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

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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-ylidene] and AgPF₆ at room temperature for 2 h led to isolation of bicyclic imidazolidin-2-one **4** in 93% yield as a single diastereomer. 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)-catalyzed⁹ oxidative diamination of alkenes with HN–R–NH functionality and for the Pd(0)-¹⁰ or Cu(I)-catalyzed¹¹ diamination of alkenes with di-tert-butyl diaziridinone 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 vicinal 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.

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Supporting Information Available: Experimental procedures and scans of NMR spectra for *N*-allylic carbamates (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

We initially targeted *N*- δ -allenyl ureas as substrates and cationic gold(I) complexes as catalysts 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 allenes¹² and alkenes¹³ 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 CH₂Cl₂ 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).

Optimization of the gold(I)-catalyzed dihydroamination of **1** revealed the pronounced effect of the silver salt, in particular AgPF₆, on the conversion of **3** to **4** in (Table 1). Employment of AgSbF₆, AgClO₄, AgOAc, or AgBF₄ 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-ylidene] 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 AgPF₆ 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 AgPF₆ relative to closely related silver salts as a cocatalyst for the conversion of **3** to **4** in the gold catalyzed dihydroamination of **1** was confirmed employing isolated, purified **3** (Table 2). Treatment of **3** with a catalytic 1:1 mixture of (5)AuCl and either AgSbF₆, AgClO₄, or AgBF₄ 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 AgPF₆ (Table 2, entry 4).

In a preparative-scale experiment, reaction of **1** with a catalytic 1:1 mixture of (5)AuCl and AgPF₆ (5 mol %) at room temperature for 2 h led to isolation of **4** in 93% yield with $\geq 98\%$ 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 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 $\geq 98\%$ diastereomeric purity (Table 3, entry 8).¹⁵

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 Supporting Information), reaction of *N*- γ -allenyl urea **20** with a catalytic mixture of (2)AuCl (10 mol %) and AgPF₆ (50 mol %) in toluene at 120 °C for 96 h led to exclusive formation of imidazolidin-2-one **21**, which was isolated in 86% yield with $\geq 98\%$ 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 as a 24:1 mixture of diastereomers (Scheme 1).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Lucet D, Gall TL, Mioskowski C. *Angew. Chem* 1998;110:2724. *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. [PubMed: 17552509] (b) Salituro FG, Baker CT, Court JJ, Deininger DD, Kim EE, Li B, Novak PM, Rao BG, Pazhanisamy S, Porter MD, Schairer WC, Tung RD. *Bioorg. Med. Chem. Lett* 1998;8:3637. [PubMed: 9934485] (c) Spaltenstein A, Almond MR, Bock WJ, Cleary DG, Furfine ES, Hazen RJ, Kazmierski WM, Salituro FG, Tung RD, Wright LL. *Bioorg. Med. Chem. Lett* 2000;10:1159. [PubMed: 10866371] (d) Kazmierski WM, Furfine E, Gray-Nunez Y, Spaltenstein A, Wright L. *Bioorg. Med. Chem. Lett* 2004;14:5685. [PubMed: 15482948] (e) Heidempergher F, Pillan A, Pincirolì V, Vaghi F, Arrigoni C, Bolis G, Caccia C, Dho L, McArthur R, Varasi M. *J. Med. Chem* 1997;40:3369. [PubMed: 9341912] (f) Reichard GA, Stengone C, Paliwal S, Mergelsberg I, Majmundar S, Wang C, Tiberi R, McPhail AT, Piwinski JJ, Shih N-Y. *Org. Lett* 2003;5:4249. [PubMed: 14601972] (g) Shue HJ, Chen X, Shih N-Y, Blythin DJ, Paliwal S, Lin L, Gu D, Schwerdt JH, Shah S, Reichard GA, Piwinski JJ, Duffy RA, Lachowicz JE, Coffin VL, Liu F, Nomeir AA, Morgan CA, Varty GB. *Bioorg. Med. Chem. Lett* 2005;15:3896. [PubMed: 16019209] (h) Shue H-J, Chen X, Schwerdt JH, Paliwal S, Blythin DJ, Lin L, Gu D, Wang C, Reichard GA, Wang H, Piwinski JJ, Duffy RA, Lachowicz JE, Coffin VL, Nomeir AA, Morgan CA, Varty GB, Shih N-Y. *Bioorg. Med. Chem. Lett* 2006;16:1065. [PubMed: 16290143]
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 VG, Barluenga J, Aznar F. *Synthesis* 1974:504. (c) Barluenga J, Aznar F, de Mattos MCS, Kover WB, Garcia-Granda S, Pérez-Carreño E. *J. Org. Chem* 1991;56:2930. (d) Chong AO, Oshima K, Sharpless KB. *J. Am. Chem. Soc* 1977;99:3420. (e) Becker PN, White MA, Bergman RG. *J. Am. Chem. Soc* 1980;102:5676.
4. de Figueiredo RM. *Angew. Chem. Int. Ed* 2009;48:1190.
5. Cochran BM, Michael FE. *Org. Lett* 2008;10:5039. [PubMed: 18841990]
6. (a) Zabawa TP, Kasi D, Chemler SR. *J. Am. Chem. Soc* 2005;127:11250. [PubMed: 16089447] (b) Zabawa TP, Chelmer SR. *Org. Lett* 2007;9:2035. [PubMed: 17447781]
7. Bar GLJ, Lloyd-Jones GC, Booker-Milburn KI. *J. Am. Chem. Soc* 2005;127:7308. [PubMed: 15898768]
8. (a) Streuff J, Hövelmann CH, Nieger M, Muñoz K. *J. Am. Chem. Soc* 2005;127:14586. [PubMed: 16231907] (b) Muñoz K, Hövelmann CH, Campos-Gómez E, Barluenga J, González JM, Streuff J, Nieger M. *Chem. Asian J* 2008;3:776. [PubMed: 18357591] (c) Muñoz K, Hövelmann CH, Streuff J. *J. Am. Chem. Soc* 2008;130:763. [PubMed: 18081279] (d) Muñoz K, Streuff J, Chávez P, Hövelmann CH. *Chem. Asian J* 2008;3:1248. [PubMed: 18655067] (d) Muñoz K. *J. Am. Chem. Soc*

- 2007;129:14542. [PubMed: 17985900] (e) Hövelmann CH, Streuff J, Brelot L, Muñiz K. Chem. Commun 2008:2334.
9. Muñiz K, Streuff J, Hövelmann CH, Núñez A. Angew. Chem.Int. Ed 2007;46:7125.
- 10-. (a) Du H, Zhao B, Shi Y. J. Am. Chem. Soc 2007;129:762. [PubMed: 17243803] (b) Du H, Yuan W, Zhao B, Shi Y. J. Am. Chem. Soc 2007;129:11688. [PubMed: 17803307] (c) Xu L, Du H, Shi Y. J. Org. Chem 2007;72:7038. [PubMed: 17676910] (d) Xu L, Shi Y. J. Org. Chem 2008;73:749. [PubMed: 18095707]
11. Zhao B, Du H, Shi Y. Org. Lett 2008;10:1087. [PubMed: 18302393]
12. Zhang Z, Liu C, Kinder RE, Han X, Qian H, Widenhoefer RA. J. Am. Chem. Soc 2006;128:9066. [PubMed: 16834380]
13. (a) Han X, Widenhoefer RA. Angew. Chem 2006;118:1779. Angew. Chem. Int. Ed 2006;45:1747. (b) Bender CF, Widenhoefer RA. Org. Lett 2006;8:5303. [PubMed: 17078703] (c) Bender CF, Widenhoefer RA. Chem. Commun 2006:4143.
14. Treatment of **1** with either AgPF₆ or (**5**)AuCl alone or with a mixture of AgPF₆ and **5** or HBF₄ and **5** in CH₂Cl₂ led to no detectable formation of either **3** or **4** after 2 h at room temperature.
15. The other isomer epimeric of **19** is at the methyl-containing stereocenter on the 6-membered ring.
16. Although the beneficial effect of the high loading of AgPF₆ is unclear, control experiments 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** (See Supporting Information).

Scheme 1.

Table 1Effect 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

entry	L	X	time (h)	3.4 ^a	dr(4) ^a

^aDetermined by ¹H NMR analysis of the crude reaction mixture.

Table 2Effect of counterion on the Au(I)-catalyzed intramolecular hydroamination of **3**.

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

^aDetermined by ¹H NMR analysis of the crude reaction mixture.

Table 3

Intramolecular dihydroamination of *N*- γ - and *N*- δ -ureas catalyzed by a mixture of (5)AuCl (5 mol %) and AgPF₆ (5 mol %) in CH₂Cl₂ at room temperature.

1 Ar = C₆H₄NO₂ (**1**)

2 Ar = Ph (**6**)

3 Ar = C₆H₄OMe (**7**)

entry	substrate ^a

5	X = CH ₂ (12)
6	X = O (13)
7	X = NTs (14)
8

^a Ar = 4-CH₃NO₂ 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.