 2 h at room temperature. Furthermore, silver was not required for efficient dihydroamination; treatment of **6** with a catalytic amount of $[(\mathbf{5})Au(NCAr_F)]^+$ SbF_6^- [$NCAr_F$ = N≡C-3,5-$C_6H_3(CF_3)_2$] (5 mol %) in CH_2Cl_2 for 16 h led to quantitive formation of **9** (see the Supporting Information).

(15) The beneficial effect of the high loading of $AgPF_6$ is unclear. Control experiments, however, ruled out the presence of a silver(I) or acid-catalyzed pathway for intramolecular hydroamination of the 2-vinylpyrrolidine intermediate formed in the gold(I)-catalyzed dihydroamination of **22**. Furthermore, dihydroamination of **22** catalyzed by the silver-free complex $[(\mathbf{2})Au(NCAr_F)]^+$ SbF_6^- [$NCAr_F$ = N≡C-3,5-$C_6H_3(CF_3)_2$] was not significantly less effective than was dihydroamination of catalyzed by (**2**)AuCl/$AgPF_6$ (see the Supporting Information).

(16) (a) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (b) Zhang, Z.; Widenhoefer, R. A. *Org. Lett.* **2008**, *10*, 2079. (c) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (d) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (f) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409. (g) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

(17) Kovács, G.; Ujaque, G.; Lledós, A. *J. Am. Chem. Soc.* **2008**, *130*, 853.